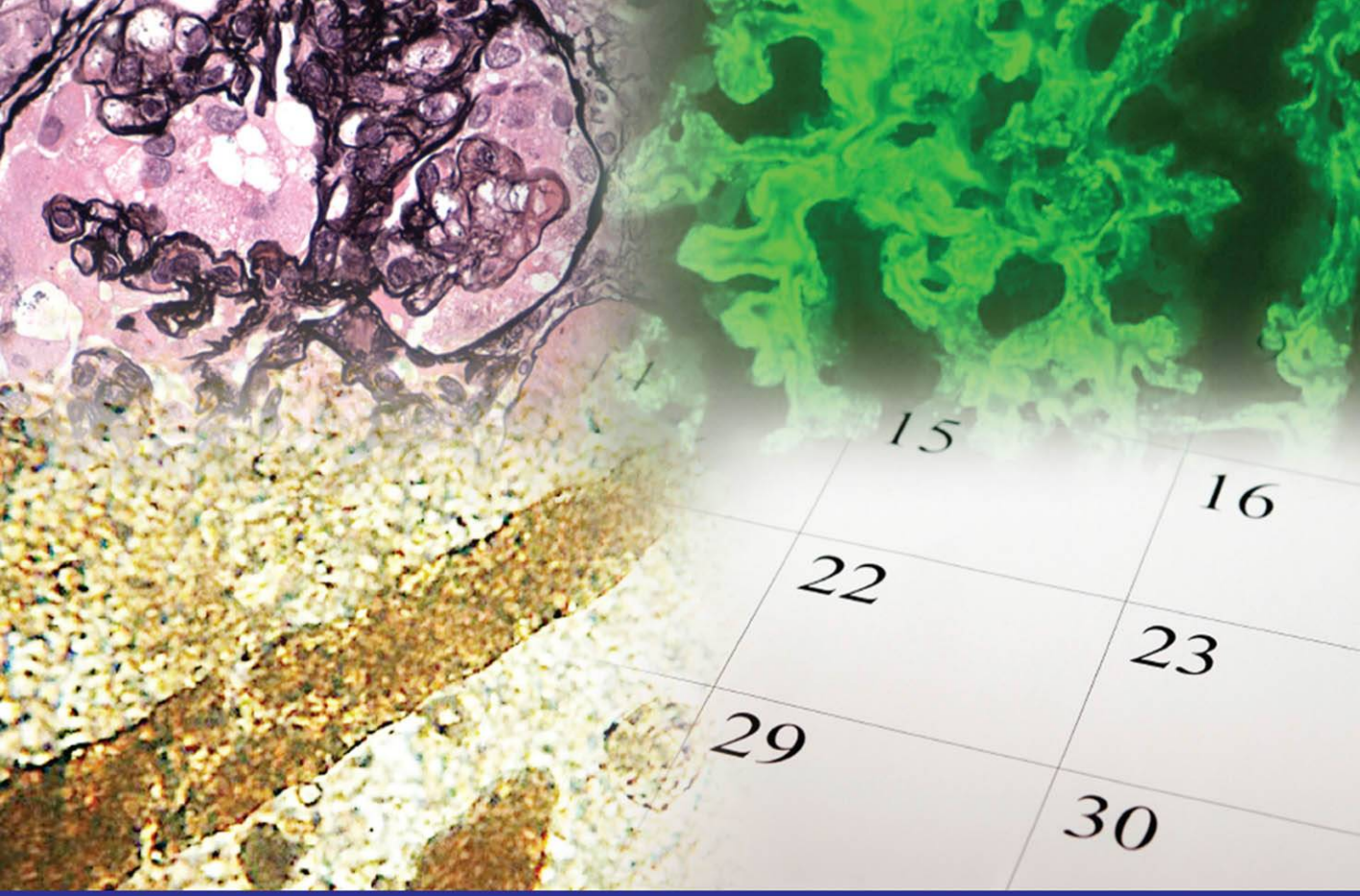

NEPHROLOGY IN 30 DAYS

SECOND EDITION

ROBERT F. REILLY, JR. • MARK A. PERAZELLA

Mc Graw Hill Education
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Nephrology in 30 Days

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Nephrology in 30 Days

Second Edition

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Dedication

To my wife Sheli, my parents Robert Sr. and Nancy, my son Rob, and my brothers Steven and Fred whose help and support are invaluable in both my life and career.

RFR, Jr.

To my parents Joe and Santina Perazella who remain ardent supporters, to my wife Donna who continues to support my academic efforts, to my brothers Joe and Scott who make life interesting, and to my boys Mark and Andrew who always make me proud.

MAP

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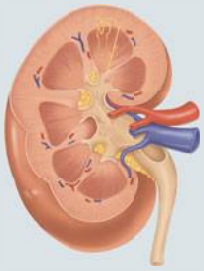

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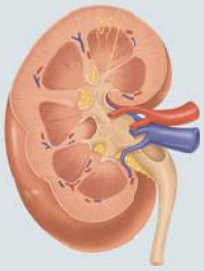

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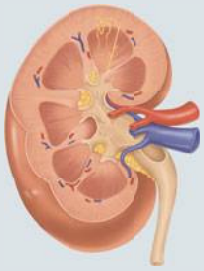


Preface

Much has changed in the world of Nephrology since our first edition of Nephrology in 30 days. Significant advances have occurred in our understanding of fluid, electrolyte, and acid-base disorders, as well as structural kidney disease. Newer, more accurate formulas are available to estimate glomerular filtration rate, the role of WNK kinases in distal tubular sodium and potassium handling has been further clarified, hyponatremia guidelines were revised, vaptans are now available for clinical use, new forms of metabolic acidosis have been reported, genetic disorders of magnesium transport provide insight into how magnesium is reabsorbed in the distal convoluted tubule, FGF-23 and Klotho were shown to play keys roles in phosphorus homeostasis, the mechanism of nephrogenic systemic fibrosis is clearer, concerns have been raised regarding use of erythropoietic stimulating agents, the mechanisms and antigens involved in membranous glomerulonephritis and Balkan nephropathy were elucidated, the treatment of glomerular diseases and vasculitis continues to advance, approaches to and classifications of both chronic kidney disease and acute kidney injury have changed, and renal toxicities of newer drugs have been identified.

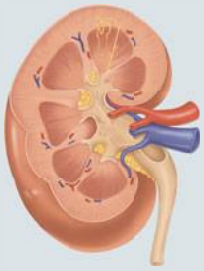
These are only a few of the advances in Nephrology covered in the second edition. Perhaps more than any other subspecialty of medicine, kidney disease has no specialty boundaries. It is, therefore, imperative that physicians early in their training as medical students, physician assistants, house officers, and subspecialty fellows gain a solid understanding of basic aspects of nephrology. Kidney disease, disturbances of fluid and electrolyte balance, and disorders of acid-base and mineral metabolism homeostasis can be confusing to many trainees and non-nephrology physicians. This book was conceived to remove that confusion. *Nephrology in 30 Days* provides a comprehensive and concise text for physicians in training and practitioners.

This textbook is an ideal tool for health care providers to rapidly attain a complete understanding of the basics of nephrology, allowing an educated approach to diagnosis and management of kidney disease and its associated complications. As the title suggests, those who read the book will gain this knowledge within 30 days. Such a time frame is ideal for medical students, physician assistants, and medical residents rotating on the clinical nephrology service elective. The book will be a foundation for them to build upon by intelligently utilizing other sources of information such as primary literature from journals and more detailed reference textbooks. It will also serve as an efficient resource for non-nephrology practitioners in internal medicine and other fields of medicine and surgery.

Nephrology in 30 Days is broken down into three major sections. The first section discusses electrolyte and acid-base disturbances. Experts in the field review disorders of sodium and potassium balance, use of intravenous fluids, pathogenesis and treatment of diuretic resistance, and respiratory and metabolic acidosis/alkalosis. The second section deals primarily with disturbances of mineral metabolism. Concise discussions of calcium, phosphate, and magnesium homeostasis are presented. Clinical disease states associated with these divalent disorders are reviewed, as are the pathogenesis and treatment of nephrolithiasis. The last section is dedicated to structural kidney disease. Acute kidney injury and chronic kidney disease are explored separately. Aspects of urinalysis and examination of the urine sediment are reviewed. Diseases of various structures within the kidney are also examined. Included are the glomerulopathies, both primary and those due to systemic processes, tubulointerstitial diseases, and abnormalities of the urinary tract including infection and obstruction. Finally, essential hypertension and secondary causes of hypertension

are reviewed. Importantly, renal imaging and genetic causes of kidney disease are covered within each of the chapters where they figure prominently.

Homer Smith in his book *From Fish to Philosopher stated* "What engineer, wishing to regulate the composition of the internal environment of the body on which the function of every bone, gland, muscle, and nerve depends, would devise a scheme that operated by throwing the whole thing out sixteen times a day and rely on grabbing from it, as it fell to earth, only those precious elements which he wanted to keep?" Hopefully, after reading this book the reader will begin to comprehend the wonderful complexity and ingenuity of the engineer that is the kidney.



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RFR, Jr.

I wish to thank Dr. Robert Reilly who had the vision to conceive of the first edition of our book and remains an excellent co-editor to work with on the second edition. I would like to extend my gratitude to the numerous mentors and colleagues who continue to influence my career in medicine and nephrology. While it is impossible to name them all, some of the many are Peter Aronson, Asghar Rastegar, John Hayslett, Stefan Somlo, Peggy Bia, Stephen Huot, Ursula Brewster, Steven Coca, Gary Desir, Rex Mahnensmith, Aldo Peixoto, Chirag Parikh, David Geller, Lloyd Cantley, Richard Formica, William Asch, Ali Abu-Alfa, Gilbert Moeckel, Glen Markowitz, John Aruny, Anushree Shirali, and Jeff Turner. Thanks to Jim Shanahan of McGraw-Hill for his support on the second edition of *Nephrology in 30 Days*. Finally, I would like to extend my most sincere thanks to the medical students, house officers, and in particular my beloved nephrology fellows who I have had the distinct honor to train and who, in the process, have also taught me a great deal.

MAP

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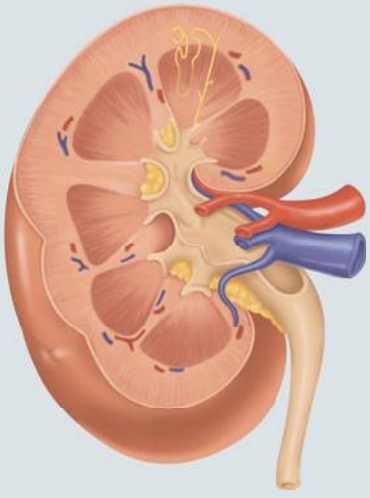
CHAPTER 1

Introduction

• *Mark A. Perazella*

Recommended Time to Complete: 1 Day



Guiding Questions

1. What are the essential functions of the kidney?
2. The nephron is the basic unit of the kidney. What are its major components?
3. How does the glomerular capillary loop prevent the filtration of macromolecules?
4. What factors are integral to the formation of glomerular ultrafiltrate?
5. How is glomerular filtration rate (GFR) regulated in normal subjects on a day-to-day basis?
6. What factors maintain renal perfusion and GFR during states of severe intravascular volume depletion?
7. How is GFR best measured in the clinical setting?
8. Are there accurate estimates of GFR that can substitute for a 24-hour urine collection?

INTRODUCTION

The kidney is designed to perform a number of essential functions. First, it contributes importantly to the maintenance of the extracellular environment that is essential for normal cellular function. The kidney achieves an optimal extracellular environment through excretion of waste products such as urea, creatinine, uric acid, and other substances. Balanced excretion of water and electrolytes is another important role of the kidney. Second, the kidney regulates systemic and renal hemodynamics through the production of various hormones, as well as the regulation of salt and water balance. Hormones such as renin, angiotensin II (AII), prostaglandins (PGs), endothelin, nitric oxide, adenosine, and bradykinin regulate vascular reactivity and renal blood flow. Third, the kidney produces other hormones that influence various end-organ functions. Red blood cell production is stimulated by renal erythropoietin synthesis, which is controlled by a highly regulated oxygen sensor in the proximal nephron. Hence the kidney can be viewed as a "critmeter", which monitors and controls red blood cell production and the hemoglobin and hematocrit. Bone metabolism is influenced by renal production of calcitriol, as well as proper balance of calcium and phosphorus. Finally, the kidney participates in gluconeogenesis during fasting to prevent hypoglycemia. It also contributes to the catabolism of various peptide hormones filtered by the glomerulus such as insulin.

To perform these functions, the kidney is uniquely constructed to filter, reabsorb, and secrete a variety of substances in a very precise manner through integrated regulation of renal hemodynamics and tubular handling of water and solutes. Secretion of hormones such as erythropoietin and calcitriol closely link kidney function with control of red cell mass and bone metabolism. Metabolism of peptide hormones and clearance of medications

is another important kidney function to maintain health. Disturbances in these processes lead to several harmful and potentially life-threatening clinical syndromes.

KEY POINTS

Functions of Kidney

1. The kidney maintains the extracellular environment through excretion of waste products and proper electrolyte and water balance.
2. Several hormones are produced in the kidney that act to control renal hemodynamics, stimulate red cell production, and maintain normal bone homeostasis.

MORPHOLOGY OF THE KIDNEY

Gross examination of the kidney reveals an outer portion, the cortex, and inner portion, the medulla (Figure 1.1). Blood is supplied to the kidney via the renal artery (or arteries) and is drained via the renal vein. As is discussed next, the glomeruli, which are the filtering units of the nephron, are found within the cortex. Tubules are located in both cortex and medulla. The medulla consists of an inner and outer stripe. Collecting tubules form a large part of the inner medulla and papilla. Urine is formed by glomerular filtration and modified by the tubules, leaves the collecting ducts and drains sequentially into the calyces, renal pelvis, ureter, and finally into the bladder.

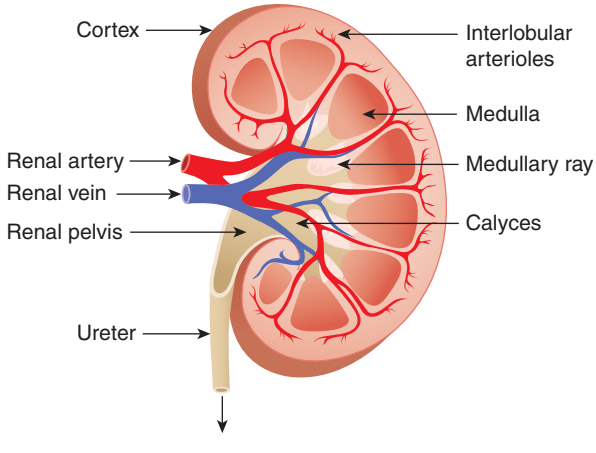


FIGURE 1-1. Anatomy of the kidney. Shown are the cortex, medulla, calyces, renal pelvis, and ureter.

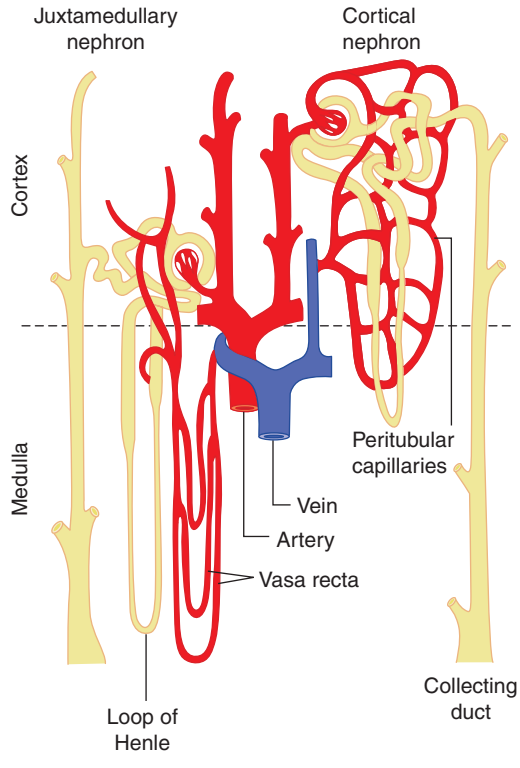


FIGURE 1-2. The nephron. The nephron consists of a glomerulus and series of tubules. Nephrons can be subdivided into those in cortex and those in the juxtamedullary region. The glomerulus is composed of a capillary tuft interposed between the afferent and efferent arteriole. Tubules are supplied by a peritubular capillary network that includes the vasa recta, which runs parallel to the loop of Henle.

The nephron is the basic unit of the kidney. There are approximately 1.0 to 1.3 million nephrons in the normal adult kidney. The nephron consists of a glomerulus and a series of tubules (Figure 1.2). The glomerulus is composed of a tuft of capillaries with a unique vascular supply. Glomerular capillaries are interposed between an afferent and efferent arteriole. They reside in the cortex and corticomedullary junction. Within the tubular lumen glomerular filtrate is modified by tubular cells. Tubules are lined by a continuous layer of epithelial cells, each of which possesses characteristic morphology and function depending on its location in the nephron. The tubules are present both in cortex and medulla.

An ultrafiltrate of plasma is formed by the glomerulus and passes into the tubules where it is modified by reabsorption (removal of a substance from the ultrafiltrate)

and secretion (addition of a substance to the ultrafiltrate). Different tubular segments alter fluid contents by varying reabsorption and secretion. Division of the nephron is based on morphology, as well as permeability and transport characteristics of the segments. For example, the proximal tubule and loop of Henle reabsorb the bulk of filtered water and solutes. In the distal nephron, and particularly in collecting tubules, fine adjustments in urinary composition are undertaken. Also, there is heterogeneity of cell types within the cortical collecting tubule. In this segment, the principal cell reabsorbs sodium and secretes potassium while the intercalated cell secretes hydrogen ion and reabsorbs potassium.

The formation of urine occurs as glomerular filtrate is sequentially modified in tubular segments. Plasma is ultrafiltered by the glomerulus and passes from the Bowman space into the proximal tubule. This nephron segment consists anatomically of an initial convoluted segment, followed by a straight segment, and the pars recta that enters the outer medulla. The loop of Henle, which possesses a hairpin configuration, follows the pars recta and includes a thin descending limb, and thin and thick ascending limb. The loops of Henle are not uniform in their length. Approximately 40% are short loops that don't enter the medulla or enter only the outer medulla. These loops do not have a thin ascending limb and are located predominantly in outer cortex. The remaining loops of Henle are long and extend into the medulla and may reach the inner medulla and papilla. Long loops are located in the juxtamedullary region. Both short and long loops are found in midcortex.

The thick ascending limb of the loop of Henle has a cortical segment that returns to its own glomerulus. This tubule, which has specialized epithelial cells known as the macula densa, approximates the afferent arteriole, forming the juxtaglomerular (JG) apparatus. As is discussed later, the JG apparatus participates importantly in regulation of GFR.

Four cortical tubular segments follow the macula densa. They are the distal convoluted tubule, the connecting segment, the initial collecting tubule, and the cortical collecting tubule. The connecting segments drain into a single cortical collecting tubule, which then connects to the medullary collecting tubule. In cortex, initial collecting tubules drain into collecting ducts, whereas deeper connecting tubules drain into connecting segments. These are called *arcades*. From this segment, urine drains into the calyces, renal pelvis, ureters, and bladder.

KEY POINTS

Morphology of the Kidney

1. On gross examination, the kidney is composed of cortex, inner and outer medulla, calyces, pelvis, and ureter.
2. The nephron is the basic unit of the kidney. It is composed of a glomerulus and a series of tubules.
3. The tubules are divided into proximal tubule, loop of Henle, distal convoluted tubule, connecting segment, initial collecting tubule, and cortical and medullary collecting tubule.
4. Following modification of the glomerular ultrafiltrate by the tubules, urine is sequentially drained into the calyces, renal pelvis, ureter, and bladder.

RENAL CIRCULATION

Renal blood flow exceeds most other organs and, on average, the kidneys receive approximately 20% of the cardiac output. This calculates to approximately 1 L/min of blood and 600 mL of plasma. Of this, 20% of plasma is filtered into the Bowman space, giving a filtration rate of approximately 120 mL/min. Renal arteries carry blood into the kidney where it passes through serial branches, which include the interlobar, arcuate, and interlobular arteries. Blood enters the glomerulus through the afferent arteriole. A plasma ultrafiltrate is formed within the capillary tuft and passes into the Bowman space. Blood remaining in the capillaries exits the glomerulus via the efferent arteriole. In cortex, blood in postglomerular capillaries flows adjacent to the tubules, while branches from the efferent arterioles of juxtamedullary glomeruli enter the medulla and form the vasa recta capillaries. Blood exits the kidney through a venous system into the systemic circulation.

The circulatory anatomy within the kidney determines the final urine composition. First, GFR importantly influences the amount of solute and water that is excreted. Second, peritubular capillaries in cortex modify proximal tubular reabsorption and secretion of solutes and water. They also return reabsorbed solutes and water to the systemic circulation. Third, creation of the countercurrent gradient for water conservation is dependent on vasa recta capillary function. These capillaries also return reabsorbed salt and water to the systemic circulation.

KEY POINTS

Renal Circulation

1. The kidney receives 20% of the cardiac output or 1 L of blood per minute.
2. Renal circulatory anatomy allows precise modulation of salt and water balance.

GLOMERULAR ANATOMY

As stated previously, the glomerulus is comprised of a capillary network with an afferent and efferent arteriolar circulation. This design sets the glomerular circulation apart from other organ systems and allows modification of urine composition to meet the demands of various, often extreme diets. The glomerular capillary tuft sits within the parietal epithelial cell space, known as the *Bowman capsule*. The parietal epithelium is continuous with the visceral epithelial cells (podocytes), which cover the glomerular capillary tuft. The glomerular capillary loop is comprised of endothelial cell, glomerular basement membrane (GBM), and podocyte, all of which are supported structurally by mesangial cells. The GBM consists of a fusion of endothelial and visceral epithelial cell basement membrane components, which include type IV collagen, laminin, nidogen, and heparan sulfate proteoglycans. It functions to maintain normal glomerular architecture, anchor adjacent cells, and restrict passage of various macromolecules. The podocyte is attached to the GBM by discrete foot processes, which have pores containing slit diaphragms. The slit diaphragm is a thin membrane that acts as the final filtration barrier.

Glomerular Filtration

A key function of the glomerulus is to act as a filtration barrier that permits the passage of water and other solutes and restricts the movement of certain molecules. For example, filtration of water, sodium, urea, and creatinine are integral to proper toxin clearance, volume balance, and electrolyte homeostasis. In contrast, restriction of filtration of large proteins (albumin, immunoglobulin G) prevents the development of hypoalbuminemia, negative nitrogen balance, and infection. The glomerular capillary wall restricts solute movement by using both size and charge selectivity.

Size selectivity is maintained by GBM and podocyte foot process slit diaphragms. The GBM contributes to size selectivity through the creation of functional pores present in the spaces between the cords of type IV collagen. Two populations of pores are present in glomerular capillary wall: a more common small pore (radius 42 Å) and a less numerous larger pore (70 Å). Other capillary loop elements, however, provide additional size selectivity. This is known because isolated GBM studies demonstrate more permeability in GBM than intact glomerulus, suggesting an important role of glomerular epithelial cells. Also, molecules that pass through the GBM are restricted from passage into the Bowman space by epithelial slit diaphragms. A number of podocyte proteins (nephrin, podocin, synaptopodin, podocalyxin, α-actin 3) interact to form the slit diaphragms and maintain podocyte integrity as a filtration barrier. Mutation in genes that synthesize these proteins as well as effacement of foot processes by disease states is associated with filtration barrier loss and the development of proteinuria. Glomerular endothelial cells, however, contribute very little to size selectivity, as their fenestrae are wide and do not restrict macromolecules until they reach a radius larger than 375 Å.

Macromolecule filtration is also prevented by charge selectivity. Electrostatic repulsion is created by anionic sites in the GBM and endothelial cell fenestrae. Heparan sulfate proteoglycans, which are synthesized by glomerular endothelial and epithelial cells, provide the bulk of negative charge. The charge barrier was first noted when the differential effect of similar-sized dextrans with various charges (neutral, cationic, anionic) on filtration was noted. Neutral and cationic dextrans undergo greater filtration than anionic dextrans, despite similar molecular weight (Figure 1.3). This finding supports a glomerular charge barrier. In humans, albumin is restricted from filtration based on both size and charge selectivity. When glomerular injury occurs, impairment of both size and charge selectivity results. An increased number of larger pores, the development of rents and cavities in the GBM, and a defect in charge selectivity allow proteinuria in diseases such as membranous nephropathy, diabetic nephropathy, and focal glomerulosclerosis. Loss of charge selectivity plays a major role in the protein leak that occurs with minimal change disease, although loss of size selectivity may contribute. It is interesting to note that small solute and water clearance are impaired in this setting, likely a result of loss of capillary surface area, while protein losses continue through large pores unimpeded because of loss of anionic charge repulsion.

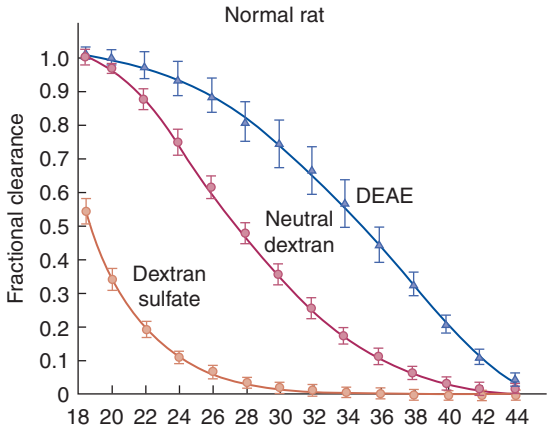


FIGURE 1-3. Filtration curves for neutral, cationic, and anionic dextrans. The curves show that filtration of anionic dextrans is impeded by negative charge in the glomerular capillary wall supporting the conclusion that the glomerular capillary wall impedes protein movement via a charge and size barrier. (From Brenner BM, Bohrer MP, Baylis C, and Deen WM. *Kidney Int.* 12:229-237, 1977, with permission.)

Other Glomerular Functions

In addition to filtration, the glomerulus has other roles in kidney. Endothelial cells secrete hormones (endothelin, prostacyclin, and nitric oxide) that influence vasomotor tone in the renal circulation. They also participate in inflammation by expressing adhesion molecules that enhance inflammatory cell accumulation. Glomerular epithelial cells remove macromolecules that penetrate the GBM and enter the subepithelial space. As noted previously, they synthesize key components of the GBM.

An area of the glomerulus not discussed previously but nonetheless an important member of the glomerular architecture is the mesangium. Two cell types comprise the mesangium. The mesangial cell has contractile properties that originate from its smooth muscle-like microfilaments. It can also synthesize PGs and react to AII. These properties make the mesangial cell ideally suited to regulate glomerular hemodynamics through changes in glomerular capillary surface area and in the vasomotor tone of the renal microcirculation. Mesangial cells are also involved in immune-mediated glomerular diseases. They produce various cytokines (interleukin [IL]-1, IL-6, chemokines) and proliferate following exposure to platelet-derived growth factor (PDGF) and epithelial growth factor (EGF), leading to mesangial hypercellularity and matrix expansion, as well as glomerular injury. Circulating macrophages and monocytes that enter and exit the mesangium constitute the second cell type. They function primarily as phagocytes to remove macromolecules that cannot pass through the GBM and remain in the capillary wall. They may also, however, contribute to inflammation in immune-mediated diseases.

KEY POINTS

Glomerular Anatomy

1. The glomerular capillary loop is comprised of an endothelial cell and epithelial cell (podocyte) whose basement membranes fuse to form a common GBM.
2. Both size and charge selectivity restrict passage of macromolecules into the Bowman space. Loss of either of these from disease processes results in proteinuria.
3. Size selectivity is determined by the GBM and, most importantly, the podocyte slit diaphragm.
4. Charge selectivity is anionic and provided by heparan sulfate proteoglycans in GBM and endothelial cell fenestrae.
5. Mesangial cells modulate glomerular hemodynamics and participate in phagocytic functions.

GLOMERULAR FILTRATION RATE

Urine formation requires that an initial separation of ultrafiltrate from plasma occurs across the glomerular capillary wall into the Bowman space. The major determinant of ultrafiltrate formation is Starling forces across the capillary wall. These forces are proportional to glomerular capillary permeability and the balance between hydraulic and oncotic pressure gradients. Thus, GFR can be described by the following formulas:

$$\text{GFR} = (\text{capillary porosity} \times \text{surface area}) \times (\Delta \text{ hydraulic pressure} - \Delta \text{ oncotic pressure})$$

$$\text{GFR} = (\text{capillary porosity} \times \text{surface area}) \times ([P_{GC} - P_{Bs}] - s[\pi_p - \pi_{bs}])$$

$$\text{GFR} = (\text{capillary porosity} \times \text{surface area}) \times (P_{GC} - P_{Bs} - \pi_p)$$

where P_{GC} and P_{Bs} are the hydraulic pressures in glomerular capillary and the Bowman space, respectively. Also, s is the reflection coefficient of proteins across the capillary wall (a measure of permeability) and $\pi_p - \pi_{bs}$ are the oncotic pressure of plasma in glomerular capillaries and

TABLE 1-1. Determinants of Glomerular Filtration (Primates)

	GLOMERULAR PRESSURES (mmHg)	
	AFFERENT ARTERIOLE	EFFERENT ARTERIOLE
Hydraulic Pressure		
Capillary	46	45
Interstitium	10	10
Mean gradient	36	35
Oncotic Pressure		
Capillary	23	35
Interstitium	0	0
Mean gradient	23	35
Mean gradient favoring filtration	+13	0
	(mean = +6 mmHg)	

the Bowman space, respectively. Because π_{bs} is zero (the filtrate is essentially protein free) and the capillary wall is completely permeable (making $s = 1$), the last equation (GFR = [capillary porosity × surface area] × [$P_{GC} - P_{Bs} - \pi_p$]) represents the formula for GFR. In general, hydraulic pressure in the capillaries and the Bowman space remains constant while oncotic pressure in plasma rises progressively with formation of a protein-free ultrafiltrate. Thus, at some point along the capillary loop, the net filtration gradient falls to zero and filtration equilibrium occurs (Table 1.1). In contrast to other primates, humans only require a net gradient favoring filtration of approximately 4 mmHg to maintain glomerular filtration. It is also notable that plasma oncotic pressure entering the efferent arteriole and peritubular capillary is elevated, an effect that increases peritubular capillary oncotic pressure and enhances proximal tubular fluid and sodium reabsorption.

As one can see from examining the GFR equation, alterations in renal plasma flow rate (RPF) or any of the factors noted in the formula above can change the GFR. RPF is an important determinant of GFR in the presence of filtration equilibrium, as it influences glomerular capillary hydrostatic pressure. Thus, GFR rises or falls in proportion to changes in RPF. Because of the unique design of the glomerulus, capillary hydrostatic pressure is influenced by variables such as the aortic (renal artery) pressure, as well as afferent and efferent arteriolar resistances. Resistance in these vessels is controlled by a combination of myogenic control, tubuloglomerular feedback (TGF) from the macula densa, and vasodilatory/vasoconstrictor hormones (AII, norepinephrine, PGs, endothelin, atrial natriuretic peptide [ANP], nitric oxide). Changes in resistance of these arterioles have opposite effects on P_{GC} and thus allow rapid regulation of P_{GC} and GFR. For example, an increase in afferent arteriolar resistance decreases P_{GC} and GFR, while an increase in efferent resistance increases both. In addition, arteriolar tone affects RPF. An increase in the resistance of either glomerular arteriole will elevate total renal resistance and diminish RPF. Thus, the afferent arteriole regulates RPF and GFR in parallel, while the efferent arteriole regulates them inversely. This will determine the direction of change in the filtration fraction (FF), which is the fraction of RPF that is filtered across the glomerulus (FF = GFR/RPF). Changes in efferent tone change the FF, whereas changes in afferent tone do not. GFR can then increase, not change or decrease based on the magnitude of efferent constriction.

To be complete, factors considered less important in the regulation of GFR than the systemic arterial pressure, arteriolar tone, and RPF are noted below. In health, changes in capillary permeability are typically minimal and have no effect on GFR. Severe glomerular injury, however, can reduce permeability and impair GFR. Reductions in the capillary surface area by disease (glomerulonephritis) or vasoactive hormones (AII, antidiuretic hormone, PGs) can develop. These effects lead to a net decline in GFR. Alterations in hydrostatic pressure in the Bowman space, as occurs with complete urinary tract or tubular obstruction, initially reduces GFR through an elevation in hydrostatic pressure. Finally, increasing plasma oncotic pressure may counter hydrostatic pressure and reduce GFR. Clinical examples are therapy with hypertonic mannitol and severe intravascular volume depletion with marked hemoconcentration.

KEY POINTS

Glomerular Filtration Rate

1. Formation of glomerular ultrafiltrate is dependent on glomerular capillary permeability and the balance between hydrostatic and oncotic pressure gradients.

2. Arterial pressure, RPF, and afferent and efferent arteriolar tone importantly influence GFR.
3. Changes in resistance of afferent and efferent arterioles have opposite effects on P_{GC}. This allows rapid regulation of GFR.

REGULATION OF RENAL PLASMA FLOW RATE AND GLOMERULAR FILTRATION RATE

Regulation of GFR (and RPF) occurs primarily through changes in arteriolar resistance. In the normal host, autoregulation and TGF interact to maintain RPF and GFR at a constant level. In disease states such as true or effective volume depletion, however, these two intrarenal processes contribute minimally and are superceded by actions of systemic neurohormonal factors. A more detailed description of the regulation of renal hemodynamics follows.

Autoregulation

Autoregulation of the renal circulation serves the purpose of maintaining a relatively constant RPF and GFR. Since GFR is determined primarily by P_{GC}, variations in arterial perfusion pressure would be expected to promote large changes in GFR. The phenomenon of autoregulation, however, prevents large swings in RPF and GFR expected from changes in arterial perfusion pressure. Changes in afferent arteriolar tone likely play a major role in autoregulation, as RPF and GFR vary in parallel (versus changes in efferent tone where RPF and GFR vary inversely). An increase in afferent arteriolar tone prevents the transmission of high arterial pressures to the glomerulus, whereas low arterial pressure is associated with reduced afferent arteriolar tone. These changes in afferent tone maintain the P_{GC} and GFR constant despite swings in perfusion pressure. In general autoregulation maintains GFR constant until either the mean arterial pressure exceeds 70 mmHg or falls below 40 to 50 mmHg.

Myogenic stretch receptors in the afferent arteriolar walls are thought to play an important part in renal autoregulation. Increased wall stretch with high arterial pressure promotes vasoconstriction, perhaps mediated by enhanced cell calcium entry. The absence of voltage-gated calcium channels in efferent arterioles supports the less important or nonexistent role of this arteriole in autoregulation.

Tubuloglomerular Feedback

Changes in GFR are also mediated by alterations in tubular flow rate sensed by the macula densa. Specialized cells in the macula densa, located at the end of the thick ascending limb of Henle, sense changes in tubular fluid chloride entry into the cell. Increases in renal perfusion pressure are associated with an increase in GFR, which is associated with enhanced sodium chloride delivery to the macula densa. To counterbalance this increase in GFR, macula densa cells send signals to the afferent arteriole that promote vasoconstriction. This reduces P_{GC} and returns GFR toward normal and reduces sodium chloride delivery to the macula densa. In contrast, reduced sodium chloride delivery to the macula densa, as occurs with prerenal azotemia, has the opposite effect—afferent arteriolar vasodilatation occurs and GFR increases. This phenomenon is called *tubuloglomerular feedback.*

The mediator(s) of TGF are not well understood. It is likely that multiple factors act to mediate the signal to the afferent arteriole. Factors that play a role include AII (more as a permissive role), adenosine, thromboxane, and nitric oxide. Adenosine and thromboxane increase when excessive chloride entry is sensed by the macula densa, thereby constricting the afferent arteriole. These substances are reduced when chloride delivery is low, allowing afferent arteriolar vasodilatation. Nitric oxide is also thought to modulate the TGF response to sodium chloride delivery, allowing TGF to be reset by variations in salt intake. For example, lowered sodium chloride delivery increases nitric oxide, whereas increased sodium chloride delivery reduces nitric oxide.

Neurohumoral Factors

Daily maintenance of renal hemodynamics in normal hosts is subserved primarily by autoregulation and TGF. These factors also participate in regulation of GFR in disease states such as renal artery stenosis (low renal perfusion) and hypertension (increased renal perfusion). In more severe states, however, the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), as well as other vasoconstrictor (endothelin) and vasodilator (PGs, nitric oxide) substances are produced. For example, severe intravascular volume depletion, whether true (vomiting) or effective (congestive heart failure), stimulates the production of catecholamines and the RAAS to maintain circulatory integrity. The net renal effect of an outpouring of these mediators varies based on

the severity of the initiating disease process, the degree of stimulation of neurohumoral substances, and other coexisting processes. Stimulation of both the SNS and RAAS reduces renal perfusion pressure but may have no net effect on GFR. As an example, the patient with congestive heart failure who has this type of neurohumoral response maintains relatively normal GFR because the afferent arteriolar constriction induced by the SNS is balanced by the preferential constriction of the efferent arteriole by AII. Also, renal vasoconstriction is balanced by the production of vasodilatory substances such as PGs (PGE_2, PGI_2) and nitric oxide. Administration of an inhibitor of PG synthesis (nonsteroidal antiinflammatory drugs) tips the balance in favor of vasoconstriction and reduced GFR. Severe states of volume depletion (e.g., hypovolemic and cardiogenic shock) will overcome all attempts by the body at preservation of renal perfusion, resulting in severe renal ischemia and renal failure.

KEY POINTS

Regulation of RPF and GFR

1. Autoregulation and TGF regulate minute-to-minute changes in GFR by modulating afferent arteriolar tone.
2. Neurohumoral substances, such as the SNS, RAAS, nitric oxide, PGs, and endothelin influence GFR in disease states that disturb intravascular volume status.

CLINICAL ASSESSMENT OF GLOMERULAR FILTRATION RATE

Measurement of GFR is essential to the management of patients with kidney disease. Functioning renal mass is best assessed by measuring total kidney GFR, a reflection of the sum of filtration rates of functioning nephron units. Serial GFR measurement allows identification of kidney disease, progression (or improvement) of kidney dysfunction, appropriate drug dosing, and initiation of dialysis when renal failure supervenes. To measure GFR precisely, the substance employed as a marker should be freely filtered by the glomerulus and not reabsorbed, secreted, or metabolized by the kidney. The following formula is used to measure GFR:

$$\text{GFR} = \frac{\text{urine concentration A} \times \text{volume}}{\text{plasma concentration A}}$$

where A is the substance that meets the criteria as an ideal marker. The compound that is the best marker of GFR is inulin. Because of its characteristics, inulin clearance accurately reflects GFR. Inulin is not employed as a clinical marker of GFR, however, because it requires intravenous infusion, most clinical laboratories are unable to assay inulin, and it is expensive. Thus, other less-optimal markers are employed to measure GFR. They are briefly reviewed.

Creatinine

Endogenously produced creatinine is the marker most commonly employed to measure GFR. Creatinine is produced from the metabolism of skeletal muscle creatine. It is released into plasma at a stable rate in normal subjects and freely filtered at the glomerulus. Unfortunately, creatinine also enters urine via secretion by the organic cation transporter in proximal tubule, overestimating GFR by 10% to 20%. As kidney function declines, the rate of tubular creatinine secretion increases. In this circumstance creatinine clearance may overestimate true GFR. Administration of cimetidine, which competitively blocks tubular cell creatinine secretion enhances the accuracy of this test while combining creatinine and urea clearance gives a close estimate of GFR. Nonetheless, creatinine clearance is widely employed in clinical practice. It is calculated by the following formula that uses a serum sample for creatinine concentration and a 24-hour urine specimen for creatinine concentration and urine volume:

$$\text{CrCl} = \frac{\text{UCr} \times \text{volume}}{\text{PCr}}$$

where Cr is creatinine, Cl is clearance, U is urine, and P is plasma. In addition to the inaccuracy of the creatinine clearance method to measure GFR, there are problems with patient collection (undercollection) of the urine sample.

Iothalamate

The inaccuracy of creatinine clearance stimulated a search for other more accurate markers for GFR. Radiolabeled iothalamate provides an accurate estimate of GFR. It correlates tightly with inulin clearance and is used in clinical studies to replace inulin as the marker of choice to assess GFR. As with inulin, however, iothalamate is not widely available in all centers for clinical practice. It is also expensive and somewhat cumbersome to employ.

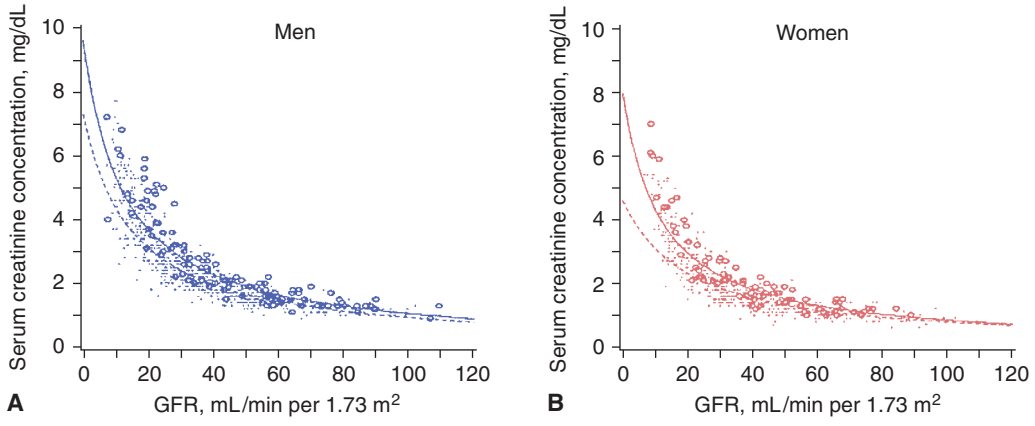


FIGURE 1-4. The relationship between serum creatinine concentration and GFR in men (A) and women (B). The relationship between serum creatinine concentration and GFR is not a linear one. Serum creatinine concentration is insensitive to changes in GFR within the range of GFRs between 60 and 120 mL/minute as a result of increasing tubular secretion. (From Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130:461-470, with permission.)

Glomerular Filtration Rate Estimates

Although serum creatinine concentration is used to assess kidney function, it is a poor marker of renal function. It is more useful when plotted as 1/serum creatinine, when used to follow changes in kidney function over time. Serum creatinine concentration is inaccurate for various reasons (reviewed in Chapter 16) and alone is suboptimal to measure kidney function. Figure 1.4 graphically illustrates this. In both men and women, serum creatinine concentration raises little as the GFR falls from 120 to 60 mL/min. Large changes in GFR result in minimal changes in serum creatinine concentration largely because creatinine secretion by renal tubules increases. Once GFR has declined to 40 to 60 mL/min creatinine secretion cannot increase further and fairly small changes in GFR result in large changes in serum creatinine concentration. Because of this problem, formulas were created using serum creatinine concentration, as well as other clinical and laboratory data to more accurately estimate GFR. These include the Cockcroft-Gault formula (estimates creatinine clearance), both the full and abbreviated forms of the Modification of Diet in Renal Disease (MDRD) formula, the Chronic Kidney Disease-EPI (CKD-EPI) formula, and the Berlin Initiative Study (BIS) formula. These formulas are discussed in Chapter 16.

Cystatin C

Problems with serum creatinine as a marker of kidney dysfunction (varying muscle mass, recent meat ingestion, etc.) have spurred the evaluation of alternative agents for estimation of GFR. One of these is cystatin C, a ubiquitous protein secreted by most cells in the body. It is a protein encoded by the CST3 gene. Cystatin C is freely filtered at the glomerulus, where it is reabsorbed and catabolized by the tubular epithelial cells, with only small amounts excreted in the urine. Cystatin C levels are therefore measured not in the urine, but in the bloodstream. Based on these characteristics, is being employed as a biomarker of kidney function. Equations have been developed linking estimated GFR to serum cystatin C levels. Most recently, some proposed equations have combined creatinine and cystatin. In addition, cystatin C has also been studied as a useful marker for predicting new-onset or deteriorating cardiovascular disease.

KEY POINTS

Clinical Assessment of Glomerular Filtration Rate

1. The gold standard measurement of GFR is inulin clearance because of its characteristics as a substance that is freely filtered at the glomerulus and not secreted, reabsorbed, or metabolized in tubules.

2. Endogenous creatinine is employed to estimate GFR, but is inaccurate and overestimates GFR as a result of its secretion by proximal tubular cells via the organic cation transporter.
3. Iothalamate is an accurate marker, but it has limited use in clinical practice.
4. Estimates of GFR using equations such as the Cockcroft-Gault, MDRD, CKD-EPI, and BIS formulas are available.
5. Cystatin C is another serum marker of kidney function that may be more accurate than serum creatinine.

Additional Reading

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SECTION I

Fluids, Electrolytes and Acid-base

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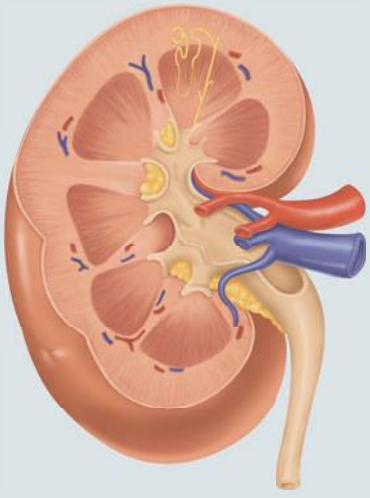

CHAPTER

2

Disorders of Sodium Balance

• *Robert F. Reilly Jr.*

Recommended Time to Complete: 2 Days

Guiding Questions

1. How does the kidney regulate extracellular fluid (ECF) volume differently from sodium concentration?
2. What effector systems regulate renal sodium excretion?
3. What is effective arterial blood volume (EABV)?
4. Can you describe the forces involved in edema formation?
5. How does edema form in congestive heart failure (CHF), cirrhosis, and nephrotic syndrome?
6. What are the most common renal and extrarenal causes of total body sodium depletion?

INTRODUCTION

One of the more difficult concepts to grasp in nephrology is that disorders of ECF volume are the result of disturbances in sodium balance and that disorders of sodium concentration (hypo- and hypernatremia) are the result of disturbances in water balance. The control of ECF volume is dependent on the regulation of sodium balance. Sodium concentration alone is not reflective of ECF volume status. This is illustrated graphically by the cases in Figure 2.1. Patient A has diarrhea (sodium concentration of diarrheal fluid is approximately 80 mEq/L) but does not have free access to water and the ECF volume as a result is depleted 3 L from its starting point of 14 L. The serum sodium concentration rises to 170 mEq/L. Patient B has an equivalent amount of diarrhea but is awake, alert, and has free access to water. Patient B drinks enough free water to increase ECF volume from 11 to 13.2 L. Sodium losses in the diarrheal fluid coupled with free water replacement results in a serum sodium concentration of 130 mEq/L. The serum sodium concentration is high in case A and low in case B, yet in both patients ECF volume is decreased. These cases illustrate that serum sodium concentration, in and of itself, does not provide information about the state of ECF volume. In both patients, sensor mechanisms detect ECF volume depletion and effector mechanisms are activated to increase renal sodium reabsorption.

ECF volume reflects the balance between sodium intake and sodium excretion and is regulated by a complex system acting via the kidney. The average intake of sodium in developed countries is between 150 and 250 mEq/day and must be balanced by an equivalent daily sodium excretion.

States where ECF volume is increased are related to a net gain of sodium and often present with edema in the presence or absence of hypertension. States where ECF

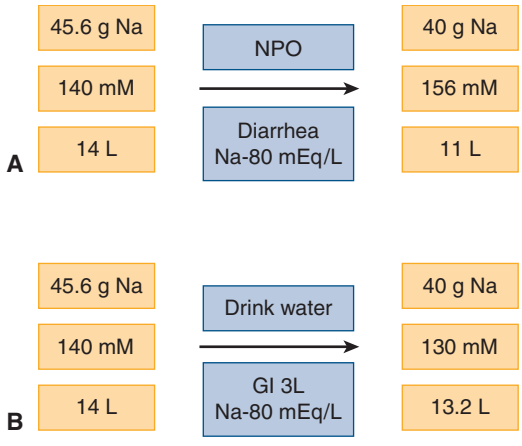

FIGURE 2-1. Sodium concentration does not reflect ECF volume status. Both of the patients shown have decreased ECF volume but in case A (no fluids taken in) serum sodium concentration is increased, while in case B (losses replaced with water) the serum sodium concentration is decreased. *Abbreviations:* GI, Gastrointestinal; NPO, nothing by mouth (nil per os).

TABLE 2-1. Sensors and Effectors of Sodium Balance

SODIUM AND VOLUME SENSORS	EFFECTORS
Low-pressure receptors (atria and veins)	Glomerular filtration rate
High-pressure receptors (aortic arch and carotid sinus)	Peritubular physical factors (ionic, osmotic, and hydraulic gradients)
Hepatic volume receptor	Sympathetic nervous system
Cerebrospinal fluid sodium receptor	Renin-angiotensin-aldosterone system
Renal afferent arteriole receptors	Atrial natriuretic factor
	Other natriuretic hormones

volume is decreased reflect a total body sodium deficit and are often a result of sodium and water losses from the gastrointestinal or genitourinary tracts and commonly present with decreased blood pressure.

A normal person maintains sodium balance without edema, hypertension, or hypotension across a broad range of sodium intake (10 to 1000 mEq/day). A variety of sensors detect alterations in sodium balance and effectors respond by adjusting renal sodium excretion (Table 2.1). Sodium sensors respond to the adequacy of intravascular filling and the effector limb modifies sodium excretion accordingly. When patients are edematous, however, there is sodium retention even in the setting of expanded total body sodium and water content.

This phenomenon led to the postulation of an important but confusing concept known as the *effective arterial blood volume* (EABV) that is defined based on the activity of the sodium homeostasis effector mechanisms in kidney. EABV is a concept rather than an objectively measured volume. Because stimulation of the sensory limb of the system cannot be directly measured, its activity is inferred based on the response of the effector limb. It is an estimate of the net level of stimulation of all sodium and volume sensors. Volume sensors in the arterial and venous circulation, including the renal vessels, monitor the sense of fullness of the vascular tree. Ultimately, it is the relationship between cardiac output and peripheral vascular resistance that is sensed. EABV can also be defined based on how far the mean arterial pressure (estimated as the diastolic blood pressure plus one-third of the pulse pressure) is displaced from its set-point. In many edematous disorders the set-point is normal, as in CHF and cirrhosis of the liver, and the mean arterial pressure tends to be low. In nephrotic syndrome, the set-point is increased by kidney disease and the mean arterial pressure is high. Despite the fact that mean arterial pressure is high, it still remains below the set-point. In both situations the kidney retains salt and water in an attempt to return blood pressure to its set-point. In clinical practice, however, net renal sodium handling determines the state of the EABV. When the kidney retains sodium, it is inferred that EABV is decreased and when the kidney excretes sodium, it is inferred that EABV is increased.

KEY POINTS

Extracellular Fluid and Sodium Concentration

1. Disorders of ECF volume result from disturbances in sodium balance and disorders of serum sodium concentration (hypo- and hypernatremia) result from alterations in water balance.
2. ECF volume control is dependent on the regulation of sodium balance. Regulation of ECF volume reflects the balance between sodium intake and sodium excretion.

3. Serum sodium concentration is not reflective of ECF volume status.
4. ECF volume expansion is related to a net gain of sodium and often presents as edema.
5. A variety of sensors detect alterations in sodium balance and effectors respond by modifying renal sodium excretion. Sodium and volume sensors respond to the adequacy of intravascular filling and the effector limb adjusts renal sodium excretion accordingly.
6. EABV is a concept and not a volume that is objectively measured. It is an estimate of the net level of activation of all sodium sensors. It is inferred that EABV is decreased when the kidney retains sodium and that EABV is increased when the kidney excretes sodium.

EFFECTOR SYSTEMS

Regulation of Sodium Transport in Kidney

When ECF volume is decreased, renal sodium excretion is minimized by decreasing the amount of sodium filtered and increasing tubular sodium reabsorption. ECF volume depletion stimulates the release of angiotensin II (AII), aldosterone, and arginine vasopressin (AVP), as well as activates the sympathetic nervous system resulting in salt and water retention. Thirst and the craving for salt are also stimulated. AII and aldosterone act synergistically to stimulate salt appetite and AII is a strong stimulator of thirst. Extrarenal salt losses are minimized by decreased sweating and fecal losses. Decreased ECF volume decreases intravascular volume and results in decreased renal perfusion. The resultant decline in glomerular filtration rate (GFR) decreases the filtered sodium load (amount presented to the proximal tubule). Tubular sodium reabsorption is increased by activation of the renin-angiotensin-aldosterone system (RAAS), activation of the sympathetic nervous system, changes in peritubular physical forces, and suppression of natriuretic peptides.

The filtered sodium chloride load is 1.7 kg/day. This is 11 times the amount of sodium chloride in the ECF. Less than 1% of the filtered load is excreted in the final urine under the control of a complex system of effector mechanisms that regulate sodium reabsorption along the nephron. The cellular and molecular mechanisms of action of these effector systems in each nephron segment are discussed below.

Proximal Tubule

The proximal tubule reabsorbs 60% to 70% of the filtered sodium chloride load. Physical factors, the sympathetic nervous system, and the RAAS regulate sodium reabsorption in this segment. The principal pathway for sodium entry into the proximal tubular cell is the Na^+-H^+ exchanger (isoform NHE3).

Physical factors regulate sodium reabsorption through changes in filtration fraction (FF) that create hydrostatic and oncotic gradients for water movement. The FF is the ratio of the GFR to renal plasma flow rate (RPF) shown in the equation below:

$$FF = \frac{GFR}{RPF}$$

Efferent arteriolar constriction by AII increases the FF via 2 mechanisms. It reduces renal blood flow (decreases RPF) and increases glomerular capillary pressure, which is the main determinant of GFR (raises GFR). The resultant increase in FF increases oncotic pressure and decreases hydrostatic pressure in the peritubular capillary. Recall that the kidney has 2 capillary networks in series. Blood leaving the glomerular capillary network via the efferent arteriole then enters the peritubular capillary network that bathes the proximal tubule. These changes promote the movement of salt and water from the tubular lumen to the interstitial space and finally into the peritubular capillary. In addition, AII reduces medullary blood flow, which has similar effects on driving forces in medullary nephron segments.

The RAAS also has direct effects on tubular transport mediated via NHE3 and the Na^+-K^+-adenosine triphosphatase (ATPase). AII and aldosterone both upregulate NHE3. The AII effect may be mediated via protein kinase C, whereas aldosterone was shown to increase insertion of preformed transporter proteins into the apical membrane. The Na^+-K^+-ATPase, which is present in the basolateral membrane of all nephron segments and is the major pathway by which sodium exits tubular cells, is also stimulated by AII. The sympathetic nervous system and insulin also stimulate the movement of NHE3 to the apical membrane and increase proximal tubular sodium reabsorption.

Systemic blood pressure itself also plays a key role in proximal tubular sodium reabsorption. As blood pressure rises the renal excretion of NaCl increases in an attempt to reduce ECF fluid volume and normalize blood pressure. This phenomenon is known as *pressure natriuresis*. Pressure natriuresis is not mediated by an increase in

filtered sodium load. An acute rise in blood pressure does not change the amount of sodium filtered by the glomerulus as a result of autoregulation of the renal microvasculature. As blood pressure increases, the afferent arteriole constricts so as to maintain glomerular capillary hydrostatic pressure constant. Afferent arteriolar constriction results from both a direct myogenic reflex and tubuloglomerular feedback (discussed below). Acute rises in blood pressure are sensed in the vasculature and a signal is transmitted to the proximal tubule to reduce sodium chloride reabsorption. This is mediated by removal of NHE3 from the luminal membrane of proximal tubule via a 2-step internalization process, regulated in part by AII, shown in Figure 2.2. NHE3 first moves from the microvillar membrane to the intermicrovillar cleft (first step) and then from the intermicrovillar cleft to subapical endosomes (second step). A fall in AII concentration plays a role in the first step. Na^+-K^+-ATPase activity is also decreased via a similar process of internalization.

Increased NaCl delivery to the thick ascending limb of Henle is sensed by macula densa cells. The macula densa is a specialized region near the junction of the cortical thick ascending limb and distal convoluted tubule (DCT). The macula densa is in close proximity to the granular renin-producing cells in the afferent arteriole, and together this region is referred to as the *juxtaglomerular* (JG) *apparatus*. The JG apparatus mediates a process known as *tubuloglomerular feedback*. When increased sodium chloride delivery is sensed by the macula densa a signal is transmitted to the afferent arteriole to constrict and single-nephron GFR decreases. Renin release by the JG apparatus is suppressed and AII levels fall if the signal is sustained. Conversely, when sustained sodium chloride delivery is sensed by the macula densa renin release is stimulated and the RAAS activated. Tubuloglomerular feedback serves 2 purposes. First, it maintains sodium chloride delivery to distal nephron segments (DCT, connecting tubule, and collecting duct) relatively constant over a wide range of conditions in the short term. It is in distal nephron where the final fine-tune regulation of sodium and water balance occurs. Additionally, in the long term the JG apparatus is responsible for controlling renin secretion at a rate that is optimal so as to maintain sodium balance.

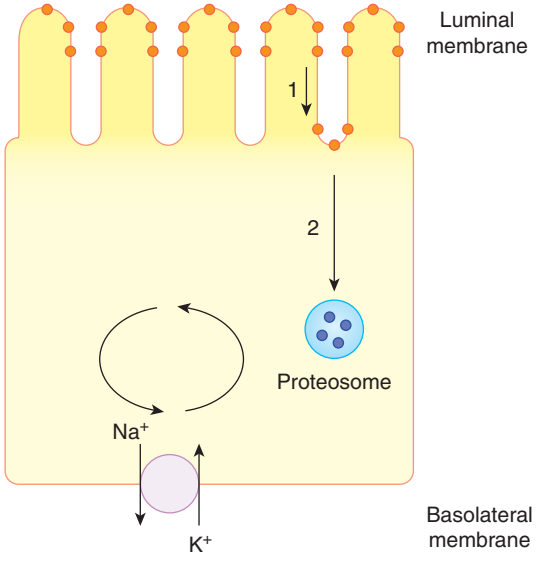

FIGURE 2-2. Sodium transporters in proximal tubule and pressure natriuresis. NHE3 (*filled circles*) is internalized in 2 steps in response to elevated blood pressure. In step 1, NHE3 moves from microvilli to the intermicrovillar cleft, a process that is regulated by AII. In step 2, NHE3 moves from the intermicrovillar cleft to proteosomes and is degraded. The Na^+-K^+-ATPase is regulated in a similar fashion.

Thick Ascending Limb of Henle

The thick ascending limb of Henle reabsorbs 20% to 30% of the filtered sodium chloride load. Sodium and chloride enter the thick ascending limb cell via the Na^+-K^+-$2Cl^-$ cotransporter, which is inhibited by loop diuretics. Because sodium and chloride concentrations in urine are much higher than potassium, for the transporter to operate maximally there must be a mechanism present for potassium to recycle back into the tubular lumen. A ROMK potassium channel in the luminal membrane mediates potassium recycling. Sodium leaves the cell via the Na^+-K^+-ATPase and chloride via a chloride channel.

The rate of NaCl reabsorption in this segment is load dependent. The higher the delivered NaCl load the higher the reabsoprtion. Sodium reabsorption is increased by activation of the sympathetic nervous system and β-adrenergic agonists, AVP in some species, parathyroid hormone, calcitonin, and glucagon. Prostaglandin E_2 inhibits sodium reabsorption.

Distal Convoluted Tubule

The DCT reabsorbs 5% to 10% of the filtered sodium load. Sodium and chloride enter the DCT cell via the thiazide-sensitive Na^+-Cl^- cotransporter (NCC) and sodium exits via the Na^+-K^+-ATPase. For mineralocorticoids to play a

role in the regulation of sodium transport in any nephron segment, that segment must also express the mineralocorticoid receptor and type 2 11β-hydroxysteroid dehydrogenase (HSD). The mineralocorticoid receptor is expressed in the entire DCT, while type 2 11β-HSD is expressed in the later half (DCT2) of the DCT. DCT2 also contains the epithelial sodium channel (ENaC). Type 2 11β-HSD degrades cortisol to the inactive cortisone in mineralocorticoid target tissues. This is required to maintain mineralocorticoid specificity, given the facts that the mineralocorticoid receptor binds glucocorticoids and that glucocorticoids circulate at much higher concentrations than mineralocorticoids.

Genetic studies of a rare monogenic disorder provide insight into NCC regulation. Familial hyperkalemic hypertension (FHH), also known as pseudohypoaldosteronism type II (PHA II), is an autosomal dominant disease characterized by hypertension, hyperkalemia, and extreme sensitivity to thiazide diuretics. Mutations in 2 members of the WNK (with no lysine [K]) kinase family, WNK1 and WNK4, cause the disease. Three members of this gene family WNK1 (also known as *long WNK1*), 2, and 4 are expressed in kidney. In addition, an alternatively spliced isoform of WNK1, kidney-specific WNK1 (KS-WNK1) is also expressed. Their expression pattern varies: long WNK1 (L-WNK1)—all along the distal nephron; KS-WNK1—in the DCT and decreases gradually in the connecting tubule; WNK3—along the entire nephron; and WNK4—DCT1 to the collecting duct. WNK4 reduces expression of NCC in the cell membrane. It does this via a kinase-dependent mechanism that does not involve changes in the synthesis or processing of NCC. Mutations in WNK4 lead to NCC overactivity via a loss of function mechanism of WNK4. Recently, other kinases including SPAK (Ste20p-related proline-alanine rich kinase) and OSR1 (oxidative stress response) have been identified as intermediates in the pathway between WNK4 and NCC. WNK4 inhibits the ROMK potassium channel. ROMK inhibition is not dependent on WNK4 kinase activity but occurs through clathrin-dependent endocytosis of the channel. Mutations result in a gain of function of this process with further increases in endocytosis from the luminal membrane.

In collecting duct, WNK4 increases claudin phosphorylation, resulting in increased paracellular chloride transport and stimulation of ENaC activity. FHH mutations further increase both of these processes and augment NaCl reabsorption. Interestingly, the WNK4 mutations of FHH increase NCC activity but decrease ROMK activity. This not only explains the hypertension and hyperkalemia of FHH but also shows that WNK4 can differentially regulate NCC and ROMK.

Aldosterone production is stimulated by both hypovolemia and hyperkalemia. In hypovolemia the distal nephron must reabsorb sodium but not increase potassium secretion, whereas in hyperkalemia the goal is to secrete potassium without an effect on sodium homeostasis. How 1 hormone can mediate 2 apparently disparate functions has been termed the *aldosterone paradox*. When aldosterone concentrations are elevated, how does the distal nephron know whether to reabsorb sodium (stimulate NCC and inhibit ROMK) or excrete potassium (stimulate ROMK and inhibit NCC)? WNK4 may be the master switch that regulates the balance between NaCl reabsorption and potassium secretion in the distal nephron. With hypovolemia both AII and aldosterone are stimulated. AII even in the presence of WNK4 stimulates NCC. Experimental studies have also shown that AII stimulates the phosphorylation of SPAK and NCC. AII thereby activates NCC in DCT1 directly and in DCT2 indirectly via aldosterone. AII also inhibits ROMK activity through WNK4 dependent and independent mechanisms. The combined interaction of AII with aldosterone favors the electroneutral reabsorption of sodium with chloride.

By contrast, in hyperkalemia, aldosterone is stimulated but AII is not. WNK4-mediated inhibition of NCC in DCT1 is maintained because type II 11β-HSD is not expressed in DCT1. This inhibition of sodium reabsorption in DCT1 results in sodium delivery further downstream to the connecting segment and collecting duct where sodium reabsorption via an electrogenic process (ENaC) can stimulate potassium secretion. S1169 phosphorylation mediated by Sgk1 (serum and glucocorticoid-regulated kinase) releases WNK4 inhibition of ENaC and ROMK in the connecting segment and collecting duct. In addition, Sgk1 phosphorylates Nedd4-2 on 3 motifs. This creates binding sites for the 14-3-3 protein that blocks interaction of Nedd4-2 with ENaC and prevents its ubiquitinization and subsequent removal from the luminal membrane.

L-WNK1 is expressed in a variety of chloride-transporting epithelia, including kidney, colon, sweat ducts, pancreas, and bile ducts. L-WNK1 does not appear to bind NCC but rather interacts with WNK4 and inhibits its ability to downregulate NCC. In FHH, mutations in L-WNK1 increase its expression and further augment

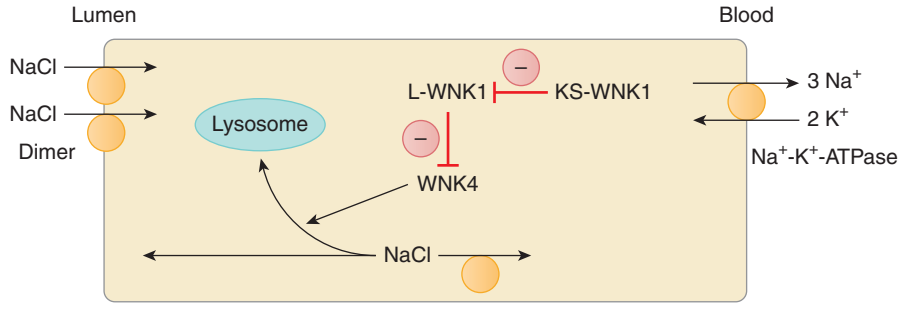

FIGURE 2-3. Simplified model of DCT sodium transport and FHH. The FHH phenotype is caused by mutations in both WNK4 and WNK1. WNK4 impairs delivery of the NCC to the luminal membrane by shunting the protein to a lysosomal compartment and mutations that decrease its activity increase NCC expression in the cell membrane. L-WNK1 interacts with WNK4 and decreases its activity. KS-WNK1 interacts with L-WNK1 and decreases its activity.

its ability to inhibit WNK4, resulting in increased NCC activity. KS-WNK1 is stimulated by aldosterone and antagonizes the effects of L-WNK1. WNK3 increases NCC activity and inhibits the activity of ROMK and KCl cotransporters in the distal nephron and may also play a role in hypovolemia. In the model of DCT sodium transport shown in Figure 2.3, delivery of NCC to the luminal membrane is inhibited by WNK4, while L-WNK1 inhibits the activity of WNK4, and KS-WNK1 inhibits L-WNK1. Mutations in either L-WNK1 or WNK4 result in increased NCC activity and the FHH phenotype.

Cortical Collecting Duct

The collecting duct reabsorbs 1% to 3% of the filtered sodium load. The RAAS is the major regulator of NaCl reabsorption in this segment. Sodium enters the cortical collecting duct (CCD) cell via ENaC and exits via the basolateral Na^+-K^+-ATPase (shown in Figure 2.4). ENaC is composed of 3 subunits (α, β, γ). Aldosterone and possibly AII increase ENaC abundance in CCD. Aldosterone also upregulates the Na^+-K^+-ATPase and the mitochondrial enzyme citrate synthetase.

As in the DCT, studies of monogenic disorders causing hypertension led to important insights into ENaC regulation. Liddle syndrome is an autosomal dominant disorder characterized by the onset of hypertension at an early age, hypokalemia, and metabolic alkalosis. Linkage studies revealed that Liddle syndrome resulted from mutations in β- and γ ENaC subunits that increased ENaC activity. The mutations clustered in a PY motif, which is involved in protein-protein interaction, at the C-terminus of the protein. The PY motif of ENaC interacts with Nedd4-2.

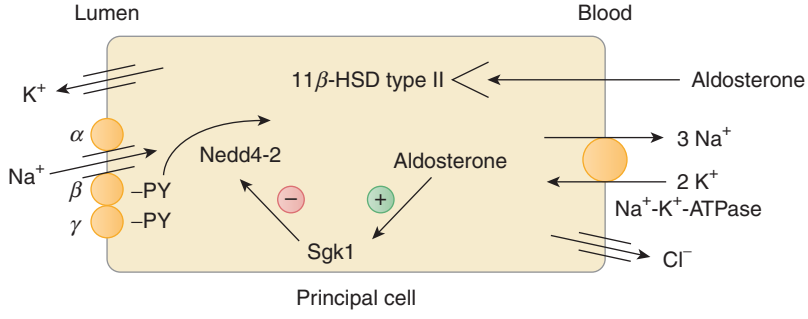

FIGURE 2-4. Model of cortical collecting duct sodium transport and Liddle syndrome. In Liddle syndrome, mutations in β- and γ ENaC subunits increase ENaC activity. Mutations occur in a PY motif involved in protein–protein interaction. The PY motif interacts with Nedd4-2 that ubiquitinates ENaC and leads to its internalization and proteosome-mediated degradation. Nedd4-2 is phosphorylated by Sgk1, which is upregulated by aldosterone. After phosphorylation Nedd4-2 no longer interacts with ENaC resulting in increased ENaC expression in the cell membrane.

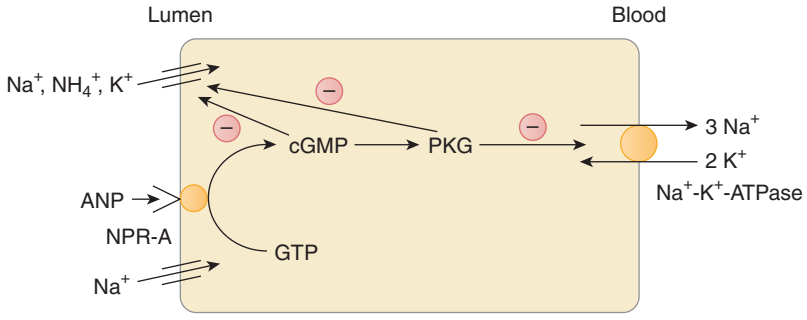

FIGURE 2-5. Sodium transport in IMCD. Sodium enters the cell via either ENaC or a cyclic guanosine monophosphate (GMP) gated-cation channel that transports sodium, potassium, and ammonium, and exits via the Na^+-K^+-ATPase. Natriuretic peptides such as atrial natriuretic peptide (ANP) bind to their receptors (NPR-A to -C) and catalyze the conversion of guanosine triphosphate (GTP) to cyclic GMP (cGMP). cGMP inhibits the cation channel directly and via phosphorylation of protein kinase G (PKG). Natriuretic peptides also inhibit the Na^+-K^+-ATPase either through PKG (ANP) or prostaglandin E_2.

Nedd4-2 ubiquitinates ENaC that leads to its internalization and proteosome-mediated degradation. Nedd4-2 is activated via phosphorylation by Sgk1, which is upregulated by aldosterone. Once Nedd4-2 is phosphorylated it no longer interacts with ENaC. In summary, these studies revealed that aldosterone upregulates Sgk1, Sgk1 phosphorylates and inactivates Nedd4-2, Nedd4-2 does not ubiquitinate ENaC, and ENaC remains active in the cell membrane. Aldosterone increases the synthesis of Sgk1 messenger ribonucleic acid (mRNA) within 30 minutes; after several hours it also increases synthesis of the α subunit of ENaC and Na^+-K^+-ATPase mRNA.

Medullary Collecting Duct

In inner medullary collecting duct (IMCD), there are 2 transport pathways whereby sodium enters the cell (Figure 2.5). The first is ENaC also expressed in CCD and the second is a cyclic guanosine monophosphate (GMP)-gated cation channel that transports sodium, potassium, and ammonium. Sodium exits the cell via the Na^+-K^+-ATPase.

The cyclic GMP-gated cation channel is inhibited by natriuretic peptides, the major effector pathway regulating sodium transport in IMCD. Although natriuretic peptides also increase GFR (via dilation of the afferent arteriole and constriction of the efferent arteriole), their major natriuretic effect is in IMCD. Natriuretic peptides are a family of proteins that include atrial natriuretic peptide (ANP), long-acting ANP, vessel dilator, kaliuretic peptide, brain-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and urodilatin. They act on target cells by binding to three types of receptors, natriuretic peptide receptors (NPR) A, B, and C. NPR-A and NPR-B are isoforms of particulate guanylate cyclase that catalyze the conversion of guanosine triphosphate (GTP) to cyclic GMP after ligand binding. NPR-B may be a specific receptor for CNP. ANP acts through NPR-A. The primary sites of production of these peptides are: ANP, cardiac atrium; BNP, cardiac ventricles; CNP, endothelial cells; and urodilatin, distal tubule of kidney. ANP also inhibits the basolateral Na^+-K^+-ATPase. All of the other effector systems discussed above are antinatriuretic, these peptides constitute the major effector system that results in natriuresis. They are important in protecting against ECF volume expansion, especially in CHF.

KEY POINTS

Effector Systems

1. As ECF volume decreases, renal sodium excretion is minimized by reducing the filtered sodium load and increasing tubular sodium reabsorption. This is mediated via release of AII, aldosterone, and AVP, as well as activation of the sympathetic nervous system.
2. In proximal tubule physical factors, the sympathetic nervous system and the RAAS regulate sodium reabsorption. Physical factors operate through changes in FF, thereby altering hydrostatic and oncotic pressure gradients for sodium and water movement. The RAAS also has direct effects on tubular sodium transport mediated via NHE3 and Na^+-K^+-ATPase.

3. Systemic blood pressure itself also plays a key role in proximal tubular sodium reabsorption through pressure natriuresis that involves internalization of NHE3.
4. The thick ascending limb of Henle reabsorbs 20% to 30% of the filtered sodium chloride load and reabsorption is load dependent.
5. The DCT reabsorbs 5% to 10% of the filtered sodium load. Activity of NCC is regulated via WNK1 and WNK4. WNK4 reduces NCC expression in the cell membrane.
6. WNK4 may function as a master switch that integrates aldosterone action in distal nephron.
7. The CCD reabsorbs 1% to 3% of the filtered sodium load under regulation by the RAAS. Aldosterone acts on both sodium entry (ENaC) and exit (Na^+-K^+-ATPase) pathways.
8. Aldosterone increases ENaC activity through the phosphorylation of Sgk1. Sgk1 phosphorylates and blocks the activity of Nedd4-2, a protein that ubiquitinates ENaC causing its removal from the cell membrane.
9. Natriuretic peptides constitute the major effector system resulting in natriuresis. They act primarily by inhibiting the IMCD cyclic GMP-gated nonspecific cation channel and the Na^+-K^+-ATPase.

DISORDERS ASSOCIATED WITH INCREASED TOTAL-BODY SODIUM (EXTRACELLULAR FLUID VOLUME EXPANSION)

Hypervolemic states (increased ECF volume) are associated with increased total-body sodium and commonly present with edema with or without hypertension. Edema is the accumulation of excess interstitial fluid. Interstitial fluid is that part of the ECF not contained within blood vessels. Edema fluid resembles plasma in terms of its electrolyte content and has a variable protein concentration. Edema may be localized as a result of local vascular or lymphatic injury or can be generalized as in CHF, cirrhosis, and nephrotic syndrome. On physical examination, edema is detected by applying pressure with the thumb or index finger on the skin of the lower extremities or presacral region. If edema is present an indentation or "pitting" results.

TABLE 2-2. Pathophysiology of Edema Formation

INCREASED FORMATION	DECREASED REMOVAL	ILL-DEFINED MECHANISMS
Increased capillary hydrostatic pressure	Decreased plasma colloid osmotic pressure	Idiopathic cyclic edema
Venous/lymphatic obstruction	Nephrotic syndrome	Pregnancy
Congestive heart failure	Malabsorption	Hypothyroidism
Cirrhosis of the liver	Cirrhosis of the liver	
Primary salt excess (nephrotic syndrome)	Impaired lymphatic outflow	
Increased capillary permeability		
Trauma—burns		
Allergic reactions		

Edema is generated by an alteration in physical forces originally described by Starling that determine fluid movement across the capillary endothelium. Alterations in these forces explain the development of both localized and generalized edema. Major causes of edema are classified according to the mechanisms responsible and are illustrated in Table 2.2. The interaction between hydrostatic and oncotic pressure governs water movement across the capillary wall. An increase in hydrostatic pressure or a decrease in oncotic pressure within the capillary favors fluid movement out of the blood vessel and into the interstitium resulting in edema formation. Increases in capillary permeability also favor edema formation. The final common pathway maintaining generalized edema is retention of excess salt and water by the kidney.

Table 2.3 shows the pathophysiology of ECF volume expansion based on the presence or absence of hypertension and edema.

Hypertension Present, Edema Present

With kidney disease and a decreased GFR, hypertension and edema are often present. The decrease in renal function results in sodium retention and ECF volume

TABLE 2-3. Pathophysiology of Extracellular Fluid Volume (Total-Body Sodium) Expansion

Hypertension Present—Edema Present
Kidney disease
Hypertension—Present, Edema—Absent
Mineralocorticoid excess Primary aldosteronism Renal artery stenosis Renin-producing tumors
Glucocorticoids binding to the mineralocorticoid receptor Cushing disease Licorice Apparent mineralocorticoid excess
Increased distal sodium reabsorption Liddle syndrome Familial hyperkalemic hypertension
Hypertension—Absent, Edema—Present
Decreased cardiac output Congestive heart failure Constrictive pericarditis Pulmonary hypertension
Decreased oncotic pressure Nephrotic syndrome
Peripheral vasodilation Cirrhosis High-output heart failure Pregnancy
Increased capillary permeability Burns Sepsis Pancreatitis

expansion. If the expansion is severe enough, hypertension and edema result.

In acute glomerulonephritis the renal lesion results in primary NaCl retention. The stimulus for NaCl retention and the molecular mechanisms whereby it occurs remain unknown. Studies in children with acute poststreptococcal glomerulonephritis showed that renin activity is low, supporting the conclusion that ECF volume is expanded. In addition, studies of patients with acute nephritis also showed increased concentration of ANPs, as would be expected if ECF volume were expanded. Expansion of ECF volume induces hypertension and edema that, in turn, suppresses renin production and stimulates release of ANPs.

Hypertension Present, Edema Absent (Excess Aldosterone or Aldosterone-Like Activity)

These disorders are caused by renal sodium retention stimulated by excess mineralocorticoids (primary aldosteronism as a result of an aldosterone-producing tumor, renal artery stenosis, and renin-producing tumors of the JG apparatus), glucocorticoids binding to the mineralocorticoid receptor (Cushing syndrome, licorice, and apparent mineralocorticoid excess), or genetic diseases that result in increased sodium reabsorption in the distal nephron (Liddle syndrome and FHH). Liddle syndrome is caused by overactivity of the sodium channel in CCD. FHH is caused by overactivity of the thiazide-sensitive NaCl cotransporter and ENaC as a result of mutations in WNK kinases.

In all of these conditions, the kidney is able to maintain ECF volume homeostasis, but at the cost of hypertension. The relationship between defects in renal salt excretion and the subsequent development of hypertension is best explained by the computer models of Guyton and his collaborators. For long-term increases in blood pressure to occur, there must be a reduction in the kidney's ability to excrete salt and water. In normal individuals, raising arterial pressure results in increased sodium excretion and a return of blood pressure to normal. This effect is mediated via pressure natriuresis (discussed earlier). A steady state is reestablished where sodium intake equals sodium excretion at a normal blood pressure. Increases in salt intake may transiently raise blood pressure but if the pressure natriuresis mechanism is intact blood pressure must always return to normal, as shown in Figure 2.6. Pressure natriuresis is the key component of a feedback system that stabilizes blood pressure and ECF volume. Activation of neurohumoral systems, especially the RAAS, shifts the curve to the right, blunting the pressure natriuresis response. Suppression of the RAAS increases the kidney's ability to excrete sodium with minimal to no change in blood pressure (shifts the curve to the left). Long-term increases in blood pressure can only occur if the curve is shifted to the right. This rightward shift results in sustained hypertension that is a "trade-off" that allows the kidney to excrete normal amounts of sodium but at the expense of hypertension. Rightward shifts of the curve

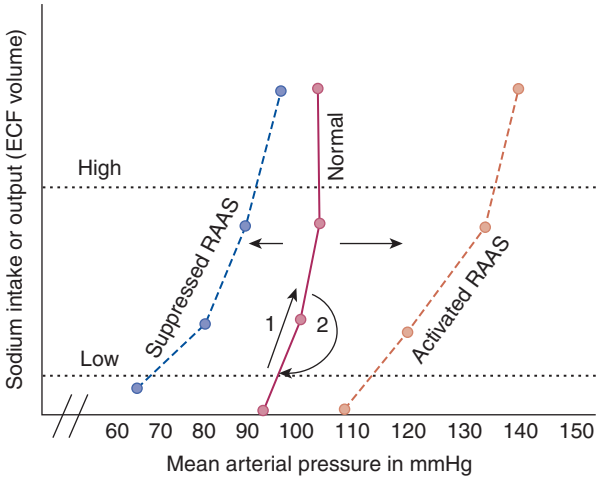

FIGURE 2-6. Pressure volume regulation in hypertension. Increases in sodium intake may transiently raise blood pressure (shown by the arrow at number 1), but if the pressure natriuresis mechanism is intact, blood pressure must always return to normal (illustrated by the curved line at number 2). Activation of the RAAS shifts the curve to the right blunting the pressure natriuresis response. Suppression of the RAAS shifts the curve to the left of normal and increases the kidney's ability to excrete sodium with minimal change in blood pressure even at high sodium intakes. Hypertension can only occur if the pressure natriuresis (pressure volume) curve is shifted to the right. Sustained hypertension is the "trade-off" that allows the kidney to excrete ingested sodium but at the cost of hypertension.

are caused by diseases that increase preglomerular resistance, increase tubular sodium reabsorption, or reduce the number of functioning nephrons.

With nephron loss remaining, nephrons must excrete greater amounts of sodium to maintain balance. Compensatory changes that must occur to achieve this include increased single-nephron GFR and decreased tubular sodium reabsorption. Decreased sodium reabsorption leads to increased NaCl delivery to the macula densa and suppression of renin release. In this situation, because renin is already maximally suppressed, the kidney's ability to excrete a salt load (such as with a high-salt diet) is impaired and requires a higher blood pressure. This explains the higher prevalence of "salt-sensitive" hypertension in patients with kidney disease. Renal arteriolar vasodilation and a sustained increase in single-nephron GFR damage surviving nephrons and lead to glomerulosclerosis. When this process becomes severe, the pressure natriuresis curve shifts to the right and hypertension develops. Damage to surviving nephrons is key in shifting the pressure natriuresis curve to the right. Studies in dogs with surgically induced nephron loss (five-sixths nephrectomy) show that sustained increases in sodium intake shift the curve to the right and induce "salt-sensitive" hypertension that resolves with sodium restriction.

Hypertension Absent, Edema Present (Decreased Effective Arterial Blood Volume)

CHF, nephrotic syndrome, and cirrhosis of the liver are characterized by edema; however, hypertension is absent. In these disorders, a primary abnormality results in decreased EABV that stimulates effector mechanisms, resulting in renal sodium retention. The primary abnormality varies depending on the disease.

In CHF the primary abnormality is decreased cardiac output. There is a secondary increase in peripheral vascular resistance to maintain blood pressure. Plasma volume is expanded. Because most of this increase is on the venous side of the circulation, however, arterial underfilling is sensed by baroreceptors. Effector systems are activated resulting in stimulation of the sympathetic nervous system and the RAAS, as well as the nonosmotic release of AVP. Plasma concentrations of renin, aldosterone, AVP, and norepinephrine are increased. The net effect is renal salt and water retention so as to compensate for arterial underfilling. The intensity of the neurohumoral response is proportional to the severity of the heart failure. Sodium concentration correlates inversely with AVP concentration and the severity of hyponatremia is a predictor of cardiovascular mortality. Despite the fact that ANP concentrations are elevated in patients with CHF, there is resistance to their action. This is likely related to an increase in sodium reabsorption in nephron segments upstream of the IMCD. Natriuresis is restored by renal denervation, probably because of decreased proximal tubular sodium reabsorption and increased distal sodium delivery.

In cirrhosis of the liver the primary abnormality is thought to be decreased peripheral vascular resistance that leads to a secondary increase in cardiac output. Plasma volume in cirrhotic patients is increased and the increase occurs before the development of ascites. Splanchnic vasodilation is present early in the course of cirrhosis and results in arterial underfilling and activation of neurohumoral mechanisms that lead to salt and

water retention. There is a direct correlation between the degree of decrease in peripheral vascular resistance and the increase in plasma volume. As in CHF the severity of hyponatremia is a predictor of clinical outcome. Splanchnic vasodilation may be mediated by nitric oxide. Shear forces in splanchnic arteriovenous shunts stimulate nitric oxide production. Studies in cirrhotic rats showed that endothelial nitric oxide was increased in the aorta and mesenteric arteries. When nitric oxide synthase inhibitors were administered to these animals there was a reversal of the increase in nitric oxide, the hyperdynamic circulation, and neurohumoral activation. Water excretion increased and the serum sodium concentration rose. Others have argued that the primary event in cirrhosis is hepatic initiated salt and water retention due to activation of a volume sensor in the hepatic circulation. They note that renal salt retention and ECF volume expansion precede the development of systemic vasodilation and ascites formation, and that shunting procedures induce natriuresis despite further increases in peripheral vasodilation.

Two hypotheses were proposed to explain the edema of nephrotic syndrome: the underfill hypothesis and the overflow hypothesis. The underfill hypothesis, which is the most commonly taught, states that edema forms in nephrotic syndrome as a result of decreased EABV. The decreased EABV is secondary to decreased capillary oncotic pressure that results from hypoalbuminemia. The reduced oncotic pressure leads to increased fluid movement into the interstitium (edema) and reduces ECF volume. Effector mechanisms are activated increasing renal salt and water reabsorption that maintains edema.

The overflow hypothesis argues that edema in nephrotic syndrome is a result of a primary increase in renal sodium reabsorption as occurs with glomerulonephritis. This would result in ECF volume expansion and suppression of the RAAS. Although measurement of ECF volume would be expected to resolve this issue, ECF volume determinations are often not reproducible and controversy exists as to whether the measurement should be normalized per kilogram of dry or wet weight.

Studies of counterregulatory hormone activity show conflicting results. Approximately one-half of nephrotic patients have elevated plasma renin activity (underfill subgroup). Plasma and urinary catecholamine concentrations are often increased, which is compatible with the underfill hypothesis. Plasma vasopressin concentrations correlate with blood volume and are reduced by albumin infusion (underfill subgroup). Other authors point out that natriuresis precedes the increase in plasma albumin concentration in patients with minimal change disease who respond to steroid therapy, blood pressure is often increased and falls with clinical remission in children with nephrotic syndrome, renin and angiotensin activity are suppressed in many patients, and in animal models of unilateral nephrosis sodium is retained in the affected kidney, which argues that there is a primary defect in sodium reabsorption and supports the overfill hypothesis.

One analysis of 217 nephrotic patients showed that plasma volume was reduced in 33%, normal in 42%, and increased in 25%. Based on this study it is likely that subgroups of patients exist, some with decreased ECF volume (underfill hypothesis) and others with increased ECF volume (overfill hypothesis). The underfilled nephrotic patient will have decreased EABV, activation of the RAAS, and lack hypertension. The overfilled nephrotic patient will demonstrate hypertension, suppression of the RAAS, and may be more likely to have a lower GFR. Attempts to better subdivide these groups may have important implications regarding therapy. The overfilled patient is likely to respond well to diuretics, whereas diuretics may further reduce renal perfusion in the underfilled patient.

Disorders that increase capillary permeability, such as burns and sepsis, may also cause edema in the absence of hypertension, although other mechanisms may also play a role. Burns can result in localized or generalized edema. Localized edema is the result of thermal injury and release of vasoactive substances that cause capillary vasodilation and increased permeability. This effect may persist for 24 to 48 hours. Diffuse edema occurs when full-thickness burns involve more than 30% of body surface area. This is a result of reduced capillary oncotic pressure resulting from loss of plasma proteins into the wounds. Extensive third-degree burns can result in loss of as much as 350 to 400 g of protein per day. In addition, there are increased insensible losses from damaged skin that may be as high as 300 mL/h/m^2 of burned skin. All of these factors contribute to decreased EABV that leads to increased renal salt and water reabsorption further increasing the edema.

Septic patients with severe inflammatory response syndrome (SIRS) caused by the increased release of inflammatory mediators may develop edema. There is an

increase in capillary permeability, as well as precapillary vasodilation. The resultant increase in capillary hydrostatic pressure associated with increased capillary permeability, which increases interstitial oncotic pressure, results in edema formation. In addition, large amounts of intravenous fluids are often administered to maintain systemic blood pressure, which may worsen the edema. Positive pressure ventilation and positive end-expiratory pressure (PEEP) ventilation may also worsen edema by decreasing venous return and reducing cardiac output. This results in activation of the sympathetic nervous system and the RAAS, leading to increased renal salt and water reabsorption. Lymphatic drainage through the thoracic duct is also impeded by increased intrathoracic pressure.

Approach to the Edematous Patient

A careful history, physical examination, and selected laboratory tests will reveal the cause of edema. The clinician encountering the edematous patient should first ask whether edema is generalized or localized. Localized edema is often caused by vascular or lymphatic injury. One next searches for evidence of heart, liver, or kidney disease in the patient's history. The location of the edema may help narrow the differential diagnosis. Left-sided CHF results in pulmonary edema. In right-sided CHF and cirrhosis of the liver, edema may accumulate in the lower extremities or abdomen (ascites).

On physical examination the presence of an S3 gallop suggests CHF. One also looks for stigmata of chronic liver disease, such as palmar erythema, spider angiomas, hepatomegaly, and caput medusae. Laboratory studies that should be obtained include serum blood urea nitrogen (BUN), creatinine concentrations, liver function tests, serum albumin concentration, urinalysis for protein excretion, chest radiograph, and electrocardiogram.

Treatment of the Edematous Patient

Treatment is first directed at halting the progression of the underlying disease. Therapies that aid in reversing the underlying pathophysiology, such as angiotensin converting enzyme inhibitors in CHF should be used when possible. A low-salt diet is critical to the success of any regimen. If these measures are unsuccessful a diuretic may be required. The clinical use of diuretics is discussed in detail in Chapter 3.

KEY POINTS

Disorders Associated with Increased Total-Body Sodium

1. Hypervolemic states (increased ECF volume) are associated with increased total-body sodium and commonly present with edema with or without hypertension.
2. Edema is the accumulation of excess interstitial fluid and is detected by noting an indentation or "pitting" of the skin after applying pressure with the thumb or index finger on the skin of the lower extremities or presacral region.
3. Edema is generated by an alteration in Starling forces that govern fluid movement across the capillary endothelium. An increase in hydrostatic pressure or a decrease in oncotic pressure favors fluid movement out of the capillary resulting in edema formation.
4. The pathophysiology of ECF volume expansion is divided into 3 general categories based on the presence or absence of edema and hypertension.
5. Kidney disease is the major cause of ECF volume expansion with both hypertension and edema.
6. ECF volume expansion associated with hypertension and absence of edema occurs with excess concentrations of mineralocorticoids, when glucocorticoids bind to the mineralocorticoid receptor, and with genetic diseases that increase sodium reabsorption in distal nephron.
7. Disorders characterized by a decreased EABV, such as CHF, nephrotic syndrome, and cirrhosis of the liver, are major causes of ECF volume expansion associated with edema in the absence of hypertension.

DISORDERS ASSOCIATED WITH DECREASED TOTAL-BODY SODIUM (EXTRACELLULAR FLUID VOLUME DEPLETION)

Sodium is the most abundant extracellular ion. As a result it determines ECF osmolality and volume. Sodium depletion means ECF volume depletion. Sodium depletion does not imply hyponatremia and conversely hyponatremia does not imply sodium depletion. The serum sodium concentration is primarily determined by changes in water metabolism (see Chapter 3). Table 2.4 illustrates the manifestations of sodium and ECF volume depletion.

When sodium excretion exceeds input, negative sodium balance and decreased ECF volume results. Given that the normal kidney can rapidly lower sodium excretion to near zero, decreased sodium intake alone never causes decreased ECF volume. Sodium depletion results from ongoing sodium losses from kidney, skin, or gastrointestinal tract. If the kidney is the source of sodium loss then urine sodium concentration exceeds 20 mEq/L and the fractional excretion of sodium (FENa) will be increased. If losses are from skin or gastrointestinal tract and the kidney is responding normally, the urine sodium concentration is less than 20 mEq/L and the FENa will be low, less than 1%.

Renal sodium losses are caused by either intrinsic kidney disease or external influences on renal function. Kidney diseases associated with sodium wasting include nonoliguric acute kidney injury, the diuretic phase of acute kidney injury, and "salt-wasting nephropathy." Salt-wasting nephropathy occurs after relief of urinary tract obstruction, with interstitial nephritis, medullary cystic disease, or polycystic kidney disease. External factors causing natriuresis include solute diuresis from sodium bicarbonate, glucose, urea, and mannitol; diuretic administration; and mineralocorticoid deficiency as a result of primary hypoaldosteronism or decreased renin secretion.

Gastrointestinal losses are external or internal. External losses occur with diarrhea, vomiting, gastrointestinal suction, or external fistulas. Internal losses or "third spacing" result from peritonitis, pancreatitis, and small-bowel obstruction. Skin losses also are external or internal. External losses result from excessive sweating, cystic fibrosis, and adrenal insufficiency. Burns cause excessive internal and external losses.

To protect blood pressure and tissue perfusion during ECF volume depletion, a variety of compensatory mechanisms are activated. These mechanisms maintain blood pressure, minimize renal sodium excretion, and in the process, maintain ECF volume.

Approach to the Patient with Decreased Extracellular Fluid Volume

As in the patient with an increased ECF volume, a careful history, physical examination, and selected laboratory tests often reveal the cause and extent of ECF volume depletion. Clinical signs and symptoms of total-body sodium deficit are shown in Table 2.4. The history focuses on identification of potential sources of sodium loss. The patient is questioned regarding polydipsia and diuretic use (kidney), diarrhea and vomiting (gastrointestinal tract), and sweating (skin). Physical examination can reveal the extent of ECF volume depletion (postural changes in blood pressure and pulse, degree of hypotension) as well its cause (intestinal obstruction or gastrointestinal fistula). Laboratory tests also aid in determining whether the sodium loss is renal or extrarenal. The presence of a decreased urine sodium concentration, a decreased FENa, concentrated urine, and a BUN-to-creatinine ratio greater than 20:1 suggests that sodium losses are extrarenal and the kidney is responding appropriately. The one exception to this caveat is the patient in whom diuretics were recently discontinued. Even though sodium losses occurred via the kidney, once the diuretic effect has dissipated, the kidneys reabsorb salt and water appropriately in order to restore ECF volume. Conversely, an elevated urine sodium concentration suggests that the kidney is the source of the sodium loss.

Treatment of the Patient with Decreased Extracellular Fluid Volume

In mild depletion states, treatment of the underlying disorder and replacement of normal dietary salt and water intake are sufficient to correct deficits. When blood pressure and tissue perfusion are compromised or the oral route of replacement cannot be used, intravenous fluid administration is required. The use of intravenous fluids is reviewed in more detail in Chapter 5 and only general guidelines are discussed here.

The amount and rate of repletion depend on the clinical situation. Cerebral perfusion and urine output are used as markers of tissue perfusion. Response of blood pressure and pulse to postural changes are adequate

TABLE 2-4. Manifestations of Extracellular Fluid Volume (Total-Body Sodium) Depletion

SYMPTOMS	SIGNS
Increased thirst	Orthostatic fall in blood pressure
Weakness and apathy	Orthostatic rise in pulse
Headache	Decreased pulse volume
Muscle cramps	Decreased jugular venous pressure
Anorexia	Dry skin and decreased sweat
Nausea	Dry mucous membranes
Vomiting	Decreased skin turgor

noninvasive indicators of ECF volume status. Response to a rapid infusion of normal saline or direct measures of cardiovascular pressures are also used.

Fresh-frozen plasma and packed red cells are the most effective initial intravascular volume expander because they remain within the intravascular space. Increased cost and potential infectious complications limit their use. Isotonic sodium chloride (normal saline) is an effective volume expander. Its space of distribution is confined to the ECF. Because of its widespread availability, low cost, and lack of infectious complications normal saline is often used when rapid increases in ECF volume are required. Five percent dextrose in water (D_5W) is a poor intravascular volume expander. Once the glucose is metabolized, which happens quickly, the remaining water is distributed in total-body water. It should never be used to expand the intravascular space as only approximately 8% of the administered volume remains intravascular.

Depending on the source of sodium loss, other electrolyte deficiencies may also need to be corrected. Potassium is lost with gastrointestinal causes such as diarrhea or vomiting. Magnesium may be deficient with thiazide diuretic use and diarrheal illnesses.

KEY POINTS

Disorders Associated with Decreased Total-Body Sodium

1. Total-body sodium determines ECF volume. Sodium depletion is synonymous with ECF volume depletion.
2. Sodium depletion results from kidney, skin, or gastrointestinal tract losses.
3. If the kidney is the source of sodium loss, urine sodium concentration exceeds 20 mEq/L.
4. Urine sodium concentration is less than 20 mEq/L or FENa is less than 1% if losses are from skin or gastrointestinal tract and the kidneys are responding appropriately.
5. Renal sodium loss is caused by intrinsic kidney disease or external influences on the kidney.
6. Treatment of the underlying disorder and replacement of normal dietary salt and water intake are sufficient to correct deficits with mild sodium depletion. Intravenous fluid administration is required when blood pressure and tissue perfusion are compromised or oral replacement cannot be used.

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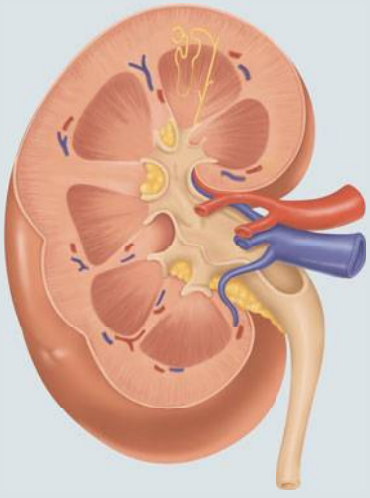

CHAPTER

3

Disorders of Water Balance—Hypo and Hypernatremia

• *Robert F. Reilly Jr.*

Recommended Time to Complete: 2 Days

Guiding Questions

1. What is the difference between tonicity and osmolality?
2. How does the kidney excrete free water and defend against hyponatremia?
3. How does one formulate a clinical approach to the patient with hyponatremia?
4. What is the definition of SIADH?
5. Can you outline a treatment approach for the correction of hyponatremia that minimizes potential complications?
6. How does the body defend against the development of hypernatremia?
7. What is the differential diagnosis of the hypernatremic patient?
8. How does one treat the patient with hypernatremia?

INTRODUCTION

One of the more difficult concepts to grasp in nephrology is that changes in serum sodium concentration result from derangements in water balance, whereas disorders of extracellular fluid (ECF) volume regulation are related to total-body sodium balance. This is best explained by the fact that serum sodium is a concentration term and reflects only the relative amounts of sodium and water present in the sample. Low serum sodium concentration (shown in the equation below) denotes a relative sodium deficit and/or a relative water excess. Sodium concentration is not a measure of total body sodium content.

$$[\text{Serum } Na^+] = \frac{eNa^+ + eK^+}{TBW}$$

As seen in the formula above (Rose modification of the Edelman equation) the serum sodium concentration is equal to exchangeable sodium (eNa^+) and potassium (eK^+) divided by total-body water (TBW). As a result hyponatremia may occur from either a decrease in the numerator or an increase in the denominator. Although one might conclude that hyponatremia more likely results from a decrease in the numerator, in clinical practice, relative water excess most commonly causes hyponatremia. Nonosmotic arginine vasopressin (AVP) release is the key pathophysiologic process in most cases. Regulation of water homeostasis is dependent on (a) an intact thirst mechanism, (b) appropriate renal water handling, and (c) intact AVP release and response.

Renal-free water excretion is the major factor controlling water metabolism and the major factor controlling renal free water excretion is AVP. Above a plasma osmolality (P_{osm}) of 283, AVP increases by 0.38 pg/mL per 1 mOsm/kg increase in P_{osm}. In turn, urine osmolality (U_{osm}) responds to increments in AVP. A rise in AVP of 1 pg/mL increases U_{osm} approximately 225 mOsm/kg. The 2 major afferent stimuli for thirst are an increase in P_{osm} and a decrease in ECF volume. Thirst is first sensed when P_{osm} increases to 294 mOsm/kg (the osmolar threshold for thirst). At this osmolality AVP is maximally stimulated (concentration >5 pg/mL) and is sufficient to maximally concentrate urine. AVP and angiotensin II directly stimulate thirst.

Osmolality is an intrinsic property of a solution and is defined as the number of osmoles of solute divided by the number of kilograms of solvent. It is independent of a membrane. Tonicity or "effective osmolality" is equal to the sum of the concentration of solutes with the capacity to exert an osmotic force across a membrane. It is a property of a solution relative to a membrane. The tonicity of a solution is less than osmolality by the total concentration of "ineffective solutes" that it contains. Solutes that are freely permeable across cell membranes such as urea are ineffective osmoles. From a cellular viewpoint, tonicity determines the net osmolar gradient across the cell membrane that acts as a driving force for water movement.

Sodium is the most abundant cation in ECF and its concentration is the major determinant of tonicity and osmolality. Furthermore, water moves freely across cell membranes allowing the maintenance of osmotic equilibrium between various compartments, therefore ECF tonicity reflects tonicity of the intracellular fluid (ICF). P_{osm} is calculated from the following formula:

$$P_{osm}\,(\text{mOsm/kg}) = 2 \times \text{Na(mEq/L)} + \frac{\text{BUN(mg/dL)}}{2.8} + \frac{\text{glucose (mg/dL)}}{18}$$

To calculate tonicity one includes only the sodium and glucose terms in the equation. It is measured directly by freezing point depression or vapor pressure techniques.

Body tonicity, measured as P_{osm}, is maintained within a narrow range (285 to 295 mOsm/kg). This is achieved via regulation of water intake and excretion. Disturbances in body tonicity are reflected by alterations in serum sodium concentration and clinically present as either hypo- or hypernatremia.

KEY POINTS

Tonicity and Osmolality

1. Changes in serum sodium concentration are indicative of a problem in water balance, while changes in ECF volume are related to total body sodium.
2. Renal free water excretion is the major factor controlling water metabolism.
3. The most abundant cation in ECF is sodium, therefore its concentration is the major determinant of ECF tonicity and osmolality.

HYPONATREMIA

Hyponatremia, defined as a serum sodium concentration less than 135 mEq/L, is the most frequent electrolyte abnormality and is seen in up to 15% of hospitalized patients. It is especially common in critical care units. Hyponatremia is caused by either (a) excess water intake (water intoxication) with normal renal capacity to excrete solute-free water or (b) continued solute-free water intake with a decreased renal capacity for solute-free water excretion. It occurs whenever free water intake exceeds free water losses.

In subjects with normal renal function excessive water intake alone does not cause hyponatremia unless it exceeds approximately 1 L/h. As a general rule one's maximal free water excretion is equal to approximately 10 to 15% of glomerular filtration rate (GFR). With a GFR of 180 L/day, maximal free water excretion equals

approximately 24 L/day or 1 L/h. In patients with a normal GFR, hyponatremia caused by excessive water intake is observed only rarely, such as in psychotic patients who drink from faucets or showers. A reduction in GFR, however, will limit free water excretion. An individual whose GFR is 20% of normal will become hyponatremic on drinking more than 4.8 L/day. Often patients with psychogenic polydipsia have some degree of renal impairment.

Almost all hyponatremic patients have impaired renal free water excretion. An understanding of how the kidney excretes free water is critical for understanding the pathophysiology of hyponatremia.

Essential features of renal free water excretion are the following:

1. **Normal delivery of tubular fluid to distal diluting segments of the nephron**. An adequate GFR without excessive proximal tubular reabsorption is required to deliver tubular fluid to the diluting segments of the kidney (thick ascending limb of the loop of Henle and distal convoluted tubule [DCT]). Although tubular fluid remains isotonic in the proximal tubule, proximal fluid reabsorption is an important determinant of water excretion. Normally 60-70% of glomerular filtrate is reabsorbed in the proximal tubule and the remaining 30-40% is isotonic to plasma as it enters the loop of Henle. Thus, if proximal tubular reabsorption increases, as in volume depletion, free water excretion is limited. To use an extreme example, a patient with acute kidney injury and a GFR of 5 mL/min forms only 7.2 L of glomerular filtrate daily. If 30% is delivered to the diluting segments, that means a total of only 2.2 L is delivered daily. Even if the distal nephron were completely impermeant to water, only 2.2 L of urine is excreted (only part of this total is free water).
2. **Normal function of the diluting segments (ascending limb of the loop of Henle and DCT)**. Tubular fluid is diluted in the water-impermeable ascending limb of the loop of Henle and DCT by the reabsorption of sodium chloride. Sodium is transported on the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of Henle and the thiazide-sensitive NaCl cotransporter in DCT. It is in the diluting segments, where U_{osm} declines to less than P_{osm}, that free water is generated.
3. **Absence of AVP**. Arginine vasopressin must be suppressed so as to prevent solute-free water reabsorption in the collecting duct. This factor is of primary importance because the renal interstitium remains slightly hypertonic even during a water diuresis. Therefore, if the collecting duct were water permeable, osmotic equilibration of fluid between the tubular lumen and interstitium would concentrate the urine and impair water excretion.

AVP is released from the posterior pituitary, enters the bloodstream, binds to its receptor (V_2) in the basolateral membrane of the collecting duct, adenylate cyclase is activated, cyclic adenosine monophosphate (AMP) generated, and water channels (aquaporins—AQP2) insert into the apical membrane increasing membrane water permeability. AVP also increases the expression of the UT-1 urea transporter in the inner medullary collecting duct facilitating urea reabsorption and increasing the osmolality of the medullary interstitium.

AVP is released in response to osmotic and nonosmotic stimuli. An increase in ECF osmolality as little as 1% stimulates AVP release and the relationship of AVP to P_{osm} is linear (Figure 3.1). Nonosmotic stimuli are associated with changes in autonomic neural tone such as physical pain, stress, hypoxia, and decreases in effective arterial blood volume. The nonosmotic pathway is less sensitive and requires a 5% to 10% decrement in blood volume to stimulate AVP release. Once the threshold is reached, however, the rise in AVP concentration is geometric (Figure 3.1). Defense of

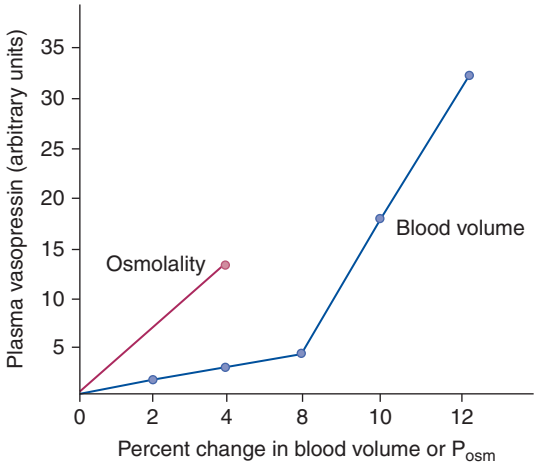

FIGURE 3-1. Changes in plasma AVP induced by alterations in osmolality or blood volume. Note that response to changes in osmolality are linear, whereas response to changes in blood volume approximates an exponential curve.

volume has priority. AVP concentration increases and stimulates renal water reabsorption protecting volume at the expense of hyponatremia. It is more important for the body to maintain blood volume than to maintain tonicity. The volume-depleted patient may become profoundly hyponatremic because nonosmotic stimuli for AVP release predominate over osmotic stimuli. AVP also has a pressor effect mediated via the V_1 receptor, contributing perhaps 10% to mean arterial pressure during volume depletion. Thus, AVP is normally osmoregulatory, but during stress becomes a volume regulatory hormone. As a general principle the kidney will always act to preserve blood and ECF volume at the expense of electrolyte and acid–base homeostasis. Nonosmotic AVP release is the key pathophysiologic process in the majority of patients with hyponatremia.

4. **Adequate solute intake**. Although the kidney has an enormous capacity to generate free water, it cannot excrete pure water. The lowest U_{osm} attainable in humans is 50 mOsm/kg. One of the main roles of the kidney is to eliminate the dietary osmolar load (approximately 10 mOsm/kg). The volume of urine required to achieve this is expressed in the equation below:

$$\text{urine volume} = \frac{\text{osmolar intake or excretion}}{U_{osm}}$$

In the steady state, osmolar intake and excretion are equal and either can be used. In theory a 70 kg person with a standard osmolar dietary load and a maximally dilute urine could generate 14 L of urine per day (700 mOsm/50 mOsm). If solute intake is very low, however, as in someone drinking only beer (beer drinker's potomania), hyponatremia could develop despite the fact that urine is maximally dilute. For example, if solute intake were only 150 mOsm/day with a maximally dilute urine, urine volume would be only 3 L. In this situation water intake could exceed renal free water excretion and hyponatremia could develop.

KEY POINTS

Hyponatremia

1. Hyponatremia is defined as a serum sodium concentration less than 135 mEq/L and is the most common electrolyte abnormality in hospitalized patients.
2. Hyponatremia occurs whenever free water intake exceeds free water losses.
3. Almost all patients with hyponatremia have impaired renal free water excretion.
4. Essential features of renal free water excretion are delivery of tubular fluid to distal diluting segments of the nephron, normal function of the diluting segments, suppression of AVP, and adequate solute intake.

Etiology

Hyponatremia most commonly results from an inability to maximally dilute the urine coupled with continued water intake. Before implicating a defect in renal free water excretion as the cause of hyponatremia, the presence of hypoosmolality must be documented because hyponatremia can occur with an elevated or normal serum osmolality.

Hyponatremia with a normal serum osmolality or "pseudohyponatremia" is a laboratory artifact. Plasma is made up of 2 fractions—an aqueous fraction and a particulate fraction. Pseudohyponatremia results from a decrease in the aqueous fraction. Many modern autoanalyzers dilute an aliquot of serum before measuring sodium concentration (indirect potentiometry). When correcting for this dilution an assumption is made that the sample is 93% aqueous and 7% particulate. If the aqueous fraction is less than 93%, pseudohyponatremia occurs. Conditions that reduce the aqueous fraction below the usual 93% of plasma (the remaining 7% is the particulate fraction made up of proteins and lipids) decrease the total amount of sodium per aliquot of plasma. Sodium concentration, however, in the aqueous fraction is normal. Three conditions that reduce the aqueous fraction are hyperlipidemia, hypercholesterolemia, and hyperproteinemia. This is not a common problem. A clue to the presence of hypertriglyceridemia is a report from the lab of lipemic serum. Lipemic serum means that after centrifugation of whole blood the supernatant is cloudy. For each 460 mg/dL increase in triglyceride concentration the serum sodium concentration falls by 1 mEq/L. Elevations in lipoprotein X concentration do not result in lipemic serum. Lipoprotein X is elevated in patients with intrahepatic and extrahepatic cholestasis and in those with lecithin cholesterol acyltransferase (LCAT) deficiency. Excess production of paraproteins as in multiple myeloma and administration

of intravenous immunoglobulin also increase the particulate fraction and may result in pseudohyponatremia. Immunoglobulin (Ig) G preparations that contain maltose or sucrose may also cause hyponatremia secondary to water translocation from the intracellular space. Measurement of serum sodium concentration by ion-sensitive electrode (direct potentiometry) will yield a normal sodium concentration.

Translocational hyponatremia is caused by water shifting out of cells in response to a nonsodium solute. Serum osmolality is elevated. Water moves down an osmotic gradient from ICF to ECF when nonsodium solute increases ECF osmolality and creates a driving force for water movement. The most common cause is hyperglycemia. Mannitol and glycine infusion also cause translocational hyponatremia. For each increase in serum glucose of 100 mg/dL above its normal concentration, serum sodium concentration falls by 1.6 mEq/L. This is a calculated correction factor. In practice this rule of thumb works well for glucose concentrations up to 400 mg/dL or in patients who are on dialysis with little or no residual renal function. At higher concentrations the correction factor is likely larger (2.0 to 4.0 mEq/L), which may be because of a combination of water translocation out of cells and free water loss in urine. Glycine has been used as an irrigation fluid in patients undergoing transurethral resection of the prostate (TURP). Systemic glycine absorption can result in the post-TURP syndrome. This is characterized by a variety of symptoms including confusion, nausea, vomiting, chest pain, hypotension, paresthesia, and anxiety. Newer bipolar resection systems that permit sodium chloride use as an irrigating solution are associated with a lower incidence of hyponatremia and post-TURP syndrome. For each 100 mg/dL rise in glycine concentration the serum sodium concentration falls by 3.8 mEq/L. An elevated serum osmolar gap may be a clue to the presence of pseudo or translocational hyponatremia.

The remaining causes of hyponatremia alter external water balance and are associated with low serum osmolality (*true hyponatremia*). True hyponatremia is caused by either (a) excess water intake (water intoxication) with normal renal capacity to excrete free water or (b) continued solute-free water intake with a decreased renal capacity for solute-free water excretion. The most common pathophysiologic mechanism is nonosmotic AVP release that prevents maximal urinary dilution. Rarely, severely depressed urine flow rate, as with low GFR, increased proximal tubule fluid reabsorption, or decreased solute intake limits urine dilution resulting in positive water balance and hyponatremia.

A clue to the source of the increased AVP concentration lies in the evaluation of the patient's volume status. Common causes are edematous states, extrarenal and renal sodium and water losses, serum inappropriate antidiuretic hormone (SIADH), and psychogenic polydipsia.

The presence of edema is indicative of increased total-body sodium. Hyponatremia results because the increase in total-body water exceeds the increase in total-body sodium. In these circumstances, effective circulating volume is decreased and volume/pressure receptors are activated, releasing AVP (note the similarity to signal for sodium retention). Thus a decreased effective arterial blood volume is sensed despite an absolute increase in total-body salt and water. The increase in AVP is "appropriate" to the sensed signal. Major causes of hyponatremia with increased total-body sodium are congestive heart failure, hepatic cirrhosis, nephrotic syndrome, and advanced chronic or acute kidney injury. The hallmark of these disorders on physical examination is dependent edema.

Renal and extrarenal salt and water losses are characterized by signs and symptoms of decreased ECF volume such as thirst, orthostatic hypotension, tachycardia, and decreased skin turgor. In this setting AVP release is "appropriate" to defend ECF volume. Total-body sodium loss exceeds total-body water loss. Common etiologies of hyponatremia with decreased ECF volume include gastrointestinal losses (excessive salt and water loss causes sufficient hypovolemia to stimulate baroreceptors to increase AVP release); third spacing of fluids; burns; pancreatitis; diuretic overuse or abuse; salt-wasting nephropathy; adrenal insufficiency; osmotic diuresis; and the hyponatremia hypertensive syndrome. Tuberculosis remains the most common cause of adrenal insufficiency worldwide. Adrenal insufficiency often presents with subtle findings and as a result the diagnosis is often delayed. Renal salt wasting has been reported with cis-platinum thought to be a result of proximal tubular injury. The hyponatremia hypertensive syndrome is a result of unilateral renal artery stenosis. It is characterized by hyponatremia, hypertension, hypokalemia, polydipsia, and polyuria. It has been most commonly described in elderly women.

With extrarenal fluid loss the sodium concentration of the lost fluid is less than the serum sodium concentration. If this is the case, how does the patient become

hyponatremic? The answer lies in the fact that thirst is intact and that the replacement fluid has a lower sodium concentration than the fluid lost.

Hyponatremia from diuretics is almost always a result of thiazide rather than loop diuretics, as thiazides interfere with urinary dilution but not urinary concentrating ability. By contrast, loop diuretics interfere with both diluting and concentrating ability, and result in medullary washout of solute and diminished AVP-induced free water reabsorption. Diuretic-induced volume depletion decreases GFR and increases proximal tubular salt and water reabsorption, thereby decreasing water delivery to distal segments. Potassium depletion may result in intracellular sodium shifts, and alters the sensitivity of the osmoreceptor mechanism leading to AVP release. Most patients have an associated hypokalemic metabolic alkalosis. Older women are at highest risk, and this generally occurs in the first 2 to 3 weeks of therapy. Mineralocorticoid- and glucocorticoid-deficient states lead to volume depletion with enhanced proximal tubular reabsorption and nonosmotic stimulation of AVP release.

Hyponatremia in the presence of a clinically normal ECF volume is most commonly the result of SIADH, drug-induced euvolemic hyponatremia, or psychogenic polydipsia. The term *clinically normal* should be stressed. If total-body sodium and total-body water were truly normal, then serum sodium concentration must also be normal. In reality, total-body water is increased as a result of "inappropriate" AVP release. "Inappropriate" implies that AVP is released despite the absence of the 2 physiologic stimuli for its release: increased serum osmolality; and decreased effective arterial blood volume. This state of mild volume expansion results in urinary sodium wasting and a clinically undetectable decrease in total body sodium. SIADH is characterized by hyponatremia, a low serum osmolality, and an inappropriately concentrated urine (less than maximally dilute). Urine sodium concentration is generally increased but it can be low if the patient develops ECF volume depletion. The patient must be clinically euvolemic with no evidence of adrenal, renal, or thyroid dysfunction; and not taking a drug that stimulates AVP release or action. SIADH is caused by malignancies, pulmonary, or central nervous system disease (Table 3.1). The most common tumor-producing SIADH is small cell cancer of the lung. In some patients with small cell lung cancer and hyponatremia, the tumor produces natriuretic peptides and not AVP. This is an important disorder to diagnose because hyponatremia will worsen if normal saline is administered. Why do patients with SIADH continue to drink fluid despite a low serum sodium concentration? One study suggested that the osmotic threshold for thirst was reset downward and that thirst occurred around a lower set-point.

TABLE 3-1. Disease Processes Causing Syndrome of Inappropriate Antidiuretic Hormone

CARCINOMAS	PULMONARY DISEASES	CNS DISORDERS
Lung (small cell)	Viral pneumonia	Encephalitis
Duodenum	Bacterial pneumonia	Meningitis
Pancreas	Pulmonary abscess	Acute psychosis
	Tuberculosis	Stroke
	Aspergillosis	Porphyria (AIP)
	Mechanical ventilation	Tumors
		Abscesses
		Subdural injury
		Guillain-Barré syndrome
		Head trauma

Abbreviations: AIP, acute intermittent porphyria; CNS, central nervous system.

Several disorders may be clinically difficult to distinguish from SIADH. Nephrogenic syndrome of inappropriate antidiuresis is the result of a gain of function mutation in the V_2 receptor. It mimics SIADH but when measured, AVP levels are undetectable. Cerebral salt wasting is a disorder associated with a variety of intracranial lesions characterized by a high urine sodium and hyponatremia and could result from disruption of sympathetic input to the kidney or elaboration of natriuretic peptides from the brain. The majority of described cases are more likely related to SIADH than to cerebral salt wasting. The diagnosis of cerebral salt wasting requires ongoing renal salt loses in the presence of hypovolemia. These patients are often administered large volumes of normal saline or

TABLE 3-2. Drug-Induced Euvolemic Hyponatremia

STIMULATE AVP RELEASE	OTHER MECHANISMS
Nicotine	Chlorpropamide: enhance renal effect of AVP
Clofibrate	Tolbutamide
Vincristine	Cyclophosphamide
Isoproterenol	Morphine
Chlorpropamide	Barbiturates
Antidepressants (SSRIs)	Carbamazepine
Antipsychotic agents	Acetaminophen
Ecstacy	NSAIDs: inhibit PG that antagonize AVP

Abbreviations: AVP, arginine vasopressin; PG, prostaglandins; NSAIDs: nonsteroidal antiinflammatory drugs; SSRI, selective serotonin reuptake inhibitors.

3% saline and in this setting renal excretion of the salt load is expected.

A variety of drugs impair renal free water excretion by potentiating the action or release of AVP and may result in drug-induced euvolemic hyponatremia. Table 3.2 provides a partial list of drugs that induce euvolemic hyponatremia. This is most commonly caused by the SSRI (selective serotonin reuptake inhibitor) group of antidepressants. Although hyponatremia can present more than 3 months after the start of an SSRI, it generally occurs in the first 2 weeks of therapy and the elderly are at increased risk. SSRIs stimulate water reabsorption in the collecting duct via a non-antidiuretic hormone (ADH)-mediated modulation of aquaporin 2. High dose (>50 mg/kg) cyclophosphamide was at one time a common cause of drug-induced euvolemic hyponatremia. Current low-dose regimens (<20 mg/kg) rarely result in hyponatremia. This is likely the result of the metabolites mafosfamide and 4-hydroperoxy-cyclophosphamide that increase interleukin (IL)-1 and tumor necrosis factor (TNF)-α that downregulate the V_2 receptor and aquaporin 2. Drug-induced hyponatremia can also occur after desmopressin administration for the treatment of enuresis. The elderly with mild hyponatremia or those taking other drugs that may impair renal water excretion are at increased risk of severe hyponatremia. As a result, several European countries have removed the enuresis indication for intranasal desmopressin.

In hypothyroidism the ability of the kidney to excrete free water is impaired by a decrease in GFR, an increase in proximal tubular reabsorption, and an increase in AVP secretion. In secondary adrenal insufficiency hyponatremia results because glucocorticoids are required to maximally suppress AVP release.

Psychogenic polydipsia or water intoxication is the result of excess water intake with normal renal capacity for free water excretion. It is differentiated from SIADH in that the U_{osm} is maximally or near maximally dilute. This commonly occurs in patients with psychiatric disease on psychotropic medications that result in dry mouth and increased water intake. Schizophrenia is associated with psychogenic polydipsia more than twice as often as non-schizophrenic psychiatric illnesses. Hyponatremia with a low U_{osm} is also seen in those with beer drinker's potomania whose renal free water excretion is limited by solute intake.

KEY POINTS

Etiology of Hyponatremia

1. Hyponatremia with a normal serum osmolality is known as "pseudohyponatremia" and is a laboratory artifact.
2. Translocational hyponatremia is caused by water shifting out of cells in response to a nonsodium solute. Serum osmolality is elevated. Hyperglycemia is the most common cause.
3. The remaining causes of hyponatremia are associated with a low serum osmolality (*true hyponatremia*). True hyponatremia is caused by either (a) excess water intake with normal renal capacity for solute-free water excretion or (b) continued solute-free water intake with a decreased renal capacity for solute-free water excretion.
4. The most common pathophysiologic mechanism is nonosmotic AVP release.
5. Edematous states, extrarenal and renal sodium and water losses, SIADH, drug-induced euvolemic hyponatremia, and psychogenic polydipsia are the most common causes of true hyponatremia.
6. Hyponatremia from diuretics is almost always a result of thiazide diuretics because thiazides interfere with urinary dilution but not urinary concentrating ability.
7. SIADH is characterized by hyponatremia, low serum osmolality, and an inappropriately concentrated urine (less than maximally dilute) in the absence of renal, adrenal, or thyroid disease.

Signs and Symptoms

Gastrointestinal complaints of anorexia, nausea, and vomiting occur early, as do headaches, muscle cramps, and weakness. Thereafter, altered sensorium develops. There may be impaired response to verbal and painful stimuli. Inappropriate behavior, auditory and visual hallucinations, asterixis, and obtundation can be seen. Seizures develop with severe or acute hyponatremia. In far advanced hyponatremia, the patient may exhibit decorticate or decerebrate posturing, bradycardia, hyper- or hypotension, respiratory arrest, and coma. Severity of symptoms correlates both with the magnitude and rapidity of the fall in serum sodium concentration. Central nervous system pathology is caused by cerebral edema.

Central nervous system symptoms result from a failure in cerebral adaptation. When P_{osm} falls acutely, osmotic equilibrium is maintained by either extrusion of intracellular solutes (regulatory volume decrease [RVD]) or water influx into brain. Neurologic symptoms result when osmotic equilibrium is achieved via the latter process. Because the brain is surrounded by a rigid case, small increases in its volume result in substantial morbidity and mortality. If solute extrusion is successful and osmotic equilibrium maintained, the patient remains asymptomatic despite low serum sodium concentration and osmolality. Sodium extrusion from brain by Na^+-K^+-adenosine triphosphatase (ATPase) and sodium channels is the first pathway activated (minutes) in RVD. If this is not adequate to lower brain osmolality then calcium-activated stretch receptors are stimulated. This activates a potassium channel that leads to potassium extrusion (hours).

In contrast, chronic hyponatremia is characterized by fewer and milder neurologic symptoms. This is because of additional regulatory mechanisms. Studies in rats after 21 days of hyponatremia show that brain water content is normal. In this setting, loss of organic osmolytes from brain, such as glutamate, glutamine, taurine, and myo-inositol, play an important role.

Hyponatremia was recently associated with osteoporosis, gait disorders, and attention deficits. One-third of total body sodium is in bone and 40% of this is exchangeable. Mild hyponatremia in a large population based study was associated with a 3-fold increased risk of osteoporosis. Gait disorders have been described with sodium concentrations equal to or less than 134 mEq/L and attention deficits with sodium concentrations equal to or less than 132 mEq/L. Hyponatremia impairs tests of tandem gait and attention to the same degree as a blood alcohol concentration of 0.06%.

Hospital-associated hyponatremia is independently associated with increased hospital mortality; prolongation of length of hospital stay; and an increased likelihood of discharge to a facility other than home regardless of whether hyponatremia was present on admission or occurred during the hospital stay. A serum sodium concentration equal to or less than 127 mEq/L increased the risk of death 15-fold. Hyponatremia is also an independent predictor of 30-day mortality in patients with acute ST segment elevation myocardial infarction.

KEY POINTS

Signs and Symptoms of Hyponatremia

1. The severity of hyponatremic symptoms correlates with the magnitude and rapidity of the fall in serum sodium concentration.
2. Central nervous system pathology is a result of cerebral edema and a failure in cerebral adaptation.
3. Chronic hyponatremia is characterized by fewer and milder neurologic symptoms.
4. Hyponatremia was recently associated with osteoporosis, gait disturbances, and cognitive impairment.

Diagnosis

The diagnostic approach to the hyponatremic patient is divided into 3 steps.

Step 1: What Is the Serum Osmolality?

The first question one needs to answer in the evaluation of the hyponatremic patient is: What is the serum osmolality? This does not necessarily mean that one needs to directly measure serum osmolality but one at least needs to think of the question. The answer divides hyponatremic patients into 3 broad categories.

1. Isoosmolar or pseudohyponatremia results when the aqueous fraction of plasma is decreased and the particulate fraction is increased. This may result from hypertriglyceridemia (triglyceride [TG] >1500 mg/dL), increases in lipoprotein X, or hyperproteinemia (multiple

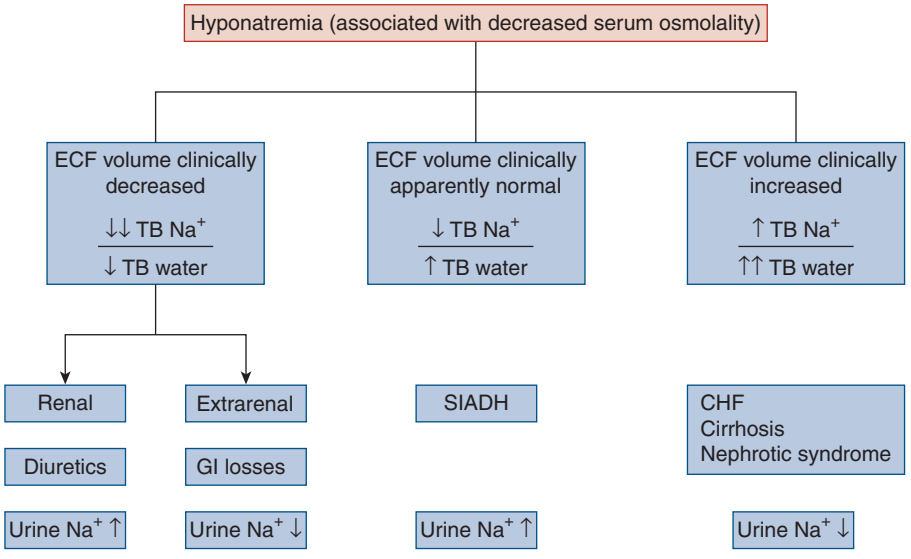

FIGURE 3-2. Clinical approach to the patient with true hyponatremia. Patients with true hyponatremia (associated with a low serum osmolality) can be subdivided into 3 categories based on ECF volume status. *Abbreviations:* CHF, Congestive heart failure; GI, gastrointestinal; TB, total-body.

myeloma, Waldenström macroglobulinemia, administration of intravenous immunoglobulin).

2. Hyperosmolar or translocational hyponatremia caused by glucose, mannitol, or glycine infusions. The most common cause of translocational hyponatremia is hyperglycemia.
3. Hypoosmolar or "true hyponatremia" makes up the vast majority of cases, further subdivided by Steps 2 and 3.

Step 2: What Is the Extracellular Fluid Volume (Total-Body Sodium Content)? Is Dependent Edema Present?

In the patient with true hyponatremia the second question one asks is what is the apparent ECF volume status? An approach to the evaluation of true hyponatremia is shown in Figure 3.2. States of increased ECF volume are relatively easy to identify on physical examination because they are characterized by dependent edema. If edema is present then the diagnosis is either congestive heart failure, cirrhosis, nephrotic syndrome, acute kidney injury, or chronic kidney disease.

Step 3: What Is the Urine Sodium Concentration?

In the absence of dependent edema the next step is to determine if the patient's ECF volume is decreased or normal. States of severe ECF volume depletion are often clinically apparent. Milder degrees of ECF volume contraction, however, may be difficult to distinguish from euvolemia on physical examination. In the patient with decreased ECF volume a urine sodium concentration less than 20 mEq/L and a U_{osm} greater than 400 mOsm/kg suggests extrarenal sodium loss. The fractional excretion of sodium (FENa) can also be used to assess renal sodium handling. The FENa is that fraction of the filtered sodium load that is excreted by the kidney. It is calculated using the formula:

$$\text{FENa} = \frac{\text{urine}\,[Na^+] \times \text{plasma}\,[Cr]}{\text{plasma}\,[Na^+] \times \text{urine}\,[Cr]} \times 100$$

Sodium concentrations are expressed in mEq/L and creatinine concentrations are expressed in mg/dL. A FENa less than 1% suggests ECF volume depletion. A urine sodium concentration greater than 20 mEq/L, a FENa greater than 2%, and a U_{osm} less than 400 mOsm/kg suggests renal sodium loss. If the patient appears euvolemic, one should consider SIADH, drug-induced euvolemic hyponatremia, psychogenic polydipsia, and hypothyroidism.

KEY POINTS

Diagnosis of Hyponatremia

1. Hyponatremia may be associated with a normal, elevated, or decreased serum osmolality.
2. In patients with decreased serum osmolality (true hyponatremia) an evaluation of ECF volume status subdivides patients into 3 groups: increased; normal; or decreased ECF volume (total-body sodium).
3. Increased ECF volume and total-body sodium is identified by the presence of dependent edema on physical examination.
4. Patients with decreased ECF volume are further subdivided based on urinary sodium excretion into those with renal or extrarenal salt and water losses.
5. The most common cause of hyponatremia in the "clinically euvolemic" patient is SIADH.

Treatment

The major sequelae of hyponatremia are neurologic. Neurologic injury is secondary to either hyponatremic encephalopathy or improper therapy (too rapid or overcorrection). Clinical studies show that in more than 90% of cases neurologic injury is secondary to hyponatremic encephalopathy. Hypoxia is the major factor contributing to neurologic injury. Because RVD involves active ion transport that is adenosine triphosphate (ATP)-dependent, it is blunted by hypoxia. As a result sodium accumulates in brain and worsens cerebral edema. Hypoxia is also a major stimulus for AVP secretion. AVP directly stimulates water entry into neurons. In addition, AVP decreases ATP generation and decreases intracellular pH that further decreases Na^+-K^+-ATPase activity. Respiratory arrest and seizures often occur suddenly in hyponatremic encephalopathy and patients who suffer a hypoxic event rarely survive without permanent neurologic injury. Predictive factors for neurologic injury include young age, female sex, reproductive status (premenopausal women), and presence of encephalopathy. Premenopausal women are at 25-fold increased risk for permanent neurologic injury from hyponatremic encephalopathy compared to postmenopausal women or men. This led to speculation that RVD is not as efficient in young women. In one study, premenopausal women had a respiratory arrest at higher serum sodium concentrations compared to postmenopausal women, 117 ± 7 mEq/L versus 107 ± 8 mEq/L, respectively.

Treatment is dependent on the acuity and severity of hyponatremia, as well as the patient's ECF volume status. Caution is exercised not to raise the serum sodium concentration too quickly in patients with chronic hyponatremia (duration >48 hours) as a devastating neurologic syndrome, central pontine myelinolysis (CPM), can result from rapid correction. Destruction of myelin sheaths of pontine neurons results in flaccid quadriplegia, dysarthria, dysphagia, coma, and death. The consequences are catastrophic and no treatment is currently available. Demyelination may be the result of excessive neuronal dehydration. Chronic hyponatremia downregulates expression of SNAT 2 (sodium-coupled neutral amino acid transporter-2). This pathway is particularly important in cell volume recovery in these cells.

In CPM lesions are characterized by oligodendrocyte and myelin loss. Oligodendrocytes may be particularly susceptible to injury with rapid sodium correction. It is associated with increases in serum sodium concentration to normal within 24 to 48 hours, an increase in the serum sodium concentration greater than 10 mEq/L in the first 24 hours and greater than 18 in the first 48 hours, and elevation of serum sodium concentration to hypernatremic levels in patients with liver disease. Alcoholics and patients with liver disease may develop CPM with increases in serum sodium concentration less than 10 mEq/day. In acute liver failure, glutamine accumulation in the brain contributes to cerebral edema. The combination of glutamine and hyponatremia-induced cerebral edema depletes the brain of myoinositol, which is the most abundant intracellular organic osmolyte. Profoundly reduced levels of myoinositol in patients with cirrhosis may explain their increased susceptibility to CPM. The clinical course may be characterized by 3 phases: (a) symptomatic hyponatremia; (b) improvement in hyponatremia encephalopathy with correction of the sodium concentration; (c) only to be followed a few days later by symptoms of CPM.

Because the neurologic insult may result from a rapid water shift out of brain cells, it is possible that it could be interrupted at an early stage by shifting water back into brain cells. This was done successfully in an animal model. The optimal protective effect was obtained provided that the final sodium correction gradient was reduced below 25 mEq/L/24 hours and was effective up to 24 hours after the onset of osmotic injury. The quickest

way to do this is through the administration of dD-AVP (a synthetic analogue of AVP, 1-deamino-8-D-arginine vasopressin, also known as desmopressin). The risk of relowering the serum sodium concentration may be low in the first few days of the correction process. This has also been reported in humans with administration of 1 to 2 μg of desmopressin intravenously every 6 to 8 hours. As serum sodium concentration rises during the correction phase, the brain regains extruded osmolytes. This process takes up to 5 to 7 days to complete.

On the other hand acute hyponatremic encephalopathy is a true medical emergency that must be dealt with promptly and aggressively. This is often the result of acute water intoxication in psychotic patients, a large fluid intake associated with ecstasy use, or exercise-induced hyponatremia in marathon runners. During a marathon race an average of 0.5 kg of glycogen and triglyceride are metabolized. This generates 1.0 to 1.5 L of free water. This plus over vigorous hydration during the race can contribute to hyponatremia. It should be kept in mind that delayed water absorption from the gastrointestinal tract may worsen the clinical situation even after the patient is under clinical observation. The patient with seizures or coma should be treated with boluses of 3% saline, either 100 mL or 2 mL/kg, repeated up to 2 times in order to raise the sodium concentration by 4 to 6 mEq/L.

A recent manuscript dealt with the special problem of acute hyponatremia in critically ill patients with acute neurologic and neurosurgical disorders. In this group of patients, treatment is recommended if the sodium concentration declines below 131 mEq/L, and if associated with symptoms, 3% saline is used. The authors used a sliding scale protocol for a sodium concentration equal to or less than 133 mEq/L or a decline in sodium concentration equal to or greater than 6 mEq/L over a 24- to 48-hour period. Initially, either NaCl tablets at a dose of 3 g every 6 hours is given orally or through a nasogastric tube, or 3% saline at 20 mL/h is administered. The dose of 3% saline is increased every 6 hours by 10 to 20 mL/h to a maximum of 80 mL/h, depending on the serum sodium concentration. The goal is to maintain a sodium concentration of 136 to 140 mEq/L. Saline is withheld for 6 hours for a sodium concentration greater than 140 mEq/L.

The patient evolving hyponatremia chronically (>48 hours) is not corrected faster than 6 mEq/L per 24 hours. One should be especially cautious if liver disease or hypokalemia are present as these subgroups of patients appear to be at particularly high risk for CPM. In the severely symptomatic patient with seizures, delirium, or coma, this 6 mEq/L increase can be front-loaded into the first few hours. One should admit the symptomatic patient to the intensive care unit and precautions should be taken to ensure a secure airway. Serum sodium concentration is increased with either the infusion of 3% saline (513 mEq Na/L) or a combination of a loop diuretic and normal saline. Hypertonic saline is discontinued when the serum sodium concentration increases above 120 mEq/L or when symptoms resolve. Serum electrolytes are monitored every 2 hours. Water restriction alone has no role in the management of the symptomatic patient as it corrects the serum sodium concentration too slowly.

A variety of formulas can be used to calculate the sodium requirement. They allow one to calculate the amount of sodium that would need to be added or water that would need to be removed to return the serum sodium concentration to normal. Although both sodium and water have either been removed or added in the process of generating the hyponatremia, these formulas work well in clinical practice. The most commonly employed formula is

$$\text{Na}^+ \text{ requirement} = \text{total-body water} \times (\text{desired serum } \text{Na}^+ - \text{current serum } \text{Na}^+)$$

Total-body water is equal to 0.6 times the body weight in men and 0.5 times the body weight in women. Based on the requirement, one then calculates the infusion rate of 3% saline solution. Alternatively, one can estimate the effect on serum sodium concentration of 1 L of any infused solution using the following formula:

$$\frac{\text{infusate } \text{Na}^+ - \text{serum } \text{Na}^+}{\text{total-body water} + 1}$$

One can then adjust the rate of infusate to achieve the desired increase in serum sodium concentration. This formula often underestimates the increase in sodium concentration in patients with concentrations less than 120 mEq/L. In many of these cases, urinary free water loss accounts for the excessive increase. Seizures may cause a transient rise in serum sodium concentration as a result of water shift into muscle caused by an increase in intracellular osmolality and contribute to rapid correction.

In the hypovolemic patient, one discontinues diuretics, corrects gastrointestinal fluid losses, and expands the ECF with normal saline. Replacing the ECF volume

deficit is important because this eliminates the stimulus for nonosmotic AVP release and leads to production of a maximally dilute urine. To calculate the sodium deficit one can use the following equation:

$$Na^+ \text{ deficit} = (\text{total-body water}) \times (140 - \text{current serum sodium concentration})$$

One can replace one-third of the deficit over the first 12 to 24 hours and the remainder over the ensuing 48 to 72 hours. If vomiting, diarrhea, or diuretics caused the volume depletion, potassium deficits also must be corrected.

In the asymptomatic euvolemic patient, one often begins treatment by restricting water. The following example illustrates the degree of reduction in total-body water required to restore the serum sodium concentration to normal. A 75-kg man has a total-body water of 45 L and a serum sodium concentration of 115 mEq/L. The formula below is used to calculate the desired total-body water (TBW).

$$\frac{\text{Actual serum } Na^+}{\text{Normal serum } Na^+} \times \text{current TBW} = \text{desired TBW}$$

The desired total-body water is 36.9 L. Subtracting the desired from the current total-body water reveals that 8.1 L of water must be removed to restore the serum sodium concentration to 140 mEq/L. Fluid restriction rarely increases the serum sodium concentration by more than 1.5 mEq/L/day. One can estimate the response to water restriction based on the ratio of the sum of sodium and potassium in urine versus serum. This is a reflection of the amount of free water in the urine. If the ratio is 0.5 or less, then there is free water in the urine and the patient is likely to have an increase in sodium concentration with fluid restriction. If the ratio is 0.5 to 1.0, then less free water is present and fluid will need to be drastically restricted. If the ratio is greater than 1.0, then no free water is present and the patient will not respond. When the cause of SIADH is not reversible, demeclocycline can be used (600 to 1200 mg/day) providing that the patient has normal liver function.

The hypervolemic patient is managed with salt and water restriction. Negative water balance is achieved if daily fluid intake is less than the excretion of free water in urine. If congestive heart failure is the cause, an increase in cardiac output will suppress AVP release.

The vaptans are V_2 receptor antagonists that enhance renal free water excretion without increasing sodium or potassium excretion. This class of drugs is also referred to as *aquaretics*. They are approved for use in euvolemic hyponatremia caused by SIADH, hypothyroidism, and adrenal insufficiency, as well as hypervolemic hyponatremia from congestive heart failure. Two vaptans are available for clinical use in the United States: conivaptan and tolvaptan. Conivaptan is available for intravenous administration. It inhibits both V_2 and V_{1a} receptors. V_{1a} receptors are expressed in vascular smooth muscle cells, liver, and platelets. Vasopressin binding to the V_{1a} receptor results in vasoconstriction, platelet aggregation and increased gluconeogenesis. Conivaptan has an effect 2 to 4 hours after the start of administration. It is metabolized by CYP3A4 and as a result should not be administered in patients on drugs that are strong inhibitors of CYP3A4, such as ketoconazole, ritonavir, and clarithromycin. A 20-mg bolus is followed by an infusion at 20 mg daily for 3 additional days. The infusion can be increased to 40 mg if the 20 mg dose is ineffective. Tolvaptan has 29-fold higher affinity for the V_2 receptor compared to the V_{1a} receptor and is given orally. It is administered starting at a dose of 15 mg daily and can be increased to 30 or 60 mg. It has an onset of action within 2 to 4 hours and a half-life of 12 hours. Its main side effect is thirst. As with conivaptan, one should avoid concomitant use with strong CYP3A inhibitors. Moderate inhibitors of CYP3A will increase the effect of the drug, whereas inducers of the enzyme will reduce its effect.

Common management errors in the treatment of the hyponatremic patient and recommendations include the following:

1. A fear of CPM often leads to a delay in correction or too slow a rate of correction of hyponatremia. Neurologic sequellae are far more commonly related to too slow a rate of correction rather than rapid correction.
2. The belief that 3% saline can only be used in a patient who is seizing. Hypertonic saline should be employed in hyponatremic encephalopathy. Every effort should be made to prevent seizure and respiratory arrest, once these sequelae develop permanent neurologic injury is the rule.
3. Be cognizant of patients who are at high risk for CPM, especially those with abrupt withdrawal of a stimulus that inhibits free water excretion, such as liver transplantation, correction of adrenal insufficiency, and elderly women on thiazides (diuretic is discontinued and ECF volume repleted). Magnetic resonance imaging is the study of choice to diagnose CPM but

may take up to 1 to 2 weeks after the onset of signs and symptoms to show characteristic abnormalities.

4. Be aware of patients who are at high risk for hyponatremic encephalopathy, such as premenopausal women in the postoperative setting. Postoperative patients should never receive free water. In the postoperative setting vasopressin levels remain elevated for 48 hours or more resulting in water retention. Neurologic symptoms commonly develop at a serum sodium concentration equal to or less than 128 mEq/L in acute hyponatremia. The intravenous fluid of choice in this setting is normal saline or Ringer's lactate. Electrolytes are monitored daily.
5. Patients with SIADH should never be treated with normal saline alone. Normal saline administration in this setting results in a further fall in serum sodium concentration. The kidney is capable of generating free water from normal saline. For example, a patient with SIADH and a U_{osm} of 600 mOsm/kg, who is administered 1 L of normal saline (approximately 300 mOsm), will excrete that osmolar load in 500 mL of urine (300 mOsm given/600 mOsm/kg – U_{osm} = 500 mL final urine volume). This results in the generation of 500 mL of free water (the remainder of the 1 L given) and a further fall in serum sodium concentration.
6. Failing to recognize that treatment of hypokalemia may make the hyponatremic patient more vulnerable to overcorrection. When potassium is repleted sodium will move out of cells, increasing its concentration. The rate of 3% saline will need to be slowed if potassium is repleted to try to account for this phenomenon. This may be the reason why hypokalemia is associated with CPM.

KEY POINTS

Treatment of Hyponatremia

1. The morbidity and mortality of hyponatremia are related to neurologic injury that occurs as a result of hyponatremic encephalopathy or improper therapy (too rapid or overcorrection).
2. The major factor contributing to neurologic injury is hypoxia. Premenopausal women are at highest risk.
3. Treatment is dependent on the acuity and severity of hyponatremia, and the patient's ECF volume status.
4. Severe symptomatic hyponatremia is treated emergently with the goal of raising serum sodium concentration by 4 to 6 mEq/L. Chronic hyponatremia (>48 hours) is not corrected faster than 6 mEq/L in a 24-hour period. If liver disease and hypokalemia are present caution should be exercised, as these patients are at high risk for CPM.
5. Every effort should be made to prevent seizure and respiratory arrest, once these sequelae develop permanent neurologic injury is the rule.
6. Postoperative patients should not receive free water.
7. Patients with SIADH should never be treated with normal saline alone.

HYPERNATREMIA

Pathophysiologic Mechanisms

Hypernatremia is defined as a serum sodium concentration greater than 145 mEq/L. It occurs when AVP concentration or effect is decreased or water intake is less than insensible, gastrointestinal and renal water losses. Therefore, hypernatremia results when there is a failure to take in enough free water in either the presence or absence of a urinary concentrating defect. This is most commonly seen in those patients who depend on others for access to water or who lack thirst sensation. Infrequently, hypernatremia results from salt ingestion or administration of hypertonic saline solutions.

With free water loss, the serum osmolality and sodium concentration increase as shown in Figure 3.3. The rise in serum osmolality stimulates thirst and AVP release from the posterior pituitary. Stimulation of thirst results in increased free water intake. AVP binds to its receptor in the basolateral membrane of collecting duct and stimulates water reabsorption.

The normal renal concentrating mechanism in humans allows for excretion of urine that is as much as 4 times as concentrated as plasma (1200 mOsm/kg H_2O). Because the average daily solute load is approximately 600 mOsm, this solute is excreted in as little as 0.5 L of urine. Note that even under maximal antidiuretic conditions, one must drink at least this volume of water per day in order to maintain water balance. Thirst is an integral component of the water regulatory system. Normal function of the renal concentrating mechanism

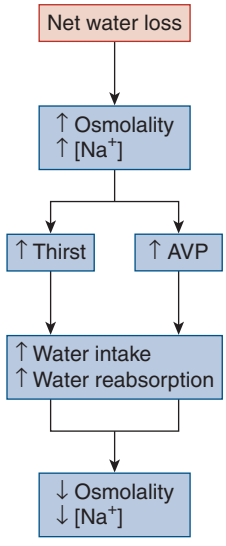

FIGURE 3-3. Normal response to water loss, which involves stimulation of thirst and increased renal water reabsorption.

requires that its various components be intact. These include the following:

1. **Ability to generate a hypertonic interstitium.** The loop of Henle acts as a countercurrent multiplier with energy derived from active chloride transport in the water-impermeable thick ascending limb of the loop (mediated via the Na^+-K^+-$2Cl^-$ cotransporter). The transporter serves the dual process of diluting tubular fluid and rendering the interstitium progressively hypertonic from cortex to papilla.
2. **AVP secretion.** This hormone renders the collecting duct permeable to water and allows fluid delivered from the distal tubule to equilibrate with the concentrated interstitium. AVP is a nonapeptide produced by neurons originating in the supraoptic and paraventricular nuclei of the hypothalamus. These neurons cross the pituitary stalk and terminate in the posterior pituitary. AVP is processed and stored in neurosecretory granules along with neurophysin and copeptin.
3. **Normal collecting duct responsiveness to AVP.** Abnormalities in the renal concentrating process obligate excretion of a larger volume of urine to maintain solute balance; for example, with 600 mOsm of solute to be excreted and the inability to increase U_{osm} above plasma, a urine flow of 2 L/day is obligated. Failure to replace these water losses orally leads to progressive water depletion and hypernatremia.

KEY POINTS

Hypernatremia

1. Hypernatremia results when there is a failure to take in enough free water in either the presence or absence of a concentrating defect. It is most commonly seen in those who depend on others for access to water or who lack thirst.
2. Thirst is an integral component of the water regulatory system.
3. The normal concentrating mechanism function requires the ability to generate a hypertonic interstitium, AVP secretion, and normal collecting duct responsiveness to AVP.

Etiology

Diabetes insipidus (DI) is the result of decreased pituitary AVP production (central) or decreased renal AVP responsiveness (nephrogenic). Central DI does not occur until greater than 80% of vasopressin-producing neurons are destroyed.

Central DI may be idiopathic or secondary to head trauma, surgery, or neoplasm. Urine volume ranges from 3 to 15 L/day. Patients tend to be young with nocturia and a preference for cold water. The kidneys should respond to exogenous AVP with a rise in U_{osm} of 100 mOsm/kg above the value achieved following water deprivation. Patients with complete central DI are unable to concentrate urine above 200 mOsm/kg with dehydration, whereas patients with partial DI are able to concentrate urine but not maximally. Treatment consists of administering AVP. The best therapy is long-acting, nasally administered dD-AVP. An important point is that thirst is stimulated by the increased P_{osm} so effectively that serum sodium concentration is only slightly elevated and the most common clinical presentation is polyuria. Psychogenic polydipsia also presents with polyuria; however, the serum sodium concentration is often mildly decreased rather than increased.

One-third to one-half of central DI cases are idiopathic. A lymphocytic infiltrate is present in the posterior pituitary and pituitary stalk. Some of these patients have circulating antibodies directed against vasopressin-producing neurons.

Familial central DI is rare and inherited in 3 ways. The most common is an autosomal dominant disorder resulting from mutations in the coding region of the AVP gene. The mutant protein fails to fold properly and accumulates in the endoplasmic reticulum resulting in neuronal death. Because neurons die slowly vasopressin deficiency is not present at birth but develops over years. It often gradually progresses from a partial to complete defect. A similar clinical presentation is seen with X-linked inheritance, although the evidence for this mode of inheritance is weak. Autosomal recessive central DI is a very rare disorder caused by a single amino acid substitution resulting in the production of an AVP with little to no antidiuretic activity.

In nephrogenic DI the collecting duct does not respond appropriately to AVP. The most common inherited form of nephrogenic DI is an X-linked disorder in which cyclic AMP is not generated in response to AVP. It is caused by a number of mutations in the V_2 receptor. Aquaporin-2 gene mutations also result in nephrogenic DI and may be inherited in an autosomal dominant or recessive fashion. In dominant cases heterotetramers form between mutant and wild type aquaporin-2 water channels that are unable to traffic to the plasma membrane. This usually results in complete resistance to AVP.

Acquired nephrogenic DI is much more common but often less severe. Chronic kidney disease, hypercalcemia, lithium treatment, obstruction, and hypokalemia are its causes. Aquaporin-2 expression in principal cells of the collecting duct is markedly reduced. Lithium is used in the treatment of manic-depressive psychosis. Nephrogenic DI may occur in up to 40% of patients on long-term therapy. It can occur in as short as 8 weeks. Concomitant use of an SSRI increases risk 2.86-fold. Lithium is a potent inhibitor of synthase kinase 3β that reduces adenyl cyclase activity. In rats administered lithium for 25 days aquaporin-2 and -3 expression decreases to 5% of control levels. Both hypokalemia and hypercalcemia are associated with a significant downregulation of aquaporin-2. Rats treated with a potassium-deficient diet for 11 days show a 30% decrease in aquaporin-2 expression. Aquaporin-2 expression normalizes after 7 days of a normal potassium diet. Hypercalcemia induced by excessive vitamin D administration in rats results in a concentrating defect that is caused by downregulation of both aquaporin-2 and the Na^+-K^+-$2Cl^-$ cotransporter.

A number of drugs may cause a renal concentrating defect. Ethanol and phenytoin impair AVP release resulting in a water diuresis. Lithium and demeclocycline cause tubular resistance to AVP while amphotericin B and methoxyflurane injure the renal medulla. Thus, a concentrating defect (inability to conserve water) can be secondary to a lack of AVP, unresponsiveness to AVP, or renal tubular dysfunction. Other specific causes and mechanisms for concentrating defects include sickle cell anemia or trait (medullary vascular injury), excessive water intake or primary polydipsia (decreased medullary tonicity), severe protein restriction (decreased medullary urea), and a variety of disorders affecting renal medullary vessels and tubules.

DI can also be caused by peripheral AVP degradation in peripartum women. Vasopressinase is an enzyme produced by the placenta that degrades AVP and oxytocin. It appears in plasma of women early in pregnancy and increases in concentration throughout gestation. After delivery, which is curative because of loss of the placenta, vasopressinase rapidly becomes undetectable. Although only case reports of DI from vasopressinase are published to date, it is unclear how frequently this condition actually occurs. These patients often respond to desmopressin (dD-AVP), which is not degraded by vasopressinase.

KEY POINTS

Etiology of Hypernatremia

1. DI may be central because of decreased pituitary production and release of AVP or nephrogenic secondary to decreased renal responsiveness to AVP.
2. Central DI is idiopathic or secondary to head trauma, surgery, or neoplasm.
3. Acquired nephrogenic DI occurs most commonly with lithium administration. Aquaporin-2 expression in principal cells of collecting duct is markedly reduced.
4. A variety of drugs cause renal concentrating defects.

Signs and Symptoms

Cellular dehydration occurs as water shifts out of cells. This results in neuromuscular irritability with twitches, hyperreflexia, seizures, coma, and death. In children, severe acute hypernatremia (serum sodium concentration >160 mEq/L) has a mortality rate of 45%. Two-thirds of survivors have permanent neurologic injury. In adults, acute hypernatremia has a reported mortality as high as 75% and chronic hypernatremia 60%. Hypernatremia is often a marker of serious underlying disease. Of note, the

brain protects itself from the insult of hypernatremia by increasing its own osmolality, in part due to increases in free amino acids. The phenomenon is referred to as the *generation of "idiogenic osmoles."* The therapeutic corollary is that water repletion must be slow with chronic hypernatremia to allow inactivation of these solutes and thus avoid cerebral edema.

KEY POINTS

Signs and Symptoms of Hypernatremia

1. Symptoms of hypernatremia result from a shift of water out of brain cells.
2. In chronic hypernatremia, the brain generates "idiogenic osmoles" that reduce the gradient for water movement.

Diagnosis

Although hypernatremia can occur in association with hypovolemia, hypervolemia, and euvolemia, patients most commonly present with hypovolemia. Those who are euvolemic may be mildly hypernatremic, but their most common complaint is polyuria. Many disorders may result in hypernatremia; however, decreased thirst, inability to gain access to water, and drugs are the most common causes (Figure 3.4).

A high serum sodium concentration generally results from free water loss that is not compensated for by an increase in free water intake. Free water loss may be renal or extrarenal in origin. Extrarenal losses originate from skin, respiratory tract, or from the gastrointestinal tract. Renal losses are the result of a solute (osmotic) or water diuresis. A solute or osmotic diuresis most commonly results from glucose excretion in uncontrolled diabetes mellitus. A water diuresis is secondary to central or nephrogenic DI. If thirst is intact, patients with renal losses present with the chief complaint of polyuria, defined as the excretion of more than 3 L of urine daily.

An increased serum sodium concentration is a potent stimulus for thirst and AVP release. After a thorough history and physical examination are performed, the clinician must answer several questions in the hypernatremic patient. First, is thirst intact? If the serum sodium concentration is elevated above 147 mEq/L the patient should be thirsty. Second, if the patient is thirsty is the

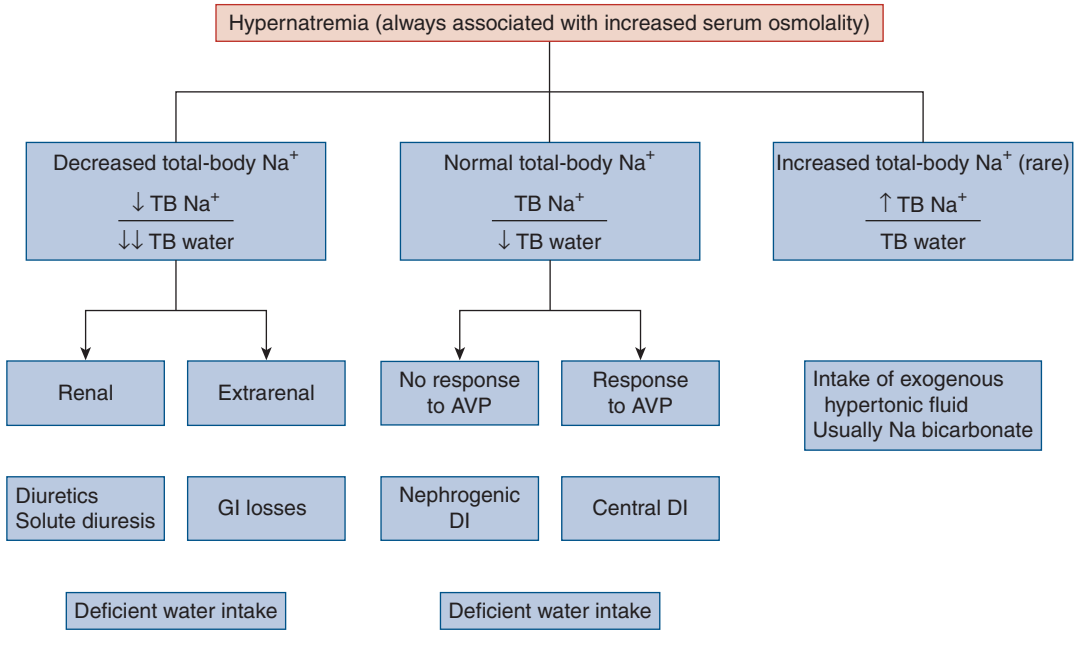

FIGURE 3-4. Clinical approach to the patient with hypernatremia. Patients with hypernatremia can also be categorized based on ECF volume status. The majority have decreased or normal ECF volume (total-body sodium). *Abbreviations:* GI, Gastrointestinal; TB, total-body.

patient capable of getting to water? The next step is to evaluate the hypothalamic-pituitary-renal axis. This involves an examination of U_{osm}. If the hypothalamic-pituitary-renal axis is intact a rise in serum sodium concentration above 147 mEq/L maximally stimulates AVP release and results in a U_{osm} greater than 700 mOsm/kg. If U_{osm} is greater than 700 mOsm/kg, then free water losses are extrarenal. A U_{osm} less than plasma indicates that the kidney is the source of free water loss as a result of either central or nephrogenic DI. These disorders are differentiated by the response to exogenous AVP. Either 5 units of aqueous vasopressin subcutaneously or 10 μg of dD-AVP intranasally increases U_{osm} by 50% or more in central DI but has no effect on U_{osm} in nephrogenic DI. In central DI the onset is generally abrupt, urine volume remains fairly constant over the course of the day, nocturia is common, and patients have a preference for drinking cold water.

U_{osm} in the intermediate range (300 to 600 mOsm/kg) may be secondary to psychogenic polydipsia, an osmotic diuresis, and partial central or nephrogenic DI. Psychogenic polydipsia is generally associated with a mildly decreased rather than increased serum sodium concentration. Partial central and nephrogenic DI may require a water deprivation test to distinguish. In the water deprivation test water is prohibited and urine volume and osmolality measured hourly and serum sodium and osmolality every 2 hours. The test is stopped if either the U_{osm} reaches normal levels (>700 mOsm/kg), the P_{osm} reaches 300 mOsm/kg, or the U_{osm} is stable on 2 successive readings despite a rising serum osmolality. In the last 2 circumstances, exogenous vasopressin is administered and the U_{osm} and volume measured. In partial central DI, the U_{osm} generally increases by greater than 50 mOsm/kg. In partial nephrogenic DI, the U_{osm} may increase slightly but generally remains below serum osmolality. An osmotic diuresis is suspected if the total osmolar excretion exceeds 1000 mOsm/day. Total osmolar excretion is calculated by multiplying the U_{osm} by the urine volume in a 24-hour collection.

KEY POINTS

Diagnosis of Hypernatremia

1. Hypernatremia occurs most commonly in association with hypovolemia.
2. The euvolemic patient is only mildly hypernatremic but will complain of polyuria.
3. A high serum sodium concentration results from free water loss that is not compensated for by an increase in free water intake. Free water loss is renal or extrarenal in origin.
4. The clinician should first examine whether thirst and access to free water are intact.
5. The next step is to evaluate the hypothalamic-pituitary-renal axis. This involves an examination of U_{osm}. If U_{osm} is greater than 700 mOsm/kg, then free water losses are extrarenal.
6. A U_{osm} less than plasma indicates that the kidney is the source of free water loss from either central or nephrogenic DI. These disorders are differentiated by response of U_{osm} to exogenous AVP.

Treatment

Treatment of hypernatremia is divided into 2 parts: restoring plasma tonicity to normal and correcting sodium imbalances, and providing specific treatment directed at the underlying disorder.

When restoring plasma tonicity to normal and correcting sodium imbalances, sodium may need to be added or removed while providing water. A formula to calculate the total amount of water needed to lower serum sodium concentration from one concentration to another can be used. This does not take into account, however, changes in sodium balance, as it is based on a rough estimate of total-body water as 60% of weight (kg) in men and 50% of weight (kg) in women:

$$\text{water needed (L)} = (\text{total-body water}) \times ([\text{actual sodium}/\text{desired sodium}] - 1)$$

Water deficits are restored slowly so as to avoid sudden shifts in brain cell volume. Water deficits are corrected preferably with increased oral intake or with intravenous administration of hypotonic solution. The serum sodium concentration should not be lowered faster than 12 mEq/day or 0.5 mEq/h. The formula above calculates the amount of free water replacement needed at the time the patient is first seen. It does not take into account ongoing free water losses that may be occurring from the kidney while one is attempting to correct the deficit. If urine volume is high or U_{osm} low, then one must add ongoing renal free water losses to the replacement calculation.

To determine ongoing renal free water losses one must calculate the electrolyte-free water clearance. For this purpose urine is divided into 2 components: an isotonic

component (the volume needed to excrete sodium and potassium at their concentration in serum); and an electrolyte-free water component. This is shown in the formula below:

$$\text{urine volume} = C_{\text{Electrolytes}} + C_{H_2O}$$

$$C_{\text{Electrolytes}} = \frac{\text{urine } [Na^+] + [K^+]}{\text{serum } [Na^+]} \times \text{urine volume}$$

where C_{H_2O} is the urine volume from which the electrolytes were removed during the elaboration of a hypotonic urine. This is best illustrated with a case.

CASE 3.1

A 70-kg male with a history of nephrogenic DI is found unconscious at home and is brought to the emergency department. The serum sodium concentration is 160 mEq/L. A Foley catheter is placed and urine output is 500 mL/h. Urine electrolytes reveal a sodium concentration of 60 mEq/L, a potassium concentration of 20 mEq/L, and a U_{osm} of 180 mOsm/kg. How much water must be administered in order to correct the serum sodium concentration to 140 mEq/L?

$$\begin{aligned}\text{Water needed (L)} &= (0.6 \times \text{body weight in kg}) \\ &\quad \times ([\text{actual sodium/desired sodium}] \\ &\quad - 1) \\ &= (0.6 \times 70) \times ([160/140] - 1) \\ &= 42 \times 0.14 \text{ or } 6 \text{ L}\end{aligned}$$

One next determines the time frame over which the deficit will be corrected. If the serum sodium concentration were decreased by 8 mEq/L in the first 24 hours then 2.4 L of water is administered at a rate of 100 mL/h. If water were given at this rate in the form of 5% dextrose in water (D_5W) serum sodium concentration would increase not decrease. The reason for this is that the replacement calculation did not include the large ongoing free water loss in urine.

To include renal free water losses, one must calculate the electrolyte-free water clearance as illustrated below:

$$\begin{aligned}C_{\text{Electrolytes}} &= \frac{\text{urine } [Na^+] + [K^+]}{\text{serum } [Na^+]} \times \text{urine volume} \\ &= \frac{60 + 20}{160} \times 500 \text{ mL/h} \\ &= \frac{80}{160} \times 500 = 250 \text{ mL/h}\end{aligned}$$

$$C_{H_2O} = \text{urine volume} - C_{\text{Electrolytes}}$$

$$C_{H_2O} = 500 - 250 = 250 \text{ mL/h}$$

The ongoing renal free water losses of 250 mL/h must be added to the replacement solution, 100 mL/h, in order to correct the serum sodium concentration.

Treatment is also directed at the underlying disorder. In the patient with nephrogenic DI, significant hypernatremia will not develop unless thirst is impaired or the patient lacks access to water. The goal of treatment is to reduce urine volume and renal free water excretion. As discussed earlier urine volume is equal to osmolar excretion or intake (they are the same in the steady state) divided by the U_{osm}. Urine volume can be reduced by decreasing osmolar intake with protein or salt restriction or by increasing U_{osm}. Thiazide diuretics inhibit urinary dilution and increase U_{osm}. By inhibiting renal prostaglandin synthesis, nonsteroidal antiinflammatory drugs (NSAIDs) increase concentrating ability. Prostaglandins normally antagonize the action of AVP. Their effects are partially additive to those of thiazide diuretics. Electrolyte disturbance such as hypokalemia or hypercalcemia should be corrected. Early in the course of lithium-induced nephrogenic DI, amiloride may be of some benefit. Amiloride prevents lithium entry into the cortical collecting duct principal cell and can limit its toxicity.

The patient with central DI and a deficiency of AVP secretion is treated with hormone replacement (Table 3.3). Intranasal desmopressin is most commonly used. The initial dose is 5 µg at bedtime and is titrated upward to a dose of 5 to 20 µg once or twice daily. Desmopressin can also be

TABLE 3-3. Treatment of Central Diabetes Insipidus

CONDITION	DRUG	DOSE
Complete		
	dD-AVP	5 to 20 µg intranasally q12-24h 0.1 to 0.4 mg orally q12-24h
Incomplete		
	Chlorpropamide	125 to 500 mg/day
	Carbamazepine	100 to 300 mg bid
	Clofibrate	500 mg qid

Abbreviations: bid, Twice a day; qid, 4 times a day.

administered orally. In general a 0.1-mg tablet is equivalent to 2.5 to 5.0 μg of the nasal spray. Serum sodium concentration must be followed carefully during dose titration to avoid hyponatremia. Desmopressin is expensive. As a consequence, drugs that increase AVP release or enhance its effect can be added to reduce cost. These drugs can also be used in patients with partial central DI. Chlorpropamide and carbamazepine enhance renal AVP action. Clofibrate may increase AVP release. As with nephrogenic DI, thiazide diuretics and NSAIDs can also be employed.

KEY POINTS

Treatment of Hypernatremia

1. Treatment of hypernatremia is directed at restoring plasma tonicity to normal, correcting sodium imbalances, and providing specific treatment directed at the underlying disorder.
2. Water deficits are restored slowly to avoid sudden shifts in brain cell volume. The serum sodium concentration is not lowered faster than 12 mEq/day.
3. If urine volume is high or U_{osm} low, then one must account for ongoing renal free water losses.
4. In the patient with nephrogenic DI, urine volume is reduced by decreasing osmolar intake with protein or salt restriction, or by increasing U_{osm} with thiazide diuretics.
5. Hormone replacement therapy with desmopressin (dD-AVP) is the cornerstone of treatment of central DI.

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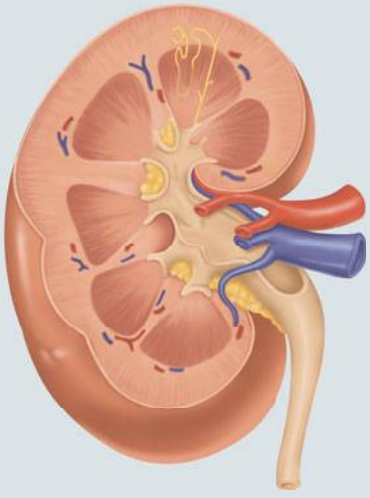
CHAPTER 4

Diuretics

• *Mark A. Perazella and Mandana Rastegar*

Recommended Time to Complete: 1 Day



Guiding Questions

1. What is the difference between diuresis and natriuresis?
2. How do diuretics reach their site of action?
3. Where do diuretics act in the nephron?
4. Which diuretics act in proximal tubule and what is their mechanism of action?
5. What transporter in the loop of Henle reabsorbs NaCl?
6. Which diuretics act in distal collecting tubule?
7. How do diuretics that act in cortical collecting duct (CCD) induce natriuresis?
8. What are some of the common adverse effects of various diuretics?
9. What is diuretic resistance and how does one assess for the cause of resistance?
10. How does diuretic resistance develop in the setting of chronic loop diuretic therapy?
11. How does one treat various causes of diuretic resistance?

INTRODUCTION

The primary renal effect of diuretics is to increase the amount of urine formed or diuresis (water, sodium, urea, and other substances). A large part of this effect is a result of enhanced natriuresis, which is defined as an increase in renal sodium excretion. Diuretics were initially described as a useful therapy to reduce edema in the 16th century. The first agent known to increase urine output was mercurous chloride. In 1930, the antimicrobial sulfanilamide was noted to increase renal Na^+ excretion and reduce edema formation in patients with congestive heart failure (CHF). It is interesting that most diuretics were discovered serendipitously when they were noted to increase urine output and change urine composition. These changes in urine were considered an adverse effect of drugs intended for other purposes. Targeted disruption of various renal transporters was not part of the development of these drugs as the mechanism of transport was unknown; instead, diuretics were developed empirically. Diuretics are the most commonly prescribed medications in the United States. They are used to treat a variety of clinical disease states, including hypertension, edema, CHF, hypokalemia and hyperkalemia, hypercalcemia, and nephrolithiasis.

To understand the actions of diuretics, one must first appreciate renal handling of sodium and water. This subject is reviewed in detail in Chapter 2, but is briefly reviewed here. The kidneys regulate extracellular fluid (ECF) volume by modulating NaCl and water excretion. Sodium intake is balanced by the renal excretion of sodium. A normal glomerular filtration rate (GFR) is important for the optimal excretion of sodium and water. Following formation and passage of glomerular ultrafiltrate into the Bowman space, delivery of sodium and water to the proximal tubule is the first site of tubular

handling. Along the nephron sodium is reabsorbed by several different transport mechanisms and absorption is regulated by a number of different factors. For example, various hormones (renin, angiotensin II, aldosterone, atrial natriuretic peptide [ANP], prostaglandin, and endothelin) and physical properties (mean arterial pressure, peritubular capillary pressure, and renal interstitial pressure) modify renal handling of sodium and water. Direct effects on tubular transport along the nephron underlie the major influence of these factors on renal sodium and water handling. Sodium reabsorption is driven primarily by Na^+-K^+-adenosine triphosphatase (ATPase) located on the basolateral membrane of all tubular epithelial cells. This pump provides energy required by transporters located on the apical (luminal) membrane that reabsorb sodium from glomerular filtrate. Cell-specific transporters are present on these tubular cells.

Diuretics act to enhance renal sodium and water excretion by inhibiting these transporters at different nephron sites (Figure 4.1). They act to reduce sodium entry into the tubular cell. With the exception of spironolactone and eplerenone, all diuretics exert their effects from the luminal side of the cell. Thus most diuretics must enter tubular fluid to be effective. Secretion across the proximal tubule via either organic acid or base transport pathways is the primary mode of entry (except for mannitol, which undergoes glomerular filtration). Diuretic potency depends significantly on drug delivery to its site of action, as well as the nephron site where it acts. Other factors that influence diuretic action are the level of kidney function (GFR), state of the effective arterial blood volume (CHF, cirrhosis, and nephrosis), and treatment with certain medications such as nonsteroidal antiinflammatory drugs (NSAIDs) and probenecid. Diuretics may also have a variety of adverse effects, some that are common to all diuretics and others that are unique to specific agents (Table 4.1).

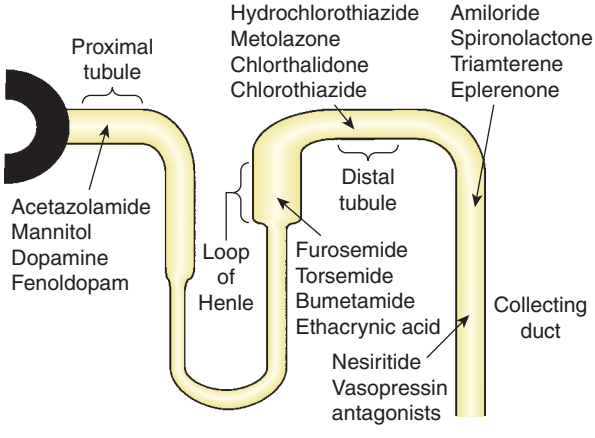


FIGURE 4-1. Sites of diuretic action in the nephron. Sodium chloride reabsorption is reduced by various diuretics in proximal tubule, loop of Henle, distal convoluted tubule, and cortical collecting duct.

KEY POINTS

Diuretics

1. Diuretics increase renal sodium and water excretion.
2. Diuretics were developed empirically based on observed effects on urine volume and change in urine composition.
3. Several hormones control renal sodium and water excretion through effects on tubular transport.
4. The majority of diuretics enter the urine by tubular secretion and act on the luminal surface to reduce sodium reabsorption.

SITES OF DIURETIC ACTION IN THE KIDNEY

Proximal Tubule

The initial site of diuretic action in the kidney is the proximal tubule. Transport of sodium in the proximal tubular cell is driven by Na^+-K^+-ATPase activity, which drives sodium reabsorption by the Na^+-H^+ exchanger on the apical membrane. The Na^+-K^+-ATPase uses energy derived from adenosine triphosphate (ATP) to extrude 3 Na^+ ions in exchange for 2 potassium ions. This results in a reduction of intracellular Na^+ concentration. Sodium can then move down its electrochemical gradient from tubular lumen into the cell via the Na^+-H^+ exchanger in exchange for an H^+ that moves out of the cell against its electrochemical gradient. Secretion of H^+ by this exchanger is associated with reclamation of filtered bicarbonate. Two diuretics that impair sodium reabsorption in this nephron segment are mannitol and acetazolamide. Each acts differently to reduce sodium reclamation. Mannitol, an osmotic diuretic, is mainly employed for prophylaxis to prevent ischemic or nephrotoxic renal injury and to reduce cerebral edema. It is a nonmetabolizable osmotic

TABLE 4-1. Adverse Effects of Diuretic Drugs

Proximal Tubule Diuretics
Carbonic anhydrase inhibitors (acetazolamide)
Hypokalemia, metabolic acidosis
Drowsiness, fatigue, lethargy, paresthesias
Bone marrow suppression
Calcium phosphate stones
Osmotic diuretics (mannitol)
Hypokalemia, hyperkalemia (cell shift)
Expansion of the ECF, CHF
Nausea and vomiting, headache
Osmotic nephropathy
Loop Diuretics (Furosemide, Bumetanide, Torsemide, Ethacrynic Acid)
Hypokalemia, hypomagnesemia, hyponatremia
Metabolic alkalosis, hypovolemia
Ototoxicity, diarrhea
Blood dyscrasia (thrombocytopenia, agranulocytosis)
Distal Convoluted Tubule Diuretics (Thiazides, Chlorthalidone, Indapamide, Metolazone)
Hypokalemia, hypomagnesemia, hyponatremia
Hypercalcemia, hyperuricemia
Metabolic alkalosis, hypovolemia
Mild hyperglycemia, hyperlipidemia
Hypersensitivity, interstitial nephritis
Leukopenia, thrombocytopenia, aplastic and hemolytic anemia
Cortical Collecting Duct Diuretics
Mineralocorticoid receptor antagonists (spironolactone*, eplerenone)
Hyperkalemia
Gynecomastia*, hirsutism*, menstrual irregularities*, testicular atrophy*
Sodium channel inhibitors (amiloride†, triamterene‡)
Hyperkalemia
Glucose intolerance†, megaloblastic anemia‡, urinary crystals‡

agent that is freely filtered by the glomerulus and enters the tubular space where it raises intratubular fluid osmolality. This effect drags water, which is accompanied by sodium from tubular cells into the tubular fluid. Mannitol is poorly absorbed with oral administration and is active only when given intravenously. It acts in the kidney within 10 minutes and has a terminal half-life ($t_{1/2}$) of approximately 1.2 hours in patients with normal renal function. Toxicity develops when filtration of mannitol is impaired, as in acute and chronic kidney disease. Retained mannitol causes increased plasma osmolality, which can exacerbate CHF, induce hyponatremia, and cause a hyperoncotic syndrome. As a result of these effects, mannitol is contraindicated in patients with CHF and moderate-to-severe kidney disease. In addition, mannitol may cause acute kidney injury (AKI) from osmotic nephropathy in high-risk individuals.

The carbonic anhydrase (CA) inhibitor acetazolamide is prescribed to alkalinize the urine (certain drug overdoses), prevent and treat altitude sickness, and decrease intraocular pressure in certain forms of glaucoma. The CA inhibitors disrupt bicarbonate reabsorption by impairing the conversion of carbonic acid (H_2CO_3) into CO_2 and H_2O in tubular fluid. Excess bicarbonate in the tubular lumen associates with Na^+, the most abundant cation in tubular fluid, and exits the proximal tubule. Acetazolamide and other CA inhibitors exert their effect within 30 minutes and maintain a $t_{1/2}$ of approximately 13 hours. Over time, the effect of these drugs diminishes as a result of the reduction in plasma and filtered bicarbonate. Metabolic consequences of CA inhibitors include metabolic acidosis and hypokalemia. Hypokalemia results from enhanced delivery of sodium and bicarbonate to the principal cell, which promotes potassium secretion through a change in membrane potential. Calcium phosphate stones may also develop as a complication of therapy (urinary alkalinization). These drugs should be avoided in patients with cirrhosis (increases serum ammonia [NH_3]) and those with uncorrected hypokalemia. Because downstream nephron segments such as the loop of Henle, distal convoluted tubule (DCT), and cortical collecting duct (CCD) avidly reabsorb sodium, these 2 drugs are relatively weak diuretics.

Thick Ascending Limb of the Loop of Henle

In this nephron segment, the Na^+-K^+-$2Cl^-$ cotransporter on the apical surface of tubular cells, powered by

Na^+-K^+-ATPase on the basolateral membrane reabsorbs significant amounts of NaCl (20% to 30% of the filtered sodium load). In addition to NaCl, potassium, calcium, and magnesium are reclaimed in this tubular segment. It is not surprising that the most potent diuretics, the loop diuretics, retard the action of this transporter. Loop diuretics consist of those that are sulfonamide derivatives (furosemide, bumetanide, and torsemide) and ethacrynic acid, a non–sulfa-containing loop diuretic. These drugs are used primarily to treat states of volume overload refractory to other diuretics including CHF, cirrhosis-associated ascites and edema, and nephrotic syndrome. Other indications are hypercalcemia and hypertension associated with moderate-to-severe kidney disease, which is often a sodium retentive state. Rarely, these drugs are employed to help correct hyponatremia in patients with the syndrome of inappropriate antidiuretic hormone (SIADH).

Loop diuretics can be administered as either oral or intravenous (IV) preparations. They are well absorbed orally, unless significant bowel edema is present as in severe CHF, cirrhosis, and nephrotic syndrome. Loop diuretics act within 20 to 30 minutes and have a $t_{1/2}$ of approximately 1 to 1.5 hours. In healthy subjects given IV furosemide or an equivalent oral dose twice the IV dose, there was no difference in cumulative urine volume, natriuresis, or potassium and chloride excretion. The major difference between the two modes of administration was a 30-minute peak natriuretic action with IV furosemide compared with a 75-minute peak for oral therapy. This difference is likely a consequence of the rapid increase in plasma levels with IV dosing. In patients with chronic kidney disease, the dose of loop diuretic to promote effective natriuresis is higher than in patients with normal kidney function. This is a result of several factors—most important is that a reduced GFR is associated with a reduction in filtered sodium load. For example, the filtered sodium for a patient with a GFR of 100 mL/min is 15 mEq/min, whereas it is only 0.15 mEq/min in a patient with kidney disease and a GFR of 10 mL/min. In advanced chronic kidney disease (creatinine clearance = 17 mL/min), the maximal diuretic response to IV furosemide occurs at 160 to 200 mg, much higher than required in subjects with normal renal function. Decreased delivery of loop diuretic to its site of action is another factor in renal failure that limits efficacy at lower administered doses.

In normal subjects, the dose equivalency for the various loop diuretics is as follows:

bumetanide 1 mg = torsemide 10 mg
= furosemide 40 mg

The maximum dose of each drug varies based on the indication and the underlying disease state. Table 4.2 notes the approximate ceiling doses for the loop diuretics based on the associated clinical condition. Ceiling dose is defined as the dose that provides maximal inhibition of NaCl reabsorption, reaching a plateau in the diuretic dose-response curve. Adverse effects from loop diuretics are related in part to their therapeutic effect on natriuresis and changes in urine composition. These include hypokalemia, hypocalcemia, hypomagnesemia, volume contraction (which can result in hypotension and shock), and metabolic alkalosis. Groups most susceptible

TABLE 4-2. Ceiling Doses of Intravenous and Oral Loop Diuretics in Various Clinical Conditions

CLINICAL CONDITION	FUROSEMIDE (mg)		BUMETANIDE (mg)		TORSEMIDE (mg)	
	IV	PO	IV	PO	IV	PO
Kidney disease						
GFR 20 to 50 mL/min	80	60 to 80	2 to 3	2 to 3	20 to 50	20 to 50
GFR <20 mL/min	200	240	8 to 10	8 to 10	50 to 100	50 to 100
CHF	40 to 80	160 to 240	2 to 3	2 to 3	20 to 50	20 to 50
Nephrotic syndrome	120		3		50	50
Cirrhosis	40 to 80	80 to 160	1	1 to 2	10 to 20	20 to 50

Abbreviation: PO, oral (per os).

to these untoward effects, in particular volume contraction, are the elderly and patients with hypertension who lack clinical edema. Loop diuretics must also be used cautiously in patients with cirrhosis, to avoid precipitation of the hepatorenal syndrome and in patients treated with digoxin who are at high risk for lethal arrhythmias when hypokalemia develops. Ototoxicity is another complication of high plasma drug levels. Ethacrynic acid is associated with severe ototoxicity and rarely employed except in patients with sulfonamide allergy. Furosemide, torsemide, and bumetanide are contraindicated in patients with sulfonamide allergy. Rarely, mild hyperglycemia occurs in patients as a consequence of inhibition of insulin release by loop diuretics.

Distal Convoluted Tubule

The DCT contains the thiazide-sensitive Na^+-Cl^- cotransporter (NCC), which reabsorbs sodium and chloride delivered from the loop of Henle. This segment reabsorbs approximately 5% to 10% of the filtered sodium load. Thiazide and thiazide-like diuretics inhibit NCC. Drugs include hydrochlorothiazide (HCTZ), metolazone, chlorthalidone, indapamide, and the IV preparation chlorothiazide. Through inhibition of NCC, this class of drugs is used primarily to treat hypertension, particularly in patients with salt-sensitive hypertension. Additional uses include treatment of osteoporosis and nephrolithiasis. Although not intuitively obvious as a therapy for these states, thiazide-type diuretics increase calcium reabsorption in the proximal tubule and the DCT. This increases total-body calcium to enhance bone density in patients with osteoporosis and decreases urinary calcium concentration, thereby reducing renal stone formation. Finally, as is discussed later, thiazides are used in combination with loop diuretics to enhance diuresis and natriuresis in patients who develop diuretic resistance.

Thiazide diuretics are less potent than loop diuretics. They are available as both oral (HCTZ, metolazone, chlorthalidone, and indapamide) and IV (chlorothiazide) preparations. They are well absorbed following oral administration with an onset of action within approximately 1 hour. The $t_{1/2}$ is variable between drugs and they have durations of action from 6 to 48 hours, depending on the drug. Although the HCTZ dose ranges from 12.5 to 50 mg/day, most of the benefit occurs with 25 mg/day. Adverse effects develop more frequently with higher doses. Metolazone dosing ranges from 2.5 mg/day up to 10 mg twice daily. Patients treated with metolazone should measure their weight daily to avoid excessive diuresis and volume contraction. Chlorthalidone has a longer half-life (40 hours) and is used most commonly at 25 to 50 mg/day, whereas indapamide is administered at 1.25 to 2.5 mg/day ($t_{1/2}$ = 14 hours). Bioavailability is reduced in patients with kidney disease, liver disease, and CHF. Patients with kidney disease, especially those with a GFR less than 25 to 40 mL/min, have limited drug delivery to its site of action. Metolazone, however, appears to maintain efficacy at lower levels of GFR.

Adverse effects associated with thiazide-type diuretics include hypokalemia, hypomagnesemia, hyponatremia, and metabolic alkalosis. As with loop diuretics, hypokalemia can be life-threatening in patients with heart disease and those on digoxin. Patients with cirrhosis are at risk for encephalopathy from associated hypokalemia and elevated plasma NH_3 levels. Hypercalcemia can develop in patients at risk, such as those with primary hyperparathyroidism and bed-bound patients. Hyponatremia occurs in patients with excessive antidiuretic hormone (ADH) concentrations that are treated with a thiazide diuretic. This results from the thiazide's effect to diminish the kidney's diluting capacity without affecting concentrating ability, allowing ADH to enhance water reabsorption. Hypersensitivity reactions are noted including pancreatitis, hemolytic anemia, and thrombocytopenia. Finally, because of increased proximal uric acid reabsorption promoted by thiazide diuretics, patients can develop hyperuricemia and clinical gout.

Cortical Collecting Duct

The CCD reabsorbs approximately 1% to 3% of the filtered sodium load. Reabsorption of NaCl and secretion of potassium is controlled primarily by aldosterone and the prevailing plasma potassium concentration. Intratubular flow rate and sodium concentration also participate in this process. The CCD principal cell is constructed to perform this function based on the presence of an apical epithelial Na^+ channel (ENaC) and potassium channel (ROMK) and a basolateral Na^+-K^+-ATPase. Sodium is reabsorbed through ENaC and potassium secreted through ROMK following stimulation of the Na^+-K^+-ATPase (and opening of ENaC and ROMK) by aldosterone and an increased plasma potassium concentration. Medications that inhibit either ENaC transport or Na^+-K^+-ATPase function increase NaCl excretion while minimizing potassium loss. Potassium-sparing diuretics such

as spironolactone and eplerenone competitively inhibit the mineralocorticoid receptor and blunt aldosterone-induced NaCl reabsorption and potassium secretion. These drugs are indicated to treat hypertension, especially hypertension caused by either primary or secondary hyperaldosteronism. They are also useful to reduce edema and ascites in patients with cirrhosis and improve cardiac dysfunction in patients with CHF characterized by an ejection fraction less than 40%. In contrast, amiloride and triamterene reduce NaCl reabsorption and potassium secretion by blocking ENaC. They are employed to reduce potassium losses associated with non–potassium-sparing diuretics and thereby prevent hypokalemia. Most often, they are given in combination with thiazide diuretics (HCTZ and amiloride, HCTZ and triamterene). They may also be added to a regimen that includes loop diuretics.

The potassium-sparing diuretics, in particular spironolactone and eplerenone, work best when aldosterone concentrations are elevated. Spironolactone, which is available only in oral form, is well absorbed. The drug undergoes hepatic metabolism. It has a $t_{1/2}$ of approximately 20 hours and requires up to 2 days to become effective. The dose range is 25 to 200 mg/day. Eplerenone is a relatively new oral potassium-sparing diuretic that has similar renal effects as spironolactone. It differs from spironolactone in that it has a shorter $t_{1/2}$ (4 to 6 hours), is metabolized by the liver (CYP3A4), and excreted primarily (67%) by the kidneys. It is most effective when dosed twice per day. The dose range is 25 to 100 mg/day. Amiloride is well absorbed with oral administration. It has a $t_{1/2}$ of 6 hours and is excreted by the kidney. Triamterene is similar to amiloride except for a shorter $t_{1/2}$ (3 hours). All drugs that act in the CCD are weak diuretics, which is not unexpected because of the limited Na^+ reabsorption that occurs in this nephron segment.

The most common and concerning adverse effect of these drugs is hyperkalemia. The groups at highest risk are patients with moderate-to-severe kidney disease and those taking either potassium supplements or medications that impair potassium homeostasis such as the angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and NSAIDs. Other patients who are at risk include those with diabetes mellitus (hyporeninemic hypoaldosteronism) and tubulointerstitial kidney disease. Spironolactone therapy is complicated by gynecomastia and amenorrhea. This occurs because it binds to estrogen and androgen receptors, especially when the dose equals or exceeds 100 mg/day. Eplerenone is specific for the mineralocorticoid receptor and is free of these adverse effects. In addition to hyperkalemia, amiloride causes a mild metabolic acidosis. Nausea and vomiting can also develop with either amiloride or triamterene therapy. Rarely, as with other diuretics, hyponatremia may occur in the elderly.

KEY POINTS

Sites of Diuretic Action

1. Mannitol and acetazolamide reduce sodium reabsorption in proximal tubule. As a result of increases in sodium reabsorption at downstream sites, they are weak diuretics.
2. In the thick ascending limb of Henle, loop diuretics induce a significant natriuresis by inhibiting the Na^+-K^+-$2Cl^-$ transporter. Loop diuretics are employed to treat volume overload (CHF, cirrhosis, and nephrotic syndrome), hypertension complicated by chronic kidney disease, hypercalcemia, and some forms of hyponatremia.
3. Hypokalemia, volume contraction, and metabolic alkalosis are relatively common adverse effects of loop diuretics.
4. Thiazide-type diuretics are used primarily to treat hypertension; however, they are also useful for osteoporosis, nephrolithiasis, and combination therapy for patients with loop diuretic resistance.
5. Hypokalemia, hyponatremia, hypomagnesemia, and hyperuricemia are common side effects of the thiazide diuretics.
6. In CCD, the principal cell reabsorbs sodium and secretes potassium under the stimulation of aldosterone, plasma potassium concentration, urinary flow rate, and sodium delivery.
7. Spironolactone and eplerenone reach the mineralocorticoid receptor from the peritubular (blood) side, whereas amiloride and triamterene block apical ENaC from the urinary space. Despite different mechanisms of action, these drugs ultimately enhance NaCl excretion and inhibit potassium excretion.
8. Hyperkalemia is the primary adverse effect of diuretics that act in CCD. Patients with moderate-to-severe kidney disease and diabetes mellitus, as well as patients on medications that impair renal potassium excretion are at highest risk.

DIURETIC RESISTANCE

The desired goal of diuretic therapy is typically to reduce ECF volume in disorders such as CHF (peripheral and pulmonary interstitial edema), cirrhosis (ascites and peripheral edema), and nephrotic syndrome (peripheral and renal edema) and control blood pressure in patients with hypertension. Inability to achieve these goals despite appropriate diuretic therapy (standard doses) is the definition of diuretic resistance. Identification of the problem is the first step. Assessing diuretic resistance requires a logical approach to the problem (Table 4.3). The second step requires appropriate diagnosis of the cause of edema. It is essential to ensure that the patient has generalized renal-related edema rather than localized edema from venous or lymphatic obstruction. Cyclic edema, a problem generally found only in women and interstitial edema caused by fluid redistributed from the plasma compartment, as seen with calcium channel blocker therapy, are other forms of edema not amenable to diuretic treatment.

TABLE 4-3. Approach to Patients with Diuretic Resistance

Step 1: Define diuretic resistance as failure to resolve edema or hypertension with standard diuretic doses.
Step 2: Identify cause of edema as renal-related edema versus edema from other causes (obstruction of veins or lymphatics, cyclic edema, calcium channel blocker therapy).
Step 3: Examine for incomplete therapy of the primary disorder requiring diuretic therapy.
Step 4: Assess patient compliance with salt-restricted diet and diuretic regimen.
Step 5: Consider pharmacokinetic alterations of the diuretic including incomplete or delayed medication absorption and/or impaired kidney function (acute or chronic renal failure).
Step 6: Consider pharmacodynamic alterations of the diuretic regimen, including severity of the edema state, activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, and compensatory hypertrophy of the distal nephron sites (particularly the DCT).
Step 7: Explore for adverse drug interactions including concurrent traditional NSAID or selective cyclooxygenase (COX)-2 inhibitor therapy.

The next step (step 3) is to examine whether the primary disorder requiring diuretic therapy is adequately treated. Clinical disorders associated with impaired diuretic response include CHF, cirrhosis with ascites, nephrotic syndrome, hypertension, and kidney disease. These disease states and their specific causes of diuretic resistance are covered in more detail later in this chapter, but an example of resistance as a result of inadequate therapy of the primary disorder includes suboptimal management of CHF. These patients often require afterload reduction with an antagonist of the renin-angiotensin-aldosterone system (RAAS) in addition to diuretic therapy. In patients with severe congestive cardiomyopathies and decompensated heart failure, an IV inotropic agent such as dobutamine or milrinone may be indicated to improve cardiac pump function and renal perfusion. Excessive reductions in arterial blood pressure may also induce diuretic resistance. Allowing the blood pressure to increase can be beneficial in this situation.

A common cause of diuretic resistance that should not be overlooked is poor compliance with dietary salt restriction or the actual diuretic regimen. Step 4 mandates a thorough history to identify either of these problems. Direct questioning about diet, in particular ingestion of canned foods or fast foods, is often illuminating. Many patients also believe that drinking large amounts of certain beverages (Gatorade, PowerAde, and others) is healthy. This behavior can overcome diuretic effect on edema formation. Adverse effects from diuretics, such as impotence and muscle cramps, may promote noncompliance. These symptoms should be inquired about in all patients.

Step 5 requires a search for alterations in pharmacokinetics as the source of diuretic resistance. One common cause of ineffective diuresis is poor absorption of the agent. Patients with edematous states may also have bowel edema. This hampers gastrointestinal absorption of the oral diuretic, causing incomplete or delayed drug absorption. In patients with poor cardiac output, vascular disease of the intestinal tree, and advanced cirrhosis, blood flow to the intestinal absorptive sites may be inadequate to allow appropriate drug absorption. The presence of kidney disease (reduced GFR) decreases the concentration of diuretic that is secreted in active form into the tubular lumen, the site of their action. It also increases the fraction that is eliminated by hepatic excretion or glycosylation.

Step 6 includes pharmacodynamic causes of diuretic resistance. The most important cause in this category is extreme renal sodium retention from various mechanisms. Pronounced activation of the RAAS and sympathetic nervous system (SNS) reduces diuretic response by lowering GFR (reduced filtered load of sodium) and increasing NaCl reabsorption along all nephron segments. Angiotensin II enhances NaCl reabsorption in proximal tubule, loop of Henle, and DCT, whereas aldosterone increases NaCl reabsorption in the proximal convoluted tubule (PCT), DCT and CCD. Stimulation of the RAAS and SNS occurs for 2 basic reasons. First, the underlying disease state, which includes conditions such as CHF, cirrhosis, and nephrotic syndrome, decreases effective arterial blood volume. This activates the RAAS, SNS, and other pathways that enhance renal sodium reabsorption. Second, diuretics also may reflexively activate the RAAS and SNS, perpetuating diuretic resistance. An important participant in the development of diuretic resistance is compensatory changes in distal nephron tubular cells following chronic therapy with loop diuretics. Increased delivery of NaCl to the DCT induces hypertrophy and hyperplasia of tubular cells (Figure 4.2) and increases the density of both Na^+-K^+-ATPase pump sites and NCC cotransporters. This intranephronal adaptation enhances the intrinsic capacity of the DCT to reabsorb Na^+ and Cl^-. Experimental animal data suggests that treatment with loop diuretics increases reabsorption of NaCl 3-fold in DCT. As is discussed later, these changes in the DCT underlie the enhanced natriuretic response noted when a thiazide diuretic is added to a loop diuretic.

The final step in the assessment of diuretic resistance is to inquire about use of medications that may blunt diuretic action. Two particularly important culprits are the traditional NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors. These drugs impair intrarenal prostaglandin synthesis by the COX-2 isoenzyme, which is important in the kidney to maintain renal blood flow and GFR and to block NaCl reabsorption in all nephron segments. Reduced natriuresis and increased blood pressure, as well as diuretic resistance result in patients with at risk physiology (hypertension, CHF, cirrhosis, nephrotic syndrome, and chronic kidney disease). Other drugs that impair diuretic response do so by reducing delivery of active diuretic to the site of action by competing for secretion through proximal tubular cell transport pathways. Probenecid, cimetidine, and trimethoprim are examples of drugs that compete for these pathways and reduce secretion of diuretic into urine, where they reach their site of action.

All of these factors need to be considered to adequately diagnose and successfully treat the patient suffering from either uncontrolled hypertension or refractory edema (or both) associated with diuretic resistance.

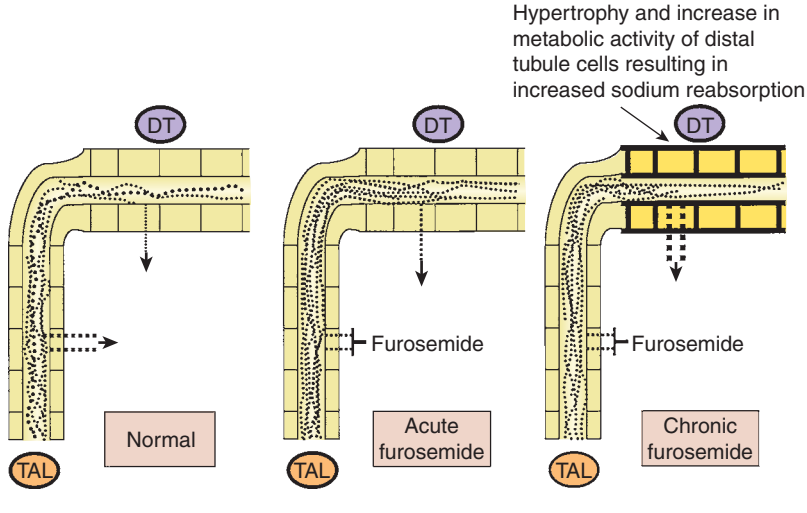


FIGURE 4-2. Intranephronal adaptation of DCT cells with chronic loop diuretic therapy. Hypertrophy and hyperplasia of DCT cells and increased density of Na^+-K^+-ATPase pump sites and NCC cotransporters induce diuretic resistance. *Abbreviation:* TAL, Thick ascending limb.

KEY POINTS

Diuretic Resistance

1. Diuretic resistance is defined as the inability to control blood pressure or reduce edema formation despite appropriate diuretic therapy (standard doses).
2. The logical approach to diuretic resistance includes assessment of variables such as verification of renal-related edema, appropriate therapy of the primary disorder, dietary and diuretic compliance, pharmacokinetic and pharmacodynamic issues, and therapy with antinatriuretic medications.
3. Activation of the RAAS and SNS promote renal sodium retention, while intranephronal adaptation by DCT cells with chronic loop diuretic therapy blunts diuretic response.
4. Concomitant therapy with NSAIDs and selective COX-2 inhibitors reduce prostaglandin-induced NaCl excretion and perpetuate diuretic resistance.

CLINICAL CONDITIONS ASSOCIATED WITH SPECIFIC CAUSES OF DIURETIC RESISTANCE

In addition to the previously noted general causes of diuretic resistance, certain clinical conditions that can be associated with poor diuretic response are encountered in practice. Each of these disease states induces diuretic resistance through effects on circulatory and renal hemodynamics and/or tubular transport function in various nephron segments.

Congestive Heart Failure

The hemodynamics associated with CHF results in sodium and water retention from reduced renal perfusion, activated RAAS and SNS, and enhanced arginine vasopressin (AVP) release. The severity of cardiac dysfunction dictates the degree of tubular NaCl and fluid reabsorption. It is therefore intuitive that the ideal treatment of CHF is directed at improving cardiac function. When this fails or is only partially successful, assessment of other factors of diuretic resistance in this clinical condition need to be considered. Impaired absorption of diuretic across the gastrointestinal (GI) tract contributes to suboptimal response to the drug. A 50% decrease in peak urinary diuretic concentrations following oral administration was noted in patients with CHF. Bowel edema, reduced bowel wall perfusion, and disturbed GI motility can alter GI tract absorption.

Nephrotic Syndrome

Sodium and fluid retention in patients with nephrotic syndrome develops from activated RAAS and SNS, increased concentrations of AVP, and direct stimulation of the Na^+-H^+ exchanger isomer 3 (NHE3) transport in proximal tubule by excessive urinary protein concentration. The presence of renal dysfunction exacerbates nephrotic syndrome as it reduces the filtered load of NaCl. Primary renal sodium retention is an important cause of edema formation in a subgroup of these patients. Either complete or partial remission of the primary renal lesion (reduce proteinuria) and ACE inhibitors or ARBs are basic steps to improve renal sodium and fluid excretion. Diuretic resistance occurs by several mechanisms. Because loop and thiazide diuretics are highly protein bound, the volume of distribution of drug increases as a result of hypoalbuminemia. This reduces the concentration of drug in the circulation and the amount delivered to the kidney. Also, albumin directly stimulates the organic anion transport pathway that transports these drugs from blood into the proximal tubular cell. Thus, hypoalbuminemia hampers urine diuretic concentrations independent of renal delivery. Collecting duct resistance to ANP-associated natriuresis also contributes to diuretic resistance. Finally, because albumin binds diuretics, excessive concentrations of albumin in the tubule fluid blunt the ability of these drugs to inhibit NaCl transport in the loop of Henle.

Cirrhosis

Edema formation and ascites occur most commonly with advanced cirrhosis or during acute decompensation of chronic liver disease. Enhanced proximal tubular NaCl and fluid reabsorption, stimulated by an activated RAAS and SNS, reduces NaCl delivery to more distal sites where loop diuretics act. In addition, secondary hyperaldosteronism stimulates avid NaCl uptake by the DCT and CCD. These mechanisms are integral to reduced diuretic response in patients with early cirrhosis. Patients with advanced cirrhosis and gross ascites have, in addition to the aforementioned factors, other causes of diuretic resistance. Intestinal edema limits drug absorption, while the

volume of distribution of drug is increased significantly with hypoalbuminemia and a markedly expanded ECF volume. Unrecognized reductions in GFR also contribute to suboptimal diuresis. Finally, spontaneous bacterial peritonitis, hypotension, and bleeding from varices can exacerbate the tenuous hemodynamics in the cirrhotic and underlie the development of diuretic resistance.

Hypertension

Essential hypertension remains primarily a disturbance in renal salt handling. Thereby, salt restriction and diuretic therapy are the most appropriate initial management options. Although dietary sodium restriction and diuretics are successful in many patients, as much as a third of patients remain resistant to therapy. In this situation, a lapse in dietary salt restriction, usually from ingestion of processed, canned, or fast foods that contain excessive amounts of sodium, is present. In some patients, the RAAS is activated prior to diuretic therapy. Treatment of these patients with a diuretic further activates the RAAS as well as the SNS, promoting renal NaCl retention and peripheral vasoconstriction. These effects can induce hypertension resistant to standard diuretic therapy. The addition of moderate-to-severe kidney disease to hypertension is a frequent cause of diuretic resistance. Salt restriction alone or with a diuretic is typically insufficient to control blood pressure. This is particularly true if the GFR is below the 25 to 40 mL/min and the patient is receiving a thiazide diuretic. Reduced drug delivery and limited diuretic effect on natriuresis underlies resistance to thiazides, although metolazone maintains fairly good efficacy in these patients.

Kidney Disease

As GFR declines, the diuretic and natriuretic effect of diuretics diminishes. Thiazide diuretics, with the exception of metolazone, are generally ineffective with a GFR below 30 mL/min, whereas escalating doses of loop diuretics are required to promote an adequate, albeit reduced diuresis. Reduction in filtered sodium, reduction in delivered drug, and accumulation of endogenous organic anions with uremia are responsible for diuretic resistance. Endogenous organic anions compete with diuretics for the organic anion transport pathway, thereby reducing secretion of drug into tubular fluid. Thus, diuretic can't reach its site of action in a concentration sufficient to inhibit NaCl reabsorption.

KEY POINTS

Clinical Conditions Associated with Specific Causes of Diuretic Resistance

1. Diuretic resistance in CHF is a result of multiple factors. The hemodynamics of cardiac dysfunction, as well as reduced drug absorption from bowel wall edema, GI dysmotility, and reduced perfusion contribute to NaCl retention and impaired diuretic response.
2. Nephrotic syndrome promotes diuretic resistance because of hypoalbuminemia and albuminuria. Activation of the RAAS and SNS, as well as direct stimulation of NH_3 in proximal tubule, induces NaCl retention. Reduced drug delivery to renal sites of action, decreased collecting duct responsiveness to ANP, and binding of diuretic in tubular fluid reduces efficacy.
3. Extreme activation of the RAAS and SNS promote diuretic resistance in cirrhosis. Bowel edema, an expanded volume of distribution, and reduced GFR also contribute to NaCl retention and diuretic resistance.
4. AKI or chronic kidney disease (CKD) causes suboptimal response to diuretics from a reduction in filtered sodium and impaired delivery of diuretics to their respective sites of action. Thiazide diuretics with the exception of metolazone become ineffective at a GFR less than 30 mL/min.

TREATMENT OF DIURETIC RESISTANCE

Once diuretic resistance is identified and appropriate steps to assess the cause of the resistant state are undertaken, a number of maneuvers can be used to improve diuretic response. Therapy is based on the recognized cause of diuretic resistance and the underlying clinical condition.

Intravenous Diuretic Therapy

Initial treatment of patients with diuretic resistance is escalation of the oral dose of loop diuretic (assuming the patient was switched from a thiazide-type diuretic previously). Table 4.2 lists ceiling doses for oral loop diuretics. The dosing interval for loop diuretics must be no longer than 8 hours (based on time of drug effect), or a rebound increase in sodium reabsorption (postdiuretic NaCl retention) will occur. IV therapy is often required to restore diuretic efficacy in patients with absorptive

problems such as bowel edema, altered GI motility, and reduced bowel perfusion. Ceiling doses for IV diuretics are also noted in Table 4.2. The major limitation of high-dose loop diuretic therapy is drug-related toxicity. Ototoxicity occurs in patients receiving very high-dose or prolonged high-dose therapy. This adverse effect is typically reversible, but is rarely associated with an irreversible defect. Myalgias may complicate high-dose bumetanide therapy; while thiamine deficiency was described in patients receiving chronic furosemide for CHF.

TABLE 4-4. Dosing Guidelines for Continuous Infusions of Loop Diuretics

DIURETIC	BOLUS DOSE (mg)	INFUSION RATE (mg/kg/h)
Furosemide	20 to 80	2 to 100 (up to 1.0 mg/kg/h)
Torsemide	25	1 to 50 (up to 0.5 mg/kg/h)
Bumetanide	1.0	0.2 to 2 (up to 0.02 mg/kg/h)

Continuous Diuretic Infusion

Patients who are failing or responding marginally (ie, refractory edema) to high-dose IV loop diuretics may benefit from continuous diuretic infusion. This therapy has several potential advantages. Trough concentrations of loop diuretic are avoided, and postdiuretic NaCl retention is averted. Generally, titration of diuretic dose is more easily achieved with continuous infusion. Prior to initiating infusion, it is important to begin with a bolus to quickly achieve therapeutic drug concentrations and to confirm that the patient is diuretic responsive.

Several smaller studies have reported continuous infusions to be more efficient, achieving approximately 30% more natriuresis for the same IV bolus dose. The efficacy is greatest for bumetanide (which has the shortest $t_{1/2}$) and least for torsemide (which has the longest $t_{1/2}$).

However, a 2011 multicenter, prospective, double-blind, randomized control trial of 308 patients with acute decompensated heart failure comparing continuous infusion to bolus therapy did not confirm prior findings. In this study, patients were assigned to receive furosemide bolus every 12 hours or a continuous infusion at either low dose (home oral dose equivalent) or high dose (2.5 times greater dosage). The study demonstrated that global assessment of symptoms, changes in kidney function, or net fluid removal were not significantly different among patients who received bolus therapy versus continuous infusion. However, there was a significant difference in net fluid loss (diuresis), improved dyspnea, and weight reduction in patients receiving high-dose furosemide therapy.

In this study (the Diuretic Optimization Strategies Evaluation [DOSE] trial), patient randomization often occurred after diuretics were initially administered and also dose adjustments were only made 48 hours after being assigned to a treatment arm. Together, these factors pose limitations to the interpretation of the trial results, which were largely negative.

Therefore, when choosing the appropriate diuretic regimen, infusion versus bolus therapy, for a patient with acute decompensated heart failure, it is critical to note that individual patients may have different responses to a specific treatment and that regimens should be customized to the patient, based on serial physical examinations, their response to treatment, and changes in kidney function, as opposed to a assigning a patient to a standard protocol.

Finally, most but not all studies note that toxicity is reduced with continuous infusion as the spike in peak concentrations is obviated. Thus, the occurrence of ototoxicity and myalgia are lessened. Table 4.4 reviews the starting bolus dose and continuous infusion dose range for loop diuretics. Careful observation to avoid overdiuresis and other electrolyte abnormalities is required.

Combination Diuretic Therapy

The addition of a second class of diuretics can often overcome diuretic resistance. In general, the patient who is failing the ceiling dose of a loop diuretic benefits from addition of a thiazide diuretic. While the combination of a loop and proximal tubule diuretic increases efficacy, addition of a DCT diuretic to a loop diuretic is synergistic and more potent. This enhanced efficacy results from several effects, none of which is caused by a change in the bioavailability or pharmacokinetics of either drug. The longer half-life of thiazide diuretics attenuates the postdiuretic NaCl retention of loop diuretics. High-dose IV chlorothiazide improves delivery of sodium from proximal tubule to loop of Henle by inhibiting CA. The most important effect of thiazides in improving loop diuretic efficacy is their ability to blunt NaCl reabsorption by the hypertrophic and hyperplastic DCT cells (Figure 4.3). Patients with CHF, cirrhosis, and nephrotic syndrome are likely to gain benefit from a CCD diuretic like spironolactone or eplerenone. This

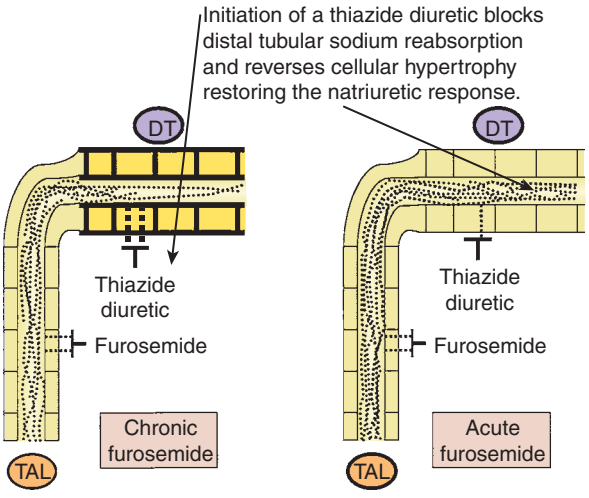


FIGURE 4.3 Combination therapy with a thiazide-type diuretic and loop diuretic improves diuretic response. Enhanced NaCl reabsorption by hypertrophic and hyperplastic DCT cells is inhibited by the addition of a thiazide-type diuretic to a loop diuretic. *Abbreviation:* TAL, Thick ascending limb.

diuretic class modulates the activated RAAS in these patients and reduces the development of potentially harmful hypokalemia.

Thiazide diuretics should be added to loop diuretics that are at their ceiling dose. Also, either proximal tubule or DCT diuretics can be added depending on the underlying clinical condition and desired effect. For example, patients with a severe metabolic alkalosis and edema may benefit from acetazolamide, as long as hypokalemia is corrected prior to administration. In patients with an activated RAAS and concurrent hypokalemia (without advanced kidney disease), a CCD diuretic should be considered. Patients with CHF have improved heart failure management and survival with the addition of spironolactone or eplerenone. Table 4.5 notes the diuretic doses that are appropriate for use in combination with a loop diuretic. Combination diuretic therapy can promote vigorous diuresis with severe hypovolemia, as well as electrolyte disturbances. Cautious prescription and close monitoring for adverse effects is required. Patients should be counseled to perform daily weights and contact their physician with any changes greater than 2 lb/day. In addition, electrolytes and renal function should be measured within 5 to 7 days of initiating combination therapy.

Cardiovascular Agents

Several drugs available as an infusion increase renal blood flow, GFR, and natriuresis through both cardiovascular and direct renal effects. Acute dopamine infusion at very low doses (1 to 3 μg/kg/min) stimulates renal dopamine receptors (DA_1 and DA_2) and stimulates natriuresis. A dose of 5 μg/kg/min stimulates β-adrenergic receptors and increases cardiac output, thereby enhancing renal perfusion and diuresis. Doses greater than 5 μg/kg/min are associated with tachycardia and increased systemic vascular resistance, and potentially reduce natriuresis. After 24 hours of dopamine infusion, however, natriuresis wanes. The addition of dopamine to diuretics is of limited benefit and is associated with potentially serious tachyarrhythmias. As a result, dopamine is rarely employed. Fenoldopam is a selective DA_1 receptor agonist that is approved to treat severe (urgent or malignant) hypertension. It lowers blood pressure by vasodilating the vasculature. It also induces a natriuresis by binding renal DA_1 receptors and inhibiting the action of NHE3. Its renal effects are 6 times more potent than dopamine. Fenoldopam may be useful to treat diuretic resistance in the setting of AKI and is being evaluated for nephroprotective effects in critically ill postcardiac surgery patients with AKI. However, the high drug cost limits its use in the clinical arena.

TABLE 4-5. Dosing Guidelines for Diuretics Added to Loop Diuretics for Combination Therapy

Class of Diuretic	Dose Range (mg/day)
Proximal Tubule Diuretics	
Acetazolamide	250 to 375; up to 500 (IV)
Distal Convoluted Tubule Diuretics	
Chlorothiazide	500 to 1000 (IV)
Metolazone	2.5 to 10 (oral)
Chlorthalidone	25 to 50 (oral)
Indapamide	1.25 to 2.5 (oral)
Hydrochlorothiazide	25 to 100 (oral)
Collecting Tubule Diuretics	
Amiloride	5 to 10 (oral)
Spironolactone	100 to 200 (oral)
Eplerenone	25 to 100 (oral)

Dobutamine is an inotropic agent and dopamine derivative that does not cause systemic or mesenteric vasoconstriction. It increases cardiac output and reflexively reduces systemic vascular resistance. These effects improve renal blood flow in the patient with congestive cardiomyopathy and enhance urinary sodium and fluid excretion following diuretic administration. The combination of dopamine and dobutamine produces synergistic effects, providing a rationale for combining low doses of dopamine (2 to 5 μg/kg/min) and dobutamine in critically ill patients with impaired cardiac pump function.

ANP is a hormone produced by myocardial atrial (and ventricular less commonly) cells when volume expansion increases cardiac wall stress. Brain natriuretic peptide (BNP) is similar to ANP. Although it was initially identified in the brain, it is also synthesized in heart, particularly the ventricles. Both peptides are released in response to the high filling pressures associated with heart failure. These hormones have natriuretic and diuretic effects and also lower blood pressure by reducing RAAS, SNS, and endothelin activity. Diuresis and natriuresis occurs through increases in GFR (increased Na^+ filtration), stimulation of cyclic guanosine monophosphate (GMP) in inner medullary collecting duct (closing nonspecific cation channels), stimulation of dopamine secretion in proximal tubule, and inhibition of angiotensin II and aldosterone production. Based on these characteristics, ANP and in particular, BNP (nesiritide) are infused intravenously to treat heart failure resistant to other medical management. Nesiritide is administered as an IV bolus of 2 μg/kg, followed by a continuous infusion of 0.01 μg/kg/min titrated up to a maximum dose of 0.03 μg/kg/min. This therapy often increases natriuresis, increases cardiac index, lowers cardiac filling pressure, and reduces blood pressure. The major adverse effects, based on a metaanalysis of 3 studies, are reversible hypotension, increased AKI (but not dialysis requirement), and worsened short-term mortality. Because of these complications, as well as the high drug cost, nesiritide is not commonly employed to enhance diuresis in clinical practice. A large prospective trail of nesiritide versus standard therapy in patients with acute decompensated heart failure demonstrated that although this drug did not increase AKI or mortality, it also was not superior to standard therapy in regards to dyspnea improvement or short-term (30-day) mortality. This trial further questions the utility of nesiritide as an additional therapy for patients with acute decompensated heart failure.

Vasopressin (V_2) receptor antagonists represent a class of agents that target the AVP receptor in kidney. Because AVP increases water reabsorption in CCD by increasing the number of aquaporins (water channels) in the apical membrane, V_2 antagonists facilitate a water diuresis. IV V_2 receptor antagonist (conivaptan) and oral receptor V_2 receptor antagonist (tolvaptan) are available clinically and approved for treatment of hyponatremia, because of their ability to enhance free water clearance. Although these agents successfully correct hyponatremia and induce aquaresis, they have little or no effect in clinical outcomes such as mortality.

KEY POINTS

Treatment of Diuretic Resistance

1. High-dose IV diuretics overcome decreased GI absorption that can occur with oral agents. Ototoxicity needs to be monitored in patients receiving high-dose loop diuretics.
2. Combining a loop diuretic with an agent that acts at another nephron segment effectively overcomes diuretic resistance. Certain clinical conditions warrant choice of one class of diuretic over another. For example, a patient with edema and metabolic alkalosis may benefit from the addition of acetazolamide to a loop diuretic.
3. Combination diuretic therapy must be monitored closely for hypovolemia and electrolyte disturbances. Hypokalemia is a particular concern when loop diuretics are combined with either proximal tubule diuretics or DCT diuretics.
4. Dopamine and fenoldopam increase diuresis and natriuresis through increases in renal blood flow, GFR, and direct tubular effects. Low doses are effective, whereas higher doses add little benefit but are associated with dangerous tachyarrhythmias.
5. Dobutamine is an inotropic agent that improves cardiac output and lowers systemic vascular resistance. These effects improve renal blood flow and GFR, thereby enhancing response to diuretics. The combination of dobutamine and dopamine is more effective in increasing natriuresis than either drug alone.
6. ANP and nesiritide increase diuresis and natriuresis through multiple effects along the nephron. These drugs are rarely used to treat refractory CHF because of hypotension, potential for increased AKI, and increased short-term mortality.

7. V_2 antagonists are agents that successfully correct hyponatremia from SIADH and CHF treated with diuretics. They act by blocking the binding of ADH to the V_2 receptor, reducing the number of aquaporins available to reabsorb water in CCD. Despite correction of hyponatremia and enhanced free water clearance in CHF, clinical outcomes such as mortality are unchanged.
8. Continuous IV loop diuretic therapy may be a favorable option in patients who are failing to respond to bolus IV loop diuretic therapy. Patients should be assessed individually and regularly to determine the response and risk-to-benefit ratio of either diuretic regimen.

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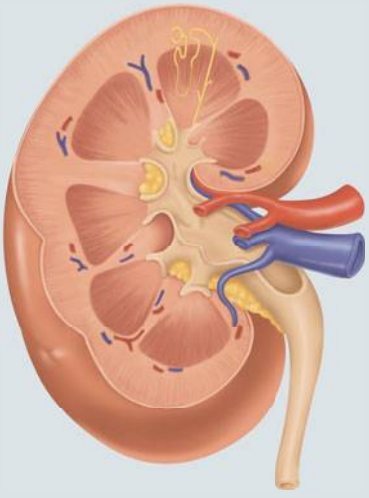

CHAPTER

5

Intelligent Use of IV Fluids

• *Robert F. Reilly Jr.*

Recommended Time to Complete: 1 Day

Guiding Questions

1. How are sodium and water distributed across body fluid compartments and what forces govern their distribution?
2. What options are available for volume resuscitation?
3. What are the guiding principles behind intravenous fluid replacement?
4. How does one assess the degree of intravascular and extracellular fluid volume depletion?
5. How does one manage the critically ill patient with extracellular fluid (ECF) volume depletion?

INTRODUCTION

Every physician and physician in training must master the ability to use intravenous solutions for expansion of the intravascular and ECF volume. Proper understanding of solutions available (colloid vs. crystalloid), their space of distribution, their cost and potential adverse effects, as well as an assessment of the patient's volume status are essential for their proper use. Mistakes are made when there is improper understanding of the patient's volume and electrolyte status.

Hypovolemia is a common problem in hospitalized patients, especially those in critical care units. It can occur in a variety of clinical settings including those characterized by obvious fluid loss as with hemorrhage or diarrhea, as well as in patients without obvious fluid loss as a result of vasodilation with sepsis or anaphylaxis. In one study, inadequate volume resuscitation was viewed as the most common management error in patients that died in the hospital after admission for treatment of injuries.

UNDERSTANDING BODY FLUID COMPARTMENTS

Total-body water constitutes 60% of lean-body weight in men and 50% of lean-body weight in women. It is distributed between intracellular fluid (ICF) (66.7%) and ECF (33.3%) compartments (Figure 5.1). The ECF compartment is further subdivided into intravascular and interstitial spaces. Twenty-five percent of the ECF compartment consists of the intravascular space, with the remaining 75% constituted by the interstitial space.

Osmotic forces govern the distribution of water between ICF and ECF. The ECF and ICF are in osmotic equilibrium, and if an osmotic gradient is established,

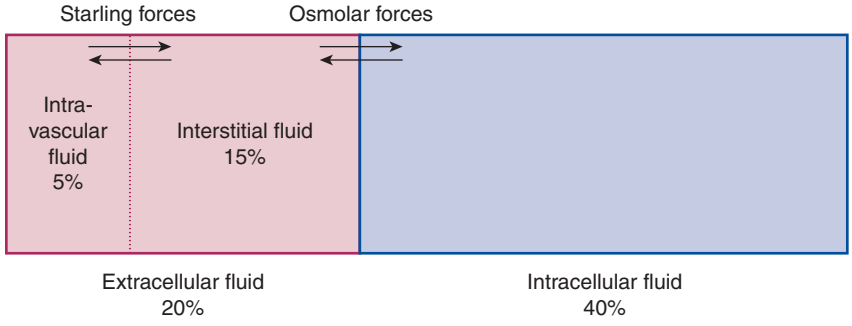

FIGURE 5-1. Body fluid compartments. Total-body water consists of ICF and ECF. ICF is 40% of lean-body weight and ECF is 20% of lean-body weight. The major driving force for fluid movement between these compartments is osmosis. The ECF can be further subdivided into the intravascular and interstitial spaces that constitute 5% and 15% of total-body weight, respectively. Starling forces are the major driving force for fluid movement between these compartments.

water will flow from a compartment of low osmolality to a compartment of high osmolality. For example, if a solute is added to the ECF such as glucose that raises its osmolality, water will flow out of the ICF until the osmotic gradient is dissipated. Water movement into and out of cells, particularly in brain, with resultant cell swelling or shrinking is responsible for the symptoms of hyponatremia and hypernatremia.

Urea distributes rapidly across cell membranes and equilibrates throughout total-body water and is, with one exception, an ineffective osmole. Equilibration of urea across the blood–brain barrier can take several hours and in this circumstance urea may function as a "transiently effective" osmole. If urea is rapidly removed from the ECF with initiation of hemodialysis in a patient with end-stage renal disease, the potential exists for the development of "dialysis disequilibrium syndrome." Patients at increased risk are those with a blood urea nitrogen (BUN) greater than 100 mg/dL that have rapid rates of urea removal during their first or second hemodialysis session. As urea concentration falls during hemodialysis a transient osmotic gradient for water movement into brain is established. This results in headache, nausea, vomiting, and, in some cases, generalized seizures. Dialysis disequilibrium can be minimized by initiating hemodialysis with low blood flow rates and for short periods of time.

Each compartment has one major solute that acts to hold water within it: ECF—sodium salts; ICF—potassium salts; and intravascular space—plasma proteins. It is important to appreciate that the serum sodium concentration is a function of the ratio of the amounts of sodium and water present and does not correlate with ECF volume, which is a function of total-body sodium. This is illustrated by the 3 examples discussed below in which ECF volume is increased in all 3 cases but serum sodium is high, low, and normal.

If one adds NaCl to the ECF, it remains within the ECF increasing its osmolality resulting in water movement out of cells. Equilibrium is characterized by hypernatremia, an increase in ECF osmolality (NaCl addition), and ICF osmolality (water loss). As a result ECF volume increases and ICF volume decreases. Therefore, even though sodium is restricted to the ECF, its administration results in an increase in osmolality of both ECF and ICF, and a reduction in ICF volume. The osmolar effects of NaCl administration are distributed throughout total-body water even though NaCl is confined to the ECF. If one adds 1 L of water to the ECF there is an initial fall in ECF osmolality, promoting water movement into cells. Equilibrium is characterized by hyponatremia and an expansion of both ECF and ICF volumes. One-third of the water remains in the ECF and only 8% in the intravascular space.

Finally, if one adds 1 L of isotonic saline to the ECF, the saline is confined to the ECF and it will increase by 1 L. The intravascular volume will increase by 250 mL. Because there is no change in osmolality there is no shift of water between the ECF and ICF and serum sodium concentration remains unchanged.

Starling forces govern movement of water between intravascular and interstitial spaces (Figure 5.2). Expansion of the interstitial space results in the clinical finding of edema. Edema fluid resembles plasma in electrolyte content, although its protein content may

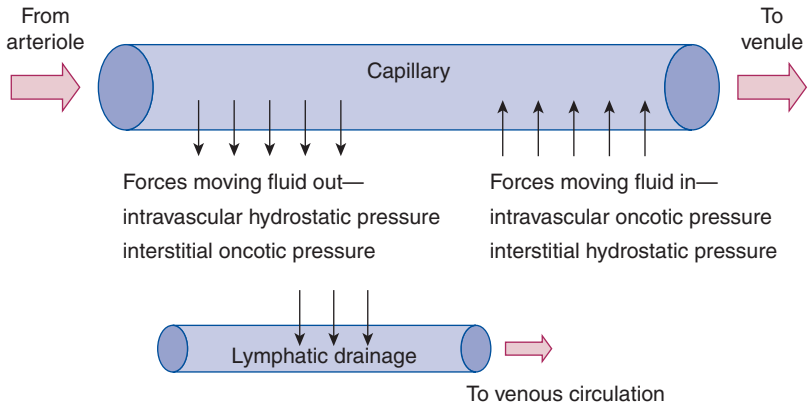

FIGURE 5-2. Starling forces across the capillary bed. Starling forces that move fluid out of the capillary are intravascular hydrostatic pressure (most important) and interstitial oncotic pressure. Forces acting to move fluid into the capillary are the intravascular oncotic pressure (most important) and interstitial hydrostatic pressure. Fluid in the interstitial space drains back to the venous system via lymphatics.

vary. The interstitial space must be expanded by 3 to 5 L before edema in dependent areas is detected. Edema may be localized as a result of vascular or lymphatic injury, or it may be generalized as in congestive heart failure (CHF). Forces governing edema formation are summarized by the equation below in which K_c reflects the surface area and permeability of the capillary. LR is the lymphatic return. P_c and P_t are the hydrostatic pressures in the capillary and tissue, respectively, whereas π_c and π_t are the oncotic pressure in the capillary and tissue, respectively.

$$\text{Net accumulation} = K_c \times [(P_c - \pi_c) - (P_t - \pi_t)] - \text{LR}$$

The most common abnormalities leading to edema formation are an increase in capillary hydrostatic pressure or a decrease in capillary oncotic pressure. In CHF, for example, the P_c increases. In cirrhosis, the P_c increases (secondary to portal hypertension) and the π_c declines. Table 5.1 lists the specific causes of edema, classified according to the major mechanism(s) responsible. The final common pathway maintaining generalized edema is renal retention of excess sodium and water.

TABLE 5-1. Mechanism of Edema Formation

INCREASED HYDROSTATIC PRESSURE	DECREASED CAPILLARY ONCOTIC PRESSURE
Venous/lymphatic obstruction	Nephrotic syndrome
Congestive heart failure	Malabsorption
Cirrhosis of the liver	Cirrhosis of the liver

KEY POINTS

Body Fluid Compartments

1. Total-body water constitutes 60% of lean-body weight in men and 50% of lean-body weight in women. It is distributed between ICF (67.7%) and ECF (33.3%) compartments.
2. Twenty-five percent of the ECF compartment consists of the intravascular space, with the remaining 75% constituted by the interstitial space.
3. Osmotic forces determine water distribution between ICF and ECF.
4. Each compartment has 1 major solute that acts to hold water within it: ECF—sodium salts; ICF—potassium salts; and intravascular space—plasma proteins.
5. Serum sodium concentration is a function of the ratio of sodium to water and does not correlate with ECF volume, which is a function of total-body sodium.
6. Starling forces govern water movement between intravascular and interstitial spaces.
7. The most common abnormalities leading to edema formation are an increase in capillary hydrostatic pressure or a decrease in capillary oncotic pressure.

REPLACEMENT OPTIONS: COLLOID VERSUS CRYSTALLOID

Despite the fact that adequate volume replacement is essential in the management of critically ill patients, the optimal replacement fluid remains a focus of considerable debate. Clinicians can choose between a wide array of crystalloids and colloids. Crystalloid solutions consist of water and dextrose and may or may not contain other electrolytes. Their composition varies depending on the type of solution. Some of the more commonly used crystalloid solutions and their components are shown in Table 5.2, and include 5% dextrose in water (D_5W), normal saline (0.9%), one-half normal saline (0.45%), and Ringer's lactate. Ringer's lactate is used more commonly in surgical services and normal saline in medical services.

Colloid solutions consist of high-molecular-weight molecules such as proteins, carbohydrates, or gelatin. Colloids increase osmotic pressure and remain in the intravascular space longer compared to crystalloids. Osmotic pressure is proportional to the number of particles in solution. Colloids do not readily cross normal capillary walls and result in fluid translocation from interstitial space to intravascular space.

Colloids are referred to as *monodisperse*, like albumin, if the molecular weight is uniform, or *polydisperse*, if there is a range of different molecular weights, as with starches. This is important because molecular weight determines the duration of colloidal effect in the intravascular space. Lower-molecular-weight colloids have a larger initial oncotic effect but are rapidly renally excreted and, therefore, have a shorter duration of action. Hydroxyethyl starch (HES), dextran, and albumin are the most commonly used colloids. Gelatins are not commercially available in the United States.

HES is a glucose polymer derived from amylopectin. Hydroxyethyl groups are substituted for hydroxyl groups on glucose. The substitution results in slower degradation and increased water solubility. Naturally occurring starches are degraded by circulating amylases and are insoluble at neutral pH. HES has a wide molecular weight range. Duration of action is dependent on rates of elimination and degradation. Lower-molecular-weight species are eliminated rapidly by the kidney. The rate of degradation is determined by the degree of substitution (the percentage of glucose molecules having a hydroxyethyl group substituted for a hydroxyl group). Substitution occurs at positions C2, C3, and C6 of glucose, and the location of the hydroxyethyl group also affects the degradation rate. Characteristics associated with a longer duration of action include higher molecular weight, a high degree of substitution, and a high C2:C6 ratio.

Hetastarch is a HES with a high molecular weight (480 kDa), slow elimination kinetics, and is associated with an increase in bleeding complications after cardiac and neurosurgery. The higher the molecular weight and the slower the elimination rate, the more likely that HES will cause clinically significant bleeding. Newer HES preparations with lower molecular weights and more rapid elimination kinetics may be associated with fewer complications. Hetastarch use is also associated with an increased risk of acute kidney injury (AKI) in septic patients and in brain-dead kidney donors. Several randomized controlled trials and a recent systematic review showed that HES increases the risk of AKI in septic patients. In one study, the median time to AKI was 16 days. The incidence of AKI is increased with increases in the cumulative dose. Given these findings, hetastarch cannot be recommended in patients with impaired kidney function. The threshold level of glomerular filtration rate below which hetastarch should be avoided is unknown. Table 5.3 compares

TABLE 5-2. Commonly Used Crystalloid Solutions

PREPARATION	OSMOLALITY (mOsm/L)	GLUCOSE (g/L)	SODIUM (mEq/L)	CHLORIDE (mEq/L)	LACTATE (mEq/L)
D_5W	252	50	–	–	–
0.9% NS	308	–	154	154	–
0.45% NS	154	–	77	77	–
Ringer's lactate	272	–	130	109	28

Abbreviations: D_5W, 5% dextrose in water; NS, normal saline.

TABLE 5-3. Albumin Versus Hetastarch

	ALBUMIN	HETASTARCH
Molecular weight	69,000	480,000
Made from	Human sera	Starch
Compound	Protein	Amylopectin
Preparations	5% and 25%	6%

albumin to hetastarch. Hetastarch is available as a 6% solution in normal saline. One liter of hetastarch will initially expand the intravascular space by 700 to 1000 mL. Other commercially available HES preparations include Voluven, Hextend, and Hespan.

Two recent editorials in *Anesthesia and Analgesia* discussed the unfortunate ramifications of the discovery that data published in the journal by Professor Joachim Boldt were fabricated. The study in question involved use of 2 different bypass pump priming solutions (albumin and a modern HES preparation) and their effects on postoperative inflammatory markers. Three readers of the manuscript noticed that the standard deviations of the interleukin (IL)-6 measurements were too narrow. A subsequent investigation revealed that there were no original patient data or laboratory measurements to support the findings. Reinhart and Takala point out that this discovery casts a shadow over all previous work done by Dr. Boldt. They note that of the 56 randomized controlled trials of HES 130/0.4, one-third were published by Dr. Boldt. They conclude that if these trials were excluded that the remaining data are insufficient to conclude that the newer HES preparation is safer than older HESs.

Dextrans are glucose polymers produced by bacteria grown in the presence of sucrose with an average molecular weight of 40 to 70 kDa. In addition to expanding the intravascular volume, dextrans also have anticoagulant properties. Several studies show that they decrease risk of postoperative deep venous thrombosis and pulmonary embolism. Dextran infusion decreases von Willebrand factor levels and factor VIII:c more than can be explained by plasma dilution alone. Dextrans also enhance fibrinolysis and protect plasmin from the inhibitory effects of α_2-antiplasmin. In clinical studies comparing dextran to unfractionated heparin, low-molecular-weight heparin, and heparinoids in the prophylaxis of postoperative deep venous thrombosis, dextran was associated with increased blood loss after transurethral resection of the prostate and hip surgery. Dextran 40 use is also associated with acute kidney injury in the setting of acute ischemic stroke.

Two large metaanalyses by the Cochrane Injuries group and by Wilkes and Navickis reviewed albumin as an intravascular volume expander. The Cochrane group compared albumin to crystalloid in critically ill patients with hypovolemia, burns, and hypoalbuminemia. The pooled relative risk of death was increased by 68% in the albumin group. The authors found no evidence that albumin reduced mortality and a strong suggestion that it increased risk of death. Wilkes and Navickis showed that the relative risk of death was increased with albumin administration in patients with trauma, burns, and hypoalbuminemia but the increase in all cases was not statistically significant. Given these concerns and the higher cost of albumin compared to crystalloids and other synthetic colloids, routine albumin use as a plasma volume expander cannot be supported with 2 possible exceptions. In patients with cirrhosis and spontaneous bacterial peritonitis, the addition of intravenous albumin to antibiotics alone was shown to reduce the incidence of renal impairment and death in a randomized controlled trial. The dose of albumin administered was 1.5 mg/kg initially and 1 mg/kg on day 3. A planned subanalysis by the Saline versus Albumin Fluid Evaluation (SAFE) study investigators comparing albumin to saline administration on organ function and mortality in patients with severe sepsis was reported. The unadjusted relative risk of death with albumin versus saline was 0.87 (95% confidence interval 0.74 to 1.02) in patients with severe sepsis. After adjustment for baseline factors with multivariant logistic regression the adjusted odds ratio was 0.71 (95% confidence interval 0.52 to 0.97). The authors concluded that albumin may have reduced the risk of death in patients with severe sepsis. Albumin is available in 2 concentrations: (a) a 5% solution that contains 12.5 g of albumin in 250 mL of normal saline and has a colloid osmotic pressure of 20 mmHg and (b) a 25% solution that contains 12.5 g of albumin in 50 mL of normal saline and has a colloid osmotic pressure of 100 mmHg. After 1 L of 5% albumin is infused, the intravascular space is expanded by 500 to 1000 mL.

Advocates of colloids argue that crystalloids excessively expand the interstitial space and predispose patients to pulmonary edema. Crystalloid advocates point out that colloids are more expensive, have the potential to leak into the interstitial space in clinical conditions where capillary walls are damaged, as in sepsis, and increase tissue edema. Despite decades of research, however, in many

clinical situations there is no difference in pulmonary edema, mortality, or length of hospital stay between colloids and crystalloids.

KEY POINTS

Replacement Options

1. Crystalloids contain water and dextrose and may or may not contain other electrolytes. The most commonly used crystalloids are normal saline and Ringer's lactate.
2. Colloid solutions consist of high-molecular-weight molecules. Colloids increase osmotic pressure and remain in the intravascular space longer compared to crystalloids.
3. Hetastarch is associated with an increased risk of acute kidney injury in septic patients and in brain-dead kidney donors. Its use cannot be recommended in patients with impaired kidney function. Further studies are needed to establish the threshold level of glomerular filtration rate below which hetastarch should be avoided.
4. Given the higher cost of albumin compared to crystalloids and other synthetic colloids and the possible association with higher mortality rates, the routine use of albumin as an intravascular plasma volume expander cannot be recommended with the exception of patients with cirrhosis and spontaneous bacterial peritonitis. Whether patients with severe sepsis may benefit from albumin versus crystalloids remains an area of active research and debate.
5. In critically ill patients, there is little difference in pulmonary edema, mortality, or length of hospital stay with either colloid or crystalloid use in the majority of studies.
6. Recent findings of scientific misconduct have raised questions regarding the safety of newer HES preparations.

GENERAL PRINCIPLES

One must first decide on the amount of sodium and volume to be replaced based on the physical examination and clinical situation. As a general rule, the fluid deficit is 3 to 5 L in the patient with a history of volume loss, 5 to 7 L in the patient with orthostatic hypotension, and 7 to 10 L in the septic patient. Because colloids are initially confined to the intravascular space, approximately one-fourth of these volumes are required if colloids are used. For most clinical indications crystalloids and colloids are equivalent. In the bleeding patient, crystalloids are preferred. In the patient with total-body salt and water excess (CHF, cirrhosis, nephrosis), colloids minimize sodium overload. Albumin should only be used in specialized situations such as large-volume paracentesis.

In the hypotensive patient, a solution must be employed that will remain in the intravascular and/or extracellular space. D_5W should not be used as only 8% of the administered volume remains intravascularly. Crystalloids, such as normal saline and Ringer's lactate, or colloids are the replacement fluid of choice.

In patients with identifiable sources of fluid loss, it is important to be aware of the electrolyte content of body fluids (Table 5.4). Of note, sweat and gastric secretions are relatively low in sodium and potassium, whereas colonic fluids are high in potassium and bicarbonate.

Normal maintenance requirements for fluids and electrolytes must also be considered and added to deficits. Insensible water losses average 500 to 1000 mL/day or approximately 10 mL/kg/day. Insensible water losses are less in the ventilated patient breathing humidified air. The average maintenance requirements for sodium, potassium, and glucose are 50 to 100 mEq/day, 40 to 80 mEq/day, and 150 g/day, respectively. Potassium should be repleted carefully in patients with chronic kidney disease and acute kidney injury.

KEY POINTS

General Principles

1. The amount of sodium and fluid replaced is based on the physical examination and clinical situation.
2. For most clinical indications crystalloids and colloids are equivalent.
3. D_5W must not be used in the hypotensive patient.
4. One needs to be aware of normal daily losses of water and electrolytes.
5. Caution should be exercised in repleting potassium in patients with chronic kidney disease and acute kidney injury.

ASSESSING EXTRACELLULAR FLUID VOLUME

ECF volume is notoriously difficult to assess based on history and physical examination. Signs and symptoms, such as dry mouth, thirst, diminished axillary sweat, decreased

TABLE 5-4. Electrolyte Content of Body Fluids

	SODIUM (mEq/L)	POTASSIUM (mEq/L)	CHLORIDE (mEq/L)	BICARBONATE (mEq/L)
Sweat	30 to 50	5	50	–
Gastric	40 to 60	10	100	0
Pancreatic	150	5 to 10	80	70 to 80
Duodenum	90	10 to 20	90	10 to 20
Ileum	40	10	60	70
Colon	40	90	20	30

capillary refill, and decreased skin turgor, are often unreliable. Axillary sweat is more commonly related to the patient's anxiety level than volume status. Decreased skin turgor is also seen with aging and rapid loss of body weight, as well as the rare genetic disorder pseudoxanthoma elasticum. Perhaps the most reliable physical finding of ECF volume depletion is orthostatic hypotension. The American Autonomic Society and the American Academy of Neurology define orthostatic hypotension as a decline in systolic blood pressure of greater than or equal to 20 mmHg or a decrease in diastolic blood pressure of greater than or equal to 10 mmHg. An increase in pulse was not included in their definition, although this commonly occurs in patients without autonomic dysfunction.

Fluid resuscitation is initiated with boluses of crystalloid or colloid with periodic reassessment of clinical end points such as heart rate, urine output, and blood pressure. In patients with advanced chronic kidney disease or end-stage renal disease, one cannot use urine output as a measure of the adequacy of fluid resuscitation. Patients who do not respond or who have severe comorbid illness of the heart or lungs are considered for invasive monitoring. Central venous pressure and pulmonary artery occlusion pressure measurements via a central venous or pulmonary artery catheter are commonly used to assess left ventricular preload and response to fluid therapy. In the first 6 hours of treatment of the septic patient, the Surviving Sepsis Campaign Guidelines for Early Goal-Directed Therapy recommends fluid boluses to achieve a central venous pressure (CVP) of 8 to 12 mmHg in the nonventilated patient, and 12 to 15 mmHg in the ventilated patient, a mean arterial pressure equal to or greater than 65 mmHg, central venous oxygen saturation greater than 70%, and a urine output equal to or greater than 0.5 mL/kg/h. In general, approximately 50% of patients in these circumstances will respond with a meaningful increase in stroke volume, cardiac output, and blood pressure. However, it has now been conclusively demonstrated in multiple studies that CVP and pulmonary artery occlusion pressure (so-called static variables) are poor predictors of response to a fluid challenge.

This is not surprising given that these pressure variables are surrogate measures of left ventricular diastolic volume or preload and can be affected by factors that alter ventricular compliance, such as myocardial infarction, myocardial ischemia, and ventricular hypertrophy, that occur commonly in critically ill patients. For a fluid challenge to be effective (increase stroke volume), 2 conditions must be met: (a) the fluid bolus must increase preload, and (b) both ventricles must be operating on the ascending limb of the Frank-Starling curve. If the ventricles are operating on the plateau phase of the Frank-Starling curve, then additional fluid will only serve to expand the ECF volume and lead to worsening edema and pulmonary congestion. If venous capacitance is increased, additional fluid may not increase preload, and if ventricular contractility is reduced, the slope of the ascending portion of the Frank-Starling curve is decreased. Once on the plateau phase of the Frank-Starling curve the only ways to increase cardiac output are to (a) increase heart rate, (b) increase contractility, or (c) reduce afterload.

This is an important distinction because increasing evidence is emerging to indicate that volume overload in the patient with AKI, as well as the patient with acute lung injury may be harmful. In patients with AKI a greater than 10% increase in body weight is associated with increased mortality. There is also an association of mortality with the proportion of days in which fluid overload is present.

In patients with acute lung injury, a conservative fluid management protocol applied for 7 days shortened the duration of both intensive care unit stay and time on the ventilator.

Given the problems with use of CVP and pulmonary artery occlusion pressure to assess likelihood of response to a fluid challenge, current research in this field has focused on a search for more reliable predictors of response to a fluid challenge in the critically ill patient. The pulse pressure and systolic pressure variation are derived from analysis of the arterial waveform with digital software and stroke volume variation is determined from pulse contour analysis. These methods take advantage of the fact that intermittent positive pressure ventilation causes cyclic changes in stroke volume of the right and left ventricles. With inspiration, venous return to the right ventricle is decreased (reduced preload) and right ventricular afterload is increased as a result of increased intrathoracic and intraalveolar pressures, resulting in a reduction of right ventricular stroke volume. After 2 to 3 seconds these changes are transmitted to the left ventricle and left ventricular stoke volume is reduced during expiration. These hemodynamic effects are exaggerated in the hypovolemic patient, and the greater the variation, the more likely the patient is to respond to a fluid challenge. If the variation in these parameters exceeds 11% to 13%, the patient is more likely to respond to fluids. Cyclic changes are greater when the patient is operating on the linear (steep) portion of the Frank-Starling curve, and as a result the stroke volume is preload dependent.

Pulse contour analysis continuously measures cardiac output through analysis of the arterial waveform. It is based on the concept that the area under the systolic part of the waveform is proportional to both stroke volume and the mechanical properties of the artery. Stroke volume is derived from the integral change from end diastole to end systole over time. This requires a specific device.

These methods, although highly accurate, do have limitations. The patient must be (a) well sedated and not breathing spontaneously; (b) free of significant arrhythmias, such as atrial fibrillation and frequent premature ventricular contractions; and (c)have a tidal volume between 8 and 10 mL/kg at the time of the measurement. In addition, because these measures are affected by cardiac contractility, vasopressors should not be titrated during the measurement process. These methods also do not provide information about the absolute level of intravascular volume but rather the response to a fluid bolus.

KEY POINTS

Assessing Extracellular Fluid Volume

1. ECF volume is difficult to assess based on history and physical examination.
2. Orthostatic hypotension may be the most reliable sign of volume depletion.
3. Volume repletion is initiated with boluses of crystalloid or colloid with periodic reassessment of clinical end points, such as heart rate, urine output, and blood pressure.
4. Volume overload in the patient with acute lung injury and AKI may be deleterious.
5. Central venous pressure and pulmonary artery occlusion pressure measurement are often used to assess preload. However, both are poor predictors of response to a fluid challenge in critically ill patients.
6. Dynamic variables, such as stroke volume variability, pulse pressure variability, and systolic pressure variability, are better predictors of response to a fluid challenge in ventilated patients. It is important to recognize that these approaches also have limitations.

THE SEPTIC PATIENT

In septic shock, cardiac output is generally high and systemic vascular resistance low. Tissue perfusion is compromised by both systemic hypotension and maldistribution of blood flow in the microcirculation. Septic shock is more complex than other forms of shock that are related to global hypoperfusion. With global hypoperfusion, as in cardiogenic shock or hypovolemic shock, a decrease in cardiac output results in anaerobic metabolism. In septic shock, however, maldistribution of a normal or increased cardiac output impairs organ perfusion, and inflammatory mediators disrupt cellular metabolism. In this setting adenosine triphosphate (ATP) stores are depleted despite maintenance of tissue oxygenation and lactic acid levels can be elevated despite normal tissue partial pressure of oxygen (PO_2).

Shock is characterized by hypotension, which is defined as a mean arterial pressure less than 60 mmHg. The primary goals of fluid resuscitation in septic shock are normalization of tissue perfusion and oxidative metabolism. Large fluid deficits are present in the septic patient. As much as 4 L of colloid and 10 L of crystalloid

are required. Survival in the septic patient is associated with increased cardiac output and blood and plasma volumes. Volume repletion significantly improves cardiac output and enhances tissue perfusion. Fluid resuscitation alone, in the absence of inotropic agents, increases cardiac index by 25% to 40%. In as many as 50% of septic patients with hypotension, shock is reversed with volume replacement alone. When crystalloids and colloids are titrated to the same filling pressure they are equally effective.

Acute respiratory distress syndrome develops in one-third to two-thirds of patients with septic shock. A major challenge for the clinician managing the patient with septic shock is balancing the potential benefits of intravascular volume expansion on vital organ perfusion, such as brain and kidney, with the potentially adverse impact of worsening pulmonary edema. On theoretical grounds both crystalloids and colloids could worsen pulmonary edema. With crystalloid infusion plasma oncotic pressure may fall acting as a driving force for water movement out of the intravascular space and lung water accumulation. With colloid infusion if microvascular permeability is increased, colloid particles could migrate into the interstitium, thereby acting as a driving force for water movement, and worsen pulmonary edema. Despite these potential problems studies have shown that there is no significant difference in the development of pulmonary edema between crystalloids and colloids when lower filling pressures are maintained.

KEY POINTS

The Septic Patient

1. In septic shock, tissue perfusion is compromised by systemic hypotension and maldistribution of blood flow.
2. Large fluid deficits are present in the septic patient. As much as 4 L of colloid and 10 L of crystalloid may need to be administered in the first 24 hours.
3. Fluid resuscitation is initiated with boluses of crystalloid or colloid with periodic reassessment of clinical end points.
4. When crystalloids and colloids are titrated to the same filling pressure they are equally effective.
5. A major challenge for the clinician managing the patient with septic shock is balancing the benefits of intravascular volume expansion on vital organ perfusion with the potential adverse impact of worsening pulmonary edema.

THE CARDIAC SURGERY PATIENT

Patients undergoing cardiac surgery are at risk for intraoperative and postoperative bleeding. Cardiopulmonary bypass induces multiple platelet abnormalities, including decreased platelet count, decreased von Willebrand factor receptor, and desensitization of platelet thrombin receptors. Several studies indicate that increased postcardiopulmonary bypass blood loss requiring reoperation is an independent risk factor for prolonged intensive care unit stay and death.

Trials comparing HES to albumin show increased postoperative bleeding and higher transfusion requirements in those receiving HES. One large retrospective study revealed a 25% lower mortality in those receiving albumin versus HES. In this study, the authors estimated that albumin use would save 5 to 6 lives per 1000 patients undergoing cardiopulmonary bypass. Other studies showed increased blood loss with HES, even in low-risk patients.

Whether this is related to a beneficial effect of albumin or a deleterious effect of HES is unknown. Cardiopulmonary bypass activates inflammatory mediators and complement. There is an increase in free radical generation and lipid peroxidation. Albumin has significant antioxidant properties and inhibits apotosis in microvascular endothelium. Free fatty acid production contributes to erythrocyte crenation, which, in turn, inhibits platelet function. This process is inhibited by albumin. Albumin also coats the surface of the extracorporeal circuit, decreasing the polymer surface affinity for platelets and reducing platelet granule release. HES reduces von Willebrand factor more than can be explained by hemodilution alone. Platelet dysfunction is mediated in part by the HES-induced fall in von Willebrand factor coupled with the decrease in von Willebrand receptor function induced by cardiopulmonary bypass.

KEY POINTS

The Cardiac Surgery Patient

1. There is an increased risk of bleeding in patients undergoing cardiopulmonary bypass.
2. Cardiopulmonary bypass induces multiple platelet abnormalities.
3. Increased postoperative bleeding and higher transfusion requirements are noted in cardiopulmonary bypass patients receiving HES. Whether this is related to a beneficial effect of albumin or a deleterious effect of HES remains to be determined.

THE GENERAL SURGICAL PATIENT

The postoperative patient is often in pain, may be nauseous, vomiting, and is under stress. All of these factors act to increase arginine vasopressin (AVP) release. This may continue for up to 4 days after surgery. As a result, it is prudent not to administer free water to these patients so as to avoid potential hyponatremia. Protocols that administer only enough fluids to maintain postoperative weight constant and avoid postoperative weight gain have been shown to reduce complications after abdominal and colorectal surgery.

KEY POINTS

The General Surgical Patient

1. The postoperative patient is at increased risk for hyponatremia as a result of AVP release.
2. Avoid hypotonic fluids in the postoperative setting.
3. Protocols that avoid the typical 3- to 7-kg increase in weight in the immediate postoperative period and attempt to maintain weight constant are associated with reduced morbidity.

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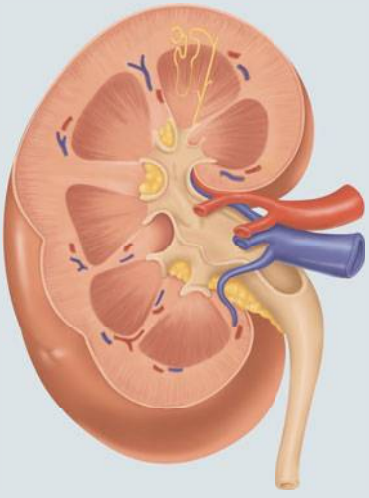

CHAPTER 6

Disorders of Potassium Homeostasis

• *Mark A. Perazella and Mandana Rastegar*

Recommended Time to Complete: 1 Day

Guiding Questions

1. What role does potassium (K^+) play in cellular function?
2. How does the body avoid a lethal cardiac arrhythmia following the ingestion of a potassium-rich meal?
3. What are the major factors that influence cellular shift of potassium and how do they accomplish their effect?
4. What is the major site of K^+ secretion by the kidney?
5. What are the 4 key factors that modulate renal K^+ excretion?
6. Does diet play a major role in the development of either hypo- or hyperkalemia?
7. What are the general categories of causes of hypokalemia?
8. What are the 3 general categories of causes of hyperkalemia?
9. Treatment of clinical disorders of potassium balance is best guided by what 2 factors?
10. What is the most appropriate method of potassium supplementation in patients with severe hypokalemia?
11. What 3 treatment steps are employed to treat patients with severe hyperkalemia?

INTRODUCTION

Potassium is found in nearly all food sources. It is the predominant intracellular cation in the body. A high cellular concentration is required to maintain normal function of a number of cellular processes. These include nucleic acid and protein synthesis, regulation of cell volume and pH, cell growth, and enzyme activation. In particular, a high intracellular K^+ concentration is necessary for the maintenance of the resting membrane potential. The resting membrane potential, in concert with the threshold membrane potential, sets the stage for generation of the action potential. This process is ultimately required for proper functioning of excitable tissues. Hence, these actions allow normal functioning of cardiac and skeletal muscles. Regulation of K^+ homeostasis is achieved mainly through cellular

shifts of potassium, as well as renal K^+ excretion. These 2 regulatory mechanisms are under the control of a variety of factors that are reviewed in subsequent sections. Disturbances in these homeostatic mechanisms result in either hypokalemia or hyperkalemia. Both of these disturbances in K^+ balance promote a variety of clinical symptoms and physical findings that are predominantly caused by disruption of action potential formation, leading to neuromuscular dysfunction and inhibition of normal cell enzymatics. Rapid recognition and treatment of these disorders are required to avoid serious morbidity and mortality.

POTASSIUM HOMEOSTASIS

Total-body K^+ stores in an adult are between 3000 and 4000 mEq (50–60 mEq/kg body weight). Total-body K^+ content is also influenced by age and sex. As compared with a young male, an elderly man has 20% less total-body K^+ content. Also, age-matched females have 25% less total-body K^+ than males. Potassium is readily absorbed from the gastrointestinal (GI) tract and subsequently distributed in cells of muscle, liver, bone, and red blood cells. Maintenance of total-body K^+ stores within narrow limits is achieved by zero net balance between input and output, as well as by regulation of K^+ between the extracellular fluid (ECF) and intracellular fluid (ICF). The bulk (90%) of dietary potassium is excreted in urine and the rest in feces (10%) in an adult. In contrast to sodium (Na^+), K^+ is predominantly an intracellular cation, with 98% of body K^+ located inside the cell. Hence, only 2% of K^+ is present in the ECF. As a result, there is a dramatic difference in K^+ concentration intracellularly (145 mEq/L) versus extracellularly (4 to 5 mEq/L). Despite this fact, however, the serum K^+ concentration is employed as an index of potassium balance because it is the most readily available clinical test. In general, it is a reasonably accurate reflection of total-body potassium content. In disease states, however, the serum potassium concentration may not always represent total-body K^+ stores. The clinician must keep this is mind when assessing patients with abnormal laboratory values.

KEY POINTS

Potassium

1. K^+ is the most abundant intracellular cation in the body. It plays a key role in cell growth, nucleic acid, and protein synthesis.
2. Proper functioning of these various cellular processes depends on maintenance of high K^+ concentration within cells.
3. Generation of an action potential in neuromuscular tissue is a key function of K^+ movement between ICF and ECF.
4. Total-body K^+ stores range between 4000 and 5000 mEq and are determined by age, sex, and body size.
5. To maintain net zero K^+ balance, approximately 90% of K^+ is excreted by the kidneys, while 10% is excreted by the GI tract.
6. Serum K^+ concentration is the marker used to estimate total-body K^+ balance.

ROLE OF POTASSIUM IN THE RESTING MEMBRANE POTENTIAL

Movement of cations, such as K^+ and Na^+, into their respective compartments requires active and passive cellular transport mechanisms. The location of K^+ and Na^+ in their respective fluid compartments is maintained predominantly by the action of the Na^+-K^+-adenosine triphosphatase (ATPase) pump in the cell membrane. This enzyme hydrolyzes adenosine triphosphate (ATP) to create the energy required to pump Na^+ out of the cell and K^+ into the cell in a 3:2 ratio. Potassium moves out of the cell at a rate dependent on the electrochemical gradient, this creates the resting membrane potential (E_m). As seen below, the Goldman-Hodgkin-Katz equation calculates the membrane potential on the inside of the membrane using Na^+ and K^+. Three factors determine the E_m: (a) the electrical charge of each ion; (b) the membrane permeability to each ion; and (c) the concentration of the ion on each side of the membrane. Inserting the intracellular K^+ (145) and Na^+ (12) concentrations and extracellular K^+ (4.0) and Na^+ (140) concentrations into the formula results in a resting membrane potential of –90 mV. The cell interior is –90 mV, largely as a result of the movement of K^+ out of the cell via the Na^+-K^+-ATPase pump.

$$E_m = -61 \log \frac{3/2\,(140) + 0.01\,(12)}{3/2\,(4.0) + 0.01\,(145)} = -90 \text{ mV}$$

The resting potential sets the stage for membrane depolarization and generation of the action potential. Any change in serum K^+ concentration alters the action potential and excitability of the cell. Thus, regulation of K^+

distribution must be efficient, because a small movement of K^+ from the ICF or ECF results in a potentially fatal change in serum K^+ concentration. Physiologic and pathologic factors influence K^+ distribution between ICF and ECF.

CELLULAR DISTRIBUTION OF POTASSIUM

Many foods have a high K^+ content that can raise serum K^+ concentrations, sometimes to levels that significantly disturb cell function and, as a result, are potentially lethal. To maintain the serum K^+ concentration within a safe range, cellular movement of K^+ is the first response of the body following ingestion of a potassium-rich meal. This is a key feature of K^+ homeostatic mechanisms because renal excretion of K^+ requires several hours. The critical importance of this process is illustrated in the following case.

CASE 6.1

A 70-kg man drinks 3 glasses of orange juice (40 mEq of K^+). In the absence of cellular shift, the K^+ would remain in the ECF (17 L) and raise the serum K^+ concentration by 2.4 mEq/L. The excess K^+, however, is rapidly shifted into cells and gradually excreted by the kidneys over the next several hours. This prevents a potentially lethal acute rise in serum K^+ concentration.

Not surprisingly, insulin, which is secreted following a meal to maintain proper glucose balance, is also integral to cellular K^+ homeostasis. As such, serum K^+ concentration is maintained in the normal range by the physiologic effects of insulin. This role of insulin to move K^+ into cells is well suited as renal K^+ excretion does not occur immediately following ingestion of a meal containing large amounts of potassium. Movement of K^+ into cells allows rapid lowering of the serum K^+ concentration until the K^+ load is fully excreted by the kidneys. Insulin stimulates K^+ uptake into cells by increasing the activity and number of Na^+-K^+-ATPase pumps in the cell membrane. Two K^+ ions are transported into the cell, while 3 Na^+ ions are moved out of the cell by this energy-requiring transporter. The intracellular shift of K^+ is independent of glucose transport. A deficiency of insulin, as occurs in many patients with type 1 diabetes mellitus, is associated with hyperkalemia from impaired cellular uptake of K^+. The following clinical experiment illustrates the effect of insulin on cellular K^+ homeostasis.

Infusion of somatostatin, an inhibitor of pancreatic insulin release, in normal subjects reduced basal insulin concentrations to very low levels. Serum K^+ concentrations were measured with KCl infusion during baseline, infusion with somatostatin, and infusion with somatostatin plus insulin. An exaggerated rise in serum K^+ concentration developed with somatostatin; this effect was completely reversed by insulin infusion.

As noted with insulin, endogenous catecholamines and β_2-adrenergic agonists promote K^+ movement into cells through stimulation of the Na^+-K^+-ATPase. Activation of the β_2 receptor underlies the effect on this active enzyme pump to move K^+ into cells. Receptor activation is signaled through adenylate cyclase to generate cyclic adenosine monophosphate (AMP). This second messenger system ultimately stimulates the Na^+-K^+-ATPase pump to shift K^+ into cells. Medications such as albuterol, a β_2-adrenergic agonist used for asthma, can lower serum K^+ concentration through stimulation of cell uptake, whereas propranolol, an antihypertensive medication that blocks β_2-adrenergic receptors, may cause hyperkalemia through inhibition of K^+ movement into cells. Intoxication with a medication such as digoxin may raise serum K^+ concentration by disrupting the Na^+-K^+-ATPase, thereby blocking cellular K^+ uptake. The clinical observation described below demonstrates the effect of digoxin on Na^+-K^+-ATPase function and serum K^+ concentration.

CASE 6.2

An elderly male with a history of heart disease presents to the emergency department with severe weakness, nausea, and vomiting. Severe digoxin intoxication is documented on blood testing. Serum K^+ concentration is 7.1 mEq/L, previous serum K^+ concentration was 4.9 mEq/L. This case shows the effect of digoxin intoxication on cellular K^+ balance, an effect mediated through inhibition of the Na^+-K^+-ATPase.

Other physiologic factors that modulate cellular K^+ movement include exercise, changes in extracellular pH, in particular metabolic acidosis and alkalosis, as well as changes in plasma osmolality. Exercise has a dual effect on cellular K^+ movement. A transient rise in serum K^+ concentration occurs primarily to increase blood flow to muscle. This homeostatic effect occurs because local release of K^+ vasodilates vessels and improves perfusion of ischemic muscles (provides more oxygen). A counterbalancing effect of endogenous catecholamine secretion also develops with exercise; this moves K^+ back into the ICF (activation of β_2-adrenergic receptors) and restores the serum K^+

concentration to normal. The level of exercise influences the cellular release of K^+. For example, a 0.3- to 0.4-mEq/L rise with slow walking, a 0.7- to 1.2-mEq/L rise with moderate exercise, and as much as a 2-mEq/L rise with exercise to the point of exhaustion. Rest is associated with rapid correction of the rise in serum K^+ concentration, mainly through the actions of the Na^+-K^+-ATPase. Physical conditioning reduces the rise in K^+ concentration, presumably through an improvement in pump activity.

Changes in pH also influence serum K^+ concentration. Metabolic acidosis is associated with an exit of K^+ from cells in exchange for protons (H^+) as the cells attempt to buffer the ECF pH. The exchange of K^+ for H^+ maintains electroneutrality across membranes. In this setting, up to 60% of excess protons are buffered within cells. An opposite effect is observed with metabolic alkalosis as K^+ enters the ICF to allow H^+ to enter the ECF and reduce alkalemia. In general, the serum K^+ concentration increases or decreases by 0.4 mEq/L for every 0.1 decrease or increase in pH. There is a wide variability, however, in the change in serum K^+ concentration with pH change in metabolic acidosis (0.2 to 1.7 mEq/L for every 0.1 fall in pH). Furthermore, this effect is more prominent with mineral (nonanion gap) metabolic acidoses than organic anion acidoses. The explanation for the differential effects of these types of acute acidoses on cellular K^+ movement is based on the presence of different types of ion transporters in cell membranes. In mineral metabolic acidosis, multiple ion transporters work in a coordinated fashion to buffer extracellular acidosis. The fall in extracellular pH inhibits both the Na^+-H^+-antiporter activity and Na^+-HCO_3^-, which causes a slowing of Na^+-K^+-ATPase and a reduction in cellular K^+ uptake. In addition, HCO_3^--Cl^- exchanger activity, which is increased to buffer extracellular H^+, is coupled to Cl^--K^+-cotransport. This results in increased movement of K from the cell to extracellular space. These buffering pathways for acute mineral metabolic acidosis lead to increased extracellular K^+ and hyperkalemia. In the setting of metabolic alkalosis, K^+ moves in the opposite direction and hypokalemia can develop from intracellular shift. In contrast, in the setting of organic acidosis (lactic acidosis), K movement into and out of the cell is balanced. For example, the decline in extracellular pH increases extracellular K through the mechanisms discussed for mineral acidosis except that a strong influx of H^+ and lactate occurs through the monocarboxylate (H^+-A^-) transporter, resulting in a larger fall in intracellular pH and HCO_3^-. This tends to increase intracellular Na^+ via Na^+-H^+-antiporter and Na^+-HCO_3^- cotransporter, stimulating Na^+-K^+-ATPase and movement of K^+ into cells. These effects tend to have no net change in extracellular K and no clinically significant hyperkalemia.

An increase in plasma osmolality, as occurs with hyperglycemia in diabetes mellitus, raises serum K^+ concentration as a result of a shift of K^+ out of cells. Potassium movement from cells is induced by the increase in intracellular K^+ concentration that occurs as water leaves the cell. As the intracellular K^+ concentration rises, an increased driving force for passive diffusion of K^+ out of the cell develops and extracellular K^+ increases. In general, the serum K^+ concentration rises by 0.4 to 0.8 mEq/L for every 10 mOsm/kg increase in the effective osmolality. As will be discussed later, other hyperosmolar substances can cause a shift of K^+ out of cells. There exists a small amount of data suggesting that aldosterone may increase cellular uptake of K^+ through stimulation of the Na^+-K^+-ATPase pump. The role of aldosterone on cellular K^+ movement, however, is controversial, and probably of only minor importance. As is noted later, the major effect of aldosterone is to enhance renal K^+ excretion.

KEY POINTS

Cellular Distribution of Potassium

1. K^+ is distributed between ECF and ICF by a number of physiologic factors.
2. Insulin and β_2-adrenergic agonists act to move K^+ into cells by stimulating the activity of Na^+-K^+-ATPase.
3. Metabolic alkalosis and acidosis shift K^+ into and out of cells in exchange for H^+ to buffer pH changes.
4. Hyperosmolality increases serum K^+ concentration through the creation of a diffusional driving force for K^+ to exit the cell.

POTASSIUM HANDLING BY THE KIDNEY

Proximal Tubule

K^+ handling in kidney occurs through the processes of glomerular filtration and both tubular reabsorption and secretion. In proximal nephron, 100% of K^+ reaches the tubule as K^+ is freely filtered by the glomerulus. Approximately 60% to 80% of filtered K^+ is reabsorbed by proximal tubule. Uptake of K^+ occurs via passive rather than active transport mechanisms. Potassium is reabsorbed by a K^+ transporter and through paracellular pathways coupled with Na^+ and water. Any process that affects Na^+

and water movement in proximal tubule will also influence K^+ reabsorption. For example, volume depletion will increase Na^+ and water reabsorption, also increasing K^+ uptake, whereas volume expansion will inhibit passive diffusion of Na^+-coupled K^+ transport.

Loop of Henle

In the loop of Henle, K^+ is both secreted and reabsorbed. Ultimately, 25% of the filtered K^+ is reabsorbed in this nephron segment. Potassium is secreted into the lumen and the K^+ concentration at the tip of the loop of Henle may exceed the amount filtered. In contrast, K^+ is actively and passively reabsorbed in the medullary thick ascending limb. Active K^+ transport occurs by the $1Na^+$-$1K^+$-$2Cl^-$ cotransporter (Figure 6.1), which is powered by the enzymatic activity of Na^+-K^+-ATPase on the basolateral membrane. Secondary active cotransport is driven by the steep Na^+ gradient across the apical membrane created by this enzyme pump. To allow continued cotransport, K^+ must recycle across the apical membrane from the cell into the tubular lumen. This provides a continuous supply of K^+ ions for cotransport with Na^+ and Cl^-, and negates the limiting effect of low luminal K^+. Medications such as loop diuretics and certain genetic disorders impair the transport function of this cotransporter resulting in Na^+ and K^+ wasting.

Distal Nephron

Following K^+ handling in the previously described nephron segments, approximately 10% of filtered K^+ reaches the distal tubule. In contrast to the other nephron segments, net K^+ secretion occurs in distal tubule. This develops because of the high luminal Na^+ concentration and low luminal Cl^- concentration, which stimulates the K^+-Cl^- cotransporter to secrete K^+. In connecting tubule (CT), cortical collecting duct (CCD), and medullary collecting duct (MCD), K^+ is both secreted and reabsorbed. The CT and CCD are the major sites of K^+ secretion in kidney.

Two major cell types modulate K^+ movement in this nephron segment.The principal cell is uniquely designed to secrete K^+ (Figure 6.2). The apical membrane of this cell contains epithelial Na^+ channels (ENaCs) and 2 types of K^+ channels (ROMK and big K or maxi-K channels), which act in concert with basolateral Na^+-K^+-ATPase to reabsorb Na^+ and secrete K^+. Potassium secretion by principal cells normally is mediated by ROMK channels, but flow-induced increases in potassium secretion are mediated by big K (BK) channels. Reabsorption of Na^+ through ENaC increases K^+ secretion through its channel by creating an electrochemical gradient for K^+ movement from cell to tubular lumen. An electrical gradient develops as a result of Na^+ entry into the principal cell without an accompanying anion, creating a lumen negative charge that stimulates K^+ secretion. Also, the entry of Na^+ into cells increases basolateral Na^+-K^+-ATPase activity to lower intracellular Na^+. Transporting 3 Na^+ ions out of the cell and 2 K^+ ions into the cell increases intracellular K^+ concentration and creates a diffusional gradient favoring K^+ exit from cells through apical K^+ channels into the tubular lumen.

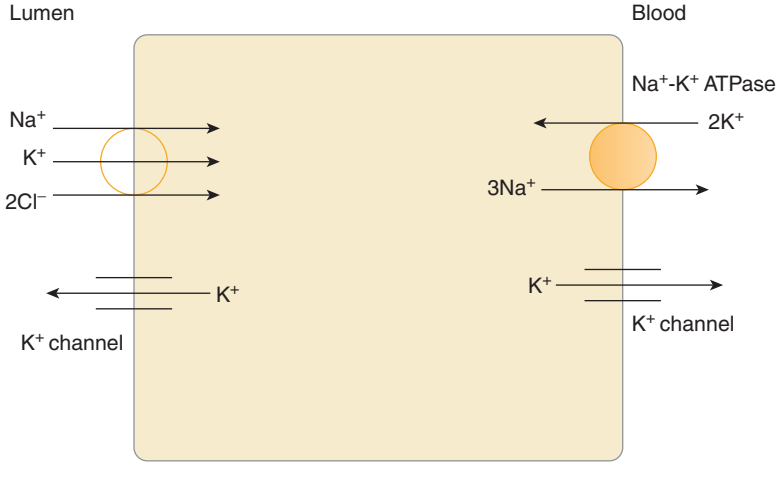

FIGURE 6-1. Na^+-K^+-ATPase. The Na^+-K^+-ATPase on the basolateral membrane provides the energy required to drive secondary active K^+ transport by the $1Na^+$-$1K^+$-$2Cl^-$ cotransporter in the thick ascending limb of Henle.

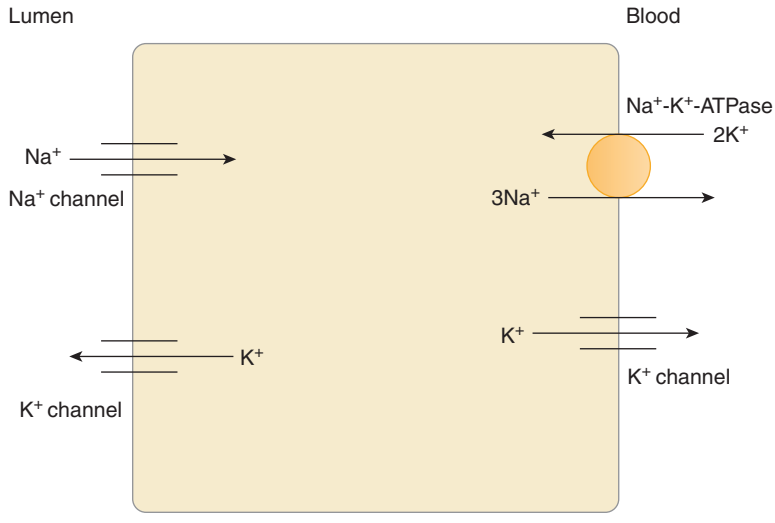

FIGURE 6-2. Cell model of the principal cell. The principal cell functions to regulate renal K^+ excretion. Reabsorption of Na^+ through epithelial sodium channel increases K^+ secretion via ROMK by creating an electrochemical gradient for K^+ movement from cell to tubular lumen.

Increased urinary flow also enhances K movement out of cells through opening BK (maxi-K) channels. Blockade of the Na^+ channel (amiloride, trimethoprim) reduces renal K^+ excretion by blocking generation of the electrochemical gradient. Administration of an aldosterone receptor antagonist (spironolactone, eplerenone) reduces apical Na^+ channel function, as well as Na^+-K^+-ATPase activity, which limits K^+ secretion from cells to urine. The other cell in the distal nephron involved in K^+ movement, the intercalated cell, promotes K^+ reabsorption. An H^+-K^+-ATPase on the apical surface of this cell reabsorbs K^+ in exchange for H^+ (Figure 6.3).

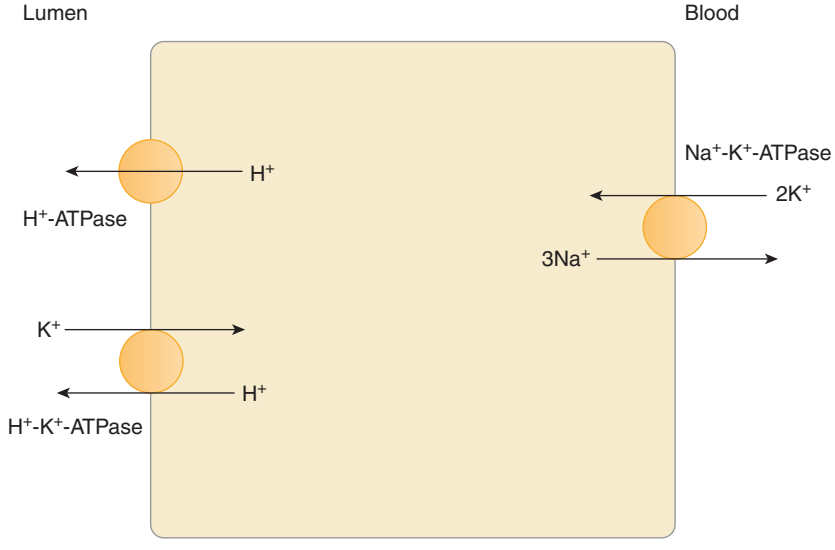

FIGURE 6-3. Cell model of the intercalated cell. The intercalated cell promotes K^+ reabsorption via the H^+-K^+-ATPase located on the apical surface. This action stimulates K^+ reabsorption in exchange for H^+ ion.

TABLE 6-1. Factors That Influence Renal Potassium Excretion

Aldosterone
Plasma potassium concentration
Tubular flow rate
Tubular sodium concentration
Antidiuretic hormone
Glucocorticoids
Metabolic alkalosis
Metabolic acidosis
Impermeant anions in the urine (sulfate, bicarbonate, carbenicillin)

Factors Controlling Renal Potassium Excretion

Although a number of factors influence renal K^+ excretion (Table 6.1), this discussion focuses on 4 clinically relevant factors that control K^+ secretion in principal cells. Most important is the mineralocorticoid aldosterone, which acts through binding its steroid receptor. This hormone stimulates Na^+ entry through ENaC and enhances basolateral Na^+-K^+-ATPase activity. This dual effect on the cell creates both an electrical potential for K^+ secretion (lumen negative charge stimulates K^+ movement from cell to urine), as well as a diffusional gradient for K^+ secretion (raising intracellular K^+ concentration).

Regulation of sodium reabsorption and potassium secretion is controlled by aldosterone, yet different physiologic needs (volume depletion or hyperkalemia) increase aldosterone production. The molecular switch that controls aldosterone's stimulation of one process versus the other is the WNK (with no lysine) kinase system (Figure 6.4). The system is comprised of 2 important kinases: WNK1 (both L and KS) and WNK4. L-WNK1 stimulates both ENaC-mediated and sodium chloride cotransporter (NCC)-mediated Na^+ transport; the former occurs through serum glucocorticoid kinase1 (Sgk1), and the latter through the blockade of WNK4. However, because both of these kinases independently suppress ROMK activity, they actually synergize to inhibit potassium secretion. The end result is increased Na^+ reabsorption with minimal K^+ secretion. In contrast, KS-WNK1 suppresses NCC transport via its dominant-negative effect on L-WNK1, stimulates ROMK activity via the same antagonistic mechanism, and enhances

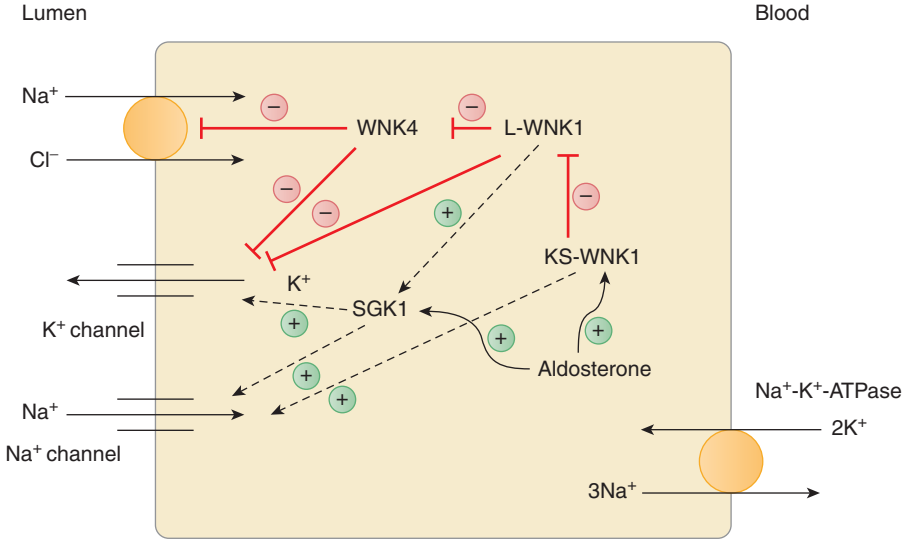

FIGURE 6-4. Effects of WNK1 and WNK4 on apical sodium and potassium transporters in the distal convoluted tubule. In the setting of hyperkalemia, aldosterone induces the transcription of KS-WNK1, which changes Na^+ reabsorption from the Na^+-Cl^- cotransporter to ENaC. This augments potassium secretion by increasing distal flow and luminal Na^+ concentration. KS-WNK1 also enhances K^+ secretion by increasing ROMK surface abundance, via its effect on L-WNK1. (Adapted from Subramanya AR, Yang CL, McCormick JA, Ellison DH. WNK kinases regulate sodium chloride and potassium transport by the aldosterone-sensitive distal nephron. *Kidney Int*. 2006;70:630-634.)

ENaC-mediated Na^+ transport through a different process, thereby increasing K^+ secretion, but minimally increasing Na^+ reabsorption. Thus, in the setting of *hyperkalemia*, aldosterone simultaneously downregulates electroneutral transport via NCC and enhances electrogenic transport via ENaC and ROMK. The inhibition of NCC activity by KS-WNK1 would increase flow to downstream nephron segments and augment electrogenic sodium and potassium exchange. Increased flow would also activate BK (maxi-K) channels, which play a central role in flow-stimulated K^+ transport. Consequently, the inhibitory effect of KS-WNK1 on NCC activity would effectively maximize the dual function of aldosterone as a mediator of both sodium reabsorption and kaliuresis. With *volume depletion* the opposite would be seen where NCC is stimulated and ROMK is inhibited, thereby facilitating Na^+ reabsorption without major kaliuresis.

The plasma K^+ concentration also influences K^+ secretion by the kidney. As the plasma K^+ concentration rises above 5 mEq/L, it produces effects on the principal cell that are similar to aldosterone as described above. This likely represents a protective mechanism to maintain renal K^+ excretion even when aldosterone is deficient or absent. On the luminal side (urinary space), both urine flow rate and Na^+ delivery influence K^+ secretion. High flow rates enhance K^+ secretion by maintaining a low urine K^+ concentration and a favorable diffusional gradient for intracellular K^+. Urinary Na^+ delivery to the principal cell promotes K^+ secretion by enhancing the entry of Na^+ ions through ENaC and creating a favorable electrochemical gradient. Thus, an increase in urine flow rate and Na^+ delivery, as created by use of a loop diuretic will increase K^+ in the urine. In contrast, disease states such as congestive heart failure or true intravascular volume contraction reduce urine flow rate or Na^+ delivery, and as a result impair renal K^+ excretion. The impact of urine flow rates and Na^+ delivery on renal K^+ excretion are less important, however, than aldosterone or the plasma K^+ concentration.

KEY POINTS

Potassium Handling by the Kidney

1. K^+ is freely filtered by the glomerulus.
2. The proximal tubule reabsorbs 60% to 80% of filtered K^+, the loop of Henle reabsorbs approximately 25%, and the distal nephron is the primary site of renal K^+ secretion.
3. In distal nephron, the principal cell in CCD is the primary regulator of K^+ excretion.
4. Several factors modulate K^+ excretion.
5. Aldosterone and plasma K^+ concentration primarily influence K^+ secretion by the principal cell.
6. The WNK kinase system is the molecular switch that determines whether aldosterone will function to increase K^+ secretion or enhance Na^+ reabsorption.
7. Urinary Na^+ concentration and urine flow rate also regulate K^+ secretion by the principal cell, but are less important than aldosterone and plasma K^+ concentration. BK or maxi-K channels facilitate K^+ secretion during increased urinary flow.

CLINICAL DISORDERS OF POTASSIUM HOMEOSTASIS

Clinical disorders of K^+ balance are common problems in patients with a variety of medical conditions, especially those that require therapy with certain medications. In general, the causes of these disturbances promote K^+ imbalance by interrupting cell shift or renal excretion of K^+. Other factors that contribute include variations in dietary K^+ intake and disturbed GI K^+ handling.

Hypokalemia

Hypokalemia is typically defined as a serum (or plasma) K^+ concentration less than 3.5 mEq/L. Falsely low serum K^+ levels, or pseudohypokalemia, is a rare cause of hypokalemia. Patients with various leukemias and extremely elevated white blood cell (WBC) counts (>1000,000/L) develop pseudohypokalemia due to the uptake of K^+ by abnormal WBCs when the specimen remains at room temperature. Causes of hypokalemia (Table 6.2) can be broadly categorized as (a) reduced dietary intake, (b) increased cellular uptake, (c) increased renal excretion, and (d) excessive GI losses. Inadequate ingestion of K^+ alone is rarely a cause of hypokalemia because of the ubiquitous presence of this cation in foods. More often, diet only contributes to another primary cause of serum K^+ deficiency and rarely causes hypokalemia alone. Hypokalemia may develop from a shift of K^+ into cells from the effects of excessive production of endogenous insulin or catecholamines. Exogenous administration of insulin

TABLE 6-2. Causes of Hypokalemia

Dietary Potassium
Inadequate oral intake (in combination with other factors)
Cellular Uptake of Potassium
Insulin
Catecholamines (β_2-adrenergic) Endogenous catecholamines Epinephrine Dopamine Aminophylline Isoproterenol
Chloroquine intoxication
Metabolic alkalosis
Hypokalemic periodic paralysis
Hypothermia
Cell growth from vitamin B_{12} therapy
Renal Excretion of Potassium
Hyperaldosteronism (primary or secondary)
Corticosteroid excess
High urine flow rate from diuretics
High distal delivery of urine sodium
Renal tubular acidosis
Drugs Amphotericin B Diuretics Aminoglycosides Lithium Cisplatinum, ifosfamide, pemetrexed Some penicillins
Tenofovir, cidofovir, adefovir
Genetic renal diseases Bartter syndrome Gitelman syndrome Liddle syndrome Apparent mineralocorticoid excess syndrome
Gastrointestinal Potassium Loss
Vomiting
Diarrhea
Ostomy losses
Skin Loss of Potassium
Strenuous exercise
Severe heat stress

induces shift of K^+ into cells and precipitates hypokalemia. A classic example is the patient with diabetes mellitus who presents with ketoacidosis and is administered a continuous insulin infusion. Serum K^+ concentration often falls dramatically because of the effect of insulin on cellular K^+ uptake, as well as correction of the hyperosmolar state. β_2-Adrenergic agonists used for asthma (albuterol) or labor (ritodrine) can lower serum K^+ concentration through cell uptake mediated by β_2 receptors. A clinical scenario where hypokalemia may develop from a β_2-adrenergic agonist is the patient with severe asthma who requires frequent nebulized treatments to correct bronchospasm.

Metabolic alkalosis may also promote cell shift of K^+ and precipitate hypokalemia. Typically, this acid–base disorder is precipitated by vomiting and diuretic use, both of which contribute to hypokalemia through renal K^+ losses. Hypokalemic periodic paralysis is an inherited disorder associated with severe hypokalemia from cellular uptake of K^+, a phenomenon often precipitated by stress, exercise, or a large carbohydrate meal. The mutation is in the α_1 subunit of the dihydropyridine-sensitive calcium channel. Hypothermia and chloroquine intoxication are rare causes of hypokalemia secondary to the shift of potassium into cells. Finally, rapid synthesis of red blood cells induced by vitamin B_{12} or iron therapy may cause hypokalemia. This phenomenon occurs because newly formed cells use available K^+ to develop the high intracellular K^+ concentration common to all cells.

Renal K^+ losses contribute significantly to the development of hypokalemia. A number of medications promote K^+ excretion by the kidney via actions in various nephron segments. In proximal tubule, K^+ reabsorption is impaired by different mechanisms. For example, acetazolamide, induces bicarbonaturia and promotes K^+ wasting by blocking carbonic anhydrase. Osmotic diuretics increase flow through the proximal tubule, reducing Na^+ and water reabsorption and thus paracellular K^+ reabsorption. Drugs such as aminoglycosides, cisplatin, ifosfamide, and tenofovir, injure proximal tubular cells and cause K^+ wasting by increasing Na^+ delivery to the distal nephron, enhancing principal cell K^+ secretion. The loop of Henle reabsorbs K^+ via the $1Na^+$-$1K^+$-$2Cl^-$ transporter. Loop diuretics inhibit the function of this transporter and reduce K^+ reabsorption significantly. Aminoglycosides also cause a Bartter-like syndrome with K^+ wasting via stimulation of the calcium

sensing receptor in loop cells and subsequent inhibition of $1Na^+$-$1K^+$-$2Cl^-$ transporter.

In distal tubule, thiazide diuretics block the activity of the Na^+-Cl^- cotransporter, thereby increasing delivery of Na^+ and urine volume to principal cells in CCD. As discussed previously, these luminal effects increase K^+ secretion. Fludrocortisone, a mineralocorticoid agonist, binds the aldosterone receptor and stimulates renal K^+ secretion in principal cells. The antifungal agent amphotericin B causes K^+ loss from the kidney through a rather unique mechanism. Through interactions with membrane sterols, it disrupts cell membranes and allows K^+ to leak out of the principal cell into the urinary space following its diffusional gradient. Primary or secondary hyperaldosteronism, as well as corticosteroid excess, may induce severe hypokalemia through stimulation of mineralocorticoid receptors and associated K^+ secretion in CCD. Primary or acquired forms of renal tubular acidosis (RTA) cause hypokalemia through tubular dysfunction proximally (type 2 RTA) or distally (type 1 RTA). Nonreabsorbable anions, by increasing lumen negative charge, increase the driving force for K^+ secretion in the CCD. These include carbenicillin, hippurate in patients who sniff glue (toluene), and β-hydroxybutyrate in patients with diabetic ketoacidosis.

Inherited renal disorders also cause hypokalemia. In the loop of Henle, various mutations cause dysfunction of the $1Na^+$-$1K^+$-$2Cl^-$ cotransporter, the apical K^+ channel, the basolateral Cl^- channel, or the β subunit (Barttin) that traffics the Cl^- channel to the basolateral membrane. An activating mutation in the calcium sensing receptor on the basolateral membrane of the loop of Henle causes inhibition of ROMK and renal Na^+ and K^+ wasting. Various Bartter syndrome phenotypes accompany each mutation, ultimately leading to K^+ wasting and hypokalemia. A mutation of the gene encoding the thiazide sensitive Na^+-Cl^- cotransporter causes the inherited disorder known as Gitelman syndrome. As seen with a thiazide diuretic, Gitelman syndrome causes renal K^+ wasting and hypokalemia. Liddle syndrome promotes severe hypokalemia by causing overactivity of the epithelial Na^+ channel in the principal cell, an effect that favors unregulated renal potassium secretion. Mutations in subunits of the epithelial Na^+ channel (β and γ) underlies this genetic disorder.

Until recently, the cause for renal potassium wasting associated with hypomagnesemia was unknown. However, a decrease in intracellular magnesium, caused by overall magnesium deficiency, releases magnesium-mediated inhibition of ROMK channels and allows increases in potassium secretion. Along with this effect, an increase in distal sodium delivery or elevated aldosterone levels may be required for significant K wasting in magnesium deficiency. GI losses of K^+, such as vomiting, diarrhea, and excessive ostomy output, may cause excessive K^+ losses from the body. In rare cases, excessive skin K^+ losses from extreme heat or strenuous exercise may cause hypokalemia.

Figure 6.5 describes a practical algorithm to assess the cause of hypokalemia. After excluding pseudohypokalemia and cell shift, hypokalemia is first evaluated by measuring the patient's blood pressure. Hypokalemia associated with hypertension is then classified based on concentrations of renin and aldosterone. In patients with hypokalemia that is associated with normal or low blood pressure, the next step in evaluation entails measuring urinary K^+ concentration to identify renal or extrarenal causes. Finally, acid–base status determines further classification of hypokalemia. Most have hypokalemia that is associated with either a metabolic acidosis or alkalosis.

The clinical manifestations of hypokalemia represent the effects of serum K^+ deficits on action potential generation in excitable tissues, protein synthesis, enzyme function, and regulation of cell pH and volume. Impaired neuromuscular function precipitates a spectrum of clinical findings ranging from muscle weakness to frank paralysis. Respiratory failure results from diaphragmatic muscle weakness while ileus is a GI manifestation of disturbed smooth muscle contractility. Cardiac disturbances include a variety of atrial and ventricular arrhythmias as well as abnormal myocardial contractile function. Arrhythmias that develop from hypokalemia are a major clinical concern as they may be fatal in patients on digoxin or in those with underlying cardiac disease. Renal manifestations of hypokalemia include impaired urinary concentration (polyuria), increased renal ammonia production and bicarbonate reabsorption (perpetuating metabolic alkalosis), and renal failure from either tubular vacuolization (hypokalemic nephropathy) or myoglobinuria (rhabdomyolysis). Finally, other metabolic perturbations associated with hypokalemia include hyperglycemia from decreased insulin release, and impaired hepatic glycogen and protein synthesis.

Treatment of hypokalemia is guided by 2 factors. First, the physiologic effects of the K^+ deficit need to be

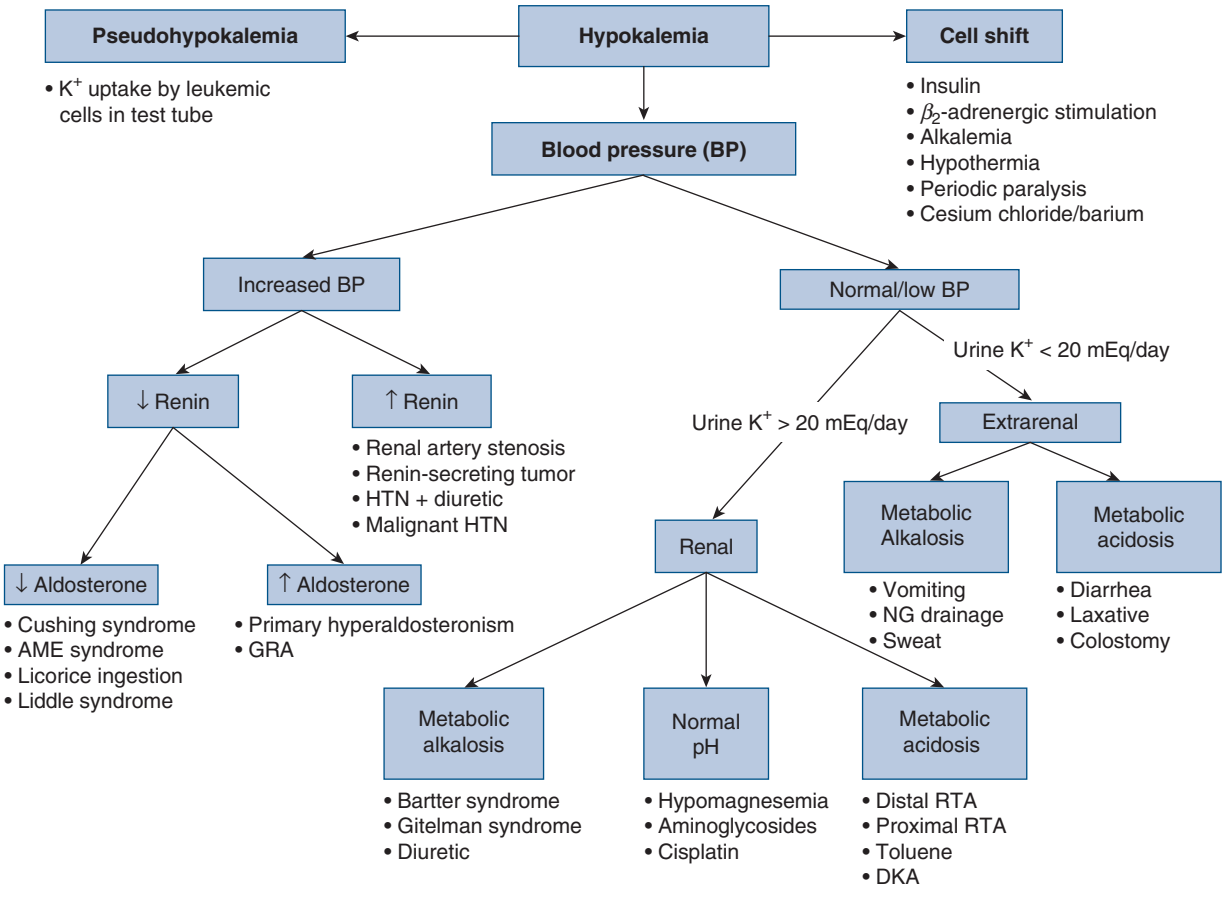

FIGURE 6-5. Clinical algorithm to evaluate hypokalemia. After excluding pseudohypokalemia and cell shift, blood pressure and various serum and urine tests are employed to classify hypokalemia. *Abbreviations:* AME, apparent mineralocorticoid excess; DKA, diabetic ketoacidosis; GRA, glucocorticoid-remediable aldosteronism; HTN, hypertension; NG, nasogastric; RTA, renal tubular acidosis.

determined and, second the cause of hypokalemia (cell shift versus renal or GI excretion) and approximate K^+ deficit need to be estimated. Physiologic effects of hypokalemia are best judged by (a) physical examination of neuromuscular function and (b) electrocardiographic interrogation of the cardiac conduction system. Muscle weakness is often present with significant hypokalemia, while paralysis signals severe hypokalemia. The presence of prominent u waves on the electrrocardiogram (ECG) (Figure 6.6) suggests a serum K^+ concentration in the 1.5 to 2.0 mEq/L range. The K^+ deficit is approximated by the knowledge of the underlying mechanism of hypokalemia (less with cell shift, more with renal/GI losses) and the prevailing serum K^+ concentration. Potassium concentrations in the 3.0 to 3.5 mEq/L range usually represent a total-body deficit in the 200 to 400 mEq range. Correction with oral potassium chloride (KCl: 40 to 80 mEq/day) is preferred with mild-to-moderate deficits such as these. In the 2.0 to 3.0 mEq/L range, K^+ deficits can reach 400 to 800 mEq. Intravenous KCl (20 to 40 mEq/L in 1 L of 0.45 normal saline) at a rate of no more than 20 mEq/h, in addition to oral KCl, is often required to correct severe K^+ deficits. Faster rates may injure veins (sclerosis) and cause cardiac dysrhythmias and must be avoided. Obviously, correction of the underlying etiology of hypokalemia is part of the treatment strategy.

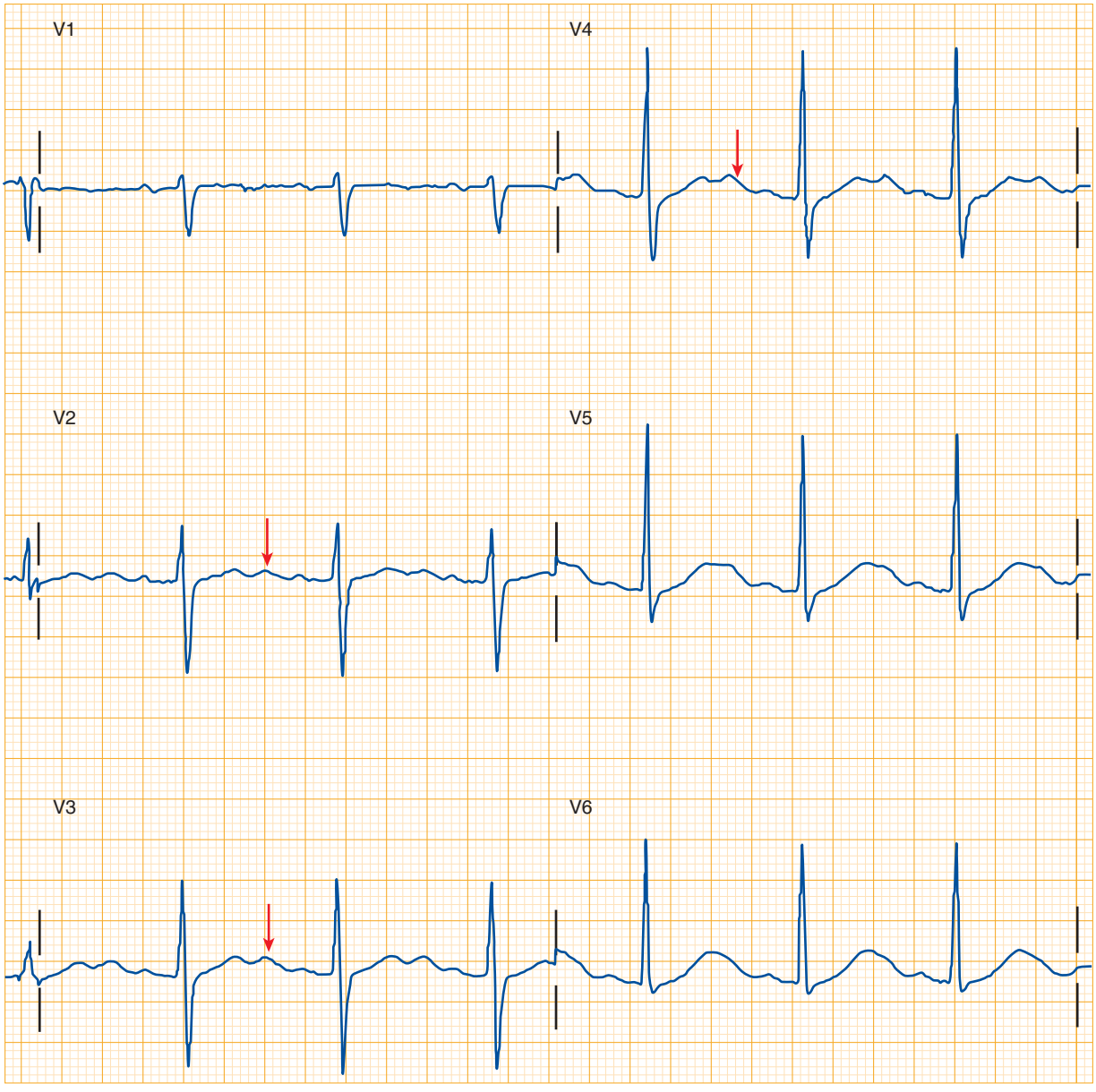

FIGURE 6-6. ECG of a patient with hypokalemia. The presence of prominent u waves on ECG signals profound hypokalemia. The u waves are illustrated by the arrows.

KEY POINTS

Hypokalemia

1. The multiple causes of hypokalemia are related to both disturbances in cellular K^+ homeostasis and renal K^+ excretion. Reduced dietary K^+ intake rarely causes hypokalemia.
2. Clinical manifestations of hypokalemia are primarily a result of neuromuscular and cardiac effects of potassium on excitable cells. Findings include muscle weakness and cardiac arrhythmias.
3. The significance of the total K^+ deficit is determined by the combination of the mechanism of

hypokalemia (cell shift vs. renal/GI K^+ loss) and the serum (or plasma) K^+ concentration.

4. Electrocardiographic evidence of hypokalemia is confirmed by the presence of u waves.
5. Treatment of hypokalemia is determined by severity of the K^+ deficit. Intravenous KCl is given with severe deficits, whereas oral KCl is employed for mild-to-moderate deficits.

Hyperkalemia

Hyperkalemia is defined as a serum (or plasma) K^+ concentration greater than 5.5 mEq/L. Rarely, the serum K^+ concentration may be falsely elevated (pseudohyperkalemia) because of release of K^+ from cells in the test tube. Lysis of cells following prolonged tourniquet application during venipuncture, and release of K^+ from large cell numbers (WBCs >100,000 cells; platelets >1,000,000 platelets) are examples of spurious hyperkalemia. Another cause of a falsely elevated serum K^+ is familial pseudohyperkalemia, which is a relatively rare autosomal dominant inherited condition. In the setting of room temperature, a cell membrane leak of K^+ develops. This repesents temperature-related defect in membrane ion (K^+) channels. As with hypokalemia, causes of hyperkalemia (Table 6.3) are broadly categorized as (a) increased dietary intake, (b) decreased cellular uptake, and (c) decreased renal excretion. Excessive K^+ intake alone does not cause hyperkalemia, but does contribute to other more important causes of K^+ overload, such as those with renal excretory defects. Shift of K^+ from the intracellular space to the ECF occurs in a variety of clinical states. As will be seen, disturbances in insulin, β_2-adrenergic actions, acidemia, and elevations in plasma osmolality all promote the shift of K^+ from ICF to ECF. Deficient concentration of either endogenous or exogenous insulin reduces K^+ entry into cells. This is a frequent cause of hyperkalemia in patients with insulin-dependent diabetes mellitus. Therapy with β_2-adrenergic antagonists (propranolol, labetalol, carvedilol) to treat hypertension and heart disease can raise serum K^+ through inhibition of β_2-receptor-mediated cell uptake. Nonanion gap (mineral) metabolic acidosis also promotes cell shift of K^+ out of cells and hyperkalemia. Hyperkalemic periodic paralysis is an inherited disorder associated with impaired cellular uptake of K^+ and hyperkalemia. The mutation is in the α subunit of the skeletal muscle sodium channel. Hyperosmolality, as develops

TABLE 6-3. Causes of Hyperkalemia

Dietary Potassium
Excessive oral or intravenous intake (in combination with other factors)
Cellular Release of Potassium
Lack of insulin (fasting, diabetes mellitus)
β_2-Adrenergic blockade Propranolol Labetalol Carvedilol
Metabolic acidosis
Hyperkalemic periodic paralysis
Succinylcholine
Hyperosmolality Hyperglycemia Mannitol
Aminocaproic acid, lysine
α-Adrenergic agonist
Phenylephrine
Midodrine
Digoxin toxicity
Cell lysis (hemolysis, rhabdomyolysis, tumor lysis)
Severe exercise
Renal Retention of Potassium
Hypoaldosteronism Hypoadrenalism Hyporeninemic hypoaldosteronism Heparin ACE inhibitors, angiotensin receptor blockers NSAIDs
Low urine flow rate
Low distal delivery of urine sodium
Renal tubular resistance to aldosterone Obstructive uropathy Systemic lupus erythematosis Sickle cell disease
Drugs Amiloride Triamterene Spironolactone, eplerenone, drospirenone Trimethoprim Pentamidine Calcineurin inhibitors

(*continued*)

TABLE 6-3. Causes of Hyperkalemia (Continued)

Genetic renal diseases
Pseudohypoaldosteronism type 1
Pseudohypoaldosteronism type 2 (Gordon syndrome)
Advanced Renal Failure

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal antiinflammatory drugs.

in diabetes mellitus with hyperglycemia and in patients treated with certain hyperosmolar substances (mannitol, dextran, hydroxyethylstarch), can shift K^+ out of cells via solvent drag and elevate serum K^+ concentration. Severe lysis of red blood cells (hemolysis), muscle cells (rhabdomyolysis), and tumor cells (tumor lysis) causes hyperkalemia from massive release of K^+ from these cells.

Decreased K^+ excretion by the kidneys contributes significantly to the development of hyperkalemia. Several medications reduce renal K^+ excretion. The major action of these drugs is to blunt the kaliuretic mechanisms of the principal cell. Drugs such as the nonsteroidal antiinflammatory drugs (NSAIDs) (including selective cyclooxygenase-2 [COX-2] inhibitors), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and heparin, reduce aldosterone synthesis. Spironolactone and eplerenone compete with aldosterone for its steroid receptor and diminish K^+ secretion. Drospirenone, a spironolactone analog used for contraception and premenstrual dysphoric disorder, competitely inhibits aldosterone receptor binding and may cause hyperkalemia in high risk patients (chronic kidney disease [CKD], other drugs that impair renal K^+ excretion). Amiloride, triamterene, trimethoprim, and pentamidine all block the apical Na^+ channel (ENaC) on the principal cell and reduce the electrochemical gradient for K^+ secretion. Inhibition of Na^+-K^+-ATPase by digoxin, cyclosporine, and tacrolimus also impair renal K^+ secretion. Several clinical diseases affect the ability of the kidneys to excrete potassium. Advanced renal failure limits K^+ secretion by reduction in the number of functioning nephrons. Aldosterone deficiency from adrenal dysfunction, diabetes mellitus, or other forms of hyporeninemic hypoaldosteronism also impairs renal K^+ excretion. This has been called a type 4 RTA. Hyperkalemia also develops from tubular resistance to aldosterone or cellular defects in tubular K^+ secretion (obstructive uropathy, systemic lupus erythematosis, and sickle cell nephropathy). Inherited renal disorders such as pseudohypoaldosteronism types 1 and 2 manifest a K^+ secretory defect, hyperkalemia, and hypertension. Finally, limited distal delivery of urinary Na^+ and sluggish urine flow rates, as seen with severe volume depletion may impair K^+ secretion by the principal cell.

Figure 6.7 describes a practical clinical algorithm to assess the cause of hyperkalemia. After excluding pseudohyperkalemia and shift of K^+ out of cells, hyperkalemia is evaluated by measuring urinary K^+ excretion and the transtubular K^+ gradient (TTKG). The TTKG provides a more accurate assessment of the tubular fluid K^+ concentration at the end of the cortical collecting tubule and whether hyperkalemia is a result of a defect in renal excretion or other process. The TTKG is calculated by measuring urinary and plasma K^+ and osmolality (osm), respectively and plugging the values into the following formula:

$$\text{TTKG} = \text{Urine } K^+ \div (\text{urine osm}/\text{plasma osm}) \div \text{plasma } K^+$$

Reduced urine K^+ excretion and a TTKG less than 5 suggest a renal defect in K^+ excretion. Patients who fall into this category are evaluated further by measuring plasma aldosterone and renin concentrations to determine the ultimate cause of hyperkalemia. In hyperkalemic patients, calculation of TTKG may be most useful in distinguishing patients who have mineralocorticoid deficiency *versus* resistance by observing a change in TTKG after administration of physiologic or pharmacologic doses of mineralocorticoid. Those with an elevated K^+ excretion and TTKG greater than 5 are categorized as nonrenal causes of hyperkalemia, as noted in Figure 6.7. The clinical manifestations of hyperkalemia are derived from the pathologic effects of high serum K^+ concentration on the generation of action potentials in excitable tissues, in particular heart and neuromuscular tissues. Hyperkalemia promotes various cardiac conduction disturbances that ultimately effect the rate and rhythm of the heart. These include various atrioventricular (AV) nodal blocks, ventricular tachycardia and fibrillation, and asystole. Myocardial contractility is also impaired in this setting, and contributes to hypotension and shock. Various degrees of muscle weakness and paralysis are also important clinical signs of hyperkalemia.

Hyperkalemia is potentially lethal and must be promptly identified and treated. As with hypokalemia,

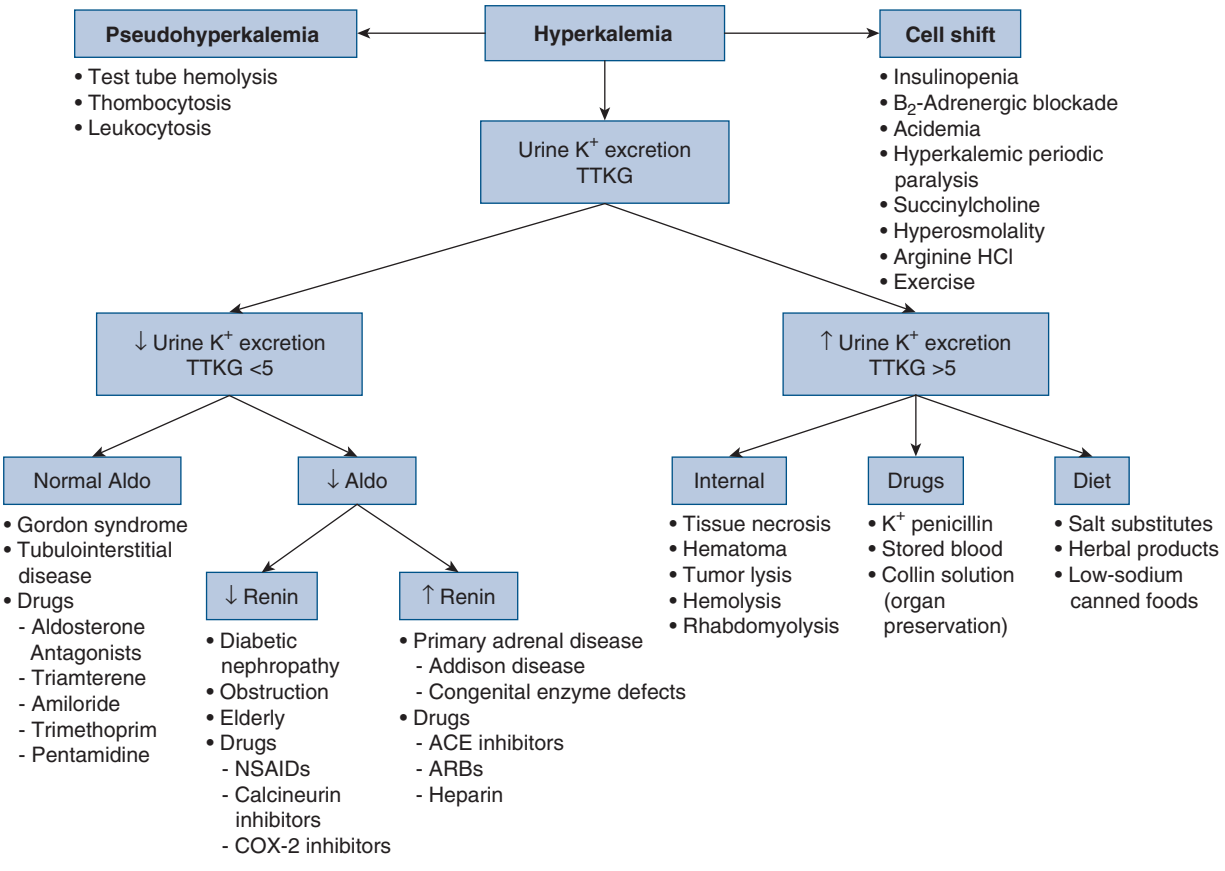

FIGURE 6-7. Clinical algorithm to evaluate hyperkalemia. After excluding pseudohyperkalemia and cell shift, urine K^+ excretion and transtubular potassium concentration gradient (TTKG) are used to initially classify hyperkalemia. Renin and aldosterone are used to further classify renal causes of hyperkalemia. *Abbreviations:* Aldo, aldosterone; ARBs, angiotensin receptor blockers.

treatment of hyperkalemia should be guided by 2 factors. First, the physiologic effects of the excess K^+ state need to be determined and, second the cause of hyperkalemia (cell shift versus impaired renal excretion) should be identified and aggressively treated. Physiologic effects of hyperkalemia are noted by signs of neuromuscular dysfunction and ECG evidence of the cardiac conduction disturbances. Significant hyperkalemia often manifests as muscle weakness of varying severity. Well-characterized ECG changes can suggest the presence of hyperkalemia; however, the ECG should not be used as a tool to diagnose hyperkalemia. One of the earliest ECG changes shown experimentally is tenting of the T waves. As the serum K^+ concentration increases, the QRS complex widens, the p wave disappears, and a sine wave pattern (Figure 6.8) develops, ultimately leading to ventricular fibrillation or asystole. In clinical series; however, the relationship between serum potassium concentration and ECG manifestations is less precise. In a series of 127 patients with serum potassium concentrations ranging between 6 and 9.3 mEq/L, no serious arrhythmias were documented and only 46% of ECGs were noted to have QRS widening, conduction defects, and peaking of T waves. Furthermore, multiple case reports of patients with end-stage renal disease (ESRD) on hemodialysis who, despite significantly elevated potassium levels, do not note significant ECG changes. Consequently, the absence of ECG changes cannot rule out potentially severe and lethal hyperkalemia in hemodialysis patients. Overall, the likelihood of identifying ECG changes increases with increasing levels of potassium and aggressive therapy is required to prevent a fatal outcome (Table 6.4).

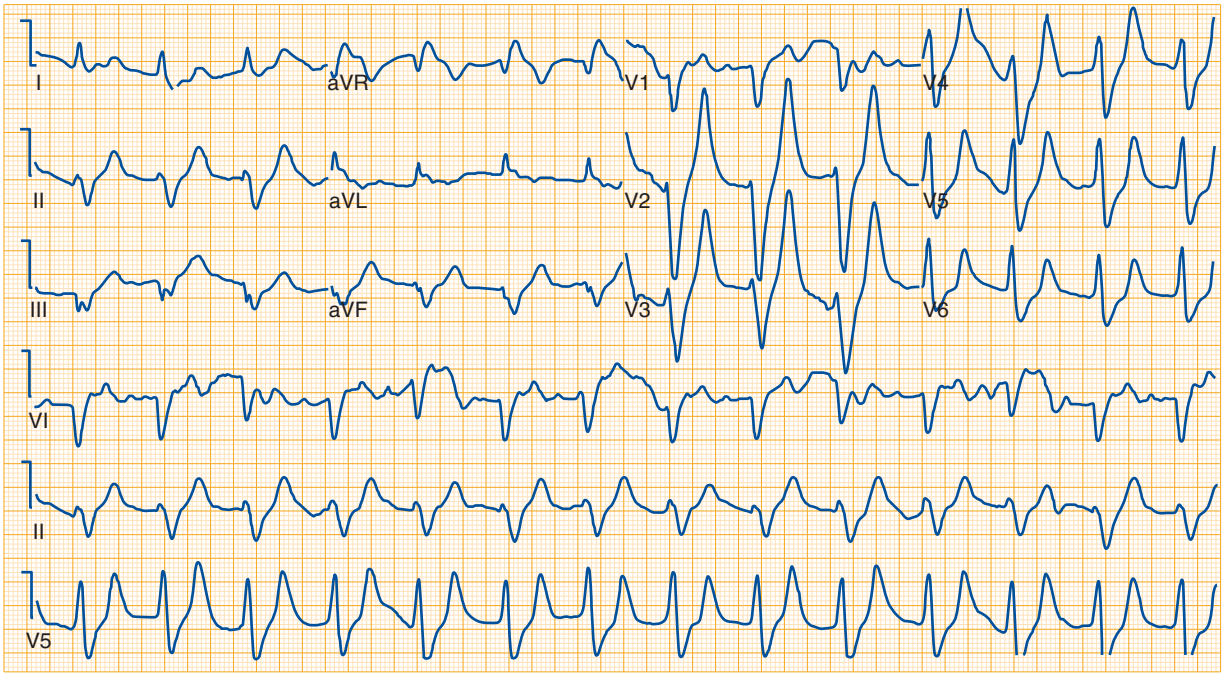

FIGURE 6-8. ECG of a patient with hyperkalemia. Peaked T waves, widening of the QRS complex, and loss of the p wave (shown here) are ECG changes consistent with hyperkalemia. The development of a sine wave indicates imminent cardiac arrest.

TABLE 6-4. Treatment of Hyperkalemia

TREATMENT	DOSE	ONSET	DURATION	MECHANISM
Calcium gluconate (10%)	10 to 20 mL IV	1 to 5 minutes	30 to 60 minutes	Stabilize excitable membranes
Insulin and glucose	10 U of IV insulin and 25 g of glucose	30 minutes	4 to 6 hours	Cell uptake
Albuterol (β_2 agonist)	20 mg in 4 mL of normal saline for nebulization	30 minutes	1 to 2 hours	Cell uptake
Terbutaline (β_2 agonist)	7 µg/kg by subcutaneous injection	10 to 15 minutes	1 to 2 hours	Cell uptake
Sodium bicarbonate	50 to 75 mEq IV	30 to 60 minutes	1 to 6 hours	Cell uptake
Sodium polystyrene sulfonate	30 to 45 g oral	2 to 4 hours	4 to 12 hours	GI excretion
Hemodialysis	1 to 2 mEq/L potassium bath	Immediate	2 to 8 hours from the blood	Removal

Abbreviations: IV, intravenous; U, units.

Treatment of hyperkalemia should include 3 main objectives: stabilize excitable tissues, shift K^+ into cells to lower serum K^+ concentration, and remove K^+ from the body. Stabilization of excitable membranes, in particular cardiac tissues, is the first priority. This is best accomplished by administering intravenous calcium (Ca^{2+}) as either Ca^{2+} gluconate or Ca^{2+} chloride under cardiac monitoring. For patients on digoxin, the calcium should be given as a slower drip. Following Ca^{2+} therapy, the serum K^+ concentration is lowered rapidly employing methods to shift K^+ into cells. Effective therapies include intravenous regular insulin (10 to 20 U) with 25 to 50 g of glucose in nondiabetics (to prevent hypoglycemia). Insulin acts within 30 minutes and lasts approximately 4 to 6 hours. It lowers the serum K^+ concentration by approximately 0.5 to 1.0 mEq/L. High-dose β_2-adrenergic agonists (albuterol 20 mg nebulized) will lower serum K^+ concentration by approximately 0.6 mEq/L within 30 minutes. Its effect lasts for 1 to 2 hours. Terbutaline, another can be administered by subcutaneous injection (7 μg/kg) and produce a K^+-lowering effect superior (~1.3 mEq/L mean reduction) to high-dose nebulized albuterol. In patients who can tolerate a sodium load and who have a severe nonanion gap metabolic acidosis, sodium bicarbonate shifts K^+ into cells.

The cation-exchange resin, sodium polystyrene, is mixed with 33% sorbitol and given orally to increase GI K^+ excretion. Because of colonic necrosis associated with sodium polystyrene-sorbitol, in particular 70% sorbitol, caution is recommended for its use. This agent should not be given as a retention enema and should not be administered to patients with underlying GI diseases, including intestinal surgery and reduced gut motility and obstructive bowel disease. High-dose loop diuretics increase renal K^+ excretion in patients with reasonably good kidney function. Hemodialysis is an efficient modality to quickly remove K^+ from the body in patients with significant renal impairment. Correction of the primary cause of hyperkalemia and adjustment in dietary K^+ intake should also be undertaken.

KEY POINTS

Hyperkalemia

1. Hyperkalemia is caused principally by the combination of disturbances in cellular K^+ uptake and impaired renal K^+ excretion. Excessive dietary K^+ intake contributes to hyperkalemia when renal K^+ excretion is decreased.
2. Clinical manifestations of hyperkalemia are primarily a result of the disruption of the normal generation of the resting membrane potential in excitable tissues. Thus, neuromuscular and cardiac functions are impaired, resulting in muscle weakness and life-threatening cardiac arrhythmias.
3. Electrocardiographic evidence of hyperkalemia is confirmed by the presence of peaked (tented) T waves, widening of the QRS, loss of the p wave, and formation of the ominous sine wave. However, ECG can be normal or lack classic findings in the setting of severe hyperkalemia.
4. Treatment of hyperkalemia is based on the principles of stabilization of excitable cell membranes, shifting of K^+ into cells, and removal of K^+ from the body using native kidneys, colonic excretion, or dialysis.
5. Rapid recognition and treatment of hyperkalemia is required to avoid serious morbidity and mortality.

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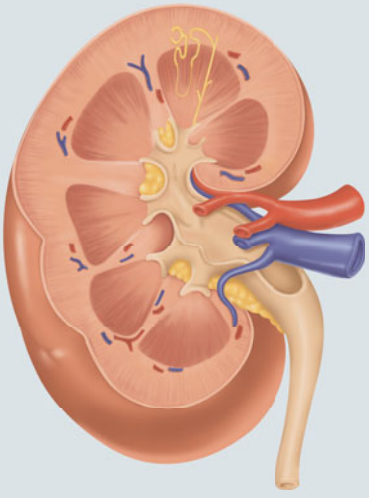

CHAPTER 7

Metabolic Acidosis

• *Adam M. Franks and Joseph I. Shapiro*

Recommended Time to Complete: 2 Days

Guiding Questions

1. Why is evaluation of acid–base status important?
2. What is "buffering?"
3. What determines the pH in the intracellular and extracellular spaces?
4. How does one assess acid–base balance?
5. What processes are involved in renal acid excretion?
6. What stepwise approach can be used to identify acid–base disturbances?
7. What is metabolic acidosis and how does it occur?
8. What are the compensatory mechanisms for metabolic acidosis?
9. What are the biochemical and physiologic effects of metabolic acidosis?
10. What is the serum anion gap (SAG) and how is it used in the differential diagnosis of metabolic acidosis?
11. What is the urine anion gap and what is it used for?
12. How does one diagnostically approach metabolic acidosis?
13. What is the treatment of metabolic acidosis?

ACID–BASE CHEMISTRY AND BIOLOGY

Acid–base disorders are one of the most common problems encountered by the clinician. Although the degree of acidosis or alkalosis that results is rarely life threatening, the careful evaluation of the patient's acid–base status often provides insight into the underlying medical problem. Moreover, the pathophysiology and differential diagnosis of these disorders can be approached logically with a minimum of laboratory and clinical data. Without exaggeration, we would say that analysis of the acid–base disturbance makes one's clinical approach to a patient substantially easier. In Chapters 7 to 9, we summarize the "physiologic approach" to acid–base disorders, which we believe is simple, logical, and clinically relevant. Acid–base homeostasis consists of the precise regulation of CO_2 tension by the respiratory system and plasma bicarbonate (HCO_3^-) concentration [HCO_3^-] by the kidney. The kidney regulates the plasma [HCO_3^-] by altering HCO_3^- reabsorption and elimination of protons (H^+). The pH of body fluids is determined by CO_2 tension and [HCO_3^-]. These body fluids can generally be readily sampled and analyzed with a blood gas instrument that determines CO_2 tension (in arterial blood, $PaCO_2$), pH, and [HCO_3^-], the latter that

is generally calculated (see below). Primary abnormalities of CO_2 tension are considered respiratory disturbances, whereas primary derangements of $[HCO_3^-]$ are referred to as metabolic disturbances.

Understanding clinical acid–base chemistry requires an appreciation of buffers. For diagnostic purposes, we can define an acid as a chemical that donates a H^+, and a base as a H^+ acceptor. For an acid (HA) and its conjugate base (A^-), we describe its strength (or tendency to donate a H^+) by its dissociation constant K_{eq} and the formula:

$$[HA] = K_{eq} \times [H^+][A^-] \qquad \text{(Eq. 1)}$$

If we rearrange this equation and apply a log transformation, we arrive at the following:

$$pH = pK + \log_{10} \frac{[A^-]}{[HA]} \qquad \text{(Eq. 2)}$$

We use the term *buffering* to describe the capacity of a solution to resist a change in pH when a strong (ie, highly dissociated) acid or alkali is added. As a concrete example, say we added 100 mL of 0.1 M HCl to 900 mL of distilled water. The $[H^+]$ of what was previously distilled water would increase from 10^{-7} to 10^{-2} M. In other words, the pH would fall from 7.0 to 2.0. In contrast, if we added 100 mL of 0.1 M HCl to 900 mL of a 1 M phosphate *buffer* (pK = 6.9 at pH 7.0), most of the dissociated H^+ from HCl would associate with dibasic phosphate (HPO_4^{2-}) and the ratio of dibasic to monobasic ($H_2PO_4^-$) phosphate would only be slightly changed. As a result, the pH would fall by only 0.1. In this latter example, the hydrochloric acid (HCl) was *buffered* by the phosphate solution, whereas in the case where HCl was added to distilled water, no such buffering occurred.

In higher animals, such as mammals, the most important buffer in the extracellular space is the bicarbonate buffer system. Inorganic phosphate and proteins are less important buffers in the extracellular space. In the intracellular space inorganic phosphate is quantitatively the most important buffer followed by bicarbonate and intracellular proteins (Figure 7.1). Although intracellular pH (pHi) is probably more important in predicting physiologic and clinical consequences than extracellular pH, it is extremely difficult to measure in vivo. Because extracellular acid–base status is still informative, we focus our clinical efforts on classifying disease states using this information, which can readily be obtained. Specifically, we focus our attention on the bicarbonate buffer system (Figure 7.1). It is generally assumed that equilibrium conditions apply to the bicarbonate buffer system in blood

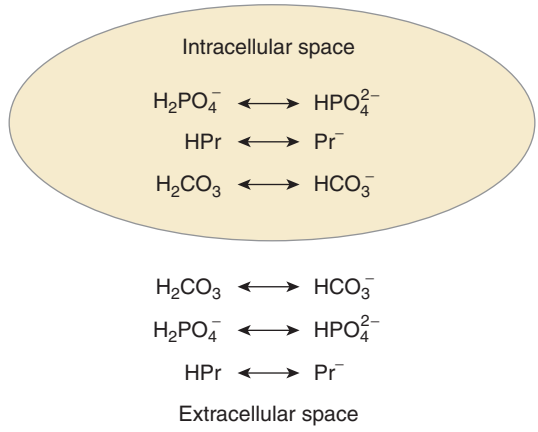

FIGURE 7-1. Relative importance of different buffers in intracellular and extracellular spaces. Note that in the intracellular space, phosphate and proteins play a greater role than they do in the extracellular space, where the bicarbonate buffer system is most important.

because of the abundance of carbonic anhydrase (CA) in red blood cells and the high permeability of the red blood cell membrane to components of the bicarbonate buffer system. Therefore, we can express the following equations:

$$H^+ + HCO_3^- \xrightarrow{K_{eq}} H_2CO_3 \qquad \text{(Eq. 3)}$$

or

$$[H^+] = K_{eq} \times \frac{[H_2CO_3]}{[HCO_3^-]} \qquad \text{(Eq. 4)}$$

Furthermore, H_2CO_3 is defined by the partial pressure of CO_2 and the solubility of CO_2 in physiologic fluids that is, for all intents and purposes, a constant *S*. We can, therefore, rearrange Equation 4 to read:

$$[H^+] = K \times \frac{S \times PCO_2}{[HCO_3^-]} \qquad \text{(Eq. 5)}$$

Taking the antilog of both sides we get:

$$pH = pK + \log_{10} \frac{[HCO_3^-]}{S \times PCO_2} \qquad \text{(Eq. 6)}$$

which is called the *Henderson-Hasselbalch equation*. In blood (at 37°C), the *pK* referred to in Equation 6 is 6.1 and the solubility coefficient for CO_2 (*S*) is 0.03. Therefore, we can simplify this expression to:

$$pH = 6.1 + \log_{10} \frac{[HCO_3^-]}{0.03 \times PaCO_2} \qquad \text{(Eq. 7)}$$

This formula allows us to view acid–base disorders as being attributable to the numerator of the ratio (metabolic processes), the denominator (respiratory processes), or both (mixed or complex acid–base disorders).

KEY POINTS

Acid–Base Chemistry and Biology

1. Evaluation of acid–base status provides insight into underlying medical problems.
2. Many cellular functions are dependent on optimum pH of body fluids.
3. The pH is defined as the negative logarithm of $[H^+]$.
4. Interplay among body buffers, lungs, and kidneys is responsible for maintaining pH within normal limits.
5. The most important buffer in the extracellular space is bicarbonate and in the intracellular space is inorganic phosphate.
6. Lungs excrete CO_2 and kidneys excrete H^+s to maintain serum bicarbonate and pH in the normal range.

ASSESSING ACID–BASE BALANCE

A myriad of enzymatic reactions involve the loss or gain of protons that occur with ongoing catabolism and anabolism. To understand whether acid or base is produced, however, one simply examines the initial substrates and final products. To do this, it is helpful to think of acids and bases as "Lewis" acids and bases; in other words, to consider acids as electron acceptors rather than as proton donors. In concrete terms, when a substrate is metabolized to something more anionic (eg, glucose is metabolized to lactate through the Embden-Meyerhof glycolytic pathway), acid is generated. Conversely, if a substrate is metabolized to something more cationic (eg, lactate is metabolized to CO_2 and H_2O via the tricarboxylic acid [TCA] cycle), acid is consumed (Figure 7.2). Because of the importance of the bicarbonate buffer system in overall acid–base homeostasis, we generally consider the addition of a proton as equivalent to the decrease in total-body HCO_3^- and loss of a proton as a gain in HCO_3^-.

The classic normal values for an arterial blood gas are pH: 7.4; $[HCO_3^-]$: 24 mEq/L; and $PaCO_2$: 40 mmHg. The kidneys regulate serum $[HCO_3^-]$ and acid–base balance by reclaiming filtered HCO_3^- and generating new HCO_3^- to replace that lost internally in titrating metabolic acid and externally (eg, from the gastrointestinal tract). Approximately 1 mmol of H^+/kg body weight per day is generated from the metabolism of a normal "Western diet." To maintain acid–base homeostasis, the kidney must excrete this acid load. The role of the kidney in acid–base homeostasis can be divided into 2 basic functions: (a) the reabsorption of filtered bicarbonate; and (b) the excretion of the acid load derived from dietary metabolism.

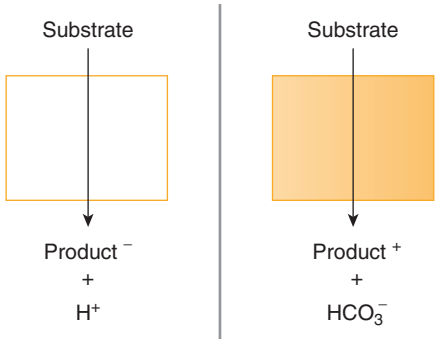

FIGURE 7-2. "Black box" approach to acid–base metabolism. The left panel shows that when a substrate is metabolized to a more electronegative product, a proton is generated. Conversely, the right panel demonstrates that when a substrate is metabolized to a more electropositive product a proton is consumed and a bicarbonate generated.

KEY POINTS

Assessing Acid–Base Balance

1. When a substrate is metabolized to something more anionic (eg, glucose is metabolized to lactate through the Embden-Meyerhof glycolytic pathway), acid is generated.
2. If a substrate is metabolized to something more cationic (eg, lactate is metabolized to CO_2 and H_2O via the TCA cycle), acid is consumed.
3. The kidneys regulate serum $[HCO_3^-]$ and acid–base balance by reclaiming filtered HCO_3^- and generating new HCO_3^- to replace that lost internally in titrating metabolic acid and externally (eg, from the gastrointestinal tract).

ACID EXCRETION BY THE KIDNEY

Our understanding of renal acid excretion has evolved considerably in the past decade. In particular, we have identified the specific ion pumps and transporters that

are involved in tubular proton secretion in different portions of the nephron. It is clear that the major ion transporters and pumps include the sodium-proton exchanger (Na^+-H^+ exchanger, which exchanges 1 H^+ for 1 sodium ion), the sodium-phosphate cotransporter (which transports 3 sodium ions with 1 HPO_4^{2-} molecule), and the vacuolar H^+-adenosine triphosphatase (ATPase) (which pumps H^+ directly into the tubular lumen). Other important transport proteins include chloride-bicarbonate exchangers, the "colonic" H^+-K^+-ATPase, and the Na^+-K^+-ATPase. These transport proteins are expressed to varying degrees in different cell types and nephron segments of the kidney, depending on the specific functions of these cells.

Regarding overall acid–base handling by the kidney, there is a strong relationship between acid secretion and the reclamation of filtered bicarbonate, as well as the production of new bicarbonate by the kidney as one would anticipate based on our earlier discussion. First, plasma is filtered at the glomerulus and HCO_3^- enters the tubular lumen. Each HCO_3^- molecule that is reclaimed requires the epithelial secretion of one H^+. This H^+ secretion occurs via the Na^+-H^+ exchanger on the luminal membrane or through an electrogenic H^+-ATPase. On an integrated physiologic level, we can think of the HCO_3^- reabsorption processes establishing a *plasma threshold* for bicarbonate; that is, that level of plasma HCO_3^- at which measurable HCO_3^- appears in urine. This concept of a *plasma threshold* is well established for renal glucose handling; historically, the appearance of glucose in urine was used as a surrogate for elevated blood glucose levels before blood glucose monitoring became widespread. Continuing this analogy to renal glucose handling, we can also define the maximal net activity of tubular HCO_3^- reabsorption as the T_{max}. The T_{max} and plasma threshold for HCO_3^- are, of course, intimately related. As the T_{max} for HCO_3^- increases, the plasma threshold for HCO_3^- increases. Conversely, decreases in T_{max} result in decreases in the plasma threshold. Quantitatively, to eliminate HCO_3^- from urine with a glomerular filtration rate of 100 mL/min and a plasma [HCO_3^-] of 24 mEq/L, the tubules must secrete about 2.4 mmol of H^+ per minute. Ergo, HCO_3^- reclamation by the tubules involves a considerable amount of H^+ secretion.

Bicarbonate reclamation is closely related to sodium reabsorption and is, therefore, sensitive to a number of other influences that impact sodium reabsorption. In particular, states of extracellular fluid (ECF) volume expansion and decreases in PCO_2 decrease the apparent T_{max} for HCO_3^-, whereas ECF volume contraction and increases in the partial pressure of carbon dioxide (PCO_2) increase the apparent T_{max} for HCO_3^-. Parathyroid hormone inhibits proximal tubule HCO_3^- reabsorption and lowers the apparent T_{max} and plasma threshold for HCO_3^-. The majority of HCO_3^- reabsorption (approximately 80% to 90%) takes place in proximal tubule. The enzyme CA is expressed intracellularly, as well as on the luminal membrane of the proximal tubule cell, which allows the secreted H^+ to combine with tubular fluid HCO_3^- to form carbonic acid (H_2CO_3). This H_2CO_3 rapidly dissociates to form H_2O and CO_2, which then can reenter the proximal tubule cell. Intracellularly, water dissociates into H^+ and OH^-. Intracellular CA catalyzes the formation of HCO_3^- from CO_2 and OH^-. Bicarbonate leaves the cell via several bicarbonate transport proteins, including the sodium-bicarbonate cotransporter, as well as the Cl^--HCO_3^- exchanger. In proximal tubule, where the reclamation of HCO_3^- filtered from the blood occurs, HCO_3^- is formed inside the renal tubular cells when either H^+ secretion or ammonium (NH_4^+) synthesis occurs. The HCO_3^- is then transported back into blood predominantly via the basolateral Na^+-$3HCO_3^-$ cotransporter.

Proton secretion by distal nephron is aided by the production of an electrogenic gradient. This gradient, which is produced by removal of sodium from the luminal fluid in excess to anion reabsorption, favors H^+ secretion. There is also direct pumping of H^+ into the tubular lumen. Na^+-H^+ exchange, as well as the activities of the vacuolar H^+-ATPase and the Na^+-K^+-ATPase in intercalated and principal cells accomplish these tasks. Chloride exchange with bicarbonate on the basolateral side of these distal tubular cells allows for proton secretion to be translated into bicarbonate addition to blood, as discussed earlier. The epithelial membrane in the distal nephron must not allow backleak of H^+ or loss of the electrogenic gradient. Under normal circumstances, urine pH can be as low as 4.4. This represents a 1000:1 gradient of [H^+] between the cell and tubular lumen.

Net acid excretion (NAE) is the total amount of H^+ excreted by the kidneys. Quantitatively, we can calculate NAE to be the amount of H^+ (both buffered and free) excreted in urine minus the amount of HCO_3^- and citrate that failed to be reclaimed. Because H^+ secretion into the tubule lumen results in a 1:1 HCO_3^- addition to the ECF, NAE equals the amount of new HCO_3^- generated.

NAE is accomplished through 2 processes that are historically separated on the basis of a colorimetric indicator (phenolphthalein) that detects pH changes effectively between pH 5 and 8. That acid, which can be detected by titrating sufficient alkali into urine to achieve color changes with this indicator, is called *titratable acid* and is

mostly phosphate in the $H_2PO_4^-$ form. Nontitratable acid excretion occurs primarily in the form of NH_4^+. This form of acid excretion is not detected by phenolphthalein since the pK (ionization constant of acid; approximately 9) for NH_4^+ is too high. Even though most clinicians equate NAE with an acidic urine, it is important to recognize that a low urine pH does not necessarily mean that NAE is increased. For example, at a urine pH of 4.0, the free H^+ concentration is only 0.1 mmol. In a 70-kg person on an average Western diet, one can see that free protons would make up only a small fraction of the approximately 70 mmol of net acid that need to be excreted per day. The majority of NAE is in the form of protons bound to buffers, either phosphate or NH_4^+. This makes it possible to elaborate a much-less-acid urine but still achieve adequate NAE. In fact, there are several pathologic conditions (discussed later) in which the urine pH is relatively acid but NAE is insufficient. In subjects that consume a typical Western diet, adequate NAE occurs through the hepatic synthesis of glutamine, which is then taken up by the proximal tubule, where it is deaminated to synthesize NH_4^+ (which generates HCO_3^-), as well as H^+ and NH_4^+ secretion in the distal and collecting tubules.

NAE is influenced by several factors, including the serum potassium concentration (serum K^+ elevations decrease NH_4^+ excretion, while decreases enhance distal nephron H^+ secretion), $PaCO_2$ (see below), and the effects of aldosterone. Quantitatively, NAE is usually evenly divided between titratable acid and NH_4^+ excretion.

However, our capacity to increase NAE is mostly dependent on enhanced ammoniagenesis and NH_4^+ excretion. The older view that NH_4^+ excretion was accomplished by simple passive trapping of NH_4^+ in the tubular lumen has been revised. We now understand that the excretion of NH_4^+ is more "active." First, hepatic synthesis of glutamine is sensitive to a number of factors including protein absorption from the gastrointestinal (GI) tract. This is probably why patients on total parenteral nutrition may develop metabolic acidosis unless they receive supplemental base-generating substrate such as acetate. In proximal tubule cells, there is deamination of glutamine to form alpha-ketoglutarate (αKG) and two NH_4^+. The further metabolism of αKG to CO_2 and H_2O generates 2 new HCO_3^- molecules. Proximal tubule cells actively secrete NH_4^+ into the lumen, probably via the luminal Na^+-H^+ exchanger. NH_4^+ can substitute for H^+ and be transported into the urine in exchange for sodium. NH_4^+ is subsequently reabsorbed in the medullary thick ascending limb of Henle where it can be transported, instead of K^+, via the Na^+-K^+-$2Cl^-$ cotransporter. This increases medullary interstitial concentrations of NH_4^+. Interstitial NH_4^+ enters the collecting duct cell, substituting for K^+ on the basolateral Na^+-K^+-ATPase. The NH_4^+ is next secreted into the tubular lumen, possibly by substitution for H^+ in the apical Na^+-H^+ exchanger or H^+-K^+-ATPase, and is ultimately excreted into the final urine. Alternatively the nonerythroid proteins RhBg and RhCg may act as NH_4^+-H^+ exchangers in the basolateral and luminal membranes, respectively. It is important to note that the net generation of any HCO_3^- from αKG metabolism is dependent on this excretion of NH_4^+. Quite simply, if this NH_4^+ molecule is not excreted in urine, it is returned via the systemic circulation to the liver, where it will be used to form urea at the expense of generating 2 H^+s. In this case, the HCO_3^- molecules that were generated by the metabolism of αKG are neutralized and no net generation of HCO_3^- results.

Because routine clinical measurement of urinary NH_4^+ concentrations never became standard, our appreciation of NH_4^+ in net acid–base balance during pathophysiologic conditions was delayed until surprisingly recently; however, assessment of NH_4^+ is key in understanding NAE. It turns out that urinary $[NH_4^+]$ is estimated by calculations based on urinary electrolyte concentrations (either urinary anion gap or urinary osmolar gap) that are routinely measured. This is discussed later in this chapter.

KEY POINTS

Acid Excretion by the Kidney

1. Each HCO_3^- reclaimed from the proximal tubular lumen requires the epithelial secretion of one H^+. Largely, a Na^+-H^+ exchanger on the luminal membrane accomplishes this, although an electrogenic H^+-ATPase is also involved.
2. NAE by the kidney is the amount of H^+ (both buffered and free) excreted in the urine minus the amount of HCO_3^- and citrate excreted in the urine.
3. NAE is accomplished primarily through elimination of titratable acid (which is mostly phosphate) and nontitratable acid (in the form of NH_4^+).
4. NH_4^+ excretion is dependent on the hepatic synthesis of glutamine, as well as glutamine deamination and urinary NH_4^+ secretion and trapping.
5. An acidic urine (low urine pH) does not necessarily mean that NAE is increased.
6. Proton secretion by distal nephron is facilitated by the production of an electrogenic gradient that is produced by removal of sodium from the luminal fluid.

CLINICAL APPROACH TO THE PATIENT WITH AN ACID–BASE DISORDER

The approach to acid–base disorders often confounds practitioners of medicine; however, if one follows a fairly standard approach, acid–base disorders can be dissected fairly easily. We suggest 7 steps when confronting a suspected acid–base disorder. The information necessary to approach a suspected acid–base disorder involves a blood gas (which gives pH, partial pressure of arterial oxygen [PaO_2], $PaCO_2$, and calculated [HCO_3^-] values) and serum chemistry panel (which gives serum Na^+, K^+, Cl^-, and total CO_2 content). It is these data on which subsequent decisions are based. The total CO_2 content (TCO_2), which is the sum of the serum [HCO_3^-] and dissolved CO_2 (usually determined on a venous serum sample), is often referred to as the "CO_2"; however, it must not be confused with the $PaCO_2$, which refers to the partial pressure of CO_2 in arterial blood. Since the serum [HCO_3^-] or TCO_2 includes a component of dissolved CO_2, it is often 1 to 2 mEq/L higher than the calculated [HCO_3^-] derived from arterial blood gases. The 7 steps are:

1. What is the blood pH (is the patient acidemic or alkalemic)? Based on a normal sea level pH of 7.40±0.02, a significant decrease in pH or acidemia means that the primary ongoing process is an acidosis. Conversely, an increase in pH or alkalemia indicates that the primary ongoing process is an alkalosis.
2. What is the primary disturbance? To identify the primary disturbance, one must examine the directional changes of $PaCO_2$ and serum [HCO_3^-] from normal. If pH is low and [HCO_3^-] is low, then metabolic acidosis is the primary disturbance. Conversely, if pH is high and [HCO_3^-] is high, then metabolic alkalosis is the primary disturbance.
3. Is compensation appropriate? This step is essential for one to understand whether the disturbance is simple (compensation appropriate) or complex (mixed). With metabolic acidosis, the $PaCO_2$ (in mmHg) must decrease; conversely, with metabolic alkalosis, the $PaCO_2$ must increase. Inadequate compensation is equivalent to another primary acid–base disturbance. It is important to recognize that compensation is never complete; compensatory processes cannot return one's blood pH to what it was before one suffered a primary disturbance.
4. What is the SAG (discussed in detail later in this chapter)? Calculating the SAG provides insight into the differential diagnosis of metabolic acidosis (anion gap and nonanion gap metabolic acidosis) and can also indicate that metabolic acidosis is present in the patient with an associated metabolic alkalosis.
5. How does the change in SAG compare to the change in serum bicarbonate concentration (discussed more fully in Chapter 9)? If the change in the SAG is much larger than the fall in serum bicarbonate concentration, one can infer the presence of both an anion gap metabolic acidosis and metabolic alkalosis. If the fall in serum bicarbonate concentration is, however, much larger than the increase in the SAG (and the SAG is significantly increased), one can infer the presence of both an anion gap and nonanion gap metabolic acidosis.
6. What is the underlying cause of the disturbance? Identifying the underlying cause of the disturbance is the whole purpose of analyzing acid–base disorders. One must remember that acid–base disorders are merely laboratory signs of an underlying disease. The pathologic cause of the acid–base disorder is usually obvious once the individual primary disturbances are identified.
7. What is the appropriate therapy to initiate? The acid–base disturbance must be directly addressed in several clinical situations. Ultimately, treatment of the underlying cause with the appropriate therapy is most important.

METABOLIC ACIDOSIS

Pathophysiologic Mechanisms and Compensation

Metabolic acidosis is characterized by a primary decrease in [HCO_3^-]. This systemic disorder may occur in several ways:

1. Addition of a strong acid that consumes HCO_3^-.
2. Loss of HCO_3^- from the body (usually through the GI tract or kidneys).
3. Rapid addition of nonbicarbonate-containing solutions to ECF, also called *dilutional acidosis*.

In the latter 2 situations, in which HCO_3^- is lost or diluted, an organic anion is not generated. In this case, electroneutrality is preserved by reciprocal increases in serum chloride concentration. These forms of metabolic acidosis are generally referred to as *hyperchloremic*

or *nonanion gap metabolic acidosis*; however, when an organic acid consumes HCO_3^-, the organic anion that is produced is often retained in ECF and serum. In this circumstance, the serum chloride concentration does not increase. This important concept is discussed in detail below.

The first line of defense against the fall in pH resulting from metabolic acidosis is the participation of buffer systems. This always occurs to some degree. As a general rule, nonbicarbonate buffers buffer about one-half of an acid load; however, with more severe acidosis, the participation of nonbicarbonate buffers can become even more important. Bone contributes importantly to buffering in chronic metabolic acidosis. The attendant calcium loss from bone that results in reduced bone density and increased urinary calcium excretion are major deleterious consequences of chronic metabolic acidosis.

The second line of defense is the respiratory system. The $PaCO_2$ declines in the setting of metabolic acidosis. This is a normal, compensatory response. Failure of this normal adaptive response indicates the concomitant presence of respiratory acidosis. An excessive decline in $PaCO_2$, producing a normal pH, indicates the presence of concomitant respiratory alkalosis. Both situations are considered to be complex or mixed acid–base disturbances (see Chapter 9). The respiratory response to metabolic acidosis is mediated primarily by pH receptors in the central nervous system (CNS). Peripheral pH receptors probably play a smaller role. This explains the small time delay prior to the establishment of respiratory compensation observed in animals and humans subjected to experimental metabolic acidosis. The normal, compensatory fall in $PaCO_2$ (in mmHg) should be between 1 and 1.5 times the fall in serum $[HCO_3^-]$ (in mEq/L). Even with extremely severe metabolic acidosis; however, the $PaCO_2$ cannot be maintained below 10 to 15 mmHg.

The kidney provides the third and final line of pH defense. This mechanism is, however, relatively slow compared to the immediate effect of buffering and respiratory compensation, which begins within 30 minutes. In contrast, the renal response requires 3 to 5 days to become complete. In the presence of normal renal function, acidosis induces increases in NAE by the kidney. This increase in NAE is primarily a result of increases in NH_4^+ excretion rather than the minimal changes in phosphate (titratable acid) excretion. Acidosis increases the deamination of glutamine that generates NH_4^+. Excretion of the NH_4^+ and the ultimate catabolism of αKG, leads to generation of new HCO_3^-. In fact, there is both transcriptional and translational upregulation of key enzymes involved in glutamine metabolism that are induced by acidosis. Chronic metabolic acidosis also increases renal endothelin 1 that activates the Na^+-H^+ exchanger on the proximal tubule brush border. Therefore, acidosis induces both the generation of new HCO_3^- via the glutamine system and the enhancement of HCO_3^- reabsorption and titratable acid formation. Interestingly, the decreases in $PaCO_2$ that occur from respiratory compensation, actually limit renal correction in metabolic acidosis.

KEY POINTS

Metabolic Acidosis

1. Metabolic acidosis is a systemic disorder characterized by a primary decrease in serum $[HCO_3^-]$.
2. This occurs in 3 ways: the addition of strong acid that is buffered by (ie, consumes) HCO_3^-; the loss of HCO_3^- from body fluids, usually through the GI tract or kidneys; and the rapid addition to the ECF of nonbicarbonate-containing solutions (dilutional acidosis).
3. In hyperchloremic or normal anion gap metabolic acidosis no organic anion is generated.
4. Organic anions are generated when an organic acid consumes bicarbonate leading to increased anion gap metabolic acidosis.
5. Fall in $PaCO_2$ is a normal compensatory response to simple metabolic acidosis.
6. Increases in NAE by the kidney develop in response to metabolic acidosis. The increase in NAE is mostly a result of increases in NH_4^+ excretion that take up to 5 days to become maximal.

BIOCHEMICAL AND PHYSIOLOGIC EFFECTS OF METABOLIC ACIDOSIS

In the short term, mild degrees of acidemia are often well tolerated. In fact, some physiologic benefit, such as increased P_{50} for hemoglobin favoring O_2 delivery to tissues, occurs. If acidosis is severe (pH <7.10); however, myocardial contractility and vascular reactivity are depressed; in this setting, hypotension often progresses to profound shock. These consequences of acidosis result from well described molecular mechanisms. First,

acidosis depresses both vascular and myocardial responsiveness to catecholamines. In the case of the vasculature, supraphysiologic concentrations of catecholamines may restore reactivity, but the myocardial depression created by acidosis will eventually overcome this effect as pH continues to fall.

Metabolic acidosis induces an intracellular acidosis, and this appears to be particularly deleterious to physiologic function in cardiac myocytes. In addition, metabolic acidosis impairs the ability of cardiac myocytes to use energy. Some of this results from a blockade of glycolysis at the level of phosphofructokinase, but direct inhibition of mitochondrial respiratory function also occurs. On a physiologic level, intracellular acidosis impairs contractile responses to normal and elevated cytosolic calcium concentrations. Specifically, intracellular acidosis significantly shifts the sensitivity of troponin C to calcium. Perhaps even more important, acidosis induces impairment of actin-myosin crossbridge cycling. This results directly from increases in inorganic phosphate concentration in the monovalent form ($H_2PO_4^-$). This increase in $H_2PO_4^-$ results both from the acidic environment, as well as an impairment of myocardial energy production that increases the total intracellular concentration of inorganic phosphate. Metabolic acidosis and hypoxia synergistically impair myocardial myocyte metabolism, a phenomenon consistent with the monovalent inorganic phosphate hypothesis.

With mild degrees of acidosis, it may be difficult to discern an increase in ventilatory effort. More severe metabolic acidosis, pH less than 7.2, increases the ventilatory effort. This is readily apparent as respirations become extremely deep and rapid, a clinical sign known as *Kussmaul respiration*. Mild degrees of acidosis do not markedly impair hemodynamic stability in subjects with otherwise normal cardiovascular function, but severe metabolic acidosis often leads to hypotension, pulmonary edema, and, ultimately, ventricular standstill. Bone effects of even mild chronic metabolic acidosis are prominent. This acid–base disturbance leaches calcium from bone, resulting in hypercalciuria and bone disease. Treatment of renal tubular acidosis (RTA) or the acidosis of chronic kidney disease hinges on these important effects.

Decreased blood pH (acidemia), serum [HCO_3^-] (primary response), and $PaCO_2$ (compensatory response) are the laboratory findings that are the hallmark of simple metabolic acidosis. We reiterate that if the $PaCO_2$ does not fall by 1 to 1.5 times the decline in serum [HCO_3^-], this implies the coexistence of respiratory acidosis. We would argue that the profound clinical implications of this make this more than a semantic argument. It is, in fact, common for subjects with profound metabolic acidosis to eventually tire of their extraordinary respiratory effort. In this setting, the $PaCO_2$ rises to a level consistent with inadequate compensation, often just prior to respiratory arrest. Ergo, this must be considered as respiratory acidosis in order to mobilize the appropriate, emergent clinical response (see Chapter 9). Normal or increased serum potassium in the face of decreased total-body potassium stores occurs commonly with metabolic acidosis. This occurs because acidosis shifts potassium from the intracellular fluid to the ECF and renal potassium excretion increases in many states of metabolic acidosis. As is discussed in the next section, metabolic acidosis is classified as an anion gap (organic) or nonanion gap (hyperchloremic) metabolic acidosis. In general, metabolic acidosis states are characterized by the retention of an organic anion generated in concert with HCO_3^- consumption (organic acidosis) and others are not (hyperchloremic). As screening of serum for such organic anions is not practical on a routine, immediate basis, a calculation performed on the serum electrolytes called the anion gap is employed.

KEY POINTS

Biochemical and Physiologic Effects of Metabolic Acidosis

1. With marked acidemia (pH <7.10), myocardial contractility is depressed and peripheral resistance falls.
2. Acidosis depresses both vascular and myocardial responsiveness to catecholamines, as well as innate myocardial contractility. Both myocardial β-receptor densities, as well as physiologic responses to β-agonists, are decreased by metabolic acidosis.
3. Decreased myocardial calcium sensitivity results in contractile dysfunction.
4. Metabolic acidosis and hypoxia act additively or synergistically to impair myocardial function, a phenomenon consistent with the monovalent inorganic phosphate hypothesis.
5. Chronic metabolic acidosis causes hypercalciuria and bone disease.

USE OF THE SERUM AND URINE ANION GAP IN THE DIFFERENTIAL DIAGNOSIS OF METABOLIC ACIDOSIS

The SAG is used to determine whether an organic or mineral acidosis is present. This very simple concept that we discuss in some detail allows the clinician to use simple electrolyte determinations to accurately infer whether an organic anion is present in high concentration. We calculate the SAG as:

$$SAG = [Na^+] - [C1^-] - [TCO_2] \qquad \text{(Eq. 8)}$$

In this equation, we use the TCO_2 as an index of serum $[HCO_3^-]$. We rather arbitrarily define "unmeasured" as not being in the equation. In other words, unmeasured cations (UCs) are those cations that are not Na^+ (eg, K^+, Mg^{2+}, Ca^{2+}) and unmeasured anions (UAs) are anions that are not Cl^- or HCO_3^- (eg, sulfate $[SO_4^{2-}]$, $H_2PO_4^-$, HPO_4^-, albumin, and organic anions). The SAG, UAs, and UCs are expressed in units of mEq/L. Equation 9 is written as such to maintain electroneutrality:

$$[Na^+] + UC = [C1^-] + [TCO_2] + UA \qquad \text{(Eq. 9)}$$

When we combine equations 8 and 9, the following equation for SAG is derived:

$$SAG = UA - UC \qquad \text{(Eq. 10)}$$

For ease of computation, we consider a normal SAG to be approximately 10 mEq/L; actually it is somewhere between 6 and 10 mEq/L. We further assume that every proton generated causes a stoichiometric reduction in serum $[HCO_3^-]$. With these assumptions, it is clear that the addition of organic acid will cause an increase in the SAG, whereas addition of mineral acid (HCl) will not (Figure 7.3).

The SAG is extremely useful in the differential diagnosis of metabolic acidosis. We stress, however, that it must be interpreted with some caution. Although an organic acidosis should theoretically produce anions in concert with protons (discussed above), the relationship between the increase in SAG and the fall in bicarbonate concentration depends primarily on the clearance mechanisms for the anion and the volume of distribution for both bicarbonate and the anion. In general, the SAG is most useful when it is extremely elevated. A major increase in the anion gap (eg, SAG >25 mEq/L) always reflects the presence of an organic acidosis.

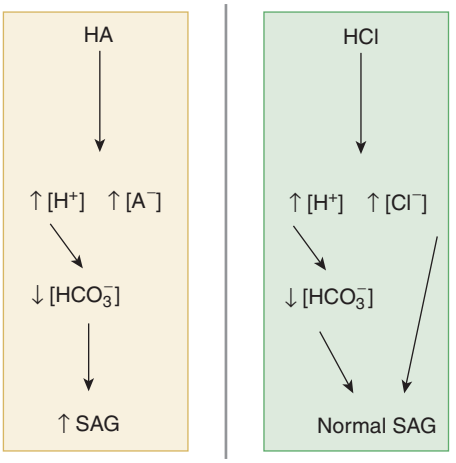

FIGURE 7-3. Organic acidosis is associated with an increase in SAG (*left panel*) whereas mineral acidosis is not (*right panel*). Note that addition of organic acid (HA) causes an increase in $[H^+]$ which, in turn, results in a decrease in $[HCO_3^-]$. Because $[Cl^-]$ and $[Na^+]$ do not change, the SAG defined as $[Na^+] - [Cl^-] - [HCO_3^-]$ increases. In contrast, when HCl is added, the decrease in $[HCO_3^-]$ is matched by an increase in $[Cl^-]$ and the SAG does not change.

Unmeasured anions include SO_4^{2-}, $H_2PO_4^-$, HPO_4^{2-}, albumin and organic anions. UCs include K^+, Mg^{2+}, and Ca^{2+}. A low SAG is seen in 4 clinical circumstances: (a) a reduction in the concentration of UAs (primarily albumin); (b) underestimation of the serum sodium concentration (severe hypernatremia); (c) overestimation of the serum chloride concentration (bromide intoxication and marked hyperlipidemia); and (d) increased nonsodium cations (hyperkalemia, hypermagnesemia, hypercalcemia, lithium toxicity, or a cationic paraprotein). For each 1 g/dL decrease in serum albumin concentration the SAG decreases by 2.5 mEq/L. Therefore, in patients with hypoalbuminemia, the SAG should be adjusted upward based on this correction factor.

As discussed earlier, one cannot routinely measure urinary NH_4^+ concentration. Therefore, we must use the same type of reasoning employed for the SAG to develop a method to estimate NH_4^+ concentration based on the electrolyte content of urine. Because of electroneutrality we presume:

$$[Na^+] + [K^+] + UC = [C1^-] + UA \qquad \text{(Eq. 11)}$$

Furthermore, when urine pH is less than 6, the urine does not contain appreciable amounts of bicarbonate.

More relevant, the UC is made up mostly of NH_4^+. Therefore, we can define the urinary anion gap (UAG) as:

$$UAG = [Na^+] + [K^+] - [C1^-] \qquad \text{(Eq. 12)}$$

It is clear that the UAG will be negative when urinary $[NH_4^+]$ is high. It turns out that low concentrations of urinary NH_4^+ are associated with a positive UAG. Although the SAG is useful in many settings of clinical acid–base diagnosis and therapy, we must stress that the UAG is limited to a few clinical situations; specifically, it is used to differentiate renal (principally tubular acidosis) from nonrenal causes of nonanion gap metabolic acidosis (such as diarrhea). It must be kept in mind that if the urine contains anions such as ketoanions or hippurate (toluene poisoning), which obligate the loss of sodium and potassium in the urine, the urine anion gap will be falsely positive.

KEY POINTS

Use of the Serum and Urine Anion Gap in the Differential Diagnosis of Metabolic Acidosis

1. The SAG is a concept used in acid–base pathophysiology to infer whether an organic or mineral acidosis is present.
2. Venous serum electrolytes are used to calculate the SAG as:

$$SAG = [Na^+] - [Cl^-] - [TCO_2].$$

3. The addition of organic acid will cause an increase in the SAG, whereas addition of mineral acid (HCl) will not.
4. The UAG is used to estimate the quantity of NH_4^+ in urine.
5. The UAG is used in the differentiation of renal from nonrenal causes of non–anion gap metabolic acidosis.

DIFFERENTIAL DIAGNOSIS OF METABOLIC ACIDOSIS

The first step in the differential diagnosis of metabolic acidosis is examination of the SAG. An anion gap metabolic acidosis is characterized by retention of an organic anion (elevated anion gap). In contrast, a hyperchloremic or nonanion gap metabolic acidosis is not associated with retention of an organic anion (normal anion gap).

INCREASED ANION GAP METABOLIC ACIDOSIS

There are 3 forms of anion gap metabolic acidosis that are characterized by ketonemia or ketonuria and these include diabetic ketoacidosis, starvation ketosis, and alcoholic ketoacidosis (AKA) (Table 7.1). In all of these disorders, impaired lipid metabolism leads to generation and accumulation of short-chain fatty ketoacids, specifically, β-hydroxybutyric and acetoacetic acids. These ketoacids are relatively strong acids that produce acidosis, as well as an increase in the anion gap. The initial step in the evaluation of the patient with anion gap metabolic acidosis is an examination of blood and urine for ketones.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a common form of anion gap metabolic acidosis. This entity results from a nearly absolute deficiency of insulin along with increases in glucagon. We should stress that the amount of insulin needed for catabolism of short-chain fatty acids is significantly less than that necessary for glucose homeostasis; ergo, DKA is a common presentation in patients with insulin-dependent diabetes mellitus but is rather unusual in patients with noninsulin-dependent diabetes mellitus. Patients with noninsulin-dependent diabetes

TABLE 7-1. Causes of Increased Anion Gap (Organic) Metabolic Acidosis

Increased Acid Production
Lactic acidosis
Ketoacidosis
Diabetic ketoacidosis
Starvation
Alcoholic ketoacidosis
Inborn errors of metabolism
Toxic alcohol ingestions
Pyroglutamic acidosis
Salicylate overdose
Other intoxications (eg, toluene, isoniazid)
Failure of Acid Excretion
Acute kidney injury
Chronic kidney disease

mellitus present with marked increases in serum glucose concentrations without ketosis (nonketotic hyperglycemic coma). This entity is also associated with an increase in the anion gap, but the chemical nature of the accumulated anion(s) has surprisingly not yet been well characterized.

DKA is diagnosed by the combination of anion gap metabolic acidosis, hyperglycemia, and demonstration of increased serum (or urine) ketones; however, the presence of serum and urine ketones is not specific for DKA. In fact, elevated ketones may accompany starvation and AKA, where there may be some associated acidosis (see below), as well as isopropyl alcohol intoxication that is characterized by ketosis without significant acidosis.

Starvation

Starvation produces some metabolic processes that are similar to those seen with DKA. As carbohydrate availability becomes limited, hepatic ketogenesis is accelerated and tissue ketone metabolism is reduced. This produces increases in the serum (and urine) concentration of ketoacids and ketones. At first, there is minimal associated acidosis as renal NAE maintains balance. With more prolonged starvation the serum [HCO_3^-] often declines; however, it does not generally fall below 18 mEq/L because ketonemia promotes insulin release.

Alcoholic Ketoacidosis

AKA is a relatively common form of acidosis seen in inner city hospitals. The acid–base disturbance results from the combination of alcohol toxicity and starvation; ethanol itself leads to an increase in cytosolic nicotinamide adenine dinucleotide (NAD^+), but without glucose (the starvation component), ketogenesis and decreased ketone usage results. The serum glucose concentrations can actually range over a wide spectrum. In some cases they are very low (ie, <50 mg/dL), but occasionally they may be moderately high (eg, 200 to 300 mg/dL). In the latter circumstance, clinicians may confuse AKA with DKA. Patients with AKA often present with complex acid–base disorders (see Chapter 9) rather than simple metabolic acidosis. A marked increase in the SAG is a hallmark of this disorder.

AKA may be a difficult diagnosis to make. When the acidosis is severe, however, the majority of ketoacids circulating in the serum may not be detected by the Acetest assay, which is relatively insensitive to β-hydroxybutyric acid. Therefore, a high index of suspicion must be held in the appropriate clinical setting. Assays are now available to directly measure β-hydroxybutyric acid.

Lactic Acidosis

Anaerobic metabolism results in the production of lactic acid. Aerobic tissues metabolize carbohydrates to pyruvate that then enters an oxidative metabolic pathway (TCA) in mitochondria. This results in the regeneration of NAD^+. When tissues perform anaerobic glycolysis, however, NAD^+ cannot be regenerated from electron transport. To regenerate NAD^+, the reaction, catalyzed by lactate dehydrogenase (LDH),

$$H^+ + \text{pyruvate} + NADH \rightarrow \text{lactate} + NAD^+$$

(NADH = reduced form of nicotinamide adenine dinucleotide) must proceed and lactate is generated. Despite consumption of an H^+, the net effect of glycolysis is to generate lactic acid from carbohydrates and as discussed earlier, generate H^+. Normally, lactate (L isomer) production is closely matched by lactate metabolism to glucose (Cori cycle) or aerobic metabolism to CO_2 and H_2O, and circulating concentrations are maintained in a very low range. Under certain pathologic conditions, there may be a substantial increase in lactate concentrations and a concomitant development of metabolic acidosis, known as *lactic acidosis*. These include those with local or systemic decreases in oxygen delivery, impairments in oxidative metabolism, or impaired hepatic clearance. Of these, local or systemic decreases in O_2 delivery as a result of hypotension are most common and are referred to as *type A lactic acidosis*.

Type B lactic acidosis is caused by a variety of disorders in which there is no evidence of hypoperfusion or tissue hypoxia. These include genetic disorders that result in mitochondrial dysfunction, mitochondrial toxins, liver disease, malignancy, and drugs. Mangosteen is a tropical fruit whose juice contains α-mangostin that is a potent inhibitor of mitochondrial function. The most common malignancies associated with type B lactic acidosis are leukemias and lymphomas that likely to overproduce lactic acid. Thiamine is an important cofactor for pyruvate dehydrogenase and lactic acidosis has been reported in patients on parenteral nutrition that was not supplemented with thiamine.

Drugs can also cause type B lactic acidosis. Propofol is an anesthetic and sedating agent commonly used in intensive care units. Patients on high doses (>4 mg/kg) for prolonged periods (>48 hours) are at risk for developing

the "propofol-related infusion syndrome" (PRIS). PRIS is characterized by lactic acidosis, bradycardia, heart failure, renal failure, rhabdomyolysis, and hyperlipidemia. Propofol inhibits oxidative phosphorylation, mitochondrial metabolism, and fatty acid uptake. Nucleoside analog reverse transcriptase inhibitors used in highly active antiretroviral therapy such as didanosine, stavudine, and zidovudine, inhibit mitochondrial DNA polymerase γ resulting in biochemical and ultrastructural mitochondrial damage that can result in lactic acidosis. Metformin used in the treatment of diabetes mellitus has been rarely associated with lactic acidosis (3 cases per 100,000 patient years). Although rare, when it occurs it is fatal in up to 50% of cases and as a result the drug carries a black box warning stating its use is contraindicated in men with a serum creatinine concentration greater than 1.5 mg/dL and in women with a serum creatinine concentration greater than 1.4 mg/dL. High concentrations of metformin block mitochondrial uptake and metabolism of pyruvate and inhibit oxidative phosphorylation. Metformin is renally excreted and has a large volume of distribution. High concentrations of the drug can be seen in those with low GFR, intentional overdose, and acute kidney injury. As a result, it is recommended that metformin be stopped 48 hours before administration of iodinated contrast. Recently, several authors recommended modifying the black box warning. Shaw recommends not using metformin in those with an estimated GFR (eGFR) less than 30 mL/min/1.73 m^2, while Herrington suggests reducing the dose by 50% in those with an eGFR from 30 to 59 mL/min/1.73 m^2 and in the elderly. Metformin is readily dialyzable, however, because of its large volume of distribution; to reduce drug levels by 90%, at least 15 hours of dialysis is required.

Lactic acidosis is one of the most common forms of anion gap metabolic acidosis. It must be considered as a possible cause of any anion gap metabolic acidosis, particularly if the clinical circumstances include hemodynamic compromise, sepsis, tissue ischemia, or hypoxia. Measurement of the serum lactate concentration employs a spectrophotometric assay using the LDH reaction. Please note that D-lactic acidosis will be missed with this approach because LDH does not recognize D-lactate. D-Lactic acidosis occurs with blind intestinal loops colonized with D-lactate–producing organisms. The clinician must suspect this diagnosis in the appropriate clinical setting and confirm D-lactic acidosis with alternate measurement methods (eg, ^{1}H nuclear magnetic resonance [NMR] spectroscopy, high-performance liquid chromatography [HPLC], specific enzymatic method for D-lactate).

Renal Failure

After eliminating ketoacidosis and lactic acidosis as potential causes for an anion gap metabolic acidosis, one next examines the serum blood urea nitrogen (BUN) and creatinine concentrations to determine if organic anion accumulation is the result of kidney failure. Normally, the kidney is responsible for excretion of the approximately 1 mEq/kg/day of H^+ generated by dietary protein. If the kidney fails to do this, one develops metabolic acidosis. With both acute and chronic renal failure, there is some retention of anions (including phosphate, sulfate, and some poorly characterized organic anions), and the SAG is typically elevated; however, it is common to find that the increase in SAG is less than the fall in bicarbonate concentration. In short, renal failure typically gives a mixed anion gap and nonanion gap metabolic acidosis. Metabolic acidosis in the setting of acute and chronic renal failure is generally not severe unless a marked catabolic state occurs, or another acidotic condition (eg, nonanion gap acidosis from diarrhea) supervenes.

Toxic Alcohol Ingestions

Toxic alcohol ingestion should be considered in all patients with an unexplained anion gap metabolic acidosis. Delays in diagnosis and therapy of these intoxications are likely to be accompanied by permanent organ damage and death. These entities are also important to recognize because they often require hemodialysis to remove the offending agent and their metabolites. The most important toxic alcohols include methanol and ethylene glycol. These are often taken as a suicide attempt, but they may be inadvertently ingested by children or inebriated adults. Although the clinical syndrome ultimately results in very severe metabolic acidosis, it must be stressed that the patient's acid–base status may initially be normal if they present to the hospital early after ingestion.

Because these toxic alcohols are osmotically active, the serum osmolar gap (defined as the difference between measured serum osmolarity and calculated serum osmolarity) is used to identify these patients:

$$\text{Calculated serum osmolarity} = 2[\text{Na}] + \frac{[\text{glucose}]}{18} + \frac{[\text{BUN}]}{2.8} \qquad \text{(Eq. 13)}$$

where [Na] is in mEq/L and [glucose] and [BUN] are in mg/dL.

This osmolar gap is generally elevated soon after ingestion because of the presence of the toxic alcohol in serum; however if the ingestion is remote, it may not be substantially elevated. Although useful in suggesting this diagnosis, elevations in serum osmolar gap are neither sensitive nor specific for toxic alcohol ingestions. In fact, ethanol is the most common cause of an elevated serum osmolar gap. Therefore, it should be measured and its contribution to the osmolar gap calculated. The contribution of ethanol to the osmolar gap is estimated by dividing its concentration in mg/dL by 4.6.

Methanol intoxication typically presents with abdominal pain, vomiting, headache, and visual disturbances. This latter symptom derives from the toxicity of formic acid, a methanol metabolite, to the optic nerve. Metabolism is folic acid dependent. Methanol toxicity can be seen with ingestions as small as 30 mL and more than 100 mL of methanol is generally fatal unless treated promptly.

Ethylene glycol is a major component of antifreeze. It apparently has a sweet taste that makes it appealing to children, and inebriated adults. Ethylene glycol intoxication presents very similarly to that of methanol; both produce CNS disturbances and severe anion gap metabolic acidosis. In contrast to methanol, however, ethylene glycol does not usually produce retinitis, but it may cause both acute and chronic renal failure. The lethal dose for ethylene glycol may be as little as 100 mL. The clinical presentation often consists of 3 stages: (a) CNS depression that lasts for up to 12 hours associated with metabolic acidosis; (b) cardiopulmonary failure; and (c) oliguric acute kidney injury that may be heralded by flank pain. Detection of oxalate crystals in urine is common in cases of ethylene glycol ingestion but may take up to 8 hours to appear. Oxalate monohydrate crystals may be erroneously interpreted as hippurate crystals by the clinical laboratory.

Consideration of either ethylene glycol or methanol ingestion is important because they require very similar and immediate treatment. Neither ethylene glycol nor methanol are particularly toxic in their own right. It is the metabolism of these agents through the enzyme alcohol dehydrogenase that produces toxic metabolites. Therefore, blockade of their metabolism by the administration of agents that block alcohol dehydrogenase (ethanol or fomepizole) should be considered early. Moreover, because both the parent compounds and metabolites are low molecular weight and have small volumes of distribution, hemodialysis is generally employed. It is important to note that if ethanol is used to block metabolism of the parent compound and dialysis is also prescribed, the dose of ethanol must be adjusted to compensate for its concomitant removal by the dialysis procedure. As with ethanol, fomepizole requires dose adjustment during hemodialysis. With ethylene glycol intoxication pyridoxine and thiamine promote the conversion of glyoxylate to the less toxic metabolites glycine and β-hydroxyketoadipate, respectively.

Other toxic alcohols that the clinician should be aware of include diethylene glycol and propylene glycol. Diethylene glycol is a clear, odorless solvent that has been associated with several epidemic poisonings. The most recent occurred in 2006 when a Chinese pharmaceutical company included it as a glycerin substitute in cough syrup marketed in Panama. More than 300 deaths may have resulted from its toxicity. Diethylene glycol is metabolized to 2-hydroxyethoxyacetaldehyde by alcohol dehydrogenase and subsequently to 2-hydroxyethoxyacetic acid by aldehyde dehydrogenase. Toxicity is manifested by anion gap metabolic acidosis, acute kidney injury, and neurologic dysfunction that can involve the peripheral and central nervous systems. Propylene glycol is used as a solvent for a variety of medications, including lorazepam and phenobarbital. Propylene glycol can be metabolized to D- and L-lactic acid, as well as methylglyoxal. It is renally excreted and accumulates with reduced kidney function. Risk factors associated with toxicity include renal dysfunction and higher infusion rates. An osmolal gap greater than 10 suggests potential toxicity.

Salicylate Intoxication

Salicylate overdoses are also common. Salicylate intoxication may occur as a suicide attempt, but often, especially in the elderly, may result from routine use. Aspirin or methylsalicylate intoxication may lead to serious and complex acid–base abnormalities. In younger subjects with salicylate intoxication, metabolic acidosis may be simple, whereas in older subjects a complex acid–base disturbance involving respiratory alkalosis and metabolic acidosis is more likely. Elderly subjects often demonstrate a major discordance between blood concentrations and symptoms. CNS toxicity almost always accompanies extremely elevated blood concentration (serum salicylate concentrations >50 mg/dL).

Salicylates stimulate respiration and produce a component of respiratory alkalosis, especially early in the course of toxicity in adults. The acids responsible for the metabolic acidosis and increase in the SAG are primarily endogenous acids (eg, lactate and ketoanions) whose metabolism is affected by toxic amounts of salicylates that uncouple oxidative phosphorylation. Salicylic acid contributes to a minor degree.

The diagnosis of salicylate toxicity should be considered when a history of aspirin use, nausea, and tinnitus are present. Suspicion should also be raised by clinical findings of unexplained respiratory alkalosis, anion gap metabolic acidosis, or noncardiogenic pulmonary edema. Advanced age and a delay in the diagnosis of salicylate toxicity are associated with significant morbidity and mortality. Efforts to remove the salicylate include urine alkalinization to a urine pH of 8.0 with sodium bicarbonate in milder cases. Systemic pH should be carefully monitored and kept below 7.6. Hemodialysis is indicated if the salicylate level is greater than 100 mg/dL, or if the patient has altered mental status, a depressed GFR, is fluid overloaded, or has pulmonary edema. Glucose should be administered because cerebrospinal fluid (CSF) glucose concentrations are often low despite normal serum glucose concentration. Acetazolamide should be avoided because it is highly protein bound and may increase free salicylate concentration.

Pyroglutamic Acidosis

This rare organic acidosis occurs as a result of accumulation of pyroglutamic acid (5-oxoproline). Pyroglutamic acid is an intermediate in the γ-glutamyl cycle. The γ-glutamyl cycle is involved in the synthesis and metabolism of glutathione. Glutathione is formed from glycine and γ-glutamyl cysteine through the action of glutathione synthase. The activity of γ-glutamyl cysteine synthase is inhibited by glutathione. Glutathione depletion results in increased synthesis of γ-glutamyl cysteine, which is metabolized to pyroglutamic acid. Accumulation of pyroglutamic acid can occur in rare genetic syndromes involving enzymes in the pathway or can be acquired. The acquired form presents with an unexplained elevation in the anion gap and altered mental status. It is thought to occur in clinical situations characterized by glutathione depletion such as critical illness, the malnourished, and with acetaminophen use. Definitive diagnosis can be made by measuring 5-oxoproline concentration in blood or urine.

Other Intoxications

Several other intoxications produce anion gap metabolic acidosis. These include toluene, strychnine, paraldehyde, iron, isoniazid, papaverine, tetracyclines (outdated), hydrogen sulfide, and carbon monoxide. These substances interfere with oxidative metabolism and produce lactic acidosis. Citric acid (present in toilet bowl cleaner) is an exception; the citrate itself causes an increase in SAG. Citric acid toxicity is associated with marked hyperkalemia. Toluene is another exception; it may produce a distal RTA in concert with an elevation of serum hippuric acid (a metabolite of toluene) concentration. Hippurate is rapidly eliminated from the body by the kidney and as a consequence the anion does not accumulate leading to a nonanion gap metabolic acidosis. This, rather than a distal RTA, is the likely mechanism of the normal SAG metabolic acidosis seen with toluene ingestion.

Inborn Errors of Metabolism

Inborn errors of metabolism represent an unusual but important cause of organic acidosis. In some cases (eg, mitochondrial myopathies, some glycogen storage diseases), lactic acidosis develops without evidence for hypoxia or hypoperfusion. In other conditions (eg, maple syrup urine disease, methylmalonic aciduria, propionic acidemia, and isovaleric academia), the accumulation of other organic acids occurs in concert with metabolic acidosis. Although many of these diseases present shortly after birth, some conditions may be first suspected in adulthood.

HYPERCHLOREMIC METABOLIC ACIDOSIS

In contrast to SAG acidosis, hyperchloremic metabolic acidosis is not associated with accumulation of organic anions (Table 7.2). Rather, loss of HCO_3^- (renal or GI), as well as some miscellaneous causes, add HCl to blood and lower serum HCO_3^- and raise serum Cl^- concentration. The UAG can be used to differentiate renal from GI causes of nonanion gap metabolic acidosis if the diagnosis is not obvious based on history and physical examination. The UAG is equal to the sum of urinary sodium and potassium minus urine chloride. It will be negative in situations where urinary $[NH_4^+]$ is elevated and the kidney is responding appropriately to metabolic acidosis (nonrenal causes). The UAG is negative because NH_4^+, when excreted

TABLE 7-2. Causes of Hyperchloremic Metabolic Acidosis

Gastrointestinal Loss of HCO_3^-
Diarrhea
Gastrointestinal drainage and fistulas
Urinary diversion to bowel
Chloride containing anion-exchange resins
$CaCl_2$ or $MgCl_2$ ingestion
Renal Loss of HCO_3^-
Renal tubular acidosis
Carbonic anhydrase inhibitors
Hypoaldosteronism
Potassium-sparing diuretics
Miscellaneous Causes of Hyperchloremic Acidosis
Recovery from ketoacidosis
Dilutional acidosis
Addition of HCl
Parenteral alimentation
Sulfur ingestion

in urine, is accompanied by Cl^- to maintain charge neutrality. In situations where the kidney is responsible for the metabolic acidosis the UAG will be positive. This may occur with either RTA or renal failure. Renal failure is identified by elevated serum concentrations of BUN and creatinine. The UAG can be misleading in 2 clinical circumstances. The first is when decreased sodium delivery compromises distal acid excretion. Therefore, to use the UAG, urine sodium concentration must be greater than 20 mEq/L. Decreased distal sodium delivery impairs collecting duct H^+ secretion and the UAG cannot be used if delivery of sodium to this segment is decreased. The second occurs when an anion (usually a ketoanion or hippurate) is excreted with sodium or potassium. Urinary sodium and potassium may be elevated leading to a positive urine anion gap and the impression that the kidney is not responding appropriately. The urinary osmolar gap (UOG) is not affected by the excretion of other anions and may need to be used in this situation. UOG is equal to the measured minus the calculated urine osmolality.

$$\text{Calculate } U_{osm} = 2(Na + K) + BUN/2.8 + \text{glucose}/18 \quad \text{(Eq. 14)}$$

The UOG is not affected by UAs in the urine as they are associated with cations (sodium or potassium). Dividing the UOG by 2 will approximate the urinary $[NH_4^+]$. A value less than 20 implies that the kidney is not responding appropriately to metabolic acidosis.

GASTROINTESTINAL LOSS OF HCO_3^-

Diarrhea

The concentration of HCO_3^- in diarrheal fluid is usually greater than the concentration of HCO_3^- in serum. Although it seems like it should be obvious, the diagnosis of diarrhea to explain nonanion gap metabolic acidosis may be difficult in the very young or very old who are unable to provide historical details. In children, the distinction between diarrhea and an underlying RTA may be very important. In this situation, the UAG provides helpful information. When diarrhea causes metabolic acidosis, a significantly negative UAG (ie, <10 mEq/L), reflecting the presence of ample urinary NH_4^+ concentrations, is present. In contrast, patients with all forms of distal RTA have positive UAGs reflecting the relatively low urinary $[NH_4^+]$ present in these conditions. Some patients with GI bicarbonate losses will have a urine pH greater than 6 as a result of complete titration of NH_3 to NH_4^+. The urine anion gap in these patients will be negative, helping to distinguish them from those with RTA.

Gastrointestinal Drainage and Fistulas

Intestinal, pancreatic, and biliary secretions have high HCO_3^- and relatively low Cl^- concentrations. The intestine produces approximately 600 to 700 mL of fluid per day, but this may be increased in states of disease. Biliary secretions amount to more than 1 L/day. This fluid usually contains $[HCO_3^-]$ as high as 40 mEq/L. Pancreatic secretions are an even greater potential source of bicarbonate loss, as the volume may exceed 1 to 2 L/day and contain $[HCO_3^-]$ up to 100 mEq/L.

Because of the high $[HCO_3^-]$, drainage of these fluids or fistulas can cause significant metabolic acidosis. One interesting variation to this phenomenon occurs with kidney pancreas transplantation when the exocrine pancreas is drained through the bladder. This procedure almost universally leads to substantial metabolic acidosis as the NAE of the transplanted kidney is essentially nullified by the combination with pancreatic secretions. For this reason, most kidney pancreas transplants are now performed with intestinal drainage of the exocrine pancreas.

Urinary Diversion to Bowel

Surgical approaches to bladder and ureteral disease include creation of alternative drainage of urine through in situ bowel and/or conduits produced from excised bowel. In both of these settings, active Cl^-/HCO_3^- exchange by bowel mucosa can impair renal NAE. Because of this, a nonanion gap metabolic acidosis may complicate both of these procedures. In fact, metabolic acidosis is almost certain when an ureterosigmoidostomy is performed. The contact time of the urine with the intestinal mucosa is an important factor in generation of the acidosis. In patients with an ileal conduit and a nonanion gap metabolic acidosis an ileal loop obstruction may be present.

Chloride Containing Anion-Exchange Resins

Cholestyramine, a resin used to bind bile acids, can also bind HCO_3^-. Because of this, Cl^-/HCO_3^- exchange across bowel mucosa may be facilitated, and metabolic acidosis may develop. This is most likely in conditions of chronic kidney disease where new HCO_3^- generation is impaired.

$CaCl_2$ or $MgCl_2$ Ingestion

Calcium and magnesium are not absorbed completely in the GI tract. As was the case for cholestyramine, unabsorbed Ca^{2+} or Mg^{2+} may bind HCO_3^- in the intestinal lumen and facilitate Cl^-/HCO_3^- exchange. In this way, a nonanion gap metabolic acidosis may result.

RENAL LOSS OF HCO_3^-

Renal Tubular Acidosis

There is no topic in nephrology that confuses students and clinicians more than RTA. The RTAs are a group of functional disorders that are characterized by impaired renal HCO_3^- reabsorption and H^+ excretion. We distinguish these conditions from the acidosis of renal failure by requiring that the impairment in NAE be disproportionate to any reduction in GFR that may be present. In most cases, RTAs occur in patients with a completely normal or near-normal GFR.

RTAs can be approached in several different ways. We prefer to separate them based on whether the proximal (bicarbonate reabsorption) or distal (NAE) nephron is primarily involved. From a clinical standpoint, it is then most simple to divide the distal RTAs into those that are associated with hypokalemia and those that are associated with hyperkalemia. The hyperkalemic type can then be further divided into those caused by hypoaldosteronism and those characterized by a general defect in sodium reabsorption.

Some mention should be made about the numbering system used to describe RTAs. Distal RTA associated with hypokalemia, also called classic distal RTA, was described first and is referred to as type I RTA. Proximal RTA is referred to as type II RTA. There is no type III RTA. Finally, distal RTA with hyperkalemia secondary to hypoaldosteronism is often referred to as type IV RTA.

Proximal (Type II) Renal Tubular Acidosis

Proximal RTA is a relatively uncommon disease. In proximal RTA, bicarbonate reabsorption in proximal tubule is impaired, and the plasma threshold for HCO_3^- is decreased. When plasma $[HCO_3^-]$ exceeds the plasma threshold for HCO_3^-, the delivery of HCO_3^--rich fluid to distal nephron sites leads to substantial bicarbonaturia. This is associated with profound urinary losses of both potassium and sodium. When plasma $[HCO_3^-]$ falls below the plasma threshold for HCO_3^-, however, NAE increases and a steady state is achieved. Thus, patients with proximal RTA typically manifest a mild metabolic acidosis with hypokalemia. The serum $[HCO_3^-]$ is generally between 14 and 20 mEq/L. If one treats patients with sodium bicarbonate, however, bicarbonaturia recurs, and urinary potassium losses become severe. Diagnostically, patients with suspected proximal RTA undergo an infusion with bicarbonate to correct the serum $[HCO_3^-]$. Proximal RTA can be diagnosed in this setting when fractional HCO_3^- excretion (ie, the fraction of filtered HCO_3^- that is excreted in the urine) exceeds 15%.

Proximal RTA may occur as an isolated disturbance of HCO_3^- reabsorption, but more commonly coexists with other defects in proximal nephron function (eg, reabsorption of glucose, amino acids, phosphate, and uric acid). In the situation where proximal tubule function is deranged for these other substances, the term *Fanconi syndrome* is used. In addition to the mild metabolic acidosis usually associated with proximal RTA, Fanconi syndrome is complicated by osteomalacia and malnutrition. Proximal RTA may occur as an inherited disorder (Lowe syndrome, cystinosis, and Wilson disease) and present in infancy. Alternatively, it may be acquired in the course of other diseases, following exposure to proximal tubular toxins (heavy metals), or in the setting of drug therapy (imatinib mesylate, tenofovir, and ifosfamide). In the past, mercurial diuretics were commonly associated with the development of Fanconi syndrome. Now the most common

acquired causes include medications (nucleotide analogs) and multiple myeloma (light chains cause proximal tubular dysfunction).

Inherited disorders of transporters involved in bicarbonate transport can also cause proximal RTA. Mutations in the basolateral sodium bicarbonate cotransporter (NBCe1/SLC4A4) have been described and are associated with a variety of ocular abnormalities, including band keratopathy, cataracts, and glaucoma.

Distal (Type I) Renal Tubular Acidosis

Although classic type I distal RTA was initially characterized by an impairment in urinary acidification, all distal RTAs result in an impairment in NAE. This impairment in NAE is largely a result of reduced urinary NH_4^+ excretion. Type I distal RTA may be associated with either hypokalemia or hyperkalemia. Distal RTA associated with hyperkalemia is the most common form of RTA. It is generally the result of hypoaldosteronism. All distal RTAs are characterized by a positive UAG in the setting of acidosis, reflecting inadequate NH_4^+ excretion.

Hypokalemic type I distal RTA is best considered a disorder of collecting duct capacity for effective proton secretion such that patients cannot achieve the necessary NAE to maintain acid–base balance. Patients with hypokalemic type I distal RTA usually present with hyperchloremic metabolic acidosis but are unable to acidify their urine (below pH 5.5) despite systemic acidosis. We stress that the failure to acidify the urine does not fully explain the defect in NAE, which is primarily caused by an associated defect in NH_4^+ excretion. The 2 mechanisms that were suggested for impaired acidification by distal nephron in hypokalemic distal RTA are (a) backleak of acid through a "leaky" epithelium and (b) proton pump failure (ie, the H^+-ATPase cannot pump sufficient amounts of H^+). Hypokalemic type I distal RTA may be inherited or may be associated with other acquired disturbances. Some of the same conditions that can cause hypokalemic distal RTA (eg, urinary obstruction, autoimmune disorders) can also cause hyperkalemic distal RTA because of a defect in sodium reabsorption, suggesting that the mechanistic analysis discussed above might be somewhat artificial. In its primary form, hypokalemic type I distal RTA is quite unusual, and generally is diagnosed in young children. The afflicted children typically present with extremely severe metabolic acidosis, growth retardation, nephrocalcinosis, and nephrolithiasis. Hypokalemia, which is usually present, may actually be caused by the associated sodium depletion and stimulation of the renin-angiotensin-aldosterone axis. Therefore, renal potassium losses decrease considerably when appropriate therapy with sodium bicarbonate is instituted. This is completely different from patients with proximal RTA where urinary potassium losses increase during therapy because of the bicarbonaturia associated urinary potassium losses. Inherited causes include mutations in genes that encode the β1 subunit of the H^+-ATPase (*ATP6V1B1*); the α4 subunit of the H^+-ATPase (*ATP6V0A4*); and the basolateral Cl^-/HCO_3^- exchanger isoform kAE1 (*SLC4A1*). H^+ pump mutations are associated with sensorineural deafness and the Cl^-/HCO_3^- exchanger mutations with ovalocytosis.

Hyperkalemic distal RTAs can develop from several mechanisms. These include (a) a defect in sodium reabsorption where a favorable transepithelial voltage cannot be generated and/or maintained, and (b) hypoaldosteronism. Hyperkalemic distal RTA from decreased sodium reabsorption is more common than either classic hypokalemic type I distal RTA or proximal RTA. Urinary obstruction is the most common cause of this form of distal RTA. Other causes include cyclosporin nephrotoxicity, renal allograft rejection, sickle cell nephropathy, and many autoimmune disorders, such as lupus nephritis and Sjögren syndrome. In contrast to hypoaldosteronism, urinary acidification is impaired in these subjects. Also, hyperkalemia plays a less-significant role in the pathogenesis of the impaired NH_4^+ excretion, which is more closely tied to impaired distal nephron function. Distal RTA from hypoaldosteronism results from either selective aldosterone deficiency or complete adrenal insufficiency. Probably the most common form of RTA is a condition called hyporeninemic hypoaldosteronism that is most often seen in patients afflicted with diabetic nephropathy. In patients with this form of RTA, urinary acidification assessed by urine pH is normal, but NAE is not. The defect in NAE in some of these patients can be explained by impaired NH_4^+ synthesis in the proximal nephron resulting directly from the hyperkalemia. Hyperkalemia also interferes with NH_4^+ recycling in the thick ascending limb of Henle where it competes with NH_4^+ for transport on the potassium site of the Na-K-2Cl cotransporter. Other patients with hyporeninemic hypoaldosteronism have a more complex pathophysiology.

Another contrasting point between proximal RTA and hypokalemic type I distal RTA is the amount of alkali therapy needed. Patients with hypokalemic distal RTA only need enough alkali to account for the amount of acid

generated from diet and metabolism. Therefore, approximately 1 mmol/kg/day is generally sufficient in these patients, whereas patients with proximal RTA require enormous amounts of bicarbonate and potassium supplementation. Some authors actually discourage trying to treat such patients with alkali.

Carbonic Anhydrase Inhibitors

CA inhibitors (eg, acetazolamide) inhibit both proximal tubular luminal brush border and cellular CA. This disruption of CA results in impaired HCO_3^- reabsorption similar to that of proximal RTA. Topiramate and zonisamide are antiseizure medications that cause a mild-to-moderate proximal RTA through this mechanism. As a result, patients taking topiramate have a 2- to 4-fold increased incidence of calcium phosphate kidney stones, which is discussed further in Chapter 13.

Potassium-Sparing Diuretics

Aldosterone antagonists (eg, spironolactone and eplerenone) or sodium channel blockers (eg, amiloride and triamterene) may also produce a hyperchloremic acidosis in concert with hyperkalemia. Trimethoprim and pentamidine may also function as sodium channel blocker and cause hyperkalemia and hyperchloremic metabolic acidosis. This is most often seen in human immunodeficiency virus (HIV)-infected patients.

MISCELLANEOUS CAUSES OF HYPERCHLOREMIC ACIDOSIS

Recovery from Ketoacidosis

Patients with DKA generally present with a "pure" anion gap metabolic acidosis. In other words, the increase in the anion gap roughly parallels the fall in bicarbonate concentration; however, during therapy, renal perfusion is often improved and substantial loss of ketoanions in urine may result. Therefore, many patients afflicted with DKA may eliminate the ketoanions faster than they correct their acidosis, leaving them with a nonanion gap or hyperchloremic metabolic acidosis. Rarely, this phenomenon may even occur in patients who drink enough fluid to maintain GFR close to normal as they develop DKA.

Dilutional Acidosis

The rapid, massive expansion of ECF volume with fluids that do not contain HCO_3^- (eg, 0.9% saline) can dilute the plasma and cause a mild, nonanion gap metabolic acidosis. This is occasionally seen with trauma resuscitation or during treatment of right ventricular myocardial infarction.

Addition of Hydrochloric Acid

Therapy with HCl or one of its congeners (eg, NH_4^+ chloride or lysine chloride) will rapidly consume HCO_3^-, and thus, cause a hyperchloremic metabolic acidosis.

Parenteral Alimentation

Amino acid infusions may produce a hyperchloremic metabolic acidosis in a manner similar to addition of HCl. In fact, this is actually quite common if alkali-generating compounds (eg, acetate or lactate) are not administered concomitantly with amino acids; however, replacement of the chloride salt of these amino acids with an acetate salt easily avoids this problem. It turns out that it is metabolism of sulfur-containing amino acids that obligates excretion of acid because neutrally charged sulfur is excreted as sulfate. In general, 1 g of amino acid mixture generally requires 1 mEq of acid to be excreted. Ergo, the acetate content of parenteral alimentation should probably match the amino acid content on a mEq/g basis.

KEY POINTS

Differential Diagnosis of Metabolic Acidosis

1. The diagnosis of lactic acidosis must be considered in all forms of metabolic acidosis associated with an increased anion gap, particularly those cases associated with local or systemic decreases in oxygen delivery, impairments in oxidative metabolism, or impaired hepatic clearance.
2. Diabetic ketoacidosis results from lack of sufficient insulin necessary to metabolize glucose and excess glucagon that causes the generation of short-chain fatty ketoacids. The diagnosis of DKA is made by finding the combination of anion gap metabolic acidosis, hyperglycemia, and demonstration of serum (or urine) ketoacids.
3. Ethylene glycol and methanol ingestion are important causes of an anion gap metabolic acidosis that are associated with an elevated osmolar gap.
4. Metabolic acidosis in the setting of acute and chronic renal failure is generally not severe.
5. GI loss of bicarbonate and RTA are 2 main causes of nonanion gap metabolic acidosis.

6. In the setting of nonanion gap metabolic acidosis, a negative urine anion gap would reflect GI bicarbonate loss, whereas in all forms of distal RTA the urine anion gap will be positive.
7. Proximal RTA (type II) is caused by impairment in proximal tubular reabsorption of bicarbonate.
8. Distal RTA is caused by impaired NAE and can be either hypokalemic or hyperkalemic.

TREATMENT OF METABOLIC ACIDOSIS

As stated earlier, the reason we analyze acid–base disorders is to obtain information as to the clinical condition underlying the acid–base abnormality. The fundamental principles of acid–base therapy are that a *diagnosis must be made* and *treatment of the underlying disease state* initiated. That said, some direct therapy of the acidosis is sometimes indicated. With most of the hyperchloremic states of metabolic acidosis, gradual correction of the acidosis is effective and beneficial. Oral bicarbonate or an anion whose metabolism results in bicarbonate generation is generally preferred. One gram of sodium bicarbonate is equivalent to 12 mEq of HCO_3^-. To administer 1 mEq/kg/day, doses will generally exceed 5 g/day in adults. Commercially available sodium or mixed sodium and potassium citrate solutions (eg, Shohl solution, Bicitra, or Polycitra) contain 1 to 2 mEq of HCO_3^- equivalent per milliliter. Citrate solutions may be better tolerated than sodium bicarbonate tablets or powder (baking soda); however, citrate can increase GI absorption of aluminum and should, therefore, not be administered along with aluminum-based phosphate binders.

The acute treatment of metabolic acidosis associated with an increased anion gap with intravenous sodium bicarbonate is controversial. Unfortunately, there is little in the way of randomized clinical data to guide us. Based primarily on experimental models, it appears that bicarbonate therapy may actually be deleterious in this setting, especially if the acidosis is associated with impaired tissue perfusion. The so-called paradoxical intracellular acidosis that results when bicarbonate is infused during metabolic acidosis probably accounts for a portion of these deleterious effects. This "paradoxical" intracellular acidosis is a direct consequence of the greater permeability of cell membranes to CO_2 than to HCO_3^-. The addition of HCO_3^- to blood (or an organism) produces CO_2. When metabolic acidosis is present, more CO_2 is produced for a given dose of sodium bicarbonate than if there were no acidosis. In fact, studies performed in a closed, human blood model demonstrate that the production of CO_2 from administered HCO_3^- is directly dependent on the initial pH. When ventilation is normal, the lungs rapidly eliminate this extra CO_2; however, when pulmonary ventilation, or more commonly tissue ventilation, is impaired (by poor tissue perfusion), this CO_2 generated by infused HCO_3^- may diffuse into cells (far more rapidly than the original HCO_3^- molecule) and paradoxically decrease the pHi (Figure 7.4). Experimentally, administration of sodium bicarbonate in models of metabolic acidosis is associated with a fall in pHi in several organs, including heart. Bicarbonate infusion in these settings also causes hemodynamic compromise. In addition to this "paradoxical" intracellular acidosis, hypertonic sodium bicarbonate ($NaHCO_3$) therapy in the form of 50-mL ampules of 1 M $NaHCO_3$ may promote hypertonicity. The hypertonic state itself may impair cardiac function, especially in patients undergoing resuscitation for cardiac arrest. Based on these data, we do not support therapy with intravenous sodium bicarbonate for acute anion gap metabolic acidosis in the emergency situation. This area, however, remains controversial.

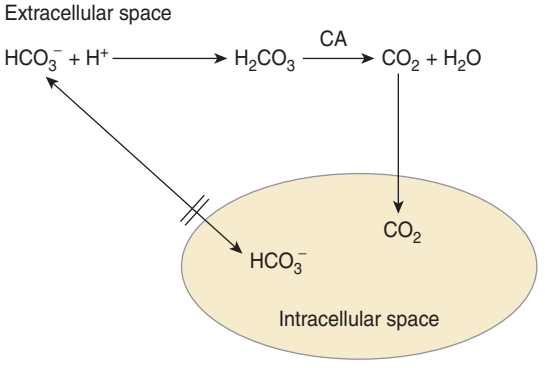

FIGURE 7-4. Mechanism of "paradoxical" intracellular acidosis following administration of sodium bicarbonate. Note that the sudden addition of bicarbonate causes increases in $PaCO_2$ accompanying the increase in $[HCO_3^-]$. This occurs, in part, because abundant CA allows for the virtually instantaneous dehydration of H_2CO_3 in blood. Because most cell membranes are permeable to CO_2 but are not nearly as permeable to HCO_3^-, the intracellular PCO_2 increases faster than $[HCO_3^-]$ and the intracellular pH transiently falls.

To address the concerns for sodium bicarbonate discussed above, alternatives have been developed, including non-CO_2–generating buffers such as THAM and Carbicarb (a 1:1 mixture of disodium carbonate and sodium bicarbonate). Dichloroacetate, which is specifically designed to decrease lactate production in lactic acidosis, was used in animals with some success. Clinical data with these agents are limited, and these agents are not Food and Drug Administration (FDA) approved for routine clinical use. Perhaps more concerning is that none of these agents are still protected by patents, and it is unclear who (if anyone) will bear the cost of studies necessary to demonstrate their clinical safety and efficacy.

KEY POINTS

Treatment of Metabolic Acidosis

1. Hyperchloremic metabolic acidosis is usually effectively treated by gradual correction of acidosis with administration of bicarbonate.
2. Acute treatment of an anion gap metabolic acidosis with intravenous sodium bicarbonate may be deleterious, especially in conditions associated with impaired tissue perfusion.
3. The administration of sodium bicarbonate in animals with metabolic acidosis is associated with a fall in pHi in several organs, as well as additional hemodynamic compromise.

Additional Reading

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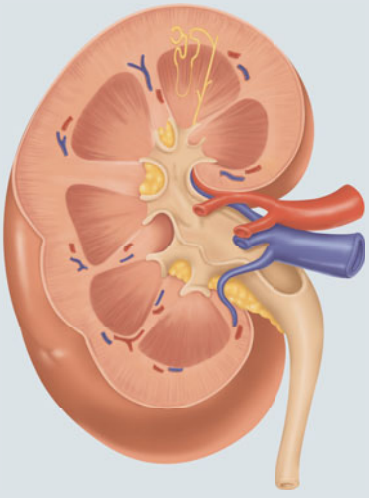

CHAPTER 8

Metabolic Alkalosis

• *Adam M. Franks and Joseph I. Shapiro*

Recommended Time to Complete: 1 Day

Guiding Questions

1. What is metabolic alkalosis and how does it occur?
2. What are the compensatory mechanisms for metabolic alkalosis?
3. How is metabolic alkalosis maintained?
4. What are the clinical features of metabolic alkalosis?
5. How does one differentiate various causes of metabolic alkalosis?
6. How does one treat metabolic alkalosis?

PATHOPHYSIOLOGY OF METABOLIC ALKALOSIS

Metabolic alkalosis is an acid–base disorder that occurs as the result of a process that increases pH (alkalemia) from a primary increase in serum bicarbonate concentration ($[HCO_3^-]$). The primary elevation of serum $[HCO_3^-]$ is caused by the pathophysiologic processes outlined below.

Net H^+ Loss from Extracellular Fluid

A loss of protons from the body occurs primarily through either the kidneys or the gastrointestinal (GI) tract. When H^+ losses exceed the daily H^+ load produced by metabolism and diet, a net negative H^+ balance results. Because the H^+ loss results in the generation of a HCO_3^-, increases in serum $[HCO_3^-]$ result. GI loss of protons generally occurs in the stomach; in this setting, H^+ secretion by the luminal gastric parietal cell H^+-adenosine triphosphatase (ATPase) leaves a HCO_3^- to be reclaimed at the basolateral surface. The coupling between net acid excretion (NAE) and bicarbonate generation in the kidney was discussed at length in Chapter 7. Finally, H^+ shifts into cells may accompany significant potassium depletion. Again, this should produce a rise in extracellular fluid (ECF) $[HCO_3^-]$. Regarding this last mechanism, we should point out that evidence of intracellular acidosis developing during experimental potassium depletion has not been consistently observed in experimental settings, and it is certainly possible that increases in NAE serves as the predominant mechanism for metabolic alkalosis with potassium deficiency.

Net Bicarbonate or Bicarbonate Precursor Addition to Extracellular Fluid

HCO_3^- administration or addition of substances whose metabolism generates HCO_3^- (eg, lactate, citrate) at a rate greater than that of metabolic H^+ production also leads to an increase in ECF $[HCO_3^-]$. In the presence of normal

kidney function, however, ECF [HCO_3^-] will not increase significantly. This occurs because as serum [HCO_3^-] exceeds the plasma threshold for HCO_3^- reabsorption, the kidney excretes the excess HCO_3^-. As a result serum bicarbonate will not rise unless there is a change in renal bicarbonate handling (maintenance factor). The need for maintenance factors in the pathogenesis of metabolic alkalosis is discussed in more detail below.

Loss of Fluid from the Body That Contains Chloride in Greater Concentration and Bicarbonate in Lower Concentration Than Serum

If this type of fluid is lost, ECF volume must contract. If this contraction is substantial enough, a measurable increase in serum [HCO_3^-] develops. Protons are not lost in this setting in contrast to losses noted with vomiting or nasogastric suction. Bicarbonate is now distributed in a smaller volume, resulting in an absolute increase in ECF [HCO_3^-]. This is referred to as *contraction alkalosis*.

KEY POINTS

Pathophysiology of Metabolic Alkalosis

1. Metabolic alkalosis is a systemic disorder characterized by increased pH as a result of a primary increase in serum bicarbonate concentration.
2. Primary elevation of serum bicarbonate concentration is caused by net H^+ loss or net addition of bicarbonate precursors to the ECF.

COMPENSATORY MECHANISMS FOR METABOLIC ALKALOSIS

The first line of pH defense during metabolic alkalosis is, again, buffering. When HCO_3^- is added to ECF, protons react with some of this HCO_3^- to produce CO_2 that is normally exhaled by the lungs. Through this chemical reaction, the increase in serum and ECF [HCO_3^-] is attenuated. It has been shown that the intracellular fluid (ICF) contributes the majority of H^+ used in this buffering process.

Respiratory compensation also occurs with metabolic alkalosis. Under normal conditions, control of ventilation occurs in the brainstem and is most sensitive to interstitial H^+ concentration (see Chapter 9). Respiratory compensation to metabolic alkalosis follows the same principles as respiratory compensation to metabolic acidosis. Of course, the direction of the change of partial pressure of arterial carbon dioxide ($PaCO_2$) is different (ie, hypercapnia as a result of hypoventilation rather than hypocapnia as a result of hyperventilation occurs) and constraints regarding oxygenation must limit the magnitude of this hypoventilatory response. With metabolic alkalosis, the $PaCO_2$ should increase 0.6 to 1.0 times the increase in serum [HCO_3^-]. Absence of compensation in the setting of metabolic alkalosis constitutes the coexistence of a secondary respiratory disturbance.

The third line of defense is renal excretion. This can be described as follows: The normal kidney has a powerful protective mechanism against the development of significant increases in ECF [HCO_3^-], namely the *plasma threshold* for [HCO_3^-], above which proximal reabsorption fails and HCO_3^- losses in urine begin. Mathematically, the plasma [HCO_3^-] can be estimated at a given time following addition of HCO_3^- to the body by:

$$[HCO_3^-]_t = [HCO_3^-]_{PT} + ([HCO_3^-]_{t0} - [HCO_3^-]_{PT}) \times \exp(-t \times GFR/V_d)$$

where $[HCO_3^-]_t$ is the plasma bicarbonate at time t, $[HCO_3^-]_{PT}$ is the plasma threshold for bicarbonate, $[HCO_3^-]_{t0}$ is the bicarbonate concentration after adding bicarbonate to the body, GFR is the glomerular filtration rate, V_d is the volume of distribution for bicarbonate, and exp is the exponential function.

In nonmathematical terms, once the plasma threshold (PT) is exceeded, bicarbonate excretion in urine is proportional to the glomerular filtration rate (GFR). If a patient has a GFR of 100 mL/min and the bicarbonate concentration is 10 mEq/L above the PT, bicarbonate will be lost in the urine initially at a rate of 1 mEq/min! Therefore, the corrective response by the kidney to excrete excessive HCO_3^- in urine usually corrects metabolic alkalosis unless there is a maintenance factor that prevents this. Exceptions to this rule occur when renal function is dramatically impaired and/or when the ongoing alkali load truly overwhelms the renal capacity for bicarbonate elimination. These exceptional situations are both uncommon and easily identified. Therefore, we usually approach the pathophysiology of metabolic alkalosis by addressing initiation factors (ie, factors that initiate the process) and maintenance factors (those that prevent renal excretion of excess bicarbonate). In some cases, as will be seen, the same factor may be responsible for both initiation and maintenance.

KEY POINTS

Compensatory Mechanisms for Metabolic Alkalosis

1. The first line of defense is buffering. When HCO_3^- is added to ECF, H^+ reacts with HCO_3^- to produce CO_2 that is normally exhaled in expired gas. Most of the H^+ used in this buffering comes from the ICF.
2. A rise in $PaCO_2$ is the normal compensatory response to simple metabolic alkalosis.
3. In virtually all cases of metabolic alkalosis, the kidney participates in the pathogenesis by not excreting the excess bicarbonate.

THE MAINTENANCE OF METABOLIC ALKALOSIS

A number of factors increase the apparent tubular maximum concentration (T_{max}) for HCO_3^-. As a result, they increase net HCO_3^- reabsorption by the kidney. Figure 8.1 shows this schematically.

Arterial Blood Volume Decrease

Volume depletion either absolute (eg, salt losses through vomiting or bleeding) or effective (eg, congestive heart failure, nephrotic syndrome, hepatic cirrhosis) increases the T_{max} and PT for HCO_3^-. This occurs through both proximal (increased proximal tubule reabsorption of Na^+ and water) and distal (mineralocorticoid effect) mechanisms. Catecholamines and angiotensin II stimulate the Na^+-H^+ exchanger isoform in the luminal membrane of proximal tubule (NHE3). Proton excretion into urine generates bicarbonate that is transported across the basolateral membrane into blood. Mineralocorticoids act distally to directly stimulate the H^+-ATPase, and indirectly raise the driving force for proton excretion by increasing lumen electronegativity (through stimulation of the epithelial sodium channel).

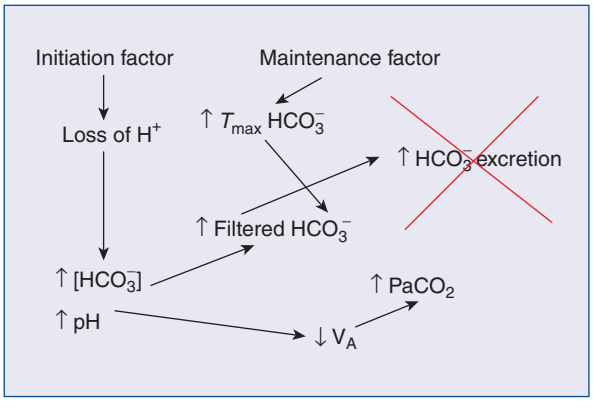

FIGURE 8-1. The importance of maintenance factors in the pathophysiology of metabolic alkalosis. In this figure, we see that proton loss (eg, from vomiting) leads to increases in pH and $[HCO_3^-]$. These increases in $[HCO_3^-]$ are accompanied by increases in HCO_3^- filtration and loss in urine. If a maintenance factor (eg, volume depletion, primary mineralocorticoid excess) is present, however, that raises the tubular transport of HCO_3^- (T_{max}), increased renal losses of HCO_3^- are prevented, and metabolic alkalosis is maintained. Note that the higher pH causes a decrease in alveolar ventilation (V_A; see Chapter 9) and the $PaCO_2$ increases.

Chloride Depletion

Sodium and chloride losses result in ECF volume depletion. Studies show that chloride is independently (ie, besides being a marker for ECF volume) involved in HCO_3^- reabsorption. In fact, even despite ECF expansion, chloride depletion increases the PT for HCO_3^-, thereby raising ECF $[HCO_3^-]$.

Aldosterone

Mineralocorticoids increase distal sodium reabsorption which, in turn, increases renal HCO_3^- generation and effectively raises the *PT* and T_{max} for HCO_3^-. These effects can occur in the absence of decreases in effective arterial blood volume. Aldosterone's predominant effect is in distal nephron. Figure 8.2 shows a model of 2 of the 3 major cell types in the collecting duct, the principal cell and the α intercalated cell. The principal cell is responsible for sodium reabsorption and potassium secretion. The α intercalated cell mediates acid secretion and, therefore, bicarbonate reabsorption and generation. Potassium secretion is passive and dependent strictly on the electrochemical gradient. Potassium secretion can be increased by raising intracellular potassium, lowering luminal potassium, or making the lumen more electronegative. Indeed, the major factors that control distal potassium secretion operate by changing these driving forces. Stimulation of the Na^+-K^+-ATPase by aldosterone, increases intracellular potassium. Aldosterone also increases distal sodium reabsorption by causing the insertion of sodium channels, as well as synthesis of new sodium channels. In the long term, aldosterone also increases the expression of the Na^+-K^+-ATPase in most epithelial cells, and directly stimulates the H^+-ATPase present in the luminal

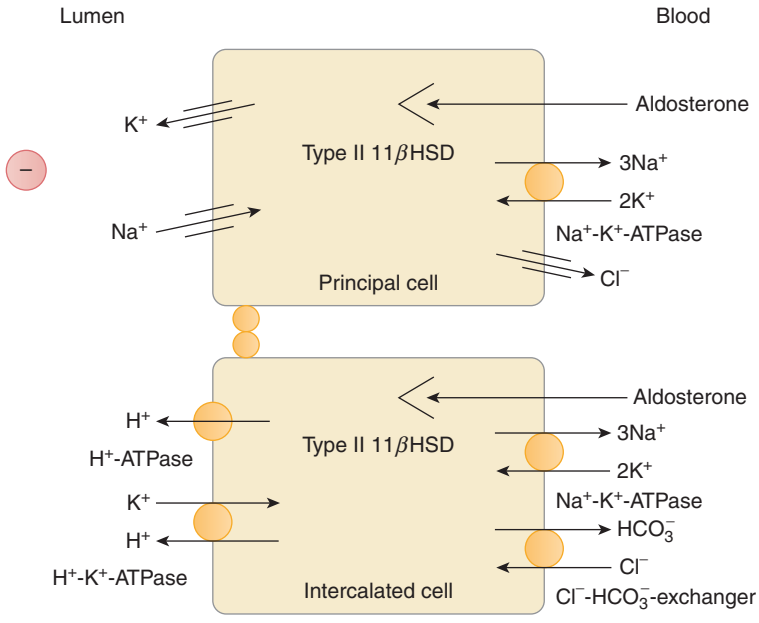

FIGURE 8-2. Collecting duct cell model. Proteins involved in sodium, potassium, and acid–base homeostasis are shown in both principal cells and α intercalated cells.

membrane of the intercalated cell. It also acts indirectly by increasing lumen electronegativity (through sodium reabsorption). Aldosterone binds to its receptor in the cytoplasm; this complex then translocates to the nucleus and stimulates gene transcription.

Surprisingly, it was found that glucocorticoids have similar affinity to that of aldosterone for the mineralocorticoid receptor. In addition glucocorticoids circulate at many times the concentration of aldosterone. So how could aldosterone ever have an effect? The answer to this question lies in the fact that target tissues for aldosterone, such as collecting duct cells, possess the enzyme type II 11β-hydroxysteroid dehydrogenase (HSD) that degrades active cortisol to inactive cortisone. If this enzyme is congenitally absent (apparent mineralocorticoid excess), inhibited (licorice), or overwhelmed (Cushing syndrome), then glucocorticoids can exert a mineralocorticoid-like effect in collecting duct.

Potassium Depletion

Potassium depletion also may increase the apparent T_{max} and PT for HCO_3^- and, thus, act as a maintenance factor for metabolic alkalosis. One potential mechanism for this is that potassium depletion may promote a relative intracellular acidosis, which makes renal H^+ excretion more favorable; however, there is considerable evidence against this appealing concept. For one, there are orders of magnitude in concentration differences involved when we compare protons to potassium ions. The $[H^+]$ in ECF is only approximately 40 nM (although intracellular concentrations may be slightly higher), whereas potassium concentrations may change by 1 to 2 mmol/L. More problematic is the observation that investigators failed to detect a decrease in renal intracellular pH during experimental potassium depletion with ^{31}P nuclear magnetic resonance (NMR) spectroscopy. Moreover, in human studies, metabolic alkalosis can be corrected almost completely without correction of potassium depletion. More likely mechanisms for the increased T_{max} for HCO_3^- resulting from K depletion follow. First, potassium depletion results in cellular potassium depletion in the proximal tubule. This, in turn, would be expected to hyperpolarize the basolateral membrane and increase the driving force for bicarbonate exit via the Na^+-$3HCO_3^-$ cotransporter. Second, potassium depletion upregulates H^+-K^+-ATPase in the collecting duct's intercalated cell. It is likely that this upregulation results in increased H^+ secretion in this segment. This, in turn, would result in HCO_3^- generation and addition to ECF.

Hypercapnia

The apparent T_{max} and PT for HCO_3^- are raised by increases in $PaCO_2$. This is probably related to the decreases in intracellular pH that occur during acute and chronic hypercapnia. Analogous to our discussion in Chapter 7, increases in $PaCO_2$ that occur during metabolic alkalosis as part of normal respiratory compensation impair the ability of the kidney to return serum bicarbonate concentration to normal.

KEY POINTS

Maintenance of Metabolic Alkalosis

1. Pathogenesis of metabolic alkalosis requires factors, which initiate or generate it and those that maintain it.
2. Several factors increase the apparent T_{max} for HCO_3^- and thus, increase net HCO_3^- reabsorption by the kidney. These include decreases in effective arterial blood volume, chloride depletion, increases in aldosterone, potassium depletion, and hypercapnia.
3. The most important maintenance factor is volume depletion.

CLINICAL FEATURES OF METABOLIC ALKALOSIS

Signs and symptoms of metabolic alkalosis are nonspecific. Patients who present with muscle cramps, weakness, arrhythmias, or seizures, especially in the setting of diuretic use and vomiting, should prompt consideration of metabolic alkalosis. Most signs and symptoms are caused by the decreases in ionized calcium that occur as the increased pH causes plasma proteins to bind calcium more avidly. At a pH above 7.6, malignant ventricular arrhythmias and seizures may be seen. It is interesting to note that humans tolerate alkalosis less well than acidosis.

Examination of arterial blood gases will demonstrate an increased pH, increased $[HCO_3^-]$, and increased $PaCO_2$, with the increase in $PaCO_2$ being between 0.6 and 1 times the increase in $[HCO_3^-]$. Serum electrolytes reveal increased total CO_2 content (TCO_2), which is the sum of the serum $[HCO_3^-]$ and dissolved CO_2, decreased chloride concentration, and, typically, decreased potassium concentration. Hypokalemia occurs predominantly from enhanced renal losses. Renal potassium excretion results from maintenance factors involved in the pathogenesis of the metabolic alkalosis. Elevated concentrations of mineralocorticoids (or substances with mineralocorticoid-like activity) are almost always involved as a maintenance factor. Severe metabolic alkalosis may also be associated with an increased serum anion gap (SAG) (increases by 3-5 mEq/L). This is a result of small increases in lactate concentration resulting from enhanced glycolysis secondary to disinhibition of phosphofructokinase. The majority of the increase in SAG, however, is a result of the increased electronegativity of albumin with elevated pH.

KEY POINTS

Clinical Features of Metabolic Alkalosis

1. There are no specific signs or symptoms of metabolic alkalosis. Many of the symptoms may be related to associated hypocalcemia.
2. Severe alkalosis (pH >7.6) can cause malignant arrhythmias, as well as seizures.

DIFFERENTIAL DIAGNOSIS

The first step in evaluation of patients with metabolic alkalosis is to subdivide them into those that have ECF chloride depletion as a maintenance factor (chloride responsive) (Table 8.1) from those that do not (chloride

TABLE 8-1. Causes of Chloride-Responsive Metabolic Alkalosis

Gastrointestinal Causes
Vomiting or gastric drainage
Villous adenoma of the colon
Chloride diarrhea
Renal Causes
Diuretic therapy
Posthypercapnia
Poorly reabsorbable anions
Exogenous Alkali Administration or Ingestion
Bicarbonate administration
Milk–alkali syndrome
Transfusion of blood products (sodium citrate)

TABLE 8-2. Causes of Chloride-Resistant Metabolic Alkalosis

With Hypertension
Primary aldosteronism
Renal artery stenosis
Renin-producing tumor
Cushing syndrome
Licorice or chewing tobacco
Apparent mineralocorticoid excess
Congenital adrenal hyperplasia
Liddle syndrome
Without Hypertension
Bartter syndrome and Gitelman syndrome
Current diuretic use
Profound potassium depletion
Hypercalcemia (nonhyperparathyroid etiology)
Poststarvation (refeeding alkalosis)
Transfusion of blood products (sodium citrate)

resistant) (Table 8.2). This is accomplished by measuring urinary chloride. At first glance this might be surprising because urinary sodium concentration and fractional excretion of sodium are examined most commonly as indicators of volume depletion. These may be misleading in metabolic alkalosis, however, especially if the kidney is excreting bicarbonate (generation phase) that will obligate increased sodium excretion. Urine chloride concentration allows one to classify patients into chloride-responsive and chloride-resistant categories (Figure 8.3). In general, chloride-responsive metabolic alkalosis corrects when volume expansion or improvement of hemodynamics occur. In contrast, chloride-resistant metabolic alkalosis does not correct with these maneuvers. Patients with chloride-responsive metabolic alkalosis typically have urine chloride concentrations less than 20 mEq/L, whereas patients with chloride-resistant metabolic alkalosis have urine chloride concentrations exceeding 20 mEq/L.

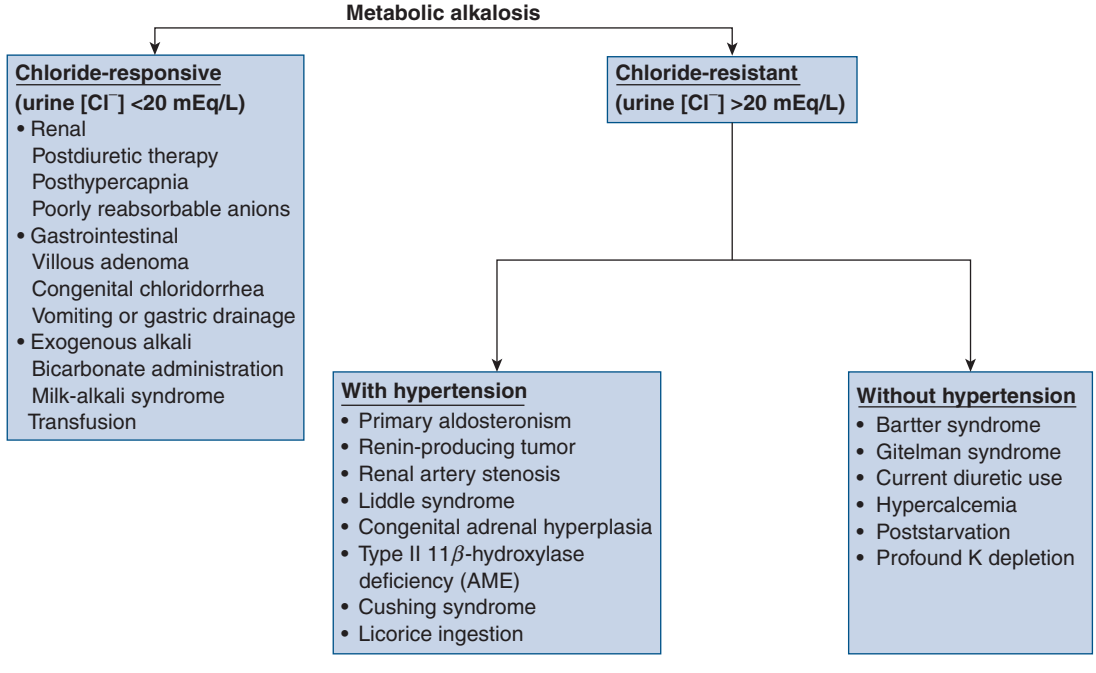

FIGURE 8-3. Differential diagnosis of metabolic alkalosis. The differential diagnosis of metabolic alkalosis based on the urine [Cl^-] is shown. The urine [Cl^-] is used to separate chloride-responsive causes of metabolic alkalosis (where the urine [Cl^-] is <20 mEq/L) from chloride-resistant causes of metabolic alkalosis where the urine [Cl^-] is generally greater than 20 mEq/L. These chloride-resistant causes can be further separated by whether the patient is hypertensive or not. *Abbreviation:* AME, apparent mineralocorticoid excess.

CHLORIDE-RESPONSIVE METABOLIC ACIDOSIS

Vomiting and Gastric Drainage

Patients with persistent vomiting or nasogastric suctioning may lose up to 2 L/day of fluid containing a proton concentration of 100 mmol/L. Given that for each H^+ secreted a HCO_3^- molecule is generated, gastric parietal cells can excrete up to 200 mmol of HCO_3^- per day. This constitutes a very significant initiation factor; however, it is the sodium, chloride, and potassium losses that allow metabolic alkalosis to be maintained. It is notable that potassium losses are more significant in urine than in vomitus, which generally contains only approximately 10 mEq/L of potassium.

Metabolic alkalosis that develops with vomiting is often mild. Similar to protracted vomiting, gastric drainage (generally via a nasogastric tube) also causes a metabolic alkalosis. The same phenomenon can also occur in patients after gastrocystoplasty; a procedure that involves implantation of a gastric mucosal patch in the urinary bladder. The gastric mucosa retains its ability to secrete protons, which are then excreted in the urine.

Colonic Villous Adenoma

Rarely, a colonic villous adenoma has significant secretory potential. This type of adenoma may produce profound diarrhea that contains excessive amounts of protein, sodium, potassium, and chloride. These diarrheal losses of sodium, potassium, and chloride, and the relatively low HCO_3^- concentration in the fluid, may lead to metabolic alkalosis—in contrast to the typical metabolic acidosis that more commonly complicates diarrheal states.

Congenital Chloridorrhea

Congenital chloridorrhea is a rare congenital syndrome arising from a defect in small- and large-bowel chloride absorption. This causes chronic diarrhea with a fluid that is rich in chloride leading to metabolic alkalosis. This disorder is the result of a mutation in the solute carrier family 26 member 3 gene (SCLC26A3). SCLC26A3 is a Cl-bicarbonate and Cl-sulfate exchanger and is expressed in the apical membrane of colonic epithelium.

Diuretic Therapy

Loop diuretics that exert their effects in the thick ascending limb of Henle (loop diuretics, eg, furosemide, bumetanide) and thiazide diuretics that act in distal convoluted tubule (eg, hydrochlorothiazide, and metolazone) may facilitate volume depletion, as well as directly stimulate renin secretion (loop diuretics). These diuretics can, thus, provide both initiation and maintenance factors to produce metabolic alkalosis. If the diuretic is still active, urinary chloride concentration is typically elevated. If the diuretic is cleared from the circulation and is no longer active (typically 24 to 48 hours after a dose), urinary chloride concentration is low, reflecting a normal renal response to volume depletion. Metabolic alkalosis associated with hypokalemia is a common complication of diuretic use, and should suggest the possibility of diuretic abuse. Diuretics are commonly abused in patients with anorexia nervosa.

Posthypercapnia

The kidney responds to chronic elevations in $PaCO_2$ by raising the plasma HCO_3^- concentration. If hypercapnia is subsequently corrected rapidly, as occurs with intubation and mechanical ventilation, the elevated serum HCO_3^- concentration will persist for at least several hours until renal correction is complete. Note that sufficient chloride must be present to allow for this renal correction. Many patients with diseases leading to hypercapnia are also treated with diuretics that may cause chloride depletion.

Poorly Reabsorbable Anions

Large doses of some β-lactam antibiotics, such as penicillin and carbenicillin, may result in hypokalemic metabolic alkalosis. The initiation and maintenance factor is the delivery of large quantities of poorly reabsorbable anions to the distal nephron with attendant increases in H^+ and potassium excretion.

Cystic Fibrosis

Metabolic alkalosis may develop in children with cystic fibrosis as a consequence of chloride losses in sweat that has a low $[HCO_3^-]$. The maintenance factor is the resultant volume depletion caused by these losses. In some cases, this may be the initial manifestation of the disease.

Alkali Administration

As discussed earlier, the normal kidney rapidly excretes alkali. Ergo, a sustained metabolic alkalosis requires a maintenance factor. In these settings, continuous and/or massive administration of alkali may cause metabolic

alkalosis. This alkali load may be in the form of HCO_3^- or, more commonly, in the form of substances whose metabolism yields HCO_3^-, as with citrate or acetate. In particular, it is clear that patients with chronic kidney disease whose ability to excrete a HCO_3^- load is decreased may develop sustained metabolic alkalosis following alkali administration. Baking soda is the richest source of exogenous alkali, containing 60 mEq of bicarbonate per teaspoon. Many patients ingest baking soda as a "home remedy" to treat dyspepsia and various GI problems. There has been at least 1 case report of metabolic alkalosis in a hemodialysis patient who was free-basing cocaine. In this case, the alkali load was likely a result of sodium hydroxide (NaOH) and baking soda in the preparation.

Milk–Alkali Syndrome

The milk–alkali syndrome was classically noted in patients with GI upset who consumed a diet rich in milk and cream along with "Sippy Powders" that contained sodium bicarbonate, magnesium carbonate, and bismuth subcarbonate. Patients presented with hypercalcemia, hyperphosphatemia, increased serum bicarbonate concentration, and an elevated blood urea nitrogen (BUN) and creatinine. In the current era, calcium carbonate ingestion, with or without vitamin D, is the most common cause. As a result some have suggested renaming this syndrome the "calcium–alkali" syndrome. Hyperphosphatemia is no longer commonly found as it was largely a result of the milk and cream consumption. Volume depletion (or at least the lack of ECF volume expansion) along with hypercalcemia-mediated suppression of parathyroid hormone (PTH) secretion contribute to the maintenance of metabolic alkalosis. Activation of the calcium-sensing receptor by elevated calcium concentration in blood and urine may also contribute to the pathophysiology. Activation of the calcium-sensing receptor in the basolateral membrane of the thick ascending limb inhibits luminal NaCl reabsorption resulting in a loop diuretic-like effect. Calcium-sensing receptor activation in the luminal membrane of the collecting duct reduces water channel (AQP2) insertion and promotes water loss. The resulting hypercalcemia also decreases renal blood flow and glomerular filtration, further impairing renal correction of metabolic alkalosis. Nephrocalcinosis may develop with chronic antacid ingestion, a pathologic factor that decreases GFR further, and thus more profoundly reduces the kidney's ability to excrete an alkali load.

Transfusion of Blood Products

Infusion of more than 10 units of blood containing the anticoagulant citrate can produce a moderate metabolic alkalosis, analogous to alkali administration discussed earlier. In many cases, some degree of prerenal azotemia may contribute to the maintenance of metabolic alkalosis. Through an identical mechanism, patients given parenteral hyperalimentation with excessive amounts of acetate or lactate may also develop metabolic alkalosis.

CHLORIDE-RESISTANT METABOLIC ALKALOSIS

Renal Artery Stenosis

Renal artery stenosis is a frequent clinical problem that develops in the elderly and those with advanced vascular disease. The most common cause of a chloride-resistant metabolic alkalosis with associated hypertension is renovascular disease. This is discussed in more detail in Chapter 21.

Primary Aldosteronism

With primary aldosteronism, excess aldosterone acts as both the initiation and maintenance factor for metabolic alkalosis. Several mechanisms are involved; some are the result of increased sodium reabsorption and potassium secretion, whereas others are independent of sodium or potassium transport. Increased H^+ secretion promotes reclamation of filtered HCO_3^- and generation of new HCO_3^-, which is ultimately retained in the ECF. Interestingly, although the increased ECF volume tends to mitigate the alkalosis by decreasing proximal tubular bicarbonate reabsorption, distal processes aid in maintenance of an elevated plasma HCO_3^- threshold. In primary aldosteronism, the clinical features of a hypokalemic metabolic alkalosis are produced, often in concert with hypertension that results from ECF volume expansion.

Recent data suggest that primary aldosteronism may occur in as many as 14% of adult hypertensive patients; however, most of these patients do not have a significant metabolic alkalosis. Primary aldosteronism may be caused by an adrenal tumor, which selectively synthesizes aldosterone (Conn syndrome) or hyperplasia (usually bilateral) of the adrenal cortex. The diagnosis of a primary mineralocorticoid excess state depends on the demonstration that ECF volume is expanded (eg, nonstimulatable plasma renin activity) and nonsuppressible

aldosterone secretion is present (eg, demonstration that exogenous mineralocorticoids and a high-salt diet or acute volume expansion with saline do not suppress plasma aldosterone concentration).

This is done in 3 steps. First, patients that are suspected of having the disorder are screened with an early morning plasma aldosterone and renin level and the aldosterone-to-renin ratio (ARR) is calculated. Clinical suspicion should be high in patients with hypertension that does not respond to 3 or more agents of different classes; spontaneous or low-dose diuretic-induced hypokalemia; a first-degree relative with primary aldosteronism; or a known adrenal mass. This step requires the discontinuation of all potassium-sparing diuretics for at least 6 weeks. If possible other drugs that affect aldosterone and renin concentrations should be held such as β blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, central antiadrenergics, and nonsteroidal antiinflammatory agents. This is often difficult, given the degree of hypertension in these patients, and clinical judgment needs to weigh the risks of stopping any of these agents. In addition, potassium deficits must be repleted. Primary aldosteronism is suggested by a high ARR. A variety of different cutoffs, from 20 to 50, have been used. The higher the cutoff the lower the sensitivity and the higher the specificity. Aldosterone concentration should be equal to or greater than 15 ng/dL and renin suppressed.

The second step is a confirmatory test. This can be either a saline suppression test, a 24-hour urine for aldosterone after a salt load, or a fludrocortisone suppression test. The saline suppression test has the advantage that the patient can be carefully monitored during the procedure. Two liters of normal saline are administered intravenously over 4 hours. If the plasma aldosterone concentration (PAC) remains above 10 ng/dL after the infusion the diagnosis is confirmed. PAC should suppress to less than 5 ng/dL in normals. With salt loading, the patient consumes a 5-g sodium diet for 3 days. This can be achieved by administering two 1 g NaCl tablets 3 times a day for 3 days. On the third day a 24-hour urine is collected for sodium, potassium, and aldosterone. A 24-hour urine aldosterone excretion greater than 12 µg in the presence of a normal serum potassium concentration and a urinary sodium excretion greater than 200 mEq/day confirms the diagnosis. The patient must be monitored closely as the salt load may significantly increase blood pressure and increase renal potassium excretion. Serum potassium concentration must be monitored closely and potassium supplemented as needed. In the fludrocortisone suppression test, 0.1 mg of fludrocortisone is administered every six hours with salt supplements for 4 days. PAC is then measured after the patient is upright for 30 minutes. A value greater than 8 ng/dL confirms the diagnosis.

The third step, adrenal venous sampling, differentiates those with an adrenal adenoma from patients with bilateral adrenal hyperplasia. During a continuous adrenocorticotropic hormone (ACTH) infusion at 50 µg/h, samples for aldosterone and cortisol are drawn from the right and left adrenal veins, as well as the inferior vena cava (IVC). To verify that blood was indeed collected from the adrenal veins the adrenal vein to IVC cortisol ratio should be greater than 5. If ACTH is not infused, then a ratio of adrenal vein to IVC cortisol concentration of greater than 3 is often used. The aldosterone-to-cortisol ratio is then determined in each adrenal vein and a value greater than 4 is indicative of a unilateral adenoma.

It is important to realize the limitations of adrenal computed tomography (CT) scans for the diagnosis of primary aldosteronism. Diagnostic accuracy in general is low with a high rate of false negatives and false positives. The exception is in patients younger than the age of 40 years with a unilateral nodule larger than 1 cm and a normal contralateral gland. Its greatest utility may be in the detection of the rare patient with an adrenal carcinoma, which are generally large in size (>4 cm).

In some families, glucocorticoid-remediable aldosteronism (GRA) develops from a gene duplication fusing regulatory sequence of an isoform of the 11β-hydroxylase gene to the coding sequence of the aldosterone synthase gene. The diagnosis of this entity should be entertained in subjects in whom family members also have difficult to control hypertension. Clinical confirmation is generally pursued with the measurement of elevated concentrations of 18-OH-cortisol and 18-oxocortisol in urine prior to genetic analysis. Patients with GRA can often be successfully treated with glucocorticoid supplementation.

Cushing Syndrome

Cushing syndrome is characterized by excessive corticosteroid synthesis. Tumors that secrete ectopic ACTH are more likely to cause hypokalemia and metabolic alkalosis than pituitary tumors. Most corticosteroids (specifically cortisol, deoxycorticosterone, and corticosterone) also have significant mineralocorticoid effects and produce hypokalemic metabolic alkalosis. Hypertension typically

is present. Collecting duct cells contain type II 11β-HSD that degrades cortisol to the inactive metabolite cortisone. Cortisol secretion in response to ectopic ACTH may be so high, however, that it overwhelms the metabolic capacity of the enzyme. In addition, type II 11β-HSD may be inhibited by ACTH.

Bartter and Gitelman Syndrome

Bartter syndrome is characterized by hyperreninemia, hyperaldosteronemia in the absence of hypertension or sodium retention. This rare condition generally presents in childhood. Histologically, hyperplasia of the juxtaglomerular apparatus was observed, but this is not specific. The disorder is caused by an abnormality in thick ascending limb chloride reabsorption (cell model shown in Figure 8.4). This results in high distal nephron sodium and chloride delivery, renin-angiotensin-aldosterone system activation, and development of hypokalemic metabolic alkalosis. The primary disturbance was initially felt to be an abnormality in the prostaglandin system; however, it is now clear that increased renal prostaglandins in these patients is secondary. Genetic studies have elucidated the molecular basis of the disease. Bartter syndrome is caused by 1 of 6 abnormalities. Specifically, inherited inactivity of the apical Na^+-K^+-$2Cl^-$ transporter, the ROMK potassium channel, the basolateral chloride channel (CLC-K_b), the β-subunit of the basolateral chloride channel (barrtin), a gain-of-function mutation in the calcium-sensing receptor, or mutations in both basolateral chloride channels ClC-Ka and ClC-kb (proteins that are each essential to medullary thick ascending limb of Henle function) can all result in Bartter syndrome. A pseudo-Bartter syndrome can occur as a result of treatment with aminoglycosides. Aminoglycosides can bind to and activate the calcium-sensing receptor. Stimulation of the receptor inhibits ROMK and the Na^+-K^+-$2Cl^-$ transporter.

A closely related condition, Gitelman syndrome, is caused by mutations in the thiazide-sensitive NaCl transporter important in distal tubule function. Gitelman syndrome may present in adults, and is probably more common than Bartter syndrome. The two syndromes can be difficult to distinguish. Some have advocated using the administration of a thiazide diuretic to differentiate them. In Gitelman syndrome, urinary chloride would not

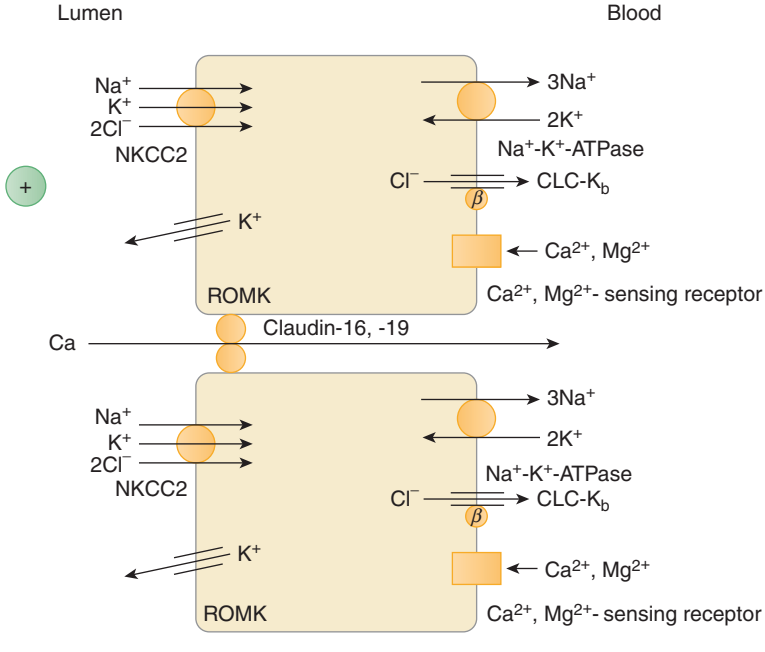

FIGURE 8-4. Thick ascending limb cell model. Proteins involved in ion transport in the thick ascending limb are shown. Abnormalities of 6 of these proteins result in Bartter syndrome and are discussed in the text.

increase, whereas in Bartter syndrome, urinary chloride would be expected to increase.

Both Bartter and Gitelman syndromes can closely mimic diuretic abuse. In fact, Bartter syndrome and Gitelman syndrome can be functionally imitated by the pharmacologic administration of loop and thiazide diuretics, respectively. Therefore, it is important to consider surreptitious diuretic use as an alternative to these diagnoses, especially if patients present de novo as adolescents or adults with previously normal serum potassium and bicarbonate concentrations. Measuring diuretic concentrations in urine is often part of the initial workup.

Liddle Syndrome

Liddle syndrome is a rare autosomal dominant disorder resulting from a mutation in either the β- or γ-subunit of the sodium channel expressed in the apical membrane of the collecting duct. The mutation increases sodium reabsorption by blocking removal of the channel from the membrane. The molecular mechanism was discussed in Chapter 2. Metabolic alkalosis, hypokalemia, and severe hypertension characterize this genetic disorder.

Licorice and Apparent Mineralocorticoid Excess

Glycyrrhizic and glycyrrhetinic acid, which are found in both licorice and chewing tobacco, may cause a hypokalemic metabolic alkalosis accompanied by hypertension, and thus, simulate primary aldosteronism. Recent studies demonstrate that this chemical inhibits type II 11β-HSD activity and "uncovers" the mineralocorticoid receptor, which is normally "protected" by this enzyme from glucocorticoid stimulation. As glucocorticoids circulate at much higher concentrations than mineralocorticoids and produce comparable stimulation of the mineralocorticoid receptor, the result is a clinical syndrome similar to primary aldosteronism without elevated PAC. Apparent mineralocorticoid excess (AME) is an autosomal recessive disorder that results from mutations in the type II 11β-HSD gene.

Profound Potassium Depletion

Severe hypokalemia (serum $[K^+]$ <2 mEq/L) may result in metabolic alkalosis. Urine chloride concentration exceeds 20 mEq/L in this setting. In some reports, affected individuals did not demonstrate mineralocorticoid excess, and their alkalosis did not correct with sodium repletion until potassium was repleted. This indicates that severe hypokalemia may sometimes convert a chloride responsive to a chloride-resistant metabolic alkalosis. We should stress, however, that correction of metabolic alkalosis without repletion of potassium deficits was shown. Therefore, although hypokalemia contributes to the maintenance of metabolic alkalosis and should be corrected, potassium supplementation does not appear necessary to correct metabolic alkalosis.

Hypercalcemia (Suppressed Parathyroid Hormone)

Patients with hypercalcemia from malignancy or sarcoid and not from hyperparathyroidism, may develop a mild metabolic alkalosis. This is likely to be a result of the calcium-mediated suppression of PTH, which may raise the PT for HCO_3^- reabsorption.

Poststarvation (Refeeding Alkalosis)

After a prolonged fast, administration of carbohydrates may produce a metabolic alkalosis that persists for weeks. The initiation factor for this form of metabolic alkalosis is not known, but increased renal sodium reabsorption secondary to ECF volume depletion is responsible for maintenance of the alkalosis.

KEY POINTS

Chloride-Resistant Metabolic Alkalosis

1. Metabolic alkalosis is classified based on urine chloride concentration into chloride responsive and chloride resistant.
2. The most common causes of chloride-responsive metabolic alkalosis are diuretics and vomiting.
3. Chloride-resistant metabolic alkaloses are caused by conditions associated with increased aldosterone concentration or an aldosterone-like effect (type II 11β-HSD associated disorders or a sodium channel mutation).

APPROACH TO THE PATIENT WITH CHLORIDE-RESISTANT METABOLIC ALKALOSIS

As shown in Figure 8.3, patients are initially subdivided based on the presence or absence of hypertension. Those patients with hypertension can then be further

TABLE 8-3. Renin and Aldosterone Concentrations in Patients with Chloride-Resistant Metabolic Alkalosis and Hypertension

	RENIN CONCENTRATION	ALDOSTERONE CONCENTRATION
Primary aldosteronism	Decreased	Increased
GRA	Decreased	Increased
Renal artery stenosis	Increased	Increased
Renin-producing tumor	Increased	Increased
Cushing syndrome	Decreased	Decreased
Licorice ingestion	Decreased	Decreased
AME	Decreased	Decreased
Liddle syndrome	Decreased	Decreased

Abbreviations: GRA, glucocorticoid-remediable aldosteronism; AME, apparent mineralocorticoid excess.

categorized based on their renin and aldosterone concentrations shown in Table 8.3. Many of these disorders are discussed in more detail in Chapter 21.

TREATMENT

Treatment of metabolic alkalosis, as with all acid–base disturbances, hinges on correction of the underlying disease state; however, the severity of the acid–base disturbance itself may be life-threatening in some cases, and requires specific therapy. This is especially true in mixed acid–base disturbances where pH changes are in the same direction (such as a respiratory alkalosis from sepsis and a metabolic alkalosis secondary to vomiting). In these circumstances increased pH may become life threatening resulting in seizures or ventricular arrhythmias that require rapid reduction in systemic pH through control of ventilation. In this clinical condition, intubation, sedation, and controlled hypoventilation with a mechanical ventilator (sometimes using inspired CO_2 and/or supplemental oxygen to prevent hypoxia) is often lifesaving.

In the past, administration of either HCl, arginine hydrochloride, or ammonium chloride was used to correct metabolic alkalosis, these agents can result in significant potential complications. Hydrochloric acid may cause intravascular hemolysis and tissue necrosis, while ammonium chloride may result in ammonia toxicity. In addition, their effect is not rapid enough to prevent or treat life-threatening complications. Therefore, in the setting of a clinical emergency, controlled hypoventilation must be employed. Once the situation is no longer critical, partial or complete correction of metabolic alkalosis over the ensuing 6 to 8 hours with HCl administered as a 0.15 M solution through a central vein is preferred. Generally, the "acid deficit" is calculated assuming a bicarbonate distribution space of 0.5 times body weight in liters, and about half of this amount of HCl is given with frequent monitoring of blood gases and electrolytes.

In less-urgent settings, metabolic alkalosis is treated after examining whether it is chloride-responsive or not. Chloride-responsive metabolic alkalosis is responsive to volume repletion. Coexistent hypokalemia should also be corrected. Chloride-resistant metabolic alkaloses are treated by antagonizing the mineralocorticoid (or mineralocorticoid-like substance) that maintains renal H^+ losses. This sometimes can be accomplished with spironolactone, eplerenone, or other distal K^+-sparing diuretics like amiloride.

It is not unusual that the actual cause of metabolic alkalosis is a result of a therapy that is essential in the management of a disease state. The hypokalemic metabolic alkalosis that develops from loop diuretic use in the nephrotic syndrome patient is an example where continued diuretic use is needed to manage the patient's severe edema. A creative approach to such clinical scenarios is the addition of the proximal diuretic acetazolamide, which will decrease the PT for HCO_3^- by inhibiting proximal tubule HCO_3^- reabsorption. The prescription of a proton pump inhibitor will decrease gastric H^+ losses in the patient who requires prolonged gastric drainage. In those with far advanced chronic kidney disease and severe metabolic alkalosis, hemodialysis may be required.

KEY POINTS

Treatment of Metabolic Alkalosis

1. With life-threatening pH elevation (eg, pH >7.6 with seizures and ventricular arrhythmias), rapid pH reduction is accomplished by control of ventilation.
2. HCl or its congeners do not work fast enough to prevent or treat life-threatening complications.
3. Once the situation is no longer critical, partial or complete correction of metabolic alkalosis over 6 to 8 hours with HCl administered as a 0.15 M solution through a central vein can be carried out.

4. Chloride-responsive metabolic alkalosis corrects with volume replacement and improved hemodynamics.
5. Chloride-resistant metabolic alkalosis may need treatment with mineralocorticoid receptor antagonists or sodium channel blockers.

Additional Reading

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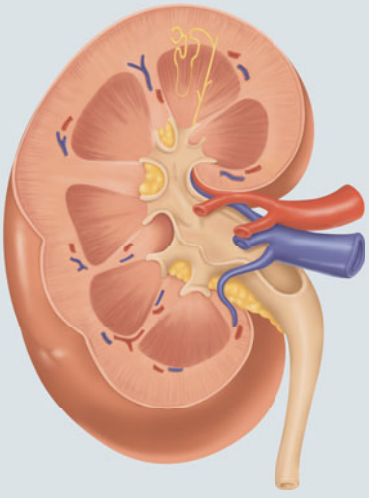
CHAPTER 9

Respiratory and Mixed Acid–Base Disturbances



• *Adam M. Franks and Joseph I. Shapiro*

Recommended Time to Complete: 1 Day

Guiding Questions

1. How is respiration controlled?
2. What is ventilation?
3. What is respiratory acidosis and how does it occur?
4. What mechanisms are involved in compensation for respiratory acidosis?
5. What is respiratory alkalosis and how does it occur?
6. What mechanisms are involved in the compensation for respiratory alkalosis?
7. What are clues to the presence of a mixed acid–base disturbance?
8. How do we approach the patient with a mixed acid–base disorder?

RESPIRATORY DISTURBANCES

Introduction

Breathing is an automatic, rhythmic, and centrally regulated process by which contraction of the diaphragm and rib cage moves gas in and out of the airways and alveolae of the lungs. Respiration includes breathing, but it also involves the circulation of blood, allowing for O_2 intake and CO_2 excretion.

Two patterns are involved in the control of breathing: automatic and volitional. The automatic component is largely under the control of partial pressure of carbon dioxide (PCO_2). The control center for this breathing resides in the brainstem within the reticular activating system (Figure 9.1). There are 2 major regions that control automatic ventilation: the medullary respiratory areas and the pontine respiratory group. Interestingly, less is known about volitional control than automatic control of respiration; consequently, we restrict our discussion to automatic breathing.

Two main types of chemoreceptors—central and peripheral—are involved in the control of automatic breathing. The most important ones are located in the medulla of the central nervous system (CNS). The main peripheral chemoreceptors are within the carotid bodies, although less-important receptors were identified in the

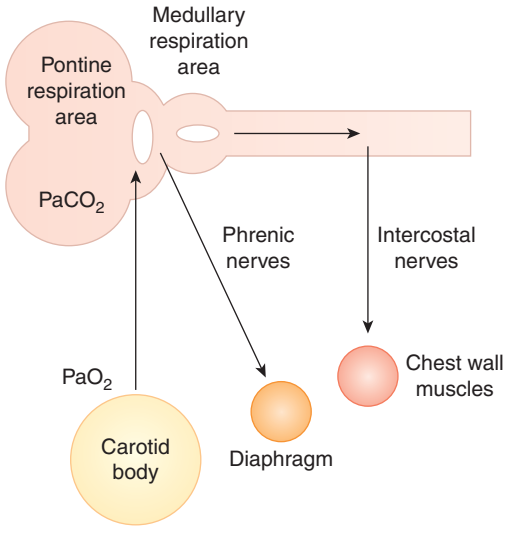


FIGURE 9-1. Control of ventilation. Schematic illustrating that central control of ventilation is largely through partial pressure of arterial carbon dioxide ($PaCO_2$)-sensitive chemoreceptors in the pons and medulla, whereas peripheral input is largely through partial pressure of arterial oxygen (PaO_2)-sensitive chemoreceptors in the carotid body. Output is to the diaphragm via the phrenic nerves and thoracic muscles largely via intercostal innervations.

aortic arch. Central chemoreceptors respond to changes in partial pressure of arterial carbon dioxide ($PaCO_2$) largely through changes in brain pH (interstitial and cytosolic). This is a sensitive system, and $PaCO_2$ control is generally tight. In contrast, respiratory control by oxygen tensions is much less important until partial pressure of arterial oxygen (PaO_2) falls to levels below 70 mmHg. This is a result of the hemoglobin-oxygen (Hb-O_2) dissociation curve, as Hb saturation is generally above 94% until the PaO_2 falls below 70 mmHg. O_2 control of respiration is mediated largely through peripheral chemoreceptors which, in response to low O_2, close adenosine triphosphate (ATP)-sensitive K^+ channels and depolarize glomus cells in the carotid body. The 2 systems interact, in that, with hypoxia, the central response to PCO_2 is enhanced. As we discuss later, with chronic hypercapnia, control of respiration by CO_2 is severely blunted, leaving some patients' respiration almost entirely under the control of O_2 tensions.

In addition to neural control, the physical machinery of breathing is also extremely important in gas exchange. This physical machinery involves the lungs, bones, and the thorax musculature that interact to move air in and out of the pulmonary air spaces. Just as there may be neural defects that impair respiration, abnormalities of the skeleton, musculature, airways, air spaces, or lung blood supply may impair respiration. To some degree, these abnormalities are assessed and characterized by pulmonary function tests. Although it is beyond the scope of this chapter to discuss this topic in detail, it should be clear to the reader that modern pulmonary function tests readily differentiate problems with airway resistance (eg, asthma or chronic obstructive pulmonary disease) from those of alveolar diffusion (eg, interstitial fibrosis) or neuromuscular function (eg, phrenic nerve palsy, Guillain-Barré syndrome). Figure 9.1 shows a simplified schematic of the elements involved in controlling ventilation.

Pulmonary ventilation refers to the amount of gas brought into and/or out of the lung. Pulmonary ventilation is expressed as minute ventilation (ie, how much air is inspired and expired within 1 minute) or in functional terms as alveolar ventilation (VA). The difference between these terms occurs because the portion of ventilation confined to the conductance airways does not effectively exchange O_2 for CO_2 in alveolae. Because O_2 uptake and CO_2 excretion are so critical, we can reference ventilation with regard to either of these gases. However, because CO_2 excretion is so effective and ambient CO_2 tensions in the atmosphere are so low, pulmonary ventilation generally is synonymous with pulmonary CO_2 excretion. Note that CO_2 is much more soluble than O_2 and exchange across the alveolar capillary for CO_2 is essentially complete under most circumstances, whereas some O_2 gradient from alveolus to the alveolar capillary is always present.

We should also point out that ventilation occurs at the tissue level as well. In this case, rather than inspired air removing CO_2 in its gaseous form, CO_2 produced by cells is largely (approximately 75%) converted to bicarbonate (HCO_3^-) and removed from the local cellular environment by blood flow. Although it is an extreme case, when CO_2 tensions in expired gases are monitored during cardiac arrest, the institution of effective circulation is accompanied by a sharp increase in expired CO_2.

KEY POINTS

Respiratory Disturbances

1. CNS respiratory centers receive input from chemoreceptors locally ($PaCO_2$) and peripherally (PaO_2).

2. Ventilation is determined by the integration of neural inputs, neural outputs, muscular responses, flow through airways, and gas exchange between alveolae and pulmonary capillaries.

RESPIRATORY ACIDOSIS

Respiratory acidosis is defined as a primary increase in $PaCO_2$ secondary to decreased effective ventilation with net CO_2 retention. This decrease in effective ventilation can occur from defects in any aspect of ventilation control or implementation. Table 9.1 summarizes these different causes.

Compensation for respiratory acidosis occurs at several levels. Some of these processes are rapid, analogous to what is seen with major compensatory mechanisms for metabolic acidosis or alkalosis, whereas others are slower. This allows us to clinically distinguish between acute and chronic respiratory acidosis in some cases.

With respiratory acidosis, a rise in bicarbonate concentration $[HCO_3^-]$ is a normal, compensatory response. As is the case for metabolic disorders, a failure of this normal adaptive response is indicative of the presence of metabolic acidosis in the setting of a complex or mixed acid–base disturbance. Conversely, an exaggerated increase in HCO_3^- producing a normal pH indicates the presence of metabolic alkalosis in the setting of a complex or mixed acid–base disturbance.

Mechanisms by which respiratory acidosis increases HCO_3^- concentration are as follows. First and probably foremost, increases in $PaCO_2$ and decreases in O_2 tension stimulate ventilatory drive, antagonizing the process that led to CO_2 retention in the first place. Next, mechanisms by which CO_2 transport occurs from tissues to lungs become operant. In other words, increases in $PaCO_2$ are immediately accompanied by a shift to the right of the reaction:

$$H_2CO_3 \rightarrow H^+ + HCO_3^-$$

and increases in HCO_3^- concentration result. The amount of this increase in $[HCO_3^-]$ in mEq/L is 0.1 times the increase in $PaCO_2$ in mmHg (±2 mEq/L). The kidney provides the mechanism for the majority of chronic compensation. Once $PaCO_2$ increases and arterial pH decreases, renal acid excretion and retention of bicarbonate become more avid. Some of this is a direct chemical consequence of elevated $PaCO_2$ and mass action facilitating intracellular bicarbonate formation. Other portions involve genomic adaptations of tubular cells involved in renal acid excretion. On this latter topic, enzymes involved in renal ammoniagenesis (eg, glutamine synthetase),

TABLE 9-1. Causes of Respiratory Acidosis

Acute	Airway obstruction—aspiration of foreign body or vomitus, laryngospasm, generalized bronchospasm, obstructive sleep apnea Respiratory center depression—general anesthesia, sedative overdosage, cerebral trauma or infarction, central sleep apnea Circulatory catastrophes—cardiac arrest, severe pulmonary edema Neuromuscular defects—high cervical cordotomy, botulism, tetanus, Guillain-Barré syndrome, crisis in myasthenia gravis, familial hypokalemic periodic paralysis, hypokalemic myopathy, toxic drug agents (eg, curare, succinylcholine, aminoglycosides, organophosphates) Restrictive defects—pneumothorax, hemothorax, flail chest, severe pneumonitis, hyaline membrane disease, adult respiratory distress syndrome Pulmonary disorders—pneumonia, massive pulmonary embolism, pulmonary edema, mechanical underventilation
Chronic	Airway obstruction—chronic obstructive lung disease (bronchitis, emphysema) Respiratory center depression—chronic sedative depression, primary alveolar hypoventilation, obesity hypoventilation syndrome, brain tumor, bulbar poliomyelitis Neuromuscular defects—poliomyelitis, multiple sclerosis, muscular dystrophy, amyotrophic lateral sclerosis, diaphragmatic paralysis, myxedema, myopathic disease (eg, polymyositis, acid maltase deficiency) Restrictive defects—kyphoscoliosis, spinal arthritis, fibrothorax, hydrothorax, interstitial fibrosis, decreased diaphragmatic movement (eg, ascites), prolonged pneumonitis, obesity

as well as apical and basolateral ion transport proteins (eg, Na^+-H^+ exchanger, Na^+-K^+-adenosine triphosphatase [ATPase]) are synthesized in increased amounts at key sites within the nephron. In sum, chronic respiratory acidosis present for at least 4 to 5 days will be accompanied by a $[HCO_3^-]$ increase equal to 0.4 times the increase in $PaCO_2$ (mmHg) (±3 mEq/L). Note that renal correction also never completely returns the arterial pH to the level it was at prior to CO_2 retention.

KEY POINTS

Respiratory Acidosis

1. In respiratory acidosis, the primary disturbance is an increase in $PaCO_2$ secondary to a decrease in effective ventilation with net CO_2 retention.
2. Decreases in effective ventilation can result from defects in any aspect of ventilation control or implementation.
3. In respiratory acidosis, the $[HCO_3^-]$ rises as a normal, compensatory response.
4. A failure of the normal adaptive response indicates the presence of metabolic acidosis in the setting of a complex or mixed acid–base disturbance.
5. The kidney provides the mechanism for the majority of chronic compensation.

TABLE 9-2. Causes of Respiratory Alkalosis

Hypoxia
Decreased inspired oxygen tension
Ventilation–perfusion inequality
Hypotension
Severe anemia
CNS Mediated
Voluntary hyperventilation
Neurologic disease: cerebrovascular accident (infarction, hemorrhage); infection (encephalitis, meningitis); trauma; tumor
Pharmacologic and hormonal stimulation: salicylates; ditrophenol; nicotine; xanthines; pressor hormones; pregnancy
Hepatic failure
Gram-negative septicemia
Anxiety-hyperventilation syndrome
Heat exposure
Pulmonary disease
Interstitial lung disease
Pneumonia
Pulmonary embolism
Pulmonary edema
Mechanical overventilation

RESPIRATORY ALKALOSIS

Respiratory alkalosis is defined as a primary decrease in $PaCO_2$ secondary to an increase in effective ventilation with net CO_2 removal. This increase in effective ventilation can occur from defects in any aspect of ventilation control or implementation. Table 9.2 summarizes these different causes.

With respiratory alkalosis, a fall in $[HCO_3^-]$ is a normal, compensatory response. As was the case for respiratory acidosis and the metabolic disorders, a failure of this normal adaptive response is indicative of the presence of metabolic alkalosis in the setting of a complex or mixed acid–base disturbance. Conversely, an exaggerated decrease in $[HCO_3^-]$ producing a normal pH indicates the presence of metabolic acidosis in the setting of a complex or mixed acid–base disturbance.

The mechanisms by which respiratory alkalosis decreases $[HCO_3^-]$ concentration are as follows. First and probably foremost, decreases in $PaCO_2$ will inhibit ventilatory drive, antagonizing the process that led to reductions in CO_2 tension in the first place. Decreases in $PaCO_2$ are immediately accompanied by a shift to the left of the reaction:

$$H_2CO_3 \rightarrow H^+ + HCO_3^-$$

and decreases in $[HCO_3^-]$ result. The amount of this decrease in $[HCO_3^-]$ is (in mEq/L) 0.1 times the decrease in $PaCO_2$ in mmHg (with an error range of ±2 mEq/L). Again, the kidney provides the mechanism for the majority of chronic compensation. Once $PaCO_2$ decreases and arterial pH increases, renal excretion of acid and reabsorption of bicarbonate are reduced. Some of this is a direct chemical consequence of decreased $PaCO_2$ and mass action antagonizing intracellular bicarbonate formation. Other portions involve genomic adaptations of tubular cells involved in renal acid excretion. Essentially, the reverse of what we described for metabolic compensation for respiratory acidosis occurs. In sum, chronic respiratory alkalosis present for at least 4 to 5 days will be accompanied by a $[HCO_3^-]$ decrease (in mEq/L) of 0.4 times the increase in $PaCO_2$ (mmHg) (with an error range of ±3 mEq/L). Note that renal correction also never

completely returns arterial pH to the level it was at prior to respiratory alkalosis. Moreover, decreases in [HCO_3^-] below 12 mEq/L are generally not seen from metabolic compensation for respiratory alkalosis.

KEY POINTS

Respiratory Alkalosis

1. In respiratory alkalosis the primary process is a decrease in $PaCO_2$ secondary to an increase in effective ventilation with net CO_2 removal.
2. With respiratory alkalosis, a fall in [HCO_3^-] is a normal, compensatory response.
3. A failure of this normal adaptive response is indicative of the presence of metabolic alkalosis in the setting of a complex or mixed acid–base disturbance.
4. The kidney provides the mechanism for the majority of chronic compensation.
5. Decreases in [HCO_3^-] below 12 mEq/L are generally not seen from metabolic compensation for respiratory alkalosis.

MIXED DISTURBANCES

The first clue to the presence of a mixed acid–base disorder is the degree of compensation. As discussed above, "overcompensation" or an absence of compensation are certain indicators that a mixed acid–base disorder is present. For metabolic disorders, the respiratory compensation should be immediate; in these settings, it is relatively easy to determine whether compensation is appropriate (see Chapters 7 and 8). For respiratory disorders, however, it is a bit more complex because metabolic compensation takes days to become complete. Note that mass action will produce approximately a 0.1 mEq/L change in [HCO_3^-] for every 1 mmHg change in $PaCO_2$; ergo, a complete absence of metabolic compensation for respiratory acidosis or alkalosis clearly indicates a second primary disturbance. For degrees of compensation between 0.1 and 0.4 times the change in $PaCO_2$, it is difficult if not impossible to distinguish between a failure of compensation (eg, a primary metabolic disorder) and an acute respiratory disturbance on the blood gas alone. Figure 9.2 illustrates these rules of compensation graphically. To

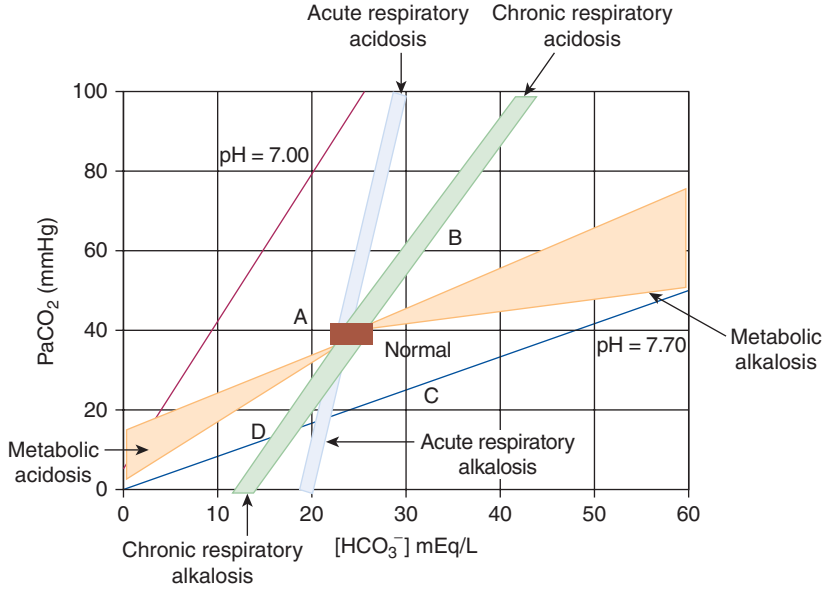


FIGURE 9-2. Acid–base nomogram. Acid–base nomogram derived from rules of compensation described in the text. Regions associated with simple acid–base disorders are identified in the shaded regions. **A,** Mixed respiratory and metabolic acidosis; **B,** mixed respiratory acidosis and metabolic alkalosis; **C,** mixed respiratory alkalosis and metabolic alkalosis; and **D,** mixed respiratory alkalosis and metabolic acidosis. Regions between acute and chronic respiratory acidosis and acute and chronic respiratory alkalosis cannot be uniquely defined (see text). Lines of constant pH 7.00 and 7.70, as well as normal range (black box), shown for reference.

further address this question, we must return to our description of the anion gap in Chapter 7. Recall that the serum anion gap (SAG) can be defined as:

$$SAG = [Na^+] - [C1^-] - [HCO_3^-]$$

but this can also be interpreted as:

$$SAG = UA - UC$$

(where UA = unmeasured anions and UC = unmeasured cations).

To use the SAG in the approach to a complex acid–base disorder, we make the stoichiometric assumption that for a pure organic acidosis:

$$\Delta SAG = \Delta[HCO_3^-]$$

Since we don't have "pre" and "post" disorder values, we further assume that the SAG started at 10 mEq/L and the $[HCO_3^-]$ started at 24 mEq/L. With these assumptions, we can diagnose simultaneous anion gap metabolic acidosis and metabolic alkalosis when the SAG is large and the decrease in $[HCO_3^-]$ is relatively small. A common clinical scenario for this occurs when vomiting accompanies an anion gap metabolic acidosis, such as lactic acidosis in the setting of bowel ischemia. Conversely, we can also diagnose simultaneous nonanion gap metabolic acidosis with anion gap metabolic acidosis if the fall in $[HCO_3^-]$ is much larger than the modestly but significantly increased SAG. Probably the most common example for this would be renal failure where some degree of nonanion gap acidosis and anion gap acidosis coexist. Figure 9.3 shows these situations schematically. Table 9.3 shows a list of clinical scenarios where complex acid–base disorders often occur.

It is appropriate at this point to reiterate the reason that one performs analysis of acid–base disorders. Quite simply, it is to gain insight into the clinical problems that the patient is facing. To this end, it is important to realize that the accurate diagnosis of a mixed disorder is more than a matter of semantics. In some cases, it may even be lifesaving. The following case illustrates this. An 8-year-old boy presents to an emergency room with history of a viral illness followed by progressive obtundation. His arterial blood gas shows a pH of 7.00, $PaCO_2$ = 38 mmHg, $[HCO_3^-]$ = 9 mEq/L. The serum glucose concentration is elevated, and both urine and blood are positive for ketones. The SAG is calculated at 25 mEq/L.

Why is it so important to accurately diagnose that the patient above has a mixed respiratory and metabolic acidosis (see Figure 9.2) rather than "uncompensated" metabolic

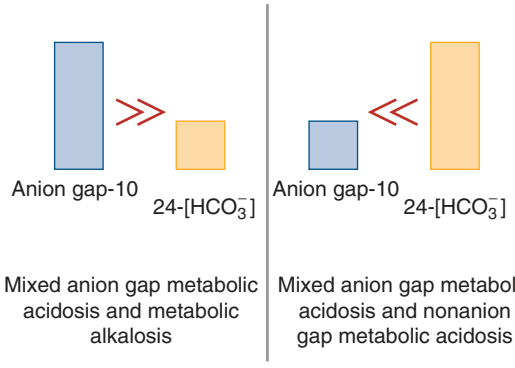


FIGURE 9-3. Diagnosis of hidden mixed acid–base disturbances. Schematic illustrating how one can diagnose hidden mixed acid–base disturbances by comparing the change in anion gap to the change in bicarbonate concentration. If the change in anion gap is much larger than the fall in bicarbonate concentration this implies the coexistence of anion gap metabolic acidosis and metabolic alkalosis (*left panel*). If the change in anion gap is much smaller than the change in the bicarbonate concentration then this implies the presence of an anion gap and nonanion gap metabolic acidosis (*right panel*).

TABLE 9-3. Syndromes Commonly Associated with Mixed Acid–Base Disorders

Hemodynamic Compromise
Cardiopulmonary arrest
Pulmonary edema
Sepsis
Liver failure
Poisonings
Ethylene glycol intoxication
Methanol intoxication
Aspirin intoxication
Ethanol intoxication
Metabolic Disturbances
Severe hypokalemia
Severe hypophosphatemia
Diabetic ketoacidosis
Bowel ischemia
Chronic obstructive pulmonary disease
Chronic kidney disease

acidosis? In the scenario described, it is likely that the child will soon stop breathing. Although the $PaCO_2$ of 38 mmHg is a "normal" value, it is not appropriate compensation and, thus, must be interpreted as another primary disorder. Understanding that this truly represents respiratory acidosis confers appropriate urgency to the clinical situation and also may prompt a search for potential causes of respiratory acidosis. In this case, the respiratory acidosis is likely secondary to neuromuscular fatigue; however, in other clinical situations it may prompt a search for causes of central respiratory depression (eg, sedative administration) or acute airway obstruction.

As was the case for simple acid–base disorders, the key reason for analyzing mixed acid–base disorders is to create short lists of differential diagnoses to further explore clinically. This is generally accomplished diagnosis by diagnosis. In other words, if a patient were found to have a triple acid–base disorder consisting of respiratory alkalosis, anion gap metabolic acidosis, and metabolic alkalosis, one would examine each of these separately and put them together in the context of the patient.

In Chapters 7 and 8, we stated that the degree of acidosis or alkalosis is rarely life-threatening by itself. Although this is true, the exceptional cases generally involve mixed acid–base disorders where both respiratory and metabolic disorders change pH in the same direction. For example, mixed respiratory acidosis and metabolic acidosis that might occur in the setting of cardiac and respiratory arrest may produce low enough pH to impair cardiac contractile function and/or vascular tone. Conversely, respiratory alkalosis in combination with metabolic alkalosis (eg, a patient with pulmonary edema treated with potassium wasting diuretics) could develop elevations in pH sufficient to cause seizures and/or cardiac arrhythmias. When these extreme conditions occur, correct therapy is directed at pH control through the control of ventilation. Once the pH is adjusted to one that is not life-threatening, the metabolic disturbance(s) are addressed. We reiterate that treatment of the acid–base disorder always involves making the correct clinical diagnosis of the underlying causes and appropriate specific therapy directed at those causes.

KEY POINTS

Mixed Acid–Base Disorders

1. Mixed acid–base disorders may result from the coexistence of primary respiratory and metabolic disorders, the coexistence of metabolic alkalosis with anion gap metabolic acidosis, and/or the coexistence of nonanion gap metabolic acidosis with anion gap metabolic acidosis.
2. To evaluate compensation, one applies the following rules:

   Metabolic acidosis: compensatory change in $PaCO_2$ (mmHg) = 1 to 1.5 × the fall in $[HCO_3^-]$ (mEq/L) or the $PaCO_2$ (mmHg) = 1.5 × $[HCO_3^-]$ + 8 ± 2.

   Metabolic alkalosis: compensatory change in $PaCO_2$ (mmHg) = 0.6 to 1 × the increase in $[HCO_3^-]$ (mEq/L).

   Acute respiratory acidosis or alkalosis: compensatory change in $[HCO_3^-]$ (mEq/L) = 0.1 × the change in $PaCO_2$ (mmHg) ± 2 (mEq/L).

   Chronic respiratory acidosis or alkalosis: compensatory change in $[HCO_3^-]$ (mEq/L) = 0.4 × the change in $PaCO_2$ (mmHg) ± 3 (mEq/L).

   Failure to achieve the appropriate degree of compensation implies a second primary disorder.
3. The most dangerous mixed disturbances occur when both metabolic and respiratory alkalosis or metabolic and respiratory acidosis coexist.
4. Stoichiometric equivalence between the change in anion gap and the reduction in $[HCO_3^-]$ is assumed with anion gap metabolic acidosis. A marked discrepancy between these measurements implies the coexistence of either anion gap metabolic acidosis and metabolic alkalosis or anion gap metabolic acidosis and nonanion gap metabolic acidosis.
5. Triple acid–base disorders are diagnosed when both respiratory and metabolic disturbances are present and either anion gap metabolic acidosis and metabolic alkalosis or anion gap metabolic acidosis and nonanion gap metabolic acidosis coexist.

Additional Reading

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SECTION II

Mineral Metabolism

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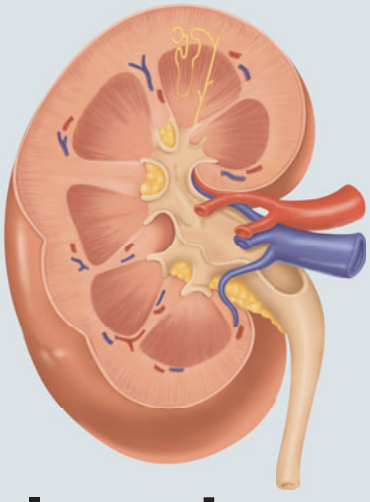

CHAPTER

10

Disorders of Calcium Homeostasis—Hypo and Hypercalcemia

• *Nishank Jain and Robert F. Reilly Jr.*

Recommended Time to Complete: 1 Day

Guiding Questions

1. How is extracellular fluid (ECF) ionized calcium regulated?
2. What roles do parathyroid hormone (PTH) and $1,25(OH)_2$ vitamin D_3 (calcitriol) play in this process?
3. What 3 pathophysiologic processes are involved in the generation of hypercalcemia?
4. Which 2 diseases make up the majority of cases of hypercalcemia and how do their presentations differ?
5. Can you devise a rational treatment plan for the hypercalcemic patient?
6. Why does the hypomagnesemic patient develop hypocalcemia?
7. How does one approach the patient with hypocalcemia?
8. What are the keys to successfully treating hypocalcemia?

REGULATION OF EXTRACELLULAR FLUID IONIZED CALCIUM

Calcium (Ca^{2+}) in the body plays a key structural role in the bony skeleton and as a messenger in extracellular and intracellular signaling. Of the 1 kg of Ca^{2+} present in the body, 99% is in bones and teeth. The remaining 1% is present in the ECF whose concentration is tightly regulated. Normal plasma concentration is 8.8 to 10.3 mg/dL (2.2 to 2.6 mM or 4.4 to 5.2 mEq/L). Sixty percent of ECF calcium is ultrafilterable (50% free and 10% complexed to anions) and the other 40% is bound to plasma proteins (mainly albumin). Ionized calcium concentration ($[iCa^{2+}]$), normally between 1.05 and 1.23 mM, is regulated by 3 hormones (PTH, calcitriol, and calcitonin), 3 target organs (kidney, bone, and parathyroid gland), and a sensor (calcium-sensing receptor) to detect ECF Ca^{2+} concentration. The vast majority of total-body

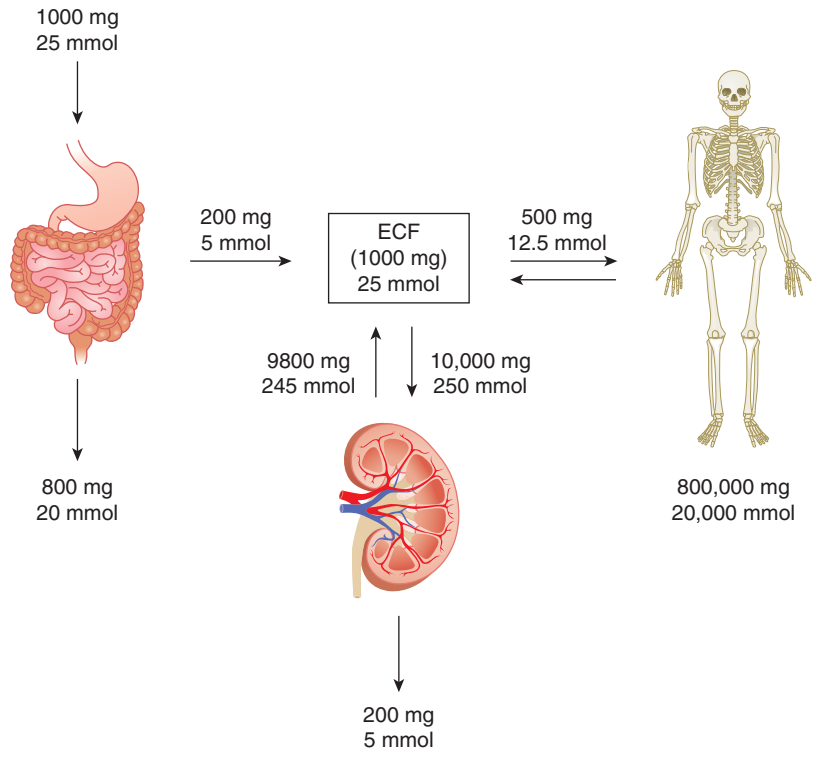

FIGURE 10-1. Calcium homeostasis. Daily calcium fluxes between ECF, intestine, kidney, and bone are shown. In the steady state, net intestinal absorption and renal calcium excretion are equal. The majority of calcium in the body is in bone. (With permission from Schrier RW, ed. *Manual of Nephrology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.)

calcium exists as hydroxyapatite in bone (99%). This reservoir is so large that one cannot become hypocalcemic without a decrease in bone calcium release as a result of a defect in either PTH or calcitriol concentration or action. The intracellular iCa^{2+} concentration (0.1 μM) is maintained at very low levels by sequestering Ca^{2+} into the endoplasmic reticulum and mitochondria, or actively extruding Ca^{2+} across plasma membranes by the Ca^{2+}-adenosine triphosphatase (ATPase) pump (present in all cells) and the sodium-calcium exchanger (NCX) (present in certain tissues).

Figure 10.1 illustrates average daily calcium fluxes between ECF and organ systems involved in its regulation (bone, intestine, and kidney). The average adult takes in 1000 mg and absorbs approximately 20% in intestine (primarily passive process). In the steady state, intestinal absorption is matched by urinary Ca^{2+} excretion. Most of the calcium absorption in the small intestine (primarily duodenum) is passive, with a small fraction absorbed by active transport. The kidney excretes approximately 2% (200 mg) of the filtered calcium load and acts as a principal regulatory organ for extracellular Ca^{2+} balance. Approximately 65% of the filtered Ca^{2+} load is reabsorbed in proximal tubule. The majority occurs across the paracellular space with a small active component. Twenty-five percent is reabsorbed in the thick ascending limb (TAL), driven by the lumen-positive potential difference generated by the actions of ROMK, as well as claudin-16 and -19. The remaining 8% is actively reabsorbed transcellularly in the distal convoluted tubule and connecting tubule. Calcium entry into the distal nephron is mediated via TRPV5 (transient receptor potential vanilloid-5) channels that are regulated by secreted klotho and PTH. Once calcium enters the cell in kidney and duodenum, it binds to calbindin (intracellular shuttling proteins) and is extruded across the basolateral membrane by NCX1. Fractional excretion of Ca^{2+} is 1% to 2%, but even small changes in distal nephron reabsorption lead to large effects on the final amount of Ca^{2+} in urine.

The calcium-sensing receptor (CaSR), a G-protein coupled receptor, is expressed in the plasma membrane of the parathyroid gland and the basolateral membrane

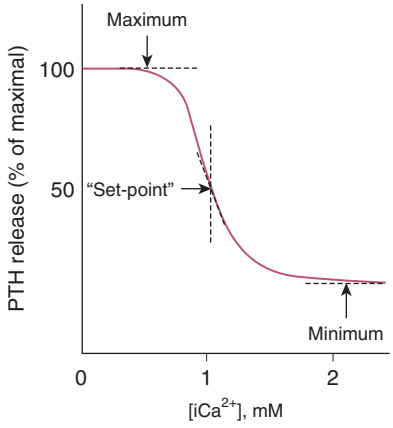

FIGURE 10-2. PTH-calcium response curve. There is an inverse sigmoidal relationship between ionized calcium concentration and PTH release from the parathyroid gland. The set-point is that ionized calcium concentration at which PTH release is inhibited by 50%. The minimum arrow illustrates that there is a basal level of PTH release even at high calcium concentration.

of the TAL of Henle in kidney. In the collecting duct, the CaSR is expressed in the apical membrane. Its activation stimulates urinary acidification and reduces water reabsorption via aquaporin-2 (AQP2) downregulation. In the parathyroid gland, it couples changes in ECF [iCa^{2+}] to the regulation of PTH secretion mediated by activating phospholipase C (PLC) and reducing intracellular cyclic adenosine monophosphate (cAMP) levels. High [iCa^{2+}] activates the CaSR and inhibits PTH release, whereas low [iCa^{2+}] has opposite effects on PTH secretion within minutes of the changes. There is an inverse sigmoidal relationship between [iCa^{2+}] and PTH secretion (Figure 10.2). The CaSR knockout mouse demonstrates marked parathyroid hyperplasia, suggesting that the receptor also plays a role in parathyroid cell growth and proliferation. A rise in PTH induces 25-hydroxyvitamin D-1α-hydroxylase, which increases serum calcitriol levels and induces intestinal Ca^{2+} absorption. Hypercalcemia induces thyroid C-cells to secrete calcitonin, a hormone that inhibits osteoclast mediated bone resorption.

Furthermore, extracellular Ca^{2+} has hormone-like action on the kidney mediated by the CaSR expressed on the basolateral membrane of TAL. Activation of CaSR by high [iCa^{2+}] results in inhibition of apical sodium entry via the furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter. Simultaneously, inhibition of the apical membrane potassium channel (ROMK) occurs by activating PLC, cAMP and arachidonic acid intermediates, resulting in a reduction of the lumen-positive voltage that drives paracellular calcium transport. This results in increased urinary calcium excretion. In addition, the ability of the kidney to concentrate urine is also impaired as a consequence of inhibition of the Na^+-K^+-$2Cl^-$ cotransporter. Hypercalciuria, also, induces collecting tubule insensitivity to vasopressin-mediated water reabsorption via a reduction of aquaporin channels in the luminal membrane.

In the distal nephron, secreted klotho cleaves the sialic acid present on galactose residues of the N-terminus of the TRPV5 channel, which acts as a binding site for galectin-1, resulting in increased TRPV5 channels in the apical membrane because of reduced caveolae-mediated endocytosis. PTH via the PTH 1 receptor inhibits the sodium-proton exchanger (NHE3) in proximal tubule and reduces bicarbonate reabsorption. PTH increases TRPV5 gene expression in the distal nephron. PTH also increases TRPV5 activity via cAMP-protein kinase A (PKA)–mediated phosphorylation. TRPV5 activity is pH sensitive. Increases in intracellular pH increase open probability of TRPV5 resulting in channel recruitment to the apical membrane. Reductions in pH have opposite effects.

Calcitriol increases calcium and phosphorus availability for bone formation and prevents hypocalcemia and hypophosphatemia. In intestine and kidney, calcitriol plays an important role in stimulating calcium transport via increasing calcium binding protein (calbindin) expression. Calbindins bind calcium and shuttle it from the apical to the basolateral membrane, thereby allowing calcium to move through the cell without an increase in free intracellular calcium concentration. Calcitriol increases sodium phosphate cotransporter expression in intestine. In bone, calcitriol has a variety of effects: (a) potentiation of PTH effects; (b) stimulation of osteoclast-mediated reabsorption; and (c) induction of monocyte differentiation into osteoclasts. In parathyroid gland, calcitriol binds to its receptor in the cytoplasm and forms a heterodimer with the retinoid X receptor and is translocated to the nucleus. The complex binds to the PTH gene promoter and decreases PTH expression, as well as inhibits parathyroid growth.

Chronic thiazide administration causes hypocalciuria thought to be mediated by a combination of increased proximal and distal Ca^{2+} reabsorption. This process is similar to that seen in patients with Gitelman syndrome. The highest incidence of thiazide-induced hypercalcemia is observed in 70- to 79-year-old women after a mean of 6 years of thiazide ingestion. Interestingly, many of these patients are eventually diagnosed with primary hyperparathyroidism

(PHPT) as the hypocalciuric effects of the thiazide are thought to uncover mild PHPT. If hypercalciuria persists after thiazide diuretics are stopped, a search for a parathyroid adenoma should be undertaken.

KEY POINTS

Regulation of Extracellular Fluid Ionized Calcium

1. PTH and calcitriol regulate ECF [iCa^{2+}].
2. Calcium concentration is sensed by the CaSR, which plays an important role in regulating PTH secretion.
3. PTH increases calcium concentration via actions in bone, intestine, and kidney.
4. PTH and hypophosphatemia enhance 1α-hydroxylase activity in proximal tubule leading to calcitriol formation.
5. Calcitriol increases availability of calcium and phosphorus for bone formation and prevents hypocalcemia and hypophosphatemia.
6. Calcitriol is the most potent suppressor of PTH gene transcription.
7. Klotho increases TRPV5 channel activity and increases calcium reabsorption in the distal nephron. Klotho-deficient mice exhibit hypercalciuria with resultant increase in serum calcitriol concentration, increased intestinal calcium absorption, osteopenia, and nephrolithiasis.

TABLE 10-1. Etiologies of Hypercalcemia

Increased Bone Resorption
Hyperparathyroidism (primary and secondary)
Malignancy
Thyrotoxicosis
Immobilization
Paget disease
Addison disease
Lithium
Vitamin A intoxication
Familial hypocalciuric hypercalcemia
Increased GI Absorption
Increased calcium intake Calcium-alkali syndrome Chronic kidney disease (calcium and vitamin D supplements)
Increased vitamin D concentration Vitamin D intoxication Granulomatous disease
Decreased Renal Excretion
Thiazide diuretics

HYPERCALCEMIA

Etiology

Hypercalcemia results from increased calcium absorption from gastrointestinal (GI) tract, increased bone resorption, or decreased renal calcium excretion (Table 10.1).

Increased GI calcium absorption is important in hypercalcemia that results from the calcium–alkali syndrome (formerly called the milk–alkali syndrome), vitamin D intoxication, and granulomatous diseases. Calcium–alkali syndrome results from excessive intake of calcium and bicarbonate or its equivalent. In addition, alkalosis stimulates calcium reabsorption in the distal nephron. Suppression of PTH secretion by hypercalcemia further increases proximal tubular bicarbonate reabsorption. The most common cause of the calcium–alkali syndrome in the past was milk and sodium bicarbonate ingestion for therapy of peptic ulcer disease, hence the former name milk–alkali syndrome. Today, the most common clinical setting is an elderly woman with history of hypertension, chronic kidney disease (CKD), osteoporosis, and an upper GI disorder, who is treated with diuretics and calcium-vitamin D supplementation. Typically, PTH and calcitriol levels are suppressed in such patients, despite the presence of CKD. Alkalosis, renal dysfunction, and hypercalcemia maintain a vicious cycle. ECF volume depletion maintains alkalosis that triggers increased GI absorption and decreased urinary calcium excretion (TRPV5 is pH sensitive), resulting in hypercalcemia. Hypercalcemia triggers volume depletion, free water loss, and nausea, perpetuating metabolic alkalosis. Bulemics taking supplemental calcium or on a high-calcium diet are also at high risk for the calcium–alkali syndrome. Treatment of these patients is often complicated by rebound hypocalcemia as a result of sustained PTH suppression from hypercalcemia. This is more likely in patients who are treated with bisphosphonates. For this reason bisphosphonates in patients with calcium–alkali syndrome should only be used in those with severe hypercalcemia resistance to more conventional therapies

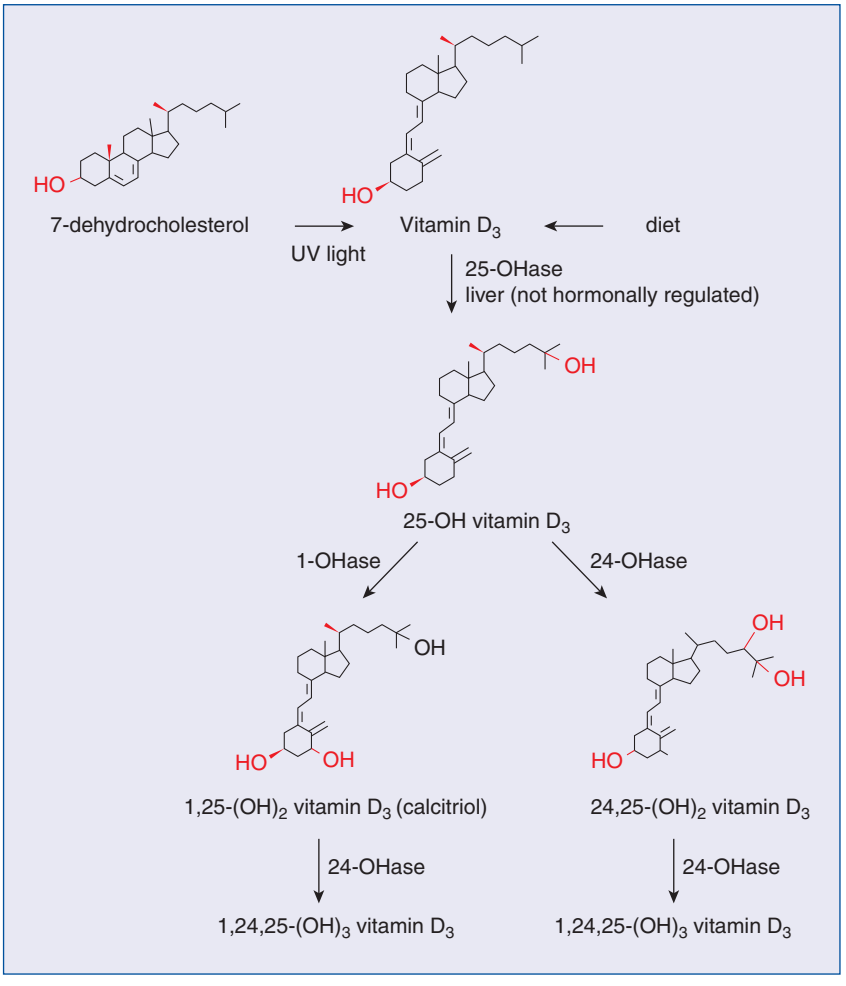

FIGURE 10-3. Vitamin D metabolism. The metabolic pathway is illustrated.

(volume expansion, loop diuretics, calcitonin). Disorders that may increase the likelihood of hypocalcemia, such as hypomagnesemia, should be corrected. Typically, patients are managed by volume resuscitation and small doses of loop diuretics for calciuresis. Bisphosphonates are not used as a first line of therapy because of the risk of rebound hypocalcemia; they are best reserved for resistant cases. Concomitant metabolic abnormalities, such as vitamin D deficiency and hypomagnesemia, should be corrected to prevent rebound hypocalcemia.

Hypercalcemia from increased calcium ingestion (reported ingestion between 1 and 9 g) alone rarely occurs in the absence of renal dysfunction or vitamin D supplementation (reported ingestion of as little as 400 to 800 units per day or calcitriol 0.25 μg per day). Vitamin D intoxication also causes hypercalcemia. Figure 10.3 shows vitamin D metabolism and formation of calcitriol in the body. Calcitriol stimulates calcium absorption in small intestine; however, bone calcium release may also play an important role in these patients. An outbreak of hypercalcemia was reported as the result of overfortification of milk from a home-delivery dairy. Other milk-associated outbreaks have resulted from the inadvertent addition of calcitriol to milk. Increased GI calcium absorption and hypercalcemia occur with granulomatous disorders, such as sarcoidosis, *Mycobacterium tuberculosis*, and *Mycobacterium avium* in patients with human immunodeficiency virus (HIV) infection. Macrophages express

1α-hydroxylase when stimulated and convert calcidiol to calcitriol. Hypercalcemia may be the initial manifestation of extrapulmonary sarcoid. Hypercalciuria may precede hypercalcemia in sarcoid. Lymphomas can produce hypercalcemia via the same mechanism. The source of calcitriol with lymphomas may be from macrophages adjacent to the tumor and not the malignant cells themselves. Lymphomas may also cause hypercalcemia via cytokine-induced activation of osteoclasts and osteolysis.

Increased bone calcium resorption is the most common pathophysiologic mechanism leading to hypercalcemia. This plays a primary role in the hypercalcemia of PHPT, malignancy, hyperthyroidism, Paget disease, and immobilization. Burn patients who are immobilized for prolonged periods (≥3 weeks) are at high risk for hypercalcemia. The 2 most common causes of hypercalcemia are PHPT and malignancy.

PHPT occurs in as many as 2 per 10,000 people in the general population. In the 1970s and 1980s the incidence was as high as 8 per 10,000 people, but has been steadily declining since. It is speculated that therapeutic radiation of the neck for thymic enlargement and acne in the 1940s and 1950s may have contributed to the higher incidence. The pathologic lesion in 90% is a solitary adenoma. Multiple adenomas can occur and parathyroid carcinoma is very rare (<1%). Of the remaining, as many as 10%, have diffuse hyperplasia and some of these have the inherited familial syndrome multiple endocrine neoplasia (MEN). MEN type I is associated with pituitary adenomas and islet cell tumors. It has an estimated prevalence of 1 per 50,000 in the general population. PHPT is the initial manifestation, occurring in general by age 40 to 50 years. The mutation resides in the menin gene. Menin is a tumor suppressor expressed in the nucleus that binds to JunD. Menin mutations occur in approximately 15% of sporadic adenomas. MEN type II is associated with medullary carcinoma of the thyroid and pheochromocytoma. It is subdivided into MEN IIa that is associated with parathyroid hyperplasia and type IIb that is not. MEN type II is caused by mutations in the RET protooncogene that is a tyrosine kinase. In developing tissues, including neural crest, kidney, and ureter, RET is a receptor for growth and differentiation.

Hypercalcemia in PHPT is the combined result of increased bone calcium resorption, increased intestinal calcium absorption, and increased calcium reabsorption in kidney. In PHPT, hypercalcemia is mild (<11.0 mg/dL), and often identified on routine laboratory testing in the asymptomatic patient. Patients present most commonly between the ages of 40 and 60 years and women are affected 2 to 3 times more often than men. The majority of patients are postmenopausal women. There are some case reports of normocalcemic PHPT, which presents with osteoporosis and/or fragility fracture with nephrolithiasis, despite the absence of hypercalcemia. Such patients have elevated serum calcitriol levels.

Secondary hyperparathyroidism-induced hypercalcemia occurs in 2 clinical settings. In the renal transplantation patient, although renal function improves, PTH concentration remains elevated as a result of increased parathyroid gland mass. Hypercalcemia generally does not persist more than a year. In the patient with end-stage renal disease and secondary hyperparathyroidism, hypercalcemia can occur with calcium and/or vitamin D supplementation. This occurs primarily in patients with low-turnover bone disease (adynamic bone disease).

Malignancy results in hypercalcemia from production of parathyroid hormone-related peptide (PTHrP), local bone resorption in areas of metastasis (cytokine mediated), or calcitriol production (lymphomas). Breast cancer, squamous cell lung cancer, multiple myeloma, and renal cell carcinoma are the most common malignancies associated with hypercalcemia. Hypercalcemia secondary to PTHrP is known as humoral hypercalcemia of malignancy (HHM). A large variety of tumors can produce PTHrP. A partial list includes; squamous cell cancers of the head, neck, and lung; breast cancer; pancreatic cancer; transitional cell carcinomas; and germ cell tumors. The first 13 amino acids of PTHrP are highly homologous to PTH, resulting in PTHrP binding to the PTH 1 receptor and affecting renal tubular Ca^{2+} reabsorption via the cAMP and PLC-mediated pathways. PTHrP may be the fetal PTH. PTH is not secreted by the parathyroid gland in utero and does not cross the placenta.

Humoral hypercalcemia of malignancy typically presents with severe hypercalcemia (calcium concentration >14 mg/dL). At the time of initial presentation the cancer is usually easily identified. PTHrP is immunologically distinct from PTH and as a result is not detected by PTH assays. An assay for PTHrP is commercially available. In patients with HHM PTH concentration will be low. Hypercalcemia from PHPT and HHM can rarely be seen in the same patient. Osteolytic metastases produce a variety of cytokines resulting in calcium release from bone. Tumor necrosis factor (TNF) and interleukin (IL)-1 stimulate the differentiation of osteoclast precursors into osteoclasts. IL-6 stimulates osteoclast production.

Approximately one-third of patients with multiple myeloma will develop hypercalcemia. Multiple myeloma presents with anemia, hypercalcemia, and localized osteolytic lesions. Release of calcium from bone results from cytokine release (IL-6, IL-1, TNF-β, macrophage inflammatory protein [MIP]-1α and MIP-1β). Myeloma cells can disturb the balance between osteoprotegerin (a decoy receptor for RANKL (receptor activator of nuclear factor kappa-B)) and RANK. This balance plays a critical role in bone remodeling and maintaining the ratio of osteoclast to osteoblast activity. The balance tips in favor of bone resorption when RANKL expression increases and osteoprotegerin decreases. Lytic bone lesions are characterized by increased osteoclast resorption without new bone formation. This is in contradistinction to bone metastases with breast and prostate cancer where areas of lysis are surrounded by new bone formation. As a result, radionuclide bone scans will show uptake at sites of metastasis but not at sites of bone involvement with multiple myeloma.

Increased bone turnover and mild hypercalcemia occur in 5% to 10% of patients with hyperthyroidism. Hyperthyroid patients may also have an increased incidence of parathyroid adenomas. Immobilization and Paget disease can cause hypercalcemia. Immobilization leads to imbalance between the rate of bone resorption and bone formation leading to hypercalcemia within days to weeks of the start of complete bed rest. It is marked by low PTH and serum calcitriol levels.

Lithium administration may cause mild hypercalcemia that results from interference with calcium sensing by the CaSR. The CaSR also binds lithium, which acts as an antagonist. Hypercalcemia is generally mild, clinically insignificant, and resolves with discontinuation of the drug. In some cases it persists and may be associated with clinical signs and symptoms. Pheochromocytoma, primary adrenal insufficiency, and familial hypocalciuric hypercalcemia (FHH) are additional rare causes of hypercalcemia. Pheochromocytoma may produce hypercalcemia via its association with MEN IIa or by the production of PTHrP. Catecholamines are also known to increase bone resorption. FHH is inherited in an autosomal dominant fashion. The mutation occurs in the CaSR, and results in a receptor that has decreased calcium affinity. As a result, elevated calcium concentrations are required to suppress PTH. It presents with mild hypercalcemia at a young age, decreased urinary calcium excretion, and a high normal or slightly elevated PTH concentration. Notably signs or symptoms of hypercalcemia are often absent. FHH is important because it can be misdiagnosed as PHPT and result in unnecessary parathyroid surgery. Patients with FHH often do not have clinical sequelae of excessive PTH activity such as hyperparathyroid bone disease or mental status changes. The presence of hypercalcemia in family members, a lack of previously normal serum calcium measurements, and low urinary calcium suggest FHH. In one study, 25% of patients that underwent unsuccessful parathyroid surgery were diagnosed with FHH. Some authors advocate using fractional excretion (FE) of calcium to distinguish FHH from PHPT with values below 1% suggestive of FHH. This is not recommended, however, given that 25% of patients with PHPT have a fractional calcium excretion below 1%.

KEY POINTS

Etiology of Hypercalcemia

1. Hypercalcemia results from increased GI calcium absorption, increased bone calcium release, and/or decreased renal calcium excretion.
2. Of the 3 pathophysiologic mechanisms, increased bone resorption is most common and important.
3. Hypercalcemia from increased GI calcium absorption rarely occurs in the absence of renal dysfunction.
4. The most common causes of increased bone calcium release are PHPT and malignancy.

Signs and Symptoms

As is the case for many electrolyte disorders, the severity and rate of rise of the calcium concentration determines the extent of clinical signs and symptoms. Patients with PHPT present with mild asymptomatic hypercalcemia incidentally discovered on routine laboratory examination.

Severe hypercalcemia is associated with prominent neurologic and GI symptoms. Central nervous system symptoms range from confusion to stupor and coma. Seizures can occur as a result of severe vasoconstriction and transient high intensity signals have been documented by magnetic resonance imaging (MRI) that resolve with return of serum calcium to the normal range. Focal neurologic symptoms mimicking a transient ischemic attack although rare are described. GI symptoms are related primarily to decreased GI motility that results in nausea, vomiting, constipation,

and obstipation. Hypercalcemia-induced pancreatitis can cause epigastric pain. As will be discussed later in this chapter, hypercalcemia decreases expression of renal water channels resulting in polyuria that leads to ECF volume depletion, decreased renal blood flow, and decreased renal function. Hypercalcemia predisposes to digitalis toxicity.

KEY POINTS

Signs and Symptoms of Hypercalcemia

1. Hypercalcemia presents with a wide range of neurologic and GI symptoms.
2. Acute kidney injury (AKI) secondary to prerenal azotemia is commonly associated with hypercalcemia.

Diagnosis

PHPT and malignancy are by far the most frequent causes of hypercalcemia, making up more than 90% of all cases. Initial evaluation of the hypercalcemic patient includes a careful history and physical examination. Of patients with PHPT, approximately 20% have signs and symptoms of disease, such as kidney stones, neuromuscular weakness, decreased ability to concentrate, depression, or bone disease. One should inquire carefully about calcium supplement use, antacids, and vitamin preparations. A recent chest radiograph is essential to exclude lung cancers and granulomatous diseases. In patients with PHPT, skeletal radiographs are rarely positive in the present era. Bone densitometry, however, is commonly abnormal. Because PHPT involves cortical more than cancellous bone, bone density is reduced to the greatest degree in the distal radius. Areas where cancellous bone predominates, such as the spine and hip, show less of a decrease.

Initial laboratory studies include electrolytes, blood urea nitrogen (BUN), creatinine, phosphorus, serum and urine protein electrophoresis, and a 24-hour urine collection for calcium and creatinine. A ratio of serum chloride to serum phosphorus concentrations of greater than 33:1 is suggestive of PHPT. This results from decreased proximal tubular phosphate reabsorption induced by PTH. Laboratory hallmarks of calcium–alkali syndrome are a low serum chloride, high serum bicarbonate, and elevated serum BUN and creatinine concentrations. A monoclonal gammopathy on serum or urine protein electrophoresis suggests multiple myeloma. If the diagnosis of multiple myeloma is suspected on clinical grounds, it is important to perform immunofixation electrophoresis (IFE) on both blood and a 24-hour urine sample so as to exclude the diagnosis. In PHPT and HHM serum phosphorus concentration is often low. In hypercalcemia resulting from calcium–alkali syndrome, thiazide diuretics, and FHH, 24-hour urinary calcium excretion will be low. Some studies suggest measuring [iCa^{2+}] in patients with PHPT or MEN type I as total calcium concentration may underestimate or miss important clinical hypercalcemia.

PHPT is generally the cause in asymptomatic outpatients with a serum calcium concentration below 11 mg/dL. Malignancy is the most common cause in symptomatic patients, with serum calcium concentration above 14 mg/dL. Factors favoring the diagnosis of PHPT include a prolonged history, development in a postmenopausal woman, a normal physical examination, and/or evidence of MEN syndrome.

After initial evaluation, an intact PTH concentration is obtained. PHPT is the most common cause of an elevated PTH. PTH concentration is generally 1.5 to 2 times the upper limit of normal. Some patients may have mildly elevated calcium with a PTH concentration that is in the upper range of normal (inappropriately elevated). Others may have a serum calcium concentration in the upper quartile of the normal range and a slightly elevated PTH concentration. Both of these subgroups of patients were demonstrated to have parathyroid adenomas. An elevated PTH concentration also may be seen, albeit rarely, with lithium and FHH. If the patient is on lithium and it can be safely discontinued, PTH concentration should be remeasured in 1 to 3 months. In all other etiologies of hypercalcemia, PTH is suppressed. PTHrP is immunologically distinct from PTH and specific assays are commercially available. C-terminal fragment PTHrP assays may be increased in pregnancy and in patients with kidney disease.

If malignancy is not obvious and PTH concentration is suppressed, one needs to rule out vitamin D intoxication or granulomatous diseases by measuring calcidiol and calcitriol concentrations. Ingestion of vitamin D or calcidiol will result in an increased calcidiol concentration and often mild to moderately elevated calcitriol concentration. Elevated calcitriol concentrations are observed with ingestion of calcitriol and in those diseases where stimulation of 1α-hydroxylase occurs, including granulomatous diseases, lymphoma, and PHPT. If hyperthyroidism is suspected, thyroid function tests should be obtained.

KEY POINTS

Diagnosis of Hypercalcemia

1. PHPT and malignancy comprise 90% of all cases of hypercalcemia.
2. PHPT is most often secondary to a parathyroid adenoma. Hypercalcemia is mild, asymptomatic, and detected on routine laboratory testing.
3. Hypercalcemia of malignancy is severe, symptomatic, and carries a poor prognosis. It is commonly caused by production of PTHrP, a peptide similar, but not identical, to PTH.
4. After a careful history, physical, and initial laboratory evaluation patients are further characterized based on PTH and PTHrP concentrations.

Treatment

Treatment of hypercalcemia depends on the degree of elevation of serum calcium concentration and is directed at increasing renal excretion, blocking bone resorption, and reducing intestinal absorption.

The first step to enhance renal calcium excretion is ECF volume expansion, subsequently; loop diuretics are added with the goal of maintaining urine flow rate at 200 to 250 mL/h. The hypercalcemic patient is invariably volume contracted. Hypercalcemia causes arteriolar vasoconstriction and reduces renal blood flow. Calcium binding to the CaSR in the TAL results in dissipation of the lumen-positive potential and reduces the driving force for calcium reabsorption. Hypercalcemia also antagonizes the effects of antidiuretic hormone in collecting duct. The subsequent volume contraction that results increases proximal sodium and calcium reabsorption and further increases serum calcium concentration. With CKD higher doses of loop diuretics are needed. If glomerular filtration rate (GFR) is low and hypercalcemia severe (≥17 mg/dL), hemodialysis may be indicated. Hemodialysis is also helpful in patients with neurologic impairment or in those with concomitant congestive heart failure. Volume expansion and loop diuretics alone may be sufficient in the patient with mild-to-moderate hypercalcemia (≤12.5 mg/dL).

When hypercalcemia is moderate or severe, bone calcium resorption must be inhibited. In the short-term, calcitonin is used because of its rapid onset (within a few hours). The usual dose is 4 IU/kg subcutaneously every 12 hours. It not only inhibits bone resorption but also increases renal calcium excretion. Its effect, however, is not large and serum calcium concentration is reduced by only 1 to 2 mg/dL. Another downside is tachyphylaxis that develops with repeated use. Therefore, another agent that decreases bone resorption in addition to calcitonin should be used.

Bisphosphonates are the drug of choice to inhibit bone resorption. Their effects are additive to calcitonin. Bisphosphonates are concentrated in bone where they interfere with osteoclast formation, recruitment, activation, and function. Bisphosphonates have a long duration of action (weeks) but their disadvantage is that they have a slow onset (48 to 72 hours). Zoledronate and pamidronate are currently the most commonly used bisphosphonates to treat hypercalcemia. Zoledronate is used at a dose of 4 to 8 mg administered intravenously over 15 minutes. It is preferred by many over pamidronate because it is more effective in reducing serum calcium concentration and produces a longer-lasting reduction in serum calcium concentration in patients with hypercalcemia of malignancy than pamidronate. Pamidronate 60 to 90 mg is given intravenously for 4 hours. The dose varies depending on the degree of hypercalcemia (60 mg when calcium concentration <13.5 mg/dL; 90 mg when calcium concentration >13.5 mg/dL). Serum calcium concentration slowly falls over days. A single dose lasts 7 to 14 days. Usually, serum calcium concentration will normalize within 7 days. Pamidronate use is not recommended in patients with advanced renal disease. Renal toxicities of bisphosphonates include focal sclerosis with pamidronate and acute kidney injury with zoledronate and pamidronate. The prevalence of osteonecrosis of the jaw with chronic use of bisphosphonates in the treatment of malignancy has been reported to be 1.5% with all nitrogen-containing bisphosphonate agents. The lesion is preceded by a dental procedure in the majority of patients.

Mithramycin cannot be used in patients with severe liver, kidney, or bone marrow disease. Its onset of action is 12 hours with a peak effect at 48 hours. Because of its severe side-effect profile (hepatotoxicity, proteinuria, thrombocytopenia, and GI upset) mithramycin is rarely used. The dose is 25 μg/kg intravenously over 4 hours daily for 3 to 4 days. In one study, hepatotoxicity was noted in 26% of patients and nausea and vomiting in 23%, as well as bleeding tendencies caused by abnormalities in several coagulation factors and platelet dysfunction.

Gallium nitrate also inhibits bone resorption. Gallium accumulates in metabolically active regions of bone. It reduces bone resorption by inhibiting the H^+-ATPase in the ruffled membrane of osteoclasts and blocking osteoclast acid secretion. It has been used to treat hypercalcemia of malignancy. One hundred to 200 mg/m^2 are given

as a continuous infusion for 5 consecutive days. Gallium nitrate is contraindicated if the serum creatinine concentration is above 2.5 mg/dL. It may be useful in patients with hypercalcemia of malignancy that fail bisphosphonates.

Agents that decrease intestinal calcium absorption are generally reserved for outpatients with mild hypercalcemia. Corticosteroids were used successfully in patients with vitamin D overdose, granulomatous diseases, and some cancers (lymphomas and multiple myeloma). Ketoconazole and hydroxychloroquine were also employed. Ketoconazole reduces calcitriol concentration by approximately 75% via inhibition of 1α-hydroxylase. Hydroxychloroquine was used in patients with hypercalcemia and sarcoidosis and works via a similar mechanism. Oral phosphorus can be tried, but is contraindicated in patients with an elevated serum phosphorus concentration or renal dysfunction. Oral phosphorus is often poorly tolerated (diarrhea) and reduces calcium concentration only slightly (1 mg/dL).

In the past, criteria for removal of a solitary parathyroid adenoma included; serum calcium concentration more than 1 mg/dL above the upper limit of normal; an episode of acute symptomatic hypercalcemia; overt bone disease; cortical bone mineral density more than 2 standard deviations below age-, sex-, and race-adjusted means; reduced renal function (more than 30%); a history of nephrolithiasis or nephrocalcinosis; urinary calcium excretion that exceeds 400 mg/day; or young age (<50 years). Some of these have been modified and include a serum calcium concentration of greater than 0.25 mmol/L above the upper limit of normal; estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2; and a T-score at any site equal to or less than –2.5 or a fracture. In the past decade, as minimally invasive parathyroidectomy techniques have improved and studies further delineate the cardiovascular risks of PHPT, it is becoming clearer that the majority of patients should have the adenoma surgically removed. Recent studies suggest that even mild PHPT is associated with increased all cause and cardiovascular mortality, hypertension, diabetes, fractures, and an increased admission rate for nonfatal cardiovascular disease.

If surgery is not performed it is recommended that serum calcium concentration be monitored every 6 months and serum creatinine concentration and bone mineral density measured yearly. Several studies report improved bone mineral density, reduction in the rate of formation of kidney stones, and improved quality of life in patients who undergo parathyroidectomy. Parathyroidectomy normalizes various bone turnover markers and should be strongly considered in elderly patients with low bone mineral density to prevent future fractures. A scoring system was developed to predict single gland versus multigland cases of PHPT: preoperative total calcium concentration equal to or greater than 12 mg/dL; intact PTH (iPTH) levels equal to or greater than twice the upper limit of normal levels; positive neck ultrasound for a single enlarged parathyroid gland; positive sestamibi scan for a single enlarged parathyroid gland; and both a positive ultrasound and sestamibi scan. A score of equal to or greater than 3 had a positive predictive value of approximately 100% for single-gland disease.

With minimally invasive surgery adenomas are first localized with a sestamibi scan and/or ultrasound preoperatively and parathyroidectomy is performed under local anesthesia. PTH assays are performed in the operating room. Given PTH's short half-life (4 minutes), PTH concentration is measured 10 minutes after removal of the suspected adenoma to verify that surgery was successful. If PTH concentration does not decline by 50% or more 10 minutes after removal of the suspected adenoma, the patient is placed under general anesthesia and more extensive neck exploration is performed looking for a second adenoma. The failure rate for the minimally invasive technique is approximately 10%. Up to 5% of patients may have a previously undetected second adenoma. In patients whose surgery is successful, the rate of kidney stone formation declines. Over the next several years bone density often increases in hip and back, but not in the distal third of the radius. Patients treated medically with bisphosphonates can have some increase in vertebral bone density, but serum PTH concentrations remain elevated. CaSR agonists can normalize serum calcium concentration, but in studies with 3 years of follow up bone density does not increase.

KEY POINTS

Treatment of Hypercalcemia

1. Initial therapy of hypercalcemia is directed at ECF volume expansion.
2. After ECF volume is expanded, a loop diuretic is added to increase renal calcium excretion.
3. If hypercalcemia is moderate-to-severe additional measures are required. Drugs that reduce calcium release from bone are added. The drug of choice in the short-term is calcitonin and in the long-term is a bisphosphonate.

4. In special circumstances mithramycin, gallium nitrate, or hemodialysis may be required.
5. Parathyroidectomy should be considered strongly in patients with PHPT even in those with mild PHPT.

HYPOCALCEMIA

Pathophysiologic Mechanisms

Hypocalcemia results from decreased intestinal calcium absorption or decreased bone resorption. Because there is a large calcium reservoir in bone, sustained hypocalcemia can only occur if there is an abnormality of PTH or a calcitriol effect in bone.

Total serum calcium is comprised of 3 components: an ionized or free fraction; calcium complexed with anions; and a protein-bound fraction. True hypocalcemia results only when the ionized calcium fraction is decreased (about half of total serum calcium concentration). The first step in evaluation of a low total serum calcium concentration is to attempt to determine whether the ionized fraction is reduced. One way to address this question is to compare the total serum calcium concentration to the serum albumin concentration. As a general rule of thumb for every 1 g/dL decrease in serum albumin concentration from its normal value (4 g/dL), one can expect a 0.8 mg/dL decrement in total serum calcium concentration. For every 1 g/dL fall in serum albumin concentration, 0.8 mg/dL must be added to the total serum calcium concentration to correct it for the degree of hypoalbuminemia. Prediction of ionized calcium from albumin-corrected total calcium should be done with caution. This correction may be unreliable in certain patient populations, such as the critically ill trauma patient and patients with CKD. Calcium binding to albumin is also affected by pH. As pH decreases ionized calcium will increase and vice versa. This effect is fairly minor and ionized serum calcium concentration will only increase 0.2 mg/dL for each 0.1 decrease in pH. If clinical suspicion of true hypocalcemia is high, then [iCa^{2+}] should be measured directly.

In CKD patients, measurement of albumin can be erroneous based on the use of bromocresol green (BCG) or bromocresol purple (BCP) methods. Hence, ionized calcium should be measured in patients with CKD and low serum bicarbonate and/or plasma albumin levels.

True hypocalcemia is the result of either decreased PTH or vitamin D concentration, or end-organ resistance to PTH or vitamin D. Less commonly, hypocalcemia results from either extravascular calcium deposition or intravascular calcium binding. Extravascular deposition occurs with pancreatitis, "hungry bone syndrome" postparathyroidectomy, or tumor lysis syndrome. Intravascular calcium binding was reported with foscarnet use (pyrophosphate analog) and after massive transfusion (citrate), usually in the presence of hepatic or renal failure. Table 10.2 lists the most common etiologies of true hypocalcemia grouped by their pathophysiologic mechanisms.

Pseudohypocalcemia occurs following gadopentetate dimeglumine and gadodiamide use during MRI because

TABLE 10-2. Etiologies of Hypocalcemia

Decreased PTH Concentration or Effect
Hypomagnesemia
Decreased PTH secretion Postsurgical Polyglandular autoimmune syndrome, type I Familial hypocalcemia Infiltrative disorders
End-organ resistance to PTH Pseudohypoparathyroidism (types I and II)
Defects in Vitamin D Metabolism
Nutritional
Malabsorption
Drugs
Liver disease
Kidney disease
Vitamin D-dependent rickets
Shift of Calcium Out of the ECF
Acute pancreatitis
Hungry bone syndrome
Tumor lysis syndrome
Miscellaneous
Osteoblastic metastases
Toxic shock syndrome
Sepsis
Pseudohypocalcemia

the dye interferes with the routine colorimetric laboratory assay (orthocresolphthalein method) used to measure serum total calcium concentration. This effect may last up to 4.5 days in patients with CKD. In one report, 18 patients were inappropriately treated with intravenous or oral calcium. In this setting, an [iCa^{2+}] should be measured before the patient is treated.

KEY POINTS

Pathophysiologic Mechanisms of Hypocalcemia

1. True hypocalcemia results from decreased GI calcium absorption, decreased bone resorption, or, less commonly, acute shift of calcium out of ECF or calcium binding within the intravascular space.
2. Given the large calcium reservoir in bone sustained hypocalcemia cannot occur without an abnormality of PTH or calcitriol action in bone.
3. When interpreting total serum calcium concentration one needs to take into account serum albumin concentration and systemic pH.

Etiology

Hypoparathyroidism is caused by several acquired and inherited disorders resulting from decreased PTH synthesis or release, or resistance to PTH action. Polyglandular autoimmune syndrome type I is the most common cause of idiopathic hypoparathyroidism. Chronic mucocutaneous candidiasis and primary adrenal insufficiency are also part of the spectrum of this disease. Mucocutaneous candidiasis presents in early childhood and involves skin and mucous membranes without systemic spread. This is subsequently followed by hypoparathyroidism after several years. Adrenal insufficiency generally develops last with an onset in adolescence. Up to half of these patients have antibodies directed against the CaSR. Mutations in the AIRE (autoimmune regulator) gene, which is a transcription factor, cause the disease. Affected patients are at risk for developing other autoimmune disorders, including pernicious anemia, vitiligo, hypothyroidism, hepatitis, and type I diabetes mellitus.

Familial hypocalcemia is the result of autosomal dominant activating mutations in the CaSR and results in a receptor that is more sensitive to ECF [iCa^{2+}]. Two patients were described with autoantibodies that activate the CaSR. One patient had Graves disease and the other Addison disease. In a cell culture system, these antibodies bound the receptor, activated second messenger systems, and suppressed PTH secretion. Such patients have autosomal dominant disease and present with hypocalcemia, hypomagnesemia, and hypercalciuria leading to nephrolithiasis. Calcium excretion in these patients is much higher than in hypoparathyroid patients. Radical neck and parathyroid surgery may be complicated by loss of parathyroid tissue. In end-stage renal disease patients who undergo parathyroidectomy for secondary or tertiary hyperparathyroidism remineralization of bone (hungry bone syndrome) may result in acute hypocalcemia. With surgical removal of a parathyroid adenoma transient hypocalcemia may result from suppression of normal gland function by the adenoma. Hypocalcemia can occur after thyroid surgery and may be either transient (11.9%) or permanent (0.9%). Patients undergoing central lymph node dissection for thyroid cancer are at high risk. Hypocalcemia or hypophosphatemia that persists for 1 week despite calcium replacement are risk factors for permanent hypoparathyroidism. Infiltrative disorders (hemochromatosis and Wilson disease) and infection with HIV can cause hypoparathyroidism.

The most common etiology of decreased PTH secretion and/or effect is severe hypomagnesemia. Hypomagnesemia decreases PTH secretion, as well as results in end-organ resistance to PTH. End-organ resistance begins to occur at a serum magnesium concentration equal to or less than 1 mg/dL. More severe hypomagnesemia (serum magnesium concentration ≤0.5 mg/dL) is required to decrease PTH secretion. Patients with hypocalcemia secondary to hypomagnesemia will not respond to calcium or vitamin D replacement until the magnesium deficit is replaced. It often takes several days after magnesium is corrected for serum calcium concentration to return to normal.

Rare genetic disorders can cause PTH end-organ resistance (pseudohypoparathyroidism types I and II). Pseudohypoparathyroidism is subdivided based on whether nephrogenous cAMP increases in response to PTH administration (Ellsworth-Howard test). In type II, there is a normal response, and in type I, there is a decreased response. In type I, the mutation arises in the G_s-α_1 protein of the adenylate cyclase complex. PTH binds to its receptor but cannot activate adenylate cyclase. The defect in type II is a result of resistance to the intracellular effects of cAMP and the mutation has yet to be identified. Some patients with type II disease will respond to theophylline.

Disorders of vitamin D metabolism are important causes of hypocalcemia. A wide variety of disorders can

interfere with this complex pathway, including decreased vitamin D intake, GI malabsorption, drugs, liver disease, kidney disease, and vitamin D-dependent rickets. Despite the fact that milk is supplemented with vitamin D in the United States, one study of noninstitutionalized adults showed that 9% had low 25(OH) vitamin D concentrations. Patients who are poorly nourished with little sunlight exposure, as well as the institutionalized elderly, are at particular risk. Postmenopausal women and adolescents are also at increased risk. Vitamin D deficiency may result from GI malabsorption given that vitamin D is a fat-soluble vitamin. Anticonvulsant drugs induce the cytochrome P450 system and increase metabolism of vitamin D. It is likely, however, that anticonvulsants cause bone loss via a variety of other mechanisms as well, including direct inhibition of bone resorption, impaired GI calcium absorption, and resistance to PTH. Vitamin D deficiency results from severe parenchymal liver disease since one of the steps involves hydroxylation in liver. Chronic kidney disease impairs 1α-hydroxylation, the final step in the formation of calcitriol. Vitamin D-dependent rickets exists in 2 forms. Type I is caused by impaired 1α-hydroxylation of calcidiol to calcitriol. Because end-organ response is intact, type I patients respond to calcitriol. Type II disease is caused by inactivating mutations in the vitamin D receptor and results in end-organ resistance to calcitriol. Serum calcitriol concentration is elevated in these patients and they respond poorly to supplemental calcitriol.

Other causes of hypocalcemia include tumor lysis syndrome, hyperphosphatemia, acute pancreatitis, and sepsis. Ionized hypocalcemia is common in patients in the intensive care unit (ICU), occurring in up to two-thirds of ICU patients, and many of these are septic. Hypocalcemia is an independent predictor of increased mortality in the ICU. However, hypocalcemia must be severe ([iCa^{2+}] <0.8 mmol/L). The mechanism of hypocalcemia in sepsis is unknown. Postulated mechanisms include a decrease in PTH concentration, decreased calcitriol concentration, and peripheral resistance to PTH action.

KEY POINTS

Etiology of Hypocalcemia

1. Hypoparathyroidism results from decreased synthesis, release, or peripheral tissue resistance to PTH.
2. The most common cause of idiopathic hypoparathyroidism is polyglandular autoimmune syndrome type I. It manifests with hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis.
3. Parathyroid and radical neck surgery can result in loss of parathyroid gland mass and hypoparathyroidism.
4. Severe hypomagnesemia is the most common cause of hypoparathyroidism.
5. Disorders of vitamin D metabolism such as nutritional deficiency, liver disease, anticonvulsant use, and CKD are important causes of hypocalcemia.

Signs and Symptoms

The degree of hypocalcemia and rate of decline of serum calcium concentration determine whether hypocalcemic symptoms occur. The point at which symptoms occur depends on multiple factors, including pH and whether other electrolyte abnormalities are present (hypomagnesemia and hypokalemia). Symptoms are primarily those of enhanced neuromuscular activation. Circumoral and distal extremity paresthesias are common complaints, as is carpopedal spasm. Altered mental status changes, irritability, and seizures may also occur. Hypotension, bradycardia, and laryngospasm may be present on physical examination. One should test for the presence of Chvostek and Trousseau signs. Chvostek sign is brought out by gently tapping just below the zygomatic arch over the facial nerve with the mouth slightly open. A positive sign, which is a facial twitch, is occasionally observed in normal patients. To test for Trousseau sign, a blood pressure cuff is inflated to 20 mmHg above systolic pressure for 3 minutes. A positive sign is flexion of the wrist, metacarpophalyngeal joints, and thumb with hyperextension of the fingers. There are case reports of patients with severe hypocalcemia and congestive heart failure (total serum calcium concentrations of 4 mg/dL or less) that reversed with correction of the hypocalcemia.

KEY POINTS

Signs and Symptoms of Hypocalcemia

1. Signs and symptoms depend on the degree and rate of decline of serum calcium concentration.
2. The serum calcium concentration at which symptoms develop varies depending on the presence or absence of other associated electrolyte or acid–base disturbances.

3. Symptoms of neuromuscular excitability predominate.
4. On physical examination one should look for the presence of Chvostek and Trousseau signs.

Diagnosis

Figure 10.4 shows an algorithm for the differential diagnosis of hypocalcemia. Common causes are hypomagnesemia (most common), CKD, and postparathyroid surgery. When total serum calcium concentration is low, one first evaluates the serum albumin concentration and, if necessary, measures ionized serum calcium concentration. After the presence of true hypocalcemia is established, blood is sent for BUN, creatinine, magnesium, and phosphorus concentrations.

Serum magnesium concentration is evaluated next. As stated previously, the most common cause of hypocalcemia is hypomagnesemia. Hypocalcemia will not correct before magnesium losses are replenished.

One then examines serum and urinary phosphorus concentrations. If kidney function is normal, hyperphosphatemia suggests hypoparathyroidism or pseudohypoparathyroidism. These disorders can easily be differentiated by measuring PTH concentration. PTH concentration is low in primary hypoparathyroidism because of gland failure, whereas with end-organ resistance as in pseudohypoparathyroidism, PTH concentration is elevated. Pseudohypoparathyroidism is further subdivided by infusing PTH and subsequently measuring urinary phosphate and cAMP concentrations.

Disorders of vitamin D metabolism are characterized by hypophosphatemia. Hypocalcemia stimulates the parathyroid gland to secrete PTH resulting in renal phosphate wasting. The FE of phosphorus will be high (>5%). If, on the other hand, the kidney is responding appropriately to phosphate depletion the FE will be below

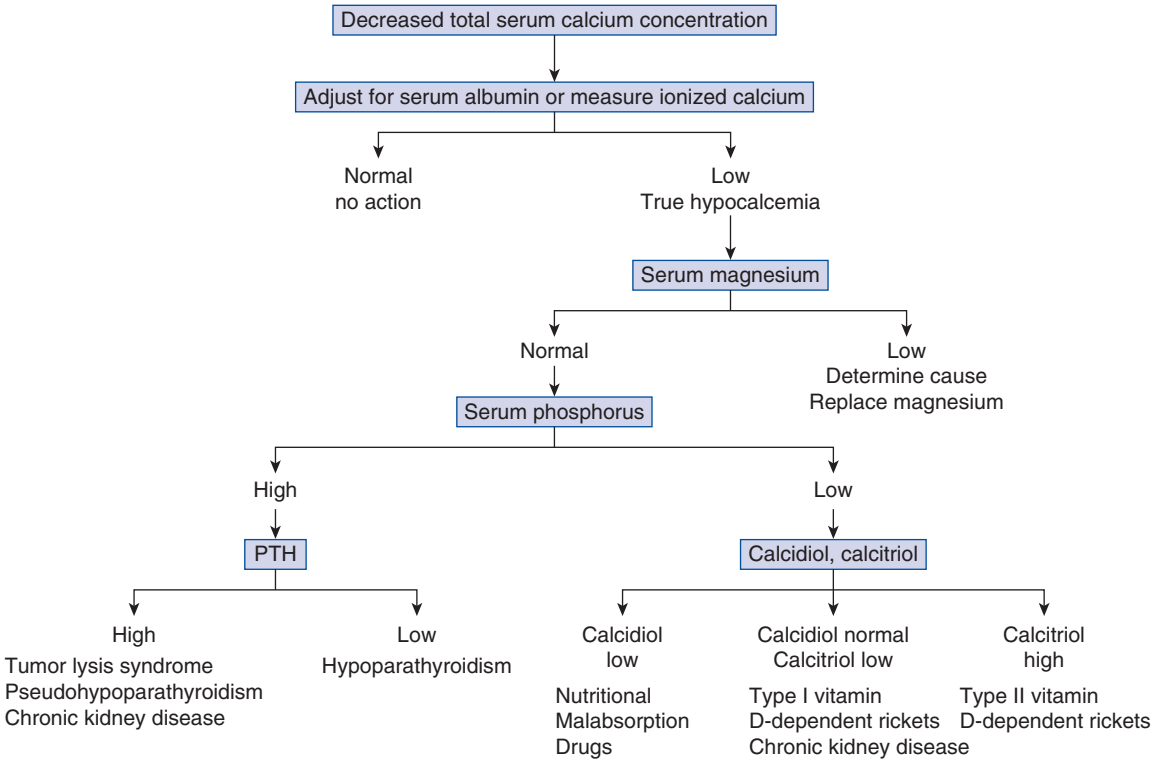

FIGURE 10-4. Evaluation of the hypocalcemic patient. After adjusting for serum albumin concentration, one evaluates serum magnesium concentration. Patients are further subdivided based on serum phosphorus, PTH, and calcidiol and calcitriol concentrations. (With permission from Schrier RW, ed. *Manual of Nephrology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.)

1%. If the FE of phosphate is high, then serum calcidiol and calcitriol concentrations are measured. Calcidiol levels are low with malabsorption, liver disease, phenobarbital, nutritional deficiency, and nephrotic syndrome. Calcitriol levels are low with CKD and increased in type II vitamin D-dependent rickets.

KEY POINTS

Diagnosis of Hypocalcemia

1. The most common causes of hypocalcemia are magnesium deficiency, CKD, and postparathyroid surgery.
2. If total serum calcium concentration is decreased, one evaluates the serum albumin concentration to attempt to estimate whether [iCa^{2+}] is decreased.
3. Hypomagnesemia is the most common cause of hypocalcemia.
4. If hypomagnesemia is not present serum phosphorus concentration and renal phosphate excretion are examined.
5. Hyperphosphatemia in the absence of CKD suggests decreased PTH concentration or effect.
6. Decreased serum phosphorus concentration is indicative of a defect in vitamin D metabolism.

Treatment

Treatment will vary depending on the degree and cause of hypocalcemia. In life-threatening circumstances, such as with seizures, tetany, hypotension, or cardiac arrhythmias, intravenous calcium at a rate of 100 to 300 mg over 10 to 15 minutes is administered. In general, intravenous calcium should be used initially in the symptomatic patient or the patient with severe hypocalcemia (total calcium corrected for albumin ≤7.5 mg/dL). Hypocalcemia that is mild in an outpatient setting is corrected with oral calcium supplementation. A vitamin D preparation may need to be added if the response to oral calcium is insufficient.

If life-threatening symptoms are not present, the administration of 15 mg/kg of elemental calcium over 4 to 6 hours can be expected to increase total serum calcium concentration by 2 to 3 mg/dL. A variety of intravenous preparations can be used, including 10% calcium gluconate (10 mL ampules [94 mg of elemental calcium]); 10% calcium gluceptate (5 mL ampule [90 mg elemental calcium]); and calcium chloride (10 mL ampule [272 mg elemental calcium]). After the first ampule is administered, generally over several minutes, an infusion is begun at 0.5 to 1.0 mg/kg/h. The infusion rate is subsequently adjusted based on serial serum calcium determinations. Magnesium deficits must first be corrected or treatment will be ineffective. In the patient who also has metabolic acidosis, hypocalcemia should be corrected first. Correction of acidosis before hypocalcemia will result in a further decrease in [iCa^{2+}] and exacerbate symptoms.

Patients with hypoparathyroidism are often treated with vitamin D supplements because administration of calcium alone is often ineffective. Serum calcium concentration should be maintained at a level where the patient is symptom free. This is generally at or just below the lower limit of normal. An elemental calcium dose of 1 to 3 g/day is usually required. Several oral preparations can be used and are shown in Table 10.3. Supplements should be taken between meals to ensure optimal absorption. Calcium citrate is more bioavailable than calcium carbonate especially in patients with increased gastric pH. If higher doses of elemental calcium are required, a vitamin D preparation should be added. In the presence of severe hyperphosphatemia, it is advisable to delay calcium supplementation until serum phosphorus concentration is below 6 mg/dL. This may not always be possible and clinical judgment must be used in the severely hypocalcemic patient.

Calcitriol is the most potent vitamin D preparation, has a rapid onset of action, a short duration of action, but is also the most expensive. A dose of 0.5 to 1.0 µg/day is often required. As one moves from calcidiol to cholecalciferol and to ergocalciferol cost decreases and duration of action increases. Some of these agents, however, may be less efficacious in the presence of renal or hepatic disease.

In hypoparathyroidism distal tubular calcium reabsorption is decreased because of a lack of PTH. The increased filtered calcium load resulting from calcium

TABLE 10-3. Oral Calcium Preparations

PREPARATION	TABLET (mg)	ELEMENTAL CALCIUM/TABLET (mg)
Calcium carbonate	500	200
Calcium citrate	950	200
Calcium lactate	650	85
Calcium gluconate	1000	90

and vitamin D replacement can lead to hypercalciuria, nephrolithiasis, and nephrocalcinosis. Patients with hypoparathyroidism excrete more calcium than normal for any given serum calcium concentration. If urinary calcium excretion exceeds 350 mg/day and serum calcium concentration is acceptable, sodium intake should be restricted, and if this is not effective, a thiazide diuretic should be added to reduce urinary calcium excretion.

Patients with hypocalcemia postparathyroidectomy require large doses of supplemental calcium. In this setting, the serum potassium must be monitored carefully, because for unclear reasons these patients are at increased risk of hyperkalemia. Treatment of hypocalcemia in the setting of the tumor lysis syndrome is directed at lowering serum phosphorus concentration.

KEY POINTS

Treatment of Hypocalcemia

1. Management of the hypocalcemic patient depends on its severity and cause.
2. Acute symptomatic hypocalcemia is treated with intravenous calcium.
3. Of the available vitamin D preparations, calcitriol is the most potent, has a rapid onset of action, and a short duration of action, but is also the most expensive.
4. Serum calcium concentration is maintained at the lower limit of normal in patients with hypoparathyroidism to minimize hypercalciuria.
5. If hypercalciuria develops salt restriction or thiazide diuretics can be employed.

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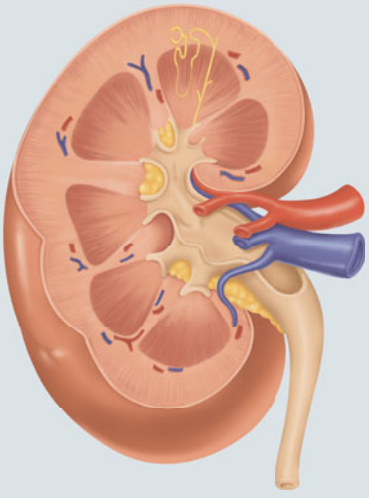

CHAPTER

11

Disorders of Phosphate Homeostasis—Hypo and Hyperphosphatemia

• *Nishank Jain and Robert F. Reilly Jr.*

Recommended Time to Complete: 1 Day

Guiding Questions

1. Of the regulators of serum phosphorus concentration, which are most important?
2. What is the most common cause of hyperphosphatemia?
3. What are the advantages and disadvantages of various phosphate binders that are available for treatment of hyperphosphatemia?
4. How does one evaluate the hypophosphatemic patient?
5. How well documented are the clinical consequences of hypophosphatemia?
6. Does the patient with moderate hypophosphatemia require phosphorus replacement?

REGULATION

Phosphorus is an important element involved in various vital functions of the body including signal transduction, cell membrane function, and energy exchange. Phosphorus circulates in the bloodstream in 2 forms: an organic fraction made up primarily of phospholipids; and an inorganic fraction. Of these 2 fractions it is the inorganic fraction, which makes up approximately one-third of total plasma phosphorus, that is assayed in the clinical laboratory. The majority (75%) of inorganic phosphorus is free in solution and exists as either divalent (HPO_4^{2-}) or monovalent ($H_2PO_4^-$) phosphate. The relative amounts of each ion depend on the systemic pH. At pH 7.4, 80% is in the divalent form based on the dissociation constant of the reaction. Approximately 1% of body weight in a 70-kg human is phosphorus (600 to 700 g). It is distributed primarily in skeleton (80% to 85%), other organs (14% in skeletal

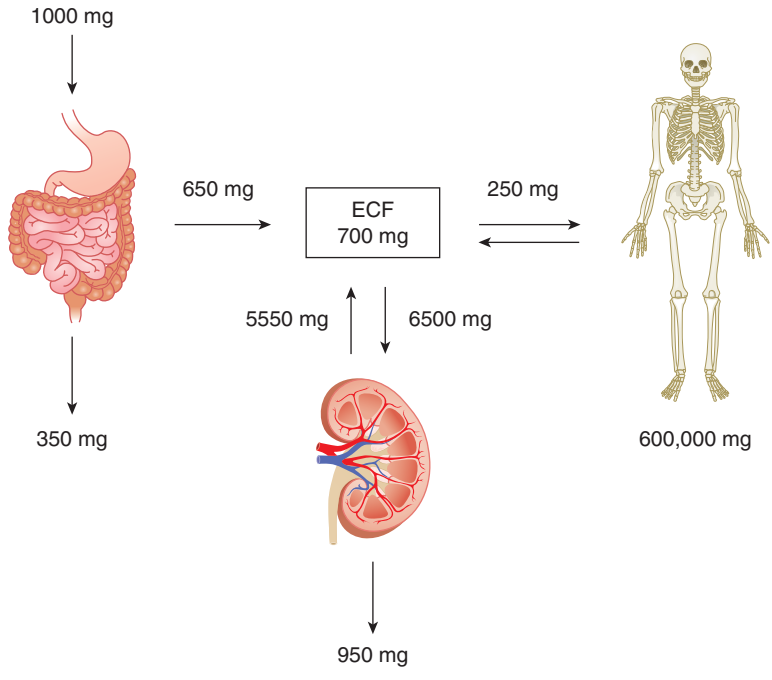

FIGURE 11-1. Phosphorus homeostasis. Daily phosphorus fluxes between extracellular fluid (ECF), intestine, kidney, and bone are shown. In the steady state, net intestinal absorption and renal excretion are equal. The majority of phosphorus in the body is in bone. (With permission from Schrier, R.W. (ed.). *Manual of Nephrology*. Lippincott Williams & Wilkins, Philadelphia, PA, 2000.)

muscle and viscera), 1% in blood and extravascular space, and a small fraction is found in the intracellular compartment where the phosphorus pool is inorganic and available for adenosine triphosphate (ATP) synthesis (Figure 11.1). Fifteen percent of phosphorus is protein bound. A typical Western diet includes 800 to 1500 mg of phosphorus daily. Diurnal variation occurs in normal individuals, with the lowest serum phosphorus concentration in the morning and a gradual rise during the day to peak in the evening. The variability in serum phosphorus concentration may be as high as 1 mg/dL and does not correlate with abundance of renal transporter proteins. This diurnal variation is intact in some patients with hyperparathyroidism but remains unknown in patients with hypophosphatemia from other causes. However, we measure random serum inorganic phosphorus concentration in the clinical setting, the normal range of which is 2.5 to 4.5 mg/dL (0.8 to 1.5 mM). Three major organs work in concert to maintain phosphorus balance: intestinal uptake; retention or release from bone; and regulated renal reabsorption.

Inorganic phosphate is absorbed along the entire length of small intestine via passive and active transport. The role of colon, at physiologic levels, is insignificant. However, in certain conditions, the colon plays a role in hypophosphatemia as the unregulated secretion (100 to 200 mg/day) is exaggerated with diarrhea. Overall, the small intestine plays a more active role in phosphorus balance than previously thought mediated by a high-affinity Pi transporter, Npt2b (type II sodium-dependent phosphate transporter). Found in the brush border membrane (BBM) of small intestine, Npt2b transports divalent Pi with a stoichiometry of 2:1 Na^+:HPO_4^{2-} across the BBM in an electroneutral fashion. Npt2b activity is regulated by dietary inorganic phosphate (Pi) intake and serum 1,25-dihydroxy-vitamin D_3 ($1,25[OH]_2D_3$) concentration. On the one hand, low dietary Pi enhances Npt2b activity through a posttranscriptional mechanism, and on the other hand, $1,25[OH]_2D_3$ enhances transporter activity by a transcription-dependent pathway mediated by the vitamin D receptor (VDR). Interestingly, parathyroid hormone (PTH) has no effect on Npt2b. Furthermore, a regulated organ crosstalk between small intestine, kidney, and bone exists, as shown in Npt2b knockout (KO) animal models, where decline in fibroblast growth

factor 23 (FGF-23) and elevation in $1,25[OH]_2D_3$ occurs to maintain serum phosphorus and calcium concentration in these animals with upregulation of Npt2a in kidney. Paracellular Pi transport in intestine is not clearly understood.

The kidney plays a key role in Pi homeostasis. It filters 200 mmol (~20 g) of Pi per day. Pi is freely filtered, as only 15% is protein bound, and the majority (85% to 90%) is reabsorbed. The latter occurs primarily in the proximal convoluted tubule (PCT) via sodium-dependent phosphate transporters (70% by Npt2a and ~30% by Npt2c, minimal by PiT-2). Reabsorption saturates and excretion increases in proportion to the filtered load at a serum phosphorus concentration within the normal range. Although, basolateral Pi transport remains poorly understood, with possible sodium independent or concentration dependent pathways, there have been recent advances in the understanding of renal Pi transport across the apical membrane.

Three types of sodium-phosphate cotransporters are expressed in kidney (Npt1, Npt2, and Npt3). Npt1 is a nonspecific anionic carrier and its physiologic role is unknown. It may play a role in urate transport. Npt2 is further subdivided into 3 isoforms: a, b, and c. Npt2b is found in the small intestine and lung. Human mutations in Npt2b present with lung calcification and normal serum calcium and Pi concentrations. Npt2a and Npt2c are found in the PCT. PiT-1 and PiT-2 belong to the Npt3 family. PiT-1 and -2 are widely expressed and likely help supply Pi to cells rather than controlling Pi balance. Table 11.1 illustrates the properties of Npt transporter isoforms. Overall, renal phosphate transport maximum (Tm) is regulated by a variety of stimuli.

PTH and phosphatonins lower the Tm. PTH induces the removal of Npt2a from the apical surface of PCT via PTH1 receptors expressed on the apical and basolateral membranes. FGF-23 and Klotho are not necessary for the phosphaturic action of PTH. It is mediated by endocytic retrieval of Npt2a from the BBM. These vesicles are shuttled to lysosomes and degraded. There is little to no recycling back to the proximal tubular cell membrane once transporters are endocytosed. New transporters must then be resynthesized and routed to the apical membrane via a subapical compartment. Acute regulation involves changes in endocytic rates. Endocytosis occurs between microvilli at intermicrovillar clefts and involves the actin cytoskeleton. Megalin may also play a role. It is mediated by a variety of protein kinases. Figure 11.2 summarizes this process.

Phosphatonins, circulating phosphaturic peptides, decrease BBM abundance of Npt2a/Npt2c in vivo and suppress 1α-hydroxylase activity in kidney. Amongst the

TABLE 11-1. Sodium Phosphate Cotransporter Isoforms

ISOFORMS	LOCATION IN HUMAN	CELLULAR LOCALIZATION	TRANSPORT MODE	OTHER TRANSPORT FUNCTIONS	HUMAN DISEASE
Npt1	Ubiquitous	Apical	Electrogenic	Cl^- channel, organic anions (urate)	Unknown
Npt2		Apical			
a	Kidney (70%)		Electrogenic		
b	Intestine		Electrogenic		Pulmonary alveolar microlithiasis
c	Kidney (~30%)		Electroneutral		Hypophosphatemic rickets with hypercalciuria in Bedouin tribe
Npt3		Basolateral	Electrogenic		
PiT-1				Osteoblast Chondrocytes Salivary glands	Increased expression at vascular calcification sites in Werner syndrome
PiT-2	Kidney (minimal Pi transport)			Salivary glands	No human disease has been identified

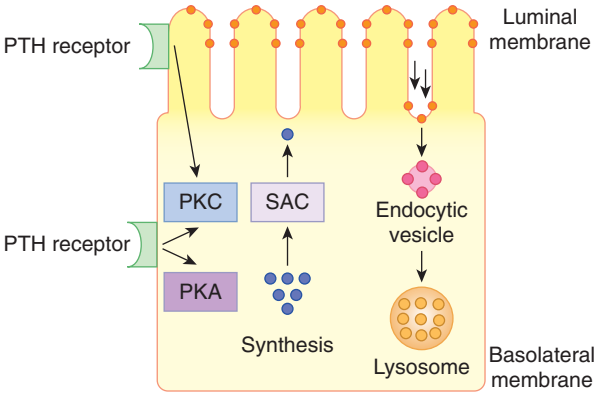

FIGURE 11-2. Cellular model of proximal tubular phosphate transport. Sodium phosphate cotransporters (Npt2a) are distributed along the luminal membrane (*dark circles*). In response to PTH, transporters localize to the intermicrovillar region where they are endocytosed and degraded in lysosomes. This appears to be a unidirectional process. New transporters must be resynthesized and routed to the apical membrane via a subapical compartment (SAC). PTH binds to receptors in both the luminal and basolateral membrane. Parathyroid hormone receptor-mediated signaling pathways (protein kinase A [PKA] and protein kinase C [PKC]) differ at the basolateral and luminal membranes.

phosphatonins such as FGF-23, secreted frizzled related protein-4 (sFRP-4), matric extracellular phosphoglycoprotein (MEPE) and dentin matrix protein-1, FGF-23 is the most studied molecule requiring a cofactor Klotho to activate its receptor, fibroblast growth factor (FGF) receptor-1, in PCT. FGF-23 is a 251-amino acid protein produced by bone cells (osteocytes and osteoblasts) in response to high Pi diet, high serum Pi or $1,25[OH]_2D_3$ concentration. Furthermore, the Klotho gene encodes a 1014-amino acid protein with a long extracellular NH_2 terminal, a single transmembrane domain, and short intracellular carboxy-terminus. Klotho exists in 2 forms: secreted; and transmembrane. It is expressed in kidney, brain, pituitary, parathyroid, ovary, testis, skeletal muscle, duodenum, and pancreas. It is highly expressed in distal tubules, and is also expressed in PCT. How bone senses changes in serum Pi concentration and alters FGF-23 secretion is unknown. Furthermore, intestinal mediators may regulate FGF-23 secretion. This hypothesis arises from the observation that hyperphosphatemia induced by dietary load increases FGF-23 levels, whereas nondietary interventions, like potassium phosphate infusion, do not.

FGF-23 when injected into experimental animals reduces calcitriol concentration within 3 hours. This occurs as a result of decreased calcitriol synthesis (decreased expression of 1α-hydroxylase) and increased degradation (increased expression of 24-hydroxylase). Serum phosphorus concentration and NaPi-2a fall after 9 to 13 hours. This effect occurs in parathyroidectomized animals indicating that it is PTH-independent. It is likely that only a part of the phosphaturic effect of FGF-23 is related to decreased calcitriol concentration. Calcitriol injection into mice results in an increase in FGF-23 concentration and FGF-23 KO mice have high serum calcitriol concentrations. Taken together, these studies indicate that FGF-23 plays a central role in feedback regulation of calcitriol concentration. It also plays a significant role in inhibiting PTH secretion from the parathyroid gland.

Pi depletion and $1,25[OH]_2D_3$ increase Pi Tm. With the discovery of novel molecules such as NHERF (sodium proton exchanger regulatory factor), we know that animals adapt to dietary Pi changes that are mediated by synchronous changes in trafficking Npt2a/Npt2c to the apical membrane in kidney. These changes are absent in NHERF null mice as they fail to correct phosphaturia and fail to increase expression of Npt2a with dietary Pi depletion. So far, the direct effect of $1,25[OH]_2D_3$ on renal Pi transport is controversial. It may alter Pi reabsorption by changing serum calcium and PTH concentrations.

Other factors that regulate renal phosphate reabsorption in humans are worth mentioning. Estrogen increases serum FGF-23 concentration and decreases Npt2a messenger ribonucleic acid (mRNA) levels, thyroid hormone increases Npt2a gene expression and glucocorticoid excess inhibits Pi reabsorption by decreasing Npt2a mRNA and protein abundance in BBM. Metabolic acidosis directly inhibits Npt2a, causing phosphaturia, in an attempt to increase net acid excretion.

Hence, Pi homeostasis is a highly regulated process involving several organs and phosphatonins play a major role in orchestrating the bone-kidney-endocrine axis.

KEY POINTS

Regulation of Phosphorus

1. Serum phosphorus consists of an organic and inorganic fraction, of these only the inorganic fraction is assayed in the clinical laboratory.

2. PTH, calcitriol, FGF-23, and dietary Pi intake regulates serum phosphorus concentration via effects on bone, intestine, and kidney.
3. PTH has both direct and indirect effects on phosphorus homeostasis. Directly, it increases bone turnover and reduces Pi reabsorption in proximal tubule. It acts indirectly in intestine via stimulation of 1α-hydroxylase with a resultant increase in calcitriol production.
4. Calcitriol enhances phosphorus transport in intestine and potentiates PTH effects in bone, which act to increase calcium and phosphorus entry into blood.
5. FGF-23 is a phosphaturic hormone that orchestrates Pi homeostasis by its control over calcitriol, PTH concentrations and renal capacity to reabsorb filtered Pi. Klotho binds to the FGF-23 receptor and acts as a cofactor required for FGF-23 signaling.
6. Npt2b mediates active transport in small intestine. Npt2a and Npt2c mediate Pi reabsorption in the proximal tubule. PiT-1 and PiT-2 transporters are widely expressed, transport Pi into cells, and play a role in ossification and smooth muscle calcification.

HYPERPHOSPHATEMIA

Etiology

Hyperphosphatemia most commonly results from decreased renal phosphate excretion. Chronic kidney disease (CKD) is the cause in greater than 90% of cases. Other causes involve abnormally increased proximal tubular phosphate reabsorption. Furthermore, an acute phosphorus load from either exogenous or endogenous sources can also cause hyperphosphatemia. Table 11.2 lists the etiologies of hyperphosphatemia, grouped by pathophysiologic categories.

As glomerular filtration rate (GFR) declines below 60 mL/min/1.73 m^2 renal phosphate excretion increases. Once GFR falls below 30 mL/min/1.73 m^2, however, phosphate reabsorption is maximally inhibited and renal excretion cannot increase further. At this point, dietary intake will exceed renal excretion and serum phosphorus concentration must increase. A new steady state is established at a higher serum phosphorus concentration. Approximately 15% of patients with a GFR of 15 to 30 mL/min/1.73 m^2 and 50% of those with a GFR less than 15 mL/min/1.73 m^2 have a serum phosphorus concentration greater than 4.5 mg/dL.

TABLE 11-2. Etiologies of Hyperphosphatemia

Decreased renal excretion
Decreased glomerular filtration rate
Acute kidney injury
Chronic kidney disease
Increased renal phosphorus reabsorption
Hypoparathyroidism
Acromegaly
Thyrotoxicosis
Drugs—bisphosphonates
Tumoral calcinosis
Acute phosphorus addition to extracellular fluid
Endogenous
Tumor lysis syndrome
Rhabdomyolysis
Severe hemolysis
Exogenous
Vitamin D intoxication
Sodium phosphate-containing bowel preparation solutions
High-dose liposomal amphotericin B
Improperly purified fresh-frozen plasma
Pseudohyperphosphatemia
Hyperbilirubinemia, hyperlipidemia, hemolysis, paraproteinemia

FGF-23 levels are augmented in early CKD stages long before hyperphosphatemia manifests in such patients. CKD patients exhibit poor response to the phosphaturic effects of FGF-23 because of decreased nephron mass or FGF-23 resistance. Furthermore, high FGF-23 and low calcitriol levels suppress Klotho expression in kidney and parathyroid gland. Decrease in Klotho provides FGF-23 resistance and perpetuates this vicious cycle of abnormal Pi metabolism in CKD patients. A progressive decline in urinary-secreted Klotho occurs during CKD progression, which is evident in early CKD stages. Inhibition of Npt2a and augmentation of TRPV5 (transient receptor potential vanilloid-5) activity by secreted Klotho is mitigated with CKD, which

may explain increased Pi reabsorption in these patients. We now know from FGF-23 KO mice that exhibit hyperphosphatemia, high $1,25[OH]_2D_3$ levels, vascular calcification, and early mortality, that reducing serum Pi concentration in these animals by either ablating the VDR or administering a low Pi diet rescues their phenotype. FGF-23 and Klotho KO models exhibit markers of oxidative stress, hypogonadism and generalized tissue atrophy. There are several overlapping aging-like phenotypes, including hypogonadism, skin atrophy, osteopenia, vascular calcification, and cognitive impairment, that present in CKD patients. Phosphate toxicity may play a pivotal role in these toxic effects.

CKD patients suffer disproportionately from cardiovascular mortality. In fact, compared to CKD patients with a serum Pi concentration less than 6.5 mg/dL, those with equal to or greater than 6.5 mg/dL levels have higher mortality. Multiple observational studies show a linear relationship between high Pi levels and high all-cause and cardiovascular mortality. There seems to be a dose–response effect in regards to serum Pi concentration and mortality in patients with CKD (all stages), end-stage renal disease (ESRD), and those with normal renal function. Based on observational data, each 1 mg/dL rise in serum Pi concentration increased all-cause mortality by 10% in patients with CKD stages 3 to 4. The REIN (Ramipril Efficacy in Nephropathy) trial showed that each 1 mg/dL rise in serum Pi concentration was associated with 85% excess risk of progression to ESRD that was consistent with the Chronic Renal Impairment in Birmingham (CRIB) study cohort. CKD patients have accelerated atherosclerosis and medial calcification. Some reports suggest that each 1 mg/dL rise in serum phosphorus concentration is associated with 21% and 25% greater prevalence of coronary artery and aortic calcification. Calcification in large arteries reduces compliance, increases pulse pressure and subsequently afterload, favoring left ventricular hypertrophy (LVH)-compromised coronary perfusion. Moreover, Pi interacts with several autocrine, paracrine, and endocrine factors to exhibit toxic effects on vascular smooth muscle cells. Vascular calcification is a complex ectopic biomineralization process where imbalance in inhibitors of mineralization, rate of cell death (providing nucleus for apatite crystals), presence of circulating nucleating factors (from increased bone turnover), and pathologic expression of bone proteins occurs in vascular smooth muscle cells.

There are other potential but uncommon causes of hyperphosphatemia. First, increased renal phosphate reabsorption is an uncommon pathophysiologic mechanism for the development of hyperphosphatemia. It occurs in hypoparathyroidism as a result of decreased PTH concentration. In acromegaly, insulin-like growth factor-1 stimulates phosphate transport. Bisphosphonates directly increase renal phosphate reabsorption, but this effect is usually offset by secondary hyperparathyroidism that results from a decrease in serum calcium concentration. Tumoral calcinosis is an autosomal recessive disease associated with hyperphosphatemia and soft-tissue calcium deposition. This condition arises either from: mutations in the GALNT3 gene that encodes a glycosyltransferase that is involved in O-linked glycosylation of FGF-23; mutations in FGF-23 that increase its cleavage by proteases; and defects in Klotho, thereby rendering FGF-23 and FGFR-1 interaction abnormal. It is the intact FGF-23 molecule that is biologically active. This results in increased FGF-23 processing and diminished phosphaturic effects.

Second, serum phosphorus concentration also increases as a result of an acute large phosphorus load. Phosphorus can be released from an endogenous source (within cells), as in tumor lysis syndrome, hemolysis, or rhabdomyolysis. Exogenous phosphorus sources reported to cause hyperphosphatemia include phosphorus-containing laxatives and enemas, high-dose liposomal amphotericin (contains phosphatidylcholine and phosphatidylserine), and solvent-detergent-treated fresh-frozen plasma (contained improper amounts of dihydrogen phosphate used as a buffer in the purification process). Oral sodium phosphate solution was commonly used as a bowel preparation agent for colonoscopy. It can be given in a small volume (45 mL 18 and 6 hours before the procedure) and is less expensive than polyethylene glycol-based solutions. These 90 mL contain 43.2 g of monobasic sodium phosphate and 16.2 g of dibasic sodium phosphate. A variety of rare renal complications occur with its use. Fatal hyperphosphatemia was reported in a renal transplantation patient, serum phosphorus concentration 17.8 mg/dL, who received a single oral dose of 90 mL and suffered a cardiorespiratory arrest 6 hours later. A case series of 5 patients was reported with acute kidney injury (mean serum creatinine concentration 4.9 mg/dL) secondary to acute calcium phosphate precipitation in distal tubules and collecting ducts and severe tubular damage. Four were prescribed angiotensin-converting enzyme

inhibitors or angiotensin receptor blockers, and 2 were taking diuretics. At 6 weeks renal function was unchanged in 4 of the 5 patients. When given to normal volunteers ages 21 to 41 years with normal renal function, oral phosphosoda caused a rise in serum phosphorus concentration to 7.6 mg/dL and a fall in serum calcium concentration to 8.4 mg/dL. There were no adverse clinical effects as a result of these changes. As many as 37% of patients with a creatinine clearance greater than 70 mL/min have an increase in serum phosphorus concentration to greater than 8.0 mg/dL. Taken together, these studies indicate that oral sodium phosphate solution should be used with caution in those older than age 55 years, those with decreased gastrointestinal (GI) motility, and in the presence of volume depletion. It should not be used at all in patients with CKD stages 3 to 5.

Fourth, spurious hyperphosphatemia occurs as a result of interference in the assay to measure serum Pi concentration. Hyperlipidemia, hyperbilirubinemia, hemolysis, paraproteinemia, and contamination of blood samples with heparin can cause spuriously elevated serum Pi levels.

KEY POINTS

Etiology of Hyperphosphatemia

1. Hyperphosphatemia results from decreased renal phosphate excretion or an acute phosphorus load from either exogenous or endogenous sources.
2. CKD is the cause in the vast majority of cases.
3. As GFR declines below 60 mL/min/1.73 m^2 renal phosphorus excretion increases. FGF-23 levels rise and urinary secreted Klotho levels decline in early CKD much before a rise in serum Pi concentration.
4. A novel role of Pi toxicity has emerged playing a central role in mortality, CKD progression, vascular calcification, tumorigenesis, and cardiovascular events.

Signs and Symptoms

Signs and symptoms of hyperphosphatemia are primarily the result of hypocalcemia. The most common explanation offered for hypocalcemia is that the calcium-phosphorus product exceeds a certain level and calcium deposits in soft tissues and serum calcium concentration falls. A calcium-phosphate product of greater than 72 mg^2/dL^2 is commonly believed to result in this so-called metastatic calcification. It is difficult, however, to find the original studies on which this belief is based.

In patients with CKD and ESRD, it is being increasingly demonstrated that serum Pi concentration orchestrates an abnormal biomineralization process in vascular smooth muscle cells of the blood vessel wall that are capable of transforming to an "osteoblast-like" phenotype. Interestingly, vascular calcification is seen even in those patients with CKD or ESRD who have normal to near-normal serum Pi concentration. Vascular calcification was shown to predict all-cause and cardiovascular mortality in such patients, and may possibly render traditional risk factor management in CKD/ESRD patients ineffective. Interestingly, vascular calcification occurs much earlier in CKD patients compared to the general population. Despite the well-established role of phosphorus and its toxic role in vascular calcification in CKD patients, it remains unclear whether phosphate binders decrease, prevent or reverse vascular calcification in patients with CKD and ESRD.

KEY POINTS

Signs and Symptoms of Hyperphosphatemia

1. Symptoms of an acute rise of serum phosphorus concentration are related to hypocalcemia.
2. CKD patients with normal serum Pi concentration already have impaired FGF-23 and Klotho, which initiates pathophysiologic processes long before a rise in serum Pi concentration.
3. Hyperphosphatemia is often associated with pruritus in CKD patients.

Diagnosis

Clinically unexplained persistent hyperphosphatemia raises the suspicion of pseudohyperphosphatemia, the most common cause of which is paraproteinemia secondary to multiple myeloma. No consistent relationship of immunoglobulin type or subclass was identified. This is a method-dependent artifact and paraprotein interference may be a general problem in some automated assays. The assay must be rerun with sulfosalicylic acid deproteinized serum so as to eliminate the

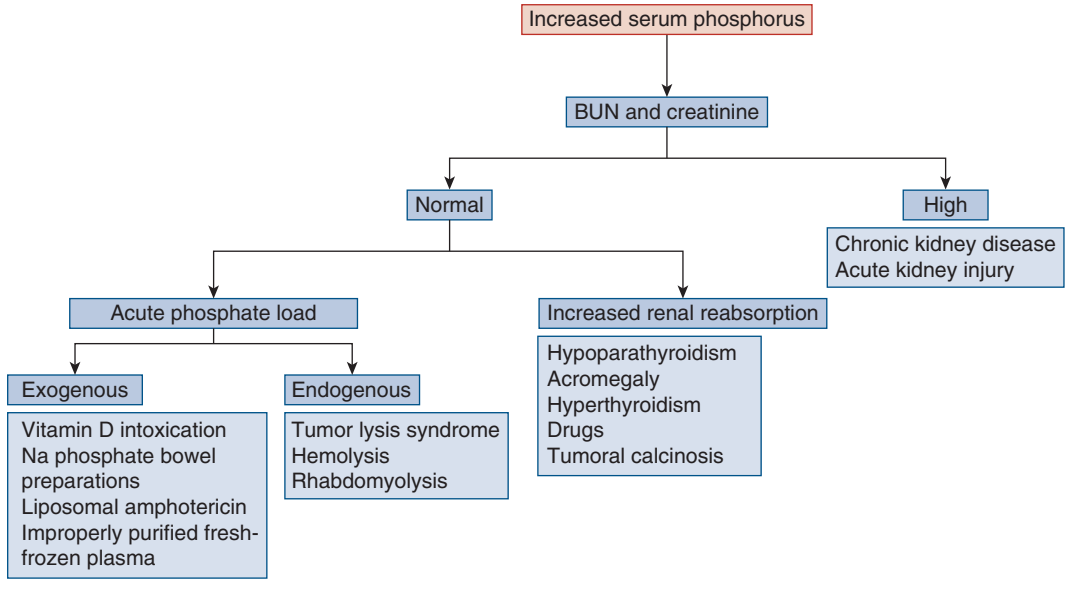

FIGURE 11-3. Evaluation of the hyperphosphatemic patient. Serum concentrations of blood urea nitrogen (BUN) and creatinine are evaluated first. Renal failure is the most common cause of hyperphosphatemia. If renal function is normal, an acute phosphorus load or increased renal phosphate reabsorption are likely responsible.

artifact. Otherwise, the cause is generally acute kidney injury or CKD. Figure 11.3 shows an algorithm for the differential diagnosis of hyperphosphatemia.

KEY POINTS

Diagnosis of Hyperphosphatemia

1. Paraproteins may result in a false elevation of serum phosphorus concentration.
2. Acute kidney injury and CKD remain the most common causes of hyperphosphatemia.

Treatment

The cornerstone of management of the hyperphosphatemic patient with CKD is reduction of intestinal phosphorus absorption. Early in CKD, hyperphosphatemia can be controlled with dietary phosphorus restriction. Dietary phosphorus absorption is linear over a wide range of intakes, 4 to 30 mg/kg/day. Therefore, absorption depends on the amount of phosphorus in the diet and its bioavailability. The majority of dietary phosphorus is contained in 3 food groups: (a) milk and related dairy products such as cheese; (b) meat, poultry, and fish; and (c) grains. Patients age 18 to 44 years consume on an average 2.1 fast-food meals per week, accounting for an estimated additional Pi consumption of greater than 1600 mg. Pi-containing additives add taste, shelf-life, and appearance, making fast-food entrees and side dishes affordable, palatable, convenient, and of high caloric density. Inorganic phosphorus salts contained in processed foods are virtually completely absorbed and patients with hyperphosphatemia should avoid these foods, including hot dogs, cheese spreads, colas, processed meats, and instant puddings. These additives have higher Pi bioavailability than natural sources (enhanced meat and poultry products have 28% higher Pi than regular products). Physiologically, animal-based food products are rich in Pi that is highly bioavailable. Plant products have lower bioavailability as they contain phytates, which are not hydrolyzed well for absorption. Hence, there is a strong and positive correlation between protein intake and phosphorus intake. Studies on healthy volunteers reveal plant products may be better than animal products with similar Pi content in the diet as a result of the differential bioavailability. Overall, dietary estimates of

TABLE 11-3. Phosphate Binders

BINDER	CALCIUM ACETATE (1 g)	CALCIUM CARBONATE (1 g)	SEVELAMER (800 mg)	LANTHANUM (750 mg)
Amount of elemental calcium	253 mg	400 mg	None	None
Amount of phosphorus bound	40 mg	44 mg	64 mg	130 mg
Cost per pill	$0.21 (667 mg)	$0.02 (1 gram)	$0.98 (800 mg)	$1.32 (750 mg)

phosphorus ingestion commonly underestimate phosphorus intake.

As CKD worsens phosphate binders must be added. Studies have been published comparing different binders, as shown in Table 11.3. The ideal binder should efficiently bind phosphate, have minimal effects on comorbid conditions, have a favorable side-effect profile, and be low in cost. Unfortunately, none of the currently available phosphate binders fulfill all of these criteria. Calcium-containing binders are low in cost but may contribute to net positive calcium balance and accelerate calcium deposition in the vasculature, and can cause oversuppression of PTH, resulting in adynamic bone disease and hypercalcemia. Aluminum-containing phosphate binders may be employed in the short-term, but should be avoided chronically in CKD patients because of aluminum toxicity (osteomalacia and dementia). Sevelamer carbonate, a synthetic calcium-free polymer, has a favorable side-effect profile but is costly. Sevelamer hydrochloride was associated with lower serum bicarbonate concentrations and hence its formulation was changed to sevelamer carbonate. Lanthanum is the newest phosphate binder with excellent binding capacity. Unfortunately, it is expensive.

In selecting between a calcium-containing binder, sevelamer carbonate, and lanthanum, one must balance cost of newer agents against potential benefits of decreased vascular calcification as recent trials have not shown mortality benefits with newer agents. Sevelamer carbonate was recently compared to calcium-based binders in a multicenter, randomized, open-label, parallel design trial among 2103 prevalent hemodialysis patients. No benefit was observed in all-cause or cause-specific mortality between sevelamer and calcium-based binders. There was a trend toward benefit of sevelamer over calcium-based binders in elderly patients older than 65 years of age. No significant difference in mortality was reported in recent metaanalyses comparing patients treated with sevelamer hydrochloride with those treated with calcium-based agents (risk difference, −2%; 95% CI, −6 to 2). Similarly, the effect of sevelamer on reducing coronary calcification in renal patients has been contradictory based on few randomized trials and a recent metaanalysis. In vitro studies have compared Langmuir equilibrium binding affinities for lanthanum carbonate and sevelamer hydrochloride. Lanthanum has higher binding affinity for phosphate than sevelamer at all pH values. Furthermore, in the presence of bile salts, sevelamer loses approximately 50% of its binding capacity as compared to lanthanum. There is a lack of data comparing lanthanum to other binders for predicting clinical outcomes and coronary calcification. Finally, magnesium-containing phosphate binders are available, but their safety and efficacy profiles are not as well studied.

In general, choice and dose of a specific agent should be based on estimation of dietary phosphorus content based on protein intake, adjusting for weekly phosphorus removal by dialysis sessions in the ESRD patient, and then selecting the appropriate agent based on its phosphorus binding capacity and cost.

KEY POINTS

Treatment of Hyperphosphatemia

1. Early in CKD, dietary phosphorus restriction alone can normalize serum phosphorus concentration. It is difficult to decrease Pi intake in the diet.
2. As GFR continues to fall phosphate binders must be added. The choice of agent should be based on estimation of phosphorus intake, weekly phosphate removal by dialysis and specific phosphorus binding capacity of the agent with special consideration to cost.

3. Calcium carbonate and calcium acetate induce positive calcium balance, sevelamer binding capacity does not increase proportionately to its dose increase, and lanthanum is costly. Aluminium is no longer used as a binder because of its chronic toxic side effects, except in the short-term.

HYPOPHOSPHATEMIA

Etiology

Hypophosphatemia results from 1 or a combination of 3 basic pathophysiologic processes: redistribution of extracellular fluid (ECF) phosphorus into intracellular fluid (ICF); decreased intestinal phosphorus absorption; or increased renal phosphorus excretion. It is quite common in alcoholics and critically ill patients. Table 11.4 shows the differential diagnosis of hypophosphatemia based on pathophysiologic process.

TABLE 11-4. Etiologies of Hypophosphatemia

Decreased net GI absorption
Decreased dietary intake
Phosphate-binding agents
Alcoholism
Shift into ICF
Respiratory alkalosis
Refeeding
Diabetic ketoacidosis
Hungry bone syndrome
Sepsis
Increased renal excretion
Primary hyperparathyroidism
Secondary hyperparathyroidism from vitamin D deficiency
X-linked hypophosphatemic rickets
Autosomal dominant hypophosphatemic rickets
Oncogenic osteomalacia
Fanconi syndrome
Osmotic diuresis
Partial hepatectomy
Pseudohypophosphatemia

The two most common causes of a phosphorus shift into cells are respiratory alkalosis and "refeeding syndrome," which are commonly seen in critically ill patients. A rise in intracellular pH that occurs with respiratory alkalosis stimulates phosphofructokinase, the rate-limiting step in glycolysis, and phosphorus is incorporated into ATP. Severe hypophosphatemia with phosphorus concentrations less than 0.5 to 1.0 mg/dL is common in alcoholics that have a combination of all 3 pathophysiologic processes that cause hypophosphatemia. To evaluate the impact of arterial pH on serum Pi concentration, a study done in 11 normal volunteers showed hyperventilation to a partial pressure of arterial carbon dioxide ($PaCO_2$) of 13 to 20 mmHg caused a fall in serum phosphorus concentration within 90 minutes from a mean of 3.1 mg/dL to 0.8 mg/dL. At the same time, urinary phosphate excretion dropped to near zero. Hypophosphatemia was reported with a rise in pH even within the normal range in ventilated chronic obstructive pulmonary disease patients. In concert with the pH rise that occurs after intubation, serum phosphorus concentration falls over the span of several hours.

With refeeding, the rapidity of onset of hypophosphatemia depends on the degree of malnutrition, caloric load, and amount of phosphorus in the formulation. In undernourished patients it develops within 2 to 5 days from either enteral or parenteral feeding. The fall is more marked in patients with liver disease. In adolescents with anorexia nervosa, decline in serum phosphorus concentration is directly proportional to the percent loss of ideal body weight. However, serum phosphorus concentration generally does not decline below 0.5 mg/dL with glucose infusion alone. Carbohydrate repletion and subsequent insulin release enhances intracellular phosphorus, glucose, and potassium uptake. Phosphorus also moves into cells with treatment of diabetic ketoacidosis (DKA), and in the "hungry bone syndrome" that occurs after subtotal parathyroidectomy for secondary hyperparathyroidism in patients with ESRD. Renal phosphate loss from osmotic diuresis contributes to the hypophosphatemia of DKA. In "hungry bone syndrome," serum calcium and phosphorus concentration often fall abruptly in the immediate postoperative period. From a clinical standpoint, hypocalcemia is the more important management issue. Catecholamines and cytokines may also cause a phosphorus shift

into cells and this may be the mechanism whereby sepsis results in hypophosphatemia.

Redistribution of Pi between extracellular and intracellular compartments occurs when erythropoietin-stimulating agents are given to patients with cirrhosis.

Decreased GI absorption alone is an uncommon cause of hypophosphatemia because dietary phosphorus intake invariably exceeds GI losses and the kidney is extraordinarily effective at conserving phosphate. Decreased dietary intake must be combined with phosphate binder use or increased GI losses as with diarrhea. In Bartter's original description of diet-induced hypophosphatemia, 75 to 100 days of a low-phosphorus diet and phosphate-binding antacids were required before symptoms developed. The primary symptom was musculoskeletal weakness that resolved with phosphorus replacement. Steatorrhea and malabsorption can result in calcitriol deficiency, secondary hyperparathyroidism, and increased renal phosphate excretion. Sorafenib, a drug approved for the treatment of advanced renal cell carcinoma, is associated with hypophosphatemia that is thought to be mediated by reduced intestinal phosphate absorption.

Increased renal phosphate excretion is seen in primary hyperparathyroidism, as well as secondary hyperparathyroidism from disorders of vitamin D metabolism. In primary hyperparathyroidism the serum phosphorus concentration is rarely below 1.5 mg/dL. Although PTH increases renal phosphate excretion, this is partially offset by PTH action to increase calcitriol that, in turn, increases GI phosphorus absorption. On the other hand, secondary hyperparathyroidism from calcitriol deficiency may be associated with severe hypophosphatemia if the patient has normal renal function. Three rare diseases associated with isolated renal phosphate wasting are worth mentioning: X-linked hypophosphatemia (XLH); autosomal dominant hypophosphatemic rickets (ADHR); and oncogenic hypophosphatemic osteomalacia. Concerns for such conditions arise when serum phosphorus concentration is less than 2.5 mg/dL and plasma FGF-23 level is greater than 30 pg/mL by intact FGF-23 assay. All 3 conditions present with low or normal calcitriol levels.

First, XLH is an X-linked dominant disorder with a prevalence of 1 in 20,000 in the general population. It is manifested by growth retardation, rickets, hypophosphatemia, dental abnormalities, and low serum calcitriol concentration. XLH is caused by mutations in the PHEX (phosphate-regulating gene with homology to endopeptidases) gene. PHEX is a member of the M13 family of metalloproteinases. The gene is expressed in bone, teeth, and parathyroid gland, but not in kidney. In bone, PHEX is expressed in the cell membrane of osteoblasts and plays a role in osteoblast mineralization. The mutated protein is not expressed in the cell membrane and is degraded in the endoplasmic reticulum. How a defect in a membrane protein expressed in osteoblasts results in renal phosphate wasting is unclear. PHEX may play a role in the activation or inactivation of peptide factors involved in skeletal mineralization, renal phosphate transport, and vitamin D metabolism. Traditional treatment for this condition is to provide phosphorus supplementation along with calcitriol. This causes FGF-23 levels to rise. Recently, phosphorus supplementation was used with cinacalcet to avoid potential long-term complications of therapy, such as nephrocalcinosis and hyperparathyroidism. In addition, Japanese patients were treated with anti–FGF-23 antibodies.

Second, ADHR occurs as a result of a gain-of-function mutation in the FGF-23 gene. FGF-23 is secreted and processed at a cleavage site into N- and C-terminal fragments. Biologic activity of FGF-23 is limited to the full-length molecule, which is degraded by protease cleavage. The enzyme responsible for FGF-23 cleavage is unknown. Mutations in ADHR occur at the proteolytic site and prevent FGF-23 cleavage.

Third, oncogenic hypophosphatemic osteomalacia (OHO) is caused by FGF-23 overproduction by mesenchymal tumors. Tumor resection is curative. Immunohistochemical staining of these tumors shows an overabundance of FGF-23. The tumor is often difficult to localize. A new technique to localize such tumors was developed by positron emission tomography (PET)-computed tomography (CT) technique using the somastatin receptor-binding compound ^{68}Ga-DOTANOC ([1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-NaI3-octreotide). A more common condition, hormone refractory prostate cancer with metastatic skeletal lesions also exhibits hypophosphatemia secondary to high FGF-23 levels.

Furthermore, there are several other conditions that can result in hypophosphatemia, which are listed in Table 11.4. Renal phosphate wasting is observed during the immediate postoperative period after partial hepatectomy. The mechanism is unclear but other phosphatonins such as MEPE may play a role. Serum FGF-23 concentrations in these patients are normal.

Drugs have also been associated with hypophosphatemia. Iron carboxymaltose can induce hypophosphatemia

by stimulating FGF-23 release. Sirolimus may induce the expression of Klotho.

Fanconi syndrome results in renal phosphate wasting. This is characterized by glycosuria in the face of a normal serum glucose and aminoaciduria. A variety of inherited diseases are associated with Fanconi syndrome, including cystinosis, Wilson disease, hereditary fructose intolerance, and Lowe syndrome. Acquired causes include: multiple myeloma; renal transplantation; and drugs. Implicated drugs include: ifosfamide; streptozocin; tetracyclines; valproic acid; didanosine (ddI); cidofovir; adefovir; tenofovir; and ranitidine. Tenofovir is being increasingly reported as a cause of Fanconi syndrome in human immunodeficiency virus (HIV)-infected patients. Tenofovir is an acyclic nucleoside phosphonate that is excreted by glomerular filtration and tubular secretion. It enters proximal tubular cells across the basolateral membrane on the human organic anion transporter 1 (hOAT1) and exits into urine on the multidrug resistance-associated protein 2 (Mrp-2). Because ritonavir inhibits Mrp-2, its use with tenofovir could result in increased toxicity. Renal injury occurs from weeks to months after starting treatment. In addition to Fanconi syndrome, decreases in creatinine clearance and nephrogenic diabetes insipidus (DI) were also reported.

The Chinese herb Boui-ougi-tou used for treatment of obesity also causes Fanconi syndrome. A urinalysis for glycosuria should be performed. Dent disease is caused either by a mutation in the $2Cl^-/H^+$ exchanger CLCN-5 or in OCRL-1, the same gene mutated in oculocerebrorenal syndrome of Lowe (OCRL) syndrome. It results in hypophosphatemia and renal phosphate wasting associated with low-molecular-weight proteinuria, hypercalciuria, nephrolithiasis, nephrocalcinosis, and CKD.

KEY POINTS

Etiology of Hypophosphatemia

1. Decreased GI absorption, phosphorus shifts from ECF into ICF and increased renal excretion are the most common pathophysiologic processes that reduce serum phosphorus concentration.
2. Intracellular phosphorus shifts are the most common cause of hypophosphatemia in hospitalized patients, more commonly seen in those that are at risk of phosphate depletion and malnourishment.
3. The most common causes of increased renal phosphorus excretion are primary and secondary hyperparathyroidism. In primary hyperparathyroidism serum phosphorus concentration is rarely below 1.5 mg/dL.
4. Several inherited disorders have been recognized, which result in hypophosphatemia such as XLH and ADHR. Tumor-induced osteomalacia (TIO) is a rare but interesting acquired cause of hypophosphatemia.
5. Several medications can also result in hypophosphatemia.

Signs and Symptoms

Hypophosphatemia causes a variety of signs and symptoms. Their severity varies with the degree of phosphorus lowering. There are a small number of studies suggesting that in certain clinical situations moderate hypophosphatemia (phosphorus concentration between 1.0 and 2.5 mg/dL) is associated with clinically significant morbidity. Moderate hypophosphatemia does not impair myocardial contractility. It increases insulin resistance but the clinical significance of this is unclear. Correction of moderate hypophosphatemia did improve diaphragmatic function in patients with acute respiratory failure. Eight intubated patients were given a short-term phosphorus infusion (10 mmol [310 mg] over 4 hours). Mean serum phosphorus concentration increased from 1.72 to 4.16 mg/dL. Transdiaphragmatic pressure increased in all patients. One can question the clinical relevance of this finding given the small number of patients and lack of clinically important end points. In a cross-sectional study a serum phosphorus concentration less than 2.4 mg/dL was associated with a 20% increase in weaning failure from a ventilator when compared to those with a normal phosphorus concentration. Continuous dialytic therapies can be associated with hypophosphatemia. In one study of 321 patients on continuous dialysis, 27% developed a serum phosphorus concentration less than 2 mg/dL during therapy. This was associated with an increased risk of developing prolonged respiratory failure requiring tracheostomy. In another study, a group of 16 patients were evaluated in the early stages of sepsis. Ten of 16 patients had significant atrial and ventricular arrhythmias. Those patients with arrhythmias had a significantly lower serum phosphorus concentration (2.8 mg/dL) than those who

did not (3.19 mg/dL). There was no increase in mortality in the hypophosphatemic patients.

On the other hand, severe hypophosphatemia (serum phosphorus concentration <1.0 mg/dL) is associated with morbidity. Failure to wean from mechanical ventilation without correction of severe hypophosphatemia was demonstrated. In one study, severe hypophosphatemia increased the length of time patients spent on a ventilator (10.5 vs. 7.1 days) and in the hospital (12.1 vs. 8.2 days). This was also shown after cardiac surgery where patients with severe hypophosphatemia required more time on the ventilator (2.1 vs. 1.1 days), a longer hospital stay (7.8 vs. 5.6 days), and cardioactive drugs for a longer period of time.

Although hypophosphatemia causes a leftward shift in the oxygen dissociation curve, the clinical significance of this is unclear. Severe hypophosphatemia produces reversible myocardial dysfunction and an impaired response to pressors. Correction of severe hypophosphatemia increases myocardial contractility by 20%. The effect of short-term correction is variable between patients with some showing minimal to no response and others showing larger responses. Severe hypophosphatemia rarely, if ever, results in clinical congestive heart failure. A variety of neuromuscular symptoms can occur including paresthesias, tremor, and muscle weakness. Hematologic disturbances include increases in red cell fragility that lead to hemolysis. Hemolytic anemia was reported in two patients with serum phosphorus concentrations of 0.1 and 0.2 mg/dL, respectively. Red cell ATP was reduced to very low levels. In vitro studies in humans show that a serum phosphorus concentration less than 0.5 mg/dL decreased chemotaxis, phagocytosis, and bacterial killing by white cells. Whether this could predispose to infection is unknown. Severe hypophosphatemia causes rhabdomyolysis in dogs only if there is a preexisting subclinical myopathy. There are very few reports of rhabdomyolysis in humans. A recent case series of 7 hospitalized patients with rhabdomyolysis indicates that the rhabdomyolysis occurred after severe burns and muscle injury.

KEY POINTS

Signs and Symptoms of Hypophosphatemia

1. Correction of moderate hypophosphatemia improves diaphragmatic function in patients with acute respiratory failure. The clinical importance of this is unclear.
2. Moderate hypophosphatemia does not impair myocardial contractility.
3. Severe hypophosphatemia impairs the ability to wean patients from mechanical ventilation and prolongs hospital stay.
4. Myocardial contractility is decreased in severe hypophosphatemia; however, this rarely, if ever, results in clinical congestive heart failure.
5. Very severe hypophosphatemia increases red cell fragility that can lead to hemolysis.
6. Severe hypophosphatemia causes rhabdomyolysis in dogs only if there is a preexisting subclinical myopathy. There are very few reports of rhabdomyolysis in humans.

Diagnosis

Figure 11.4 summarizes the diagnostic approach to the patient with hypophosphatemia. One can use the fractional excretion (FE) of phosphorus, the 24-hour urinary phosphorus, or the calculated renal threshold phosphate concentration ($TmPO_4$/GFR) to distinguish among pathophysiologic mechanisms of hypophosphatemia. The FE of phosphorus is calculated using the formula from an early morning first void specimen:

$$\frac{U_P \times P_{Cr}}{U_{Cr} \times P_P} \times 100$$

Urine and plasma creatinine and phosphorus concentrations are all expressed in mg/dL. A FE of phosphorus below 5%, a 24-urine phosphorus less than 100 mg/day, or a $TmPO_4$/GFR greater than 2.1 mg/dL indicates that the kidney is responding properly to decreased intestinal absorption or phosphorus shift into cells. If renal phosphorus wasting is the pathophysiologic reason for hypophosphatemia, then the FE of phosphorus exceeds 5% and the 24-hour urine phosphorus excretion is greater than 100 mg. FGF-23 can be assayed using Western blot or ELISA (enzyme-linked immunosorbent assay).

Hypophosphatemia should be evaluated with a panel of other tests: total serum calcium; PTH; and total 25-hydroxy vitamin D levels. In the patient with increased renal phosphorus excretion, one next evaluates the serum calcium concentration. In secondary hyperparathyroidism, serum calcium concentration is low, provided that renal function is intact. If secondary hyperparathyroidism from vitamin D deficiency is suspected, calcidiol and

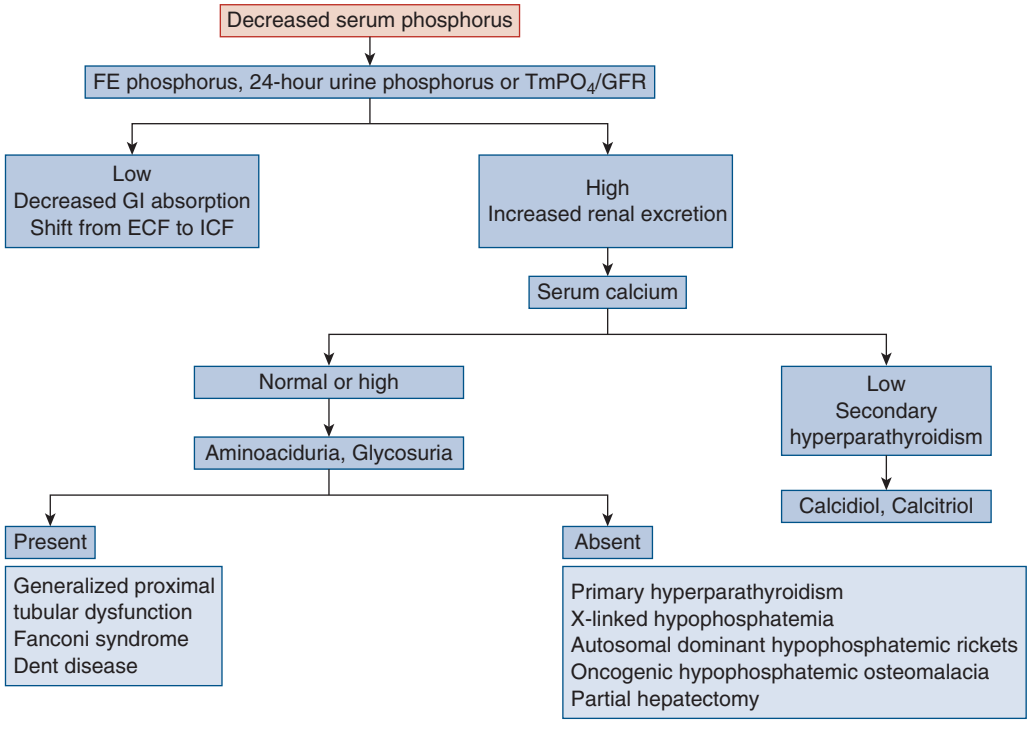

FIGURE 11-4. Evaluation of the hypophosphatemic patient. The first step in the evaluation of the hypophosphatemic patient is the evaluation of renal phosphorus excretion ($TmPO_4$/GFR). Decreased renal phosphorus excretion suggests a gastrointestinal cause or a phosphate shift from ECF to ICF. Increased renal phosphorus excretion is further subdivided based on serum calcium concentration.

calcitriol concentrations will help identify the defect. In the patient with a normal or elevated serum calcium concentration, one subdivides patients based on whether they have isolated renal phosphate wasting or a generalized proximal tubular disorder. Of the isolated phosphate wasting disorders, primary hyperparathyroidism is by far the most common. It is associated with a high serum calcium concentration and a low serum phosphorus concentration. The diagnosis is established by measuring PTH levels. Three rare disorders make up the remainder of patients in this category: XLH; ADHR; and OHO.

The generalized proximal tubular disorders are much less common and include Fanconi syndrome and Dent disease. If severe hypophosphatemia is noted, and the patient is either asymptomatic or serum phosphorus concentration remains low despite repletion, then one should consider the possibility of pseudohypophosphatemia. As is the case with pseudohyperphosphatemia, paraproteins can also result in a spuriously low serum phosphorus concentration. This artifact is avoided if deproteinized serum is analyzed.

KEY POINTS

Diagnosis of Hypophosphatemia

1. The first step in evaluation of the hypophosphatemic patient is examination of renal phosphate excretion with a FE, a 24-hour urine, or renal threshold phosphate concentration. This separates patients with renal phosphate wasting from those with decreased intake and intracellular phosphorus shifts.
2. The most common cause of hypophosphatemia from intracellular shifts in hospitalized patients is respiratory alkalosis.
3. If increased renal phosphate excretion is detected, one next examines serum calcium concentration, PTH, and 25-hydroxy vitamin D_3 levels.
4. Secondary hyperparathyroidism is the most common cause of renal phosphate wasting associated with hypocalcemia.
5. If serum calcium is normal or elevated primary hyperparathyroidism is the most common cause.

Treatment

There is little evidence that treatment of moderate hypophosphatemia (serum phosphorus concentration 1.0 to 2.5 mg/dL) is necessary, except in a mechanically-ventilated patient. Severe hypophosphatemia (≤1 mg/dL) or symptoms are indications for treatment. One must keep in mind that serum phosphorus concentration may not be a reliable indicator of total-body phosphorus stores as the majority of phosphorus is contained within cells. Hypophosphatemia is commonly associated with other electrolyte disturbances (hypokalemia and hypomagnesemia). One must cautiously replete phosphorus in patients who have impaired ability to excrete phosphorus loads (those with decreased GFR). Most hypophosphatemic patients can be corrected with up to 1 g of supplemental phosphorus per day orally. Table 11.5 lists several forms of oral phosphorus replacement therapy. Oral repletion is most commonly limited by the development of diarrhea.

Intravenous phosphorus administration may be complicated by hypocalcemia and hyperphosphatemia and is only justified in those with severe symptomatic phosphorus depletion. Sodium phosphate should be employed except in patients that require concomitant potassium supplementation. During intravenous replacement, blood chemistries, including serum phosphorus, calcium, magnesium, and potassium, should be monitored closely. Once serum phosphorus concentration has risen above 1 mg/dL, an oral preparation is begun and intravenous phosphorus is discontinued. In the severely malnourished patient, such as an adolescent with anorexia nervosa, refeeding must be accomplished slowly. Serum phosphorus concentration should be monitored closely and the patient placed on telemetry, as sudden death and ventricular arrhythmias have been reported with refeeding. Caution must be exercised when correcting hypophosphatemia in the recent renal transplantation recipient. In this situation, a newly transplanted kidney is often placed in the environment of significant secondary or tertiary hyperparathyroidism. In this setting, phosphate supplementation for hypophosphatemia has resulted in acute phosphate nephropathy. Some suggest that in this clinical setting phosphate should be replaced only in those with severe hypophosphatemia.

KEY POINTS

Treatment of Hypophosphatemia

1. Treatment of moderate hypophosphatemia should be considered in a mechanically-ventilated patient.
2. Severe hypophosphatemia (≤1 mg/dL) or symptoms are indications for treatment.
3. The safest mode of therapy is oral.
4. Intravenous phosphorus replacement carries the risk of hypocalcemia and is only warranted in patients with severe symptomatic phosphorus depletion.

TABLE 11-5. Phosphate Preparations

PREPARATION	CONTENTS	PHOSPHORUS	SODIUM	POTASSIUM
K-phos-neutral	Dibasic Na phosphate Monobasic Na phosphate Monobasic K phosphate	250 mg/tab	13 mEq/tab	1.1 mEq/tab
K-phos original	Monobasic K phosphate	114 mg/tab	–	3.7 mEq/tab
Fleets phosphosoda	Monobasic Na phosphate Dibasic Na phosphate	129 mg/mL	4.8 mEq/mL	–
Neutra-phos-K	Monobasic K phosphate Dibasic K phosphate	250 mg/cap	–	13.6 mEq/capsule
Neutra-phos	Monobasic and dibasic Na and K phosphates	250 mg/cap	7.1 mEq/capsule	6.8 mEq/capsule
IV Na phosphate	Monobasic Na phosphate	93 mg/mL	4.0 mEq/mL	–
IV K phosphate	Monobasic K phosphate	93 mg/mL	–	4.4 mEq/mL

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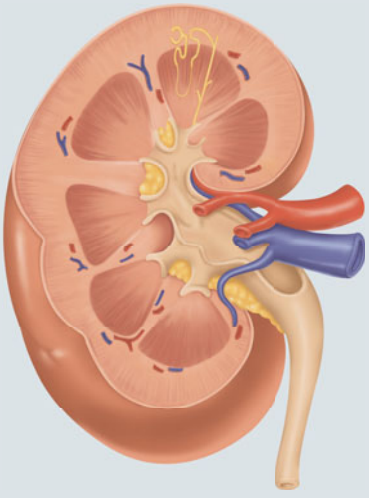

CHAPTER

12

Disorders of Magnesium Homeostasis—Hypo and Hypermagnesemia

• *Robert F. Reilly Jr.*

Recommended Time to Complete: 1 Day

Guiding Questions

1. How is extracellular fluid (ECF) magnesium concentration regulated?
2. What role does the thick ascending limb play in this process?
3. Which are the most important causes of hypomagnesemia?
4. Why is hypomagnesemia associated with both hypocalcemia and hypokalemia?
5. How does one approach the patient with hypomagnesemia?
6. What are the most common causes of hypermagnesemia?
7. Why are patients with chronic kidney disease (CKD), gastrointestinal (GI) disorders, and the elderly at increased risk for hypermagnesemia?

REGULATION

Magnesium is the fourth most abundant cation in the body and second most abundant within cells. It plays a key role in a variety of cellular processes. Magnesium is an important cofactor for adenosine triphosphatases (ATPases), and thereby in the maintenance of intracellular electrolyte composition. Ion channels involved in nerve conduction and cardiac contractility are regulated by magnesium. More than 300 enzymatic systems depend on magnesium for optimal function, including those involved in protein synthesis and deoxyribonucleic acid (DNA) replication. Magnesium deficiency is implicated in the pathogenesis of hypertension, type II diabetes mellitus, atherosclerosis, and asthma.

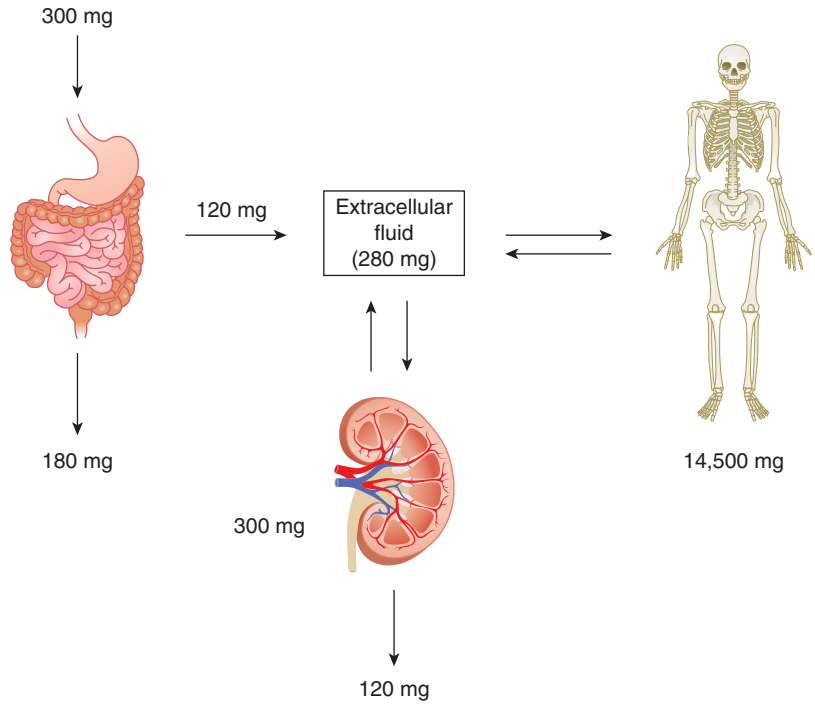

FIGURE 12-1. Magnesium homeostasis. Daily magnesium fluxes between ECF, intestine, kidney, and bone are shown. In the steady state, net intestinal absorption and renal magnesium excretion are equal.

Normal serum magnesium concentration is between 1.7 and 2.5 mg/dL. Only 1% of the 21 to 28 g of magnesium in the body is contained within the ECF. Of the remainder, 67% is in bone and 20% in muscle. Figure 12.1 shows the distribution of magnesium within the body. In bone, the majority of magnesium is complexed in hydroxyapatite crystals. Approximately 30% of magnesium in bone is exchangeable with the ECF compartment. The rate of exchange is unclear. Magnesium within muscle and red cells is largely complexed to intracellular ligands and has limited ability to move from intracellular fluid (ICF) to ECF in conditions of total-body magnesium depletion.

Magnesium is regulated by both GI tract and kidney, with kidney playing the more important role. The average North American diet contains approximately 200 to 350 mg of magnesium. The average daily requirement in men is 220 to 400 mg, and in women is 180 to 340 mg. The North American diet is only marginally adequate with respect to magnesium. The majority is complexed to chlorophyll in green leafy vegetables. Seafoods, nuts, meats, and grains are high in magnesium.

Magnesium absorption is inversely proportional to intake. Under normal circumstances 30% to 40% is absorbed. This can vary from a low of 25% with large magnesium intakes, to a high of 80% with dietary magnesium restriction. The majority of magnesium absorption occurs in small intestine via both a paracellular and transcellular pathway. Magnesium absorption is affected by water absorption and prolonged diarrheal states result in significant intestinal magnesium losses. Secretions from the upper GI tract are relatively low in magnesium (1 mg/dL), whereas those from colon are relatively high in magnesium (18 mg/dL).

The primary regulator of ECF magnesium concentration is the kidney. Only 30% of magnesium is bound to albumin. The remainder is freely filtered across the glomerulus. Renal magnesium reabsorption varies widely to maintain homeostasis. Reabsorption is reduced to near zero in the presence of hypermagnesemia or CKD. With magnesium depletion secondary to GI causes the fractional excretion of magnesium can be reduced to 0.5%. Twenty percent of magnesium is reabsorbed in the proximal tubule in adults. ECF volume status affects magnesium reabsorption in this segment. Volume contraction increases and volume expansion decreases magnesium reabsorption. The bulk of magnesium reabsorption

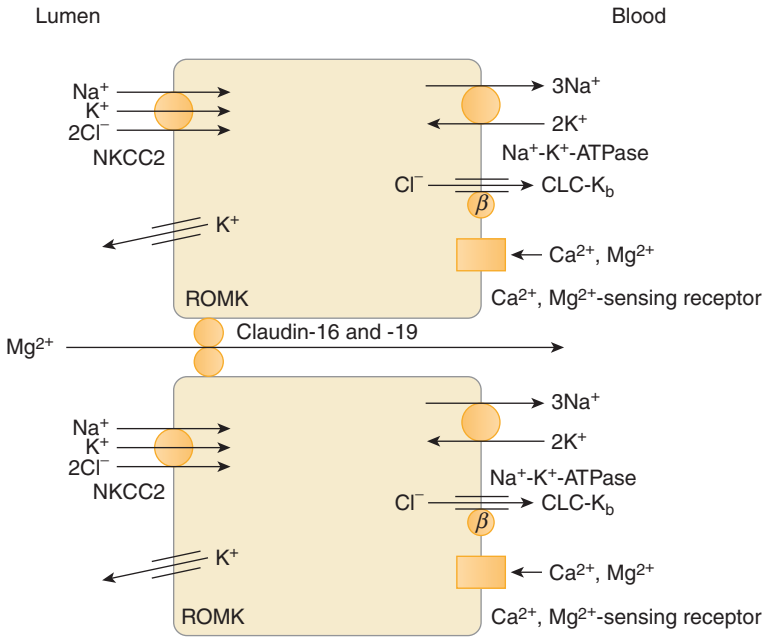

FIGURE 12-2. Thick ascending limb magnesium transport model. Six transporters expressed in the thick ascending limb of Henle are associated with a Bartter-like syndrome: type I—the sodium-potassium-chloride cotransporter, NKCC2; type II—the ROMK potassium ion channel; type III—ClC-K_b, the basolateral chloride ion channel; type IV—barttin, a β subunit required for the trafficking of CLC-K (both ClC-K_a and ClC-K_b) channels to the basolateral membrane; type V—severe gain-of-function mutations in the calcium-sensing receptor; and type VI—mutations in both ClC-K_a and ClC-k_b.

occurs in the thick ascending limb (60% to 70%). Magnesium is reabsorbed paracellularly with the lumen-positive voltage acting as driving force (Figure 12.2). The voltage is generated by potassium exiting across the apical membrane through the ROMK channel. Potassium recycling is essential for Na^+-K^+-$2Cl^-$ function, given that the luminal potassium concentration is much lower than that of sodium or chloride. The lumen-positive potential difference is also augmented via the tight junction proteins claudin-16 and -19. Mutations in the genes encoding these proteins result in the autosomal recessive disease familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC). As prourine moves through the thick ascending limb, which is permeable to sodium and chloride but not water, the sodium concentration falls from 140 mM to 30 mM. This results in a driving force for sodium and chloride to leak back into the lumen. Claudin-16 mediates sodium movement, while claudin-19 blocks chloride movement, augmenting the lumen-positive potential difference. This effect has been referred to as the dilution potential. Although a variety of peptide hormones increase magnesium reabsorption including parathyroid hormone (PTH), calcitonin, glucagon, and antidiuretic hormone (ADH), magnesium concentration at the basolateral surface of the thick ascending limb is the major determinant of magnesium reabsorption. In hypermagnesemic states, magnesium reabsorption approaches zero, and in hypomagnesemia, the loop reabsorbs virtually all of the filtered magnesium reaching it. This effect is presumably mediated via the calcium/magnesium-sensing receptor expressed along the thick ascending limb basolateral surface. The receptor senses elevated calcium and magnesium concentration and transduces this signal to the apical membrane resulting in an inhibition of potassium recycling via ROMK. This dissipates the lumen-positive voltage and decreases the driving force for magnesium reabsorption.

Approximately 5% to 10% of magnesium is reabsorbed in distal convoluted tubule (DCT) (Figure 12.3). Magnesium transport here is active and transcellular. Magnesium enters the cell passively through a channel (TRPM6) and exits actively via an unknown mechanism.

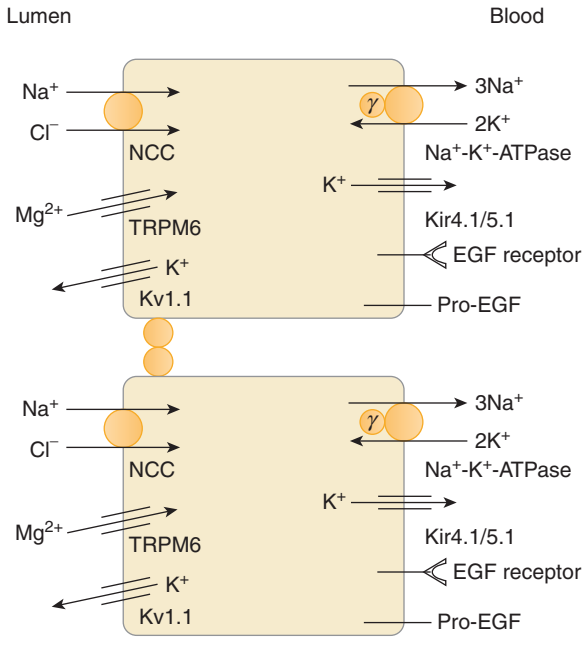

FIGURE 12-3. Distal convoluted tubule magnesium transport model. Transporters expressed in distal convoluted tubule that are associated with renal magnesium wasting include the thiazide-sensitive Na^+-Cl^- cotransporter (Gitelman syndrome); the γ subunit of the Na^+-K^+-ATPase (isolated dominant hypomagnesemia); TRMP6 a magnesium channel (primary intestinal hypomagnesemia); Kv1.1; Kir4.1/5.1; and pro-EGF (pro-epidermal growth factor).

The recent discovery that mutations in potassium channels (Kv1.1 and Kir4.1/5.1) and pro-epidermal growth factor (EGF) play a role in the pathogenesis of rare inherited disorders of renal magnesium wasting through their effects on magnesium entry into the distal convoluted tubule (DCT) via TRPM6 either directly or indirectly has shed further light on mechanisms of DCT magnesium transport. Potassium channels in the basolateral and luminal membranes affect the electrical driving force for magnesium entry across the luminal membrane. Recent studies also showed that EGF via binding to its receptor in the basolateral membrane regulates TRPM6.

Despite differences in transport mechanisms compared to thick ascending limb, PTH, calcitonin, glucagon, ADH, and hypomagnesemia increase magnesium reabsorption in DCT. Amiloride increases magnesium reabsorption in distal nephron and is used therapeutically to reduce renal magnesium loss. Thiazide diuretics, on the other hand, cause mild magnesium wasting. Distal magnesium loss is partially offset by increased proximal reabsorption due to mild ECF volume contraction. The collecting duct plays a very limited role in magnesium reabsorption.

KEY POINTS

Magnesium Regulation

1. Magnesium plays a key role in a variety of cellular process.
2. Magnesium is regulated by both GI tract and kidney, with kidney playing the more important role.
3. Twenty percent of magnesium is reabsorbed in the proximal tubule in adults. Volume contraction increases and volume expansion decreases proximal magnesium reabsorption.
4. The majority of magnesium reabsorption occurs in thick ascending limb. Magnesium is reabsorbed passively across the paracellular space with the lumen-positive voltage acting as driving force.
5. It is the magnesium concentration at the basolateral membrane of thick ascending limb that is the major determinant of magnesium reabsorption.
6. Approximately 5% to 10% of magnesium is reabsorbed in the DCT. Magnesium transport here is active and transcellular. Amiloride increases magnesium reabsorption in distal nephron and can be used therapeutically to reduce renal magnesium loss. Thiazide diuretics cause mild magnesium wasting.

HYPOMAGNESEMIA

Etiology

Hypomagnesemia is caused by decreased oral intake, increased GI losses, increased renal excretion, and magnesium shifts from ECF to ICF. GI and renal losses are the most common causes of hypomagnesemia.

Magnesium depletion was first appreciated in animals in 1932 with the report of locoism in cattle. Locoism or "grass staggers" closely resembles magnesium depletion in humans and occurs within 1 to 2 weeks after grazing on early spring grass that is high in ammonium. The ammonium complexes magnesium and phosphate, forming insoluble struvite in the intestinal lumen, preventing magnesium absorption. Cattle develop signs and symptoms of neuromuscular excitability, hypomagnesemia, hypocalcemia, and hypokalemia. In 1960, Vallee, Wacker, and Ulmer first reported magnesium deficiency in man. They described 5 patients with carpopedal spasm, Chvostek and Trousseau signs, and seizures.

GI causes of hypomagnesemia include decreased intake, malabsorption, diarrheal states, primary intestinal hypomagnesemia, and administration of proton pump inhibitors. Clinically significant magnesium depletion from decreased oral intake alone is rare because of the ubiquitous nature of magnesium in foods and the kidney's ability to conserve magnesium. Hypomagnesemia was described in a number of patients with malabsorption. Serum magnesium concentration in these patients tends to correlate with the degree of steatorrhea. Presumably intestinal free fatty acids bind to magnesium forming insoluble soaps. Magnesium malabsorption is improved with a low-fat diet. Magnesium depletion can occur in any severe diarrheal state. Fecal magnesium increases as stool water increases and colonic secretions are high in magnesium. Proton pump inhibitor use has been associated with hypomagnesemia. Urinary magnesium excretion in these patients is low suggesting a possible GI pathogenesis.

Primary intestinal hypomagnesemia is an autosomal recessive disorder characterized by hypomagnesemia and hypocalcemia. Patients present in the first 6 months of life with symptoms of neuromuscular excitability including seizures secondary to hypomagnesemia and hypocalcemia. The hypocalcemia is resistant to therapy with calcium or vitamin D analogs. Passive intestinal magnesium transport is normal and large doses of oral magnesium reverse the hypomagnesemia and hypocalcemia. Mutations in the TRPM6 gene cause this disorder. TRPM6 is a member of the transient receptor potential (TRP) channel family and is expressed in intestine and DCT. TRPM6 is the pathway whereby magnesium crosses the apical membrane of epithelial cells in intestine and DCT. Renal magnesium wasting was described in these patients consistent with TRPM6 expression in kidney.

Renal magnesium losses are caused by primary defects in renal tubular reabsorption or secondary to a variety of systemic and local factors to which the kidney is responding normally. Primary renal defects are more likely to cause severe hypomagnesemia than secondary defects. Drug- or toxin-induced injury is the most common cause of primary renal magnesium wasting. Offending drugs include aminoglycosides, *cis*-platinum, amphotericin B, pentamidine, cyclosporine, tacrolimus, and EGF receptor inhibitors such as cetuximab and erlotinib. With *cis*-platinum, hypomagnesemia may persist for years after the drug is discontinued. Cyclosporine-induced hypomagnesemia is often associated with normal or elevated serum potassium and resolves rapidly after discontinuation of the drug. Molecular studies in cultured cells showed that cyclosporine administration downregulates TRPM6. This effect is mediated by inhibition of c-fos transcription. Hypomagnesemia may occur up to 2 weeks after a course of pentamidine. Hypomagnesemia was reported after tubular damage resulting from acute tubular necrosis, urinary tract obstruction, and delayed renal allograft function. This may result from increased flow in the loop of Henle that decreases magnesium reabsorption in this segment. Cetuximab and erlotinib are chemotherapeutic agents that bind to and inhibit activation of the EGF receptor. The role of the EGF receptor in magnesium transport in DCT is discussed further below. Leptospirosis has also been associated with hypomagnesemia and renal magnesium wasting, as well as acute kidney injury and phosphate wasting.

A variety of uncommon inherited renal magnesium wasting diseases have been described. They are subdivided based on whether the genetic defect is in a protein expressed in the loop of Henle or in the DCT.

Inherited diseases affecting magnesium reabsorption in the loop of Henle include FHHNC, autosomal dominant hypocalcemia (ADH), and Bartter syndrome. In all of these disorders, the driving force stimulating passive magnesium transport (lumen-positive voltage) is dissipated.

FHHNC is characterized by renal magnesium and calcium wasting. It presents in early childhood with recurrent urinary tract infections, nephrolithiasis, and

a urinary concentrating defect. The associated hypercalciuria, incomplete distal renal tubular acidosis, and hypocitraturia result in nephrocalcinosis and a progressive decrease in glomerular filtration rate. One-third develop end-stage renal disease by early adolescence. Mutations in claudin-16 and -19 cause FHHNC. Claudin-16 and -19 are expressed in the tight junction of the thick ascending limb of Henle. Mutations in the genes encoding these proteins affect generation of the dilution potential, as discussed earlier.

Approximately 50% of patients with ADH have associated hypomagnesemia. ADH results from an activating mutation in the calcium/magnesium-sensing receptor. Activating mutations shift the receptor set-point and increase its affinity for calcium and magnesium. This signal is transduced to the apical membrane resulting in inhibition of potassium exit. The resulting reduction in lumen-positive transepithelial voltage reduces the driving force for magnesium and calcium reabsorption in the loop of Henle.

Bartter syndrome is caused by a variety of genetic defects in thick limb of the loop of Henle that present with renal salt wasting, hypokalemic metabolic alkalosis, and increased renin and aldosterone concentrations. Mutations in 6 ion transport proteins are described (Figure 12.2). All play a key role in transcellular sodium chloride transport and generation of the lumen-positive voltage that is the driving force for magnesium and calcium transport. These include Na^+-K^+-$2Cl^-$ cotransporter (NKCC2); apical membrane potassium channel (ROMK); basolateral membrane chloride channel (ClC-K_b); barttin, the β subunit of the basolateral membrane chloride channel; severe gain-of-function mutations of the calcium-sensing receptor; and mutations in both ClC-K_a and -K_b. The phenotype varies depending on the gene(s) mutated. Mutations in NKCC2 and ROMK are associated with severe salt wasting, neonatal presentation, and nephrocalcinosis. For unclear reasons hypomagnesemia is not common. Mutations in ClC-K_b present during adolescence and 50% have hypomagnesemia. Mutations in barttin are associated with sensorineural deafness and hypomagnesemia is not yet reported.

Genetic disorders resulting in magnesium wasting in the distal convoluted tubule include isolated dominant hypomagnesemia (IDH), Gitelman syndrome, autosomal recessive isolated renal hypomagnesemia (IRH), and autosomal dominant hypomagnesemia and EAST (epilepsy, ataxia, sensorineural deafness, and tubulopathy)/SeSAME (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte disorders) syndromes. IDH is an autosomal dominant disorder associated with hypocalciuria and chrondrocalcinosis. It is caused by a defect in the *FXYD2* gene that encodes the γ subunit of the basolateral Na^+-K^+-ATPase in the DCT. Mutations result in subunit retention in the Golgi complex. How a mutation in this subunit results in isolated renal magnesium wasting and increased calcium reabsorption is unclear. Hepatocyte nuclear factor (HNF) 1B is a transcription factor that regulates FXYD2. This gene is mutated in maturity onset diabetes of the young type 5 and explains the hypomagnesemia secondary to renal magnesium wasting that occurs in up to half of affected individuals. Gitelman syndrome results from loss of function mutations in the thiazide-sensitive sodium chloride cotransporter (NCC). Mutant NCC is trapped in the Golgi and not trafficked to the apical membrane. Patients present in adolescence with symptoms of hypomagnesemia and almost always have associated hypocalciuria. Gitelman syndrome results in more profound hypomagnesemia than is seen with chronic thiazide therapy. TRPM6 is downregulated with both Gitelman syndrome and thiazide administration. Autosomal recessive IRH is the result of mutations in pro-EGF. As a result pro-EGF is either mistargeted or processed by proteases and does not make its way to the basolateral membrane. EGF stimulates magnesium reabsorption in DCT in a paracrine fashion. Pro-EGF, a type 1 membrane protein, is cleaved to EGF that binds to its receptor in the basolateral membrane. EGF receptor binding stimulates magnesium transport by causing TRPM6 insertion into the luminal membrane. Patients with IRH have severe hypomagnesemia secondary to renal magnesium wasting, seizures, and mental retardation. Autosomal dominant hypomagnesemia presents with severe renal magnesium wasting, muscle weakness and cramping, tetany, tremor, and cerebellar atrophy. Mutations in the *KCNA1* gene that encodes the voltage gated potassium channel Kv1.1 were described. The channel is expressed in the luminal membrane. Mutated channels exert a dominant-negative effect on wild type channels, hence the autosomal dominant mode of inheritance. The channel is responsible for maintaining the electrical driving force for magnesium entry across the luminal membrane. This is important because magnesium concentrations are similar in the tubular lumen (1.1 mM) and within the DCT cell (0.8 mM). Magnesium entry depolarizes the cell and

Kv1.1 by extruding potassium from the cell maintains the negative membrane potential. EAST/SeSAME syndrome is caused by mutations in the *KCNJ10* gene that encodes the inward rectifying potassium channel Kir4.1. Kir4.1 is expressed in kidney, inner ear, and brain. The associated tubulopathy is similar to Gitelman syndrome with hypomagnesemia, hypocalciuria, hypokalemia, and metabolic alkalosis. Kir4.1 is expressed in the basolateral membrane and helps maintain Na^+-K^+-ATPase activity by allowing potassium recycling across the basolateral membrane.

A variety of systemic and local factors affect magnesium reabsorption in the proximal tubule, thick ascending limb of Henle, and DCT, resulting in secondary renal magnesium wasting. In proximal tubule, magnesium reabsorption is decreased by volume expansion, as might occur after saline infusion and osmotic diuresis. In the loop of Henle, magnesium reabsorption is inhibited by furosemide. This effect is mild because of an associated increase in proximal reabsorption. Hypercalcemia also results in magnesium wasting. Calcium binds to the calcium/magnesium receptor in the basolateral membrane of the loop of Henle decreasing the lumen-positive voltage that drives paracellular magnesium transport. Thiazide diuretics act in DCT to inhibit magnesium transport.

Magnesium shifts from ECF to ICF can occur as with calcium. These are uncommon causes of hypomagnesemia and can result after parathyroidectomy, refeeding, and in patients with hyperthyroidism. Hypomagnesemia develops in patients with burns because of magnesium losses through skin. Magnesium loss is proportional to the skin area burned.

KEY POINTS

Etiology of Hypomagnesemia

1. GI and renal losses are the most common causes of hypomagnesemia.
2. GI causes of hypomagnesemia include decreased oral intake, malabsorption, diarrheal states, primary intestinal hypomagnesemia, and administration of proton pump inhibitors.
3. Clinically significant magnesium depletion from decreased oral intake alone is uncommon because of the ubiquitous nature of magnesium in foods.
4. Renal magnesium losses are a result of primary defects in renal tubular reabsorption or secondary to systemic and local factors to which the kidney is responding.
5. Primary renal defects cause severe hypomagnesemia more often than secondary defects. Drug- and toxin-induced injuries are the most common causes of primary renal magnesium wasting.
6. Common secondary renal causes of hypomagnesemia include volume expansion, osmotic diuresis, furosemide, hypercalcemia, and thiazide diuretics.
7. A variety of inherited renal magnesium wasting diseases were described and can be subdivided based on whether the genetic defect is in the loop of Henle or DCT.

Signs and Symptoms

It is difficult to attribute specific symptoms to hypomagnesemia because of its common association with metabolic alkalosis, hypocalcemia, and hypokalemia. Symptoms commonly attributed to hypomagnesemia involve the neuromuscular and cardiovascular systems. Increased neuromuscular excitability manifests as weakness, tetany, positive Chvostek and Trousseau signs, and seizures. A decreased concentration of either magnesium or calcium can lower the threshold for nerve stimulation.

Magnesium affects a variety of ion channels in heart. Specifically, it regulates potassium channels that open in the absence of magnesium. It is a critical cofactor for the Na^+-K^+-ATPase and hypomagnesemia decreases pump activity. As a result, intracellular potassium decreases with hypomagnesemia and depolarizes the cardiac myocyte resting membrane potential. The threshold for generation of an action potential is reduced and the potential for arrhythmias increased. Hypomagnesemia is associated with a variety of atrial and ventricular arrhythmias. Decreased intracellular potassium also decreases the speed of potassium efflux resulting in a prolonged repolarization time. Hypomagnesemia aggravates digitalis toxicity as both decrease activity of the Na^+-K^+-ATPase. Magnesium depletion produces acute changes in the electrocardiogram such as peaked T waves and widening of the QRS complex. In severe magnesium depletion the T wave diminishes in amplitude, the QRS widens further, and the PR interval becomes prolonged. These effects are also seen with hypokalemia and may be secondary to changes in serum potassium.

Hypokalemia is frequently associated with hypomagnesemia. There are at least 2 possible explanations

for this. Magnesium is an inhibitor of ROMK, the apical membrane potassium secretory channel in the loop of Henle and distal nephron. A decrease in intracellular magnesium releases the inhibitory effect and increases potassium secretion. The second possibility is that renal magnesium and potassium losses are unrelated but both occur in patients with specific diseases, such as alcoholism, diabetic ketoacidosis, osmotic diuresis, and diuretic use.

Severe magnesium depletion alters calcium homeostasis and results in hypocalcemia. Chronic hypomagnesemia suppresses PTH release from the parathyroid gland and this effect is rapidly reversed by intravenous magnesium infusion. This suggests that magnesium's effect is more likely a result of inhibition of PTH release rather than of PTH synthesis. Balance studies show that the hypocalcemia is not associated with a net negative calcium balance, indicating that it results from alterations in internal homeostatic mechanisms. Hypomagnesemia-induced hypocalcemia may result from skeletal resistance to the effects of PTH. In vitro studies show that magnesium depletion interferes with PTH-stimulated cyclic adenosine monophosphate (cAMP) generation. End-organ resistance occurs at serum magnesium concentrations equal to or less than 1.0 mg/dL. Serum magnesium concentrations equal to or less than 0.5 mg/dL are required to decrease PTH secretion.

KEY POINTS

Signs and Symptoms of Hypomagnesemia

1. Specific symptoms are difficult to attribute to hypomagnesemia because of its common association with metabolic alkalosis, hypocalcemia, and hypokalemia.
2. Hypomagnesemia results in increased neuromuscular excitability manifested by tetany, positive Chvostek and Trousseau signs, and seizures.
3. Hypomagnesemia is associated with a variety of atrial and ventricular arrhythmias.
4. Magnesium depletion produces acute changes in the electrocardiogram as a result of its effects on a variety of ion channels in heart.
5. Hypokalemia is frequently associated with hypomagnesemia.
6. Severe magnesium depletion suppresses PTH release from the parathyroid gland and causes skeletal resistance to PTH, resulting in hypocalcemia.

Diagnosis

The 2 major sources of magnesium loss are GI tract and kidney (Table 12.1). The most common GI causes are malabsorption and diarrheal states. A careful history and physical examination should reveal the presence of these disorders. Hypomagnesemia from decreased oral intake alone and primary intestinal hypomagnesemia are rare.

Renal magnesium wasting is caused by primary defects in renal tubular reabsorption or secondary to systemic and local factors that the kidney is responding to. Drug- or toxin-induced injury is the most common cause of primary renal magnesium wasting. A careful drug exposure history is obtained for aminoglycosides, *cis*-platinum, amphotericin B, pentamidine, and cyclosporine. Drugs that bind to and inhibit the EGF receptor, such as cetuximab and erlotinib, result in renal magnesium wasting as occurs with isolated recessive hypomagnesemia. A variety of rare inherited renal magnesium wasting diseases also need to be considered.

Systemic and local factors can affect magnesium reabsorption in proximal tubule, thick ascending limb of

TABLE 12-1. Etiologies of Hypomagnesemia

Gastrointestinal Causes
Decreased oral intake
Malabsorption
Diarrhea
Primary intestinal hypomagnesemia
Proton pump inhibitor use
Increased Renal Losses
Primary Drugs Toxins Leptospirosis Miscellaneous tubular injury Genetic disorders
Secondary Osmotic diuresis, saline infusion Diuretics Hypercalcemia
Shifts from the Extracellular to the Intracellular Space
Hungry bone syndrome
Refeeding syndrome
Hyperthyroidism

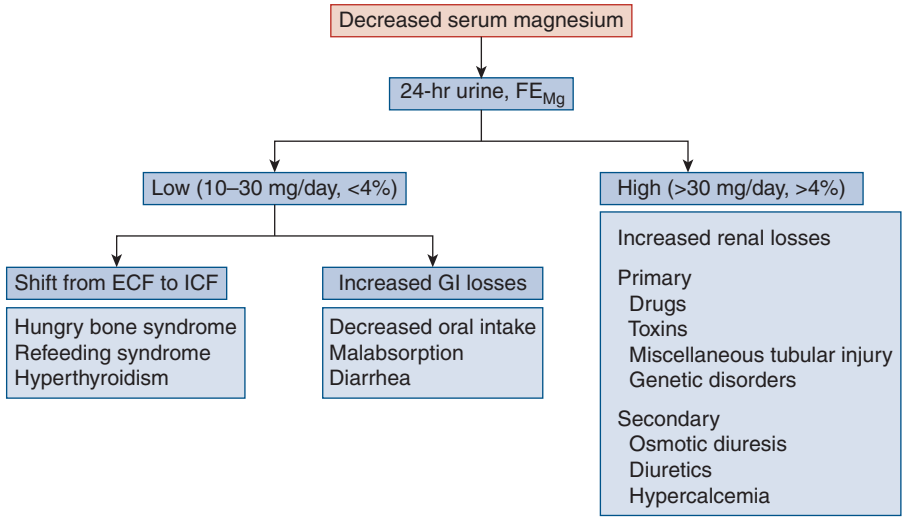

FIGURE 12-4. Evaluation of the hypomagnesemic patient. The first step in the evaluation of the hypomagnesemic patient is the evaluation of renal magnesium excretion. Decreased renal magnesium excretion suggests a GI cause or a shift in magnesium from ECF to ICF. Increased renal magnesium excretion may be primary or secondary.

Henle, and distal tubule. Osmotic diuresis reduces proximal tubular magnesium reabsorption. Loop diuretics such as furosemide cause mild renal magnesium wasting because of an associated increase in proximal tubular magnesium reabsorption secondary to volume contraction. Hypercalcemia results in renal magnesium wasting. Thiazide diuretics act in DCT to block magnesium transport because of downregulation of TRPM6. As with loop diuretics, their effect is mild as a result of enhanced proximal tubular magnesium reabsorption from ECF volume contraction.

Magnesium shifts from ECF to ICF are uncommon causes of hypomagnesemia, but should be looked for after parathyroidectomy, refeeding, and in patients with hyperthyroidism.

Figure 12.4 illustrates an approach to the evaluation of the hypomagnesemic patient. If the diagnosis is not readily apparent from the history, either a 24-hour urine for magnesium or a spot urine for calculation of the fractional excretion of magnesium is obtained. The fractional excretion of magnesium (FE_{Mg}) is calculated from the equation below:

$$FE_{Mg} = \frac{U_{Mg} \times P_{Cr}}{(0.7 \times P_{Mg}) \times U_{Cr}} \times 100$$

where U_{Mg} is urinary magnesium, P_{Cr} is plasma creatinine, P_{Mg} is plasma magnesium, and U_{Cr} is urinary creatinine. The P_{Mg} is multiplied by 0.7 since only 70% of magnesium is freely filtered across the glomerulus.

When magnesium losses are extrarenal the kidney will conserve magnesium. The 24-hour U_{Mg} excretion is less than 30 mg and the FE_{Mg} less than 4%. If renal magnesium wasting is the cause of hypomagnesemia, renal magnesium excretion is increased, and the 24-hour U_{Mg} excretion is greater than 30 mg and the FE_{Mg} greater than 4%. In a study of 74 patients with hypomagnesemia the mean FE_{Mg} in patients with renal magnesium wasting was 15% (range: 4% to 48%).

Serum magnesium concentration may not accurately reflect total-body magnesium stores. In patients with unexplained hypocalcemia, hypokalemia, or symptoms of neuromuscular excitability the possibility of normomagnesemic magnesium depletion should be considered. In this setting, especially in patients at high risk for magnesium depletion, a therapeutic trial of magnesium replacement may be warranted. Magnesium replacement carries little risk provided renal function is normal. Some authors advocate performing a magnesium-loading test. A magnesium load is administered (2.4 mg/kg over 4 hours) and its renal excretion monitored over the next 24 hours. If less than 80% of the load is excreted this is

considered evidence of total-body magnesium depletion. Unfortunately, the test is of limited use. It is often positive in the setting of diarrhea, malnutrition, and diuretic use, even in the absence of symptoms, and may be falsely negative with renal magnesium wasting.

KEY POINTS

Diagnosis of Hypomagnesemia

1. A careful history and physical examination often reveals the cause of hypomagnesemia.
2. The most common cause of primary renal magnesium wasting is drug- or toxin-induced injury.
3. If the diagnosis is not apparent from the history, a 24-hour urine for magnesium or a FE_{Mg} is obtained.
4. The possibility of normomagnesemic hypomagnesemia should be considered in patients with unexplained hypocalcemia, hypokalemia, and symptoms of neuromuscular excitability.

Treatment

The route of magnesium repletion varies depending on the severity of associated symptoms. The acutely symptomatic patient with seizures, tetany, or ventricular arrhythmias thought to be related to hypomagnesemia should be administered magnesium intravenously. In the life-threatening setting, 4 mL (2 ampules) of a 50% solution of magnesium sulfate diluted in 100 mL of normal saline (200 mg or 16 mEq of magnesium) can be administered over 10 minutes. This is followed by 50 mEq of magnesium given over the next 12 to 24 hours. The goal is to increase the serum magnesium concentration above 1 mg/dL. Magnesium is administered cautiously in patients with impaired renal function and serum concentration monitored frequently. In the setting of CKD, the dose is reduced by 50% to 75%. Because renal magnesium excretion is regulated by the concentration sensed at the basolateral surface of the thick ascending limb of Henle, an acute infusion results in an abrupt increase in concentration and often a dramatic increase in renal magnesium excretion. For this reason much of intravenously administered magnesium is quickly excreted by the kidney.

In the absence of a life-threatening condition, magnesium is administered orally. Oral administration is more efficient because it results in less of an acute rise in magnesium concentration. Table 12.2 lists some of the more common oral magnesium preparations. Slow-release magnesium chloride and magnesium lactate preparations are preferable as they cause less diarrhea. Diarrhea is the major side effect of magnesium repletion that limits therapy. A range of 25 to 100 mEq/day in divided doses is generally required. Attempts are also made to correct the underlying condition. Drugs that result in renal magnesium wasting should be minimized. Amiloride increases magnesium reabsorption in DCT and collecting duct and may reduce renal magnesium wasting or decrease the dose of magnesium replacement if diarrhea becomes problematic. Amiloride is not used in patients with impaired renal function because of the risk of hyperkalemia.

Certain cardiovascular conditions deserve special comment. Hypomagnesemia was implicated in ventricular and atrial arrhythmias in patients with cardiac disease. Patients with mild hypomagnesemia in the setting of an acute myocardial infarction (MI) have a 2 to 3-fold increased incidence of ventricular arrhythmias in the first 24 hours. This relationship persists for as long as 2 to 3 weeks after an MI. Magnesium should be maintained in the normal range in this setting.

TABLE 12-2. Oral Magnesium Preparations

PREPARATION	MOLECULAR WEIGHT	FORMULA	mg Mg/g	mEq Mg/g
Mg carbonate	84	$MgCO_3$	289	24
Mg chloride	203.3	$MgCl_2 \cdot 6H_2O$	119	10
Mg gluconate	414.6	$(CH_2OH(CHOH)_4COO)_2Mg$	58	5
Mg lactate	202.4	$Mg(C_3H_5O_3)_2$	120	10
Mg oxide	40.32	MgO	602	50
Mg sulfate	246.5	$MgSO_4 \cdot 7H_2O$	98	8

The American Heart Association Guidelines for Cardiopulmonary Resuscitation recommend use of intravenous magnesium for treatment of torsades de pointes and refractory ventricular fibrillation. Torsades de pointes is a ventricular arrhythmia often precipitated by drugs that prolong the QT interval. The exact mechanism of action of magnesium is unknown. Magnesium does not shorten the QT interval and its effect may be mediated via inhibition of sodium channels.

Hypomagnesemia is common after cardiopulmonary bypass and may result in an increased incidence of atrial and ventricular arrhythmias. Studies on prophylactic magnesium repletion in this setting are conflicting with some showing a reduction in incidence of atrial fibrillation postcardiac surgery and others no effect.

Studies of magnesium administration in the setting of ischemic heart disease show conflicting results. In animal models, magnesium limits ischemia reperfusion injury if given prior to reperfusion. Two large clinical trials examined this issue in the setting of acute MI in humans. In Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) a randomized, placebo-controlled, double-blind study in 2316 patients with acute MI, magnesium was given prior to the onset of thrombolysis. There was a 24% reduction in relative risk of mortality in the first month in the treatment group. The Fourth International Study of Infarct Survival (ISIS-4), however, showed no benefit from magnesium in the setting of acute MI. In this study magnesium was not given until after thrombolysis and an average of 8 hours after the onset of chest pain. Animal models show that benefit is lost if magnesium is administered after reperfusion.

Epidemiologic studies revealed an association between hypomagnesemia and atherosclerotic cardiovascular disease. The Atherosclerosis Risk in Communities Study (ARIC) followed a cohort of 15,792 subjects over a 4- to 7-year period. The relative risk of coronary heart disease in men and women increased as serum magnesium concentration decreased. This finding was statistically significant only in women. Men and women that developed coronary heart disease during the study had a significantly lower serum magnesium concentration. Other studies showed that as the magnesium concentration of drinking water increased the incidence of ischemic heart disease decreased. Magnesium deficiency in animal models promotes atherosclerosis. Hypomagnesemia activates macrophages, stimulates the peroxidation of lipoproteins, and increases circulating concentrations of proinflammatory cytokines. Magnesium repletion is associated with improvement in lipid profile, a decrease in insulin resistance, reduction of free radical generation, and inhibition of platelet reactivity. All of these factors play a role in the atherosclerotic process.

KEY POINTS

Treatment of Hypomagnesemia

1. The route of magnesium repletion varies depending on the severity of associated symptoms. The treatment goal is to increase the serum concentration above 1 mg/dL.
2. Magnesium is administered cautiously in patients with impaired renal function and serum concentration monitored frequently.
3. Magnesium is administered orally in the absence of a life-threatening condition. Amiloride may reduce renal magnesium wasting, but should not be used in patients with impaired renal function.
4. Magnesium should be maintained in the normal range in the setting of ischemic heart disease.
5. Hypomagnesemia is associated with an increased risk of a variety of cardiovascular conditions including atrial and ventricular arrhythmias, torsade de pointes, and atherosclerotic cardiovascular disease.

HYPERMAGNESEMIA

Etiology

The kidney is capable of excreting virtually the entire filtered load of magnesium in the presence of an increased serum magnesium concentration or a decrease in the glomerular filtration rate. For this reason hypermagnesemia is relatively uncommon. Table 12.3 lists some of the more common etiologies. It most often occurs with magnesium administration in the setting of a severe decrease in glomerular filtration rate. It was reported with magnesium-containing cathartics in patients with CKD, intravenous magnesium for postpartum eclampsia, and in patients using Epsom salts (magnesium sulfate) as a mouthwash.

The most common cause of hypermagnesemia is CKD. As glomerular filtration rate falls the FE_{Mg} increases. This allows magnesium balance to be maintained until the glomerular filtration rate falls well below 30 mL/min. Mild hypermagnesemia resulting from decreased renal magnesium excretion can occur with lithium intoxication and familial hypocalciuric hypercalcemia. This is a result of

TABLE 12-3. Etiologies of Hypermagnesemia

Intravenous Magnesium Load in the Absence of CKD
Treatment of preterm labor
Treatment of eclampsia
Oral Magnesium Load in the Presence of CKD
Laxatives
Antacids
Epsom slats
Miscellaneous
Saltwater drowning

the interaction of lithium with the basolateral calcium/magnesium-sensing receptor in the thick ascending limb of Henle. Antagonism of this receptor causes enhanced magnesium reabsorption.

Intravenous administration of magnesium can result in hypermagnesemia even in the absence of CKD. The typical setting is obstetrical with magnesium infused for the management of preterm labor or eclampsia. Typical protocols often result in serum magnesium concentrations of 4 to 8 mg/dL. Hypermagnesemia caused by oral magnesium ingestion occurs most commonly in the setting of CKD. Cathartics, antacids, and Epsom salts are frequently the source of magnesium. Advanced age, CKD, and GI disturbances that enhance magnesium absorption such as decreased motility, gastritis, and colitis are contributing factors. A rare setting where magnesium concentration may be elevated is salt water drowning. Seawater is high in magnesium (14 mg/dL) with the Dead Sea having the highest recorded concentration (394 mg/dL).

KEY POINTS

Etiology of Hypermagnesemia

1. In the presence of an increased serum magnesium concentration or a decrease in the glomerular filtration rate the kidney is capable of excreting virtually the entire filtered load of magnesium.
2. Hypermagnesemia most commonly occurs with magnesium administration in patients with severe decreases in glomerular filtration rate.
3. Hypermagnesemia with oral magnesium ingestion occurs most commonly in the setting of CKD.

Signs and Symptoms

Hypermagnesemia can result in significant neuromuscular and cardiac toxicity. Magnesium blocks the synaptic transmission of nerve impulses. Initially this results in lethargy and drowsiness. As magnesium concentration increases deep tendon reflexes are diminished (4 to 8 mg/dL). Deep tendon reflexes are lost and mental status decreases at serum magnesium concentrations of 8 to 12 mg/dL. If the magnesium concentration rises further (>12 mg/dL), flaccid paralysis and apnea may ensue. Parasympathetic blockage resulting in fixed and dilated pupils that mimics brainstem herniation was reported. Smooth muscle can be affected resulting in ileus and urinary retention.

In cardiac tissue, magnesium blocks calcium and potassium channels required for repolarization. At serum magnesium concentrations above 7 mg/dL, hypotension and electrocardiogram (ECG) changes, such as PR prolongation, QRS widening, and QT prolongation, are noted. At magnesium concentrations greater than 10 mg/dL ventricular fibrillation, complete heart block, and cardiac arrest occur.

KEY POINTS

Signs and Symptoms of Hypermagnesemia

1. At magnesium concentrations between 4 and 8 mg/dL deep tendon reflexes are diminished. Deep tendon reflexes are lost and mental status decreases at serum magnesium concentrations of 8 to 12 mg/dL. At serum magnesium concentrations greater than 12 mg/dL flaccid paralysis and apnea may ensue.
2. Magnesium blocks calcium and potassium channels required for repolarization in heart.
3. Hypotension and ECG changes such as PR prolongation, QRS widening, and QT prolongation are noted at serum magnesium concentrations above 7 mg/dL.
4. Fatal complications such as ventricular fibrillation, complete heart block, and cardiac arrest were reported at magnesium concentrations greater than 10 mg/dL.

Diagnosis

Hypermagnesemia is often iatrogenic. A careful medication history is essential to determine the source of the

magnesium, whether intravenous, as in the treatment of obstetrical disorders, or oral. Laxatives, antacids, and Epsom salts are the most common oral magnesium sources. High doses of intravenous magnesium may result in hypermagnesemia in the absence of kidney disease. Hypermagnesemia from increased GI magnesium absorption often requires some degree of renal impairment. The elderly are at increased risk, often because the degree of decrease in glomerular filtration rate is not adequately appreciated based on the serum creatinine concentration. The elderly often have decreased intestinal motility that further increases intestinal magnesium absorption.

KEY POINTS

Diagnosis of Hypermagnesemia

1. Hypermagnesemia is commonly iatrogenic.
2. Hypermagnesemia from intravenous magnesium infusion can occur in the absence of kidney disease.
3. Some degree of renal impairment is often present in patients developing hypermagnesemia from increased GI magnesium absorption.
4. The elderly are at increased risk.

Treatment

Because the majority of cases of hypermagnesemia are iatrogenic, caution should be exercised in the use of magnesium salts especially in patients with CKD, those with GI disorders that may increase magnesium absorption, and in the elderly. Patients with CKD should be cautioned to minimize magnesium-containing antacids and laxatives. If the patient has hypotension or respiratory depression, calcium (100 to 200 mg of elemental calcium over 5 to 10 minutes) is administered intravenously. The source of magnesium should be stopped. Renal magnesium excretion is increased with a normal saline infusion and/or furosemide administration. In the patient with severe CKD or end-stage renal disease dialysis is often required. Hemodialysis is the modality of choice if the patient's hemodynamics can tolerate it, since it removes more magnesium than continuous venovenous hemofiltration or peritoneal dialysis.

KEY POINTS

Treatment of Hypermagnesemia

1. Caution should be exercised in the use of magnesium salts in high-risk patients.
2. Intravenous calcium can be used if the patient has significant hypotension or respiratory depression.
3. The source of magnesium should be stopped. If renal function is normal, saline infusion and/or furosemide administration are employed if the rate of renal magnesium excretion needs to be increased.
4. In severe hypermagnesemia hemodialysis is often required in those with significant CKD or end-stage renal disease.

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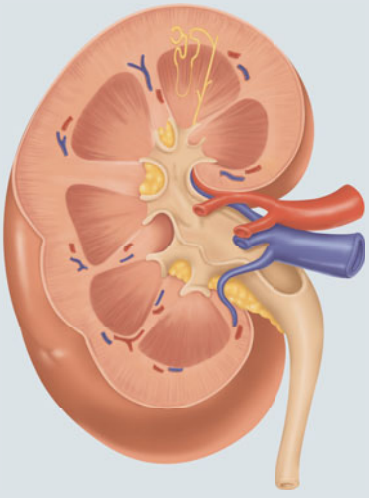
CHAPTER 13

Nephrolithiasis

• *Robert F. Reilly Jr.*

Recommended Time to Complete: 2 Days



Guiding Questions

1. Why do stones form in the urinary tract?
2. How does one evaluate the patient with renal colic and what is the likelihood that a stone will pass spontaneously?
3. What are the important risk factors for the formation of calcium-containing stones?
4. Is there an optimal approach to the patient with a single calcium-containing stone?
5. How does one evaluate and treat the patient with multiple recurrent calcium-containing stones?
6. Which risk factors are most important for the formation of uric acid stones?
7. What role does bacterial infection play in struvite stones?
8. Why is medical therapy difficult in patients with cystine stones?
9. Which prescription and nonprescription drugs form stones in the urinary tract?

INTRODUCTION

Kidney stones are a common problem facing nephrologists, urologists, and general internists in the United States. A study of nephrolithiasis rates from Rochester, Minnesota showed that in the period from 1970 to 2000 the incidence of new onset symptomatic kidney stones declined in men from 15.5 to 10.5 cases per 10,000, but increased in women from 4.3 to 6.8 cases per 10,000. The male-to-female ratio declined from 3:1 to 1.3:1 over this time. The prevalence of stone disease in the United States increased 37% between National Health and Nutrition Examination Survey (NHANES) II (1976-1980) and NHANES III (1988-1994). In the United Kingdom, hospitalizations for stone disease have increased 63% in the last decade. The prevalence of stone disease in the United States appears to be increasing in women, perhaps as a result of the obesity epidemic. Individuals with increased body mass index (BMI) are known to excrete more sodium, oxalate, uric acid, and phosphate in the urine. In addition, as BMI increases, urine pH decreases, which may increase the risk of uric acid stones. The peak incidence for the initial episode of renal colic occurs early in life between the ages 20 and 35 years. In women there is a second peak at age 55 years. By age 70 years, 11% of men and 5.6% of women will have had a symptomatic kidney stone. The recurrence rate is 40% to 50% after 5 years, 50% to 60% at 10 years, and 75% at 20 years. Nephrolithiasis is a major cause of morbidity from pain (renal colic) and renal parenchymal damage from urinary tract obstruction and infection, and results in about $5 billion of economic costs in the United States annually.

Calcium-containing stones make up 80% or more of all stones in the United States and contain calcium oxalate alone, a combination of calcium oxalate and calcium phosphate, or calcium phosphate alone. The remainder is composed of uric acid or struvite. Cystine stones are rare in adults. In more arid climates, such as the Middle East, uric acid stones are more common than calcium-containing stones. Studies based on samples received by stone analysis laboratories suggest that 10% to 20% of all stones are made up of struvite, but this is because of an overrepresentation of stones from surgical specimens.

A kidney stone is an organized mass of crystals that grows on the surface of a renal papilla. They result whenever the excretory burden of a poorly soluble salt exceeds the volume of urine available to dissolve it. Supersaturation of urine with respect to a stone-forming salt is necessary but not sufficient for stone formation. Interestingly, urine in normal patients is often supersaturated with respect to calcium oxalate, calcium phosphate, and uric acid, yet stone formation does not occur. Other factors such as inhibitors of crystallization play an important role in the pathogenesis of stone formation. Normal urine contains several inorganic and organic inhibitors of crystallization. Citrate, magnesium, and pyrophosphate are the most important of these inhibitors of crystallization.

Recent studies of intraoperative papillary biopsies have shed further insight into the pathogenesis of calcium oxalate and calcium phosphate stone formation. The initial site of crystal formation is on the basolateral surface of the thin limb of the loop of Henle in patients with idiopathic hypercalciuria that form calcium oxalate stones. Stones consist of a core of calcium phosphate (apatite) surrounded by alternating layers of matrix and calcium oxalate. The crystal nidus erodes through the surface of the renal papilla into the renal pelvis. Stones form over regions of calcium deposition on the surface of the renal papilla known as *Randall's plaques*. Why calcium phosphate precipitates in this region of the nephron has been the subject of studies by Worcester and Coe. They found that in patients with idiopathic hypercalciuria, urinary calcium excretion increases after meals as a result of reduced proximal tubular calcium reabsorption, leading to increased calcium delivery to the thin limb. These patients consistently have supersaturated urine with respect to calcium phosphate.

Calcium phosphate stones consist of greater than 50% calcium phosphate. They are seen more commonly in women and are associated with higher urinary pHs. Papillary biopsies in these patients reveal dilated ducts of Bellini that are plugged with apatite, which project out into the papillary space. These plugs are associated with a focal papillary tubulointerstitial nephritis secondary to crystal-induced injury.

KEY POINTS

Kidney Stones

1. Nephrolithiasis is a common clinical problem whose frequency varies with gender and race.
2. Calcium oxalate stones are the most common stone in the United States.
3. Supersaturation is required but not sufficient for stone formation.
4. Renal papillary biopsies have provided new insights into the mechanism of calcium oxalate and calcium phosphate stone formation.

THE PATIENT WITH RENAL COLIC

Stones form on the surface of a renal papilla; if they remain there, they do not produce symptoms. If the stone dislodges it can impact anywhere between the ureteropelvic and ureterovesicular junction, resulting in renal colic. Renal colic presents as severe flank pain that begins suddenly, peaks within 30 minutes, and remains constant and unbearable. It requires narcotics for relief and is associated with nausea and vomiting. The pattern of pain radiation may provide a clue as to where in the urinary tract the stone is lodged. Pain radiating around the flank and into the groin is common for a stone trapped at the ureteropelvic junction. Signs of bladder irritation such as dysuria, frequency, and urgency are associated with stones lodged at the ureterovesicular junction (the narrowest portion of the ureter). Pain may radiate to the testicles or vulva. Struvite stones are often incidentally discovered on plain abdominal radiograph because they are generally too large to move into the ureter. The abdominal, rectal, and pelvic examinations are directed at ruling out other potential etiologies of abdominal pain. Physical examination is remarkable for costovertebral angle tenderness and muscle spasm.

A complete blood count, serum chemistries, and urinalysis are required to evaluate patients. The white blood cell (WBC) count may be mildly elevated as a result of the stress of the acute event. A WBC count greater than 15,000/mm^3 suggests either another intraabdominal

cause for the pain or pyelonephritis behind an obstructing calculus. Elevations of the serum blood urea nitrogen (BUN) and creatinine concentrations are not common, and if present, are usually secondary to prerenal azotemia from volume depletion. Obstruction of a solitary functioning kidney, as is the case after a renal transplantation, will result in acute kidney injury. Any patient with abdominal pain should have a careful urinalysis performed. Approximately 90% of patients with renal colic will have microscopic hematuria.

If nephrolithiasis is suspected after the initial evaluation, one must next establish a definitive diagnosis. A radiograph of the abdomen can identify radiopaque stones larger than or equal to 2 mm in size (calcium oxalate and phosphate, struvite, and cystine stones). Radiolucent stones (uric acid) and stones that overlie the bony pelvis are often missed. Unfortunately, two-thirds of kidney stones trapped in the ureter will overlie the bony pelvis. As a result, an abdominal radiograph is most valuable to rule out other intraabdominal processes. It is not sensitive enough to exclude nephrolithiasis with certainty. An ultrasound examination readily identifies stones in the renal pelvis, but is much less accurate for detecting ureteral stones. The intravenous pyelogram (IVP) was formerly the gold standard for the diagnosis of renal colic. It identifies the site of the obstruction, although the stone itself may not be visualized. Structural or anatomic abnormalities and renal or ureteral complications can be detected. Major disadvantages of the IVP include the need for intravenous contrast and the prolonged waiting time required to adequately visualize the collecting system in the presence of obstruction. As a result, spiral computerized tomography (CT) is the test of choice in the majority of emergency departments. Spiral CT is highly sensitive, rapid, and does not require contrast. It may also identify the site of obstruction. Figure 13.1 is an example of a kidney stone detected on spiral CT scanning. If the patient does not have a stone, the spiral CT may also identify other causes of abdominal pain, such as appendicitis and ischemic bowel.

After a stone is identified in the ureter by spiral CT, subsequent management involves an assessment of the likelihood of spontaneous passage, the degree of pain present, and whether there is suspected urinary tract infection (UTI). The probability of spontaneous passage is related to the stone size and its location in the ureter at the time of initial presentation (Table 13.1). In general, the smaller the stone and the more distal in the ureter it is located, the higher the likelihood of spontaneous passage. In general, about half of all stones larger than 5 mm will require urologic intervention. The patient with pain who cannot be managed with oral medication cannot take fluids and who has a solitary kidney or evidence of pyelonephritis, requires hospital admission. Stones unlikely to pass spontaneously require further urologic intervention.

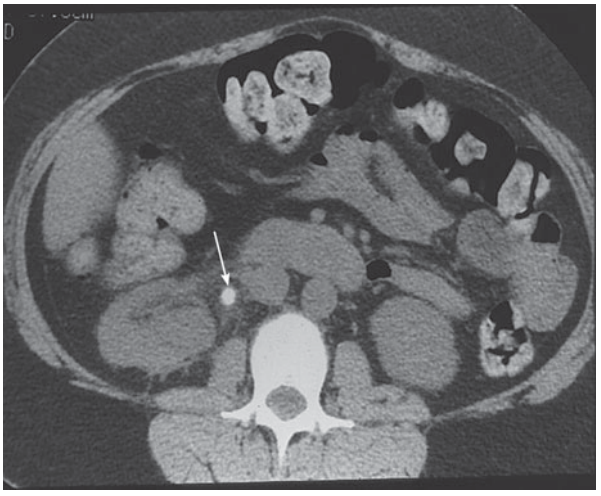


FIGURE 13-1. Spiral CT scan of a kidney stone. Shown by the arrow is a kidney stone impacted in the ureter.

α_1-Receptor antagonists and calcium channel blockers have been successfully used to aid in stone passage (medical expulsive therapy). Corticosteroids, when added, are of modest benefit. Medical expulsive therapy is more

TABLE 13-1. Likelihood of Spontaneous Kidney Stone Passage

Size
>6 mm: 0% to 25%
>4 to 6 mm: 20% to 60%
<4 mm: 50% to 90%
Location
Upper ureter
>6 mm: <1%
<4 mm: 40% to 80%
Lower ureter
<4 mm: 70% to 95%

likely to be beneficial in patients with pain that is well controlled when the stone is located in the distal ureter or the stone is smaller than 10 mm.

KEY POINTS

The Patient with Renal Colic

1. The radiation pattern of renal colic may provide a clue as to where in the ureter the stone is lodged.
2. A WBC count greater than 15,000/mm^3 is indicative of either another intraabdominal cause for pain or pyelonephritis behind an obstructing calculus.
3. Microscopic hematuria is present in 90% of patients.
4. Spiral CT is the diagnostic test of choice in the patient with suspected renal colic.
5. The size of the stone and its location in the ureter at initial presentation determine likelihood of spontaneous passage.
6. Medical expulsive therapy may be effective in those with small stones or when the stone is located in the distal ureter.

RISK FACTORS FOR CALCIUM-CONTAINING STONES

Calcium-containing stones make up the majority of stones in the United States and are generally composed of a mixture of calcium oxalate and calcium phosphate. In mixed stones, calcium oxalate predominates, and pure calcium oxalate stones are more common than pure calcium phosphate stones. Calcium phosphate precipitates in alkaline urine, whereas calcium oxalate precipitation does not vary with pH. Because urine is acidic in most patients on a standard Western diet, calcium oxalate stones are more common. Hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria, low urine volume, and medullary sponge kidney are the major risk factors for calcium-containing stone formation. Patients may form calcium-containing stones with a single or any combination of risk factors. Some patients form calcium-containing stones with no risk factors indicating that our knowledge of the stone-forming process is incomplete. Table 13.2 shows the upper limits of normal in a 24-hour urine for some of these risk factors in men and women.

Hypercalciuria is present in as many as two-thirds of patients with calcium-containing stones. It results from an increased filtered load, decreased proximal tubular reabsorption, or decreased distal tubular reabsorption. Proximal tubular calcium reabsorption is similar to sodium. Whenever proximal sodium reabsorption is decreased there is a parallel decrease in proximal calcium reabsorption and vice versa. Distal nephron calcium reabsorption is stimulated by parathyroid hormone (PTH), diuretics (thiazides and amiloride), and alkaline pH, and inhibited by acidic pH and phosphate depletion.

TABLE 13-2. Abnormal Values for Calcium Oxalate Stone Risk Factors

	mg/24 h	
SUBSTANCE	MALE	FEMALE
Calcium	>200	>200
Uric acid	>800	>750
Oxalate	>45	>45
Citrate	<320	<320

The most common cause of hypercalciuria (90%) is idiopathic. In 3 families, the absorptive hypercalciuria phenotype was localized to a region of chromosome 1 (1q23.3-q24). Although the precise mechanism is unknown, these patients have increased 1,25$(OH)_2$ vitamin D_3 (calcitriol) concentration, low PTH concentration, and reduced bone mineral density. Three potential pathophysiologic mechanisms were proposed: increased intestinal calcium absorption; enhanced bone demineralization; and decreased renal calcium or phosphorus reabsorption. Patients with idiopathic hypercalciuria can be subdivided on the basis of a fast and calcium load study into absorptive hypercalciuria types I, II, and III and renal leak hypercalciuria. This is based on the assumption that if the physiologic mechanism is identified this information will guide specific therapy. In practice, however, this is often unnecessary. Randomized controlled trials of pharmacologic intervention did not subdivide patients in this fashion.

Other important causes of hypercalciuria include primary hyperparathyroidism, renal tubular acidosis (RTA), sarcoidosis, immobilization, Paget's disease, hyperthyroidism, milk–alkali syndrome, and vitamin D intoxication. Filtered calcium load is increased in primary hyperparathyroidism as a result of bone calcium release and increased intestinal calcium absorption mediated by calcitriol. In the subset of patients with hypercalciuria

increased filtered load overcomes distal PTH action to increase calcium reabsorption. In RTA, an increased filtered calcium load results from bone calcium release in response to buffering of systemic acidosis. Acidosis also directly inhibits distal tubular calcium reabsorption. In sarcoidosis macrophages produce calcitriol via activation of 1α-hydroxylase leading to increased intestinal calcium absorption with a resultant increase in filtered load. Immobilization, Paget's disease, and hyperthyroidism result in calcium release from bone and increase the filtered load.

Citrate is an important inhibitor of calcium oxalate precipitation in urine. It complexes calcium in the tubular lumen and as a result there is less calcium available to associate with oxalate. Citrate deposits on the surface of calcium oxalate crystals and prevents them from growing and aggregating. This latter effect may be more important. Chronic metabolic acidosis as occurs with chronic diarrhea or distal RTA and an acid-loading diet high in protein enhance proximal tubular citrate reabsorption and reduce urinary citrate concentration. Hypokalemia also causes hypocitraturia. Sodium-citrate cotransporter expression in the apical membrane of proximal tubule is upregulated with hypokalemia.

Hyperuricosuria is an important risk factor for calcium-containing stone formation. Uric acid and monosodium urate decrease calcium oxalate and calcium phosphate solubility, a phenomenon known as "salting out." Uric acid can bind to macromolecular inhibitors and decrease their activity.

Oxalate in urine is derived from 2 sources. The majority (80% to 90%) comes from endogenous production in liver. The remainder is derived from dietary oxalate and ascorbic acid. The most common causes of hyperoxaluria include; enteric hyperoxaluria from inflammatory bowel disease, small bowel resection, or jejunoileal bypass; dietary excess; and the very uncommon inherited disorder primary hyperoxaluria. In enteric hyperoxaluria, intestinal hyperabsorption of oxalate occurs via 2 mechanisms. Free fatty acids bind calcium and decrease the amount available to complex oxalate increasing free oxalate, which can then be absorbed. In addition, bile salts and fatty acids increase colonic oxalate permeability. Intestinal fluid losses also decrease urine volume, and bicarbonate and potassium losses can lead to hypocitraturia.

Low urine volume is a very common risk factor for calcium-containing stone formation. The risk of stone formation in the United States is largest in areas where temperature is highest and humidity lowest (the stone belt of the Southeast and Southwest). Studies show that 3% to 12% of patients with calcium-containing stones have medullary sponge kidney. One should have a high index of suspicion for medullary sponge kidney in those who do not have any of the previously discussed risk factors for calcium-containing stone formation. It occurs in 1 in 5000 patients and involves men and women with equal frequency. The medullary and inner papillary collecting ducts are irregularly enlarged resulting in urinary stasis that promotes precipitation and attachment of crystals to the tubular epithelium. An IVP establishes the diagnosis revealing linear papillary striations or collections of contrast media in dilated collecting ducts. Patients present in the fourth or fifth decade with kidney stones or recurrent UTI that may be associated with a distal RTA.

KEY POINTS

Risk Factors for Calcium-Containing Stones

1. Important risk factors for calcium-containing stone formation are hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria, low urine volume, and medullary sponge kidney.
2. Hypercalciuria is most commonly idiopathic, but other important causes are primary hyperparathyroidism, RTA, and sarcoidosis.
3. Calcium phosphate stones suggest the diagnosis of RTA or primary hyperparathyroidism.
4. Citrate is the most important inhibitor of calcium oxalate precipitation in urine.
5. Uric acid and monosodium urate can reduce the solubility of calcium oxalate in urine.
6. Anatomic abnormalities of the urinary tract should be suspected when patients without any of the common risk factors form stones.

THE PATIENT WITH A SINGLE CALCIUM-CONTAINING STONE

The assessment of the patient with an initial calcium-containing stone includes a careful history and physical examination evaluating for a family history of stone disease, skeletal disease, inflammatory bowel disease, and UTI. Environmental risk factors such as fluid intake, urine volume, immobilization, diet, medications, and vitamin ingestion are examined. Initial laboratory studies include

blood chemistries, urinalysis, an abdominal radiograph, and renal ultrasound to assess stone burden. Stone analysis is always performed if the patient saved the stone. One study showed that in 15% of cases analyses of 24-hour urines would not have correctly predicted the chemical composition of the stone. Stone analysis is inexpensive, establishes a specific diagnosis, and can help direct therapy.

Most authors recommend the patient with a single isolated stone and no associated systemic disease be managed with nonspecific forms of treatment, including increased fluid intake and a normal calcium diet. Increasing fluid intake is the cheapest way to reduce urinary supersaturation. In a prospective randomized trial of 199 first-time stone-formers followed for a 5-year period, the risk of recurrent stone formation was reduced 55% by increasing urine volume to greater than 2 L/day with water intake. One should keep in mind that the likelihood of future stone formation is high, approximately 50% in the subsequent 5 to 8 years. In high-risk subgroups (white males), patients with significant morbidity from the initial event (nephrectomy), or patients with a solitary functioning kidney, a more aggressive approach may be warranted (see the section on the patient with multiple or recurrent calcium-containing stones).

In the past, patients with calcium-containing stones were advised to follow a low-calcium diet. Subsequent studies have called this into question, suggesting that a low-calcium diet may actually increase risk of stone formation. The postulated mechanism is that ingested calcium complexes dietary oxalate and a reduction in dietary calcium results in a reciprocal increase in intestinal oxalate absorption. This increases urinary supersaturation of calcium oxalate. Confounding factors may also play a role, however, in that high calcium diets are also associated with increased excretion of magnesium and citrate, as well as increased urine volume, factors that reduce the incidence of stone formation. A randomized prospective trial compared patients on a low-calcium diet to those on a normal calcium, low-sodium, and low-protein diet. The relative risk of stone formation was reduced 51% in those consuming a normal calcium diet. How much of this effect was a result of calcium intake is unclear, as a diet low in sodium and protein would be expected to reduce stone formation. Based on these findings the safest approach may be to recommend a normal calcium diet.

The Atkins diet adversely impacts several risk factors for calcium-containing stone formation. In one study, net acid excretion increased 56 mEq/day, urinary citrate fell from 763 mg to 449 mg/day, urinary pH declined from 6.09 to 5.67, and urine calcium increased from 160 mg to 248 mg/day. High-protein, low-carbohydrate diets are best avoided in patients with a history of calcium-containing kidney stones.

The question of whether supplemental calcium increases nephrolithiasis risk is unclear. One report suggested that any use of supplemental calcium raises the relative risk of stone disease 20%. Surprisingly, risk did not increase with increasing dose. The timing of calcium ingestion (with meals or between meals) was not addressed.

KEY POINTS

Risk Factors for Calcium-Containing Stones

1. The majority of first-time calcium-containing stone-formers can be managed by increasing fluid intake.
2. Stone analysis is cheap and may help guide future management.
3. Supplemental calcium may increase the risk of stone formation in some patients.

THE PATIENT WITH MULTIPLE OR RECURRENT CALCIUM-CONTAINING STONES

Complicated calcium-containing stone disease is defined as the presence of multiple stones, new stone formation, enlargement of existing stones, or passage of gravel. This is established based on initial evaluation and these patients require a full metabolic evaluation. Serum calcium concentration is measured and if any value is above 10 mg/dL, a PTH concentration must be obtained. Blood chemistries are evaluated for the presence of RTA. At least two 24-hour urine collections are obtained on the patient's usual diet for calcium, citrate, uric acid, oxalate, sodium, creatinine, and pH. Further therapeutic intervention depends on the results of these collections. An IVP may be indicated to evaluate the possibility of structural abnormalities predisposing to stone formation especially if the stone disease is unilateral. If a specific disease is identified, such as primary hyperparathyroidism, sarcoidosis, enteric hyperoxaluria, or primary gout, it is treated appropriately.

The patient with complicated disease is managed with both nonspecific and specific treatment. Nonspecific therapies such as increased fluid intake and a normal calcium diet were discussed above. Specific therapies vary depending on risk factor assessment derived from 24-hour urine

TABLE 13-3. Randomized Placebo-Controlled Trials

TREATMENT	DOSE	PATIENT GROUP
Water	Urine volume >2 L	Unselected
HCTZ (hydrochlorothiazide)	25 mg BID	Unselected
Chlorthalidone	25 mg daily	Unselected
Indapamide	2.5 mg daily	Hypercalciuria
Allopurinol	300 mg daily	Hyperuricosuria
K citrate	60 mEq daily	Hypocitraturia
K-Mg citrate	40 mEq daily	Unselected

testing. Treatment is based on therapies shown to be effective in randomized placebo-controlled clinical trials with a follow up period of at least 1 year, the results of which are shown in Table 13.3. This is critical because of the *stone clinic effect*. After a patient develops a symptomatic kidney stone, the next several months are often characterized by a period of decreased risk for new stone formation (stone clinic effect). At least 2 factors play a role in this process: regression to the mean; and increased adherence to nonspecific treatments (increased fluid intake). Pharmacologic agents that reduced the risk of stone formation in randomized placebo-controlled trials are thiazides, allopurinol, potassium citrate, and potassium magnesium citrate.

Hypercalciuria is the most common abnormality and is treated with thiazide diuretics. Clinical trials showing benefit used hydrochlorothiazide 50 mg daily or 25 mg bid, chlorthalidone 25 to 50 mg daily, or indapamide 2.5 mg daily. Thiazides directly increase distal tubular calcium reabsorption and indirectly increase calcium reabsorption in the proximal tubule by inducing mild volume contraction. For thiazides to be maximally effective, one must maintain volume contraction and avoid hypokalemia; they usually decrease urine calcium by 50%. If ineffective, the usual reason is a high sodium intake. Proximal sodium and calcium reabsorption is decreased and urinary calcium excretion increased with volume expansion. A 24-hour urine for sodium will detect the patient with increased sodium intake. Amiloride acts in a more distal site, collecting duct, than thiazides, and can be added if needed. Four randomized controlled trials in recurrent stone-formers showed a reduced risk for new stone formation with thiazides. Although patients in these trials had calcium oxalate stones, the majority were not hypercalciuric, suggesting that thiazides have effects in addition to decreasing urine calcium, or that reduction of urine calcium decreases the risk of recurrent stone formation even in the absence of hypercalciuria. An analysis of the relative risk of stone formation based on urinary calcium excretion of participants in the Nurses Health Study Cohort and the Health Professionals Follow-up Study suggests a possible explanation for this observation. The relative risk of stone formation increased above a urinary calcium excretion of 100 mg/day (100 to 149 mg/day: relative risk [RR] 1.26; 150 to 199 mg/day: RR 1.52; 200 to 249 mg/day: RR 1.84; 250 to 299 mg/day: RR 1.93; 300 to 349 mg/day: RR 2.68; >350 mg/day: RR 4.94).

Sodium cellulose phosphate and orthophosphate were used in patients who cannot tolerate thiazides; however, these therapies were often poorly tolerated as well. Slow-release neutral phosphate may be better tolerated from a gastrointestinal standpoint. A randomized controlled trial of potassium acid phosphate showed no effect compared to placebo.

Potassium citrate or potassium magnesium citrate are employed in patients with hypocitraturia. Each reduced the relative risk of stone formation in placebo-controlled trials. In patients taking thiazides, potassium magnesium citrate has the advantage that it replaces diuretic-induced potassium and magnesium losses. Patients with struvite stones should not receive citrate because it may increase stone growth. Citrate increases intestinal aluminum absorption in chronic kidney disease patients. The use of citrate preparations is often complicated by diarrhea. How to best use and dose citrate preparations has become more complex given recent pathophysiologic studies that highlight the key role that calcium phosphate plays in the formation of calcium oxalate and phosphate stones. Alkali to the extent that it increases urinary pH may increase urinary supersaturation of calcium phosphate. As a result Worcester and Coe have recommended a total dose of citrate equal to one-half to two-thirds of urinary ammonia excretion in mmol in patients with calcium phosphate stones until results of randomized controlled trials become available. They recommend following urinary pH, citrate concentration, and urinary supersaturation of calcium phosphate, and if supersaturation increases, potassium citrate should be discontinued or the dose reduced.

Hyperuricosuria as a sole risk factor is best treated with allopurinol, and has been shown to be of benefit in 1 randomized, controlled clinical trial in patients with hyperuricosuria without hypercalciuria. It may be of less benefit in those that also have hypercalciuria.

The degree of hyperoxaluria often provides a clue as to its etiology. Dietary hyperoxaluria is generally mild with urinary oxalate between 40 and 60 mg/24 h and is managed with a low-oxalate diet. Enteric hyperoxaluria is more severe with urinary oxalate between 60 and 100 mg/24 h. Initially, it is treated with a low-fat, low-oxalate diet. Calcium carbonate and/or cholestyramine can be added if this is unsuccessful. Enteric hyperoxaluria and calcium oxalate nephrolithiasis occurs after Roux-en-Y gastric bypass. These patients have increased urinary oxalate, decreased urinary citrate, and decreased urine volume. In severe cases, acute and chronic interstitial nephritis can occur, surrounding areas of tubular oxalate deposition, and resulting in progressive chronic kidney disease and end-stage renal disease. Gastric banding does not appear to be associated with an increased risk of stone formation.

Oxalobacter formigenes is an oxalate-degrading bacterium that resides in the colon. The absence or reduced activity of *O. formigenes* is associated with an increased risk of calcium oxalate stones. The bacteria use oxalate as a metabolic substrate, which it obtains from the intestinal lumen or by stimulating colonic epithelial cells to secrete it. Patients with ulcerative colitis and cystic fibrosis have been reported to have hyperoxaluria and a lack of *O. formigenes* in their stool cultures after prolonged antibiotic therapy. These studies raise the question as to whether administration of oxalate-degrading bacteria could be used to reduce urinary oxalate secretion. Initial studies in humans to date are conflicting.

Primary hyperoxaluria is a rare autosomal recessive disorder and urinary oxalate is often in excess of 100 mg/24 h. It is the result of 1 of 2 enzyme defects in glyoxalate metabolism that lead to enhanced conversion of glyoxalate to oxalate. Type I disease is the result of a defect in hepatic peroxisomal alanine:glyoxalate aminotransferase. Pyridoxine is a cofactor of this enzyme. Increased urinary glycolate excretion is supportive of the diagnosis, which is established based on genetic testing. Type II disease is caused by a defect in cytosolic glyoxalate reductase/D-glycerate dehydrogenase. Increased urinary excretion of L-glyceric acid is supportive of the diagnosis of type II disease, which is established with genetic testing. In patients with CKD stages 4 or 5 urinary oxalate excretion may be falsely low and serum values may need to be measured. Treatment of primary hyperoxaluria is difficult. Pyridoxine supplementation and maintenance of a high urine output can be tried. The disease often recurs in the transplanted kidney. Combined liver–kidney transplantation may be the best treatment option for children with progressive type I disease.

If metabolic evaluation fails to detect risk factors for calcium-containing stone formation an IVP is performed to rule out medullary sponge kidney. One also needs to consider whether a trial of citrate alone or citrate plus hydrochlorothiazide is warranted. Both agents are relatively inexpensive and have limited toxicity. In addition, a significant percentage of patients in randomized placebo-controlled trials of thiazides and citrate did not have hypercalciuria or hypocitraturia. There is good reason to suspect, therefore, that these therapies would be effective in these patients.

If thiazides, allopurinol, or citrate are prescribed, it is important to repeat the 24-hour urine in 6 to 8 weeks to examine the effect of pharmacologic intervention on urinary supersaturation of calcium oxalate, calcium phosphate, and uric acid. Several commercial laboratories provide this service. Computer programs (EQUIL) and algorithms are also capable of calculating supersaturation from a 24-hour urine collection.

This approach directed at specific and nonspecific risk factor reduction for calcium-containing stone disease decreases the frequency of recurrent stone formation, and reduces the number of cystoscopies, surgeries, and hospitalization.

KEY POINTS

The Patient with Multiple or Recurrent Calcium-Containing Stones

1. Complicated calcium-containing stone disease is present if the patient has multiple stones, evidence of the formation of new stones, enlargement of old stones, or passage of gravel. This subgroup of patients requires complete metabolic evaluation.
2. Therapy is based on an analysis of risk factors for calcium-containing stones.
3. Treatment is guided by results of randomized placebo-controlled trials.
4. Urinary supersaturation of calcium oxalate, calcium phosphate, and uric acid is monitored with treatment.

GENETIC CAUSES OF CALCIUM-CONTAINING STONES

Several rare genetic disorders are capable of causing hypercalciuria, nephrolithiasis, and/or nephrocalcinosis. Some of these diseases, including Bartter syndrome

(metabolic alkalosis), autosomal dominant hypocalcemia with hypercalciuria (disorders of serum calcium), familial hypomagnesemia with hypercalciuria and nephrocalcinosis (disorders of serum magnesium), and inherited forms of distal RTA (metabolic acidosis), are discussed in other parts of this book.

Dent disease is inherited in an X-linked recessive fashion and is secondary to a defect in a $2Cl^-/H^+$ exchanger gene (*CLCN5*), which is expressed in the S_3 segment of the proximal tubule and the medullary thick ascending limb. It is characterized by hypercalciuria, nephrolithiasis, nephrocalcinosis, hypophosphatemia, and low-molecular-weight proteinuria. CLC-5 expression is regulated by PTH and vitamin D. The exchanger may regulate the endocytosis and degradation of epithelial calcium channels. A few patients have been described with OCRL-1 mutations (the gene associated with the oculocerebrorenal syndrome of Lowe) that encodes a phosphatidylinositol-4,5-biphosphate-5-phosphatase.

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is an autosomal recessive disorder characterized by hypophosphatemia, rickets, elevated levels of $1,25(OH)_2$ vitamin D_3, nephrocalcinosis, and nephrolithiasis. It is caused by a mutation in the *SLC34A3* gene that encodes NaPi-IIc.

KEY POINTS

Genetic Causes of Calcium-Containing Stones

1. A variety of genetic disorders are associated with hypercalciuria and nephrolithiasis.
2. Dent disease is caused by a defect in a $2Cl^-/H^+$ exchanger gene (*CLCN5*), which is thought to be involved in endocytosis of transport proteins.

URIC ACID STONES

Uric acid stones represent 5% to 10% of stone disease in the United States. Their highest incidence is reported in the Middle East, where as many as 75% of stones contain uric acid. This is secondary in part to the arid climate and reduced urinary volumes seen as a result of the arid climate. Unlike other mammals, humans do not express uricase that degrades uric acid into the much more soluble allantoin. Consequently, uric acid is the major metabolic end product of purine metabolism. Stones made up of uric acid are by far the most frequent radiolucent stone.

Uric acid has low solubility at acidic pH. It is a weak organic acid with 2 dissociable protons. Only the dissociation of the first proton, which occurs at a pK_a (negative logarithm of acid ionization constant, which is a measure of acid strength) of 5.5, is of clinical relevance. At a pH of less than 5.5 it remains as an undissociated acid (uric acid), which is much less soluble than the salt (sodium urate). As pH increases, it dissociates into the more soluble salt, sodium urate. At pH 4.5 only 80 mg/L of uric acid is soluble, whereas at pH 6.5, 1000 mg/L of sodium urate is dissolved. Because of the dramatic increase in solubility as urinary pH increases, uric acid stones remain the only kidney stones that can be completely dissolved with medical therapy alone. Patients with uric acid stones exhibit a lower urinary pH and ammonium ion excretion than normals. As many as 75% have a mild defect in renal ammoniagenesis in response to an acid load. Urinary buffers other than ammonia are titrated more fully with a resultant urine pH approximating 4.5. Patients with defects in ammoniagenesis, such as the elderly and those with polycystic kidney disease, are at increased risk for uric acid stones. There is also a high incidence of uric acid stones in patients with type II diabetes mellitus (34%). It has been suggested that a renal manifestation of insulin resistance may be reduced urinary ammonium excretion and decreased urinary pH. Given the current epidemic of obesity and diabetes mellitus in the United States population uric acid stones may increase in frequency in the future.

The second most important risk factor for uric acid stone formation is decreased urine volume. Hyperuricosuria is the third and least important risk factor and is seen in less than 25% of patients with recurrent uric acid stones. The importance of urinary pH compared to uric acid excretion is illustrated by the fact that a threefold increase in uric acid excretion from 500 to 1500 mg would not overcome the effect of a pH change from 5 to 6 that increases uric acid solubility 6-fold.

Another determinant of uric acid solubility is cations present in urine. Uric acid solubility is decreased by higher sodium concentration, and increased by higher potassium concentration. This may explain calcium phosphate stone formation that can occur during sodium alkali therapy but not with potassium alkali therapy. The sodium load increases urinary calcium excretion and reduces uric acid solubility while potassium does not.

Because of their smooth contour, uric acid stones are more likely to pass spontaneously than calcium oxalate or phosphate stones. Although a definitive diagnosis is

established by stone analysis, uric acid stones are suggested by the presence of a radiolucent stone, or the presence of uric acid crystals in unusually acidic urine. Xanthine, hypoxanthine, and 2,8-dihydroxyadenosine stones are radiolucent but are very rare. When a radiolucent stone fails to dissolve with standard alkali therapy its presence should be suspected.

Etiologies are subdivided based on the 3 major risk factors. Low urine volume is important in gastrointestinal disorders such as Crohn's disease, ulcerative colitis, diarrhea, and ileostomies, as well as with dehydration. Acidic urinary pH plays an important role in primary gout and gastrointestinal disorders. Hyperuricosuria is subdivided based on whether hyperuricemia is present (primary gout, enzyme disorders, myeloproliferative diseases, and hemolytic anemia) or absent (dietary excess). Primary gout is an inherited disorder transmitted in an autosomal dominant fashion with variable penetrance. Hyperuricemia, hyperuricosuria, and persistently acid urine are its hallmarks. Uric acid stones are present in 10% to 20% of patients. In a sizeable group (40%) stones occur before the first attack of gouty arthritis. Because urine is always acidic in patients with primary gout, the risk of uric acid stones will vary directly with serum and urinary uric acid concentration (Tables 13.4 and 13.5).

As might be expected, therapy is directed at reversal of the 3 risk factors. First, urine volume is increased to 2 L/day or greater. Next, potassium citrate is employed to alkalinize the urine to pH 6.5. The starting dose is 10 mEq TID with meals, and one titrates upward to achieve the desired urine pH. More than 100 mEq/day is rarely required. Sodium alkali therapy is less preferable as it may cause hypercalciuria. In a study of 12 patients with uric acid stones, alkali therapy resulted in complete stone dissolution in 1 to 5 months. Increases in urinary pH above 6.5 are not necessary and should be avoided because of the potential risk of calcium phosphate precipitation. If early morning urine remains acidic acetazolamide (250 mg) is added before bedtime. If hyperuricosuria is present, one should first attempt to decrease purine consumption in the diet. Allopurinol is used in patients whose stones recur despite fluid and alkali, patients with difficulty tolerating this regimen (diarrhea), or when uric acid excretion is greater than 1000 mg/day. If allopurinol is administered in patients with massive uric acid overproduction as in the tumor lysis syndrome, adequate hydration must be ensured to avoid precipitation of xanthine and hypoxanthine.

TABLE 13-4. Risk of Uric Acid Stones in Patients with Primary Gout as a Function of Serum Urate Concentration

SERUM URATE (mg/dL)	WITH STONES (%)
5.1 to 7.0	11
7.1 to 9.0	18
9.1 to 11.0	25
11.1 to 13.0	28
>13.1	53

Adapted from Riese RJ, Sakhaee K. Uric acid nephrolithiasis: pathogenesis and treatment. *J Urol.* 1992;148:765-771.

TABLE 13-5. Risk of Uric Acid Stones in Patients with Primary Gout as a Function of Urate Excretion

URINARY URATE EXCRETION (mg/24 h)	WITH STONES (%)
<300	11
300 to 499	21
500 to 699	21
700 to 899	34
900 to 1,099	38
>1100	50

Adapted from Riese RJ, Sakhaee K. Uric acid nephrolithiasis: pathogenesis and treatment. *J Urol.* 1992;148:765-771.

KEY POINTS

Uric Acid Stones

1. Uric acid stones make up approximately 5% of kidney stones in the United States.
2. The 3 most important risk factors are decreased urine pH, decreased urine volume, and increased urinary uric acid excretion.
3. Of the 3 risk factors, low urine pH is most important.
4. Because of their uniform round shape, uric acid stones are more likely to pass spontaneously than calcium-containing stones.
5. Uric acid stones are the most common radiolucent stone.
6. Uric acid stones can be completely dissolved with medical therapy.

STRUVITE STONES

Struvite stones are composed of a combination of magnesium ammonium phosphate (struvite—$MgNH_4PO_4 \cdot 6H_2O$) and carbonate apatite ($(Ca_{10}(PO_4)_6CO_3)$). It is suggested that they comprise 10% to 15% of all stones; however, this is likely an overestimation. These percentages are based on reports from chemical stone analyses and surgical specimens are overrepresented in these studies. It is likely that their true prevalence is less than 5% of kidney stones. Prior to more recent therapeutic urologic advances, they were the cause of significant morbidity and mortality. Struvite stones are the most common cause of staghorn calculi, although any stone may form a staghorn. Urine is supersaturated with struvite in only 1 circumstance: infection with urea-splitting organisms that secrete urease. Urease-producing bacterial genuses include: *Proteus*; *Morganella*; *Providencia*; *Pseudomonas and Klebsiella. Escherichia coli* and *Citrobacter* do not express urease.

Women with recurrent UTI, patients with spinal cord injury or other forms of neurogenic bladder, and those with ileal ureteral diversions are at high risk for struvite stone formation. Struvite stones can present with fever, hematuria, flank pain, recurrent UTI, and septicemia. They grow and fill the renal pelvis as a staghorn calculus and are radiopaque as a result of the carbonate apatite component. Rarely do they pass spontaneously, and in many cases they are discovered incidentally. Loss of the affected kidney occurs in 50% of untreated patients.

For struvite stones to form, it is necessary that the urine be alkaline (pH >7) and supersaturated with ammonium hydroxide. Urea is hydrolyzed to ammonia and carbon dioxide (Figure 13.2). Ammonia hydrolyzes to ammonium hydroxide. Carbon dioxide hydrates to form carbonic acid and then loses protons to form bicarbonate and carbonate. Elevated concentrations of ammonium hydroxide and carbonate at alkaline pH never occurs under physiologic conditions and is only seen with UTI with a urease-producing organism. The stone behaves like an infected foreign body. A symbiotic relationship develops, whereby bacteria provide conditions suitable for stone growth and the stone acts as a protected environment for the bacteria.

The majority of staghorn calculi are composed of struvite. Struvite stones are larger and less radiodense than calcium oxalate stones. The association of a kidney stone and an infected alkaline urine is highly suggestive of a struvite stone. Definitive diagnosis, however, can only be established by stone analysis. If a UTI is associated with an acidic urine and a staghorn calculus, it is likely that the 2 are unrelated. All staghorn calculi should be cultured and sent for stone analysis after percutaneous nephrolithotomy or extracorporeal shock wave lithotripsy (ESWL) treatment. Stone culture is important because urine cultures are not always representative of the organism(s) present in the stone. *Proteus mirabilis* is the most common urease-producing organism isolated. If the culture is negative, one should consider the possibility of infection with *Ureaplasma urealyticum*. Some patients have stones that contain a mixture of struvite and calcium oxalate. A metabolic evaluation should be performed as these patients often have an underlying metabolic abnormality and are at higher risk for stone recurrence.

Open surgical removal is no longer the treatment of choice for staghorn struvite calculi given the high recurrence rate (27% after 6 years) and the persistence

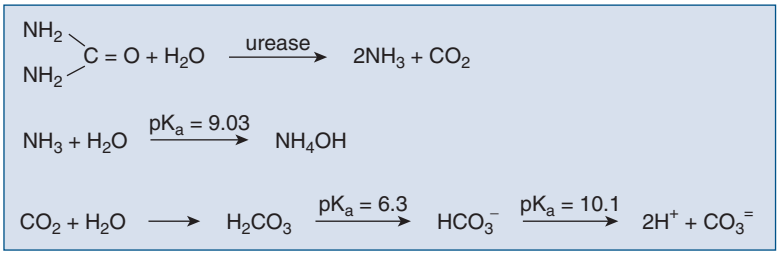


FIGURE 13-2. Pathophysiology of struvite stone formation. Struvite does not form under physiologic conditions. Urease converts urea to ammonia and carbon dioxide. Ammonia hydrates to form ammonium hydroxide. The resultant high pH converts bicarbonate to carbonate. The combination of high pH, ammonium hydroxide, and carbonate provide the conditions for formation of magnesium ammonium phosphate and carbonate apatite (struvite).

of UTI (41%). A combination of percutaneous nephrolithotomy and ESWL is currently the treatment of choice and is associated with improved outcomes compared with surgery. Total elimination of the stone is difficult. Small particles containing bacteria that can act as a nidus for further stone growth are difficult to remove. Culture-specific antimicrobial agents are employed as prophylaxis against recurrent infection after complete stone removal. If a struvite stone is not completely removed, recurrent UTIs and stone growth will occur. Most patients with residual fragments progress despite treatment with antibiotics. Reducing the bacterial population often slows stone growth but stone resolution with antibiotics alone is unlikely. Urease inhibitors (acetohydroxamic acid) can decrease urinary struvite supersaturation, reduce stone growth, and can result in dissolution of stones. Acetohydroxamic acid is associated with severe toxicities, however, including hemolytic anemia, thrombophlebitis, and nonspecific neurologic symptoms (disorientation, tremor, and headache). The half-life is prolonged in patients with chronic kidney disease (normal: 3 to 10 hours; chronic kidney disease: 15 to 24 hours). Acetohydroxamic acid should not be used if the serum creatinine is greater than 2.0 to 2.5 mg/dL or the glomerular filtration rate is less than 40 mL/min. It is teratogenic and also should not be administered in patients taking iron supplements.

KEY POINTS

Struvite Stones

1. Struvite stones are the most common cause of staghorn calculi.
2. Women with recurrent UTIs make up the majority of patients with struvite stones.
3. Struvite stones form only when urine is infected with urease-producing bacteria.
4. The stone should always be sent for culture because urine cultures may not be representative of the organisms in the stone.
5. The combination of percutaneous nephrolithotomy and ESWL has replaced open nephrolithotomy as the treatment of choice for stone removal.
6. To cure the patient, the stone must be completely removed.
7. Stone growth is suppressed by antimicrobial therapy but a cure is unlikely without urologic intervention.

CYSTINE STONES

Cystinuria is secondary to an inherited defect (autosomal recessive) in proximal tubular and intestinal reabsorption of dibasic amino acids (cysteine, ornithine, lysine, and arginine). As a consequence increased amounts of these amino acids are excreted by the kidney. Clinical disease results from the poor solubility of cystine (dimer of cyteine) in water. Stones are radiodense as a result of the sulfhydryl group of cysteine. Cystine stones are less radiodense on radiography than calcium or struvite stones, and typically have a homogeneous structure without striation. They are rare in adults, but make up as much as 5% to 8% of stones in children. The prevalence of cystinuria is approximately 1 per 7000 general population in the United States. Stones consisting entirely of cystine occur only in homozygotes. Normal adults excrete less than 20 mg of cystine per gram of creatinine per day. Most patients form their first stone before age 20 years. Men are generally more severely affected than women. Patients present with bilateral large staghorn calculi with elevated serum BUN and creatinine concentrations. Hexagonal cystine crystals are often seen in first morning void urine. Calcium oxalate and calcium phosphate stones can be seen in heterozygotes with cystine acting as a nidus. This disorder is caused by mutations in one of two genes. SLC3A1 encodes a glycoprotein, rBAT, that forms a heterodimer with the transport protein, SLC7A9. SLC7A9 encodes $b^{0,+}$AT the amino acid transport protein.

Urinary supersaturation generally occurs at cystine concentrations greater than 250 mg/L. To prevent cystine stones, urinary concentration should be maintained below 200 mg/L. Given that the pK_a of cysteine is 8.3 its solubility is difficult to influence by raising urinary pH. The goal is to keep pH in the 6.5 to 7.0 range. Homozygotes excrete an average of 800 to 1000 mg/day, consequently, 4 L of urine must be produced daily to maintain cystine solubility. Cystine crystals when seen in first morning void urine are diagnostic of cystinuria, but this is an uncommon observation. Acidifying urine to pH 4 with acetic acid and storage overnight may bring out crystals in dilute or alkaline urine. The sodium-nitroprusside test, which can detect cystine at a concentration of 75 mg/L, is a commonly employed screening test. Nitroprusside complexes with sulfide groups and the test may be falsely positive in those taking sulfur-containing drugs. A positive screening test should be followed by 24-hour urine cystine quantitation. Homozygotes excrete greater than 250 mg/g of creatinine.

The hallmark of treatment is water, water, and more water. The amount is based on the patient's cystine excretion. To reduce urinary cystine concentration below 200-250 mg/L a urine output of 4 L/day is often necessary. This requires approximately two 8 oz glasses of water every 4 hours. The patient should also drink 2 large glasses of water when awakening to void during the night. This is a difficult regimen to comply with and water alone is often ineffective when urinary cystine excretion exceeds 500 mg/day. Alkalinization is a secondary measure used in those who do not respond to water alone. A urinary pH of 6.5 to 7.0 is targeted to avoid increasing the risk of calcium phosphate stone formation. Potassium citrate is preferable to sodium citrate or bicarbonate as extracellular fluid volume expansion that occurs with sodium salts increases urinary cystine excretion. Sodium and animal protein restriction may be of small benefit.

D-Penicillamine or tiopronin (α-mercaptopropionylglycine) is used if water and alkali are ineffective. They are almost always required in patients with high urinary cystine excretion (>1000 mg/day). These drugs are thiols that bind to cysteine and form compounds that are more soluble in aqueous solution than cystine. The D-penicillamine–cysteine complex is 50 times more soluble than cystine. Tiopronin is better tolerated than D-penicillamine. In one nonrandomized trial, 31% of patients stopped therapy because of unacceptable side effects with tiopronin versus 69% of those on D-penicillamine. Side effects included fever, rash, arthralgia, leukopenia, and proteinuria. D-Penicillamine binds pyridoxine and pyridoxine (50 mg/day) should be administered to prevent deficiency. Zinc supplements help prevent the anosmia and loss of taste that can occur with D-penicillamine. The dose of tiopronin is 400 to 1200 mg daily in 3 to 4 divided doses, whereas the D-penicillamine dose is 0.5 to 2 g daily in 3 to 4 divided doses. Captopril was initially reported to be of benefit, but subsequent studies have not borne this out. Monitoring drug therapy is complicated by the fact that some urinary assays cannot distinguish between free cystine and cysteine complexed to D-penicillamine or tiopronin.

KEY POINTS

Cystine Stones

1. Cystinuria is secondary to an autosomal recessive defect in proximal tubular and jejunal reabsorption of dibasic amino acids.
2. The amino acid cysteine dimerizes to form cystine that has limited solubility in water (250 mg/L).
3. Homozygotes excrete upward of 1000 mg of cystine daily.
4. Water is the hallmark of treatment but is often of limited use in patients who excrete more than 500 mg of cystine.
5. Ancillary measures include alkalinization of the urine with potassium citrate, and agents that form dimers with cysteine including tiopronin (α-mercaptopropionylglycine) and D-penicillamine.

DRUG-RELATED STONES

A variety of prescription drugs precipitate in urine, including sulfonamides, triamterene, acyclovir, and the antiretroviral agent indinavir. Of the sulfa drugs, sulfadiazine is more likely to precipitate than sulfamethoxazole. This occurs most commonly after several days of high-dose therapy for *Toxoplasmosis gondii* or *Pneumocystis carinii* infection and presents as acute kidney injury. The risk is increased with hypoalbuminemia. Treatment involves discontinuation of the drug, alkalinization of the urine to pH greater than 7.15, and maintenance of high urine flow rate.

Triamterene is a weak base that can precipitate and form stones in the urinary tract. Triamterene and parahydroxytriamterene sulfate are the major stone constituents. In one series, 22% of reported stones contained only triamterene, 14% had more than 90% triamterene, and 42% had less than 20% triamterene mixed with calcium oxalate and uric acid. The annual incidence was estimated at 1 in 1500 patients among those prescribed the drug. Most patients were taking 75 mg for several years, but some were taking only 37.5 mg for 3 to 6 months. Triamterene should be avoided in patients with a previous history of calcium oxalate or uric acid stones. There are rare case reports of crystal-induced acute kidney injury.

Acyclovir use can result in crystal-induced acute kidney injury, especially if the drug is infused rapidly intravenously or the dose is not adjusted for renal dysfunction. The incidence is reduced by slow infusion over 1 to 2 hours with vigorous prehydration. There are rare case reports of acute kidney injury with oral therapy in those who were dehydrated or received too high a dose.

Indinavir has limited solubility at physiologic pH and 15% to 20% of the drug is excreted unchanged in urine. Microscopic hematuria occurs in up to 20% of patients. Nephrolithiasis develops in 3% of patients, and 5% will experience either dysuria or flank pain that resolves when the drug is discontinued. It has been increasingly recognized that indinavir can cause an insidious increase in serum BUN and creatinine concentrations associated with pyuria. Nelfinavir, saquinavir, atanazavir, and efavirenz may also crystallize in the urine and cause stones.

As many as 1 in 2000 stones are composed primarily of ephedrine. This results from abuse of nonprescription cold formulations or the ingestion of Ma-huang. Ma-huang is rich in ephedrine, norephedrine, pseudoephedrine, and norpseudoephedrine. Ephedrine has been removed from the market in the United States. Guaifenesin and its metabolites have been detected in kidney stones. Topiramate is an antiepileptic medication that inhibits carbonic anhydrase and causes type II RTA. Calcium phosphate and calcium oxalate stones were reported with its use.

KEY POINTS

Drug-Related Stones

1. A variety of prescriptions and nonprescription drugs can precipitate in urine and form stones.
2. A careful medication history should be a part of the evaluation of all patients with nephrolithiasis.

CONSEQUENCES OF STONES

A case control study showed that the overall incidence of chronic kidney disease was increased in patients with nephrolithiasis. A series of stone formers from France showed an increased incidence of end-stage renal disease. A high percentage of these patients had struvite stones that are known to be associated with loss of renal function. Another group examined patients in the NHANES III cohort and found an association between a history of nephrolithiasis and reduced glomerular filtration rate (GFR) that was related to an increase in BMI. Whether this can be explained by the high incidence of hypertension and diabetes in these patients or is a result of the stone disease itself is unclear.

KEY POINT

Consequences of Stones

1. Observational studies suggest an association of nephrolithiasis and chronic kidney disease. Whether this is a result of confounders or renal injury from stone disease remains to be determined.

UROLOGIC TREATMENT OF SYMPTOMATIC STONES

Stones that result in pain, urinary tract obstruction, and loss of renal function or infection may need to be removed urologically. Commonly used options include ESWL, ureteroscopy (URS) with laser lithotripsy, and percutaneous nephrolithotomy. ESWL is an option for stones that are smaller than 20 mm in the mid and upper poles, and less than 10 mm in the lower pole. URS is superior to ESWL for lower-pole stones that are 10-20 mm. ESWL is most effective for less-dense stones (<900 Hounsfield units) and when the skin to stone distance is less than 10 cm. Cystine and brushite stones are more resistant to ESWL. The patient should have a documented negative urine culture before undergoing ESWL.

KEY POINTS

Urologic Treatment of Symptomatic Stones

1. Symptomatic stones often require urologic intervention.
2. URS is superior to ESWL for lower pole stones that are 10-20 mm.
3. ESWL is most effective for less-dense stones (<900 Hounsfield units) and when the skin to stone distance is less than 10 cm. The patient should have a documented negative urine culture before undergoing ESWL.

Additional Reading

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SECTION III

Intrinsic Renal Diseases

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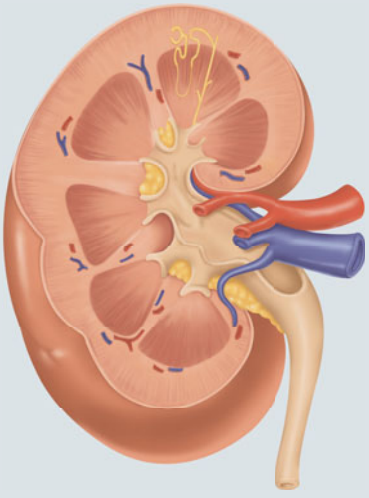
CHAPTER 14

Urinalysis and Urine Microscopy



• *Mark A. Perazella*

Recommended Time to Complete: 1 Day

Guiding Questions

1. What information does the urinalysis/urine microscopy provide about patients with kidney disease?
2. What are the various components of the urinalysis/urine microscopy?
3. Does the protein measured on the dipstick detect all urine proteins?
4. Is the dipstick test for blood specific for red blood cells?
5. Does red blood cell morphology help differentiate the site of kidney bleeding?
6. What information does the presence of cellular casts in the urine sediment provide?
7. Is the presence of uric acid or calcium oxalate crystals always indicative of a defined renal disease?
8. Is the random spot urine protein-to-creatinine ratio an accurate estimate of daily protein excretion?
9. Do patterns of urinary findings help differentiate various types of kidney disease?
10. Does quantitative examination of the urine sediment improve diagnosis and allow prognosis in patients with acute tubular necrosis?

INTRODUCTION

Kidney disease, whether acute or chronic, may present with systemic features of renal injury (hypertension, edema, uremia), renal limited manifestations (flank or loin pain, gross hematuria), or asymptomatically with only abnormalities in blood testing or urinalysis. Kidney disease is fully assessed with complete history and physical examination, directed blood testing, and examination of the urinary sediment. Although the urinary sediment evaluation does not measure level of renal function, it is extremely important in providing insight into the cause of kidney disease and may also provide prognostic information in the setting of prerenal acute kidney injury (AKI) and acute tubular necrosis (ATN). Thus, in addition to urinalysis, the clinical examination, estimates of glomerular filtration rate (GFR), radiologic testing, and renal biopsy are used in combination to assess the patient with kidney disease. This chapter reviews the components of the urinalysis/urine microscopy, as well as their interpretation in patients with kidney disease.

URINALYSIS/URINE MICROSCOPY: ROLE IN KIDNEY DISEASE

Examination of urine in patients with kidney disease provides invaluable information. It is one of the major noninvasive diagnostic tools available to the clinician. The urinalysis is comprised of several components. These include the appearance of the urine, various parameters measured on dipstick and spot collections, and examination of the urine under the microscope. As will be discussed later, urine microscopy is essential to complete the urinalysis and assess kidney disease. The full urinalysis can provide insight into the cause of kidney injury/disease, some of the functional consequences of renal injury, and the course of kidney disease following various interventions. For example, in a patient suffering from acute glomerulonephritis, the urine sediment can provide information about activity of the inflammatory process. It will not always predict eventual renal outcomes, although data support its utility in prognosis in prerenal AKI and ATN. Thus, normalization of the urine sediment may represent either resolution with full recovery of kidney function or healing of the inflammatory process with residual glomerulosclerosis and nephron loss (chronic kidney disease). In this circumstance, other testing is required to accurately predict the status of kidney disease.

Despite some of the limitations of urinalysis, it should be performed in all patients with kidney disease or suspected kidney problems. The urine specimen is examined within an hour of voiding to provide optimal information and eliminate false-positive or false-negative results. A midstream specimen is adequate in men. In women, the external genitalia should be cleaned prior to voiding to avoid contamination of the urine with vaginal secretions. Following collection, dipstick testing is performed and the sample centrifuged at 3000 rpm for 3 to 5 minutes. Urine color and appearance is noted both before and after centrifugation, as this will provide clues to potential causes of the underlying kidney process. The dipstick measures pH, specific gravity, protein (albumin), heme, glucose, leukocyte esterase, bile, and nitrite. The centrifuged specimen is decanted to remove the supernatant and placed in a separate tube. This allows examination of the sediment. A small amount of sediment is placed on a glass slide. A cover slip is applied and both stained and unstained sediment are examined at various powers (100×, 160×, and 400×) under the microscope. These aspects of urinalysis are discussed in more detail throughout the chapter.

KEY POINTS

Urinalysis/Urine Microscopy: Role in Kidney Disease

1. Abnormalities in the urinalysis may signal kidney disease in the otherwise asymptomatic patient.
2. Findings on the urinalysis provide insight into the cause of acute or chronic kidney disease.
3. The evaluation of patients with suspected or known kidney disease should include history, physical examination, directed blood testing, and radiologic studies, as well as complete examination of the urine.

URINALYSIS: COMPONENTS

Appearance

Initial examination of urine consists of assessment of urine color and appearance. Normal urine is typically clear and light yellow in color. It tends to be lighter when more dilute (large water intake or polyuric states) and darker when more concentrated (overnight water restriction, prerenal disease states). The urine may appear cloudy because of infection (white cells, bacteria, proteinaceous material) or crystalluria (uric acid or calcium-containing crystals). The urine can look white from the presence of pyuria or calcium phosphate crystals; green from drugs such as methylene blue, amitriptyline, or propofol; or black as a consequence of certain malignancies or ochronosis. Table 14.1 lists some of the substances that can alter urine color. Although these urinary colors are unusual, various shades of red or brown are more common. Intermittent excretion of red to brown urine occurs in a variety of clinical settings. Assessment of red/brown urine should proceed through the following steps:

1. Centrifuge the urine and examine the sediment and supernatant.
2. Red/brown sediment supports hematuria or ATN with muddy brown casts.
3. Red/brown supernatant should be examined further with dipstick testing for the presence of heme.

4. Heme-negative supernatant may be caused by beeturia (beet ingestion in certain hosts), porphyria, or therapy with phenazopyridine (bladder analgesic).
5. Heme-positive supernatant may result from either hemoglobinuria or myoglobinuria. These are distinguished by examination of the plasma that will be red with hemoglobinuria and clear with myoglobinuria.

Dipstick Examination of Urine

Urine dipstick allows rapid examination of the urine for several abnormalities. They include specific gravity, pH, protein, blood/heme, glucose, leukocyte esterase, nitrite, and bile. Each of these components of the dipstick, as well as their application to the evaluation of kidney disease are discussed.

Specific Gravity

The kidney can vary urine osmolality (concentration) to appropriately maintain plasma osmolality within a very narrow range. Thus, the concentration of urine varies markedly based on the status of the patient's intravascular volume. To assess whether the kidney's response is appropriate or abnormal for the patient's volume status, measures of urine concentration are employed. Specific gravity is one such available test. Importantly, the specific gravity and other measures of urine concentration are assessed in correlation with the patient's clinical state. The specific gravity is defined as the weight of a solution compared with that of an equal volume of water. As such, it is a reasonable reflection of urine concentration. It is most useful in the diagnosis of patients with disorders of water homeostasis (hyponatremia, hypernatremia) and states of polyuria. It can vary significantly, however, with measured urine osmolality under certain clinical situations. For example, the presence of large molecules in the urine such as glucose and radiocontrast media can produce large changes in specific gravity, while having minimal effects on osmolality. These potential confounders must be accounted for when interpreting the specific gravity.

Urinary pH

Urine pH reflects the degree of acidification of urine; hence it is a measure of the urine hydrogen ion concentration. Urine pH normally ranges from 4.5 to 8.0 based on the prevailing systemic acid–base balance. Examination of urine pH is most useful in the workup of a metabolic acidosis. The appropriate response to metabolic acidosis is an increase in renal acid (buffered hydrogen ion) excretion, with a reduction in urine pH to below 5. Urine pH above 5 in the setting of metabolic acidosis may signal

TABLE 14-1. Substances That May Change the Color of Urine

SUBSTANCE	COLOR
Bilirubin	Yellow-amber
Nitrofurantoin	
Chloroquine	
Sulfasalazine	
Serotonin	
Riboflavin	
Phosphate crystals (precipitated)	White
Severe pyuria	
Chyle	
Phenazopyridine	Red-brown
Heme pigments	
Hematuria	
Phenothiazines	
Senna, rhubarb, cascara, aloe	
Phenytoin	
Porphyrins	
Phenolphthalein	
Beets	
Melanin	Brown-black
Homogentisic acid	
Phenol	
Porphobilinogen	
Methyldopa	
Quinine	
Metronidazole	
Ochronosis	
Certain malignancies	
Amitriptyline	Blue-green
Methylene blue	
Biliverdin	
Propofol	
Pseudomonas infection	

kidney disease, such as one of the forms of renal tubular acidosis (RTA). Changes in urine pH to various provocative tests can help distinguish which type of RTA exists. A urine pH less than 5.5 can also suggest risk for crystal and stone formation from uric acid, as well as medications such as sulfadiazine and methotrexate. Alkaline pH (>7.0) can provide clues to various clinical disorders such as urinary infection with urease-producing organisms (*Proteus mirabilis*) and risk for crystal and stone formation from calcium phosphate and certain drugs (atazanavir, indinavir). Management of these clinical disorders is assessed by measuring urine pH following the appropriate intervention.

Urine Protein

The urine dipstick measures primarily albumin. It does not identify other proteins that may be found in the urine, such as immunoglobulins and their light chains, or proteins secreted by tubular cells. Although the dipstick test is highly specific for the identification of albumin, it is insensitive in the detection of urinary albumin levels that are less than 300 to 500 mg/day. This is an important point as this makes the dipstick an unreliable test in the detection of microalbuminuria in certain patient populations. For example, microalbuminuria is an important early manifestation of diabetic nephropathy, one that would prompt changes in disease management in this population. Waiting for dipstick positive proteinuria allows significant amounts of structural damage to occur prior to aggressively managing kidney disease. Similarly, microalbuminuria is associated with cardiovascular disease in nondiabetic patients and its detection would likely alter management in these patients. In addition to the insensitivity of the dipstick protein measurement, the semiquantitative values (trace, 1+, 2+, 3+, 4+) obtained are only rough guides to actual amounts of proteinuria. Furthermore, these values should be interpreted cautiously recognizing that urine concentration, pH, and substances such as iodinated radiocontrast can influence the dipstick reading. For example, dilute urine can underestimate the degree of proteinuria, whereas both concentrated urine and alkaline urine can overestimate proteinuria. Finally, radiocontrast can cause a false-positive dipstick reading for proteinuria. Therefore, the urine should not be tested for at least 24 hours following radiocontrast administration. Other tests to measure proteinuria are discussed later.

Urine Blood/Heme

Dipstick testing of urine for blood/heme is sensitive in detecting both red blood cells and heme pigment (hemoglobin or myoglobin) in urine. As few as 1 to 2 red blood cells per high-power field register positive on dipstick, making this test at least as sensitive as urine sediment examination. False-positive results (heme pigments) for hematuria can, however, occur. In contrast, false-negative tests are unusual and a dipstick negative for heme reliably excludes hematuria. Importantly, the dipstick test for heme is never a substitute for a thorough urine sediment examination. All patients with hematuria on dipstick should have their urine spun down and the sediment examined closely for any abnormalities, especially evidence of glomerular disease (dysmorphic red blood cells, red blood cell casts) or nephrolithiasis (monomorphic red blood cells, crystals).

Urine Glucose

Dipstick testing for glucose is a relatively insensitive measure of hyperglycemia and is not recommended for screening of patients for diabetes mellitus. Significant glycosuria does not occur until the mean plasma glucose concentration is approximately 180 mg/dL. Additionally, it depends on urine volume. Also, glucose detected semiquantitatively on urine dipstick may reflect a kidney abnormality rather than hyperglycemia. Certain disease states may alter the ability of the kidney to reabsorb filtered glucose in the proximal tubule despite normal plasma glucose concentration. This renal glycosuria can manifest as an isolated proximal tubular defect. More commonly, it can develop in association with other defects in proximal tubular reabsorption including hypophosphatemia (phosphaturia), hypouricemia (uricosuria), RTA (bicarbonaturia), and aminoaciduria. This constellation of proximal tubular dysfunction is termed *Fanconi syndrome*. This syndrome is hereditary or acquired through diseases (multiple myeloma) or drugs (proximal tubular toxins) that primarily injure proximal tubular cells in kidney. Drugs such as cidofovir, tenofovir, cisplatin, and ifosfamide cause Fanconi syndrome.

Urine Leukocyte Esterase

Positive dipstick testing for leukocyte esterase (LE) represents the presence of white blood cells in urine (pyuria). The test is positive with 2 to 3 leukocytes/

high-powered field. A positive test in the absence of white blood cells on urine microscopy suggests that the cells lysed prior to viewing. Importantly, lymphocytes do not produce LE and the dipstick will be LE negative when they are present in the urine. Although the presence of urinary white blood cells most often reflects infection of the urinary tract, it can also be indicative of diseases associated with sterile pyuria. Included are tubulointerstitial nephritis from various causes, crystalluria and nephrolithiasis, and renal mycobacterial infection. As with hematuria, a thorough examination of the urine sediment should be performed in patients with pyuria.

Urine Nitrite

The urine nitrite test is most valuable when used in conjunction with LE to assess a patient for the presence of urinary tract infection. Certain bacteria (*Enterobacteriaceae*) convert urinary nitrate to nitrite (Figure 14.1). Thus, the combination of LE and nitrite positive tests on dipstick strongly suggests infection with this family of bacteria. Bacteria that do not produce nitrate reductase will not convert nitrate to nitrite and therefore will test negative for nitrite despite urinary tract infection.

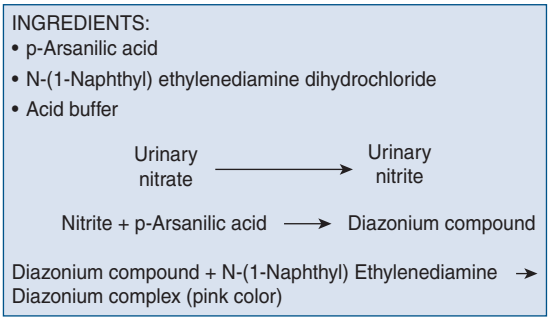


FIGURE 14-1. Laboratory components of the nitrite test used to identify bacteria in the urine. The conversion of nitrate to nitrite results in the production of a pink-colored diazonium complex.

Urine Bile

Bile present on urine dipstick reflects the filtration of serum bilirubin. Figure 14.2 illustrates normal bile pigment metabolism. The finding of bile pigment is common in patients with various forms of liver disease with associated hyperbilirubinemia. It does not represent a disturbance in kidney function although liver disease may be associated with renal failure (hepatorenal syndrome).

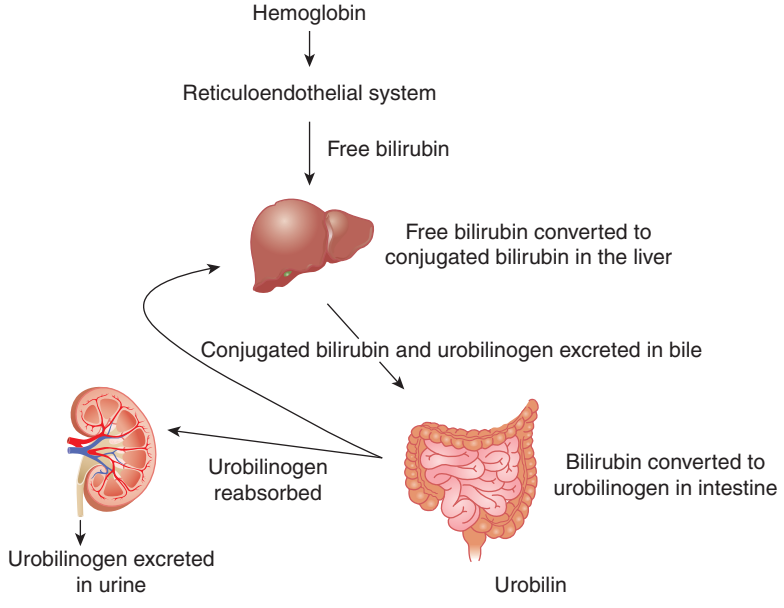


FIGURE 14-2. Pathway of normal bile pigment metabolism. Free bilirubin is converted in the liver and intestine to urobilinogen that is subsequently excreted in the urine.

TABLE 14-2. Conditions Associated with Urine Urobilinogen and Urine Bilirubin

CONDITION	URINE BILIRUBIN	URINE UROBILINOGEN
Normal	–	+
Hepatitis	+	+
Hepatotoxins	+	+
Biliary obstruction	+	–
Cirrhosis	+	+

Testing for urine bilirubin and urobilinogen separates obstructive jaundice from other forms of liver disease. In this situation, complete biliary obstruction has positive urine bilirubin with negative urobilinogen, while other forms of liver disease are positive for both substances (Table 14.2).

KEY POINTS

Urinalysis: Components

1. Dipstick of the urine provides useful information about patients with various forms of kidney disease.
2. A red or brown appearance of urine is appropriately evaluated with dipstick testing and urine sediment examination.
3. Dipstick proteinuria identifies urinary albumin excretion greater than 300 to 500 mg/day but does not measure nonalbumin proteins.
4. Glycosuria in patients with normal plasma glucose concentration suggests a proximal tubular disturbance in glucose reabsorption. This finding should stimulate investigation for other defects in proximal tubular function and, if present, evaluation for the cause of Fanconi syndrome.
5. Urinary tract infection is likely in patients with urine dipstick positive for both LE and nitrite. Isolated positive LE with a negative urine culture result should promote evaluation for causes of sterile pyuria-like tubulointerstitial nephritis and nephrolithiasis.

URINE SEDIMENT EXAMINATION

Microscopy of the urine sediment is a very important aspect of the evaluation of patients with known or suspected kidney disease. Urinary sediment should be reported both qualitatively (types of cells, casts, crystals, organisms) and quantitatively (number of casts per low-powered field and cells/crystals per high-powered field). At least 10 and up to 20 microscopic fields should be viewed and an average range reported. For example, 5 to 10 granular casts per low-powered field or 1 to 5 red blood cells per high-powered field. It is important to also recognize that normal subjects without kidney disease may also have minor amounts of abnormal elements (red blood cells, white blood cells, casts, and crystals) in the urine. A patient without kidney disease may have zero to 4 white blood cells or zero to 2 red blood cells in 1 high-powered field and 1 cast, often hyaline in 10 to 20 low-powered fields. Additionally, a few crystals made up of uric acid, calcium oxalate, or calcium phosphate may occasionally be observed. A greater number of these elements in the urine is, however, very suggestive of either systemic or renal-related disease states. Various elements found in urine on sediment examination are described below.

Cellular Elements

The most common cell types observed in urine are red blood cells, white blood cells, and epithelial cells. The urine can also contain cells from the bladder, and when contaminated during collection, vaginal squamous cells can be noted. Less commonly, tumor cells from the uroepithelium (bladder and ureteral epithelium), lymphoma, or leukemic cells that have infiltrated the renal parenchyma, and "decoy cells" associated with BK-polyomavirus–induced changes in renal tubular cells or uroepithelial cells are identified in urine sediment. The various cellular elements present in urine are reviewed below.

Red Blood Cells

The presence of red blood cells in urine, either microscopic or visible grossly, is called *hematuria*. Hematuria can be transient and benign or, alternatively, signal a disease of the kidneys or urogenital tract. Microscopic hematuria is defined as 2 or more red blood cells per high-powered field in a spun urine sediment on 2 separate urine examinations. Red cell morphology is useful to help localize the source of injury or disease within the kidneys or elsewhere in the urinary system. Monomorphic red cells, which appear round and uniform like those seen on a peripheral blood smear, typically suggest

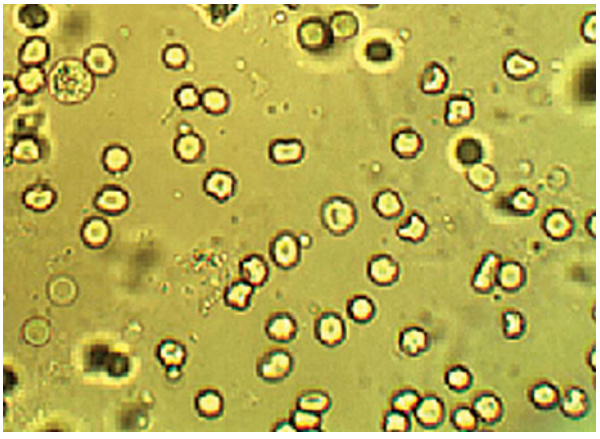


FIGURE 14-3. Monomorphic red blood cells in the urine sediment. The red cells are the smaller uniform cells without nuclei. (Courtesy of Mark A. Perazella.)

extrarenal bleeding (Figure 14.3). In contrast, dysmorphic red cells often indicate a renal lesion, in particular a glomerular process. The morphology of dysmorphic red cells is characterized by blebbing, budding, and partial loss of the cellular membrane. Acanthocytes are 1 form of dysmorphic red cell that have a ring form with vesicle-shaped protrusions (Figure 14.4). This process results in altered red cell size (smaller) and shape. Monomorphic and dysmorphic red cells may be difficult to distinguish on routine urine microscopy. Phase contrast microscopy and scanning electron microscopy of urine more accurately identify red cell morphology but are not routinely available in most clinical settings. Persistent hematuria most often signals nephrolithiasis, glomerular pathology, or malignancy of the kidneys or urinary tract.

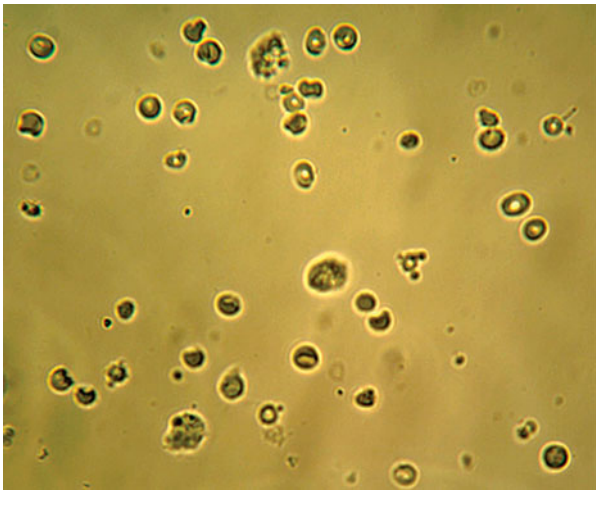


FIGURE 14-4. Dysmorphic red blood cells in the urine sediment. The red cells have blebs that indicate injury caused by passage through the glomerulus. (Courtesy of Mark A. Perazella.)

White Blood Cells

White blood cells in urine, known as *pyuria*, are larger than red blood cells and have a granular cytoplasm with multiple nuclei. Neutrophils are the most common white blood cells in urine. They have multilobed nuclei, and often signal infection of the urinary tract or kidney (Figure 14.5). Eosinophils with their bilobed nuclei, may also be observed in urine on Wright stain or Hansel stain, which stains the granules bright red. Once thought to indicate the presence of acute interstitial nephritis, urinary eosinophils are seen with various renal processes, including cholesterol emboli, glomerulonephritis, urinary tract infection, and prostatitis. Lymphocytes may also be visualized in urine. These mononuclear cells are observed in urine sediment when lymphocytes, which are present in the renal interstitium, are shed into the urine. Examples are chronic tubulointerstitial diseases such as sarcoidosis and uveitis-tubulointerstitial nephritis syndrome.

Epithelial Cells

Although epithelial cells can be shed into urine from any part of the genitourinary system, only renal tubular

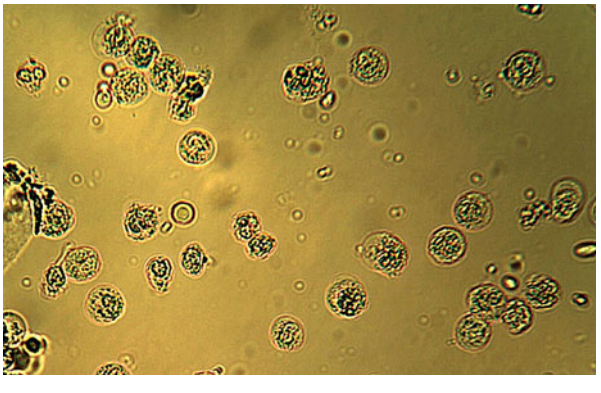


FIGURE 14-5. White blood cells in the urine sediment. White cells have a multilobed nucleus and a granular cytoplasm. (Courtesy of Mark A. Perazella.)

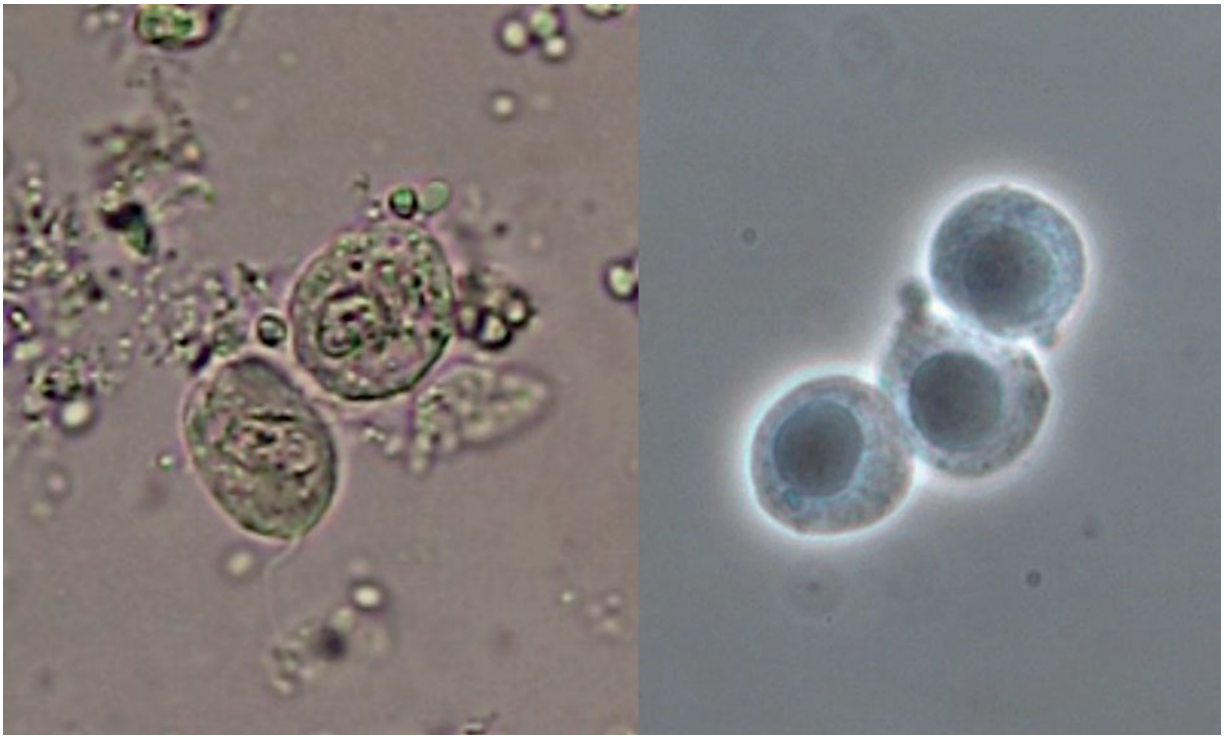


FIGURE 14-6. Renal tubular epithelial cells in the urine sediment (brightfield in the left panel and phase contrast microscopy in the right panel). Renal tubular epithelial cells have a central uniform nucleus and are larger than white blood cells. (Courtesy of Mark A. Perazella and Giovanni Fogazzi.)

epithelial cells have clinical relevance. In general, renal tubular epithelial cells are several times larger than white blood cells; however, their size varies greatly (Figure 14.6). Also, their nuclei are round and located either centrally or eccentrically in the cytoplasm. It is often difficult to distinguish these cells from uroepithelial cells from the lower urinary tract (transitional epithelium), making the presence of renal tubular epithelial cell casts diagnostically important. Renal tubular epithelial cells and casts are essentially diagnostic of either ischemic or nephrotoxic ATN, but occasionally are seen with glomerular disease. Lipid-filled tubular epithelial cells and free fat droplets (Maltese cross-appearance when polarized) are present in the urine sediment of patients with high-grade proteinuria.

Malignant Cells

Close scrutiny of urine can sometimes discover cancer present in the kidneys or genitourinary tract. Atypical lymphocytes or lymphoid cells observed in the urine sediment can represent lymphoma of the kidneys or bladder. Similarly, leukemic cells may be present in urine, signaling leukemic infiltration of the kidneys, or genitourinary tract. Tumor cells of uroepithelial origin are noted in the urine sediment when ureteral or bladder cancer is present.

Decoy Cells

Examination of the urine sediment in renal transplant patients treated with tacrolimus or mycophenolate mofetil can confirm the presence of BK-polyomavirus infection if "decoy cells" are demonstrated. These cells are renal tubular epithelial cells and other uroepithelial cells that manifest changes associated with viral infection. These cells are best visualized employing Papanicolaou-stained urine sediment or phase-contrast microscopy of unstained urine sediment (Figure 14.7). Several cellular findings characterize "decoy cells." They include (a) ground-glass nucleus; (b) chromatin margination; (c) course granules

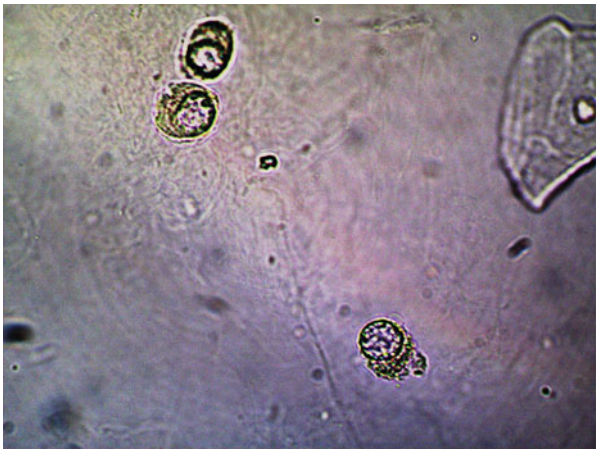


FIGURE 14-7. Decoy cells are seen in the urine sediment of a patient with BK nephropathy. (Courtesy of José Antonio Tesser Poloni and Mark A. Perazella.)

(chromatin patterns); (d) nuclear body inclusions with a peripheral halo; and (e) cytoplasmic vacuoles. Virus particles are seen when scanning electron microscopy is used.

Other Cellular Elements

Bacteria are quite commonly seen in urine sediment during infection of the urinary tract. Rarely, other infectious organisms are seen in the urine sediment. Included are *Candida albicans, Coccidioides immitis, Mycobacterium tuberculosis, Cryptococcus neoformans, Curvularia* species, and *Schistosoma haematobium*. Budding yeast (Figure 14.8) are seen on microscopy in a patient with yeast cystitis. These organisms are often found associated with white blood cells, red blood cells, abnormal epithelial cells, and cellular casts.

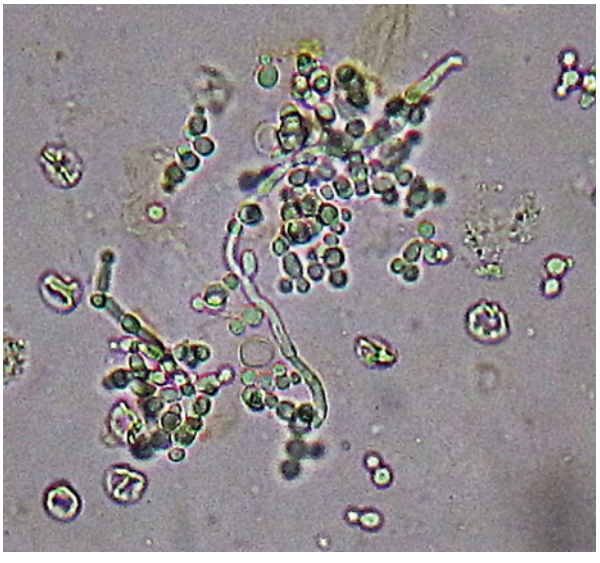


FIGURE 14-8. Budding yeast are seen in the urine sediment. (Courtesy of Mark A. Perazella.)

KEY POINTS

Urine Sediment Examination

1. Examination of the urine sediment is crucial to provide insight into the cause of kidney disease.
2. Cellular elements present in the urine sediment include red blood cells, white blood cells, epithelial cells, tumor cells, decoy cells, and various infectious agents.
3. Red blood cell morphology can distinguish glomerular bleeding (dysmorphic cells with blebbing) from nonglomerular bleeding (monomorphic cells).
4. White blood cells in urine are indicative of urinary infection or processes associated with sterile pyuria such as interstitial nephritis, nephrolithiasis, and renal mycobacterial infection.
5. Tubular epithelial cells are commonly seen in urine sediment when ATN from ischemia or nephrotoxins is present.
6. Rarely, malignant cells are observed in the urine sediment. Examples include renal and bladder lymphoma and uroepithelial tumors of the ureters and bladder.
7. "Decoy cells" in urine sediment represent epithelial cells infected with BK-polyomavirus in renal transplantation patients.

URINE CASTS

Casts observed in urine are formed within renal tubular lumens and, therefore, conform to the shape of these lumens. They are typically cylindrical with regular margins, but can be fractured during the process of spinning and placing the sediment on the glass slide. All casts have an organic matrix that is composed primarily of Tamm-Horsfall mucoprotein that is synthesized and released at the loop of Henle. Various urinary casts are observed in urine; some in normal subjects. Often, the presence of

casts in urine represents significant kidney disease, suggesting an intrarenal origin. The diverse casts that can be viewed in the urine sediment are reviewed below.

Hyaline Casts

These slightly refractile cast (Figure 14.9) are not associated with any particular disease. Hyaline casts may occur in a frequency as high as 5 to 10 per high-powered field. They are found in small volumes of concentrated urine and following diuretic therapy.

Red Blood Cell Casts

The demonstration of even 1 red blood cell cast is significant for glomerulonephritis or vasculitis. These casts are difficult to find and require thorough evaluation of the entire sediment on the microscope slide. Red blood cell casts are often found with free dysmorphic red cells (Figure 14.10). These casts typically contain red cells within a hyaline or granular cast, although sometimes the cast can be tightly packed with red blood cells.

White Blood Cell Casts

Casts containing white blood cells (Figure 14.11) are found most commonly in the urine sediment of patients with acute pyelonephritis or tubulointerstitial disease. Occasionally, these casts are also present with other inflammatory diseases of the kidney such as glomerular disorders, vasculitis, and cholesterol emboli. Like red cell casts, white blood cell casts are often found with free white cells such as neutrophils with pyelonephritis and eosinophils with acute interstitial nephritis.

Epithelial Cell Casts

Injury to the tubular epithelium with the development of necrosis causes shedding of cells into the lumen. This is the proximate cause of renal tubular epithelial cell casts

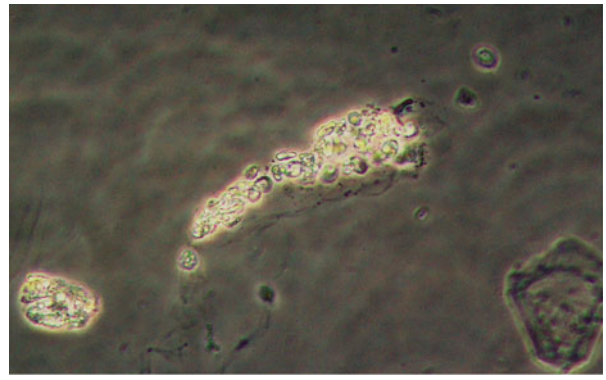


FIGURE 14-10. Red blood cell cast in the urine sediment. Red cell casts are the hallmark of glomerulonephritis. (Courtesy of José Antonio Tesser Poloni and Mark A. Perazella.)

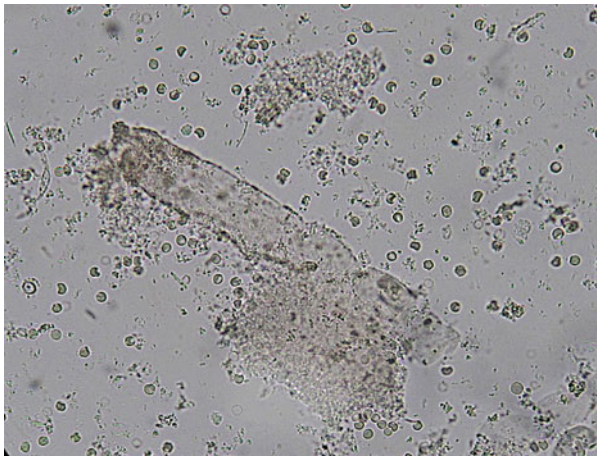


FIGURE 14-9. Hyaline cast in the urine sediment. Hyaline casts are acellular and are seen in normal urinary sediment. (Courtesy of Mark A. Perazella.)

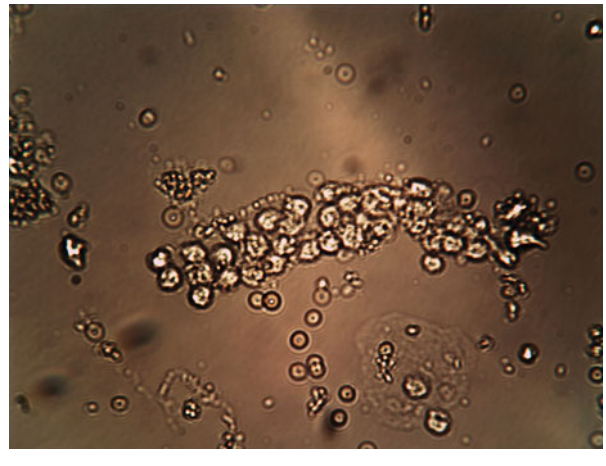


FIGURE 14-11. White blood cell cast in the urine sediment. White cell casts are often seen in diseases of the tubulointerstitium. (Courtesy of Mark A. Perazella.)

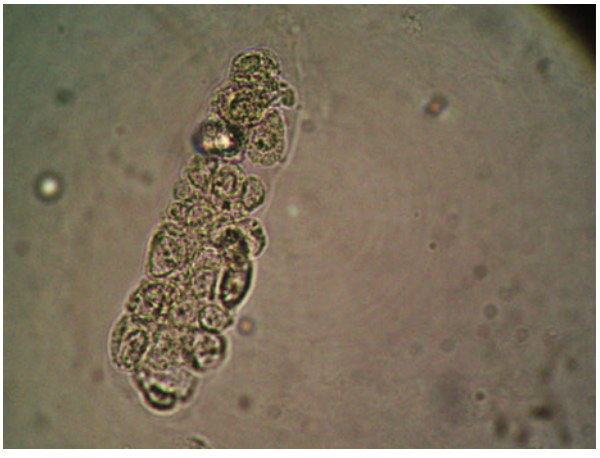


FIGURE 14-12. Renal tubular epithelial cell cast (bile stained) in the urine sediment. These casts classically reflect tubular injury from either ischemia or nephrotoxins. (Courtesy of Mark A. Perazella.)

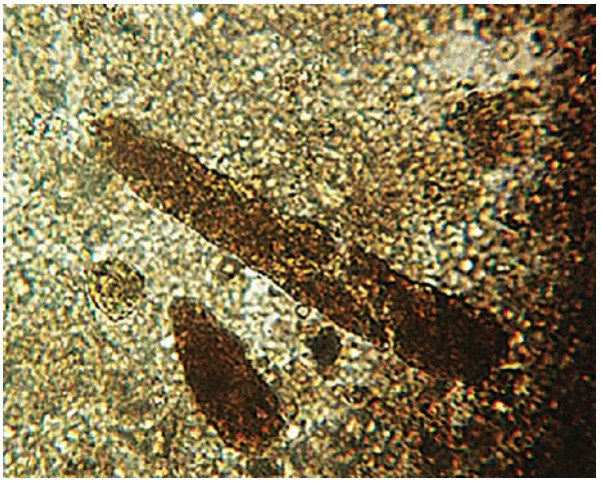


FIGURE 14-13. Granular cast in the urine sediment. Granular casts are composed of degenerating cells and reflect tubular injury. They are often seen in acute tubular necrosis. (Courtesy of Mark A. Perazella.)

in urine sediment (Figure 14.12). The casts contain tubular epithelial cells of varying sizes and shapes admixed with granular material. Renal tubular epithelial cells are also present in the sediment. Although desquamation of these cells is most indicative of tubular injury and necrosis, they are also observed with glomerulonephritis and vasculitis.

Granular Casts

Casts containing granular debris (Figure 14.13) represent degenerating cells of various origins. Although most often seen with ATN from degenerating tubular epithelial cells, they can also be degraded red blood cells or white blood cells. Thus, it is important to assess these casts along with other urinalysis findings (protein, other cell types present in urine, and their morphology), as well as the pertinent clinical data.

Waxy Casts

As the granular casts continue to degenerate, they form waxy casts (Figure 14.14). Because this is a relatively slow process, the presence of significant numbers of waxy casts suggests advanced kidney disease, either subacute in the setting of AKI or in chronic kidney disease (CKD). Once again, the company these casts keep provides useful diagnostic information.

Broad Casts

As their name implies, broad casts are wider than other casts and are thought to form in the large (dilated) tubules of nephrons with sluggish urine flow. They often are granular or waxy, and like waxy casts are indicative of advanced kidney disease.

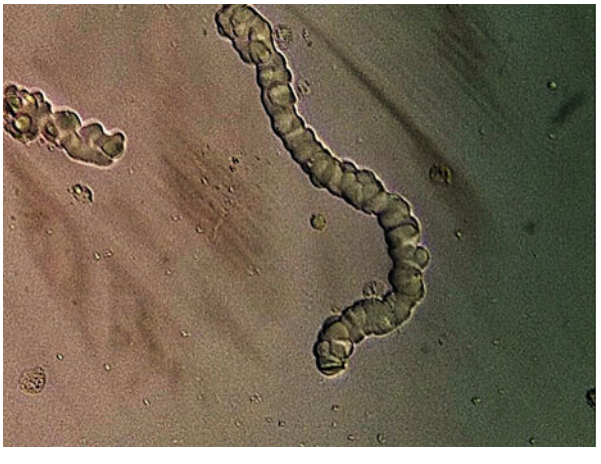


FIGURE 14-14. Waxy casts in the urine sediment. These casts are cylindrical, possess a higher refractive index and are more rigid, often demonstrating sharp edges, fractures, and broken-off ends. (Courtesy of Mark A. Perazella.)

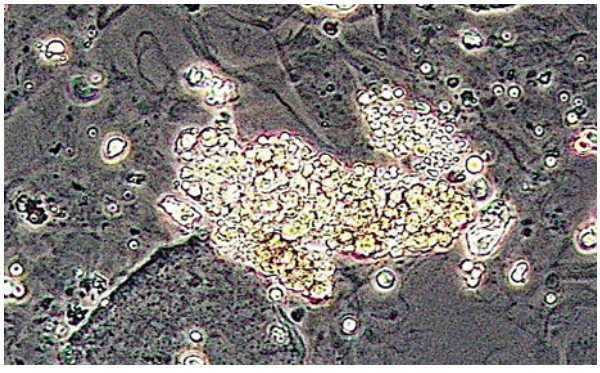


FIGURE 14-15. A cast full of lipid droplets is noted in the urine sediment. This is a lipid of "fatty" cast that is seen with nephrotic syndrome. (Courtesy of José Antonio Tesser Poloni and Mark A. Perazella.)

Fatty Casts

Tubular epithelial cells filled with lipid droplets, known as oval fat bodies and those contained in a cast matrix constitute fatty casts (Figure 14.15). These casts are found in patients with significant levels of proteinuria and lipiduria, and are part of the nephrotic syndrome. The droplets are composed of cholesterol and cholesterol esters, both of which can be seen free in the urine.

KEY POINTS

Urine Casts

1. Urinary casts are formed in the tubular space, and as such are cylindrical in shape and composed of an organic matrix consisting of Tamm-Horsfall proteins. At times, various cellular elements are contained in the casts.
2. Red blood cell casts are indicative of glomerulonephritis or vasculitis; even 1 cast is very significant.
3. White blood cell casts are seen in the setting of acute pyelonephritis or acute interstitial nephritis.
4. Renal tubular epithelial cell casts, along with granular casts and free epithelial cells are commonly seen with ATN.
5. Fatty casts develop in urine in diseases associated with high-grade proteinuria (nephrotic range). They are refractile casts containing tubular epithelial cells filled with cholesterol and cholesterol esters.

URINE CRYSTALS

The formation of crystals in urine depends on a variety of factors. The most important factors include the degree of supersaturation of constituent molecules, urine pH, and the presence or absence of inhibitors of crystallization. These crystals may form in normal subjects, as well as in patients with known disorders associated with crystalluria. Not uncommonly, crystals are admixed with both white and red blood cells. The different crystals seen in urine are reviewed.

Uric Acid Crystals

Acid urine favors the conversion of relatively soluble urate salts into insoluble uric acid. As a result of this milieu, uric acid crystals and amorphous urates form in urine and cause either asymptomatic crystalluria, renal failure from crystal-induced tubular obstruction, or frank nephrolithiasis. In particular, tumor lysis syndrome can cause severe uric acid crystalluria and acute kidney injury. Low urine volumes also contribute to the formation of uric acid crystals and stone formation. These crystals are pleomorphic and can be rhombic or rosette shaped (Figure 14.16). They can be easily identified under polarized light.

Calcium Oxalate Crystals

The formation of calcium oxalate crystals is independent of urine pH. Excess urinary oxalate, as seen with

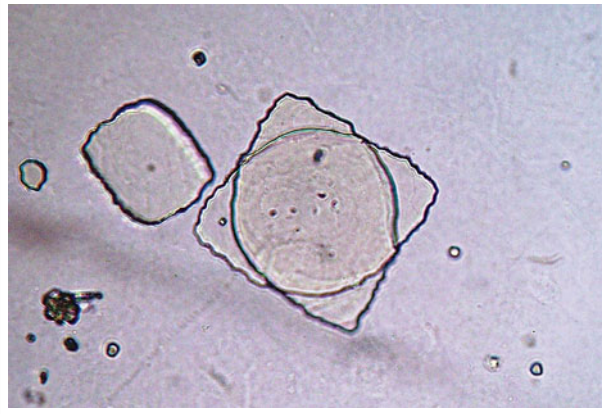


FIGURE 14-16. Uric acid crystals in the urine sediment. Uric acid crystals can be rhomboid or needle shaped and may be a normal finding in an acidic urine. (Courtesy of José Antonio Tesser Poloni and Mark A. Perazella.)

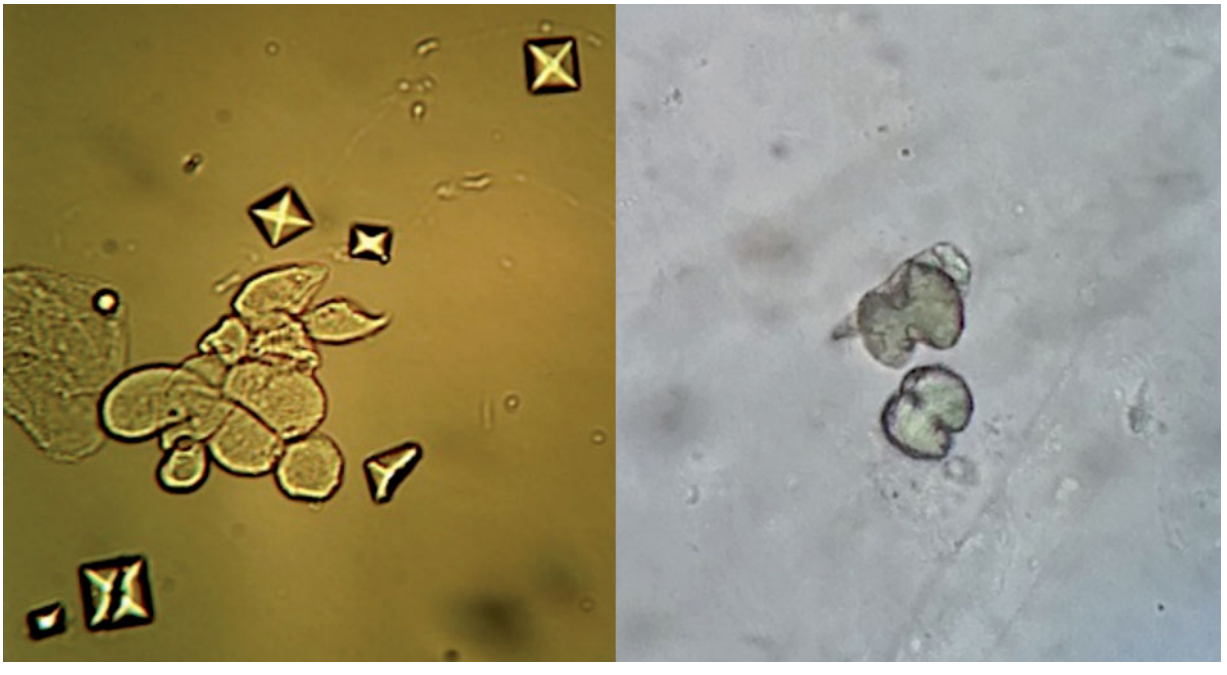


FIGURE 14-17. Calcium oxalate crystals in the urine sediment. Calcium oxalate may crystallize in a monohydrate or dihydrate form. The dihydrate form is shown in the left panel and monohydrate in the right panel. (Courtesy of Mark A. Perazella.)

ethylene glycol ingestion and short bowel syndrome, is associated with calcium oxalate crystal excretion and nephrolithiasis. Also, hypocitraturia is an important contributor to formation of calcium oxalate crystals. These crystals are envelope shaped if calcium oxalate dihydrate (Figure 14.17), or dumbbell or needle shaped if calcium oxalate monohydrate. These crystal may also be seen within cast matrix and represent acute oxalate nephropathy from enteric hyperoxaluria (bariatric surgery/small bowel disease, drugs, pancreatitis) or primary hyperoxaluria types 1 and 2.

Calcium Phosphate Crystals

In contrast to calcium oxalate crystals, an alkaline pH increases the formation of calcium phosphate crystals. Hypercalciuria also contributes importantly to calcium phosphate crystalluria. These crystals are seen in patients with RTA and can cause cloudy white urine, hematuria, and kidney stones. Calcium phosphate crystal may also be seen in patients suffering from acute phosphate nephropathy from sodium phosphate containing bowel purgatives.

Cystine Crystals

Cystine crystals are observed in urine of patients with the hereditary disorder known as cystinuria. The crystals tend to precipitate when their concentration exceeds 300 mg/L of urine. Acid urine also increases crystallization. The crystals are hexagonal; their presence in the urine is diagnostic of cystinuria (Figure 14.18).

Magnesium Ammonium Phosphate Crystals

Struvite or "infection stones" are made up of 2 constituents: magnesium ammonium phosphate and calcium carbonate-apatite. Normal urine is typically undersaturated with ammonium phosphate, however, infection with certain bacteria increase the ammonia concentration (and hence the pH) through urease production. The alkaline pH (>7) decreases the solubility of phosphate and contributes to both crystal and stone formation. The

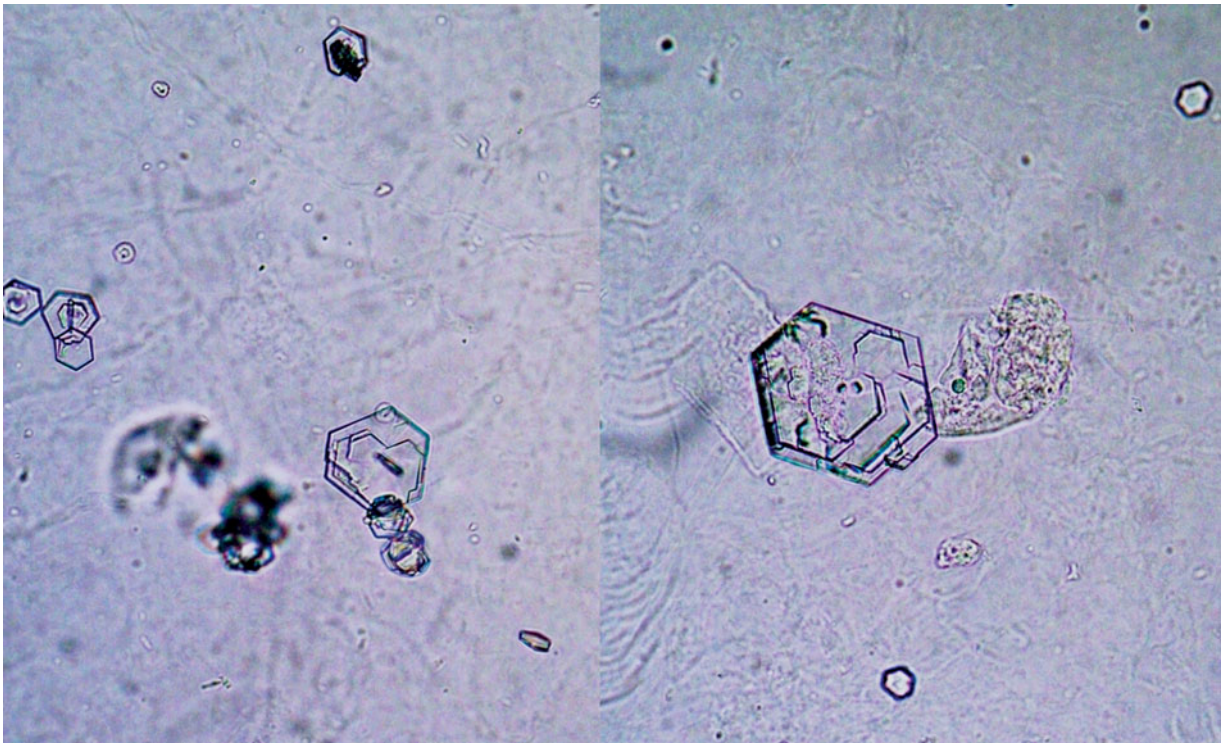


FIGURE 14-18. Cystine crystals in the urine sediment. Cystine crystals are hexagon shaped and are the hallmark of cystinuria. (Courtesy of José Antonio Tesser Poloni and Mark A. Perazella.)

triple phosphate crystals appear as coffin lid covers in the urine sediment (Figure 14.19).

Drug-Associated Crystals

A number of medications can cause crystal formation in urine. Most occur as a consequence of supersaturation of a low-volume urine with culprit drug, whereas others develop as a result of drug insolubility in either alkaline or acid urine pH. Acyclovir crystals, noted as needle-shaped crystals that polarize, occur when the drug is rapidly infused in volume-depleted patients. Excess drug dose for the level of renal function also contributes to crystalluria. This can result in AKI. Urine pH is unimportant in the development of acyclovir crystals. Acid urine pH contributes importantly to the formation of crystalluria with drugs such as methotrexate, sulfadiazine, and triamterene. Volume depletion with low urinary flow rates also enhances crystalluria with these drugs. All of these medications are associated with AKI, while both sulfadiazine and triamterene also cause renal stone formation. Indinavir and atazanavir, protease inhibitors, are also associated with crystalluria. Both volume depletion and alkaline urine enhance crystallization and nephrolithiasis from these drugs. Other therapeutic agents associated with urinary crystals include Pyridium, amoxicillin, ampicillin, aspirin, xylitol, foscarnet, cephalexin, ciprofloxacin, primidone, piridoxylate, and vitamin C.

KEY POINTS

Urine Crystals

1. A variety of crystals can be viewed in urine. Some can occur in normal subjects, as well as patients with defined disease states.
2. Urinary crystals can be asymptomatic, cause hematuria or renal failure, or form kidney stones.
3. Uric acid crystals form in acid urine. Patients may develop acute kidney injury and nephrolithiasis from uric acid crystalluria.

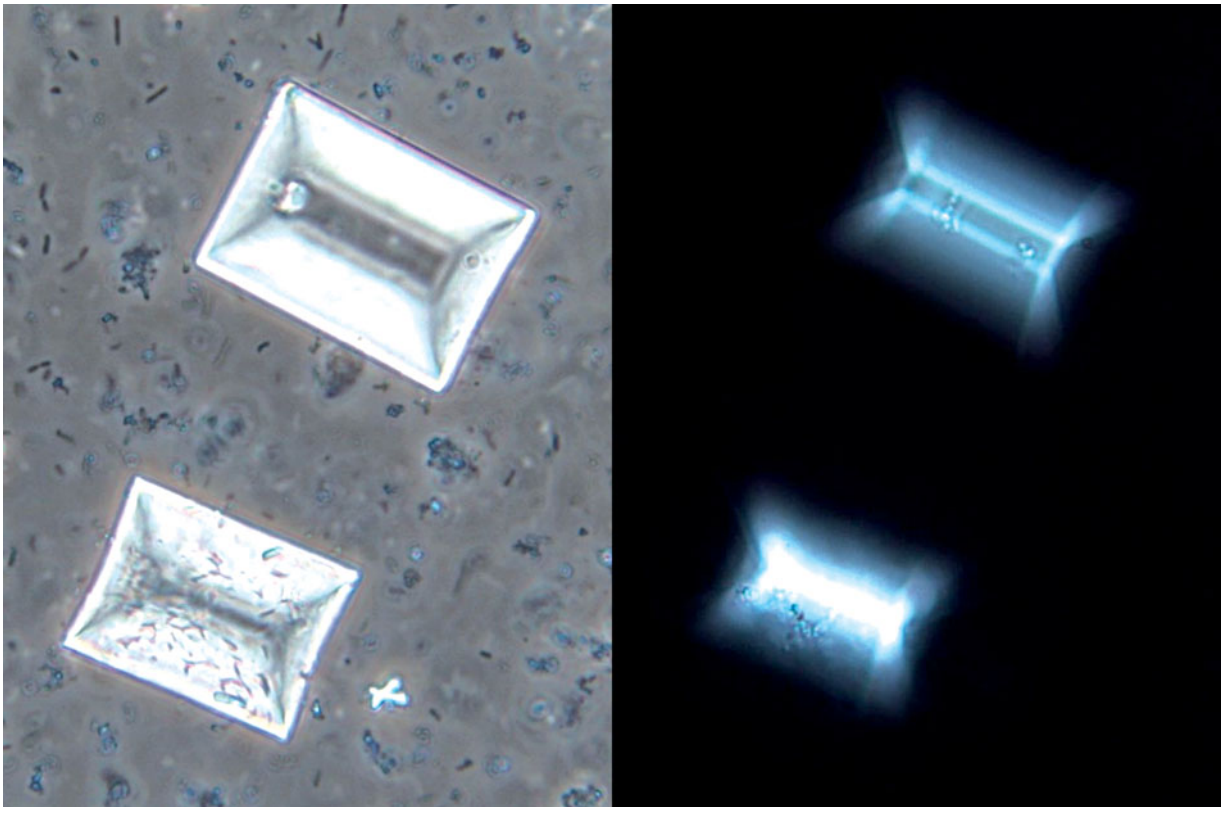


FIGURE 14-19. Triple phosphate crystals in the urine sediment (phase contrast in the left panel and polarization microscopy in the right panel). Triple phosphate crystals are shaped like a coffin lid and are only seen in urine infected with urease-producing bacteria. (Courtesy of Giovanni Fogazzi.)

4. Calcium oxalate crystals can be enveloped and dumbbell shaped, as well as needle-like, when viewed in the urine sediment. High urine oxalate and hypocitraturia are common causes of the formation of these crystals.
5. Cystine crystals signal the hereditary disease cystinuria. Crystal formation occurs with excessive cystine concentration in the urine (>300 mg/L), as well as a low urine pH (<7).
6. Medication-induced crystals develop from insoluble drug characteristics, low urine flow rates, and either acid or alkaline pH (depending on the drug). They can be associated with asymptomatic crystalluria, hematuria and pyuria, renal failure, and kidney stone formation.

TESTS OF URINARY PROTEIN EXCRETION

In addition to the aforementioned dipstick tests of urine, other important tests are required in the evaluation of patients with proteinuria and kidney disease. Perhaps one of the most important urinary markers of disease progression is urinary protein excretion. Although the dipstick protein measurement is a specific test, it provides only a rough guide to the actual degree of proteinuria. Positive protein on dipstick should stimulate more accurate assessment of proteinuria. High-risk populations like diabetics should have screening with more sensitive measures of albuminuria. The following section discusses tests that should be employed to more fully evaluate patients with known or suspected kidney disease.

Sulfosalicylic Acid Test

The sulfosalicylic acid (SSA) test, in contrast to the dipstick, detects all proteins in urine. The SSA gained its major usage in the assessment of elderly patients with renal failure, a benign urine sediment, and negative or trace protein on dipstick who were suspected of having myeloma kidney. A strikingly positive SSA test in such a patient is consistent with the presence of nonalbumin proteins, such as immunoglobulin light chains in urine. The SSA is performed by mixing 1 part urine supernatant with 3 parts (3%) SSA. The resultant turbidity is graded as zero to 4+ and approximates protein concentrations.

The rapid availability and accuracy of the random spot urine protein-to-creatinine ratio has, however, limited the use of the SSA test in clinical medicine.

Spot Protein-to-Creatinine Ratio

Several studies confirm the accuracy of the random spot measurement of protein and creatinine in estimating 24-hour urine protein excretion. The protein-to-creatinine ratio correlates closely with the 24-hour measurement of protein in g/1.73 m^2 of body surface area. The units of measure for the urine protein and creatinine are required to be identical to allow the calculation of the ratio. Because protein excretion varies during a 24-hour period, it is most optimal to measure the spot urine protein-to-creatinine ratio either in the morning or at the same time during the day. The following case illustrates the use of spot urinary protein and creatinine in the estimation of daily protein excretion.

A 41-year-old patient with diabetic nephropathy is on therapy with an angiotensin-converting enzyme (ACE)-inhibitor (lisinopril 40 mg/day). An angiotensin receptor blocker (losartan 100 mg/day) is added in an attempt to reduce proteinuria. Prior to losartan, daily urinary protein excretion was 2.1 g. A random spot urine is sent for protein and creatinine concentration to monitor response to the addition of losartan after 8 weeks of therapy. Urine protein concentration is 110 mg/dL and creatinine concentration is 90 mg/dL (110 mg/dL/90 mg/dL = 1.2); thus the ratio is 1.2. This is equivalent to a urinary protein excretion of 1.2 g/day.

Daily protein excretion above 150 mg/day, when documented on more than 1 measurement, is considered abnormal and the patient should undergo a thorough investigation to diagnose and treat the underlying kidney disease. The Work Group of the Kidney Disease Outcome Quality initiative (K-DOQI) of the National Kidney Foundation recommends use of the random spot protein-to-creatinine ratio to evaluate and monitor proteinuria in patients at risk for or with known kidney disease.

Like the spot protein-to-creatinine ratio, the random spot albumin-to-creatinine ratio is invaluable in the diagnosis of microalbuminuria and for monitoring the status of microalbuminuria in patients with diabetes mellitus. This test accurately estimates urine albumin excretion. Albumin concentrations in the 30 to 300 mg/day range are considered diagnostic of microalbuminuria. Microalbuminuria is confirmed with more than a single urine sample since several factors can increase urinary albumin excretion.

24-Hour Urine Collection

The 24-hour urine collection for protein and creatinine is considered the gold standard measure of urine protein excretion. It is more accurate than the random spot urine protein estimation and allows simultaneous calculation of creatinine clearance. In addition, it detects changes in urine creatinine excretion from vigorous exercise, high meat or vegetarian diet, creatine supplementation, and medications that effect creatinine production. All of these can confound the urine creatinine excretion and render the spot measurement less accurate. Finally, the 24-hour urine collection provides relevant information regarding nutrient and fluid intake by measuring urine volume, urea, sodium, and potassium. The benefits of this test are, however, compromised by its cumbersome nature in the ambulatory setting. Many patients are unwilling to perform these collections on a regular basis, making the random spot protein-to-creatinine ratio invaluable in monitoring proteinuria.

In patients with diseases associated with the production of monoclonal proteins (immunoglobulins or light chains) and in patients considered as potentially having these disorders, collection of 24-hour urine is required. Such diseases include multiple myeloma, primary amyloidosis, some lymphomas, and diseases associated with monoclonal light or heavy chain production. This urine collection will allow the measurement of both protein electrophoresis and immunoelectrophoresis, detecting the presence of monoclonal proteins. The 24-hour urine collection is also useful in the evaluation and treatment of patients with certain forms of

hypertension (primary aldosteronism and pheochromocytoma) and nephrolithiasis.

KEY POINTS

Tests of Urinary Protein Excretion

1. The SSA urine, which measures all urinary proteins, is useful to evaluate patients with negative dipstick protein measurement who are suspected of having a disorder associated with monoclonal immunoglobulin production.
2. The random spot protein-to-creatinine ratio accurately estimates 24-hour urine protein excretion and is recommended as the test of choice to monitor patients with proteinuric kidney disease.
3. The 24-hour urine collection for protein and creatinine is the most precise measure of proteinuria and provides insight into renal function from the creatinine clearance calculation.

URINALYSIS/URINE MICROSCOPY AND KIDNEY DISEASE: PATTERNS

As with any test in clinical medicine, urinalysis is most useful diagnostically when different components of the test are combined to allow patterns of urinary findings to associate with different kidney diseases. Often times, the combination of urinary findings will suggest only one or two renal disorders. Below are examples to illustrate the point. Table 14.3 also demonstrates the use of urinalysis and urine sediment examination in the detection of various renal disease states.

Isolated Hematuria with Monomorphic Red Blood Cells

The differential diagnosis of this combination of findings is limited to crystalluria, nephrolithiasis, or malignancy of the genitourinary system. Rarely, glomerular disorders such as immunoglobulin (Ig) A nephropathy or thin basement membrane disease may present in this way. Patients with these glomerulopathies often have, however, dysmorphic red blood cells and red blood cell casts in the urine sediment.

Hematuria with Dysmorphic Red Blood Cells, Red Blood Cell Casts, and Proteinuria

Patients with this constellation of findings are likely to have a glomerular disease or renal vasculitis. As discussed in the Chapter 17 on glomerular disease, this presentation is termed *nephritic syndrome* and strongly suggests glomerulonephritis. Importantly, the absence of these findings does not exclude glomerulonephritis. A kidney biopsy may be indicated in this situation.

Hematuria with Dysmorphic Red Blood Cells and Pyuria with White Blood Cells

This combination of urinary findings is seen with various kidney processes. Included are glomerular disease, tubulointerstitial nephritis, vasculitis, urinary obstruction, crystalluria (typically the offending crystal is also present), cholesterol embolization, and renal infarction. All these disease states can injure the kidney and cause an inflammatory lesion within the renal parenchyma.

TABLE 14-3. Urinalysis and Microscopic Examination of the Urine Sediment

TEST	PRERENAL	VASCULITIS	GN	ATN	AIN	POSTRENAL
Specific gravity	High >1.020	Normal/high 1.010–1.020	Normal/high 1.010–1.020	Isosmotic 1.010	Isosmotic 1.010	Isosmotic 1.010
Blood (dip)	Negative	Positive	Positive	±	±	Negative
Protein (dip)	Negative	Positive	Positive	Negative	±	Negative
Sediment examination	Negative, hyaline casts	RBC casts, dysmorphic RBCs	RBC casts, dysmorphic RBCs	Granular casts, RTEs	WBC casts, eosinophils	Negative, sometimes WBCs/RBCs

Abbreviations: ATN, acute tubular necrosis; AIN, acute interstitial nephritis; GN, glomerulonephritis; RBC, red blood cells; RTE, renal tubular epithelial cells; WBC, white blood cells.

Free Tubular Epithelial Cells, Epithelial Cell Casts, and Granular Casts

The patient with acute kidney injury and this combination of urinary findings is likely to suffer from ATN induced by either an ischemic event or administration of a nephrotoxin, or both. The injured tubular cells are sloughed into the tubular lumen and form a cast in combination with Tamm-Horsfall matrix protein. Marked hyperbilirubinemia can also cause this urinary sediment, usually the serum bilirubin level will exceed 10 mg/dL and the dipstick is strongly positive for bile. The cells and casts are also stained with bile.

Free White Blood Cells, White Blood Cell Casts, Granular Casts, and Mild Proteinuria

These urinary findings are seen in patients with tubulointerstitial disease. They include pyelonephritis, drug-induced tubulointerstitial nephritis, and systemic diseases such as sarcoidosis. Rarely, an acute glomerulonephritis or other inflammatory renal disease may have this sediment. Evidence of glomerular disease is, however, also usually present (heme positive, dysmorphic red blood cells) in these disease processes.

Bland Urine Sediment and High-Grade (4+) Proteinuria

This combination of findings on urinalysis suggests the patient has a glomerular lesion associated with the nephrotic syndrome. A bland urine sediment, defined as the absence of cells or casts, suggests a noninflammatory glomerular lesion. Lipiduria with Maltese crosses and fatty casts might also be present in the urine sediment. Some of the glomerular lesions that cause nephrotic syndrome include membranous glomerulonephritis, focal glomerulosclerosis, minimal change disease, membranoproliferative glomerulonephritis, mesangial glomerulonephritis, amyloidosis, and diabetic nephropathy.

QUANTITATIVE URINE MICROSCOPY

Urine microscopy is accepted as an important diagnostic tool for patients with underlying kidney disease. Along with the clinical information, laboratory data, and urinalysis, the presence of certain cells, casts, or crystals in the urine often points to the correct renal diagnosis or at the very least, to a focused differential. Where the diagnosis is unclear, a kidney biopsy or another diagnostic test is performed. The urine sediment findings in this case are qualitative. However, quantitative assessment of the urine sediment also provides important diagnostic and prognostic information when used in the evaluation of prerenal AKI and ATN, the most common causes of hospital-acquired AKI.

TABLE 14-4. Urine Microscopy Scoring System

	GRANULAR CASTS (PER LPF)		
RTE CELLS (PER HPF)	0 (0 POINT)	1 TO 5 (1 POINT)	≥6 (2 POINTS)
0 (0 Point)	0	1	2
1 to 5 (1 Point)	1	2	3
≥6 (2 Points)	2	3	4

Values denote total points awarded.

A urine microscopy scoring system (Table 14.4) as well as the number of renal tubular epithelial cells and renal tubular epithelial cell and granular casts are useful in differentiating prerenal AKI from ATN. The likelihood ratios for ATN increased with increasing numbers of renal tubular epithelial cells or granular casts. In addition, a higher urine microscopy score predicts worsening of kidney function as measured by the Acute Kidney Injury Network classification and increased risk for requiring renal replacement therapy. For example, a score of greater than or equal to 3 versus zero had an adjusted relative risk of 7.3 for worsening AKI. Finally, a higher urine microscopy score in patients with hospital-acquired AKI (including those in the intensive care unit) is associated with a higher risk for in-hospital death, with relative risks increasing with higher scores. Thus, it appears that clinicians can utilize quantitative urine sediment findings to both diagnose and prognosticate most cases of hospital-acquired AKI.

Additional Reading

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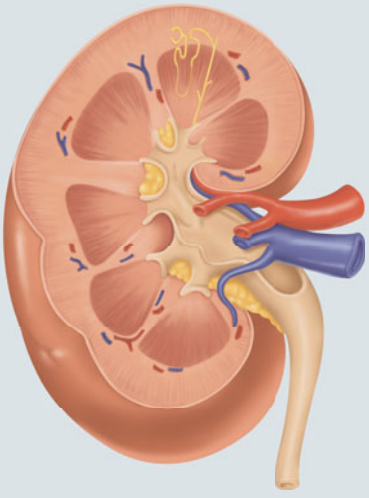

CHAPTER 15

Acute Kidney Injury

• *Mark A. Perazella and Mandana Rastegar*

Recommended Time to Complete: 2 Days

Guiding Questions

1. What is acute kidney injury (AKI)?
2. What tests are currently used to diagnose AKI?
3. What is the best measure of glomerular filtration rate (GFR)?
4. In what clinical situations are blood urea nitrogen (BUN) and serum creatinine concentration poor reflections of GFR?
5. Is community-acquired AKI more common than hospital-acquired AKI?
6. What is a simple yet useful system to categorize AKI in clinical context?
7. What are the principal causes of AKI in each category?
8. What are the clinical tools available to diagnose the etiology of AKI?
9. What are the clinical and biochemical consequences of AKI?
10. What are the best available preventive measures and treatments of AKI in the various categories?

INTRODUCTION

AKI is broadly defined as a rapid deterioration in kidney function as manifested by a reduction in GFR. The term *acute kidney injury* is intended to highlight the potential reversible nature of the injury, whereas the prior term *acute renal failure* (ARF) implicates renal impairment that is sustained. AKI is comprised of a variety of syndromes that are characterized by kidney dysfunction that occurs over hours to days. AKI can occur in the patient with completely normal kidney function or superimposed on chronic kidney disease (CKD). The loss of kidney function results in the accumulation of nitrogenous wastes within body fluids that would otherwise be excreted by the kidneys. The most commonly employed markers of AKI are serum creatinine and BUN, both of which rise in this setting. AKI may also cause disturbances in salt and water balance, potassium and phosphorus retention, acid–base homeostasis, and endocrine abnormalities. Descriptive terms in the setting of AKI include the following:

1. **Azotemia**—A buildup of nitrogenous wastes in blood.
2. **Uremia**—A constellation of symptoms and signs of multiple-organ dysfunction caused by retention of "uremic toxins" in the setting of renal failure.

Urine output is highly variable in the setting of AKI. It is often oliguric (<400 mL/day), but may be nonoliguric, with urine volumes actually exceeding 3 L/day (polyuric). In certain clinical states, urine output will be less than 100 mL/day, defined as oligoanuric or anuric (no urine output). Therefore, it is important to recognize that the presence of urine output does not exclude the possibility of AKI. In general, the level of kidney impairment in AKI includes a spectrum ranging from mild and rapidly reversible to very severe with a prolonged course and often a poor outcome. As is discussed later, the etiology of AKI, as well as the population of patients in which it occurs, determines the ultimate clinical course of AKI.

Prior to 2002 there was not a precise universal definition of AKI. In recent years, 2 evidence-based validated classification systems have been used in clinical settings to define AKI: RIFLE criteria and AKIN staging. The Acute Dialysis Quality Initiative workgroup in 2002 proposed the RIFLE criteria, an acronym that defines AKI with 3 grades of increasing severity (Risk, Injury, Failure) and outlines 2 outcomes variable (Loss and End-stage) (Figure 15.1).

In 2007, the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria, which increases the sensitivity of RIFLE–Risk by including a small absolute change in serum creatinine of greater than 0.3 mg/dL in addition to the prior criteria, which would be AKIN Stage I. AKIN Stage II is identical to the RIFLE–Injury criteria. Finally, any patient receiving renal replacement therapy (RRT) would also be classified as AKIN Stage 3 (RIFLE–Failure). Furthermore, AKIN staging requires that the abrupt change in kidney function be within 48 hours, versus 1 week with RIFLE. Both classification systems incorporate urine output criteria as seen in Figure 15.1.

The addition of an absolute change in serum creatinine of equal to or greater than 0.3 mg/dL is based on epidemiologic data that demonstrated an 80% increase in mortality risk associated with changes in serum creatinine concentrations as little as 0.3 to 0.5 mg/dL. The inclusion of a time constraint of 48 hours is based on data that showed worse outcomes associated with small changes in the serum creatinine when the rise in creatinine was observed within 24 to 48 hours.

The Kidney Disease Improving Global Outcomes (KDIGO) proposed acute kidney diseases and disorders (AKD) as another category of kidney disease that includes AKI alone, AKI superimposed on CKD, AKD without AKI, and AKD superimposed on CKD (Table 15.1). No kidney disease (NKD) is an additional category added by the group. With the additional category of AKD, kidney diseases and disorders that do not meet either AKI

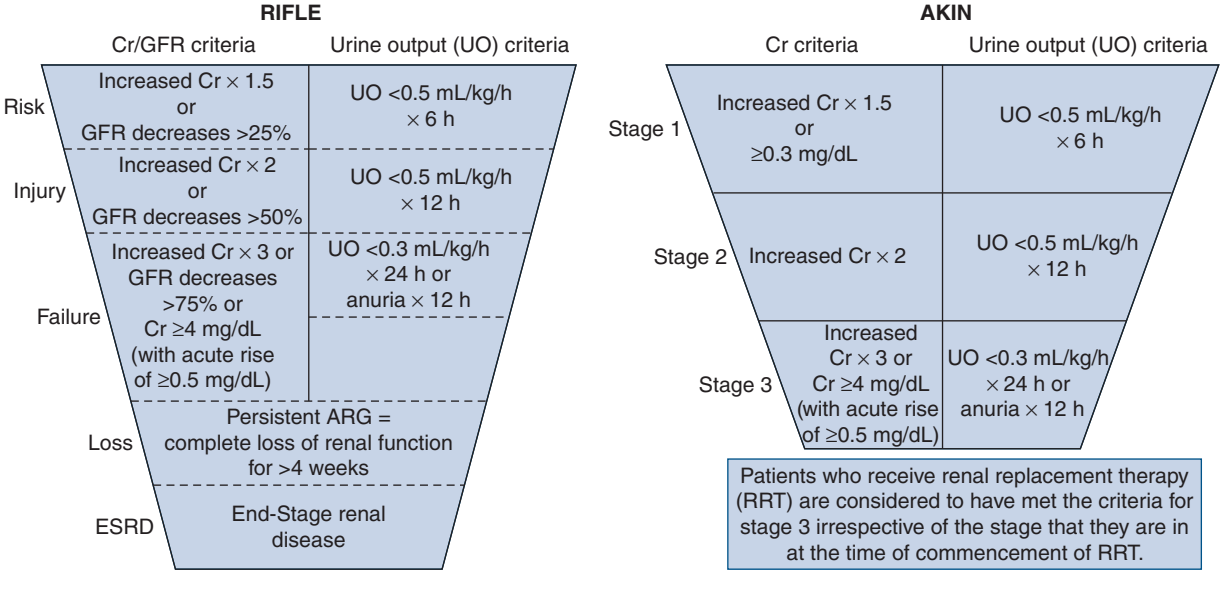

FIGURE 15-1. The RIFLE and AKIN classifications of acute kidney injury are noted. RIFLE is based on serum creatinine, estimated GFR, and urine output. AKIN is based on serum creatinine (Cr) and urine output (UO). (With permission from BioMed Central Publishing. Cruz DN, Ricci Z, Ronco C. *Clinical review: RIFLE and AKIN—time for reappraisal*. Crit Care. 2009;13:211.)

TABLE 15-1. Definitions of AKI, CKD, and AKD

	FUNCTIONAL CRITERIA	STRUCTURAL CRITERIA
AKI	Increase in SCr by 50% within 7 days, *or* Increase in SCr by 0.3 mg/dL within 2 days, *or* Oliguria	No criteria
CKD	GFR <60 mL/min per 1.73 m^2 for >3 months	Kidney damage for >3 months
AKD	AKI, *or* GFR ≤60 mL/min per 1.73 m^2 for <3 months, *or* Decrease in GFR by ≥35% or increase in SCr by >50% for <3 months	Kidney damage for <3 months
NKD	GFR ≥60 mL/min per 1.73 m^2 Stable SCr	No damage

Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no kidney disease; SCr, serum creatinine.

or CKD definition yet, but have alterations in kidney function or structure, can be identified. This approach will allow patients with these kidney disorders to have evaluation and treatment that restores kidney function or reverses kidney damage.

KEY POINTS

Acute Kidney Injury

1. AKI is defined as an abrupt reduction in GFR.
2. Accumulation of nitrogenous wastes, disturbed electrolyte and acid–base balance, and abnormal volume status may result from AKI.
3. AKI may be polyuric, nonoliguric, oliguric, or anuric based on measured levels of urine output for the 24-hour period.
4. Two classification systems are used in clinical settings to define AKI: RIFLE criteria and AKIN staging.
5. Epidemiologic data demonstrate a significant increase in mortality risk associated with changes in serum creatinine concentration of as little as 0.3 to 0.5 mg/dL.
6. In addition to AKI and CKD, AKD is another category of kidney disorder that allows the classification of patients who may need an intervention to restore kidney function or reverse kidney damage.

MEASURES OF KIDNEY FUNCTION

Although serum creatinine concentration is the most commonly employed clinical laboratory measure of kidney function, it actually is a poor reflection of true GFR in many patients. This problem exists because changes in serum creatinine concentration do not precisely correlate with changes in GFR. The concentration of serum creatinine is influenced by a number of factors.

1. In the setting of kidney disease, creatinine is cleared from the body by the kidney through both glomerular filtration and tubular secretion.
2. Certain drugs compete with tubular secretion of creatinine (trimethoprim, cimetidine) and may increase serum creatinine concentration in the absence of any change in GFR.
3. The reported serum creatinine concentration can be falsely elevated by interference with the laboratory technique used to measure creatinine (certain cephalosporins, endogenous chromophores).
4. The gender and muscle mass of the patient influence the serum creatinine concentration and can mask changes in GFR. This results because muscle is the primary source of creatine, which is converted to creatinine in the liver. Female gender and severe muscle wasting will reduce the production of creatine and limit the rise in serum creatinine that would normally accompany a reduction in GFR.

The relationship between BUN and GFR is even more confounded. First, renal handling of urea includes glomerular filtration as well as tubular secretion and reabsorption. Thus, any disease state associated with reduced tubular flow rates will increase urea reabsorption in the kidney and increase BUN. Second, multiple factors increase BUN in the absence of changes in GFR. They include protein loading (total parenteral nutrition, high-protein supplements), hypercatabolic states (infection, steroids, etc.), gastrointestinal (GI) bleeding (reabsorbed blood converted to urea), and tetracycline antibiotics (increase urea generation). Alternatively, BUN may remain very low despite significant kidney dysfunction in states such as cirrhosis (reduced urea generation), poor protein intake, and protein malnutrition, all of which are associated with decreased urea generation.

In spite of the problems associated with serum creatinine and BUN as accurate estimates of GFR, they are the most commonly employed laboratory tests to identify AKI. Clinicians use these less than optimal markers

of kidney function because they are readily available, are familiar to all physicians, and though alternative tests may identify AKI earlier, there has not yet been a commercially standard use of these. Better measures of GFR, such as technetium-labeled iothalamate, are not practical in the acute clinical situation and not widely available. Inulin clearance, the gold standard measure of GFR, is strictly a research tool. Estimates of GFR or creatinine clearance, such as those based on the Modification of Diet in Renal Disease (MDRD) formulas and Cockcroft-Gault formula, were only tested in patients with stable CKD and would probably be inaccurate in the setting of AKI with a rapidly changing GFR.

These above limitations have led to new techniques based on proteomics to identify novel biomarkers of AKI. The goals of biomarker research are earlier diagnosis of AKI, appropriate differential diagnosis of AKI, and prediction of AKI that will worsen, require RRT and associate with higher mortality. Early diagnosis would permit the appropriate preventive and preemptive strategies to be implemented, and treatment regimens offered such that permanent loss of function can be avoided. In patients who develop AKI, biomarker concentrations demonstrate changes earlier than do serum creatinine concentrations (Figure 15.2). Biomarkers may also distinguish between prerenal azotemia (prerenal AKI), acute tubular necrosis (ATN), and other glomerular disorders, allowing appropriate interventions and avoiding potentially harmful therapies such as continued aggressive intravenous fluid therapy in a patient with ATN (risk of volume overload and other end-organ consequences). Finally, the ability of biomarkers to predict outcomes such as worsening kidney function (ie, progression to higher AKIN stages), RRT requirement, and mortality is of highest interest for nephrologists caring for patients with AKI.

The expression of the NGAL (neutrophil gelatinase-associated lipocalin; also called lipocalin-2 or siderocalin) messenger ribonucleic acid and protein in the kidney has been shown to be significantly increased in the kidney tubules of patients with ischemic, septic, or posttransplantation AKI, as well as within 2 to 6 hours post–cardiopulmonary bypass surgery, and even following contrast administration. The cytokine interleukin (IL)-18, which is formed in the proximal tubules and can be detected in the urine, is a candidate biomarker for renal parenchymal injury. Patients with ATN had significantly higher levels of IL-18 in their urine than did control subjects or persons with other forms of kidney disease. Another molecule that is upregulated in postischemic injury in the proximal tubule is kidney injury molecule 1 (KIM-1). Urinary KIM-1 has been suggested as another biomarker for the diagnosis of ischemic ATN. Cystatin C is a protease inhibitor that may be an alternative to serum creatinine in the measurement of renal function of the

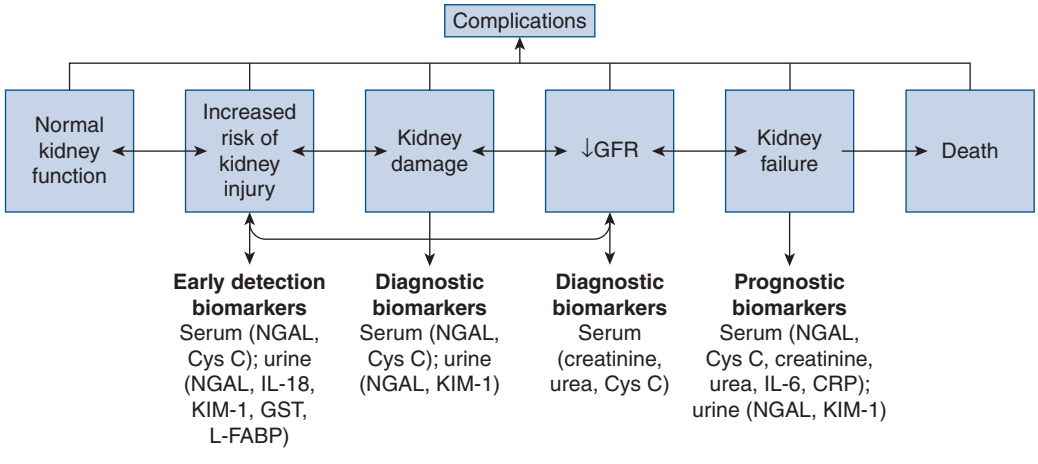

FIGURE 15-2. Evolution of acute kidney injury. Measurement of different biomarkers can detect injury before a decrease in GFR and can also be used for diagnostic and prognostic assessment. *Abbreviations:* CRO, C reactive protein; CysC, cystatin C; GFR, glomerular filtration rate; GST, glutathione-S-transferase; IL-6, interleukin-6; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver fatty-acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin. (With permission from Elsevier. Bellomo R, Kellum JA, Ronco C. *Acute kidney injury*. Lancet. 2012;380:756-766.)

GFR. In contrast to other biomarkers, serum cystatin C levels are usually noted when tissue injury has led to significant changes in the filtration function.

These biomarkers can also be utilized to better identify subsets of patients who would otherwise not be identified as having AKI with our current serum creatinine-based and urine output-based criteria. Biomarkers measured on the day of AKI diagnosis improve risk stratification and identify patients who are at higher risk for progression of AKI and worse patient outcomes. Moreover, by identifying possible mechanisms of injury, novel biomarkers increase our understanding of the pathogenesis of AKI. Further research will be needed for the development and clinical validation of new biomarkers for the eventual definition of kidney injury. As these new biomarkers evolve, so will our understanding of AKI. Presently, these biomarkers are not readily available for clinical use and are under clinical investigation. Whether a panel of biomarkers would provide complementary information and be practical in use compared with a single biomarker approach remains to be determined. Consequently, the clinician should assess the patient with suspected AKI using all of the clinical tools currently available yet recognize their limitations.

KEY POINTS

Measures of Renal Function

1. Serum creatinine and BUN are the most common tests used to identify AKI.
2. An abrupt increase in serum creatinine concentration usually reflects a decline in GFR and signals the development of AKI.
3. Unfortunately, the 2 commonly used laboratory tests suffer from a number of limitations that reduce their accuracy in the estimation of GFR.
4. Factors besides GFR that influence serum creatinine concentration include gender, muscle mass, and certain drugs.
5. In addition to the level of underlying renal function, BUN is influenced by the urea avidity of the kidney (slow urine flow rates), presence of GI bleeding, protein intake, catabolic states, protein malnutrition, and cirrhosis.
6. Novel biomarkers are in development that may allow diagnosis of AKI earlier and elucidate the underlying pathologic damage. In addition, they may also permit improved differential diagnosis of AKI causes and predict several important clinical outcomes.

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

AKI is a frequent problem in hospitalized patients, whereas it is less common in the community setting. Clearly, the actual incidence and outcomes of AKI are dependent on the definition used, as well as the patient population evaluated. A few studies have been published that evaluate the incidence and etiology of community-acquired renal failure, as well as the AKI that develops in hospitalized patients.

In a study designed to examine community-acquired AKI, renal failure was defined as an increase in serum creatinine concentration of 0.5 mg/dL in patients with a baseline less than 2.0 mg/dL, a rise of 1.0 mg/dL in patients with a baseline between 2.0 and 4.9 mg/dL, or a rise of 1.5 mg/dL in patients with a baseline greater than 5.0 mg/dL. The incidence of AKI on admission to the hospital was 0.9%. Approximately half of the patients had AKI superimposed on CKD. Prerenal AKI accounted for 70% of the cases, whereas obstructive uropathy caused 17%. Intrinsic AKI from various etiologies resulted in only 11% of the AKI cases. Overall mortality was 15% in patients with AKI. Mortality was highest in patients with intrinsic kidney failure (55%) and lowest in patients with prerenal azotemia (7%). As will be seen in the discussion of hospital-acquired AKI, the mortality of community-acquired AKI is much less when compared with that seen in the hospital.

Two studies evaluated the incidence of AKI in the hospital. It is worth noting that the incidence of hospital-acquired AKI is higher than that seen with AKI that develops in the community. In a study performed in 1979, the incidence of AKI was 4.9% of all hospital admissions when a definition of AKI similar to the one employed above was used. Once again, prerenal AKI was the most common cause of AKI (42%), whereas postoperative AKI resulted in 18%, radiocontrast material in 12%, and aminoglycosides in 7% of episodes. Overall mortality associated with AKI was 29% and mortality was highest in patients with a serum creatinine concentration greater than 3 mg/dL (64% vs. 3.8% in patients with serum creatinine concentration <2 mg/dL). As noted, this study represents trends in AKI that occurred in the late 1970s. In 1996, the same group of investigators performed a similar study to determine if the incidence of and mortality associated with AKI changed. They postulated that the population of patients studied in this time period were older, possessed higher comorbidities, and received

more nephrotoxic medications, placing them at higher risk for AKI. When compared with the study 20 years earlier, the incidence of hospital-acquired AKI increased slightly to 7.2%. Once again, decreased renal perfusion remained the most common cause of AKI (39%). This was followed by nephrotoxic drugs (aminoglycosides and nonsteroidal antiinflammatory drugs [NSAIDs]) causing 16%, radiocontrast material causing 11%, and postoperative renal impairment causing 9% of the episodes of AKI. CKD was a common underlying risk factor for AKI as compared with patients with normal kidney function. Remarkably, the overall mortality was 19.4%, lower than the mortality noted 20 years prior. This may reflect improved supportive care and advances in several lifesaving technologies. Mortality, however, remained high in patients with serious illnesses, such as sepsis (mortality 76%), when AKI developed. As seen previously, the correlation between severity of AKI and mortality was again observed.

The mortality associated with a hospitalized AKI patient depends on the severity of illness and burden of organ system dysfunction that the patient suffers from. For example, whether quantifying disease severity by number of failed organ systems or Acute Physiology and Chronic Health Evaluation (APACHE) II or III score, the mortality increases as the severity of patient illness increases. As the number of organs failed increased from zero to 4, the mortality associated with AKI increased from less than 40% to above 90%. Similarly, the mortality associated with AKI progressively increased from less than 10% with an APACHE III score less than 50, to 52% with a score of 51 to 70, to 58% with a score of 71 to 90, to 86% with a score of 91 to 110, and to 100% with a score greater than 110. As one might suspect when examining these data, the mortality associated with AKI that develops in the medical or surgical intensive care unit is extremely high.

A metaanalysis that examined long-term outcomes of AKI, defined as at least 6 months of follow-up, published in 2009 summarized that AKI (variable definitions) had an increased long-term risk for death compared to hospitalized patients without AKI (relative risk [RR] 2.62; 95% confidence interval [CI] 1.99 to 3.45). A number of other studies have reported on the long-term impact of AKI on CKD. For example, CKD patients with an eGFR <45 mL/min per 1.73 m^2 pre-hospitalization who experienced severe AKI, defined as RRT-requiring AKI, had a 26.3% rate of death during the hospitalization compared to 4.7% among CKD patients without AKI. Among this population of RRT-requiring AKI patients with underlying CKD, within 30 days of discharge 66% or survivors received a diagnosis of ESRD compared to 1.5% of non-AKI survivors. Another study examined patients with preserved kidney function, an enhanced GFR (eGFR) greater than 45 mL/min per 1.73 m^2 who did not develop AKI and those who developed RRT-requiring AKI. The RRT-requiring AKI group had a 28-fold increased risk of CKD progression. Several studies examining the outcomes of hospital-acquired reversible AKI (within 48 to 72 hours) demonstrated higher mortality rates compared with patients with nonprogressive community-acquired AKI and with control patients without AKI. Combined, these studies suggest that all forms of AKI, including the RRT-requiring forms, appear to be associated with an increased risk for development of new CKD, progression of CKD, end-stage renal disease (ESRD) and death. It is important to recall, however, that many of these studies suffer from various forms of confounding, making it hard to definitively state that AKI in and of itself leads to CKD/ESRD and mortality.

KEY POINTS

Epidemiology of Acute Kidney Injury

1. The incidence of AKI varies depending on whether it occurs in the hospital (5% to 7%) or in the community setting (0.9%).
2. Prerenal AKI is the most common cause of AKI in patients with either community- or hospital-acquired AKI.
3. Obstructive uropathy is the second leading cause of AKI in community-acquired kidney failure, whereas drug nephrotoxicity and postoperative AKI are the next most common causes in hospitalized patients.
4. The overall mortality associated with AKI is higher with hospitalized AKI (19% to 29%) than community-acquired AKI (15%).
5. The mortality associated with AKI increases as the severity of patient illness increases (up to 100%).
6. It appears that AKI is associated with increased risk for new-onset CKD, progression of CKD, ESRD, and mortality. However, confounding factors in these studies prevent definitive statements on causation.

CLINICAL ASSESSMENT OF ACUTE KIDNEY INJURY

Table 15.2 provides a list of the etiologies of AKI classified as prerenal, intrinsic renal, or postrenal. Figure 15.3 is a schematic of the various causes of AKI. A logical approach to AKI is achieved by broadly classifying the clinical causes into the following:

1. **Prerenal AKI**—A decrease in GFR that occurs as a consequence of reduced renal blood (plasma) flow and/or reduced renal perfusion pressure.
2. **Intrinsic AKI**—A decrease in GFR as a result of direct parenchymal injury in the kidney, often subdivided by the various compartments involved (vascular, glomerular, interstitial, and tubular).
3. **Postrenal AKI**—A decrease in GFR primarily as a result of an obstruction to urine flow anywhere from the pelvis and calyces to the urethra.

TABLE 15-2. Etiologies of Acute Kidney Injury

Prerenal
"True" volume depletion
Extrarenal losses
Nausea/vomiting
Diarrhea, external fistulae
Renal losses
Overdiuresis
Renal salt wasting
Diabetes insipidus
"Effective" volume depletion
Sepsis
Cardiomyopathy
Cirrhosis/hepatic insufficiency
Nephrotic syndrome
Structural renal artery/arteriolar disease
Renal artery stenosis, arteriolonephrosclerosis
Altered intrarenal hemodynamics
NSAIDs, calcineurin inhibitors, ACE inhibitors, ARBs
Intrarenal
Vascular disease
Arterial, arteriolar, venous
Glomerular disease
Acute glomerulonephritis (immune complex, vasculitis, anti-GBM)
Thrombotic microangiopathy (TTP/HUS)
Monoclonal immunoglobulin deposition disease
Acute tubular necrosis
Nephrotoxic
Ischemic
Pigment-related
Crystal-associated nephropathy
Osmotic nephropathy
Acute interstitial nephritis
Medication-induced
Infection (viral, fungal, bacterial)
Systemic diseases
Postrenal
Pelvic/ureteral obstruction
Retroperitoneal disease
Nephrolithiasis
Fungus balls, blood clots
Bladder obstruction
Structural (stones, benign prostatic hyperplasia, blood clots)
Functional (neuropathic, drugs)
Urethral obstruction

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GBM, glomerular basement membrane; HUS, hemolytic uremic syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; TTP, thrombotic thrombocytopenic purpura.

Prerenal AKI

AKI is classified as prerenal AKI when a patient exhibits a rising BUN and serum creatinine concentration caused by inadequate blood flow to the kidneys. To provide a framework to understand the concept of prerenal AKI, the following description of renal blood flow (RBF) is provided. The kidneys receive up to 25% of the cardiac output, which results in more than 1 L of RBF per minute. This high rate is necessary to not only maintain GFR, but also to preserve renal oxygen delivery (to sustain

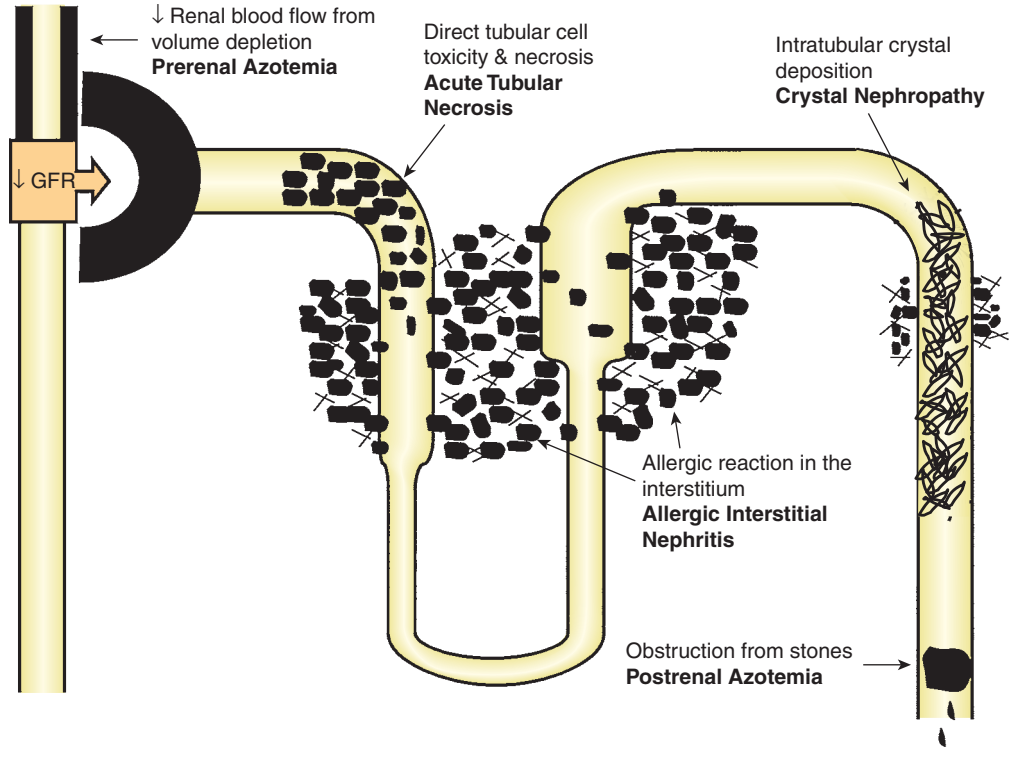

FIGURE 15-3. Etiologies of acute kidney injury. Common causes of acute kidney injury are noted in this schematic.

ion transport and other energy-requiring processes). Thus, normal kidney function is dependent on adequate perfusion. It is intuitive that a significant reduction in renal perfusion may be sufficient to diminish filtration pressure and lower GFR. Broad examples of prerenal AKI include the following causes of renal circulatory insufficiency:

1. Renal circulatory insufficiency from "true" intravascular volume depletion.
   a. Hypovolemia from hemorrhage, renal losses (diuretics), GI losses (vomiting, diarrhea), third spacing, and severe sweating.
2. Renal circulatory insufficiency from "effective" intravascular volume depletion.
   a. Impaired cardiac function from cardiomyopathy, hypertensive heart disease, valvular heart disease, pericardial disease, and severe pulmonary hypertension. Venous congestion from hypervolemia also contributes to reduced renal perfusion and reduced GFR.
   b. Impaired liver function from acute hepatic failure and severe cirrhosis with hepatorenal physiology.
   c. Impaired systemic vascular tone (inappropriate vasodilation) because of sepsis, medications, and autonomic failure.
3. Renal circulatory insufficiency caused by renal artery disease.
   a. Main renal artery disease (renal artery stenosis).
   b. Small renal vessel narrowing (hypertensive arteriolonephrosclerosis).
4. Renal circulatory insufficiency caused by altered intrarenal hemodynamics.
   a. Afferent arteriolar vasoconstriction (NSAIDs, calcineurin inhibitors).
   b. Efferent arteriolar vasodilation (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]).

Both "true" and "effective" hypovolemia activate several neurohormonal vasoconstrictor systems as

mechanisms to protect circulatory stability. These include catecholamines from the sympathetic nervous system, endothelin from the vasculature, angiotensin II (AII) from the renin-angiotensin system (RAS), and vasopressin from the neurohypophysis. All of these substances raise blood pressure through arterial and venous constriction. They also possess, however, the ability to constrict the afferent arteriole and reduce GFR, especially when systemic blood pressure is inadequate to maintain renal perfusion pressure. Structural lesions in the renal arterial and arteriolar tree can also reduce perfusion and promote prerenal azotemia. In response to these hemodynamic challenges, renal adaptive responses are stimulated to counterbalance diminished renal perfusion, whether as a result of functional or structural causes. Myogenic influences and the production of vasodilator substances constitute these adaptive processes. The myogenic reflex is activated by low distending pressures sensed in the renal baroreceptors, thereby causing afferent arteriolar vasodilation. Prostaglandins (PGE_2, PGI_2), nitric oxide, and products from the kallikrein-kinin system modify the effects of above-noted vasoconstrictors on the afferent arteriole. Disturbance of the balance between afferent vasodilation and efferent vasoconstriction can disrupt intrarenal hemodynamics and precipitate AKI. Medications such as the NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors act to cause prerenal azotemia through inhibition of vasodilatory prostaglandins in patients who require prostaglandin effects to maintain renal perfusion. Despite its vasoconstrictor properties, AII acutely preserves glomerular filtration pressure and GFR in states of reduced renal perfusion by constricting the efferent arteriole. This effect in part explains the reduction in GFR that occurs when an ACE inhibitor or an ARB is administered to a patient who is dependent on AII to constrict the efferent arteriole.

The cardiorenal syndrome (CRS) is an umbrella term that encompasses various cardiac or kidney derangements that coexist and their interplay. There are 5 subtypes of the CRS (Table 15.3). Hospital-acquired AKI caused by CRS is most often that of the type I variety. For example reduced stroke volume or cardiac output, arterial underfilling, elevated atrial pressures, and venous congestion, independently or in combination, cause impairments in the renal circulation, causing a reduction in GFR and AKI. The neurohumoral adaptations that occur to preserve perfusion to vital organs, such as activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) as well as increases in the release of vasopressin and endothelin-1, promoting salt and water retention and systemic vasoconstriction, can promote or exacerbate AKI by 2 mechanisms. First, these neurohormonal adaptations increase cardiac afterload and further reduce cardiac output and renal perfusion, and second, they increase central venous pressure, renal venous pressure and/or intraabdominal pressure, ultimately lowering GFR. Identifying AKI in the setting of heart failure is clinically relevant because reduced GFR is generally associated with a worse prognosis in these patients.

TABLE 15-3. Definition and Classification of the Cardiorenal Syndrome

CRS Type 1	Acute worsening of cardiac function leading to renal dysfunction
CRS Type 2	Chronic abnormalities in cardiac function leading to renal dysfunction
CRS Type 3	Acute worsening of renal function causing cardiac dysfunction
CRS Type 4	Chronic abnormalities in renal function leading to cardiac disease
CRS Type 5	Systemic conditions causing simultaneous cardiac and renal dysfunction

Just as there is a strong physiologic interplay between cardiac dysfunction and kidney impairment, there is a strong association with liver disease and kidney impairment. In patients with advanced, decompensated cirrhosis or fulminant hepatic failure, a unique form of AKI, termed *hepatorenal syndrome* (HRS) may occur. It is important to note, that HRS is only a fraction of all AKI cases in cirrhotic patients and is a diagnosis of exclusion (that is difficult to firmly make). Table 15.4 summarizes the diagnostic criteria for HRS. There are 2 subtypes of HRS: Type 1 HRS is characterized by rapidly progressive renal failure defined by doubling of the initial serum creatinine concentrations to a level greater than 2.5 mg/dL in less than 2 weeks. Type 2 HRS is characterized by moderate renal failure (serum creatinine from 1.5 to 2.5 mg/dL). The hallmark of HRS is profound renal vasoconstriction in the setting of systemic and splanchnic arterial vasodilation. Figure 15.4

TABLE 15-4. Hepatorenal Syndrome Criteria

Cirrhosis with ascites
Serum creatinine >1.5 mg/dL
No improvement of serum creatinine (decrease to a level of 1.5 mg/dL) after at least 2 days with diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

summarizes the hemodynamic changes that occur in HRS. Currently, there is no test that is specific for the diagnosis of HRS. The main differential diagnoses of type 1 HRS are ATN and prerenal AKI, as all of these conditions have an acute onset with progressive deterioration of kidney function. Although prerenal AKI can generally be recognized by response to intravenous fluids (albumin and saline), HRS type 1 and ATN are more problematic. Traditional markers such as urine microscopy (renal tubular cells and granular casts) and urine chemistries (fractional excretion of sodium or urea) to differentiate ATN from HRS are sometimes helpful, but can be insensitive. Therefore urinary biomarkers, including IL-18, NGAL, KIM-1, and others, are currently under investigation to differentiate between type 1 HRS and ATN. This is crucial as therapy for these 2 causes of AKI are very different—midodrine and octreotide, norepinephrine (or vasopressin) for HRS and supportive therapy for ATN. Liver transplantation (or combined liver-kidney transplantation) is the definitive therapy for HRS. Determining the etiology of AKI in cirrhotic patients is also critical for prognosis as HRS carries the worst survival among all causes of AKI in cirrhotic patients. It also heavily influences decisions such as the candidacy of a patient for liver transplantation and the utility of RRT in these patients.

In general, prompt correction of the underlying hemodynamic insult causing the reduction in renal perfusion in prerenal AKI will result in rapid correction of RBF and GFR. This ultimately prevents structural kidney

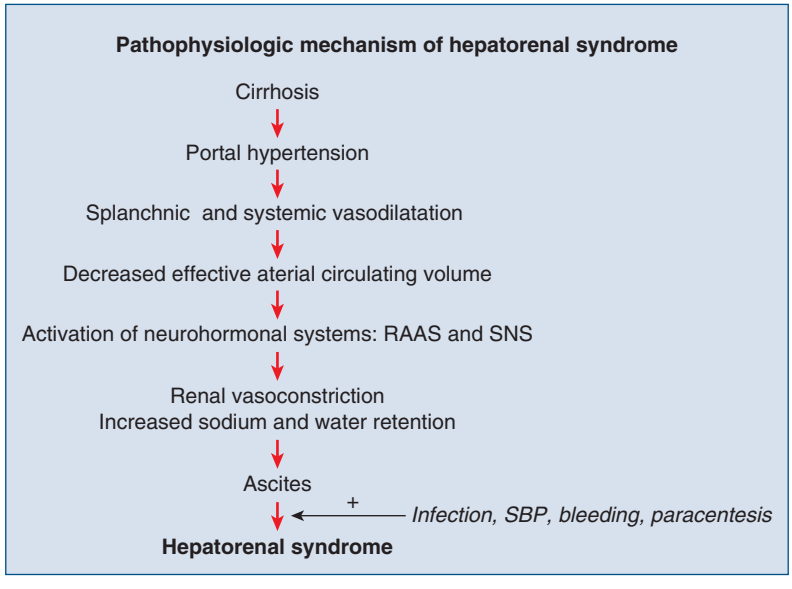

FIGURE 15-4. Pathophysiology of hepatorenal syndrome. In cirrhosis, portal hypertension gives rise to compensatory splanchnic vasodilation, which creates a state of decreased effective circulating volume. In response, the RAAS and the SNS are activated, increasing renal sodium avidity, worsening ascites, and causing severe intrarenal vasoconstriction, the hallmark of HRS. *Abbreviations:* SBP, spontaneous bacterial peritonitis; SNS, sympathetic nervous system.

damage in the form of ischemic renal tubular necrosis and preserves tubular function. Recognizing that renal tubular function remains intact is important. In prerenal azotemia, the tubules will reabsorb sodium avidly and maximally concentrate the urine. This protective mechanism preserves intravascular volume, sometimes appropriately as with "true" volume depletion and at other times inappropriately with congestive heart failure and HRS.

This tubular effect on the urine sodium and water is useful to identify prerenal azotemia as a cause or contributor to AKI. The urine sodium is usually less than 10 mEq/L and the urine osmolarity is very high (greater than plasma). The ratio of the clearance of sodium to creatinine (fractional excretion of sodium or FENa) is calculated as follows: FENa = $(U_{Na}/P_{Na}) \times (P_{Cr}/U_{Cr}) \times 100$ (expressed in percent) (where U_{Na} = urinary sodium; P_{Na} = plasma sodium; U_{Cr} = urinary creatinine; P_{Cr} = plasma creatinine). The FENa is generally useful to separate prerenal azotemia from other causes of AKI. A FENa less than 1% supports a diagnosis of prerenal azotemia and a FENa greater than 2% suggests other causes of AKI. The fractional excretion of urea (FEUrea) is employed to separate prerenal azotemia from ATN in patients who have received diuretics. It is calculated from the formula FEUrea = $(U_{Urea}/P_{Urea}) \times (P_{Cr}/U_{Cr}) \times 100$ (where U_{Urea} = urinary urea; P_{Urea} = plasma urea). A FEUrea greater than 50% suggests ATN, whereas a level less than 35% supports prerenal azotemia. The renal failure index (RFI) is another equation used to separate prerenal azotemia (<1%) from AKI as a result of other causes (>2%). Its formula is RFI = $U_{Na} \times (P_{Cr}/U_{Cr}) \times 100$. The urinalysis is unrevealing and the urine sediment is typically bland without renal tubular epithelial cells (RTEs), protein, or casts in prerenal azotemia. In fact, the absence of RTE and granular casts has a high likelihood ratio for prerenal AKI and a negative predictive value for ATN greater than 90%. As is discussed later, prolonged and uncorrected prerenal AKI can sometimes result in ATN from ischemic-induced injury. Ischemic ATN will change the clinical picture of AKI. The course of AKI will likely be protracted as compared with prerenal azotemia. In addition, injured renal tubules will no longer have the capacity to reabsorb sodium and water, resulting in a FENa greater than 2% and a urine osmolarity fixed around 300 mOsm. This entity is more fully discussed in the intrinsic renal azotemia section.

KEY POINTS

Prerenal Acute Kidney Injury

1. Prerenal AKI occurs when RBF is reduced and causes a reduction in GFR and associated AKI.
2. Prerenal AKI is broadly classified on the basis of intravascular volume depletion (true vs. effective), the presence of structural lesions in the renal arterial/arteriolar system, and altered intrarenal hemodynamics.
3. CRS type 1 is a form of prerenal AKI whose mechanism of kidney dysfunction includes both impaired renal perfusion and venous hypertension. Therapy is baed on improving cardiac output, reducing elevated neurohormones, and fluid removal to improve renal venous hypertension.
4. HRS is occurs in decompensated cirrhosis or fulminant hepatic failure and is another form of prerenal AKI. It is difficult to distinguish from ATN and requires specific therapy and ultimately liver transplantation (or combined liver-kidney transplantation).
5. The urine sodium and osmolarity, the FENa, FEUrea, and the RFI may be useful to help distinguish prerenal AKI from other causes of AKI, but they are not optimally specific or sensitive tests. The FENa, and the RFI are both less than 1% with most cases of prerenal AKI, while FEUrea is less than 35%. Urine microscopy is useful in differential diagnosis of AKI, and has good positive and negative predictive values for prerenal AKI and ATN.
6. Rapid identification and prompt correction of the prerenal disturbance often improves kidney function quickly. Thus early diagnosis is critical, raising a potential role for novel biomarkers in the AKI setting.

Intrinsic Renal Acute Kidney Injury

AKI that arises from a process that damages one of the compartments of the renal parenchyma is called *intrinsic AKI*. For ease of organization and simplicity, the renal compartments are divided into the following anatomic sites of injury:

1. Vasculature
   a. Artery (thrombosis superimposed on stenotic renal arterial lesion, thromboembolism with renal artery occlusion, renal artery dissection, large- and medium-vessel vasculitis)

   b. Arteriole (atheroemboli, vasculitis, scleroderma kidney, fibrinoid necrosis from malignant hypertension, septic emboli)
   c. Venous (renal vein thrombosis)
2. Glomerulus
   a. Acute proliferative glomerulonephritis (immune complex, vasculitis, antiglomerular basement antibody)
   b. Thrombotic microangiopathy (hemolytic uremic syndrome [HUS]/thrombotic thrombocytopenic purpura [TTP])
   c. Monoclonal immunoglobulin deposition disease (light/heavy chain, amyloid, fibrillary/immunotactoid)
3. Tubules
   a. ATN (ischemic, nephrotoxic)
   b. Pigment nephropathy (hemoglobin, myoglobin)
   c. Crystal deposition (medications, uric acid, calcium oxalate, and phosphate)
   d. Osmotic nephropathy (sucrose, intravenous immune globulin [IVIG], hydroxyethyl starch, dextran, mannitol)
4. Interstitium
   a. Acute (allergic) interstitial nephritis (drugs)
   b. Infection-induced interstitial nephritis (viral, bacterial, tuberculosis, rickettsial)
   c. Systemic diseases associated with interstitial nephritis (sarcoid, systemic lupus erythematosus [SLE], Sjögren)
   d. Malignant interstitial infiltration
   e. Idiopathic interstitial nephritis

Vasculature

Disease of the blood vessels leading to the kidneys (large- and medium-size arteries), within the renal parenchyma (small arteries and arterioles), and draining the kidneys (veins) may cause AKI. Large-vessel arterial disease that causes AKI consists of the following: (a) thrombosis superimposed on a high-grade renal artery stenosis (unilateral in a single functioning kidney or bilateral disease), (b) significant thromboembolism from the heart or an aortic aneurysm causing occlusion of the renal arteries, or (c) dissection of the renal arteries from some form of trauma or collagen vascular disorder. Patients with these renal disorders often present with flank or abdominal pain, fever, hematuria if urine is still formed, and oligoanuria or anuria. Laboratory testing reveals elevations in serum and urine lactate dehydrogenase (LDH), urinalysis with positive blood, and many red blood cells present in the urine sediment. If caught early enough, treatment of thrombosis and thromboembolism is administration of thrombolytic agents to dissolve clot and restore RBF. Long-term anticoagulation may be required to prevent further renal embolization from the heart. Surgical repair of an aortic aneurysm may be indicated, while percutaneous angioplasty with probable stent placement is a relatively noninvasive procedure to correct significant renal artery stenosis. In certain centers, surgical revascularization of the kidney may be more appropriate. A renal artery dissection clearly is an indication for surgical repair. Vasculitis may affect the large renal blood vessels in Takayasu arteritis and giant cell arteritis. More commonly, the small arterial vessels and arterioles are injured by vasculitis, as discussed below.

Embolization of atheromatous material to the interlobar, arcuate, and interlobular arteries in the kidneys induces ischemic injury in downstream tissue while also eliciting a giant cell reaction in the interstitium surrounding the occluded vessel (Figure 15.5). Debris from ulcerated plaques in the aorta and renal arteries are composed primarily of cholesterol crystals. Embolization of the crystals occurs most commonly from invasive procedures (percutaneous arterial interventions and vascular surgery) that disrupt the fibrous cap on the ulcerated plaque, however, thrombolytic therapy and therapeutic anticoagulation can also precipitate embolization. Rarely, this process occurs spontaneously in patients with significant burden of renal artery or aortic plaque. The clinical manifestations of atheroembolic disease include abrupt onset of severe hypertension, acute or subacute kidney injury, livedo reticularis, digital/limb ischemia, abdominal pain (pancreatitis or bowel ischemia), GI bleeding, muscle pain, central nervous system (CNS) symptoms (focal neurologic deficits, confusion, amaurosis fugax), and retinal ischemic symptoms. The presenting symptoms depend on the extent and distribution of the cholesterol embolization. Peripheral eosinophilia, hypocomplementemia, elevated sedimentation rate, and eosinophiluria variably accompany the syndrome, while urinary findings range from bland to varying levels of cylindruria and proteinuria (occasionally nephrotic proteinuria). Diagnosis of this syndrome can be confused by intravenous contrast

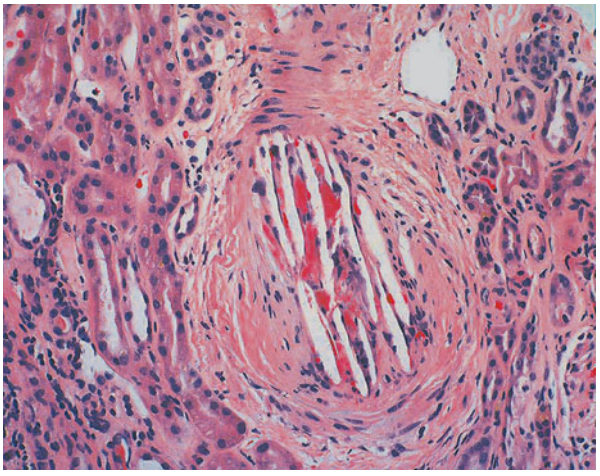

FIGURE 15-5. Atheroembolic renal disease. Clefts of atheromatous material occlude the vessel lumen and cause acute kidney injury in the setting of cholesterol emboli. (Courtesy of Michael Kashgarian.)

administration at the time of the invasive procedure. The time course of contrast nephropathy, however, is different from cholesterol emboli. Contrast-associated AKI develops within 48 hours, peaks within approximately a week, and then recovers over the next several days. In contrast, cholesterol emboli-induced AKI follows a more protracted course of renal failure with infrequent recovery, development of CKD, and sometimes progression to ESRD. In addition to the clinical and laboratory findings noted, cholesterol embolization syndrome is diagnosed with biopsy of involved organs including kidneys and skin. Treatment is based primarily on prevention by avoiding the factors known to precipitate atheroembolization, especially in patients with severe vascular disease. Supportive care with blood pressure control, amputation of necrotic limbs, aggressive nutrition, avoidance of anticoagulation (reduce risk for further embolization), and dialytic support for severe renal failure improves the dismal prognosis associated with this syndrome. Steroids have been used to treat the inflammatory lesion that accompanies renal atheroembolism. A small number of reports describe benefit with steroids, as well as iloprost.

Macroscopic polyarteritis nodosa (PAN) causes arterial injury in medium and small vessels. It is typically idiopathic or may be associated with hepatitis B antigenemia. This type of PAN presents with severe hypertension and renal failure. Diagnosis is confirmed by renal arteriogram demonstrating beading in the arterial tree of the kidney. Disease can also occur in other arterial beds, causing symptoms attributable to disease specific to the affected organ. Scleroderma is a systemic disorder characterized by narrowing of the arteries from the deposition of mucinous material. Multiple organs may be involved including the lungs, heart, GI tract, and skin. Scleroderma renal crisis manifests as AKI and severe hypertension in a patient with a flaring of their disease. ACE inhibitors are an effective therapy to control blood pressure and improve renal function. Poorly controlled or untreated hypertension can cause AKI from severe renal injury related to malignant hypertension. Fibrinoid necrosis with ischemic injury occurs in the kidney. Initial blood pressure control is associated with worsening renal function because the autoregulatory capability of the kidney is impaired and renal perfusion is solely dependent on systemic pressure. Over time, renal function improves. The thrombotic microangiopathies can also promote arteriolar as well as glomerular capillary thrombosis. Treatment is usually plasmapheresis, plasma exchange, blood pressure control, dialysis when required, and avoidance of platelet transfusions.

Renal vein thrombosis is a complication of nephrotic syndrome, especially when the underlying glomerular lesion is membranous nephropathy. Loss of anticoagulant substances in the urine (antithrombin 3, plasminogen activator inhibitor) and increased production of procoagulants (tissue plasminogen activator, fibrinogen) underlies the development of a hypercoagulable state. Thrombosis of the renal vein is thought to cause AKI through raised intrarenal pressures and reduced renal perfusion. Treatment of renal vein thrombosis is thrombolysis and anticoagulation, as well as remission of the underlying glomerular lesion and reduction in proteinuria.

KEY POINTS

Vasculature

1. Intrinsic renal disease is categorized by anatomic compartments that have been acutely injured. They include the vasculature, glomerulus, tubules, and interstitium.
2. AKI from large-vessel arterial disease occurs most commonly from thrombosis of preexisting renal artery stenosis or thromboembolism from a cardiac thrombus.

3. Atheroembolic disease causes systemic disease from occlusion of small arteries and arterioles, inducing end-organ ischemia. Renal atheroemboli is associated with AKI, hypertension, and variable findings in the urine sediment ranging from minor cylindruria to eosinophiluria and proteinuria.
4. Macroscopic PAN presents with severe hypertension and AKI. Arteriogram of the renal arteries reveals a characteristic beading pattern.
5. Scleroderma renal crisis also presents with severe hypertension and AKI. ACE inhibitors are the treatment of choice for this disease.
6. Renal vein thrombosis complicates heavy proteinuria, especially with membranous nephropathy. AKI likely results from reduced renal perfusion.

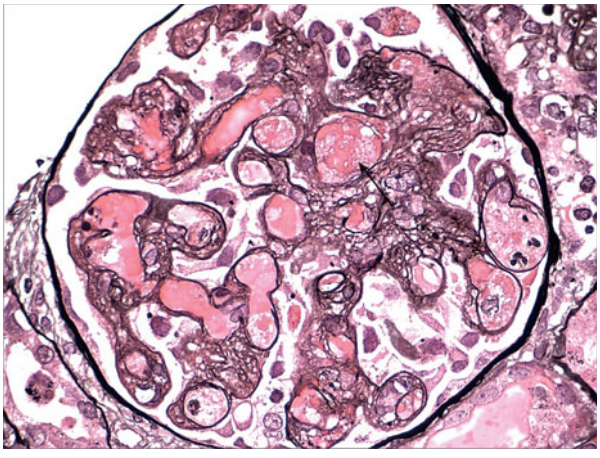

FIGURE 15-6. Histopathology of thrombotic microangiopathy. As seen in this glomerulus, capillary loops are occluded with microthrombi associated with thrombotic microangiopathy. An occluded capillary loop is shown by the arrow. (Courtesy of Glen S. Markowitz.)

Glomerulus

Glomerular diseases occur through various mechanisms. Acute proliferative glomerulonephritis may be classified as immune complex, pauci immune, or anti–glomerular basement membrane (GBM)-related disease. This group of diseases is characterized by glomerular cell proliferation and necrosis, polymorphonuclear cell infiltration, and with severe injury, epithelial crescent formation. TTP and HUS are 2 of the more common causes of thrombotic microangiopathy. Platelet deposition and endothelial injury with thrombosis of arterioles and glomerular capillaries underlie the kidney injury associated with thrombotic microangiopathies. Glomerular damage can be severe with profound ischemia and necrosis (Figure 15.6). Deposition of monoclonal immunoglobulin light and/or heavy chains may also promote glomerular lesions. The type of immunoglobulin, as well as the metabolism and packaging of the immunoglobulin determine which type of glomerular lesion develops. Light-chain deposition disease, heavy-chain deposition disease, and light/heavy-chain deposition disease have all been described to cause nodular glomerular lesions. Similarly, amyloidosis forms glomerular nodules. These diseases are separated by appearance on electron microscopy. Light- and heavy-chain diseases have granular deposits, whereas amyloidosis appears as haphazard fibrils in the 8- to 12-nm size range. The fibrillary glomerulonephritides (fibrillar and immunotactoid) are sometimes associated with mesangial expansion or glomerular nodules. They more commonly appear as a mesangial proliferative, mesangiocapillary, or membranous lesion. At times, crescents are also present. They are also distinguished from amyloidosis by a larger fibril size (fibrillary: 20 nm; immunotactoid: 30 to 50 nm) and organized microtubular fibrils (immunotactoid only) seen on electron microscopy.

Acute proliferative glomerulonephritis presents with hematuria and proteinuria, described as a nephritic sediment. Examination of the urine sediment under the microscope classically reveals dysmorphic red blood cells and red blood cell casts. AKI is typically present, as are hypertension and edema formation. The thrombotic microangiopathies may also present with a nephritic sediment. AKI may be severe, as seen with HUS or may be mild, as noted with TTP. A microangiopathic hemolytic anemia and thrombocytopenia are key features of this disease complex. The immunoglobulin deposition diseases more often manifest with nephrotic proteinuria and renal failure. On very rare occasions, these diseases will have hematuria. The glomerular diseases are covered more fully in Chapter 17 dedicated to these diseases.

KEY POINTS

Glomerulus

1. Acute proliferative glomerulonephritis may result from an immune complex disease, pauci immune vasculitis, or anti–GBM-related disease.

2. The clinical presentation of this renal lesion is hypertension, azotemia, and a nephritic urinary sediment.
3. Other glomerular lesions associated with AKI include the thrombotic microangiopathies and monoclonal immunoglobulin deposition diseases.

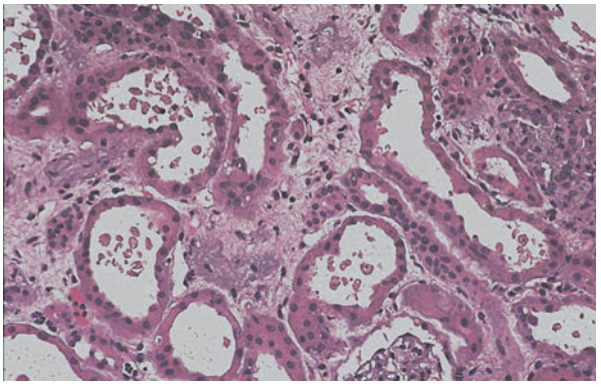

FIGURE 15-7. Histopathology of ATN. ATN is characterized by tubular injury with cellular blebbing, necrosis and sloughing of cells in the tubular lumen. (Courtesy of Michael Kashgarian.)

Tubules

ATN, also referred to as acute tubular injury (ATI), is the most common form of intrinsic renal azotemia (Figure 15.7). It probably accounts for greater than 80% of the episodes of intrinsic renal disease. It is classically divided into ischemic, which makes up 50% of ATN, and nephrotoxic ATN, which constitutes the remainder of cases. In many instances, ATN results from multiple insults acting together to induce multifactorial renal injury. The end result of either ischemic or toxic insult is tubular cell necrosis and death. Table 15.5 outlines the important factors underlying the pathogenesis of ATN.

Ischemic ATN is an extension of severe and uncorrected prerenal azotemia. Prolonged renal hypoperfusion causes tubular cell injury, which persists even after the underlying hemodynamic insult resolves. Various etiologies precipitate ischemic ATN. Surgical causes include intraoperative and postoperative hypotension with impaired renal perfusion. This occurs relatively frequently following cardiac and vascular surgical procedures. Obstructive jaundice also appears to increase the risk of ischemic ATN. In the medical intensive care unit and on the medical wards, ischemic and multifactorial ATN is common. This relates to the severe comorbidities these patients manifest. Superimposition of sepsis with or without shock, severe intravascular volume depletion from hemorrhage or GI/renal losses, or cardiogenic shock can induce severe ischemic ATN. Employment of

TABLE 15-5. Pathogenesis of Acute Tubular Necrosis

INTRARENAL HEMODYNAMICS AND VASOCONSTRICTION	TUBULAR CELL INJURY AND NECROSIS	REPERFUSION INJURY FROM INFILTRATING LEUKOCYTES AND T CELLS	ROLE OF GROWTH FACTORS IN RENAL INJURY
Elevated endothelin, increased sympathetic discharge, reduced nitric oxide, loss of renal autoregulation	Disruption of actin cytoskeleton with loss of cell polarity	Recruitment of neutrophils and adhesion of cells, release of reactive oxygen species, proteases, elastases, other enzymes	Growth factors participate in regenerative process after ischemic injury
Reduction in cortical and medullary blood flow	Generation of reactive oxygen species	Infiltration of T lymphocytes → unknown mechanism of injury	Growth factors may also promote renal injury
Ischemic tubular injury with apoptosis and cell necrosis	Tubular shedding Backleak of filtrate Cast formation with tubular obstruction	Tubular cell death, interstitial inflammatory infiltrate with fibrosis	Augmentation of tubulointerstitial injury and fibrosis

vasopressors to restore blood pressure further reduces renal perfusion. In some cases, ischemic ATN is so profound that cortical necrosis (ischemic atrophy of the renal cortex) develops.

Nephrotoxic ATN occurs when either endogenous or exogenous substances injure the tubules. Tubular toxicity occurs through direct toxic effects of the offending substance, changes in intrarenal hemodynamics, or a combination of these effects. Organic solvents and heavy metals (mercury, cadmium, lead) were a frequent cause of ATN in the past. Over time, many drugs with toxic potential were synthesized and noted to cause tubular injury by multiple mechanisms. Aminoglycoside antibiotics cause proximal tubular injury. These drugs are reabsorbed into the cell by pinocytosis. Once intracellular, they promote cell injury and death, leading to clinical ATN and AKI. It is notable that ATN from aminoglycosides rarely develop within the first week of therapy. The antifungal agent amphotericin B destroys cellular membranes through sterol interactions. A component of tubular ischemia also contributes via acute afferent arteriolar constriction. ATN develops in a dose-dependent fashion. Newer formulations (liposomal, lipid complex) are less nephrotoxic, but can also precipitate AKI in high-risk patients. Radiocontrast material is a common cause of AKI because it is so widely employed with imaging procedures. Radiocontrast nephropathy develops in patients with underlying risk factors such as kidney disease, especially diabetic nephropathy, and "true" and "effective" intravascular volume depletion. In patients with normal kidney function, the risk for contrast-induced AKI is low, less than 2%, however, the incidence may be as high as 25% in patients with preexisting renal impairment with or without a combination of other risk factors such as diabetes, congestive heart failure (CHF), advanced age, and concurrent administration of nephrotoxic drugs. Radiocontrast causes ATN through both ischemic tubular injury (prolonged decrease in RBF) and direct toxicity (osmotic cellular injury). Large volumes of contrast clearly increase risk, while low osmolar and isoosmolar radiocontrast reduce the incidence of dye-induced AKI. Drugs such as the antiviral agents, cidofovir and tenofovir cause AKI through disruption of mitochondrial and other cellular functions following their uptake from the peritubular blood into the cell via the human organic anion transporter-1 on the basolateral membrane. Other drugs noted to cause nephrotoxic ATN include several chemotherapeutic agents (platinum-based drugs, ifosfamide, mithramycin, imatinib, pentostatin, and pemetrexed), zoledronate, aminoglycosides, polymyxins, high-dose vancomycin, foscarnet, and deferasirox.

Pigment nephropathy represents the renal tubular effects of overproduction of heme moieties in serum that are filtered at the glomerulus and excreted in urine. Heme pigment, from either hemoglobinuria (massive intravascular hemolysis) or myoglobinuria (severe rhabdomyolysis), induces tubular injury by promoting the formation of reactive oxygen species, as well as by reducing renal perfusion through inhibition of nitric oxide synthesis.

Crystal deposition in distal tubular lumens causes a well-recognized syndrome of AKI following massive rises in uric acid and therapy with certain medications. Keys to developing AKI from crystal deposition are underlying kidney disease and intravascular volume depletion. Uric acid nephropathy with tubular obstruction from urate crystals develops in patients suffering from tumor lysis syndrome. Sulfadiazine promotes intratubular deposition of sulfa crystals in an acid urine, acyclovir crystal deposition occurs with large intravenous doses of the drug, while atazanavir and indinavir deposition of crystal (Figure 15.8) develops in the setting of volume contraction and urine pH above 5.5. Ciprofloxacin when administered in excessive doses (underlying kidney disease) and in the setting of alkaline urine can cause AKI from intratubular crystal deposition. Methotrexate, foscarnet, and large doses of intravenous vitamin C also promote

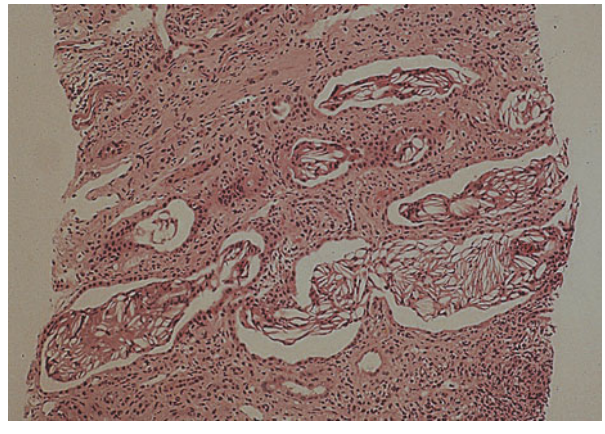

FIGURE 15-8. Indinavir nephropathy. Indinavir crystal deposition noted in the tubules of an human immunodeficiency virus (HIV)-infected patient with AKI. (Courtesy of Glen S. Markowitz.)

intratubular crystal deposition. Vitamin C, which is metabolized to oxalate, can cause deposition of calcium oxalate crystals within the tubules. Bariatric surgery (small bowel bypass) and orlistat, through induction of malabsorption, cause enteric hyperoxaluria and calcium oxalate crystal deposition (acute oxalate nephropathy). Use of sodium phosphate-containing bowel purgatives in high-risk individuals (elderly, underlying kidney disease, volume depleted, on ACE inhibitor or ARBs) has also been associated with AKI from calcium phosphate intratubular crystal deposition, an entity coined acute phosphate nephropathy.

A relatively new form of AKI was described in patients with underlying kidney disease treated with warfarin who were excessively anticoagulated (international normalized ratio [INR] >3). This can happen with other agents in the setting of supratherapeutic levels of anticoagulation. The mechanism underlying AKI appears to be excessive anticoagulation leading to glomerular hemorrhage, with subsequent tubular obstruction with red blood cell (RBC) casts (Figure 15.9). Tubular obstruction and/or heme-related tubular injury from lysosomal overload and oxidative damage appear to play an important role. Initial reversal of anticoagulation, followed by more judicious anticoagulation in those who truly require it is recommended. Unfortunately, many patients are left with CKD, sometimes requiring RRT.

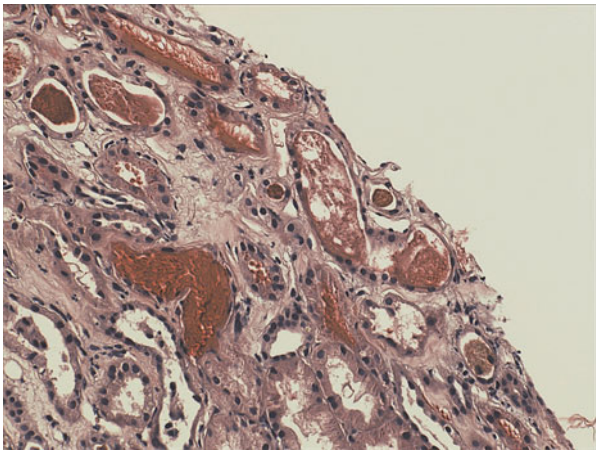

FIGURE 15-9. Histopathology of warfarin-induced nephropathy. Renal tubular obstruction from RBC casts and heme-associated injury occur in the setting of glomerular hemorrhage. (Courtesy of Gilbert Moeckel.)

Finally, the interesting and poorly recognized entity of osmotic nephrosis can promote AKI through the induction of tubular swelling, cell disruption, and occlusion of tubular lumens. The hyperosmolar nature of substances such as sucrose, dextran, mannitol, IVIG (sucrose), and hydroxyethyl starch underlies the pathophysiology of this renal lesion. All of these substances are freely filtered at the glomerulus where they are then reabsorbed by the proximal tubule through pinocytosis. Once inside the cell, they cannot be metabolized further, thereby promoting cellular uptake of water driven by the high osmolality within the cell. Cells then develop severe swelling, disturbing cellular integrity, and occluding tubular lumens. AKI results from this abnormal tubular process when patients with underlying kidney disease or other risk factors for kidney injury (intravascular volume depletion, older age) receive these hyperosmolar substances. Therapy is primarily supportive and avoidance of further exposure to these agents. Most recover, though CKD does occur.

KEY POINTS

Tubules

1. ATN is the most common cause of intrinsic renal azotemia. Ischemic insults and various nephrotoxins are the major causes.
2. Tubular injury leading to ATN also results from endogenous toxins such as heme pigment. Both massive intravascular hemolysis and rhabdomyolysis are associated with pigmenturia.
3. Crystal deposition in the distal tubular lumens is another cause of AKI. Acute tumor lysis syndrome and certain medications underlie crystal nephropathy.
4. Intratubular obstruction from RBC casts is associated with AKI in patient excessively anticoagulated with warfarin or other anticoagulants.
5. Hyperosmolar substances such as sucrose, IVIG, mannitol, dextran, and hydroxyethyl starch, induce tubular cell swelling and AKI. This entity is called *osmotic nephropathy*.

Interstitium

Disease of the renal interstitium can result from drugs, certain infectious agents, systemic diseases, and infiltrative malignancies. The syndrome of acute interstitial nephritis (AIN) is characterized by AKI and myriad

clinical findings. What is constant in AIN is the presence of a cellular infiltrate (lymphocytes, monocytes, eosinophils, plasma cells) and edema (or fibrosis) in the interstitium of the kidney (Figure 15.10). Tubulitis or invasion of lymphocytes into the tubular cells may also occur. Certain drugs (anticonvulsants, sulfonamides, etc), systemic diseases (sarcoidosis, tubulointerstitial nephritis with uveitis) and idiopathic diseases may also cause a granulomatous interstitial nephritis. Typically, the glomeruli and vasculature are spared by this process. The clinical presentation varies based on the offending agent and the host response. For example, β-lactams often cause the classic triad of fever, maculopapular skin rash, and eosinophilia. Other clinical findings include arthralgias, myalgias, and flank pain. In contrast, NSAIDs rarely develop any extrarenal manifestations. Aside from AKI, patients receiving NSAIDs do not develop a fever, rash, or eosinophilia. Other drugs, such as the sulfa-containing agents, rifampin, phenytoin, allopurinol, H_2-blockers, and fluoroquinolones, may or may not develop extrarenal manifestations. At times, there might be a slight increase in liver transaminases, representing an associated drug-induced hepatitis. The urinalysis may reveal mild proteinuria, hematuria, and leukocyturia. The urine sediment examination may be bland or demonstrate white blood cells (WBCs) (sometimes eosinophils), RBCs, and WBC casts. The Wright stain or Hansel stain may reveal eosinophils in the urine, but, unfortunately, neither of these tests is sensitive or specific for AIN. For example, the most common cause of eosinophiluria is urinary tract infection. In general renal disease occurs 2 to 3 weeks following drug exposure; however, it may occur more quickly in patients previously exposed to the inciting agent. Diagnosis is best made by renal biopsy. Characteristic findings are as described above: a cellular infiltrate and either edema or fibrosis in the interstitium. When biopsy is not possible, gallium scan of the kidneys may provide help in ruling out the diagnosis, as it is a relatively sensitive but not specific test. Positron emission tomography (PET) may be an even more sensitive and specific test for AIN, especially when the differential diagnosis is primarily between AIN and ATN. Treatment is most successful when AIN is identified early, allowing withdrawal of the offending agent prior to the development of advanced tubulointerstitial fibrosis. Therapy with steroids is controversial, but may reduce the duration of AKI and perhaps improve functional recovery in patients with severe renal impairment. Some data support that early use of steroids after drug withdrawal (<2 weeks, optimally <1 week) in AIN is associated with better recovery and less CKD. Aside from these retrospective data, there are no controlled trials to support widespread steroid use.

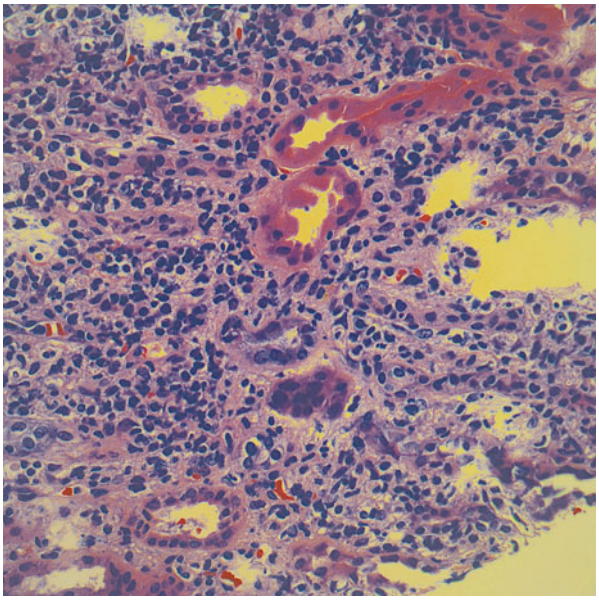

FIGURE 15-10. AIN. The renal interstitium is infiltrated with lymphocytes, plasma cells, and eosinophils in AIN. (Courtesy of Mark A. Perazella.)

Infection in the renal interstitium was described as a cause of interstitial nephritis prior to the AIN reported with the drugs noted above. Infection with bacteria such as staphylococci, streptococci, *Mycoplasma*, diphtheroids, and *Legionella* promotes AIN. Several viral agents, including cytomegalovirus, Ebstein-Barr virus, human immunodeficiency virus (HIV), Hantaan virus, parvovirus, and rubeola, also cause AIN. Finally, AIN may result from other infectious agents, such as rickettsia, leptospirosis, and tuberculosis.

A number of systemic illnesses cause disease in the renal interstitium. Sarcoidosis promotes a lymphocytic interstitial nephritis, at times associated with noncaseating granulomas. This leads to renal injury and CKD. Steroids reduce the severity of interstitial nephritis with sarcoidosis. SLE is an immune complex disease more commonly associated with a proliferative glomerulonephritis. An underrecognized histopathologic finding that occurs with SLE is AIN. The interstitial inflammatory lesion is caused by immune complex deposition in the

tubulointerstitium. This lesion responds to usual therapy given for lupus nephritis. Interstitial nephritis also occurs in Sjögren syndrome. This also appears to be an immune complex mediate disease of the renal interstitium.

Malignant infiltration of the kidney is an uncommon cause of clinical renal disease. The malignancies most often associated with interstitial infiltration are the leukemias and lymphomas. Leukemic infiltration causes nephromegaly (Figure 15.11), AKI, and sometimes urinary K^+ wasting (as a result of either tubulointerstitial damage or lysozyme production). Renal involvement from lymphomatous infiltration can be in the form of discrete nodules or diffuse interstitial infiltration. Lymphoma may also cause massive kidney enlargement and AKI. Successful treatment of the underlying malignancy typically improves the infiltrative lesion; however, irradiation of the kidneys may also provide additional benefit.

Two processes described in patients with HIV infection involve the tubulointerstitium and are worth briefly mentioning. The first is the immune reconstitution inflammatory syndrome (IRIS) where a renal (and other organ) interstitial infiltrate occurs when combination antiretroviral therapy reconstitutes the immune system (in the setting of a previous or occult opportunistic infection). The resulting exuberant immune reaction is associated with T-cell infiltration of the kidney and other organs—which can cause AKI. Treatment involves treatment of the opportunistic infection—sometimes corticosteroids are required to suppress the inflammatory response. The second is the diffuse infiltrative lymphocytosis syndrome (DILS). This is a Sjögren syndrome-like syndrome associated with multivisceral (including the kidneys) CD8 T-cell infiltration that appears to be a host-determined response to HIV. It is associated with AKI and is highly responsive to steroids.

A more complete discussion of all of the diseases that affect the tubulointerstitium is undertaken in another Chapter 18. This will include chronic interstitial nephritis and tubulointerstitial disease secondary to glomerular disease. The pathogenesis of tubulointerstitial disease will also be examined.

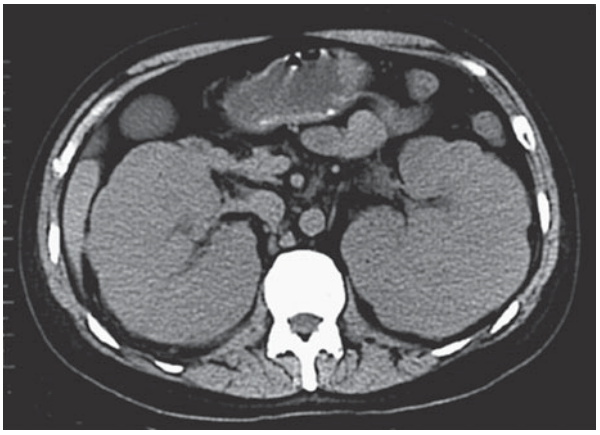

FIGURE 15-11. Computed tomography (CT) scan demonstrates bilateral kidney enlargement. Such nephromegaly is suggestive on an infiltrative process such as lymphoma (as in this case) and leukemia. (Courtesy of Mark A. Perazella.)

KEY POINTS

Interstitium

1. Acute interstitial nephritis results from a variety of medications. β-Lactams such as the penicillins produce the classic syndrome of fever, skin rash, and eosinophilia along with AKI more often than other drugs. In particular, NSAIDs lack most of the extrarenal manifestations of AIN.
2. Infectious agents such as bacteria, viruses, *Mycobacteria*, rickettsial organisms, and *Leptospira* cause AIN.
3. Acute interstitial nephritis is also a consequence of systemic diseases. Included are sarcoidosis, SLE, and Sjögren syndrome. Altered immunity associated with these diseases promotes interstitial disease in such patients.
4. Infiltration of the interstitium with malignant cells occurs most commonly with the leukemias and lymphomas. Massive nephromegaly often accompanies AKI, while tubular insufficiency may manifest as hypokalemia.
5. In HIV patients, 2 processes known as IRIS and DILS, may develop and cause a cellular infiltrate in the renal tubulointerstitium.

Postrenal Acute Kidney Injury

Anatomic obstruction of urine flow anywhere along the genitourinary system can result in AKI. The process causing postrenal AKI is called *obstructive uropathy*. The radiographic (ultrasound, intravenous or retrograde pyelogram, computed tomography [CT] scan) demonstration of a dilated urinary collecting system is termed

hydronephrosis. Abnormal kidney function (AKI, tubular defects) that occurs with urinary obstruction is called *obstructive nephropathy*. For AKI to develop, obstruction must be bilateral (both ureters or below the bladder) or unilateral in a single functioning kidney. It is important to recognize that obstruction may be complete and associated with anuria, or partial (incomplete) and associated with urine volumes varying (and fluctuating) from low to normal to polyuric levels. Either complete or partial obstruction may cause AKI, however, obstructive uropathy that is complete is typically associated with more severe renal failure and clinical manifestations (hypertension, intravascular volume overload, hyperkalemia, hyponatremia, and so on).

The pathogenesis of AKI from urinary obstruction is briefly discussed in this section. A more thorough description is presented in Chapter 19 dedicated to obstructive uropathy. Following acute obstruction, a triphasic response occurs in the renal plasma flow. An initial and short-lived (2 to 4 hours) increase in plasma flow develops as vasodilatory prostaglandins are produced in response to the rise in intratubular pressure. This represents an attempt to maintain GFR by overcoming the elevated intratubular pressure. Blood flow begins to decline after 2 to 5 hours, an effect caused by increased ureteral and tubular pressure transmitted to the renal interstitium. Intratubular pressure also returns to normal at 24 hours, after increasing acutely with obstruction. A further decline in renal plasma flow at 24 hours (30% to 50% of baseline) occurs despite normalization of ureteral and tubular pressures. This fall is a result of production of AII and thromboxane A_2, both vasoconstrictors. These substances also reduce GFR, not only by reducing renal plasma flow, but by inducing mesangial contraction and reducing the glomerular ultrafiltration coefficient. Despite all of these effects, GFR declines progressively but never reaches zero. The explanation for maintained GFR is the continued reabsorption of sodium and water (urine) along the nephron and in the lymphatics.

Obstruction of the urinary system can occur anywhere starting at the renal calyces and extending to the urethra. A wide variety of disorders cause AKI from urinary obstruction. They can be classified according to the site or level of obstruction (Table 15.6). In general, the most common causes of obstructive uropathy in the upper urinary tract (above the bladder) include stones and retroperitoneal disease, whereas in the lower tract, prostatic hyperplasia and bladder dysfunction most often obstruct urinary flow at this level. The diagnosis of obstructive uropathy should be considered in most patients with AKI because it is highly reversible when identified and treated early on. History may point to upper tract (history of nephrolithiasis or certain cancers, flank pain) or lower tract (prostatism, neuropathic bladder). Physical examination should include assessment of flank tenderness, prostatic enlargement, or palpable bladder. Straight catheterization of the bladder helps evaluate for lower tract obstruction (large residual urine in the bladder). Imaging of the kidneys with ultrasound is the most appropriate initial test

TABLE 15-6. Etiologies of Postrenal Acute Kidney Injury

Ureterocalyceal Obstruction
Retroperitoneal disease Tumor Lymph Nodes Fibrosis
Papillary necrosis
Nephrolithiasis
Fungus balls
Blood clots
Strictures Infection Granulomatous disease Prior instrumentation
Bladder Obstruction
Structural
Stones
Blood clots
Tumor
Benign prostatic hyperplasia
Functional Cerebrovascular accident Diabetes mellitus Spinal cord injuries Drugs Other neuropathic conditions
Urethral Obstruction
Urethritis
Urethral stricture
Blood clots

to evaluate the patient with AKI and possible urinary tract obstruction. In general, the sensitivity and specificity of renal ultrasonography for the detection of urinary obstruction (hydronephrosis) are high, however, several clinical situations can reduce its accuracy. Acute obstruction, typically less than 48 hours, does not allow the urinary system to fully dilate, causing a negative ultrasound study for hydronephrosis. In patients with superimposed severe intravascular volume depletion, GFR and urine formation are reduced, limiting dilation of the urinary system and the ability of ultrasound to detect obstruction. Retroperitoneal disease involving the kidneys and ureters (cancer, fibrosis, and enlarged nodes) encases the collecting system and blunts dilation. In addition, obese patients and overlying bowel gas reduce visualization of the kidneys and urinary system, potentially confounding ultrasound results. In cases such as these, where the ultrasound findings are equivocal or negative yet the suspicion for urinary obstruction is high, a CT scan may provide more information. CT scans use stems from its ability to detect the etiology of obstruction (stones, tumor, enlarged lymph nodes, and so on) despite the absence of hydronephrosis. If these studies are negative but obstruction is still considered likely, retrograde pyelography can diagnose many forms of upper tract obstruction.

Adequate treatment of obstructive uropathy hinges on early recognition. As time passes with obstruction, especially if complete, reversibility of renal impairment is compromised. Upper urinary tract obstruction is relieved by retrograde ureteral stent placement. When severe retroperitoneal disease and ureteral or bladder cancer limit ureteral stent placement, nephrostomy tube insertion is often required. Relief of lower tract obstruction with a bladder catheter or suprapubic tube (when indicated), like the procedures for upper tract obstruction noted above, is the first step in treatment. Management of electrolyte and fluid balance is the next step in patients with obstructive uropathy. Postobstructive diuresis is a phenomenon that occurs most commonly in patients with bilateral, complete obstruction. Large urine volumes can attend the diuresis that accompanies relief of obstruction. The diuresis is, in part, physiologic in that excess sodium and water are being excreted. Disturbed tubular function, however, may contribute to the excessive diuresis. Tubular abnormalities in sodium and water reabsorption can develop and persist for days (or permanently). Also, elevated levels of atrial natriuretic peptide may also induce diuresis while urea may cause an osmotic diuresis. Judicious fluid repletion is required in this circumstance, avoiding both iatrogenic contribution of postobstructive diuresis as well as underresuscitation and hypotension.

KEY POINTS

Postrenal Acute Kidney Injury

1. Anatomic obstruction of urinary flow results in an entity called obstructive uropathy. When renal defects develop in this situation, it is termed *obstructive nephropathy*.
2. Obstruction of the urinary system can be partial or complete, and either unilateral or bilateral. AKI most often complicates bilateral, complete obstruction.
3. Urine output can fluctuate between polyuria and oliguria in patients with partial obstruction. Bilateral, complete obstruction is characterized by anuria.
4. The pathogenesis of obstructive uropathy includes a reduction in GFR from both elevated intratubular pressure (resisting filtration pressure) and production of vasoconstrictor substances that reduce renal plasma flow.
5. Obstruction of the urinary system is classified as either upper tract (renal pelvis and ureters) or lower tract (bladder and urethra) according to the site of obstruction.
6. Diagnosis of obstructive uropathy entails a complete history (anuria, prostatism, history of bladder, prostate, or cervical cancer) and physical examination (suprapubic fullness, flank tenderness), as well as imaging with renal ultrasound. This imaging test is both sensitive and specific, but can be negative (no hydronephrosis) in the presence of obstruction in a few clinical situations.
7. Treatment of obstruction focuses on rapid identification to preserve renal function. Upper tract obstruction is usually managed with ureteral stent placement or percutaneous nephrostomy tube insertion. Lower tract disease is managed with a bladder catheter or suprapubic tube.
8. Postobstructive diuresis may develop following relief of complete, bilateral obstruction for several reasons. Excess sodium and water are excreted while obstruction-related tubular defects may occur and cause inappropriate sodium and water wasting. Elevated BUN concentrations may also contribute through an osmotic diuresis.

PREGNANCY AND ACUTE KIDNEY INJURY

Although pregnant patients are generally healthy and have an uncomplicated course, various forms of kidney injury can occur. Pregnancy-associated AKI can be caused by any of the previously listed causes (see Table 15.2). There are, however, several specific etiologies of AKI in pregnancy that occur; they are briefly reviewed.

Pregnancy can be associated with microangiopathic hemolytic anemia and thrombocytopenia in the setting of AKI. This would raise suspicion for either a thrombotic microangiopathy (TTP-HUS) or severe preeclampsia, usually with the HELLP syndrome (hemolysis with a microangiopathic blood smear, elevated liver enzymes, and thrombocytopenia). Preeclampsia typically occurs after 20 weeks gestation. Clinical manifestations of preeclampsia are hypertension and proteinuria with glomerular endotheliosis as the pathologic hallmark finding on kidney biopsy. Proteinuria in preeclampsia is defined as equal to or greater than 0.3 g protein in a 24-hour urine specimen. The presence of equal to or greater than 5 g of protein in a 24-hour urine collection suggests severe preeclampsia, but may also reflect previous underlying kidney pathology (ie, membranous nephropathy) or a different renal process, or a combination. A rise in serum uric acid concentrations occurs in preeclampsia, possibly caused by proximal sodium reabsorption and, secondarily, urate reabsorption. Tissue damage, oxidative stress, and inflammation may also promote hyperuricemia. Abnormal placental development and hypoperfusion alter the maternal endothelial cell function and lead to the characteristic systemic signs and symptoms of preeclampsia. The placenta requires extensive angiogenesis to establish a suitable vascular network to supply oxygen and nutrients to the fetus. There is an elaborate interplay between proangiogenic and antiangiogenic factors by the developing placenta, and the balance among these factors is important for normal placental development. Specifically, increased production of soluble fms–like tyrosine kinase 1 (sFlt-1 or sVEGFR-1), an antiangiogenic factor, is demonstrated to cause the systemic endothelial dysfunction characteristic of preeclampsia.

Thrombotic microangiopathy of pregnancy includes TTP and HUS, most commonly atypical HUS. Thrombotic microangiopathy during pregnancy is very rare, collectively TTP-HUS reportedly occur in 1 in 25,000 pregnancies, whereas preeclampsia affects approximately 5% to 8% of pregnancies, and HELLP occurs in 0.5% to 0.9% of pregnancies. TTP-HUS can develop during any stage of pregnancy. The hallmark of these thrombotic microangiopathic disorders is the development of microthrombi in the small vessels causing thrombocytopenia, hemolysis, and multiorgan damage, such as AKI and neurologic disturbances. The development of microthrombi in TTP is attributed to a deficiency in the von Willebrand factor (vWF) cleaving enzyme ADAMTS13, leading to large vWF multimers that promote platelet aggregation within the microcirculation. Levels of fibrinogen and vWF are increased and there is significant reduction in the level of ADAMTS13, between 52% and 64% of normal, which is why pregnancy is a proposed trigger for the development or exacerbation of TTP, although the mechanism is not fully understood. Pregnancy-associated HUS is considered a form of atypical HUS and is associated with several abnormalities of the complement cascade, leading to the development of microthrombi, primarily in the renal parenchyma. Differentiating HUS from TTP is difficult given their overlapping clinical presentations. Features more common in HUS include more severe renal injury with serum creatinine levels greater than 3 mg/dL, milder neurologic abnormalities, and unlike TTP, most cases of HUS develop several weeks postpartum.

The distinction between the HELLP variant of severe preeclampsia and thrombotic microangiopathy is a clinical challenge, as both are characterized by microangiopathy and thrombocytopenia. The presence of elevated liver enzymes is strongly suggestive of HELLP syndrome, and is an uncommon feature of pregnancy-associated thrombotic microangiopathy. Preeclampsia/HELLP syndrome typically resolves within days of delivery, unlike TTP-HUS.

Other causes of AKI in pregnancy include bilateral renal cortical necrosis, acute pyelonephritis, obstructing nephrolithiasis, and acute fatty liver of pregnancy (AFLP). This last cause of AKI is a rare syndrome characterized by AKI, hypoglycemia, hypofibrinogenemia, liver function test abnormalities, and a prolonged partial thromboplastin time (PTT).

KEY POINTS

Pregnancy and Acute Kidney Injury

1. AKI in pregnancy requires immediate investigation. Routine investigations of AKI in pregnancy should include complete blood count (CBC), peripheral smear, coagulation panel, LDH, liver function tests, plasma haptoglobin, uric acid, and urine dipstick for protein.

2. Preeclampsia typically occurs after 20 weeks gestation. Clinical manifestations of preeclampsia are hypertension and proteinuria with glomerular endotheliosis as the pathologic hallmark finding. The antiangiogenic factor, sFlt-1, causes the systemic endothelial dysfunction characteristic of preeclampsia.
3. Any etiology of AKI can occur during pregnancy, however, when associated with a microangiopathic hemolytic anemia, and thrombocytopenia, thrombotic microangiopathy (TTP-HUS), or severe preeclampsia, with the HELLP syndrome, must be considered.
4. The hallmark of thrombotic microangiopathies (TTP-HUS) is the development of microthrombi in small vessels causing thrombocytopenia, hemolysis, and multiorgan damage, such as AKI and neurologic changes.
5. TTP is attributed to a deficiency in the vWF cleaving enzyme ADAMTS13, whereas HUS is associated with several abnormalities of the complement cascade.
6. The presence of elevated liver enzymes is strongly suggestive of HELLP syndrome, and is an uncommon feature of pregnancy-associated thrombotic microangiopathy.

APPROACH TO THE PATIENT WITH ACUTE KIDNEY INJURY

Evaluation of the patient with AKI should be methodical to ensure that potentially reversible causes are rapidly diagnosed and treated to preserve kidney function and limit CKD. A thorough history to identify causes of and risk factors for prerenal AKI (vomiting, diuretics, diarrhea, heart failure, cirrhosis), potential nephrotoxic drugs (either prescribed or nonprescription), and risk factors for (prostate disease, cervical cancer, and so on) or symptoms of urinary obstruction (prostatism, overflow incontinence, anuria) is required. Physical examination should focus on volume status to allow initial classification into one of the broad categories of AKI. These include hypotension, an orthostatic fall in blood pressure, or flat neck veins (volume depletion), as well as edema, pulmonary rales, or an S_3 gallop (cardiac dysfunction). In situations where intravascular volume status is uncertain, measurement of cardiac filling pressures with a Swan-Ganz catheter may be useful, but is not employed commonly. More often, central venous pressures (CVPs) are measured. Although there are data that demonstrate the limitations of CVP, even when monitoring trends and response to fluid administration or removal, they remain an important tool in guiding fluid management. New noninvasive tools are under investigation that may allow safer and more accurate care of such patients. Examination for evidence of systemic disease should also be sought. For example, this includes signs of pulmonary hemorrhage (vasculitis, Goodpasture disease), skin rash (SLE, atheroemboli, vasculitis, cryoglobulins, AIN), and joint disease (SLE, rheumatoid arthritis), to name a few.

Laboratory tests are directed by the differential diagnosis postulated following a complete history and physical examination. Basic tests include a CBC to assess for anemia (microangiopathic or immune-mediated) and thrombocytopenia (TTP, HUS, disseminated intravascular coagulation [DIC]). The urinalysis is a key component of the AKI work-up. Table 15.7 outlines the various urine findings in some of the different causes of AKI. It is essential to evaluate urine specific gravity, as well as

TABLE 15-7. Urinalysis and Microscopic Examination of the Urine Sediment

TEST	PRERENAL	VASCULITIS	GN	ATN	AIN	POSTRENAL
Specific gravity	High	Normal/high	Normal/high	Isosmotic	Isosmotic	Isosmotic
Blood (dip)	Negative	Positive	Positive	±	±	Negative
Protein (dip)	Negative	Positive	Positive	Negative	±	Negative
Sediment examination	Negative, hyaline casts	RBC casts, dysmorphic RBCs	RBC casts, dysmorphic RBCs	Granular casts, RTEs	WBC casts, eosinophils	Negative, sometimes WBCs/RBCs

Abbreviations: ATN, acute tubular necrosis; AIN, acute interstitial nephritis; GN, glomerulonephritis; RBCs, red blood cells; RTE, renal tubular epithelial cells; WBCs, white blood cells.

the presence of blood (or heme), protein, or leukocyte esterase. A very high urine specific gravity (SG) typically suggests a prerenal process whereas isosthenuria (SG = 1.010) indicates intrinsic renal disease like ATN. Bland urine with no blood or protein and few or no cells/casts favor a diagnosis of prerenal AKI. Vascular causes of AKI have a variable urine tonicity and sometimes hematuria and granular casts. Glomerulonephritis will have variable urine tonicity, blood and protein (usually), and RBCs and RBC casts. ATN has an isotonic urine, variable heme (positive with rhabdomyolysis and hemolysis) and protein, RTEs, and pigmented coarsely granular casts. The urine in patients with postrenal AKI is typically isotonic and bland unless there is associated infection (pyuria) or nephrolithiasis (hematuria). Although urine chemistries sometimes help distinguish the type of pathology in the kidney, there are several instances where they are inaccurate. As stated earlier, a low urine sodium and a FENa and RFI (both <1%) generally support prerenal AKI. In contrast, urine sodium greater than 20 mEq/L and FENa and RFI both greater than 2% suggest ATN (Table 15.8). However, prerenal AKI with an elevated FENa or FEUrea occurs in the setting of glycosuria, metabolic alkalosis, bicarbonaturia, salt wasting disorders, and CKD. Similarly, ATN with low FENa and FEUrea occurs with pigmenturia, sepsis, radiocontrast, nonoliguric ATN, and severe cirrhosis or CRS. Evidence of systemic disease should prompt directed testing using antinuclear antibody (ANA) (SLE), antineutrophilic cytoplasmic antibody (ANCA) (vasculitis), hepatitis serology, serum cryoglobulins (cryoglobulinemia), complement levels, serum and urine immunoelectrophoresis (monoclonal immunoglobulin diseases), and blood cultures (endovascular infection).

Diagnostic imaging tests play an important role in the evaluation of patients with AKI. The modality most often employed is retroperitoneal ultrasonography of the kidneys, ureters, and bladder. This test provides information about kidney size (large or small) and parenchyma (echogenicity), status of the pelvis and urinary collecting system (hydronephrosis), and the presence of structural abnormalities (stones, masses, and enlarged lymph nodes). In the setting of AKI, renal ultrasound's biggest use is in rapidly confirming or excluding the presence of hydronephrosis and a diagnosis of obstructive uropathy. Doppler interrogation of the renal arteries provides important information about RBF and renal artery stenosis; however, this test is highly operator dependent. CT scan of the retroperitoneum also provides important information about the etiology of postrenal AKI when ultrasound is negative or inconclusive. Magnetic resonance imaging (MRI) with gadolinium angiography also safely provides important information about renal artery stenosis/thrombosis, but should be avoided in patient with AKI or stage 4 CKD. The entity of nephrogenic systemic fibrosis can develop in these patients, especially with certain types of gadolinium contrast (nonionic linear chelates) and in the setting of inflammation.

Percutaneous kidney biopsy is sometimes required to determine the etiology of AKI, as well as to direct appropriate therapy. Reasonable criteria to support use of kidney biopsy are the following: no obvious cause of AKI (no evidence of hypotension, nephrotoxins), prolonged oliguria (longer than 2 to 3 weeks), assess for multiple myeloma in the elderly with unexplained renal failure, extrarenal manifestations of systemic disease (SLE, vasculitis), and to determine if AIN is present in patients receiving a potentially culprit drug. Examination of the kidney tissue using light microscopy, immunofluorescence staining, and electron microscopy will facilitate an accurate diagnosis in virtually all cases of AKI. Kidney biopsy, however, should be employed judiciously so as to avoid complications such as traumatic arteriovenous malformation within the kidney, severe bleeding requiring transfusion, other organ injury (liver, spleen, bowel), and kidney loss (severe bleeding requiring embolization or nephrectomy).

TABLE 15-8. Urine Chemistries

LAB TEST	PRERENAL	ATN
Urine Na^+ (mEq/L)	<20	>20
UOsm (mOsm/kg)	>500	<400
RFI (%)	<1	>2
FENa (%)	<1	>2
FEUrea (%)	<35	>50

CLINICAL CONSEQUENCES OF ACUTE KIDNEY INJURY

Failure of kidney function precipitates clinical problems related to toxin excretion, fluid balance, acid/base homeostasis, and electrolyte/mineral regulation.

Disturbance of the homeostatic renal processes result in the following:

Retention of nitrogen wastes	⇒	azotemia and uremia
Retention of sodium	⇒	volume overload, hypertension
Retention of water	⇒	hyponatremia
Retention of metabolic acids	⇒	metabolic acidosis
Retention of potassium	⇒	hyperkalemia
Retention of phosphate	⇒	hyperphosphatemia, hypocalcemia

Clinical manifestations of AKI vary based on the severity of renal dysfunction. Uremic symptoms include anorexia, nausea/vomiting, weakness, difficulty concentrating/thinking, lethargy, and pruritus. Physical examination findings supporting uremia include asterixis, pericardial friction rub, sensory and/or motor neuropathy, and hyper- or hypotension depending on the cause of AKI. Other associated findings of severe uremia include GI ulcerations, bleeding from platelet dysfunction, infection from abnormal WBC function, impaired wound healing, and malnutrition from the catabolic state.

TREATMENT OF ACUTE KIDNEY INJURY: GENERAL PRINCIPLES

Therapy of AKI first requires identification of the etiology and pathogenesis of the inciting process (prerenal, intrarenal, and postrenal). Hence, treatment is based on diagnosis directed therapy. Also, the consequences of AKI need to be identified and rapidly managed to avoid serious adverse events (hyperkalemia, pericarditis, acidosis, and so on). Prerenal AKI is best treated by optimizing renal perfusion. Repletion of intravascular volume and correction of heart failure, liver failure, and other "effective" causes of reduced intravascular volume constitute treatment for this form of AKI. Intrarenal AKI is managed through directed therapy for the disturbed kidney compartment (vasculature, glomerulus, tubules, and interstitium). In certain situations, preventive therapy reduces renal injury; for example, volume repletion prior to any nephrotoxic or ischemic exposure. Fluid therapy (isotonic saline or sodium bicarbonate), and acetylcysteine may reduce the kidney damage associated with radiocontrast exposure in high-risk subjects. RRT has no role in preventing contrast-induced AKI. As discussed previously, management of postrenal AKI mandates rapid identification of the obstruction process and early intervention to relieve obstruction and preserve renal function.

Conservative therapies of many of the consequences of AKI are initially employed, including correction of volume overload/hypertension, hyponatremia, hyperkalemia, and acidosis. The actual therapies for these clinical situations are covered in Chapters 2, 3, 6, and 7. Conversion of patients from oliguric to nonoliguric AKI makes management easier, but probably does not improve morbidity or mortality. Azotemia and uremia, as well as the other consequences previously noted, may require RRT to allow appropriate management when conservative measures are unsuccessful.

Initiation of acute hemodialysis or continuous renal replacement therapies is required in certain patients with AKI. Continuous therapies, which can only be employed in critical care units, include continuous venovenous hemofiltration (CVVH)/continuous venovenous hemodialysis (CVVHD)/continuous venovenous hemodiafiltration (CVVHDF), slow low-efficiency dialysis (SLED), and extended daily dialysis (EDD). Emergent indications include severe hyperkalemia, uremic end-organ damage (pericarditis, seizure), refractory metabolic acidosis, and severe volume overload (pulmonary edema). Other clinical situations that mandate the commencement of RRT are uremic symptoms such as anorexia, nausea/vomiting, somnolence, restless legs, and neuropathy. Bleeding from platelet dysfunction and extreme hyperphosphatemia are other reasons to consider initiation of dialysis. Acute hemodialysis is the modality most commonly employed to treat the consequences of AKI. In patients who are critically ill and hemodynamically unstable, continuous therapies are preferred. The continuous modalities allow more precise control of volume, uremia, acid–base disturbances, and electrolyte disorders with less hemodynamic instability (hypotension). It will also allow aggressive nutritional support without associated volume overload. Peritoneal dialysis is another gentle therapy for AKI, but it is less commonly used.

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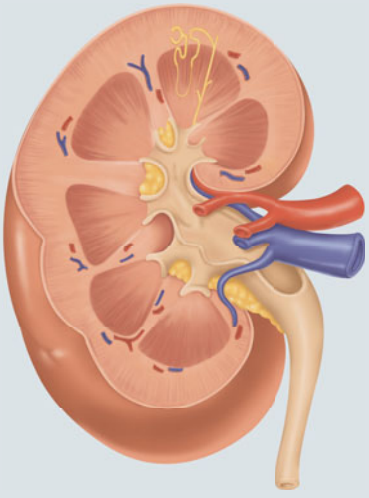

CHAPTER

16

Chronic Kidney Disease

• *Mark A. Perazella and Edgar V. Lerma*

Recommended Time to Complete: 2 Days

Guiding Questions

1. Why is the rapid growth of the chronic kidney disease (CKD) population a concern?
2. Why are estimation equations of glomerular filtration rate (GFR) used to measure kidney function?
3. Why is a staging system beneficial to appropriately care for CKD patients?
4. What are the major mechanisms of progression of kidney disease?
5. What are the most effective treatments to slow progression of CKD to end-stage renal disease (ESRD)?
6. Is cardiovascular disease (CVD) common in CKD patients?
7. What are the various categories of risk factors for the development of CVD in CKD patients?
8. What are the most common causes of anemia in CKD patients?
9. What are the options available to treat anemia of CKD patients?
10. What metabolic mineral disturbances occur in CKD patients?
11. What types of bone disease constitute the spectrum of renal osteodystrophy?
12. Why is early referral of CKD patients to nephrologists important?
13. What are the important aspects of preparation of CKD patients for initiation of renal replacement therapy (RRT)?

INTRODUCTION

CKD is a worldwide health problem. Comprehensive data on CKD provided by the Third National Health and Nutrition Examination Survey (NHANES III) note that approximately 800,000 Americans have CKD as manifested by a serum creatinine concentration of 2 mg/dL or greater. More than 6.2 million are estimated to have a serum creatinine concentration of 1.5 mg/dL or greater. Data extrapolated from the Framingham study suggest that approximately 20 million people in the United States are at risk for CKD.

The rapid growth in both the incidence and prevalence of CKD will result in a huge influx of patients into the

ESRD system. Based on data from the United States Renal Data System (USRDS), the number of point prevalent Medicare ESRD patients increased to more than 470,000 (3.2% difference) and that of the non-Medicare ESRD patients increased to 101,351 (8.3% difference) from 2008 to 2009. Expansion of the ESRD population will have a significant economic impact on the already overextended Medicare system. The per-person per-year costs (net inpatient/outpatient) attributed to CKD among Medicare patients is generally higher in those with later stages of CKD as compared to earlier stages. For instance, the costs were approximately $19,052 for Stages 4 to 5 CKD as compared with $13,120 for Stages 1 to 2 CKD (a 45% difference). These costs included medical and surgical diagnostic-related groups (DRGs), pharmacy supplies, home health agencies, and skilled nursing, among others. For ESRD, the total Medicare costs for 2009 rose to $29 billion, which accounts for 5.9% of the total allotted Medicare budget for that year. The increase in both CKD and ESRD populations may also overwhelm the ability of nephrologists and other healthcare providers to fully provide interventions that will improve the length and quality of patients' lives.

Defining and Staging Chronic Kidney Disease

Several terms are used to describe the period of kidney disease that precedes the institution of RRT such as *pre-ESRD*, *chronic renal insufficiency*, *chronic renal failure*, and *chronic renal disease*. Unfortunately, none of these terms is particularly accurate and may be confusing to nonnephrology physicians. The term *pre-ESRD* gives the impression that dialysis is an inevitable outcome of all kidney diseases. The terms *renal insufficiency*, *chronic renal failure*, *chronic renal disease*, and *pre-ESRD* have negative connotations. These terms also include the word *renal*, which is not easily understood by patients. For these reasons, *chronic kidney disease* is chosen as the defining term.

The definition and classification of CKD are based on measurement of GFR, the best overall measure of kidney function. Factors that influence GFR include both structural or functional kidney disease, as well as patient age. In general, the annual decline of GFR with age is approximately 1 mL/min/1.73 m^2 of body surface area, beginning after the patient reaches approximately 20 to 30 years of age. Although a chronic decline in GFR to a level of less than 60 mL/min/1.73 m^2 is evidence of CKD, substantial kidney damage can exist without a decrease in GFR. In this circumstance, kidney damage is defined as a structural or functional abnormality of the kidney that persists for more than 3 months. Manifestations of kidney damage can include pathologic changes or abnormalities revealed by blood, imaging, or urine tests. Using this definition, CKD is present if the GFR is less than 60 mL/min/1.73 m^2. CKD is also present if the GFR is equal to or greater than 60 mL/min/1.73 m^2, if other evidence of kidney damage also exists. Table 16.1 provides a classification and staging system based on the level of GFR.

Since the inception of the classification system in 2002, there have been a few modifications. In 2005, the Kidney Disease: Improving Global Outcomes (KDIGO) Work Group recommended adding the suffix "D" for patients with Stage 5 CKD who were on dialysis and the suffix "T" for those with a functioning kidney transplant. Three years later, the United Kingdom National Institute of Health and Clinical Excellence (NICE) group recommended subdividing Stage 3 CKD into 3a (GFR 59 to 45 mL/min/1.73 m^2) and 3b (44 to 30 mL/min/1.73 m^2) and adding the suffix "p" for those with confounding proteinuria. These modifications were based on the fact that a lower GFR in Stage 3 and the presence of proteinuria had significant implications on clinical outcomes.

This staging system provides a common language for communication between the various healthcare providers. It allows more reliable estimates of the prevalence of earlier stages and of populations at increased risk for CKD. In addition, evaluation of factors associated with a high risk of progression can be recognized. Treatments can be more effectively examined and the development of adverse outcomes in this population is more easily determined.

Glomerular Filtration Rate as an Index of Kidney Function

Serum creatinine concentration is commonly employed as an index of renal function. It is not an accurate measure of GFR, however, and it is especially inaccurate when the serum creatinine concentration is between 1 and 2 mg/dL. This is because creatinine, unlike inulin, is secreted by the renal tubules. As renal function declines, the amount of creatinine secreted by the tubules increases and raises the amount of creatinine in the urine. This acts to falsely increase the creatinine clearance (CrCl), resulting in an overestimation of GFR. Serum creatinine concentration

TABLE 16-1. Staging System and Action Plan for Chronic Kidney Disease

STAGE	DESCRIPTION	GFR (mL/min/1.73 m²)	ACTION*
0	At increased risk of CKD	≥90 with risk factors†	Screening CKD risk reduction
1	Kidney damage with normal or increased GFR†	≥90	Diagnosis and treatment Slow progression of CKD Treat comorbidities Cardiovascular disease risk reduction
2	Mild decrease in GFR	60 to 89	Estimate progression
3A	Mild to moderate decrease in GFR	44 to 59	Evaluate and treat complications
3B	Moderate to severe decrease in GFR	30 to 44	Treat complications Initiate discussions about options for possible future need for renal replacement therapy
4	Severe decrease in GFR	15 to 29	Treat complications Prepare for RRT
5	Kidney failure	<15 or dialysis	Renal replacement if uremic or other indications present

*Includes actions from preceding stages.
†Risk factors: hypertension, dyslipidemia, diabetes mellitus, anemia, systemic lupus erythematosus, and chronic analgesic ingestion.
†Kidney damage as manifested by abnormalities noted on renal pathology, blood, urine, or imaging tests.
Source: Adapted from Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Part 4. Definition and classification of stages of chronic kidney disease. *Am J Kidney Dis.* 2002;39 (suppl 2):S46–S75. Copyright 2002, with permission from Elsevier.

is also influenced by body mass, muscle mass, diet, drugs, and laboratory analytical methods. "Normal" ranges of serum creatinine quoted by laboratories are misleading because they do not take into account the age, race, sex, or body size of the individual.

Inulin clearance is the gold standard test for measuring GFR. Unfortunately, this test is cumbersome, expensive, and not widely available for clinical use. Iothalamate (^{125}I-iothalamate) clearance estimates GFR and is a reasonably accurate substitute for the inulin clearance method. It is also expensive and somewhat cumbersome to perform as a routine clinical test. A 24-hour urine collection for CrCl is the accepted alternative measure of GFR because it is widely available and is familiar to most clinicians. It is often difficult, however, for patients to perform correctly and is less accurate than either inulin or iothalamate clearance. In addition, this test often overestimates GFR in patients with advanced kidney disease.

To simplify measurement of renal function, GFR estimates from prediction equations are often used. These formulas take into account serum creatinine concentration, age, gender, race, and body size, and are better estimates of GFR than serum creatinine concentration alone. The formulas used are sufficiently accurate. The three most widely used are the Cockcroft-Gault, the Modification of Diet in Renal Disease Study (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. The Cockcroft-Gault equation noted below estimates of creatinine clearance (eCrCl):

$$\text{eCrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for females}$$

Although it provides an adequate estimate of GFR (eGFR), the MDRD equations are more accurate. MDRD equation 7 is the preferred formula but it requires

measurement of blood urea nitrogen (BUN) and serum albumin. The MDRD formula is as follows:

$$\begin{aligned}\text{eGFR} = 170 &\times [\text{serum creatinine (mg/dL)}]^{-0.999} \\ &\times [\text{age (years)}]^{-0.176} \times [0.762 \text{ if female}] \\ &\times [1.18 \text{ if African American}] \\ &\times [\text{BUN (mg/dL)}]^{-0.170} \\ &\times [\text{albumin (g/dL)}]^{+0.318}\end{aligned}$$

An abbreviated form of the MDRD equation that does not require BUN or albumin measurement was also developed and is as follows:

$$\begin{aligned}\text{eGFR} = 186 &\times [\text{serum creatinine (mg/dL)}]^{-1.154} \\ &\times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}] \\ &\times [1.21 \text{ if African American}]\end{aligned}$$

The abbreviated form is reasonably accurate. The MDRD equation was tested in more than 500 patients with a range of kidney diseases and ethnicities (European Americans and African Americans). GFR values were validated in the sample group using ^{125}I-iothalamate as the gold standard; however, certain patient groups were not well represented in the MDRD study sample. Therefore, clearance measurements are still required in groups who were underrepresented in the MDRD sample to fully validate the formula for all patients. These include patients at extremes of age and body size; the severely malnourished or obese; patients with skeletal muscle diseases, paraplegia or quadriplegia; vegetarians; and those with rapidly changing kidney function. The MDRD equation underestimates GFR in patients with relatively normal kidney function.

In 2009, the CKD-EPI was developed in an attempt to improve the accuracy of estimating equations in a more heterogenous group of patients. This formula utilized the same 4 variables as the MDRD equation. Compared with the MDRD equation, the CKD-EPI equation has less bias, particularly at GFR greater than 60 mL/min/1.73 m^2, as well as improved overall accuracy. It also allows reporting of numeric values across the range of GFR measurements. The CKD-EPI equation is as follows:

$$\begin{aligned}\text{eGFR} = 141 &\times \min(\text{serum creatinine}/k, 1)^{a} \\ &\times \max(\text{serum creatinine}/k, 1)^{-1.209} \\ &\times 0.993^{\text{age}} [\times 1.018 \text{ if female}] \\ &[\times 1.159 \text{ if black}]\end{aligned}$$

k is 0.7 for females and 0.9 for males, a is –0.329 for females and –0.411 for males.

In the absence of specific modifications for race, ethnicity or regional difference, the CKD-EPI equation is fairly accurate for GFR estimation. To account for possible differences in muscle mass and diet, race, ethnicity and other geographic variables, the MDRD Study and CKD-EPI equations have been modified for use in China and Japan. The modifications are associated with improved accuracy in these populations.

It has been proposed that utilizing both serum creatinine concentration and serum cystatin C together may improve the accuracy of GFR estimation, as compared to either marker alone. This may be particularly useful in patients with CKD 3A (45 to 59 mL/min/1.73 m^2) who do not manifest any markers of kidney damage. Cystatin C may potentially offer some advantages over measurement of serum creatinine concentration in the estimation of GFR and for the proper classification of CKD. Its use, however, is limited by higher cost and "lack of standardization" among the limited number of laboratories that offer the test.

Prevalence of Chronic Kidney Disease Stages

Prevalence estimates for each CKD stage were obtained by using a reference group comprised of patients evaluated in the NHANES III. In this sample of patients, the MDRD equation was used to estimate GFR. In addition to abnormal GFR levels, the presence of micro- or macroalbuminuria on spot urine specimens was considered sufficient evidence of kidney damage. The level of albuminuria, based on the ratio of albumin (and protein) to creatinine on spot urine samples, was used to estimate the prevalence of the first 2 stages. The reported prevalence of CKD Stages 1 to 4 in the most recent NHANES between 1999 and 2006 was 26 million (13%) out of approximately 200 million United States residents 20 years of age or older. Approximately 65% had CKD Stage 3 or 4. The USRDS estimates that nearly one-half million U.S. patients were treated for ESRD in the year 2004, and by 2010 this figure increased by approximately 40%. The elderly are a growing segment of the population and are clearly at increased risk for kidney disease. Males and African Americans with preexisting hypertension or diabetes mellitus and CKD are also at higher risk for development of ESRD.

APPROACH TO CHRONIC KIDNEY DISEASE PATIENTS

The approach to the patient involves establishing the presence of CKD, determining the stage of disease, and enacting an action plan based on the stage. The management of CKD patients requires a multidisciplinary approach

involving primary care physicians, nephrologists, endocrinologists, cardiologists, vascular surgeons, physician assistants, nurse practitioners, dietitians, and social workers. The goals of this interdisciplinary approach are to identify patients either with or at increased risk for CKD, to slow the progression of CKD to ESRD, to identify and treat comorbid conditions, to identify and prevent complications of CKD, and to prepare patients mentally and physically for RRT. As seen in Table 16.1, the action taken increases from simple screening maneuvers and risk reduction to more complex disease management.

Patients with established CKD are assessed for comorbid conditions. Medications are adjusted for the level of renal function. Blood pressure (BP) monitoring is essential to diagnose hypertension and facilitate optimal BP control. Serum creatinine concentration is measured to allow estimation of GFR. Protein- or albumin-to-creatinine ratios on spot urine samples and urinalysis are performed. Finally, imaging of the kidney by ultrasound is warranted in most CKD patients.

The approach is implemented in a stepwise fashion and individualized for each patient based on the level of kidney function. In a patient with a normal GFR (≥90 mL/min/1.73 m^2) or a mildly impaired GFR (>60 mL/min/1.73 m^2) the focus will be on delaying progression and treating comorbid conditions. Progression is best predicted by plotting the reciprocal of the serum creatinine concentration over time. This plot predicts a date when the GFR will reach target levels and can be used along with symptoms and signs for deciding the appropriate time for initiation of RRT.

KEY POINTS

Approach to Chronic Kidney Disease Patients

1. The incidence and prevalence of CKD are growing rapidly.
2. Equation estimates of GFR as well as other laboratory, pathologic, and radiographic changes allow classification and staging of CKD.
3. There are 3 equations available to estimate either CrCl (Cockcroft-Gault formula) or GFR (MDRD and CKD-EPI). The most useful equation to estimate GFR is the CKD-EPI formula.
4. Patients with CKD should be staged and then evaluated and managed using their CKD stage.
5. Management of CKD patients will focus on disease prevention, management of comorbidities, and preparation for RRT.

PROGRESSION OF CHRONIC KIDNEY DISEASE

Mechanisms of Chronic Kidney Disease Progression

Much of what we understand about the mechanisms involved in the progression of CKD has been obtained through "experimental kidney disease." Progression of CKD may be considered as a process of "glomerular adaptation." In experimental models, adaptation is characterized by an increased workload per nephron, and this is manifested as increased "single nephron GFR (SNGFR)." The increase in SNGFR is initially "adaptive," but eventually becomes "maladaptive," because it leads to further nephron injury. There are several theories that have been suggested to account for this:

1. Hemodynamic hypothesis
2. Abnormal permeability to macromolecules
3. Growth Factor Hypothesis

Hemodynamic Hypothesis

In experimental settings, ablation of kidney mass is achieved through a unilateral nephrectomy followed by ligation of the renal artery branches in the remaining functioning kidney, thereby causing an infarction of approximately two-thirds of said kidney. By reducing the number of nephrons to one-sixth, GFR reduction ensues. Following a reduction in the number of functioning nephrons, the remaining nephrons experience hyperfiltration and glomerular capillary hypertension. Although these changes are initially adaptive to maintain GFR, over time they are deleterious to renal function because of pressure-induced capillary stretch and glomerular injury. Histopathologically, this progression of events is manifested as glomerular and tubular hypertrophy followed by eventual focal glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Damage caused by glomerular hyperfiltration is notably important in the pathophysiology that underlies diabetic nephropathy.

Another experimental kidney disease model mimicking diabetes mellitus utilizes alloxan or streptozotocin to chemically ablate pancreatic islet cells. The hyperfiltering state induced by hyperglycemia upregulates local expression of the renin-angiotensin-aldosterone system (RAAS) and contributes to progressive kidney damage. In this instance, stimulation of the RAAS causes glomerular injury by further raising glomerular capillary pressure through angiotensin II (AII)-driven efferent arteriolar

vasoconstriction and facilitating pressure and stretch injury in the capillaries. Taken together, these effects lead to endothelial injury, stimulation of profibrotic cytokines by the mesangium, and detachment of glomerular epithelial cells.

Abnormal Permeability to Macromolecules

Another consequence of renal injury and activation of the RAAS is proteinuria. Glomerular capillary hypertension, caused by hyperfiltration and AII effect on efferent arterioles, leads to an increase in glomerular permeability and excessive protein filtration. Pore size is altered by AII, increasing protein leak across the glomerular basement membrane. An activated RAAS may also cause proteinuria through novel effects on nephrin expression in kidney. Nephrin, a transmembrane protein located in the slit diaphragm of the glomerular podocyte, is thought to play a key role in the function of the glomerular filtration barrier. By maintaining slit diaphragm integrity, nephrin limits protein loss across the glomerular basement membrane. When its expression is disrupted, proteinuria and its consequences may result. Data in rat models of proteinuric kidney disease suggest an important interaction between the RAAS and nephrin in modifying glomerular protein permeability. Although proteinuria is a marker for renal disease risk, it is also likely that excess protein in urine contributes to progressive kidney damage. Proteins present in the urine are toxic to the tubules, and can result in tubular injury, tubulointerstitial inflammation, and scarring. Tubular damage is caused by protein overloading of intracellular lysosomes, stimulation of inflammatory cytokine expression, and extracellular matrix protein production. These processes induce renal tubulointerstitial fibrosis and glomerular scarring. Remission or reduction in proteinuria is often associated with renoprotection and slowed progression of kidney disease.

Growth Factor Hypothesis

Although it is known that elevated glomerular capillary pressure and capillary stretch lead to scar formation in the glomerulus, an activated RAAS and other inflammatory mediators cause irreversible damage in the kidney through other mechanisms. Proinflammatory and profibrotic effects of AII and aldosterone underlie the injury that develops in the renal parenchyma.

Advanced glycation end-products (AGEs) accumulate in the mesangial area and glomerular capillary walls in diabetic nephropathy patients, and as such may have a role in perpetuating renal injury. AGEs are a heterogeneous group of compounds that are produced by nonenzymatic, sequential glycation and oxidation reactions of sugars with free amino groups on proteins, peptides, or amino acids. There are several pathways by which AGEs cause renal injury:

1. AGEs interfere with extracellular matrix proteins (collagen, elastin, and laminin) leading to alterations in both structure (induces fibrosis) and function (hydrophobicity, charge, elasticity, and turnover).
2. AGE–RAGE interactions. AGE may also produce cellular injury by a cascade of receptor-dependent (RAGE) events that leads to transformation of tubular cells into myofibroblasts, leading to development of tubular atrophy and interstitial fibrosis.
3. AGEs are also involved in receptor-independent interactions that lead to intracellular generation of reactive oxygen species (ROS). ROS activate signaling pathways (eg, mitogen-activated protein kinases, protein kinase C, Janus kinase/signal transducers and activators of transcription), which lead to proinflammatory (eg, nuclear factor kappa B [NF-κB], monocyte chemoattractant protein-1, tumor necrosis factor [TNF]-α) and profibrotic (eg, transforming growth factor [TGF]-β, connective tissue growth factor, platelet-derived growth factor [PDGF]) effects.
4. Accumulation of AGEs also leads to endothelial dysfunction (indirectly), increased thrombogenicity and accelerated atherosclerotic changes, and subsequent end-organ hypoperfusion.

Another maladaptive consequence is increased ammoniagenesis per remnant nephron. This effect promotes complement cascade activation and enhanced injury to the tubulointerstitium. These effects are thought to be related to the actions of excess aldosterone and endothelin-1 stimulated by impaired elimination of the daily acid load and subsequent acid retention (inherent in CKD). This concept has led to the notion that dietary alkali therapy may have a potential role in preserving GFR and delaying progression of CKD.

These various mediators promote fibrosis and scarring in the kidney through multiple untoward effects such as toxic radical formation, enhanced cellular proliferation, and collagen deposition in the glomerulus and tubulointerstitium. Ultimately, glomerulosclerosis and tubulointerstitial fibrosis occur and promote CKD.

TABLE 16-2. Risk Factors associated with Initiation and Progression of Chronic Kidney Disease

INITIATION FACTORS	PROGRESSION FACTORS
Systemic hypertension	Older age
Diabetes mellitus	Male gender
Cardiovascular disease	Race/ethnicity
Obesity/metabolic syndrome	Genetic predisposition
Hyperuricemia	Poor blood pressure control
Smoking	Poor glucose control
Low socioeconomic status	Proteinuria
Nephrotoxins (NSAIDs, analgesics, herbal supplements, heavy metals, etc)	Cardiovascular disease
	Dyslipidemia, smoking, obesity/metabolic syndrome, hyperuricemia, low socioeconomic status
	ETOH consumption, nephrotoxins (NSAIDs, analgesics, herbal supplements, contrast material, etc)
	Acute kidney injury

Abbreviations: ETOH, alcohol; NSAIDs, nonsteroidal antiinflammatory drugs.

RISK FACTORS FOR PROGRESSION OF CKD

The risk factors for CKD progression can be classified into (Table 16.2):

1. *Susceptibility factors*—These are the factors that predispose to CKD. These include genetic and familial predispositions, race, maternal-fetal factors, age, and gender.
2. *Initiation factors*—These are the factors that precipitate injury to the kidneys.
3. *Progression factors*—These are the factors associated with progression of damage to established kidney disease.

These factors are further classified as either modifiable or nonmodifiable, based on feasibility for intervention. Below are the modifiable risk factors for progression.

Hypertension and the RAAS

Hypertension is clearly associated with progression of CKD and is the second most common cause of ESRD. Importantly, hypertension is present in the majority of CKD patients, making it a key risk factor for progression. Most studies, with a few exceptions confirm that hypertension hastens the course of CKD to ESRD in both diabetic and nondiabetic patients. The MDRD study demonstrated that proteinuric patients, when randomized to a lower BP, manifested a slower decline in GFR. Also, significant correlation between the achieved BP and the rate of renal function decline, especially in patients with greater than 1 g/day of proteinuria, was noted. The Joint National Committee (JNC VII) recommends the following BP target goals:

1. CKD with less than 1 g/day of proteinuria: 130/80 mmHg.
2. CKD with more than 1 g/day of proteinuria: 125/75 mmHg.

Since the JNC VII Guidelines were published in 2003, several studies have questioned the recommendation of targeting a BP of 130/80 mmHg in CKD patients without albuminuria. Studies suggest that data from the general population are not necessarily applicable to the CKD population. Furthermore, some suggest that tight BP control may have adverse consequences particularly in the elderly and those with coronary artery disease. Several randomized controlled trials (RCTs) failed to demonstrate a significant benefit of aggressive lowering of in those without proteinuria. The AASK (African American Study of Kidney Disease and Hypertension) found there was notable benefit in targeting a lower BP (mean arterial pressure [MAP] ≤92 mmHg) for those with urine protein-to-creatinine ratio greater than 220 mg/g, whereas, no benefit was seen in those with urine protein-to-creatinine ratio less than 220 mg/g. A similar finding was demonstrated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, whereby a target systolic BP less than 120 mmHg was not significantly beneficial, as opposed to a target systolic BP less than 140 mmHg. Analysis of the effect of BP control on progression to ESRD was assessed in 16,128 CKD patients in the Kidney Early Evaluation Program (KEEP). In this large, diverse population, progression to ESRD started at a systolic BP of 140 mmHg rather than the recommended goal of 130 mmHg. Progression was highest in those with a systolic BP at least 150 mmHg. Thus, we may need to change target BP for CKD patients.

Proteinuria is a powerful risk factor for progression of CKD, especially as levels exceed both 1 and 3 g/day, respectively. Patients with high-grade proteinuria and

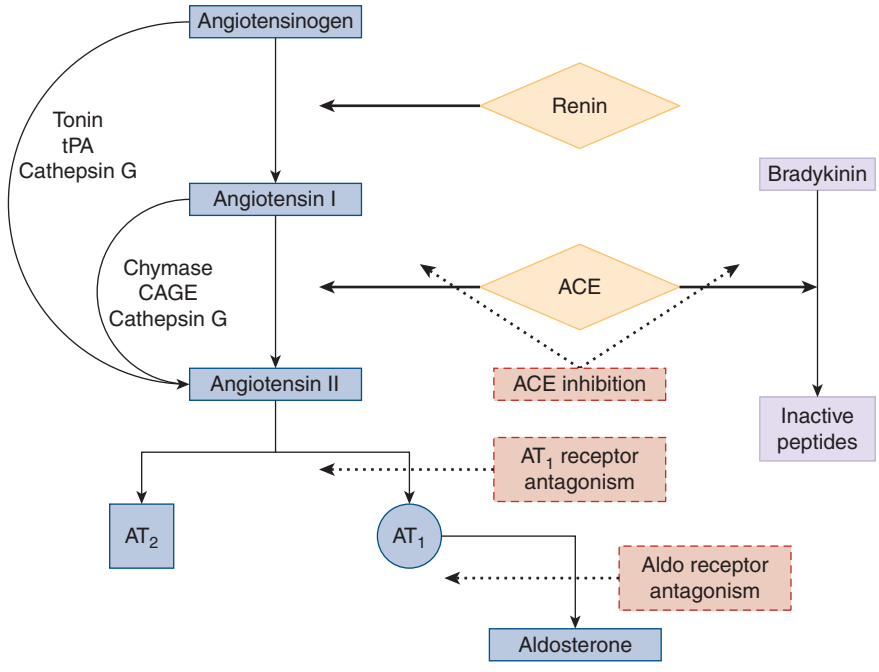

FIGURE 16-1. The RAAS. AII and aldosterone are formed by classical pathways (renin, angiotensin-converting enzyme [ACE]) and alternate pathways (tonin, tPA, cathepsin G, chymase, CAGE). The pathway is interrupted at various levels by ACE inhibitors, AT_1 receptor antagonists, and aldosterone receptor antagonists. *Abbreviations:* AT_1, angiotensin type 1; AT_2, angiotensin type 2; CAGE, chymostatin-sensitive angiotensin II-generating enzyme; tPA, tissue plasminogen activator. (Courtesy of Mark A. Perazella.)

hypertension are at highest risk to progress to ESRD. MDRD Study A data demonstrated significant benefit in kidney outcomes in patients with proteinuria greater than 1 g/day, particularly in those with GFR between 25 and 55 mL/min/1.73 m^2 and a trend toward benefit in patients with lower levels of proteinuria. This was supported by the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study, which also showed that a low BP target was beneficial in decreasing the risk of kidney outcomes in those with higher urine protein levels.

Both experimental and clinical data suggest that inhibition of the RAAS is very effective in lowering BP, reducing proteinuria, and slowing progression of kidney disease in both diabetic and nondiabetic patients. This is of particular interest as the leading cause of ESRD in the United States is diabetic nephropathy. Treatment of disease states resulting from or associated with excessive RAAS activity is best achieved by therapies that suppress AII and aldosterone production or inhibit the renal effects of these substances (Figure 16.1).

Inhibition of angiotensin-converting enzyme (ACE) activity decreases AII and aldosterone formation and potentiates the vasodilatory effects of the kallikrein-kinin system by increasing bradykinin formation (Figure 16.1). The ACE inhibitors reduce proteinuria and delay progression of kidney disease in both diabetic nephropathy and other forms of proteinuric kidney disease. In a landmark study, the effect of captopril versus conventional therapy on the occurrence of multiple renal end points (time to doubling of serum creatinine concentration, progression to ESRD, or death) was studied in 409 type 1 diabetic patients with proteinuria and CKD. A 50% reduction in the development of these renal end points was demonstrated in patients treated with captopril compared with conventional therapy, despite little difference in BP control. The beneficial effects of RAAS inhibition also extend to nondiabetic kidney diseases complicated by

proteinuria. The ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study compared the ACE-inhibitor benazepril with placebo in 583 nondiabetic patients with CKD. Benazepril was associated with an overall risk reduction of 53% in the development of the primary renal end point (doubling of serum creatinine concentration and need for dialysis) as compared with conventional antihypertensive therapy. In this trial, the absolute benefit of ACE inhibition was most marked in patients with the highest level of proteinuria. The Ramipril Efficiency in Nephropathy (REIN) study (stratum 2) confirmed these positive results in a similar group of nondiabetic patients. A 52% risk reduction in progression to kidney disease end points was seen with ramipril as compared with placebo. Renoprotection was most impressive in patients with greater than 3 g of proteinuria. A metaanalysis of data obtained from 1860 nondiabetic patients from 11 randomized clinical trials demonstrated significant renal protection with ACE inhibitors. ACE-inhibitor therapy was associated with a reduction in relative risk for the development of ESRD (0.69) and for the doubling of serum creatinine concentration (0.70). Thus, the benefit of ACE inhibition is most pronounced in patients with heavy proteinuria and a reduction in proteinuria correlates with slower declines in GFR.

AII type 1 receptor blockers (ARBs) lower BP, reduce proteinuria, and slow progression of kidney disease. Antagonism of the AT_1 receptor (see Figure 16.1) and binding of AII to the AT_2 receptor probably underlies their mechanism of action. Recently completed clinical trials suggest that ARBs reduce microalbuminuria and proteinuria and retard the progression of diabetic CKD in a fashion similar to the ACE inhibitors. The Reduction of End Points in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study compared the ARB losartan with conventional therapy in 1513 type 2 diabetics with hypertension and nephropathy. A 16% risk reduction was noted in predetermined primary composite end points (time to doubling of serum creatinine concentration, progression to ESRD, or death) in the losartan group over a mean follow-up of 3.4 years. This study demonstrated a 28% risk reduction in progression to ESRD and 25% reduction in doubling of serum creatinine concentration in patients treated with losartan. An average reduction in the level of proteinuria of 35%, despite similar BP control between the groups, was also noted. Similar findings were described in the Irbesartan Diabetic Nephropathy Trial (IDNT) study, which employed irbesartan in patients with type 2 diabetes mellitus and nephropathy. The Telmisartan Randomized Assessment Study in ACE-intolerant Subjects with Cardiovascular Disease (TRANSCEND) study, which included patients with vascular diseases and diabetes, showed that telmisartan significantly decreased the risk of composite kidney outcomes (as compared to placebo) in those with microalbuminuria (defined as urine microalbumin-to-creatinine ratio >3.4 mg/mol).

Like ACE inhibitors, interruption of the RAAS with ARBs in diabetics is a logical, albeit incomplete, strategy to provide renoprotection. In addition, both ACE inhibitors and ARBs are also associated with so-called off-target effects, which are not related to RAAS inhibition. For instance, the ARB losartan has the unique ability to increase urinary uric acid excretion. Other effects attributed to ACE inhibitors and ARBs include decreases in hemoglobin and serum cholesterol levels (especially in proteinuric subjects).

The choice between ACE inhibitors and ARBs in CKD, however, is an area of controversy. In general, the evidence for ACE inhibitors and improved kidney outcomes are older and mostly apply to type 1 diabetics. On the other hand, evidence for the use of ARBs in type 2 diabetics is contemporary. Data on cardiovascular protection in diabetic patients are noted with ACE inhibitors. Current evidence suggests that the effects of both agents are likely similar. A recent metaanalysis noted that there was insufficient evidence on the relative effects on survival when comparing both classes. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Randomized Assessment Trial (ONTARGET), which enrolled people with high cardiovascular risk (including those with diabetes and CKD), did not show a clear difference between the 2 classes of drugs. This study, however, was believed to be relatively underpowered for this comparison.

Previously, dual blockade of the RAAS with ACE inhibitors and angiotensin receptor blockers was considered to provide kidney benefit beyond therapy with either drug alone. One notable study that supported this notion was the Candesartan and Lisinopril Microalbuminuria (CALM) study. This study combined lisinopril and candesartan to treat hypertension and reduce microalbuminuria in patients with type 2 diabetes mellitus. Over 24 weeks, dual blockade safely reduced BP and reduced microalbuminuria (50%) as compared with candesartan (24%) and lisinopril (39%) monotherapy. Similarly,

a randomized double-blind crossover study in 18 type 2 diabetic patients with proteinuria demonstrated positive renal effects with combination therapy. In patients with immunoglobulin (Ig) A nephropathy, the combination of losartan and enalapril were additive in decreasing urinary protein excretion, whereas doubling the dose of either form of monotherapy had no effect on proteinuria. Over 6 months, the combination of lisinopril plus candesartan reduced proteinuria by 70% compared to monotherapy with lisinopril (50% reduction) or candesartan (48% reduction). Not all studies demonstrate that combination therapy is better than maximal dose ACE-inhibitor therapy in decreasing proteinuria. These studies suffer from small patient numbers, surrogate markers of renal protection (proteinuria), and short-term follow-up.

In a recent trial, combination RAAS blockade therapy was associated with an increase in adverse events, especially impaired kidney function and hyperkalemia, as compared with either agent alone. This occurred despite significant albuminuria reduction with combination therapy. In ONTARGET, combination therapy failed to improve cardiovascular end points despite additional BP reduction averaging systolic blood pressure 2.4 mmHg/diastolic blood pressure 1.4 mmHg. At the present time, dual RAAS blockade with an ACE inhibitor and an ARB is not recommended, a recommendation supported by the American Society of Hypertension's Position Article on combination therapies. Thus, titration of the single agent to maximal dose to control BP and proteinuria is recommended. If proteinuria remains greater than 1 g/day, a second agent to further block the RAAS is not recommended but may be useful in certain individuals. The risks and benefits of this therapy must be carefully weighed.

Aldosterone, the last hormone in the RAAS pathway is associated with renal injury through both hemodynamic and profibrotic effects. Aldosterone antagonism in animals is renoprotective when used alone or in combination with ACE inhibition. Preliminary human data suggest that the combination of an aldosterone receptor antagonist like spironolactone or eplerenone with an ACE inhibitor or ARB significantly reduce proteinuria. This therapy, however, is associated with higher risk of hyperkalemia.

Another class of drugs that act on the RAAS are the direct renin inhibitors (DRIs). Aliskiren, the first orally active DRI, decreases albuminuria when used in combination with losartan, in diabetic patients with proteinuria. This study also showed a near-significant trend toward a reduced GFR decline. However, a phase 3 study on type 2 diabetics with CKD combining aliskiren and another RAAS blocker, the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study, was terminated because of futility and an increased incidence of stroke and serious adverse events (hyperkalemia, hypotension, and ESRD or death as a consequence of CKD). At present, aliskiren is not recommended for diabetic patients, particularly in combination with ACE inhibitors or ARBs.

Finally, it is important to recognize that with close patient monitoring, RAAS inhibitors can be used safely in most patients with mild-to-moderate CKD. The 2 major concerns associated with these drugs are the development of hyperkalemia and/or further worsening of kidney function. In regards to hyperkalemia, careful dose titration, dietary changes, avoidance of potassium-altering medications (nonsteroidal antiinflammatory drugs [NSAIDs], cyclooxygenase [COX]-2 selective inhibitors, potassium-sparing diuretics, etc), and use of loop diuretics allow safe therapy in most patients. Increases in serum creatinine concentration should be tolerated as long as the concentration rises no higher than 30% above baseline and stabilizes within 2 months of therapy. Continued increases should promote drug discontinuation and a search for volume contraction, critical renal artery stenosis, and other potentially correctable problems.

Diabetes Mellitus

As the prevalence of diabetes mellitus grows in the United States, patients with this disease continue to contribute a significant number of patients to the CKD population. In fact, diabetic kidney disease is the most common cause of ESRD. Thus, it is important to identify and adequately manage these patients to reduce progression of their underlying kidney disease. As shown in the Diabetes Control and Complications Trial (DCCT), intensive insulin therapy to establish tight glucose control prevented de novo kidney disease (microalbuminuria) by 34% and reduced progression of established nephropathy (albuminuria) by 56% in type 1 diabetics. Progression of CKD in type 2 diabetics is an even bigger problem as this group makes up the majority of patients who develop ESRD. Earlier studies revealed that intensive insulin therapy to

maintain the glycosylated hemoglobin (HbA1c) level in the 7.0% to 7.6% range reduces progression of kidney disease (albuminuria/proteinuria) as compared with conventional insulin therapy.

Several trials conducted in diabetic patients to determine whether or not early and/or more intensive glycemic therapy might further decrease the frequency of CKD and ESRD. Aggressive glycemic control did not translate into better outcomes, and in certain situations, were harmful. Based on these trials, recommendations have been modified to target HbA1c approximately 7% to prevent or delay microvascular complications including overt diabetic nephropathy. Thus it appears that in diabetics with higher CKD stages, either high (>8% to 9%) or low (<7%) HbA1c levels are harmful in regards to mortality, progression of kidney disease and other clinical endpoints.

As HbA1c may not be truly accurate (falsely low as a result of decreased red blood cell [RBC] lifespan, transfusions, and hemolysis) in CKD patients, studies must adjust for this finding or develop another assay for these patients. To address this issue, research efforts are focused on glycated albumin as a measure of diabetic control in those with advanced stages of CKD.

Dietary Protein

Restriction of dietary protein reduces renal injury in the experimental setting by decreasing glomerular capillary hypertension and reducing production of profibrotic cytokines and growth factors. In humans, it is less clear that a low-protein diet is beneficial. The results of various studies are mixed. In the largest study, 2 levels of protein restriction (low and very low) failed to show a difference in GFR decline between groups after a mean follow-up of 2.2 years. Post hoc analysis identified some benefit of protein restriction when examined by achieved level of protein intake. Patients with the very low protein intake had a 1.15 mL/min/year slower decline in GFR. Two metaanalyses also suggest a benefit with protein restriction. In one, the risk of ESRD or death was reduced by 33% while another noted a small benefit in GFR change (0.53 mL/min/year) with a low-protein diet. Enthusiasm for this approach is tempered by the real risk of malnutrition in CKD patients.

Protein diets above the recommended daily intake may increase the rate of progression of kidney disease particularly in those with earlier stages of CKD. In the Nurses Health Study, the effect of protein intake over 11 years in 1624 enrolled females, divided into those with baseline GFR greater than 80 mL/min/1.73 m^2 (normal kidney function) and those with baseline GFR 55 to 80 mL/min/1.73 m^2, was examined. In those with normal baseline kidney function, there was no significant association between high protein intake and change in eGFR. However, in the latter group, protein intake was associated with a significant decrease in eGFR of approximately 1.69 mL/min/1.73 m^2 per 10-g increase in protein intake. This effect was most significant in those who consumed a diet consisting of high nondairy animal-protein content.

Current evidence supports no benefit to dietary protein restriction of less than 0.8 g/kg/day. However, high total protein intake (>1.3 g/kg/day), especially high nondairy animal-protein content, may increase the rate of GFR decline in CKD patients, and is therefore not recommended.

Hyperlipidemia

Experimental work demonstrates that low-density lipoprotein (LDL) lipids are toxic to human mesangial cells, an effect that is reversed by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). Observational studies in humans suggest that reducing serum lipid levels is associated with preservation of kidney function. Unfortunately, these studies are plagued by small patient numbers and as a result, are underpowered for drawing any conclusions. To address this problem, a metaanalysis of 13 studies revealed a trend toward reduction in proteinuria and a small decrease rate of GFR loss with lipid lowering.

Two large scale RCTs (Prevention of Renal and Vascular End-stage Disease Intervention Trial [PREVEND-IT] and European Study for Preventing by Lipid-lowering Agents aNd ACE-inhibition Dialysis Endpoints (ESPLANADE) failed to show a beneficial effect of statins on albuminuria in patients who were treated with ARBs. The SHARP (Study of Heart and Renal Protection) study, a randomized, prospective, controlled trial examining the combination of ezetimibe and simvastatin, showed that all-cause and cardiovascular mortality were not improved. Combination therapy did not decrease the risk of progression to ESRD in CKD patients who were not on dialysis at baseline, as compared with placebo. The primary mortality benefit of therapy was limited to patients with hyperlipidemia, particularly CKD Stages 3 and 4 (but not in

CKD Stage 5 or those on dialysis). Based on the results of SHARP, it appears that statin therapy does have a role—perhaps at least a statin combined with ezetimibe—in patients with CKD Stages 3 to 4. A major limitation is high cost.

Dietary Salt

CKD patients are at risk to develop salt and water overload as a consequence of reduced GFR, upregulated neurohormones, and other disturbed physiology. A direct correlation between a high sodium diet and increased arterial pressure, proteinuria, and decreased in GFR are well described.

A low-sodium diet may significantly reduce proteinuria and arterial pressure as shown in a crossover RCT where the addition of a low sodium diet to ACE inhibitor therapy significantly reduced proteinuria as compared with the addition of an ARB to ACE inhibitor therapy. Greater BP reduction was also noted with this approach. Current evidence supports lowering salt intake to less than 100 mmol (<2.4 g) per day of Na^+ to achieve these clinical end points.

Hyperuricemia

CKD patients often develop hyperuricemia and/or gout from their reduced GFR, diuretics, and other abnormalities. An association between hyperuricemia in the setting of CKD and both negative cardiovascular outcomes progression of CKD is noted.

Reduction of symptomatic or asymptomatic hyperuricemia with the use of xanthine oxidase inhibitors, such as allopurinol, may slow loss of kidney function in CKD patients with and without diabetes mellitus. In one study, this effect was independent of other risk markers, for example, albuminuria. Other uric acid-lowering drugs, such as rasburicase and losartan, are associated with improved outcomes in CKD. In an 8-week study comparing rasburicase and placebo, a single 4.5-mg dose of rasburicase significantly lowered serum uric acid levels and improved kidney function. The ARB losartan, by virtue of its ability to increase urinary excretion of uric acid, lowered serum uric acid levels and reduced doubling of serum creatinine or development of ESRD.

Smoking

Tobacco smoking may injure the kidney through various pathways. Hypertension complicates smoking, a well-known factor associated with kidney disease. Smoking also increases SNGFR and may promote progression of kidney disease through hyperfiltration and glomerular capillary hypertension. Finally, smoking raises aldosterone levels. As discussed previously, aldosterone may enhance kidney disease by increasing BP and direct profibrotic effects. In humans, smoking similarly injures the kidney and increases the risk of developing albuminuria in diabetics. Smoking cessation slows progression of kidney disease in patients with diabetic nephropathy and some nondiabetic forms of kidney disease. Given the overall negative health consequences associated with smoking, patients with CKD should be aggressively counseled to quit.

Obesity

Obesity is considered an independent risk factor for CKD. A metaanalysis of weight loss interventions in obese CKD patients showed an association between weight loss and a decrease in both proteinuria and systemic arterial pressure, with no demonstrable decrease in GFR during a mean follow up of 7.4 months. Weight loss interventions were shown to decrease proteinuria and albuminuria by 1.7 g and 14 mg, respectively. These effects were independent of BP reduction.

KEY POINTS

Progression of Chronic Kidney Disease

1. Adaptive changes to nephron injury promote various effects that ultimately contribute to progression of CKD.
2. Hypertension, hyperfiltration, hyperglycemia, high-grade proteinuria, and overactivation of the RAAS cause renal injury and progression of kidney disease to ESRD.
3. CKD patients with high levels of proteinuria are at highest risk to progress to ESRD.
4. Therapies that reduce BP to appropriate goals, reduce proteinuria, and inhibit the RAAS provide the most benefit to slow loss of renal function in diabetic and nondiabetic patients with proteinuric kidney disease.
5. ACE inhibitors and ARBs provide renoprotection in CKD patients; combination therapy with these drugs is currently not recommended. Addition of aldosterone antagonists to these 2 RAAS blockers may be beneficial in some patients, but must be done with close monitoring.

6. Tight glucose control in type 1 diabetics reduces progression of micro- and macroalbuminuria. However, tight control in type 2 diabetics may be less likely to improve renal outcomes and may be harmful.
7. Dietary protein restriction, serum lipid lowering with statins, dietary salt restriction, treatment of hyperuricemia, smoking cessation, and weight loss may also reduce progression of kidney disease in subgroups of patients.

CARDIOVASCULAR CONSEQUENCES OF CHRONIC KIDNEY DISEASE

Epidemiology

CVD is the leading cause of death in CKD patients. There is an increase in the overall prevalence of CVD in these patients. Left ventricular hypertrophy (LVH) and ischemic heart disease (IHD) are the most common manifestations of CVD in this population. This is not surprising given the shared risk factors (hypertension and diabetes mellitus) for both disease entities. Analysis of the Framingham study demonstrates that moderate CKD was associated with twice the prevalence of CVD and higher relative risks for both IHD and cerebrovascular accident (CVA) compared with individuals with normal kidney function. In a recent large cross-sectional study of 5888 elderly Medicare patients, the odds ratio for the presence of CVD was almost 2.5 times higher in CKD patients. In the Heart Outcome Prevention Evaluation (HOPE) trial, myocardial infarctions were more common in the subset of patients with CKD. A similar finding was noted in CKD patients compared with subjects from the general population in France.

Risk Factors

Many factors increase risk for CVD in CKD patients. The pathogenesis of cardiovascular damage in this group is far more complex than in the general population. Risk factors for CVD include those identified in the general population and additional ones associated with kidney disease (Table 16.3). Traditional coronary risk factors are highly prevalent in CKD patients. Diabetes mellitus is the most common cause of kidney disease in the United States and is present in more than 35% of patients with ESRD. Similarly, hypertension and dyslipidemia are rampant. A cross-sectional analysis involving patients enrolled in the MDRD trial noted that 64% were hypertensive despite therapy and more than half had elevated LDL cholesterol levels. "CKD-related" risk factors include the hemodynamic and metabolic abnormalities associated with kidney disease. Risk factors for CVD can be divided into "factors modified by CKD" such as hypertension, dyslipidemia, and hyperhomocysteinemia, and "CKD state-related risk factors" including anemia, hyperparathyroidism, malnutrition, and oxidative stress.

The uremic environment is also believed to influence the nature of atherosclerotic plaques in the CKD population. Interestingly, coronary lesions in CKD patients are uniquely characterized by increased media thickness, infiltration, and activation of macrophages and marked calcification. Nevertheless, the exact pathogenic mechanism(s) by which such uremic environment accelerates atherosclerosis is still not fully elucidated, but the notable presence of so-called nontraditional risk factors,

TABLE 16-3. Cardiovascular Risk Factors in Chronic Kidney Disease

TRADITIONAL RISK FACTORS	RISK FACTORS ALTERED BY CKD	CKD-RELATED RISK FACTORS
Hypertension	Dyslipidemia	Hemodynamic overload
Hyperlipidemia	High lipoprotein (a)	Anemia
Diabetes mellitus	Prothrombotic factors	Increased oxidant stress
Tobacco use	Hyperhomocysteinemia	Malnutrition
Physical inactivity	Hypertension	Hyperparathyroidism
	Sleep apnea	Elevated asymmetric dimethyl arginine (ADMA) levels

such as oxidative stress, inflammation, vascular calcification, and AGEs, increase as GFR declines. So-called uremic retention solutes, which may have proatherogenic properties, such as asymmetric dimethylarginine (ADMA), homocysteine, guanidine, indoxyl sulfate, and *p*-cresyl sulfate, are also seen elevated in CKD patients. Elevated levels of inflammatory biomarkers such as interleukin (IL)-6, TNF-α, Pentraxin 3, and C-reactive protein are also inversely related to the GFR level, and could probably be a result of decreased clearance.

Risk factor reduction is likely to be effective in reducing morbidity and mortality caused by CVD in patients with CKD as they are in the general population. An approach to risk reduction should target both the traditional coronary risk factors and specific risk factors related to CKD (see Table 16.3).

Traditional Risk Factors

Hypertension

Hypertension is a common problem in CKD and is associated with untoward vascular events. From a CVD perspective, the treatment of hypertension in CKD is incompletely studied. In Stages 3 to 4, antihypertensive therapy improves LVH, and a recent study of patients with polycystic kidney disease revealed better results in reduction of left ventricular mass (35% vs. 21%) in the group of patients whose target BP was 120/80 mmHg versus the conventional less than 140/90 mmHg. Patients with diabetic nephropathy have a reduction in hospitalization for first heart failure episode with AII receptor blockade. Large cohort studies reveal a protective effect associated with antihypertensive drug therapy. Exposure to calcium channel blockers or β-blockers was associated with decreased cardiovascular death in hemodialysis patients. ACE inhibitor effects are inconsistent across studies, but they are probably cardioprotective and reduce heart failure. Thus, hypertension is important in CKD because of its impact on both kidney disease progression and cardiovascular events. Lower BP targets lead to better control of LVH and likely cardiovascular outcomes.

Diabetes Mellitus

Patients with diabetes mellitus constitute a large portion of the CKD population. This comorbid condition increases their risk of CVD. In patients without significant degrees of renal dysfunction, several studies demonstrate the importance of markers of diabetic nephropathy on cardiovascular outcomes. The World Health Organization (WHO) Multinational Study of Vascular Disease in Diabetes, which included both type 1 and type 2 patients, demonstrated an almost 2-fold increase in the standardized mortality ratio of diabetic patients who had microalbuminuria. The addition of CKD increased this ratio to 2- to 3-fold depending on sex. It appears that diabetes mellitus is an independent risk factor for the development of de novo IHD and de novo heart failure in both CKD and ESRD patients.

Smoking

Smoking aggravates the excessive cardiovascular risk in CKD patients. A random sample of new ESRD patients in the United States noted that smokers had a 22% greater risk of developing coronary artery disease. Like hypercholesterolemia and older age, smoking strongly predicted the presence of carotid atherosclerosis in ESRD patients. Because smoking has a clear association with CVD in CKD patients, attempts at modifying its use are warranted. There are no published studies on the efficacy of different strategies for smoking cessation in patients with CKD or ESRD. Despite this, smoking cessation is an important preventive intervention.

Factors Modified by Chronic Kidney Disease

Dyslipidemia

The prevalence of hyperlipidemia in CKD is higher than in the general population but varies depending on the lipid, target population, course of kidney disease, and level of kidney function. Total or LDL cholesterol elevations are common in patients with CKD and nephrotic syndrome and ESRD patients on peritoneal dialysis (PD). Uremic dyslipidemia is characterized by increased plasma triglyceride with normal total cholesterol concentration. Very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) concentrations are elevated, whereas LDL and high-density lipoprotein (HDL) are decreased. Increased triglyceride and decreased HDL cholesterol concentrations are more severe in individuals with advanced CKD. Limited data suggest that lipid abnormalities increase CVD in CKD patients. For example, the incidence of myocardial infarctions in 147 CKD patients (CrCl of 20 to 50 mL/min/1.73 m^2) was approximately 2.5 times higher than in the general population. Patients with myocardial infarctions had lower HDL cholesterol concentrations and higher triglyceride, LDL cholesterol, apolipoprotein B, and lipoprotein (a) levels. Patients with CKD should be considered in the highest risk group as

defined by the National Cholesterol Education Program guidelines. LDL cholesterol concentrations greater than 100 and greater than 130 mg/dL are treatment-initiation thresholds for diet and drug therapy, respectively. Target LDL cholesterol concentrations are less than 100 mg/dL in CKD patients. Statins are the most effective therapy to reduce total and LDL cholesterol. Pharmacologic treatment of hypertriglyceridemia and of low HDL is not recommended unless LDL is also increased. Statins in combination with ezetimibe may further improve LDL cholesterol levels. Fibric acid analogs are the most effective in reducing triglycerides in CKD patients.

Serum lipid reduction with statin therapy is not beneficial to reduce mortality or cardiovascular complications (myocardial infraction [MI], CVA) in ESRD patients. The 4D (German Diabetes Dialysis Study) Study in type 2 diabetics on hemodialysis demonstrated no survival benefit for patients treated with a statin (vs. placebo), while the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) study showed no improvement in cardiovascular outcomes or mortality in ESRD patient on hemodialysis. Similarly, the SHARP study using a statin combined with ezetimibe offered no mortality (all cause and cardiovascular) benefit over placebo therapy in ESRD patients, although CKD patients did have a reduction in mortality.

Hyperhomocysteinemia

Hyperhomocysteinemia, an independent risk factor for atherosclerosis in the general population, is highly prevalent in CKD patients. It may also increase atherosclerosis in this group. Approximately 90% of ESRD patients have elevated plasma homocysteine levels, the result of impaired homocysteine metabolism. Treatment of this disorder with folates, vitamin B_6 and vitamin B_{12} supplementation seldom corrects the abnormal levels observed in ESRD patients. The clinical impact of lowering homocysteine levels with these drugs has not improved CVD outcomes. These vitamins have been demonstrated to lower homocysteine levels in CKD patients, yet have not been associated with improved CVD outcomes.

Hypervolemia

B-type natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) are used to estimate volume status in the general and heart failure populations. As concomitant congestive heart failure (CHF) portends a worse prognosis in patients with underlying CKD, early diagnosis and prevention could potentially translate into improved overall prognosis and outcomes. To achieve this goal, several cardiac biomarkers, such as cardiac troponins and BNP levels, have been examined in the CKD/ESRD population.

In individuals with normal kidney function, BNP secretion correlates with the severity of CHF and the degree of left ventricular dysfunction. In contrast, plasma BNP and NT-proBNP levels for detection and stratification of CHF tend to be less accurate in patients with CKD (GFR <60 mL/min/1.73 m^2) and ESRD. Although studies suggested the potential for natriuretic peptides to estimate excess fluid volume and dry weight in ESRD patients, their role remains limited. In general, only levels either in the normal range (normal volume status) or grossly elevated (volume overloaded) are useful in patients with kidney disease.

Chronic Kidney Disease-Related Risk Factors

Anemia

Anemia in ESRD dialysis patients is associated with adverse cardiovascular outcomes in many observational studies. Under uremic conditions, the hemodynamic changes associated with anemia are maladaptive, resulting in irreversible hypertrophy and arteriosclerosis. As noted in observational studies, a decrease in hemoglobin (Hb) level of 1 g/dL incrementally increases the risk of mortality by 18% to 25% and of LVH by approximately 50%. Anemia is also a cardiac risk factor in CKD patients. As an example, CKD patients with a 0.5 g/dL decrease in Hb concentration have a 32% increased risk of left ventricular growth. Correction of anemia may improve cardiovascular function through multiple effects. Regression of LVH occurs in CKD patients after 12 months of erythropoietin treatment aimed at normalizing hematocrit (Hct), in the absence of better BP control.

Several observational studies demonstrated cardiovascular and other benefits with anemia correction with erythropoiesis stimulating agents (erythropoietin, darbepoetin) in CKD and ESRD patients. However, as is discussed later, correction of anemia with erythropoiesis-stimulating agent (ESA) therapy in both CKD and ESRD patients has not improved most clinical outcomes, and in some cases is associated with adverse events (CVA). It is not clear if this is the result of ESA therapy itself or higher Hb targets. Regardless, a more tempered approach to anemia management with ESAs is recommended.

Hyperparathyroidism

As revealed in many observational studies, disturbances of calcium and phosphate metabolism may increase CVD in CKD patients. Elevated serum calcium and phosphate, secondary hyperparathyroidism, administration of calcium-containing phosphate-binding agents, and vitamin D supplementation were implicated as risk factors for increased cardiovascular complications, possibly through end-organ calcification. Calcifications of the coronary arteries, valves, and myocardial tissue, as well as diffuse myocardial fibrosis are common pathologic findings in uremic hearts. Hyperphosphatemia is strongly associated with mortality in ESRD patients. The adjusted relative risk of death is greater at serum phosphorus levels greater than 6.5 mg/dL and when the calcium and phosphorus product is greater than 72 mg^2/dL^2. Increased mortality is caused by an increase in cardiac deaths, suggesting that correction of hyperphosphatemia may be important to reduce cardiac morbidity and mortality, especially in the early stages of CKD.

Efforts should be made to reduce hyperphosphatemia and hyperparathyroidism through strict phosphorus control and judicious use of vitamin D derivatives. Although non–calcium-containing binders may have additional benefits to reduce surrogate end points such as coronary, vascular and valvular calcifications, reductions in cardiovascular complications have not been clearly documented. Surprisingly, correction of hyperphosphatemia with 3 phosphate binders (calcium acetate, sevelamer carbonate, lanthanum carbonate) in ESRD patients was associated with more coronary calcification as compared with placebo. Calcimimetics may also play an important role in CVD reduction by improving parathyroid hormone (PTH) levels and calcium-phosphorus products in CKD patients, but again the data are far from certain. For example, the EVOLVE (Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events) study examined ESRD patients treated with cinacalcet versus placebo. Patients were evaluated for the composite primary outcome of all-cause mortality or first nonfatal cardiovascular event, including MI, hospitalization for unstable angina, heart failure, or peripheral vascular event. Unfortunately, despite biochemical improvement, there was not a statistically significant reduction in the primary outcome. This speaks to the complexity of CVD risk factors in patients with CKD and ESRD.

KEY POINTS

Risk Factors

1. CVD is common in CKD patients and is associated with increased risk of mortality.
2. Several risk factors are present in CKD patients that increase the prevalence of CVD, including traditional factors, factors modified by CKD, and factors related to the CKD state.
3. Hypertension and diabetes mellitus are the major factors contributing the large CVD burden in CKD.
4. Anemia increases the development of LVH, a prominent risk factor for untoward cardiovascular events. However, anemia correction with ESAs has not improved CVD outcomes.
5. Calcification of the vasculature from hyperphosphatemia, a high calcium-phosphorus product, and perhaps excessive calcium intake may also contribute to CVD.
6. CVD in CKD and ESRD is complex and multifactorial, likely explaining the lack of effective single therapies to reduce cardiovascular death and other adverse outcomes.

CLINICAL MANIFESTATIONS OF CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE

Left Ventricular Hypertrophy and Coronary Artery Disease

LVH is present in nearly three-quarters of CKD patients initiating dialysis. Indirect evidence suggests that LVH develops progressively in these patients over the years preceding dialysis initiation. The prevalence of LVH approaches 40% in CKD patients; higher rates occur in patients with lower GFR values. In addition, eccentric rather than concentric LVH is found to be twice as prevalent, suggesting a prominent role for anemia in the genesis of hypertrophied left ventricles in CKD patients. In Canada, the prevalence of IHD approaches 39% to 46% in patients with CKD.

Coronary artery disease is also more severe with advanced renal dysfunction. The prevalence of calcified lesions is inversely related to GFR levels, and as compared to the general population, coronary lesions tend to be more proximal in location, and this may account for the higher post-acute MI mortality in CKD patients. Thus, it is well established that CVD is prevalent in CKD patients.

CKD patients with CVD have worse outcomes than the general population. In ESRD patients commencing dialysis, the presence of LVH is independently associated with increased mortality. The risk of death over the first year following a MI in this group is almost twice that of the general population. Similar findings are seen in CKD patients. The presence of mild-to-moderate kidney disease is associated with an increased risk of overall cardiovascular mortality.

A number of studies documented a worse outcome after a MI in CKD patients. This may be partly a result of undertreatment of these patients with state-of-the-art therapies for CVD. Fear of exacerbating underlying kidney function with inhibitors of the renin-angiotensin system, contrast material, and aspirin explain this therapeutic approach. Risk of bleeding complications from thrombolytics employed for acute coronary syndromes in CKD patients with dysfunctional platelets further reduces use of this potentially lifesaving therapy. There is also an increased risk for death after cardiac surgery. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, kidney disease conferred a higher risk of death among patients with ventricular dysfunction. Similarly, a higher risk of death and other cardiovascular events in CKD patients were noted in the HOPE trial. In summary, CKD patients appear to possess a higher risk of death from CVD.

Peripheral Vascular Disease

Peripheral vascular disease (PVD) is also prevalent in CKD patients, reaching 20% in one study. The risk for PVD is highest for CKD patients on dialysis with underlying diabetic nephropathy or premature atherosclerosis. Known predisposing factors include duration of dialysis, hypoalbuminemia, low PTH levels, and low predialysis diastolic BP. Vascular medial calcification of large peripheral arteries is commonly seen and is in part caused by diabetic vasculopathy or calcific uremic arteriolopathy. PVD is also associated with increased mortality; outcomes after revascularization are generally worse than those of the general population, reflecting advanced vasculopathy and vascular calcification.

Cerebrovascular Disease

CVAs occur at higher rates in CKD and ESRD patients. In the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS), the prevalence of cognitive impairment increased by approximately 10% per 10 mL/min per 1.73 m^2 decline in patients with eGFR less than 60 mL/min per 1.73 m^2. In a univariate model, microalbuminuria was associated with a 1.5- to 2-fold increased stroke risk. In the USRDS 2008, strokes accounted for 4% of ESRD deaths. Thus, CVA is also an important complication in this patient group.

Atrial Fibrillation

Atrial fibrillation has also been shown to be more common in CKD patients, and this has been attributed to shared risk factors such as older age, hypertension, CHF and obesity. In a cohort study of 1018 hypertensive patients, CKD was independently associated with the risk of incident atrial fibrillation. Importantly, anticoagulant treatment of atrial fibrillation in CKD and ESRD patients is difficult and often complicated by adverse events (bleeding, hemorrhagic CVA, calcific uremic arteriolopathy [CUA] if on warfarin).

ANEMIA OF CHRONIC KIDNEY DISEASE

Anemia is a common and early complication of CKD. It is characterized by normochromic normocytic RBCs. In 5222 prevalent patients with CKD, mild anemia, defined as a Hb level less than 12 g/dL, was found in 47% of the cohort. The degree of anemia was most marked in patients with the lowest GFRs. Anemia however can develop in patients with GFR levels as high as 60 mL/min. Anemia guidelines for CKD patients recommend anemia workup and treatment for all Stage 3 or 4 CKD patients. Patients with GFRs less than 60 mL/min/1.73 m^2 and Hb less than 11 g/dL (premenopausal females and prepubertal patients) or Hb less than 12 g/dL (adult males and postmenopausal females) should be evaluated. Hb is the recommended parameter for the evaluation and management of anemia, given the wider variations seen in Hct values and instability of samples.

Anemia evolves in patients with CKD for a variety of reasons (Table 16.4). Decreased RBC production, decreased RBC survival, and blood loss all contribute to anemia. The primary cause of anemia in patients with CKD is insufficient production of erythropoietin by the diseased kidneys. This is supported by a state of "relative" erythropoietin deficiency in CKD patients, as levels are inappropriately low for the degree of anemia compared with normal individuals. Finally, an improvement in the RBC count is seen almost uniformly following therapy with exogenous erythropoietin.

TABLE 16-4. Causes of Anemia in Chronic Kidney Disease

Low erythropoietin production
Iron deficiency
Inflammation/infection (cytokines, hepcidin)
Blood loss
Hemoglobinopathies
Severe secondary hyperparathyroidism
Aluminum toxicity
Folate/B_{12} deficiency
Shortened red cell survival
Other (hypothyroidism, ACE-inhibitors)

A common secondary cause of anemia is iron deficiency. Blood loss from phlebotomies associated with laboratory testing, occult gastrointestinal bleeding, decreased iron absorption, dietary restriction, and iron usage by exogenously stimulated erythropoiesis all contribute to the development and maintenance of iron deficiency. In an analysis of data from the NHANES III, 38.3% of 3453 anemic subjects with GFRs between 20 and 60 mL/min/1.73 m^2 had TSAT (transferrin saturation) values below 20%. Thus, all potential causes of iron deficiency must be fully evaluated in CKD patients. Acute and chronic inflammatory conditions (including infections) are another common cause of anemia and/or reduced response to ESA therapy in CKD and ESRD patients (Figure 16.2). Increased cytokines produced by

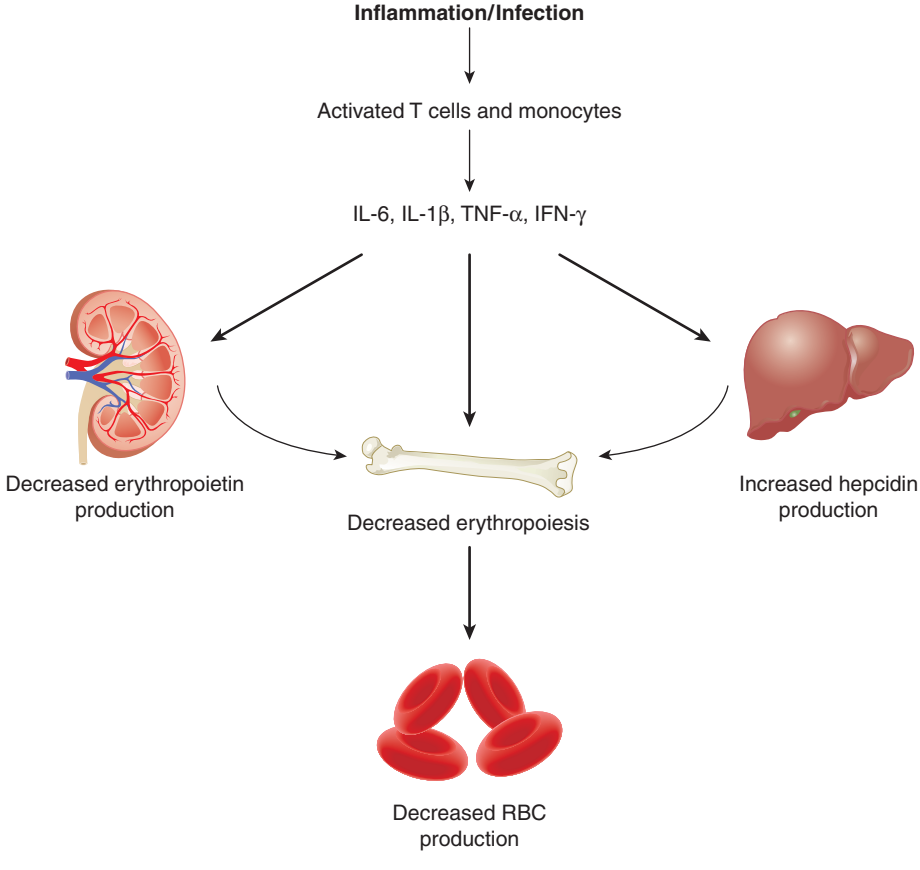

FIGURE 16-2. Effects of inflammation on development of anemia. Cytokine production stimulated by inflammation/infection decrease RBC production by reducing erythropoietin production, decreasing marrow response to erythropoietin, and increasing hepcidin production, which sequesters iron in the reticuloendothelial system, inducing a "functional" iron deficiency. *Abbreviations:* IL, interleukin; IFN, interferon; RBC, red blood cell; TNF, tumor necrosis factor. (Courtesy of Mark A. Perazella.)

these conditions reduce ESA response by RBC precursors and also increase production of hepcidin, which sequesters iron in the reticuloendothelial system and induces a functional iron deficiency. Other secondary causes of anemia in CKD include hypothyroidism, severe hyperparathyroidism, aluminum toxicity, folate and B_{12} deficiencies, shortened RBC survival, and hemoglobinopathies.

Evaluation of anemia in CKD patients should include the following tests:

- Hb and/or Hct
- RBC indices
- Reticulocyte count
- A test for occult blood in stool
- Iron parameters: serum iron, total iron-binding capacity (TIBC), percent transferrin saturation, and serum ferritin

Diagnosis of iron deficiency is not always straightforward in CKD patients. Functional iron deficiency, which refers to the imbalance between iron needed to support erythropoiesis and the amount released from storage sites, is often present. Serum ferritin values equal to or less than 30 ng/mL indicate severe iron deficiency, and are indicative of absent or low bone marrow iron. Values above 30 ng/mL have to be interpreted with caution because serum ferritin is a known acute phase reactant and can be affected by inflammatory processes. Thus ferritin can be elevated in CKD patients, particularly those on maintenance dialysis, in whom subclinical inflammation is common. TSAT generally reflects the amount of available iron necessary to support erythropoiesis. It is obtained by the formula: (serum iron/TIBC) × 100. Measurement of serum hepcidin levels is not clinically available and levels are not currently superior to standard iron tests. A ferritin concentration below 100 ng/mL is usually diagnostic of iron deficiency; however, the ferritin level may be elevated secondary to chronic inflammation or infection. Thus it is not always a reliable index of iron deficiency in CKD patients. TSAT is considered the best routinely available test of iron deficiency. A TSAT less than 20% usually indicates functional iron deficiency. Other tests, such as the proportion of hypochromic RBCs (>10% with corpuscular Hb <28 g/dL) and reticulocyte Hb content may improve the diagnosis of functional iron deficiency in CKD patients.

Effects of Anemia in Chronic Kidney Disease Patients

Anemia plays a major role in the quality of life in CKD patients and has pronounced effects on patient well-being. It may ultimately determine prognosis both prior to and after starting RRT. For these reasons, it is imperative that anemia is addressed and judiciously corrected in CKD patients, utilizing an individualized approach and not a fixed Hb target. The relationship between anemia and morbidity and mortality in dialysis patients is established by observational studies, but correction with ESAs has not improved these outcomes. As previously discussed, observational evidence similarly associates anemia and CVD in CKD patients. The effect of anemia on CVD appears to start many years prior to the development of ESRD. However, as in ESRD patients, anemia correction with ESAs in CKD patients is complicated and a judicious approach must be taken. This issue will be discussed later in the chapter.

Role of Anemia in Cardiovascular Disease and Mortality

Evidence supports a link between anemia and CVD. Anemia is independently associated with the presence of LVH in CKD patients and plays a significant role in its evolution. Evidence in favor of the connection of anemia and LVH includes data generated from a cross-sectional study of 175 patients with mean CrCl of 25.5 mL/min. A decline in Hb of 1 g/dL was associated with a 6% independent increased risk for LVH. More severe LVH is seen with lower Hb levels. Anemia may also increase oxidative stress. Other factors peculiar to CKD such as the uremic milieu, calcification, hypertension, and volume overload contribute to the maladaptive cardiac response to anemia. Cardiac fibrosis and potentially irreversible LVH may result from these factors.

Several observational studies document that correction of anemia in ESRD patients reduces left ventricular mass index, improves ejection fraction (EF), and mitigates ischemic changes that develop during stress tests. Similar limited data are available in CKD patients, although small numbers of patients with severe LVH and advanced kidney disease were studied.

Other Benefits of Anemia Correction

Correction of anemia in CKD patients includes other benefits such as the following:

1. Improved sense of well-being, quality of life, neurocognitive function, and work capacity (primarily observational studies).
2. Reduced need for packed RBC transfusion.

3. Reduced allosensitization pretransplantation.
4. Reduced hospitalization (observational studies only).

Effect of Anemia Correction on Kidney Function

Worsening of kidney function with anemia correction by recombinant human erythropoietin (rHuEpo) was an initial concern based on data from an animal model of kidney disease. Uncontrolled hypertension rather than correction of anemia was the probable cause of worsening kidney function. Studies in humans uniformly show no effect of exogenous erythropoietin therapy on renal function in CKD patients. Of interest, a beneficial effect of anemia correction on renal function was noted in small, uncontrolled studies. Correction of anemia slowed the progression of CKD and the potential mechanisms for such a desirable benefit was speculated to be a result of correction of anemia/hypoxia-induced interstitial fibrosis and the antiapoptotic effect of erythropoietin. Several in vitro studies also supported a kidney protective effect of erythropoietin. However, RCTs do not support a renoprotective effect of ESAs in patients with either CKD or acute kidney injury (AKI). Thus, anemia correction with these drugs is neither harmful nor beneficial to kidney function in CKD patients.

Effect of Anemia Correction on Blood Pressure Control

Anemia correction with ESAs may increase BP in CKD patients. Concerns for severe hypertensive crisis and seizures were prominent following initial experience with rHuEpo. The increase in BP that develops with ESA is caused by an increase in systemic vascular resistance as well as direct and indirect pressor effects of the drug. These initial concerns, however, were almost entirely alleviated when the rate of Hb correction was slowed to an average of 1 g/dL/month. Because hypertension may still develop with slower rates of anemia correction, BP monitoring should be a standard part of ESA therapy. BP control is easily achieved with adjustments in antihypertensive regimens.

Therapy of Anemia in Chronic Kidney Disease

Recombinant human erythropoietin and darbepoetin both successfully correct anemia in patients with CKD. Optimal target Hb levels are unknown. The Hb targets have changed numerous times as observational data were corrected by the publication of RCTs. Initiation and maintenance dosing of ESA therapy in CKD patients must balance the benefits of improving anemia-related symptoms and reducing RBC transfusions with the potential harms of stroke and hypertension. Although there is no clear consensus regarding actual target Hb levels in CKD patients (who are not on dialysis), the latest Food and Drug Administration (FDA) guidelines recommend initiation of ESA therapy when Hb is less than 10 g/dL, and decreasing it or interrupting the dosing regimen when it is greater than 10 g/dL. This dose adjustment should take into consideration other factors such as symptoms, comorbid conditions, requirements for blood transfusion, and transplantation status. They also recommend that the Hb target should *not* exceed 13 g/dL. KDIGO clinical anemia guidelines are similar to the FDA recommendations. KDIGO guidelines suggest initiating ESA therapy for nondialysis CKD patients when the Hb is less than 10 g/dL, once all other reversible forms of anemia have been addressed. The guidelines recommend that ESA therapy *not* be used to maintain Hb above 11.5 g/dL, although individualization is allowed for those who might benefit from a higher level, but *never* to exceed 13 g/dL. Adjuvant therapies for anemia, such as vitamins C, D, and E, folic acid, L-carnitine, and pentoxifylline are not recommended.

The above recommendations were based on several RCTs that collectively demonstrated that full correction of anemia with an ESA was potentially harmful. One of the earlier RCTs addressed the issue of full correction versus partial correction of anemia, in ESRD patients on hemodialysis with underlying symptomatic heart failure or IHD. This study was terminated early because of the concern that correction of Hct to normal levels (~40%) was associated with harm in subjects, although some tried to blame intravenous iron as the cause of the harm. A subsequent study using a target Hb of 13.5 to 14.5 g/dL noted a beneficial effect on left ventricle (LV) volume and LV mass index, but a higher (not significant) stroke incidence in those patients who achieved that Hb level with the use of erythropoietin.

Three landmark studies confirmed that a higher target Hb level in CKD patients offered no benefit and was potentially harmful. In the multicenter, randomized, open-label Cardiovascular Reduction Early Anemia Treatment Epoetin beta (CREATE) study, the high Hb group (13 to 15 g/dL) gained no clinical outcomes

benefit and more of them required dialysis as compared with the low Hb group (10.5 to 11.5 g/dL). The U.S. Correction of Hemoglobin and Outcomes in Renal Insufficiency (US CHOIR) study, which was terminated after only 16 months, also demonstrated that a Hb target of 13.5 g/dL in CKD patients was associated with increased risk of the primary composite end point (death, MI, heart failure hospitalization, and stroke) as compared with the group with a Hb target of 11.3 g/dL. Furthermore, there was no improvement in quality of life. Lastly, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study, the first randomized, double-blind, placebo-controlled trial designed to evaluate the effect of a Hb level of 13 g/dL on the risk of death, cardiovascular events, and progression to ESRD in type 2 diabetics with Stage 3 or 4 CKD, further argued against higher Hb targets. A significant increase in stroke, particularly in those with prior histories of stroke, and increased venous thromboembolic events were noted in the higher Hb group, despite only achieving 12.5 g/dL. Post-hoc analysis of the TREAT study revealed a significantly higher death rate from cancer in those who received darbepoetin and had an underlying malignancy at baseline. Thus, full correction of anemia cannot be recommended given the absence of scientific evidence supporting beneficial effects and the potentially harmful clinical outcomes described in the RCTs.

Subcutaneous injection is the preferred route of ESA administration. Self-administration is simple and well tolerated by most patients. Some patients experience minor pain at the site of injection. rHuEpo is usually given on a weekly or twice-weekly basis. More frequent dosing may be required at initiation, depending on the degree of anemia. After attaining target Hb, many patients may be subsequently maintained on weekly injections. The recommended starting dose of rHuEpo is 50 to 100 U/kg. Dosing changes for rHuEpo should not be done more frequently than every week, whereas the frequency for darbepoetin should be less. Hb is measured on a weekly basis during the initiation phase of therapy and until the target Hb level is attained. Thereafter, biweekly or monthly determinations are usually sufficient.

Darbepoetin is an erythropoietic agent with a longer serum half-life than rHuEpo. It differs structurally from rHuEpo by virtue of its higher sialic acid-containing carbohydrate content, an important determinant of the half-life of these molecules. It is generally given no more frequently than once a week; bi- or triweekly use may be sufficient to correct anemia. The starting dose for darbepoetin is 0.45 μg/kg weekly or 0.75 μg/kg every 2 weeks for those on dialysis and 0.45 μg/kg at 4-week intervals. Most patients will require either a dose of 25 or 40 μg. The safety profile of this long-acting erythropoietic agent is similar to that of rHuEpo.

As erythropoiesis is stimulated and the marrow produces RBCs, iron stores are rapidly used. Many patients will require iron supplementation to maintain erythropoietic responsiveness. Oral supplementation can be effective for nondialysis CKD patients, but intravenous iron preparations may be required. The most commonly utilized intravenous iron preparations to replete iron stores in CKD/ESRD patients are sodium ferric gluconate, iron sucrose, and ferumoxytol. Iron indices such as TSAT and ferritin are followed on a regular basis to guide iron administration. KDIGO guidelines suggest initiating iron therapy when TSAT is less than 30% and ferritin is less than 500 ng/mL. The acceptable range for TSAT is between 30% and 50%, and for ferritin, it is between 500 and 800 ng/mL. Iron therapy is unlikely to provide any further benefit by exceeding the upper limits and risks iron overload and perhaps infectious risk. Suboptimal response to ESA therapy includes inflammatory states, gastrointestinal blood loss, and primary hematologic disorders. These should be fully investigated as clinically indicated. Intravenous iron should not be administered to patient with active systemic infections.

When managing chronic anemia in CKD patients, KDIGO guidelines note that the benefits of RBC transfusions may sometimes outweigh the risks in patients in whom ESA therapy is ineffective (hemoglobinopathies, bone marrow failure, ESA resistance) and the risks of ESA therapy may outweigh its benefits (previous or current malignancy, previous stroke).

KEY POINTS

Anemia of Chronic Kidney Disease

1. Anemia commonly occurs when GFR reaches 30 to 40 mL/min in CKD patients, but may occur earlier.
2. Decreased red cell production (erythropoietin deficiency), reduced red cell survival, and enhanced blood loss (with iron deficiency) contribute to the anemia of CKD.

3. Iron deficiency is the most common cause of exogenous erythropoietin resistance in CKD patients. In anemic patients, iron therapy should be initiated when the TSAT is less than 30% and ferritin is less than 500 ng/mL. Inflammation and infection also frequently cause anemia in CKD patients.
4. Observational studies noted that correction of anemia was associated with reductions in adverse CVD and hospitalizations, improvements in well-being and neurocognitive function, and reductions in RBC transfusions and allosensitization pretransplantation. However, RCTs have failed to document improvements in mortality, CVD, hospitalizations, or quality of life.
5. Anemia is corrected in CKD patients with either subcutaneous recombinant erythropoietin or darbepoetin. Adequate iron stores are required to allow response to ESA therapy. There are no Hb targets for CKD patients; therapy should be individualized and based on symptoms, signs, and comorbidities.
6. To avoid severe hypertension and seizure, CKD patients receiving exogenous ESA therapy should have Hb corrected approximately 1 g/dL/month until target is reached.

METABOLIC MINERAL DISTURBANCES ASSOCIATED WITH CHRONIC KIDNEY DISEASE

In CKD patients, the incidence of hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism increase as GFR declines. Identification and treatment of mineral metabolism disturbances at an early stage in CKD may reduce many of their adverse consequences. These metabolic disturbances ultimately lead to a group of bone disorders collectively known as *renal osteodystrophy*.

Serum phosphorus increases as GFR declines below 60 mL/min/1.73 m^2. Approximately 15% of patients with a GFR from 15 to 30 mL/min and 50% of those with a GFR less than 15 mL/min have a serum phosphate greater than 4.5 mg/dL. PTH increases the renal excretion of phosphorus. In the short-term, this serves to maintain phosphorus homeostasis. As GFR falls below 30 mL/min/1.73 m^2 renal phosphate excretion reaches a maximum. Hyperphosphatemia directly increases PTH secretion and stimulates parathyroid cell proliferation and hyperplasia. Hyperphosphatemia also decreases expression of the calcium-sensing receptor. The calcium-sensing receptor is expressed on parathyroid cells and senses the extracellular fluid (ECF) calcium concentration. There is an inverse sigmoidal relationship between serum calcium and PTH with a nonsuppressible component of PTH secretion, even at high serum calcium levels. The PTH-calcium response curve is shifted to the right in CKD patients with secondary hyperparathyroidism. Decreased calcium sensing may be a result of reduced expression of the calcium-sensing receptor in parathyroid gland.

The conversion of 25(OH) D to its active metabolite $1,25(OH)_2$ D occurs mainly in the proximal tubule via the enzyme 1α-hydroxylase and is decreased in CKD patients. Phosphate retention is another feature of reduced GFR, which directly inhibits 1α-hydroxylase activity and prevents active vitamin D synthesis. Low 25(OH) D levels are commonly noted in CKD patients; they are more prevalent at lower GFR levels. Furthermore, delivery of 25(OH) D to the site of 1α-hydroxylase in the proximal tubule is limited in the setting of very low GFRs. Thus assessment of vitamin D nutrition by measurement of serum 25(OH) D is required.

Concentrations of $1,25(OH)_2$ vitamin D_3 decline early in the course of CKD (GFR ≤60 mL/min/1.73 m^2). $1,25(OH)_2$ vitamin D_3 is a potent suppressor of PTH gene transcription and parathyroid growth and cell proliferation. The vitamin D receptor and calcium-sensing receptor in the parathyroid are downregulated in CKD. Calcium-sensing receptor expression is also regulated by $1,25(OH)_2$ vitamin D_3. A decrease in calcium-sensing receptor expression decreases the responsiveness of the parathyroid gland to inhibition by calcium.

Hypocalcemia occurs late in the course of kidney disease, typically after changes in serum phosphorus, $1,25(OH)_2$ vitamin D_3, and PTH. Seven percent of patients with a GFR of 15 to 30 mL/min and 25% of patients with a GFR less than 15 mL/min are hypocalcemic. This divalent disorder increases PTH concentration by prolonging the half-life of the messenger ribonucleic acid (mRNA) and exacerbates secondary hyperparathyroidism.

The combination of all of the above mentioned biochemical abnormalities, particularly hyperphosphatemia, and other factors present in uremic serum, induce vascular smooth muscle cells to undergo transdifferentiation into osteoblast/chondrocyte-like cells. These cells

subsequently increase expression of bone-associated and mineralization regulating proteins, and increase extracellular matrix deposition.

Secondary hyperparathyroidism is a near universal complication of CKD that develops early in the course of the disease. PTH concentration begins to rise as the GFR falls below 40 mL/min. PTH production and secretion are regulated by phosphorus, $1,25(OH)_2$ vitamin D_3, and calcium. Alterations in these parameters, as noted above, increase the development of secondary hyperparathyroidism.

This complex interplay between biochemical abnormalities, bone and vascular calcification stimulated the KDIGO Work Group in 2006 to group these disorders under the designation of "Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)". It was thought that the consequences of mineral metabolism disorders extended far beyond bone and thus the term *renal osteodystrophy* did not accurately reflect the systemic nature of the disorder. Table 16.5 defines CKD-MBD.

The KDIGO group further expanded the term *renal osteodystrophy* to go beyond the more descriptive words that focused on bone turnover to fully assess turnover, mineralization and volume in a "TMV classification system." Initial definitions of renal osteodystrophy (see discussion below), still commonly used, were more descriptive in nature and designed to allow classification more for research purposes.

TABLE 16-5. Chronic Kidney Disease–Mineral Bone Disorder and Renal Osteodystrophy

CKD-MBD
• A systemic disorder of mineral and bone metabolism caused by CKD manifested by either 1 or a combination of the following: 1. Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism 2. Abnormalities of bone turnover, mineralization, volume, linear growth, or strength 3. Vascular or other soft tissue calcification
Renal Osteodystrophy
• An alteration of bone morphology in patients with CKD. • Bone morphology is 1 measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable only by histomorphometry of bone biopsy

Renal Osteodystrophy

Renal osteodystrophy is a group of metabolic bone disorders that develop as a consequence of kidney disease. They include osteitis fibrosa, osteomalacia, mixed uremic osteodystrophy, and adynamic bone disease. Osteitis fibrosa develops as a result of increased PTH concentration, which increases osteoblast and osteoclast number and activity (high bone turnover). Osteomalacia is caused by $1,25(OH)_2$ vitamin D_3 deficiency. It is characterized by low bone turnover with wide unmineralized osteoid seams and the absence of osteoclasts and erosive surfaces. Mixed uremic osteodystrophy has features of both osteitis fibrosa and osteomalacia. Adynamic bone disease is distinguished by a reduction in bone formation and resorption and is manifested histologically by thin osteoid seams with little or no evidence of cellular activity. It is associated with PD, higher doses of calcium carbonate as a phosphate binder, the presence of diabetes mellitus, $1,25(OH)_2$ vitamin D_3 treatment, and older age.

In patients with advanced CKD, the spectrum of renal osteodystrophy is similar to that observed in ESRD patients. Osteitis fibrosa is seen in 40% to 56%, osteomalacia in 2% to 11%, and adynamic bone disease in 27% to 48%. Few patients have normal bone histology. In patients with milder kidney disease, osteitis fibrosa and mixed uremic osteodystrophy are the most common histologic lesions found in 39.6% and 28.7% of patients, respectively. Osteomalacia is the least common abnormality (4.5% of patients). Normal bone histology is found in approximately 20% of those with less-severe kidney disease. Adynamic bone disease is noted in only 5.7% of those with milder CKD. The largest study examining 176 CKD patients with bone biopsy found osteitis fibrosa in 55.7%, mixed uremic osteodystrophy in 13.6%, and adynamic bone disease in 5.1%. Normal histology was seen in 25% and osteomalacia was observed in only 1 patient. Patients with normal histology had a significantly higher GFR than those with an abnormal bone biopsy.

Intact PTH (iPTH) is the most common biomarker used for the assessment of bone turnover and classification of renal osteodystrophy. However, wide variations exist among the many assays used in clinical practice, making it difficult to develop target iPTH values for CKD. The wide iPTH variability is likely a result of different antibodies, reactive hormone fragments, and lack of standardized assays and calibration methods. In

TABLE 16-6. Suggested Ranges for Parathyroid Hormone in Relation to Chronic Kidney Disease Stage

CKD STAGE	iPTH TARGET
Stage 3	35 to 70 pg/mL
Stage 4	70 to 110 pg/mL
Stage 5 including dialysis	150 to 300 pg/mL

Adapted from KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD.

general, iPTH levels consistently less than 65 pg/mL are associated with adynamic bone disease. iPTH levels consistently greater than 200 pg/mL are more often associated with osteitis fibrosa. Although bone biopsy is the gold standard, biomarkers such as iPTH are followed longitudinally in patients at high risk to develop renal osteodystrophy and those with bone disease that is likely to become more severe as kidney function deteriorates. Target levels for iPTH in advanced CKD were previously proposed by the Kidney Disease Outcomes Quality Initiative (KDOQI) (Table 16.6), but optimal target iPTH values are not established for patients with CKD. In general, therapy to lower iPTH is suggested when levels are above normal and consistently rising. Similarly, PTH lowering therapy is reduced when iPTH is consistently declining and indicative of over-suppression. Per the KDIGO CKD-MBD guidelines, the recommended iPTH target is 2 to 9 times the upper limit for the assay for those with Stage 5 CKD on dialysis.

The phosphatonin fibroblast growth factor 23 (FGF-23), which is secreted from osteocytes that are derived from osteoblasts, has generated renewed interest in regards to its role in bone metabolism in CKD. Serum FGF-23 levels are elevated in CKD, and serum intact FGF-23 levels increase with decreasing GFR. FGF-23 is stimulated in response to increased calcitriol, increased PTH, and increased serum phosphorus levels. It production reflects a feedback loop that inhibits calcitriol synthesis and increases calcitriol degradation, inhibits PTH secretion, and increases renal excretion of phosphorus. In the kidney and parathyroid gland, FGF-23 binds to its receptor and a coreceptor Klotho. It appears that FGF-23 and Klotho provide an important connection between bone and kidney, and bone and parathyroid glands. In this circumstance, PTH links kidney and bone and calcitriol links kidney, parathyroid gland, bone, and intestine (Figure 16.3). Thus a coupled relationship exists between all of these organs to tightly regulate calcium and phosphorus metabolism.

These complex multiorgan interactions give further credence to the notion that CKD-MBD is a systemic disorder that occurs when 1 of the major organs that control mineral homeostasis, the kidney, is affected or impaired. The exact mechanisms of these interactions are not yet fully understood, but the known association between CKD and the increased risk of CVD support that these derangements should be considered important cardiovascular risk factors.

Recent studies suggest that vascular calcification is a process that involves more than simple precipitation of calcium and phosphate. A complex series of events causes predisposed vascular smooth muscle cells to differentiate into osteoblasts or bone forming cells. Predisposing factors include the CKD-MBD milieu and chronic inflammation. Serum fetuin-A, which is a potent inhibitor of extraskeletal calcification, is reduced in CKD patients with severe vascular calcification. A direct correlation between low fetuin-A levels and decreased survival is noted in dialysis patients. Reduced levels of matrix GLA protein (warfarin), pyrophosphates, bone morphogenic proteins, and osteoprotegerin may also enhance vascular calcification.

One other consequence of CKD-MBD in ESRD patients is increased risk of hip and vertebral fractures. Those with adynamic bone disease appear to be at highest risk. Analysis of the USRDS database of whites starting dialysis between 1989 and 1996 showed the risk of hip fracture in women was 13.63 per 1000 patient years and in men was 7.45 per 1000 patient years. The relative risk for hip fracture in men and women was 4.44 and 4.40 times higher, respectively, in dialysis patients compared to age- and sex-matched controls. Although the age-specific relative risk was highest in the youngest age groups, the added risk of fracture associated with dialysis increased steadily with advancing age. Risk factors for hip fracture include age, white race, female sex, low body mass index (BMI), PVD, inability to ambulate, low albumin, and smoking. Data in CKD patients are not available, but their fracture risk is likely higher than the general population.

Treatment of Chronic Kidney Disease–Mineral and Bone Disorder and Renal Osteodystrophy

Treatment of CKD-MBD and renal osteodystrophy in CKD patients includes several targets. Hyperphosphatemia

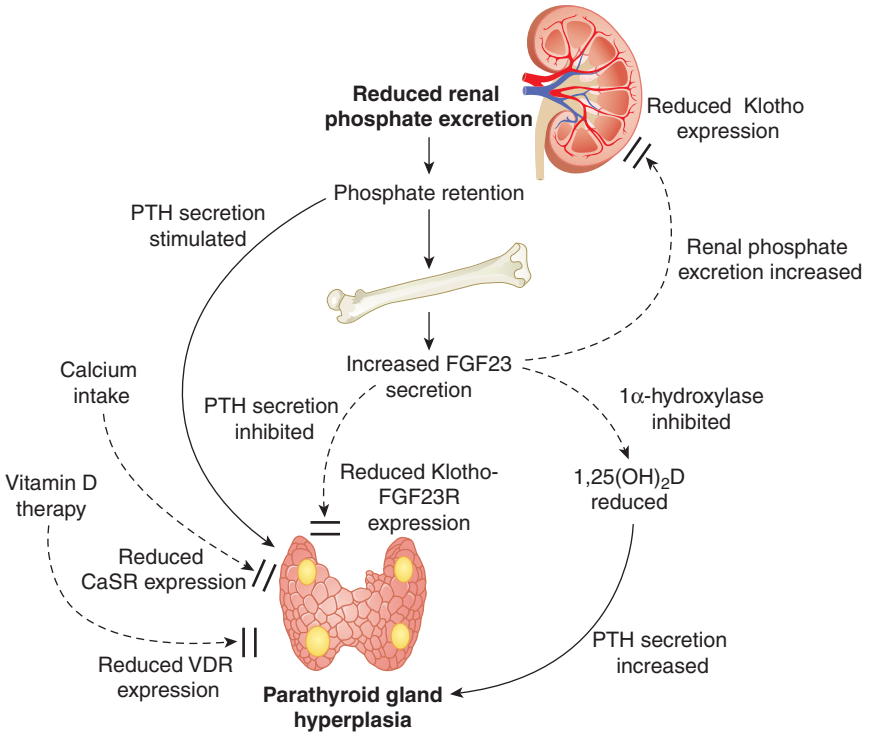

FIGURE 16-3. Mineral bone metabolism in CKD. Reduced kidney function is associated with a number of effects (phosphate retention, reduced 1α-hydroxylase activity, and reduced Klotho–FGF-23 receptor, CaSR, and VDR expression) that lead to parathyroid gland hyperplasia and other end-organ effects. *Abbreviations:* FGF, fibroblast growth factor; CaSR, calcium-sensing receptor; VDR, vitamin D receptor. (Courtesy of Mark A. Perazella.)

is initially controlled with dietary restriction. Ingestion of foods high in phosphorus should be minimized. As CKD worsens, oral phosphate binders are frequently required. The current goal of therapy in ESRD patients is to maintain the calcium-phosphorus product equal to or less than 55 and the serum phosphate equal to or less than 5.5 mg/dL. Concentrations above these increase the relative risk of mortality in ESRD patients. The recommended goals are slightly different for CKD patients. In CKD Stages 3 and 4, the serum phosphorus goal is equal to or less than 4.6 mg/dL, while the goal is equal to or less than 5.5 mg/dL for Stage 5 CKD.

The use of calcium-containing phosphate binders results in net-positive calcium balance in ESRD patients. This calcium may deposit in the vasculature and contribute to increased morbidity and mortality from ischemic coronary disease. Calcium-containing binders, although efficient and low in cost, may contribute to excess total-body calcium burden. Sevelamer carbonate, which replaced the hydrochloride-based binder, a synthetic calcium-free polymer has a favorable side effect profile but is costly. Aluminum is the most efficient binder and is relatively inexpensive, however, it has significant long-term toxicity (aluminum-related osteomalacia and dementia). Aluminum-containing phosphate binders should only be used in the short-term management of severe hyperphosphatemia (phosphate ≥8.5 mg/dL). Lanthanum carbonate, another non–calcium-containing phosphate binder provides generally safe and effective control of hyperphosphatemia. Like sevelamer, it is more costly than the calcium-containing phosphate binders. It is a disc that must be chewed and not swallowed intact.

Because hypocalcemia is a potent stimulator of PTH secretion, serum calcium should be corrected into the low-normal range. This can be achieved with oral

calcium; however, it should be employed cautiously as it may increase risk for vascular calcification and the development of adynamic bone disease when excessive amounts are consumed.

Acidosis is common in CKD patients. This disturbance increases bone loss, potentiates the effect of PTH and decreases $1,25(OH)_2$ vitamin D_3 production. Correction slows the progression of secondary hyperparathyroidism. Small studies support a potential role of bicarbonate supplementation in protecting the proximal tubule and delaying progression of kidney disease. Randomized studies have also confirmed that bicarbonate supplementation slows the rate of progression of kidney failure to ESRD in Stage 4 CKD patients. An added benefit is improved nutritional status. A serum bicarbonate goal of equal to or greater than 22 mEq/L can be achieved with 1 to 4 g of sodium bicarbonate daily with close monitoring for hypertension and fluid overload. Addition of a loop diuretic often allows continued sodium bicarbonate therapy in patients with hypertension and edema.

The optimal iPTH concentration in CKD patients is not established. In Stages 3 to 5 CKD, iPTH targets previously suggested by KDOQI are as noted in Table 16.6. However, these are no longer recommended as a result of assay problems causing wide iPTH variability. The first step in management is correction of hyperphosphatemia and hypocalcemia. If PTH remains elevated or these conditions are absent then vitamin D therapy will likely be required. In patients with low 25(OH) vitamin D levels, oral therapy with cholecalciferol or ergocalciferol may lower iPTH levels and reduce the need for active vitamin D therapy. However, if iPTH does not improve or continues to increase, active vitamin D therapy is warranted. Small doses of oral calcitriol (0.25 to 0.50 g/day) often stabilize and decrease iPTH levels. Paricalcitol (19-*nor*-1α-25-dihydroxyvitamin D_2), a vitamin D analog also effectively lowers iPTH levels with a dosing regimen of 1 to 2 µg/day. Decreases are primarily seen in patients with an iPTH less than 200 pg/mL. Pulse calcitriol therapy (2 g/week dosed 2 to 3 times per week) or pulse paricalcitol therapy (6 to 12 µg/week dosed 2 to 3 times per week) may be more effective and is associated with a lower risk of hypercalcemia. Doxercalciferol (1α-OH vitamin D) is another vitamin D option. It really offers no benefit over calcitriol or paricalcitol.

The calcimimetic cinacalcet is another drug that may be useful to control secondary hyperparathyroidism in patients with ESRD and CKD. Several studies document this drug's efficacy in suppressing both iPTH and serum calcium concentration. However, it may cause hyperphosphatemia when employed in the earlier stages of CKD. It may be particularly useful in CKD patients with secondary hyperparathyroidism that is refractory to conventional therapy (eg, vitamin D analogs and phosphate binders). RCTs examining the effect of cinacalcet on serum PTH, calcium and phosphorus levels demonstrate significant improvements in these biochemical parameters. In the largest reported trial, 1136 dialysis patients with secondary hyperparathyroidism were randomly assigned to traditional therapy plus cinacalcet or placebo for 26 weeks. Cinacalcet plus standard therapy not only decreased serum PTH levels but also calcium and phosphorus levels. In addition to decreasing PTH, cinacalcet also effects bone histology. A prospective, double-blind, placebo-controlled trial in dialysis patients with secondary hyperparathyroidism demonstrated that cinacalcet decreased bone turnover and tissue fibrosis. However, despite these improvements in biochemical data, as noted in the EVOLVE study, cinacalcet has not changed mortality or adverse cardiovascular events in these patients.

Parathyroidectomy is often reserved for treatment of ESRD patients who are refractory to medical management of secondary hyperparathyroidism. Over the past several decades, this surgical procedure has cycled several times between increased and decreased use. Over the past few years, the frequency of parathyroidectomy for secondary hyperparathyroidism has been on the decline. This trend likely reflects the utilization of various nonsurgical and pharmacologic options that suppress PTH secretion (paricalcitol, cinacalcet), as well the lack of evidence showing clear superiority of parathyroidectomy on meaningful clinical outcomes. KDIGO guidelines recommend parathyroidectomy only in symptomatic patients with advanced stages of CKD and those with Stage 5 CKD on dialysis, who have severe hyperparathyroidism unresponsive to conservative measures. Subtotal or total parathyroidectomy with autotransplantation performed by well-experienced surgeons effectively decrease PTH, calcium, and phosphorus levels. However, no RCTs directly compare medical with surgical therapy for hyperparathyroidism. Thus, the decision to perform surgery is more often related to the presence of symptoms associated with severe hypercalcemia, progressive extraskeletal calcification, CUA (with high iPTH), progressive and debilitating hyperparathyroid bone disease, or refractory pruritus. Surgery is generally effective, and with the

ability to measure intraoperative PTH levels, failure is rare. When surgical parathyroidectomy is deemed necessary but the patient is a poor operative risk, ethanol ablation of the glands can be performed using ultrasound guidance. However, some experience is required to perform this percutaneous procedure. Multiple injections are typically required to effectively control secondary hyperparathyroidism.

The devastating and highly mortal entity known as CUA or calciphylaxis requires aggressive management. The painful ischemic wounds and eschars require aggressive wound care to promote healing and prevent/reduce infection. In those with severe secondary hyperparathyroidism, either cinacalcet or surgical/percutaneous parathyroidectomy is required. Intensive dialysis to lower calcium and phosphorus concentrations, intravenous sodium thiosulfate infusions thrice weekly at the end of dialysis, and hyperbaric oxygen therapy improves pain control and heal wounds. Anecdotal evidence supports bisphosphonate therapy for CUA.

KEY POINTS

Metabolic Mineral Disturbances Associated with Chronic Kidney Disease

1. Disturbances in mineral metabolism develop early in CKD and include hyperphosphatemia, hypocalcemia, and low vitamin D concentration and secondary hyperparathyroidism.
2. Renal osteodystrophy consists of a spectrum of bone diseases in CKD patients. They include osteitis fibrosa, osteomalacia, adynamic bone disease, and mixed uremic osteodystrophy.
3. Hip and vertebral fractions are a complication of renal osteodystrophy in CKD patients.
4. Although bone biopsy is the gold standard, iPTH concentration is employed to guide management of renal osteodystrophy and use of vitamin D. However, its wide variability does not allow targets to be established for CKD patients (2 to 9 times above normal is the goal for Stage 5 CKD).
5. Phosphate binders, both calcium-containing and non–calcium-containing, are used to achieve serum phosphorus targets. Inactive and active vitamin D sterols are used to suppress iPTH levels and prevent/correct secondary parathyroid hyperplasia. Calcimimetics such as cinacalcet target parathyroid gland calcium sensing receptor and reduce PTH secretion and hyperplasia.
6. Parathyroid surgery (subtotal or total with autotransplantation) is often required to optimally control secondary hyperparathyroidism.
7. CUA should be managed with a multiinterventional approach, including wound care, antibiotics, intensive dialysis, intravenous sodium thiosulfate, and iPTH control (with cinacalcet or parathyroidectomy).

PREPARATION OF THE CHRONIC KIDNEY DISEASE PATIENT FOR RENAL REPLACEMENT THERAPY

A critical part of CKD care consists of the emotional and physical preparation of patients for the initiation of RRT. Evaluation and management of the patient with advanced CKD focuses on preparation for RRT. Importantly, improved predialysis care reduces the mortality rate for this high-risk group. To address this issue, the appropriate timing of nephrology referral, ESRD preparatory care, critical components of patient education and those resources available to patients, and the optimal time of RRT initiation is reviewed.

Nephrology Referral of Chronic Kidney Disease Patients

The population of patients with CKD is not uniformly monitored in the United States. As a result, most CKD patients are not prepared for entry into the world of ESRD. Less than half of new ESRD patients have permanent vascular access in place at the initiation of hemodialysis. Given the well-known advantages of permanent vascular access, there is room for improvement in preparatory phase of CKD patients.

A major reason for this problem is late referral (1 to 4 months prior to RRT) of CKD patients to nephrologists. Only about half of incident ESRD patients are seen by a nephrologist 1 year prior to initiation of ESRD care, and 30% are seen less than 4 months before RRT is begun. Late referral is associated with increased morbidity and a graded risk reduction for patient mortality is noted with early referral (>12 months). Multiple factors cause late referral of CKD patients to nephrology specialty care teams. Economic barriers (ie, lack of insurance), as well as patient factors that include denial, fear, and procrastination exist. Provider factors,

TABLE 16-7. Consequences of Late Referral

Severe metabolic acidosis
Severe hyperphosphatemia
Marked anemia
Hypoalbuminemia
Severe hypertension and volume overload
Low prevalence of permanent dialysis access
Delayed referral for renal transplantation
Higher initial hospitalization rate
Higher costs of initiation of dialysis
Increased 1-year mortality rate
Decreased patient choice in RRT modality selection

TABLE 16-8. Benefits of Early Referral to Nephrologist

Improved vocational outcomes
Delay in need to initiate RRT
Increased proportion of patients with permanent vascular access, particularly AVF > AVG (arteriovenous graft)
Patient modality selection differences—greater peritoneal dialysis usage
Reduced need for urgent dialysis
Reduced hospital length of stay and health care costs
Better metabolic parameters at dialysis initiation
Better patient survival

such as underappreciation of severity of kidney disease, fear of alarming the patient, lack of a multidisciplinary care team, and inadequate frequency of patient follow-up may contribute. Lack of training about both the appropriate timing and indications for referral of CKD patients to nephrologists also contributes to late referral. Finally, poor communication and feedback from nephrologists following CKD patients promotes late referral.

Late referral to the nephrologist is associated with diminished patient choice as well as adverse outcomes (Table 16.7). Patients referred late select PD as a dialysis modality less often. It also promotes delayed referral for renal transplantation evaluation and eliminates any possibility for preemptive renal transplantation. Resource usage is significantly higher when referral occurs late in the course of CKD, including higher initial hospitalization rates and cost of initiation of dialysis. Most importantly, overall patient mortality is greater. In contrast, early referral permits multidisciplinary predialysis education and improves vocational outcomes. It also delays progression of CKD, reduces requirements for urgent dialysis, and decreases hospital length of stay. Importantly, it increases native arteriovenous fistula (AVF) creation (Table 16.8). In certain patients (very elderly, older woman, short life expectancy, etc), an arteriovenous graft (AVG) may be a reasonable initial vascular access. The National Institutes of Health (NIH) Consensus Development Conference Panel published a consensus statement recommending nephrology referral of all CKD patients with a serum creatinine concentration greater than 2 mg/dL in men or greater than 1.5 mg/dL in women. The National Kidney Foundation (NKF) also recommends early referral to the nephrology team.

Components of End-Stage Renal Disease Care Preparation

A multidisciplinary clinic approach, consisting of physicians, social workers, nutritionists, and nurse coordinators, enhances the preparation of CKD patients for entry into ESRD care and initiation of RRT. The use of a multidisciplinary predialysis program to reduce urgent dialysis was studied. The proactive CKD care program reduced the number of urgent dialysis starts from 35% to 13%. It also decreased the number of hospital days during the first month of RRT and resulted in reduced costs per patient. Hence, a multidisciplinary team approach to CKD care improved preparedness for entry into the ESRD system and reduced healthcare resource usage. Education about the various dialysis options allows patients to make informed choices about the appropriate modality of RRT. As development of ESRD is emotionally traumatic news for most patients, early nephrology referral allows adequate time for the dialysis care team to assist in this aspect of CKD patient care.

The nephrologist should discuss modality options for RRT, including the specifics of hemodialysis, PD, and preemptive renal transplantation. If PD is the patient's preferred choice of RRT, the patient and/or the family can initiate PD training prior to the actual initiation of dialysis. If hemodialysis is selected, vascular access, preferably an AVF should be placed. Patients

should be counseled to protect their nondominant arm to protect veins for future AVF or AVG creation. Avoiding dialysis catheters is preferable, thus either an AVF or AVG is acceptable. KDOQI guidelines strongly encourage placement of permanent vascular access when serum creatinine concentration is greater than 4 mg/dL, the CrCl is less than 20 mL/min, or the development of ESRD is anticipated within 1 year. Preemptive renal transplantation requires a significant amount of time for planning and completion of medical testing. In some instances, the patient may elect not to initiate RRT. In this difficult situation, explicit counseling that outlines the serious consequences of this choice is mandatory and should include one or more members of the patient's family. In addition, an evaluation for major depression is required. The presence of depression precludes informed consent and requires further intervention by the family and judicial system (conservatorship). If this decision is ultimately chosen by the patient and is supported by the family, then end-of-life care should be pursued. Medical management without dialysis is a reasonable approach in patients who are poor candidates for chronic dialysis therapy.

As kidney disease progresses to ESRD, dietary modifications are necessary to avoid life-threatening volume overload, hyperkalemia, protein and caloric malnutrition, exacerbation of metabolic acidosis, and divalent ion derangements. Consultation with a renal dietician is essential to avoid or reduce the development of these complications. Medication adjustments by the nephrologist will also reduce these complications. Nutritional state should be assessed regularly and dietary counseling undertaken to optimize protein intake without inducing hyperphosphatemia, hyperkalemia, or metabolic acidosis.

To avoid information overload and patient confusion, the introduction of small amounts of new information at successive visits will reduce patient stress and improve understanding of their disease process and ultimate ESRD care plan. It is helpful for the primary provider to assess the patient's understanding of the aforementioned at follow-up visits. Reinforcement of correctly understood information and clarification of erroneous aspects of the patient's education are essential since cognitive deficits may exist in advanced uremia. Early education improves understanding by reducing anxiety and fear through preparation, allowing for choices, assuring informed consent, encouraging independence, and promoting a sense of patient self-control.

Initiation of Renal Replacement Therapy

Timely initiation of RRT is the final aspect of adequate preparation of the CKD patient. Absolute indications for dialysis include uremic serositis (especially pericarditis), uremic encephalopathy, refractory metabolic acidosis, hyperkalemia, or uncontrollable volume overload. Initiation of RRT is based on the combination of the presence of signs and symptoms of uremia, kidney function as assessed by estimated GFR (or CrCl), and patient preference. At the time of initiation of RRT, emotional and physical preparation of patients is key. This approach allows for a smooth transition and more stable entry into ESRD care or preemptive transplantation.

Early initiation of RRT for patients with advanced CKD became increasingly accepted as a beneficial approach by the nephrology community based on positive results from observational studies and publication of clinical practice guidelines. Early dialysis was believed to decrease mortality, hospitalizations, and cost of treatment. The Netherlands Cooperative Study on the Adequacy of Dialysis Study Group (NECOSAD) examined 253 patients who started RRT at different GFR levels: timely manner (GFR 7.1 ± 2.4 mL/min/1.73 m^2) and late (GFR 4.9 ± 1.7 mL/min/1.73 m^2). There was a small gain in survival time over 3 years from the time of initiation of RRT in the timely start group (2.5 months), however, there was no significant difference in survival between the 2 groups with long-term follow-up. This and other studies raised questions about the questionable benefit of earlier initiation of RRT.

Subsequently, several observational studies described increased mortality with early start dialysis. As a result of the observational nature of such studies, it was difficult to draw firm conclusions because of problems such as lead-time bias, survivor bias, and inaccuracies of estimating GFR in patients with decreased muscle mass or volume overload. To address the confounding inherent in these studies, a multicenter RCT was conducted among 828 adult patients with progressive CKD. They were randomized to either early (CrCl 10 to 14 mL/min) initiation of RRT or late (CrCl 5 to 7 mL/min) initiation of RRT. No difference in mortality was noted between the early and the late start groups and no difference in the secondary outcomes (cardiovascular events, infectious events and complications of dialysis). The effect of early initiation of RRT on survival was studies in 81,176 relatively healthy ESRD patients. The unadjusted 1-year mortality

was 6.8% in those with GFR less than 5 mL/min/1.73 m^2 as compared with 20.1% in those with GFR equal to or greater than 15 mL/min/1.73 m^2, supporting the potential harm associated with early initiation of RRT.

KEY POINTS

Preparation of the Chronic Kidney Disease Patient for Renal Replacement Therapy

1. The patient with advanced CKD requires emotional and physical preparation for the initiation of RRT.
2. Late referral to the nephrology care team is associated with increased morbidity and mortality in CKD patients.
3. A multidisciplinary clinic approach (physicians, social workers, nutritionists, and nurse coordinators) enhances the preparation of CKD patients for entry into ESRD care.
4. In patients with advanced CKD, dietary modifications are required to avoid life-threatening volume overload, hyperkalemia, acidosis, protein and caloric malnutrition, and disturbances in mineral metabolism.
5. Initiation of RRT is based primarily on the presence of signs of symptoms of uremia, and the level of kidney function.
6. Early initiation of RRT based on estimated GFR or CrCl offers no survival or overall benefits and is associated with potential harmful clinical outcomes.

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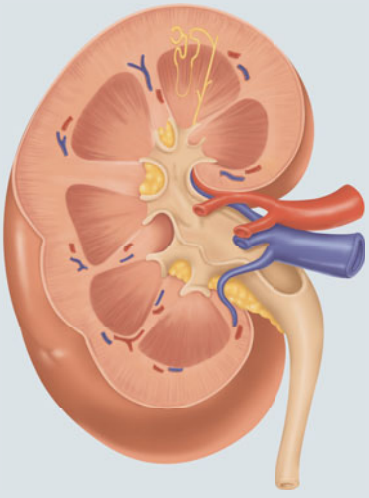

CHAPTER 17

Glomerular Diseases

• *Robert F. Reilly Jr. and Mark A. Perazella*

Recommended Time to Complete: 2 Days

Guiding Questions

1. What are the clinical presentations of glomerular disease?
2. Which primary renal diseases present as the nephrotic syndrome?
3. What are the 5 clinical stages of diabetic nephropathy?
4. Can you describe the characteristic findings on urinalysis of the patient with nephritis?
5. How does rapidly progressive glomerulonephritis (RPGN) present and what are its most common causes?
6. What is the serum antineutrophil cytoplasmic antibody test and how is it interpreted?
7. Which glomerular diseases commonly present with isolated abnormalities on urinalysis?

PRESENTATION OF GLOMERULAR DISEASES

Diseases that adversely affect the structure and function of the glomerulus present to the clinician in a limited number of ways. Glomerular diseases can be grouped into 4 clinical syndromes: the nephrotic syndrome, the nephritic syndrome, RPGN (a variant of the nephritic syndrome), and asymptomatic abnormalities on urinalysis. The differential diagnosis varies depending on the clinical syndrome.

The nephrotic syndrome is manifested by severe proteinuria (>3.0 to 3.5 g/1.73 m^2/day) and hypoalbuminemia. Associated features include, to a variable degree, edema, hyperlipidemia, and lipiduria. Nephrotic syndrome results from an increase in glomerular permeability to macromolecules. Etiologies are divided into 2 broad categories: primary renal diseases and secondary forms (infection, malignancy, medications, and multisystem diseases). The pathogenesis is not well understood. Abnormalities of the immune system appear to be the predominant mechanism in man. Circulating immune complexes may deposit in glomeruli, or the antigen may be deposited or originate in the glomerular capillary wall and immune complexes (antigen–antibody) form in situ. Less-commonly inherited diseases of the podocyte cause congenital nephrotic syndrome. Mutations in genes that produce proteins critical to the maintenance of the normal structure and function of the podocyte foot processes and slit diaphragm result in proteinuria.

The nephritic syndrome is characterized by the presence of hematuria with red blood cell casts, an increased serum blood urea nitrogen (BUN) and creatinine concentration, varying degrees of hypertension, and proteinuria.

Nephritic syndrome is secondary to an inflammatory disease of the glomerulus that is manifested by an increase in cellularity on light microscopy. The increased cellularity is secondary to proliferation of endothelial, epithelial, and/or mesangial cells or to glomerular infiltration with inflammatory cells.

RPGN is a variant of the nephritic syndrome. The serum BUN and creatinine concentration rise rapidly over days to weeks. The hallmark of RPGN on renal biopsy is the cellular, fibrocellular, or fibrous crescent and this disorder is also referred to as "crescentic" glomerulonephritis. A crescent is a histologic marker of severe injury. It develops when necrosis occurs and a rent or hole forms in either the glomerular capillary basement membrane or in the basement membrane of the Bowman capsule. When such a disruption occurs macrophages, inflammatory mediators, and plasma proteins gain access to the Bowman space. A crescent develops from the proliferation of macrophages, fibroblasts, and parietal glomerular epithelial cells. Crescents are often associated with visible areas of necrosis within the glomerular capillary. RPGN is important to recognize because irreversible glomerular damage occurs quickly in the absence of therapy.

Asymptomatic abnormalities on urinalysis include the discovery of hematuria or proteinuria on routine dipstick analysis of urine. Urine microscopy often reveals dysmorphic red blood cells and cellular casts. This chapter is subdivided into 4 sections based on the clinical syndromes described above. Individual glomerular diseases are discussed further based on their most common clinical presentation.

KEY POINTS

Presentation of Glomerular Diseases

1. Glomerular diseases present as 4 clinical syndromes: nephrotic syndrome; nephritic syndrome; RPGN (a variant of the nephritic syndrome); and asymptomatic abnormalities on urinalysis.
2. The nephrotic syndrome is manifested by severe proteinuria (>3.0 to 3.5 g/1.73 m^2/day) and hypoalbuminemia.
3. Hematuria with dysmorphic red blood cells, red blood cell casts, an increased serum BUN and creatinine concentration, varying degrees of hypertension, and proteinuria are present in the nephritic syndrome.
4. RPGN is a variant of the nephritic syndrome in which the serum BUN and creatinine concentration rise rapidly over days to weeks. The hallmark of RPGN on renal biopsy is the cellular, fibrocellular or fibrous crescent.
5. Glomerular disease may also present as asymptomatic abnormalities on urinalysis.

NEPHROTIC SYNDROME

Under normal circumstances only 30 to 45 mg of protein is excreted in urine; about one-third of that total is albumin. The upper limit of normal for urinary protein excretion is 150 mg/day and this can increase to 300 mg/day with exercise. The glomerular capillary acts as a barrier to the filtration of serum proteins. This barrier consists of 3 layers: an endothelial cell, the basement membrane itself, and an epithelial cell. There is both a size barrier (small proteins are freely filtered [molecular weight (MW) 5000 Da], and large ones are restricted [MW 100,000 Da]), as well as a charge barrier (the capillary membrane is negatively charged and repels negatively charged proteins). Disorders of the filtration barrier result in proteinuria, and if severe enough, the nephrotic syndrome. Another hypothesis purports that a large glomerular leak of protein is normal and proximal tubular cells transport albumin into cells via the megalin-cubulin receptor pathway, whereupon albumin is degraded and transported back to the systemic circulation. In this paradigm, proteinuria develops when dysfunction of apical uptake of albumin exists. The accuracy of this hypothesis is currently unknown and remains to be proven.

The nephrotic syndrome is manifested by severe proteinuria (>3.0 to 3.5 g/1.73 m^2/day) and hypoalbuminemia. Peripheral edema, an elevated serum cholesterol concentration and lipiduria are often present. Edema results from a change in Starling forces across the capillary wall. As serum albumin concentration falls plasma oncotic pressure decreases. There may also be an intrarenal defect resulting in increased sodium reabsorption as well. Albumin in the tubular lumen increases activity of the Na^+-H^+ exchanger in the proximal tubule resulting in increased sodium reabsorption. In addition, abnormal glomerular filtration of plasminogen and its conversion to plasmin activate gamma ENaC proteolytically and contribute to

sodium retention and edema formation in acute proteinuric conditions. Edema should first be treated with sodium restriction. If this is ineffective then diuretics are added. Milder diuretics that block sodium reabsorption in the distal convoluted tubule or collecting duct (thiazides, triamterene, amiloride, spironolactone, and eplerenone) are often used before more potent loop diuretics.

Hypercholesterolemia is thought to result from an increase in synthesis of hepatic proteins in response to hypoalbuminemia. This is supported by animal studies showing that the degree of cholesterol elevation is inversely related to the fall in plasma oncotic pressure. Animal studies also show that raising the oncotic pressure with albumin infusion results in a fall in serum cholesterol concentration toward normal. If the serum cholesterol concentration is elevated and the patient does not have hypoalbuminemia, the increase is probably not caused by the nephrotic syndrome. There is also a decrease in lipoprotein catabolism. Lipoprotein lipase is decreased as is lecithin-cholesterol acyltransferase (esterifies cholesterol to high-density lipoprotein [HDL]). Downregulation of lipoprotein lipase and the very-low-density lipoprotein (VLDL) receptor results in elevated triglycerides and VLDL.

A variety of coagulation abnormalities are often present in the nephrotic syndrome. Levels of factors V, VIII, α-macroglobulin, and fibrinogen are increased, while X, XI, and XII, plasminogen activator inhibitor (PAI), and antithrombin III are decreased. The platelet count tends to be increased, as is platelet aggregation. Also, the clot formed in this setting has an altered structure (closed), which makes it more resistant to fibrinolysis. The end result is that patients are hypercoagulable, and have an increased incidence of both arterial and venous thrombi. Patients at highest risk for thrombosis are the elderly and those with a serum albumin concentration less than 2.5 mg/dL. Renal vein thrombosis occurs in 5% to 35% and is more commonly associated with membranous glomerulonephritis. The presentation can be acute or chronic. Acute renal vein thrombosis is manifested by flank pain, hematuria, and a decrease in glomerular filtration rate (GFR). Chronic renal vein thrombosis is often silent and can present as a pulmonary embolus. As antithrombin III concentration is low, these patients may be relatively heparin resistant and require more heparin than usual to raise the partial thromboplastin time (PTT) into the therapeutic range.

The risk of infection with encapsulated organisms is increased possibly a result of the loss of complement factor B (alternate pathway) and γ-globulin in urine. Patients should be immunized with pneumococcal vaccine.

PRIMARY RENAL DISEASES THAT PRESENT AS THE NEPHROTIC SYNDROME

Minimal Change Disease

Minimal change disease, also known as nil disease or lipoid nephrosis, derives its name from the fact that the light microscopic appearance of the glomerulus is normal (Figure 17.1) and the tubules may become vacuolated with lipids as a result of hyperlipiduria. I immunofluorescence (IF) studies are also negative. On electron microscopy (EM) podocyte epithelial foot processes are fused (Figure 17.2). Some patients have mesangial deposits of immunoglobulin (Ig) M and C3. Heavy deposition of IgM (IgM nephropathy) associated with mesangial hypercellularity may carry a worse prognosis. This is thought to represent an intermediate lesion along a path of progression toward focal and segmental glomerulosclerosis (see below). Acute tubular necrosis is seen in a subgroup of patients with minimal change disease.

The pathogenesis may be secondary to a defect in cell-mediated immunity, because in vitro T-cell function abnormalities are described and minimal change disease can occur in association with Hodgkin disease, nonsteroidal antiinflammatory drugs (NSAIDs) and the treatment

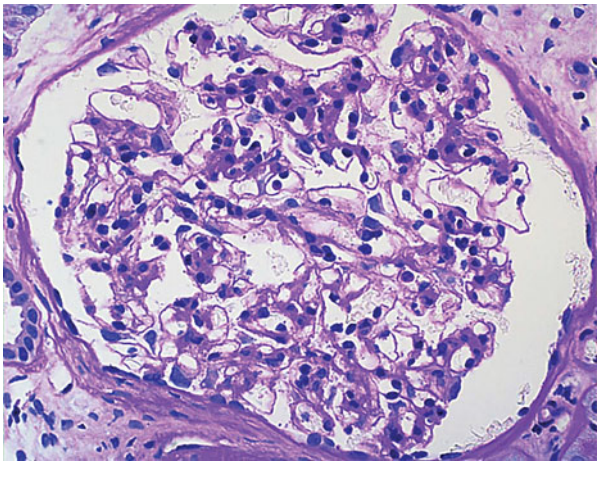

FIGURE 17-1. Minimal change disease (light microscopy). The glomerulus on light microscopy in minimal change disease is normal.

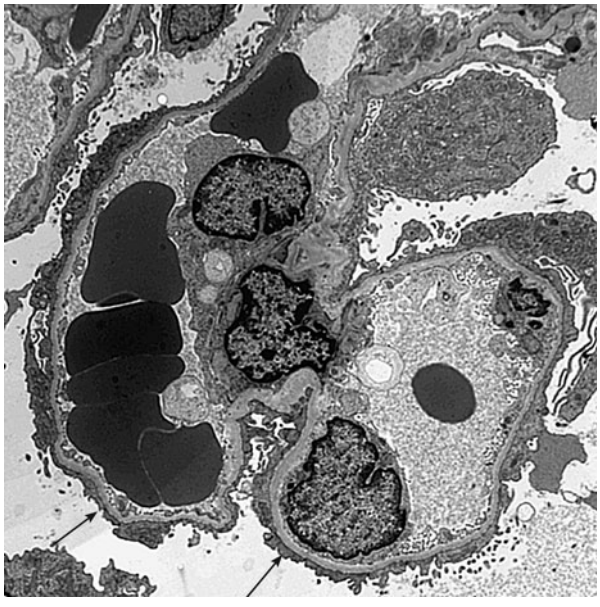

FIGURE 17-2. Minimal change disease (electron microscopy). The arrow shows fusion of the foot processes of podocytes. This is the only abnormality seen on the renal biopsy of a patient with minimal change disease.

of malignant melanoma with interferon. T-cell cultures derived from patients with minimal change disease release a vascular permeability factor. Minimal change disease may result from the production of a lymphokine that is toxic to the glomerular epithelial cell. The toxin reduces the anionic charge barrier of the membrane and injures podocyte foot processes, causing albuminuria. In adults, minimal change disease is the cause of 10% to 15% of cases of nephrotic syndrome. In children, it is the most common cause of nephrotic syndrome, with a peak incidence between ages 2 and 3 years. It accounts for more than 90% of cases of nephrotic syndrome in the pediatric population. The urine sediment is generally unremarkable, although microscopic hematuria may be present in 20% of patients. Lipiduria with free lipids, oval fat bodies (cells containing lipid), and lipid casts may be seen with severe nephrosis. Proteinuria is "selective," consisting almost entirely of albumin, suggesting that the abnormality in the glomerular basement membrane (GBM) is an alteration in the charge barrier. Hypertension is generally absent. Minimal change disease responds well to corticosteroids (within 4 weeks), although relapses are the rule. Relapses may be provoked by an upper respiratory infection. Patients with frequent relapses or those who are steroid-dependent may be treated with cyclophosphamide, chlorambucil, cyclosporine, tacrolimus, or levamisol. Oral cyclosporine and tacrolimus carry the risk of nephrotoxicity, especially in those treated for longer periods of time. The long-term prognosis with respect to the maintenance of renal function is good.

Focal Segmental Glomerulosclerosis (Focal Sclerosis)

Focal segmental glomerulosclerosis (FSGS) is characterized by sclerosing lesions associated with hyaline deposits involving parts (segmental) of some glomeruli (focal). The sclerosis results from glomerular capillary collapse with an increase in mesangial matrix (Figure 17.3). Mild-to-moderate mesangial hypercellularity may be seen. On EM subendothelial deposits and foot process fusion are present in involved glomeruli. Capillary collapse and folding and thickening of the basement membrane are present in sclerotic glomeruli. IF reveals nonspecific trapping of IgM and C3 in the sclerotic mesangium. As the disease progresses, tubular atrophy, interstitial fibrosis, and global glomerular sclerosis occur. Increasing degrees of interstitial fibrosis (>20% of biopsy surface area) is associated with a poorer prognosis. Juxtamedullary nephrons are affected initially.

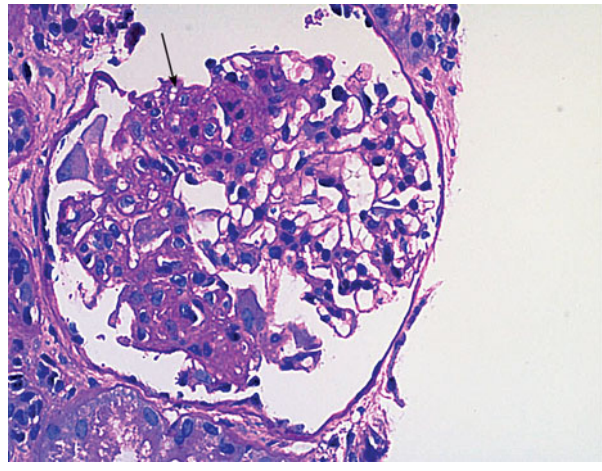

FIGURE 17-3. FSGS. The left half of this glomerulus is sclerotic (*arrow*) and the right half is normal hence the term *segmental* in FSGS. In the sclerotic region, there is glomerular capillary collapse and an increase in mesangial matrix.

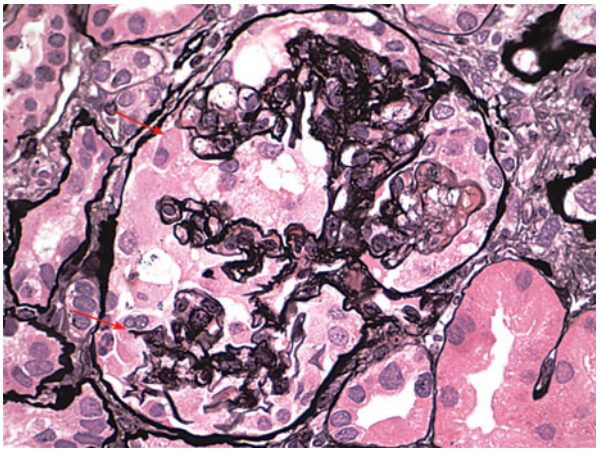

FIGURE 17-4. Collapsing FSGS (light microscopy). The glomerular tuft is retracted and covered by visceral epithelial cell hypertrophy (*arrow*). (Courtesy of Glen S. Markowitz.)

The Columbia pathologic classification of primary FSGS describes 5 histopathologic types of glomerular lesions. The variants include (a) classic FSGS or not otherwise specified (NOS); (b) tip lesion; (c) cellular; (d) perihilar; and (e) collapsing (Figure 17.4). In general, the tip and cellular variants of FSGS are more steroid responsive and have a better prognosis, whereas classic and collapsing FSGS are poorly responsive to steroids and have a poor renal prognosis.

The etiology of primary FSGS is unknown but humoral factors, glomerular hypertrophy and hyperfiltration, and injury to glomerular cells are postulated. Inherited forms of FSGS are caused by mutations in genes that encode podocyte proteins α-actinin 4, podocin, nephrin, transient receptor potential channel, subfamily 6 (TRPC6), and inverted formin-2 (IFN2). Focal sclerosis can also be secondary to vesicoureteral reflux, morbid obesity, multiple myeloma, urinary tract obstruction, analgesic nephropathy, chronic renal transplant rejection, heroin nephropathy, human immunodeficiency virus (HIV) infection, and substantial loss of nephron mass. Drugs, such as pamidronate, interferon, and anabolic androgenic steroids, are also associated with FSGS.

Focal sclerosis is the most common primary renal disease resulting in nephrotic syndrome in African Americans. Recent advances have enhanced our understanding of the common occurrence of FSGS in African Americans. An allelic varitation at the APOL-1 locus on chromosome 22 may explain the high risk of FSGS in individuals of African ancestry. APOL-1 is trypanosomolytic and this protective allelic variant has persisted over evolutionary time. Although the exact mechanism of injury is unknown, the expression of APOL-1 in podocytes is in keeping with FSGS, a disorder of podocytes. The pathogenesis of idiopathic FSGS may also be related to circulating factors that target and injure the podocyte (permeability factors). A pivotal role for soluble urokinase plasminogen activator receptor (suPAR) in idiopathic FSGS has been noted. The mechanism underlying development of FSGS with suPAR is likely related to the ability of this molecule to activate β-integrin on podocytes, which then promotes foot process effacement. Other possible circulating permeability factors include cardiotrophin-like cytokine (CLC-1) and a factor that disturbs nonmuscle myosin IIA on podocytes. With all of these molecules, the final common pathway is foot process effacement with proteinuria and eventual focal glomerular sclerosis.

In FSGS, the urinary sediment is usually remarkable for hematuria and pyuria, and up to 30% of adults may present with asymptomatic proteinuria. Blood pressure is generally elevated, GFR decreased, and the development of slowly progressive renal failure is the usual course. Approximately 50% to 60% of patients reach end-stage renal disease (ESRD) within 10 years of initial diagnosis. Patients with nonnephrotic range proteinuria have a better prognosis. The clinical course is much more rapid in patients with heroin nephropathy or HIV infection (renal failure often is present within 2 years from the time of initial diagnosis).

HIV-associated nephropathy (HIVAN) is much more common in African Americans than in whites. It generally occurs late in the course of HIV infection in patients with a higher viral titer (load) and CD4 count of less than 250 cells/mm^3. Patients present with nephrotic syndrome and an elevated BUN and serum creatinine concentrations. The kidneys are enlarged on renal ultrasound with increased echogenicity of the renal cortex. On light microscopy there is glomerular collapse, extensive lymphocytic infiltration, and cystic dilation of tubules that are filled with proteinacious material (microcysts). Tubuloreticular inclusion bodies are found within glomerular and tubulointerstitial endothelial cells. Immune complex-related diseases, such as membranoproliferative glomerulonephritis (MPGN), membranous glomerulonephritis, IgA nephropathy, and a lupus-like immune

complex glomeulopathy, are more common in whites with HIV infection and the nephrotic syndrome. HIV viral proteins induce podocyte injury and apotosis. Studies in HIVAN show that the decrease in GFR was slowed by combination antiretroviral therapy, angiotensin-converting enzyme (ACE) inhibitors, and prednisone. Prednisone should be reserved for those patients who are at low risk of infection as serious infectious complications may arise during its use. A collapsing FSGS is also a complication of drug therapy (pamidronate, interferon, and androgenic steroids).

Focal sclerosis is less responsive to corticosteroids. High-dose corticosteroids often must be employed for 6 to 9 months before a response is seen. If corticosteroids fail, second-line agents of choice are cyclosporine and tacrolimus, although cyclophosphamide and mycophenolate mofetil (MMF) can also be used. Rituximab is of unclear benefit in FSGS. A number of other agents are in early phase trials, including adalimumab (monoclonal tumor necrosis factor [TNF] inhibitor), fresolimumab (anti-transforming growth factor [TGF] monoclonal antibody), rosiglitazone, pirfenodone (TGF antagonist), natural adrenocorticotropic hormone (ACTH), and oral galactose. In general, approximately 30% to 50% of patients with sporadic or idiopathic FSGS are resistant to a reasonable course of steroids (at least 4 months). Relapses occur commonly in steroid-sensitive FSGS, and over time, steroid resistance can develop. Although complete remission is rare, partial remissions are common, which is opposite to what is seen with minimal change disease. Factors associated with a poorer prognosis include persistent high-grade proteinuria, diffuse mesangial IgM deposition, the extent of tubulointerstitial fibrosis and the degree of glomerulosclerosis on renal biopsy, and a higher serum creatinine concentration (not uniformly). African American race and a lack of response to corticosteroids are also predictors of poor outcome. As many as 50% of patients may develop a recurrence in the transplanted kidney, and greater than 80% in secondary grafts of patients where the initial graft was lost because of recurrent FSGS. Those patients with a rapid progression and high degrees of proteinuria are at increased risk of recurrence. Treatment of secondary causes of FSGS are directed at the underlying cause, such as repair of reflux, weight reduction (obesity), control of hyperfiltration (nephron loss), and HIVAN therapy with combination antiretroviral medications, and discontinuation of offending drugs.

Mesangial Proliferative Glomerulonephritis

Mesangial proliferative glomerulonephritis generally presents with isolated microscopic hematuria or proteinuria although nephrotic syndrome is also seen. On light microscopy there is an increase in mesangial cell number. Mesangial deposits of immunoglobulin and complement are present on EM. Treatment is often supportive focusing on blood pressure control and proteinuria reduction with drugs that modulate the renin-angiotensin-aldosterone system (RAAS) such as ACE inhibitors and angiotensin receptor blockers (ARBs). Initial treatment is generally with corticosteroids. Nonresponders or partial responders often do not respond to cyclosporin. Deposition of IgM in the mesangium and lack of response to corticosteroids are associated with a poor prognosis.

Membranous Glomerulonephritis

Membranous glomerulonephritis is characterized by uniform, diffuse thickening of the glomerular capillary wall without cellular proliferation (Figure 17.5). The most characteristic feature is the presence of subepithelial immune deposits on EM (Figure 17.6). The electron-dense deposits are formed in situ in the GBM. The M-type phospholipase A_2 receptor (PLA2R) appears to be the human glomerular target antigen in primary membranous glomerulonephritis. Thus, antibodies formed in the circulation may bind the PLA2R, form

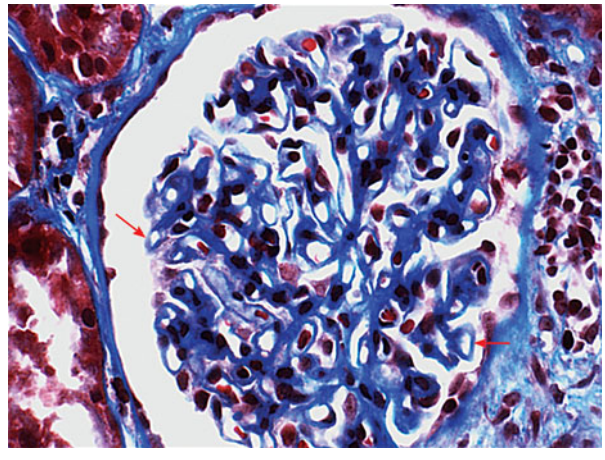

FIGURE 17-5. Membranous glomerulonephritis (light microscopy). Shown by the arrows are the diffusely thickened glomerular capillary loops characteristic of this lesion. There is no increase in cellularity.

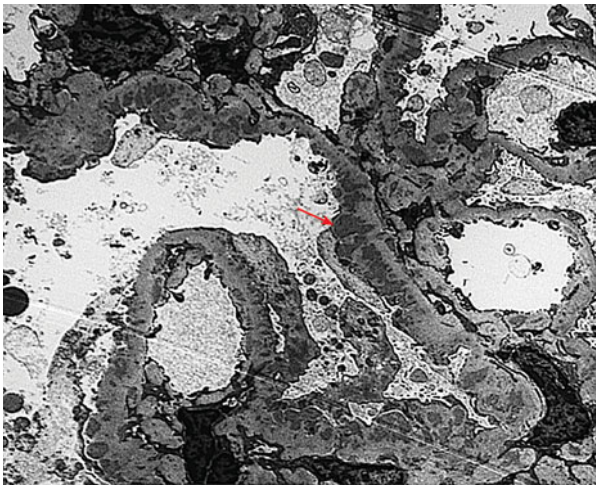

FIGURE 17-6. Membranous glomerulonephritis (EM). Immune deposits in the glomerular basement membrane are shown by the arrow. They are found in the subepithelial space.

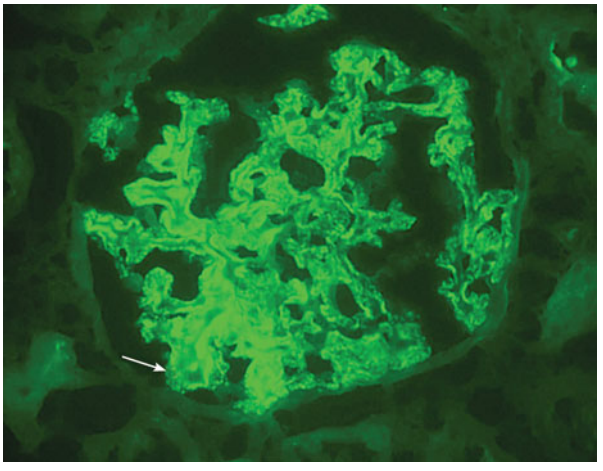

FIGURE 17-7. Membranous glomerulonephritis (IF microscopy). The staining pattern is granular and corresponds to the punctate accumulation of immune deposits in the glomerular basement membrane (*arrow*) and mesangium.

antigen–antibody (Ag-Ab) complexes that then initiate a cascade of events causing glomerular capillary loop injury. The development of glomerular injury is complement-dependent and is related to the formation of the membrane attack complex (C5b-C9). The membrane attack complex induces matrix production, release of oxidants, and podocyte injury. GBM accumulates between the deposits, which creates the appearance of spikes. With time, the basement membrane extends over the deposits, forming domes. IF microscopy shows a granular pattern (Figure 17.7). In the idiopathic lesion mesangial deposits are usually absent and IgG subtype 4 is present. In membranous glomerulonephritis from secondary causes, mesangial deposits greater than 8 polymorphonuclear cells per glomerulus and tubuloreticular inclusions are generally present, depending on the cause. Subendothelial deposits, tubulointerstitial deposits, the presence of all Igs in deposits, and mesangial or endocapillary proliferation are suggestive of a secondary cause. Many of these patients have evidence of circulating immune complexes. Histologic changes associated with a poor prognosis include interstitial fibrosis and segmental glomerulosclerosis.

Membranous glomerulonephritis is the most common primary renal disease that causes nephrotic syndrome in white adults. Nephrotic syndrome is present in 80% of cases. Hypertension is usually absent and the urinary sediment may show hematuria in approximately half of patients. A serum test measuring the M-type PLA2R antibody may become a diagnostic test to identify idiopathic membranous nephropathy (MN). The initial study demonstrated that anti-PLA2R antibodies were present in 82% of patients with idiopathic MN, but in very few secondary causes of MN such as systemic lupus erythematosus (SLE) nephritis, cancer-related MN, and hepatitis B-related MN. This antibody test may be useful in diagnosis, as well as in monitoring of disease activity and response to therapy. However, the absence of antibodies does not preclude response to therapy and the presence of antibodies does not absolutely exclude the presence of a secondary cause of MN.

As described above, this lesion is also seen in collagen vascular diseases (SLE, mixed connective tissue disease, and rheumatoid arthritis), infections (hepatitis B, malaria, secondary and congenital syphilis, leprosy, schistosomiasis, and filariasis), drugs (NSAIDs, gold, penicillamine, mercury, probenecid, captopril, and bucillamine), neoplasia (lung, colon, stomach, breast, cervix, and ovary), and miscellaneous disorders (sickle cell disease, thyroiditis, and sarcoid).

Therapy remains controversial because of the high spontaneous remission rate. Without treatment, generally one-third of patients spontaneously remit, one-third progress to renal failure, and one-third remain unchanged.

Factors associated with an increased frequency of progression to renal failure include male sex, age older than 50 years, high-grade persistent proteinuria, hypertension, and an elevated serum creatinine concentration. Excretion of IgG and α_1-microglobulin is a predictor of response to therapy, progression to renal failure, and the extent of tubulointerstitial damage on renal biopsy. An initial study suggested that corticosteroids alone decrease the rate of decline in renal function but this was not borne out by subsequent trials. The combination of alternating monthly courses of either corticosteroids and chlorambucil or corticosteroids and oral cyclophosphamide increase the rate of remission of nephrotic syndrome and the probability of survival without renal failure. The majority of therapeutic trials were conducted, however, in patients with serum creatinine concentration equal to or less than 1.7 mg/dL. Uncontrolled trials were carried out in patients with serum creatinine concentrations between 2 and 3 mg/dL. The combination of prednisone and cyclophosphamide lowered serum creatinine concentration in the short-term. It is unclear whether patients with serum creatinine concentration equal to or greater than 3 mg/dL benefit from therapy. Cyclosporine was used in patients who failed steroid therapy. The rate of remission of nephrotic range proteinuria is increased but conflicting data exist as to whether one can slow progression of disease. MMF was employed successfully in small numbers of patients. Synthetic ACTH has been noted to reduce proteinuria and induce remission of membranous glomerulonephrtitis in small studies. Rituximab has also been used successfully to induce remission of proteinuria in 60% of patients, but is expensive and complicated by infection and progressive multifocal leukoencephalopthy. Intravenous rituximab has been used to treat MN with some success. However, this drug's efficacy for MN requires comparison with cyclosporine in a randomized controlled trial.

Because of the high spontaneous remission rate, some authors recommend treating only patients with elevated serum creatinine concentration, progressive declines in GFR, and symptomatic nephrotic syndrome, as well as those patients who are at high risk for progression and patients with thromboembolic disease. Because of the association with renal vein thrombosis and thromboembolic events some recommend treating patients with profound hypoalbuminemia with anticoagulants. Patients who experience a thromboembolic event should be anticoagulated as long as they remain nephrotic.

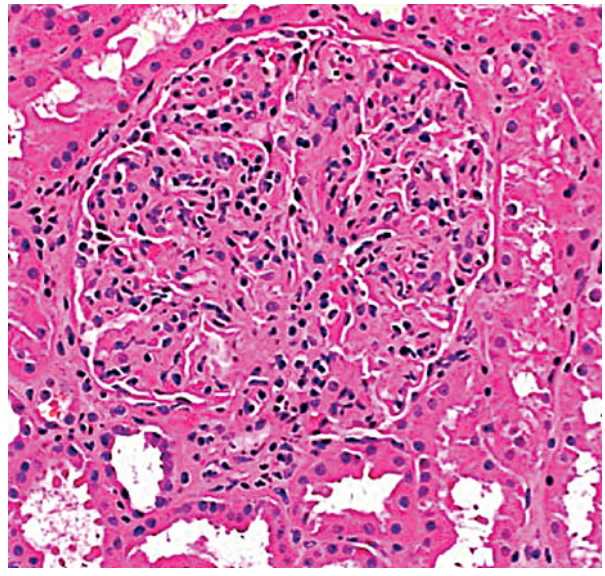

FIGURE 17-8. MPGN (light microscopy). There is an increase in both cellularity (proliferation of endothelial and mesangial cells) and mesangial matrix. Open capillary loops are difficult to visualize as a result of endothelial proliferation. The lobules of the glomerulus are distorted (lobular accentuation).

Membranoproliferative Glomerulonephritis

MPGN is characterized by diffuse proliferation of mesangial cells with the extension of mesangial matrix or cytoplasm into the peripheral capillary wall, giving rise to a thickened and reduplicated appearance. This gives rise to the double contour or "tram-track" appearance of the GBM. There is mixed mesangial and endothelial cell proliferation that results in a lobular distortion of the glomerulus (lobular accentuation) (Figure 17.8). MPGN is divided into several types based on EM.

Type I MPGN, which is the most common form of the disease, is associated with subendothelial electron-dense deposits and marked peripheral capillary interposition of mesangial cell cytoplasm and matrix. IF microscopy reveals glomerular deposition of immunoglobulin, C3, and C4. Patients may present with the nephrotic syndrome, nephritic syndrome, an overlap of these 2 syndromes, RPGN, or with asymptomatic hematuria and proteinuria. Episodic macroscopic hematuria may also occur. Blood pressure is generally increased, GFR reduced, and anemia is present disproportionate to the degree of azotemia. Complement concentrations are low especially in type II MPGN. The classical complement pathway is activated in

type I MPGN resulting in a decrease in C4 concentration. Glomerular crescents, hypertension, decreased GFR, and heavy proteinuria are poor prognostic signs. Infection (shunt nephritis, malaria, endocarditis, hepatitis B and C, and HIV), B-cell lymphomas, SLE, mixed connective tissue disease, sickle cell disease, monoclonal immunoglobulin deposition diseases (amyloidosis, light-/heavy-chain deposition disease), and α_1-antitrypsin deficiency are also associated with MPGN type I. Infection with hepatitis C is the most common cause.

Type II MPGN is characterized by intramembranous electron-dense deposits and is often called *dense deposit disease*. There are dense ribbon-like confluent deposits in the basement membranes of the glomeruli, tubules, and vasculature. In type II MPGN the alternative complement pathway is activated decreasing C3 concentration. Peripheral catabolism of C3 is increased by a circulating IgG known as C3 nephritic factor. This results in an increase in C3 degradation products especially C3c. C3c has an affinity for the lamina densa of the GBM and is deposited there. The depressed complement concentrations do not correlate with disease activity. These patients are generally resistant to therapy.

Subendothelial and subepithelial immune deposits and marked fragmentation of the GBM are found in type III MPGN. It is associated with IgA nephropathy and Henoch-Schönlein purpura (HSP) and is rarely a result of hepatitis C infection. This lesion is not corticosteroid-responsive.

More recently, given the role of the alternative pathway of complement in MPGN, a more practical approach is to reclassify this entity as immune complex-mediated and complement-mediated MPGN. Using this paradigm, immune complex-mediated MPGN occurs when there are increased circulating immune complexes (infection, autoimmune, dysproteinemia), and complement-mediated MPGN occurs when there is a disease with dysregulation of the alternative complement pathway (mutations or antibodies to complement factors or complement-regulating proteins). Examples of complement-mediated MPGN (Ig-C3+ IF staining) are classical intramembranous dense deposit disease (type II MPGN) and C3 glomerulopathy.

C3 glomerulopathy has subendothelial dense deposits that resemble type I MPGN on EM, but has only C3 staining without Ig on IF. Patients typically present with proteinuria, often in the nephrotic range (sometimes with nephrotic syndrome), hematuria, variable degrees of hypertension and kidney failure. C3 levels are usually low, C4 levels are normal, and some patients have a C3 convertase stabilizing autoantibody called C3 nephritic factor, which is also seen in dense deposit disease. Progression to ESRD occurs and this glomerulopathy can recur following kidney transplantation. Some patients develop hematuria after an upper respiratory infection (URI), leading to a presumptive clinical diagnosis of IgA nephropathy or postinfectious glomerulonephritis. Six of 9 patients who developed hematuria following a URI and glomerulonephritis on renal biopsy had mesangial C3 deposits, four of which had associated hypocomplementemia. This suggests that a form of C3 glomerulopathy occurred in these patients. Thus, this entity must be included in the differential diagnosis of acute glomerulonephritis following a URI.

SECONDARY RENAL DISEASES COMMONLY ASSOCIATED WITH NEPHROTIC SYNDROME IN ADULTS

Diabetes Mellitus

Diabetic nephropathy is the single most common cause of the nephrotic syndrome and ESRD in the United States. Type I diabetics with nephropathy have a 50-fold increase in mortality compared to those without nephropathy. Nephropathy in type I diabetes mellitus rarely develops before 10 years' disease duration, and approximately 40% of type I diabetics have proteinuria within 40 years after the onset of disease. The annual incidence of diabetic nephropathy peaks just before 20 years' disease duration and declines thereafter. Those patients who survive 30 years of diabetes mellitus without developing nephropathy are at extremely low risk of doing so in the future.

The glomeruli in patients with diabetic nephropathy may exhibit a form of nodular glomerulosclerosis known as *Kimmelstiel-Wilson disease* (Figure 17.9). The nodules form in the peripheral regions of the mesangium and can be single or multiple. They may result from accumulation of basement membrane or injury from microaneurysmal dilation of the glomerular capillary. Nodular glomerulosclerosis can occur in association with diffuse glomerulosclerosis. Diffuse glomerulosclerosis, which is universally present, results from widening of the mesangial space by an increase in matrix production. Glomerular injury in diabetes mellitus is related to the severity and duration of hyperglycemia and may be related to advanced glycosylation end-products (AGEs). Elevation of serum glucose concentration leads to glycosylation of serum and tissue proteins resulting in AGE formation that can cross-link with collagen. In animal models, administration of

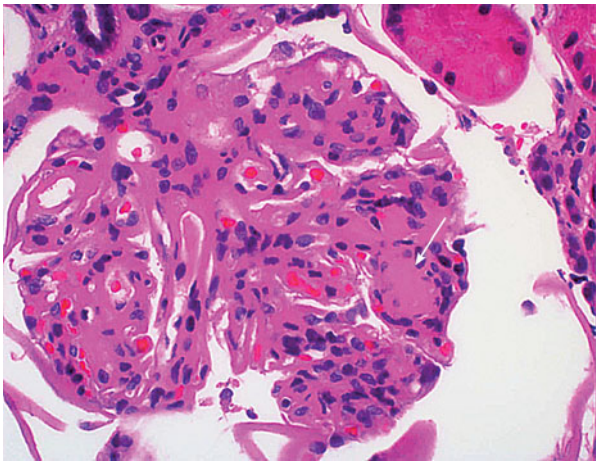

FIGURE 17-9. Diabetic glomerulosclerosis (light microscopy). The arrow shows an area of nodular glomerulosclerosis (Kimmelstiel-Wilson disease). Note also the diffuse increase in mesangial matrix throughout the glomerulus (diffuse glomerulosclerosis).

AGEs induces glomerular hypertrophy and stimulates mesangial matrix production. Upregulation of TGF-β_1 and its receptor likely play an important role in renal cell hypertrophy and stimulation of mesangial matrix production. Altered vascular endothelial growth factor (VEGF) homeostasis in the podocyte may also play a role in the pathogenesis of diabetic nephropathy. VEGF expression is increased early in diabetic nephropathy, potentially causing capillary injury, but over time, with ongoing injury and loss of podocytes, there is a decline in VEGF. This may lead to an insufficient capillary repair and a reduction in nephrin expression in podocytes and proteinuria. In addition to glomerular changes, there is diffuse accumulation of hyaline material in the subendothelial layers of the afferent and efferent arterioles.

The natural history of diabetic nephropathy is divided into 5 stages: (a) time of initial diagnosis; (b) the first decade (characterized by renal hypertrophy and hyperfiltration); (c) the second decade manifested by glomerulopathy (microalbuminuria) in the absence of clinical disease; (d) clinically detectable disease (the hallmarks of this stage are dipstick-positive proteinuria, hypertension, and a progressive decline in renal function); and (e) ESRD.

- **Stage I**—At the onset of diabetes mellitus virtually all patients experience functional changes, such as increased kidney size, microalbuminuria that reverses with the control of blood glucose concentration, and an increased GFR that decreases with initiation of insulin therapy in most patients.
- **Stage II**—GFR may be increased in Stage II, and it is postulated that this finding predicts the later development of nephropathy, but this remains controversial. The pathogenesis of the hyperfiltration is unclear but may be partly caused by hyperglycemia and activation of the RAAS. At the onset of diabetes mellitus the renal biopsy is usually normal. Within 1.5 to 2.5 years, GBM thickening begins in nearly all patients. No correlation exists between GBM thickening and clinical renal function. Mesangial expansion begins approximately 5 years after the onset of disease.
- **Stage III**—Stage III is manifested by microalbuminuria. Microalbuminuria is an albumin excretion rate between 30 and 300 mg/day (20 to 200 μg/min). This amount of albumin excretion is below the level of sensitivity of a urine dipstick. A mid-morning albumin-to-creatinine ratio above 30 mg/g correlates well with 24-hour or timed urine collections. Several groups reported that a slightly elevated urinary albumin excretion occurring in the first or second decade of diabetes mellitus is a harbinger of the later development of clinical diabetic nephropathy. These studies used thresholds ranging from 15 to 70 μg/min to classify patients. Microalbuminuria best predicts diabetic nephropathy when it is progressive over time and is associated with hypertension.
- **Stage IV**—Stage IV is defined by the presence of dipstick positive albuminuria (>300 mg/day) and is associated with a slow gradual decline in GFR that may result in ESRD. Classically, the rate of decline of GFR was stated to be 1 mL/min/month, but this number is probably now closer to 0.5 mL/min/month or less. The rate of progression can be slowed by antihypertensive therapy. It may decline further with combined treatment with ACE inhibitors and ARBs.
- **Stage V**—As the GFR continues to decline, ESRD may develop. Diabetic nephropathy is the most common cause of ESRD in the United States. Because of associated autonomic neuropathy and cardiac disease, diabetics often experience uremic symptoms at higher GFRs (15 mL/min) than nondiabetics.

Although the 5 clinical stages of diabetic nephropathy are best characterized in patients with type I diabetes

mellitus, they are similar in patients with type II disease with the following exceptions. The ability to date the time of onset of type II diabetes mellitus is more difficult than in patients with type I disease. Therefore, one needs to be more flexible in interpreting the first decade—it may be shorter than 10 years. In virtually 100% of patients with type I diabetes mellitus and diabetic nephropathy, retinopathy is present, whereas retinopathy is present in two-thirds of those with type II disease and diabetic nephropathy. Therefore, the absence of retinopathy in a patient with type II diabetes mellitus should not dissuade one from the diagnosis in the appropriate clinical setting. On the other hand, the absence of retinopathy in a patient with type I disease would argue strongly against diabetes mellitus as a potential cause of renal disease.

The urinalysis in diabetic nephropathy is generally remarkable for proteinuria with little in the way of cellular elements present. On occasion microscopic hematuria is seen. This should prompt a workup for other causes of hematuria, such as transitional cell carcinoma in the patient who is older than age 40 years (cystoscopy). The most common cause of microscopic hematuria in the patient with diabetic nephropathy is, however, diabetic nephropathy. Macroscopic hematuria or the presence of red cell casts is suggestive of another diagnosis. Broad waxy and finely granular casts can be seen as well. The presence of nephrotic range proteinuria in the diabetic patient with a preserved GFR should also raise concern that another glomerular lesion is the cause of the nephrotic syndrome. In general, proteinuria is initially mild and progresses to the nephrotic syndrome as the GFR declines in patients with diabetic nephropathy. Treatment of diabetic nephropathy requires a multidrug regimen, including tight glucose control, blood pressure control with medications that modulate the RAAS, and statin therapy to reduce lipids. This is reviewed in more detail in Chapter 16.

Systemic Amyloidosis

More than 90% of patients with primary and secondary amyloidosis have renal involvement, approximately 60% have nephrotic syndrome. In patients older than the age of 60 years with nephrotic syndrome, 10% have amyloidosis. On light microscopy, diffuse amorphous hyaline material is deposited in glomeruli (Figure 17.10). Amyloid deposits may also be present in tubular basement membranes, arterioles, and small arteries. In more advanced cases, nodule formation occurs and the light microscopy picture can resemble advanced diabetic nephropathy.

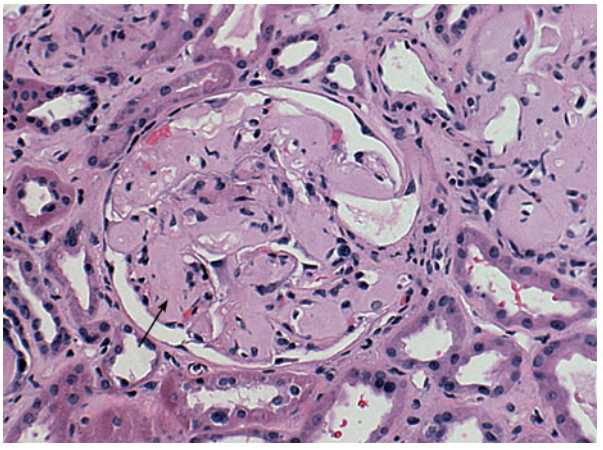

FIGURE 17-10. Amyloid (light microscopy). The arrow illustrates a diffuse increase in amorphous hyaline material (amyloid) deposited in the glomerulus. (Courtesy of Gilbert Moeckel.)

The diagnosis is confirmed by special stains (Congo red, thioflavin-T) and EM. Amyloid deposits have a characteristic apple-green birefringence under polarized light with Congo red staining. The demonstration of 8- to 12-nm nonbranching fibrils on EM is diagnostic (Figure 17.11).

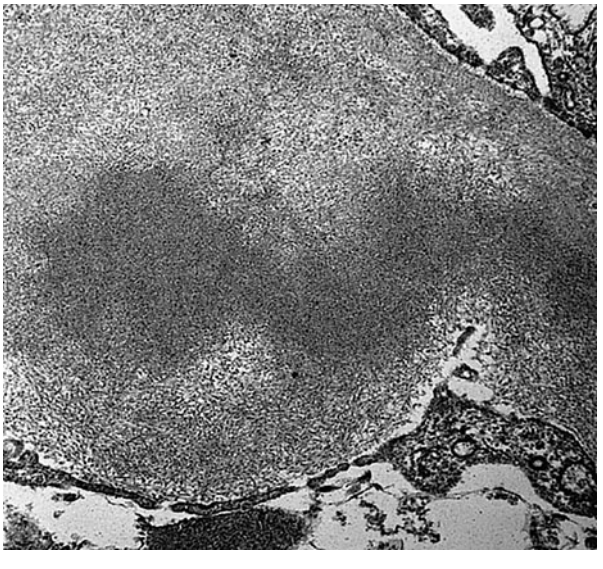

FIGURE 17-11. Amyloid (electron microscopy). Shown in the glomerulus is the deposition of nonbranching 8- to 12-nm fibers that are characteristic of amyloid. (Courtesy of Gilbert Moeckel.)

Patients present with nephrotic syndrome, decreased GFR, and an unremarkable urinary sediment, although oval fat bodies and lipid casts are sometimes seen with severe nephrosis. Clinically apparent extrarenal involvement is often absent. A monoclonal light chain is present in urine in approximately 90% of patients with primary amyloidosis. The combination of serum free light chains and serum immunofixation is diagnostic in 99% of patient with primary amyloidosis. Tissue diagnosis can be established on biopsy of the rectum, gingiva, abdominal fat pad and skin, as well as on renal biopsy.

In primary amyloidosis (AL amyloid) fibrils consist of the N-terminal amino acid residues of the variable portion of monoclonal light chains. Lambda light chains more commonly form amyloid fibrils (75%) than do kappa light chains (25%). Primary amyloid commonly involves heart, kidney, and peripheral nerves. The vast majority of patients have a paraprotein detected in serum or urine (90%). Prognosis is poor with a mean survival of less than 2 years and only a 20% 5-year survival. Cardiac disease, renal dysfunction, and interstitial fibrosis on kidney biopsy are associated with a worse prognosis. The goal of therapy is to reduce light-chain production with chemotherapy. The combination of melphalan and dexamethasone is most commonly employed with stabilization of renal function and improvement in organ system involvement in some patients. Thalidomide (or lenalidomide) and dexamethasone (alone or in combination with cyclophosphamide) is employed in those who relapse after melphalan-dexamethasone or hematopoietic stem cell transplant. However, these regimens are complicated by several toxicities. Bortezomib (with or without dexamethasone) may be an option for patients unable to tolerate melphalan-dexamethasone and those with relapse after successful response to frontline therapy. The best results are found with high-dose melphalan, followed by bone marrow or stem cell transplantation. Toxicity of this regimen is considerable and only a small subset of patients are candidates. In one study of 350 patients who carried a clinical diagnosis of AL amyloid, 10% had mutations resulting in the formation of amyloidogenic proteins that were responsible for the syndrome. Mutated genes included transthyretin, fibrinogen A α-chain, lysozyme, and apolipoprotein A-I. None of these patients had a positive family history. A genetic cause should be suspected in those whose fluorescence staining is negative for light chains and serum amyloid-associated protein A.

In secondary amyloidosis (AA amyloid) fibrils are made up of the N-terminus of serum amyloid-associated protein A. Chronic inflammation (rheumatoid arthritis, inflammatory bowel disease, bronchiectasis, heroin addicts (who inject subcutaneously)), some malignancies (Hodgkin disease and renal cell carcinoma), and familial Mediterranean fever stimulate hepatic production of serum amyloid-associated protein A, an acute-phase reactant. Monocytes and macrophages take up the protein and cleave it into smaller fragments called AA protein (the major component of secondary amyloid fibrils). Treatment is directed at the underlying process. Correction of the inflammatory or infectious process may improve proteinuria in patients with secondary amyloidosis. Colchicine in high doses is effective in patients with familial Mediterranean fever. Those with preserved renal function are more likely to respond with decreases in proteinuria.

Nonamyloid fibrillar deposits can also cause glomerular disease. They occur most commonly in elderly whites. These diseases, fibrillary glomerulonephritis and immunotactoid glomerulonephritis are only diagnosed by renal biopsy. A variety of light microscopy patterns are described, including diffuse proliferative glomerulonephritis, mesangial proliferation, membranous glomerulonephritis, and MPGN. The diagnosis is established based on EM. In fibrillary glomerulonephritis, fibrils average 20 nm in diameter and are randomly arranged. IF microscopy is positive for IgG, C3, and kappa and lambda light chains. Fibrillary glomerulonephritis is responsible for more than 90% of nonamyloid fibrillary diseases.

Immunotactoid glomerulonephritis is characterized by fibrils that are 30 to 50 nm in size. On light microscopy an MPGN type I or diffuse proliferative pattern are most common. IF microscopy is positive for IgG. IgM, IgA, C3, and C1q may also be seen. Some patients have a circulating paraprotein and hypocomplementemia is often present. Associations with chronic lymphocytic leukemia, B-cell lymphomas, hepatitis C, cryoglobulinemia, and SLE have been described. Patients with nonamyloid fibrillar deposits commonly present with nephrotic syndrome, microscopic hematuria, hypertension, and a progressive decline in GFR. There is no proven effective therapy, although corticosteroids, cyclophosphamide, and cyclosporine have been employed. Some advocate tailoring therapy based on the light microscopy pattern. There is a high rate of recurrence after renal transplantation.

Monoclonal Immunoglobulin Deposition Diseases

Monoclonal immunoglobulin deposition diseases result from the deposition of light chains, heavy chains, or the combination of both in a variety of organs including kidney. In light chain deposition disease (LCDD), immunoglobulin light chains deposit in the glomerulus and do not form fibrils. The deposits in most cases are derived from the constant region of kappa light chains. A paraprotein is detected in the urine or serum by immunofixation electrophoresis in 85% of patients. The most common presentation is nephrotic syndrome associated with hypertension and a decreased GFR. Other organs, such as heart, liver, and peripheral nerves, may be affected. Light microscopy reveals eosinophilic mesangial nodules. IF microscopy is positive for monoclonal light chains in a linear pattern in the glomerular and tubular basement membranes. Mesangial nodules also stain positive. A subset of patients have associated myeloma cast nephropathy. The prognosis of patients with LCDD is poor, and renal dysfunction predicts a poor prognosis. Some patients respond to the combination of melphalan and prednisone.

Heavy chains may also deposit in the glomerulus with a similar clinical presentation and result in heavy-chain deposition disease (HCDD). The diagnosis is established by IF with antiheavy chain antibodies. Patients with HCDD secrete an abnormal heavy chain with a deletion in the CH1 domain. If the patient produces a heavy chain that fixes complement (IgG 1 or 3) hypocomplementemia may be present. LCDDs and HCDDs may occur together, causing a third category known as "light- and heavy-chain deposition disease" (LHCDD). This disease displays similar characteristics as the other 2 deposition diseases, involving multiple organs with prominence in the kidneys. The renal lesion includes glomerular nodules, marked thickening of glomerular and tubular basement membranes, and intersitial fibrosis. EM reveals nonorganized granular, electron-dense deposits.

KEY POINTS

Secondary Renal Diseases Commonly Associated with Nephrotic Syndrome in Adults

1. The glomerular capillary acts as both a charge and size barrier to the filtration of serum proteins.
2. The nephrotic syndrome is manifested by severe proteinuria (>3.0 to 3.5 g/1.73 m^2/day) and hypoalbuminemia.
3. Patients with the nephrotic syndrome are hypercoagulable and have an increased incidence of both arterial and venous thrombi.
4. Minimal change disease is the most common cause of nephrotic syndrome in children. Proteinuria is selective and the response rate to prednisone is high.
5. FSGS is characterized by sclerosis in a portion (segmental) of some (focal) glomeruli. It is the most common primary renal disease causing nephrotic syndrome in African Americans. FSGS can be classified histologically into 5 types.
6. Membranous glomerulonephritis is characterized by thickened glomerular capillary walls, the absence of cellular proliferation, and the presence of subepithelial immune deposits. The M-type PLA2R appears to be the human glomerular target antigen in primary membranous glomerulonephritis. Therapy remains controversial because of the high spontaneous remission rate.
7. MPGN may present with the nephrotic syndrome, nephritic syndrome, an overlap of these 2 syndromes, or with asymptomatic hematuria and proteinuria. Complement concentrations are low.
8. Diabetic nephropathy is the most common cause of the nephrotic syndrome and ESRD in the United States. The natural history of diabetic nephropathy is divided into 5 stages. The rate of progression can be slowed by antihypertensive therapy and tight glucose control.
9. Nephrotic syndrome may occur in up to 60% of patients with primary and secondary amyloid. The demonstration of amyloid fibrils on EM is diagnostic.

Systemic Lupus Erythematosus

Renal involvement is common in SLE with half of patients having an abnormal urinalysis or a decreased GFR at the time of initial diagnosis, and 75% eventually manifesting kidney disease. Renal involvement includes mild mesangial proliferation, focal or diffuse proliferative glomerulonephritis, membranous glomerulonephritis, and chronic glomerulonephritis. Although SLE may present as nephrotic syndrome (membranous glomerulonephritis), it more commonly presents as nephritis and is discussed in the following section. Patients may change from 1 form of renal involvement to another.

NEPHRITIC SYNDROME (GLOMERULONEPHRITIS)

Acute nephritic syndrome or glomerulonephritis is characterized by the abrupt onset of hematuria, proteinuria, and a rise in serum BUN and creatinine concentrations. Patients are often hypertensive and may have peripheral edema. In glomerulonephritis, there is an inflammatory lesion of the glomerular capillary bed that is often immune-mediated. This is manifested clinically by red cell casts, hematuria, and proteinuria. The hallmark of glomerulonephritis on urine microscopy is the presence of dysmorphic red blood cells and red cell casts. Decreased glomerular capillary perfusion decreases GFR and results secondarily in increased reabsorption of sodium and water. Hypertension, oliguria, edema formation, and rising serum BUN and creatinine concentrations are the clinical sequelae.

Postinfectious Glomerulonephritis

Acute postinfectious glomerulonephritis (APIGN) occurs most often in children but can be seen in adults. It generally occurs 2 weeks after pharyngeal infection with specific nephritogenic strains of group A β-hemolytic streptococcal infection. The clinical presentation can vary from microscopic hematuria and proteinuria on urinalysis to the nephritic syndrome, with the abrupt onset of periorbital and lower extremity edema, mild-to-moderate hypertension, microscopic hematuria, red cell casts, gross hematuria, and oliguria. The latent interval from the time of infection to the onset of symptoms is not less than 5 days and not more than 28 days (average: 10 to 21 days). Documentation of a preceding streptococcal infection may be by throat or skin culture or serologic changes in streptococcal antigen titers. Antistreptolysin O (ASO) titers are not as sensitive in patients with skin infection and anti-DNAse B is often used in this setting. Laboratory evaluation reveals an elevated serum BUN and creatinine concentration, and low serum complement concentration (C3). The vast majority of children recover spontaneously. The recovery rate is lower in adults. In the rare patient, RPGN may develop. The serum creatinine concentration usually returns to baseline within 4 weeks, C3 concentration returns to normal in 6 to 12 weeks, and hematuria generally resolves within 6 months; proteinuria, however, may persist for years. There is no evidence that immunosuppressive therapy with corticosteroids is of benefit.

There is endothelial and mesangial cell proliferation with leukocytic infiltration in kidney, resulting in a picture of diffuse proliferative glomerulonephritis. EM reveals large immune deposits in the subepithelial space. Subendothelial deposits can occur early in the course of the disease. IF demonstrates complement and IgG. The disease is secondary to an immunologic process. Many patients have circulating immune complexes, whereas others may develop in situ immune complexes in the GBM as a result of planted bacterial antigens. Treatment includes antimicrobial agents, blood pressure control, and supportive therapy.

Several infectious agents in various organs, such as the skin, lungs, bone, and urinary tract, have been associated with APIGN. In adults, the most common infections occur in the hospital setting and are caused by staphylococcus, streptococcus, and Gram-negative rods. Many of these patients are immuncompromised with diabetes mellitus or malignancy and are elderly. One of the more common infectious agents is *Staphylococcus aureus*, which has a more rapid onset of renal injury and can present similarly to Henoch-Schönlein purpura. In addition to a presentation typical of nephritic syndrome, patients develop severe purpura, hypocomplementemia, and histopathology characterized by IgA-positive immunofluoresence (rather than IgG). In addition, in contrast to children and young adults, patients have worse outcomes with complete recovery in only approximately 50%, with many developing chronic kidney disease (CKD) and as many as 33% requiring chronic renal replacement therapy. Management consists of blood pressure control, eradication of infection, and dialysis when needed. Immunosuppressive therapy with steroids or other agents is not warranted.

Systemic Lupus Erythematosus

Renal disease in patients with SLE is associated with a number of different lesions that involve the glomerulus, blood vessels, and tubulointerstitium. This section focuses on glomerular disease.

Immune complex formation underlies the pathogenesis of SLE nephritis. The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of SLE nephritis, generated from a consensus conference in 2002, replaced the World Health Organization (WHO) classification from 1995. The ISN/RPS classification divides the lesions associated with SLE into 6 different patterns or classes (Table 17.1). Class I (minimal mesangial lupus nephritis) is normal light microscopy

TABLE 17-1. International Society of Nephrology/Renal Pathology Society Classification of Lupus Nephritis

CLASS	NAME	LIGHT MICROSCOPY	IF	EM
I	Minimal mesangial lupus nephritis (LN)	Normal	Mild mesangial staining	Few mesangial deposits
II	Mesangial proliferative LN	Mesangial proliferation with increased mesangial matrix	Mesangial staining	Mesangial deposits, few isolated subepithelial or subendothelial deposits
III III (A) III (A/C) III (C)	Focal LN Focal proliferative LN Focal proliferative and sclerosing LN Focal sclerosing LN	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli Active lesions Active and chronic lesions Chronic inactive lesions with glomerular scars	Focal capillary loop staining with or without mesangial staining	Focal subendothelial deposits with or without mesangial alterations
IV IV-S (A) IV-G (A) IV-S (A/C) IV-G (A/C) IV-S (C) IV-G (C)	Diffuse lupus nephritis Diffuse segmental proliferative LN Diffuse global proliferative LN Diffuse segmental proliferative and sclerosing LN Diffuse global proliferative and sclerosing LN Diffuse segmental sclerosing LN Diffuse global sclerosing LN	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving >50% of all glomeruli Active lesions Active lesions Active and chronic lesions Active and chronic lesions Chronic lesions Chronic lesions	Diffuse capillary loop staining with or without mesangial staining	Diffuse subendothelial deposits with or without mesangial alterations
V	Membranous LN	Capillary loop thickening	Global or segmental subepithelial staining with or without mesangial staining	Global or segmental subepithelial deposits with or without mesangial deposits
VI	Advanced sclerosis LN	Greater than 90% globally sclerosed glomeruli without residual activity	—	—

with evidence of mesangial immunoglobulin staining on IF microscopy. Class II (mesangial proliferative lupus nephritis) is characterized by mesangial proliferation, defined as increased mesangial matrix and hypercellularity (light microscopy), mesangial immunoglobulin staining (IF), and dense deposits (EM) within the mesangium. A few subepithelial or subendothelial deposits may be present on EM or IF. Focal lupus nephritis constitutes class III nephritis. On light microscopy, "focal" represents disease in some, but not all, glomeruli, whereas

"segmental" means that less than 50% of glomeruli have evident disease. As such, focal and segmental mesangial and endothelial proliferation is seen; necrosis (cell death) may also be present in these areas. Immune staining is seen in the mesangium and capillary loops on IF. Deposits in the mesangium, subendothelial, and subepithelial areas are often visualized on EM. Class III is broken down into the following subcategories based on activity/chronicity. Class III(A): focal proliferative lupus nephritis (active lesions); Class III(A/C): focal proliferative and sclerosing lupus nephritis (active and chronic lesions); Class III(C): focal sclerosing lupus nephritis (chronic inactive lesions with glomerular scars). Class IV (diffuse lupus nephritis) is an active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving more than 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. The class is divided into diffuse segmental when more than 50% of glomeruli have segmental lesions, and diffuse global when more than 50% have global lesions. Class IV-S(A): diffuse segmental proliferative lupus nephritis (active lesions); Class IV-G(A): diffuse global proliferative lupus nephritis (active lesions); Class IV-S(A/C): diffuse segmental proliferative and sclerosing lupus nephritis (active and chronic lesions); Class IV-G(A/C): diffuse global proliferative and sclerosing lupus nephritis (active and chronic lesions); Class IV-S(C): diffuse segmental sclerosing lupus nephritis (chronic lesions); and Class IV-G(C): diffuse global sclerosing lupus nephritis (chronic lesions). Crescents and thickening of capillary loops (wire loops) may also be seen (Figure 17.12). Immune staining is noted in the mesangium and capillary loops on IF, whereas EM shows deposits in all sites. Class V nephritis is a membranous lupus nephritis. It is characterized by diffuse thickening of the GBM without cellular proliferation. Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by IF or EM, with or without mesangial alterations. Class VI is advanced sclerosis lupus nephritis, which is characterized by more than 90% of glomeruli with global sclerosis and without residual activity. This represents an end-stage kidney lesion.

An abnormal urinalysis (hematuria and proteinuria) is typically seen at the time of diagnosis of SLE. Approximately 50% of patients with newly diagnosed SLE will have an abnormal urinalysis with or without renal dysfunction. In this setting, proteinuria is the most common urinary abnormality, noted in 80% of patients.

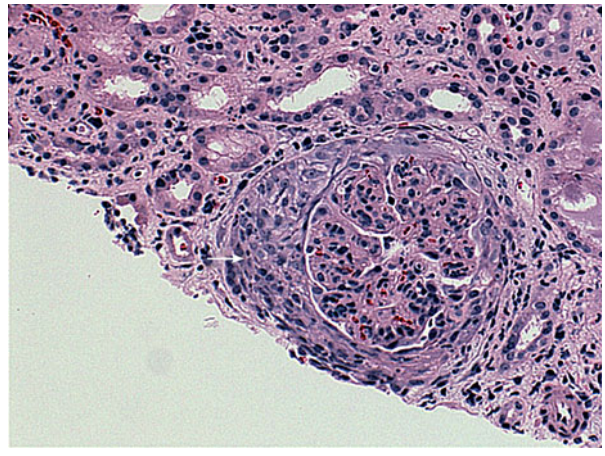

FIGURE 17-12. Lupus nephritis (light microscopy). There is an increase in cellularity as a result of mesangial and endothelial proliferation, as well as an accumulation of mesangial matrix. A crescent is seen at the arrow on the left. (Courtesy of Gilbert Moeckel.)

Hematuria and/or pyuria develop in nearly 40% of patients at sometime during the course of disease. In general, lupus nephritis develops early following diagnosis, although decreased kidney function (increased serum creatinine concentration) is relatively uncommon within the first few years of diagnosis. Younger patients appear to develop renal disease earlier. Although SLE is associated more commonly with certain human leukocyte antigen (HLA) genotypes (HLA-B8, -DR2, -DR3, and -DQW1) and complement component deficiencies (C2 and C4 deficiencies), nephritis tends to be more severe in African Americans, children, and in those patients with genetic abnormalities of Fc receptors.

The course of renal disease is typically benign for types I and II SLE nephritis. Often there are no obvious signs of renal disease, although hematuria and/or proteinuria with preserved kidney function is seen. In type III, proteinuria and hematuria are commonly present; rarely, patients may develop nephrotic range proteinuria. Mild renal dysfunction and hypertension can occur. Diffuse proliferative nephritis (type IV) is universally complicated by hematuria and proteinuria. Acute kidney injury, which can be severe, hypertension, and nephrotic range proteinuria are common. Type III and, in particular, type IV nephritis are both associated with severe and rapid loss of kidney function when left untreated. In addition to type III and type IV lesions,

poor renal prognosis is associated with high activity index and chronicity index, presence of cellular crescents and interstitial fibrosis, and severe vascular lesions. The activity index is based on 6 histologic categories of active lesions that may be reversible (cellular proliferation, leukocyte infiltration, fibrinoid necrosis, cellular crescents, hyaline thrombi or wire loops, and mononuclear cell interstitial infiltration), whereas chronicity index measures 4 histologic components of irreversible damage (glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy). MN, which has a variable course of disease, is associated with high-grade proteinuria, and 90% of patients with MN develop nephrotic syndrome at some point in the disease course. Hematuria, hypertension, and renal failure may be seen.

As an immune complex disease, the pattern of SLE-associated glomerular injury that develops is related to the site of formation of the immune deposits. Loss of self-tolerance and generation of an autoimmune response are associated with alterations in cytotoxic, suppressor, and helper T-cell numbers. Altered T-cell signaling, cytokine production, and polyclonal activation of B cells results in the production of idiotypic autoantibodies against nuclear antigens, DNA, Sm, RNA, Ro, La, and other nuclear antigens. Thus, the complexes are composed of nuclear antigens and complement fixing IgG_1 antibodies. Immune complex deposition in kidney results from either complexes formed in the circulation (mesangial and proliferative) or binding of circulating antibodies to antigens previously planted in the subepithelial space (membranous). Location of deposits determines the type of inflammatory response. Deposits in the mesangium or subendothelial space are close to the vascular space, and as a result, activate complement. This generates the chemoattractants C3a and C5a, stimulating influx of neutrophils and mononuclear cells. A proliferative glomerular lesion, including mesangial, focal, and diffuse proliferative nephritis, is created. In contrast, deposits on the subepithelial space activate complement but do not attract inflammatory cells because of their separation from the vascular space. A nonproliferative lesion complicated by proteinuria (membranous) with disease limited to the glomerular epithelial cell develops.

Diagnosis of SLE nephritis most often occurs following identification of extrarenal disease. Occasionally, renal manifestations and renal histology precede systemic disease, or recognition of atypical symptoms of SLE. In addition to urinary findings such as hematuria (with or without red blood cell casts) and proteinuria (both low and high grade), blood testing, such as serum creatinine concentration, antinuclear antibody titer, anti–double-stranded DNA, and serum complement concentration are also useful. Renal biopsy is the gold standard test to diagnose and direct therapy in lupus nephritis. In addition, biopsy allows for prediction of prognosis. Histologic features such as ISN/RPS class, activity and chronicity indices, and other findings when employed with clinical features can help guide therapy. For example, aggressive cytotoxic treatment is employed for lesions that are potentially reversible and less-aggressive approaches, employing supportive therapy in those with advanced, irreversible histopathology.

Therapy of lupus nephritis is based primarily on ISN/RPS classification, with types III and IV undergoing treatment. For induction therapy, a combination of intravenous "pulse" cyclophosphamide and intravenous methylprednisolone are more effective than either alone. Cyclophosphamide is infused monthly (0.5 to 1.0 g/m^2, titrated to maintain white blood cell count above $3000/mm^3$) for 6 months followed by infusion every 3 months for an additional 24 months. Induction therapy with oral MMF has also been shown to be successful in the treatment of lupus nephritis. It appears to be equal to cyclophosphamide, but with fewer adverse effects, in particular less infectious complications. Prolonged maintenance therapy is associated with the best outcome. Because of toxicity, a shorter maintenance course is recommended for patients with diffuse proliferative lupus nephritis with mild clinical disease. Corticosteroids are often tapered over a period of months to doses optimal to control extrarenal manifestations of SLE. Oral azathioprine (0.5 to 4 mg/kg/day) and MMF (500 to 3000 mg/day) have been employed successfully as maintenance therapies for lupus nephritis. In fact, MMF is superior to azathioprine for maintenance therapy. Plasmapheresis appears to add little benefit to routine immunosuppressive therapy, although some patients with resistant disease garner some benefit. Although early promise was seen with rituximab, current data suggest that this drug, when added to MMF is not associated with a higher complete or partial remission rate for initial therapy of proliferative lupus nephritis. Patients should be monitored for both remission (during therapy) and relapse of lupus nephritis (following therapy) with the same clinical tools as used to diagnose renal disease.

When routine treatment of lupus nephritis is unsuccessful, other modalities have been employed for both initial and maintenance therapy. African American race is associated with resistance to routine immunosuppressive regimens for diffuse proliferative glomerulonephritis. Cyclosporine stabilizes renal function and reduces proteinuria in a small number of patients with type IV lupus nephritis when used as initial therapy. Intravenous immunoglobulin promoted histologic, immunologic, and clinical improvement in 9 patients resistant to routine therapy. The efficacy of this therapy needs further evaluation in controlled studies. High-dose chemotherapy with stem cell transplantation was examined in patients with active diffuse proliferative nephritis and other severe extrarenal manifestations of SLE refractory to aggressive immunosuppressive treatment. Seven patients with this type of disease underwent this regimen. At 25 months of follow-up, all patients had no clinical or serologic evidence of SLE. Other experimental therapies for lupus nephritis on the horizon include immunoadsorption, anti-CD40 ligand (to block costimulatory pathways between T and B cells), and LJP-394, a small molecule that blocks production of anti-DNA antibodies. Large, randomized studies are required to fully test these interventions.

In addition to standard therapy of nephrotic syndrome, such as RAAS inhibition, lipid lowering, diuretics, and anticoagulation (in high-risk patients), immunosuppressive therapy may be indicated in certain situations. These include patients with severe, symptomatic nephrotic syndrome, worsening kidney function, and/or mixed membranous and proliferative lesions on renal histology. Based on an National Institutes of Health (NIH) trial comparing prednisone, cyclosporine, and cyclophosphamide for lupus membranous nephritis, 1-year remission was better with cyclosporine and cyclophosphamide than with prednisone alone. The probability of remission with cyclosporine and cyclophosphamide were lower with urinary protein excretion greater than 5 g/day. Relapse was less with cyclophosphamide than with cyclosporine. Although MMF was equivalent to cyclophosphamide in 1 trial, follow-up was short, making it unclear whether MMF would be associated with higher relapse rates. Thus, for those who meet criteria for immunosuppressive therapy, initial treatment with prednisone and either cyclophosphamide or cyclosporine is recommended. For those with resistant or relapsing disease, substituting cyclosporine for cyclophosphamide, or vice versa, is recommended.

Thrombotic Microangiopathies

The thrombotic microangiopathies consist of a spectrum of diseases that are characterized by the formation of platelet microthrombi within vessels, thrombocytopenia, and microangiopathic hemolytic anemia. Formation of microthrombi in the microcirculation leads to multisystem end-organ ischemia and 1 of 2 clinical presentations (Table 17.2), consistent with either hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP). There is, however, overlap between the 2 with regard to the clinical manifestations of the thrombotic microangiopathy. HUS and TTP can also be separated based on pathogenesis of the coagulation disorder. TTP is most often associated with either a congenital or acquired defect in a metalloproteinase-converting enzyme (ADAMTS13 [a disintegrin and metalloproteinase with thrombospondin domain 13]) for von Willebrand factor (vWF). Absence of or reduced activity of this enzyme leads to abnormally large vWF in the circulation, which promotes aggregation of platelets and formation of microthrombi. In contrast, with HUS endothelial cell damage in the vasculature is thought to be the primary event that precipitates coagulation and microthrombi formation. It is not associated with a defect in the vWF-cleaving protease, but can have abnormal vWF in the circulation during acute illness.

Renal histology in the thrombotic microangiopathies is characterized by microthrombi within small vessels,

TABLE 17-2. Clinical Features of the Thrombotic Microangiopathies

	D+ HUS	TTP
CNS symptoms	+	+++
Fever	+	+++
Colitis	+++	+
Multiorgan disease	+	+++
Hematuria/proteinuria	+++	++
Renal failure	+++	+
Death despite treatment	5%	15%
Recurrences	1%	20%

Abbreviations: +, Rare; +++, common; CNS, central nervous system; D+ HUS, diarrhea-associated hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

including small arteries, arterioles (including afferent arterioles), and glomerular capillary loops. Ischemic retraction of glomeruli and ischemic injury in the tubulointerstitium are present. Over time, glomerulosclerosis and tubulointerstitial fibrosis are seen. EM demonstrates small vessel microthrombi consisting of platelets and fibrin. No immune deposits are seen. IF staining is also negative except for fibrin deposition in vessel walls.

Hemolytic Uremic Syndrome

HUS develops from various disease processes. The sporadic or endemic variety associated with diarrhea (D+ HUS) is linked to Shiga toxin exposure. The classic example is *Escherichia coli* strain 0157:H7. This bacterium produces the culprit toxin, which is associated with acute endothelial inflammation and injury, as well as accelerated thrombogenesis, resulting in bloody diarrhea and HUS. Other organisms produce neuraminidase, a promoter of diffuse endothelial injury, and may also cause HUS. Atypical, non-diarrhea-associated HUS (D− HUS) is more heterogeneous. It consists of familial forms, including both autosomal dominant and recessive disorders that can frequently relapse. D− HUS can also occur following exposure to various drugs and therapeutic agents, including: cyclosporine; tacrolimus; mitomycin-C; gemcitabine; methotrexate; oral contraceptives; ticlopidine; irradiation; quinine; and anti–T-cell antibodies. Pregnancy (HELLP [hemolysis, elevated liver enzymes, low platelets] syndrome), certain malignancies, systemic diseases (scleroderma, SLE, antiphospholipid antibody syndrome), malignant hypertension, HIV infection, and bone marrow transplantation are associated with D− HUS. Hereditary abnormalities in the alternate complement pathway (factor H, factor I, factor B, membrane cofactor protein, thrombomodulin, and a combination of a genetic defect in factor CFHR (complement factor H-related)1 and CFHR3 coupled with autoantibodies to factor H) were also described to cause this form of HUS. Finally, an idiopathic form of D− HUS can occur.

The majority of HUS in children is associated with diarrhea (D+ HUS), whereas less than 50% of adult cases are D+ HUS. Vectors for toxin-producing bacteria are beef and fermented salami, as well as contaminated water, fruit, and vegetables. Unpasteurized apple cider, apple juice, and dairy products are also sources. Numerous outbreaks are a result of person-to-person contact. Development of HUS occurs during the warmer months. In children, bloody diarrhea from colitis is common and abdominal pain, which can be associated with intussception, bowel necrosis, and rectal prolapse can occur. The onset of HUS occurs approximately 1 week after diarrhea, presenting as pallor, lethargy, irritability, severe hypertension, and decreased urine output. Clinical or chemical pancreatitis, seizures, and other end-organ disturbances occur less commonly.

Recently, 2 newer therapies have shown promise in the treatment of HUS. The terminal complement inhibitor eculizumab was recently approved by the U.S. Food and Drug Administration for the treatment of D− HUS but has also shown promise in a small number of patients with D+ HUS. Eculizumab binds to C5 and prevents formation of the membrane attack complex (C5-C9). Eculizumab is associated with life-threatening meningococcal infection and meningococcal vaccination is required for all patients. Immunoabsorption has also resulted in clinical improvement in severely ill patients. Blood pressure control and optimal management of renal failure, often using dialysis, are key to improved outcomes. Children with HUS have a good prognosis. Approximately 90% experience functional recovery, whereas 5% die in the acute phase of illness. In those who recover, 10% are left with some form of CKD. In contrast, adults have worse outcomes. Overall mortality is up to 30%, and CKD occurs in approximately 20% to 30% of survivors, many requiring renal replacement therapy for ESRD. Mortality is highest (greater than 50%) in those with postpartum, cancer, or mitomycin-C–associated HUS. Recurrence develops in 25% of cases. The poor outcome is likely explained by the much higher incidence of D− HUS in adults.

Thrombotic Thrombocytopenic Purpura

TTP occurs most often from either congenital or acquired abnormalities in the vWF-cleaving protease (ADAMTS13). The primary defect is abnormal (enhanced) platelet aggregation caused by large, circulating vWFs present as a result of reduced protease activity, resulting in microthrombi formation. Congenital forms may be acute and nonrelapsing or, more commonly, chronic and relapsing. The chronic, relapsing form of TTP may be familial (autosomal recessive) or sporadic, both associated with a deficiency of vWF-cleaving protease. Acquired forms occur following exposure to various drugs such as ticlopidine, mitomycin-C,

oral contraceptives, quinine, cyclosporine, and cocaine. Scleroderma, pregnancy, HIV infection, and SLE are also associated with TTP. Acute, nonrelapsing forms of TTP are more commonly acquired. An autoantibody directed against the vWF-cleaving protease, that is able to inactivate the enzyme, occurs with most acquired forms of TTP.

In contrast to HUS, TTP occurs predominantly in women (70%) and is not seasonal. Peak incidence is in the third and fourth decades of life and TTP is rare in infants and the elderly. This is probably because of the more common association with acquired causes of TTP, which outnumber congenital forms. Fever and bleeding are common presenting features of TTP. Central nervous system (CNS) manifestations occur initially in approximately 50% of patients, but eventually develop in nearly 90% of those with TTP, and are the most prominent feature of the syndrome. Headache, visual symptoms, somnolence, and focal neurologic findings occur commonly. Seizures develop in 30% of patients. The CNS changes can fluctuate and be fleeting. Purpura is common, while gastrointestinal bleeding occurs from severe thrombocytopenia. Renal manifestations include hematuria, proteinuria, and azotemia. Severe acute kidney injury, in contrast to HUS, is much less common, but can occur. Heart and lung may also suffer thrombotic complications of TTP.

Current therapy for TTP involves a combination of plasma exchange and corticosteroids. The rationale of plasma infusion and plasma exchange in TTP is based on targeting the vWF-cleaving protease abnormality. Treatment with fresh-frozen plasma infusion is very effective for TTP-associated with a deficiency of the vWF protease. Alternatively, intensive plasmapheresis with plasma infusion is appropriate for disorders associated with an autoantibody to the vWF protease. Plasma exchange is associated with a response in 70% to 90% of patients with TTP. Treatment should be continued until remission is achieved. In general, at least 7 consecutive daily treatments followed by alternate day exchanges for those improving are recommended. Remission rates may be higher in those treated with high-dose methylprednisolone (10 mg/kg/day for 3 days then 2.5 mg/kg/day) versus standard dose methylprednisolone (1 mg/kg/day). Splenectomy is risky and its benefit is marginal. Platelet transfusions are generally felt to be contraindicated because they may worsen clinical signs and symptoms.

KEY POINTS

Nephritic Syndrome (Glomerulonephritis)

1. Nephritis or the nephritic syndrome is characterized by the abrupt onset of hematuria, proteinuria, and acute kidney injury. Patients often have associated hypertension and peripheral edema. The hallmark of glomerulonephritis on urinalysis is the presence of red cell casts.
2. APIGN occurs most often in children after pharyngeal infection with specific nephritogenic strains of group A β-hemolytic streptococcal infection.
3. Immune complex formation underlies the pathogenesis of SLE nephritis. Location of deposits determines the type of inflammatory response.
4. The ISN/RPS classification divides the lesions associated with SLE into 6 different types. Type III (focal proliferative glomerulonephritis) and, in particular, type IV nephritis (diffuse proliferative glomerulonephritis) are both associated with severe and rapid loss of kidney function when left untreated.
5. Therapy of lupus nephritis is based primarily on the ISN/RPS classification.
6. The thrombotic microangiopathies consist of a spectrum of diseases that are characterized by the formation of platelet microthrombi within vessels, thrombocytopenia, and microangiopathic hemolytic anemia.
7. HUS develops from various disease processes. The sporadic or endemic variety associated with diarrhea is linked to Shiga toxin exposure. The onset occurs approximately 1 week after diarrhea, presenting with severe hypertension and decreased urine output.
8. TTP is associated with either a congenital or acquired defect in a metalloproteinase-converting enzyme for vWF. CNS manifestations are the most prominent feature. Purpura is common, whereas gastrointestinal bleeding occurs from severe thrombocytopenia. Renal manifestations include: hematuria; proteinuria; and azotemia.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

RPGN is characterized by crescent formation and a rapid decline in renal function. A crescent is made up of proliferating epithelial cells that line Bowman's capsule and infiltrating macrophages (Figure 17.13). Crescents result

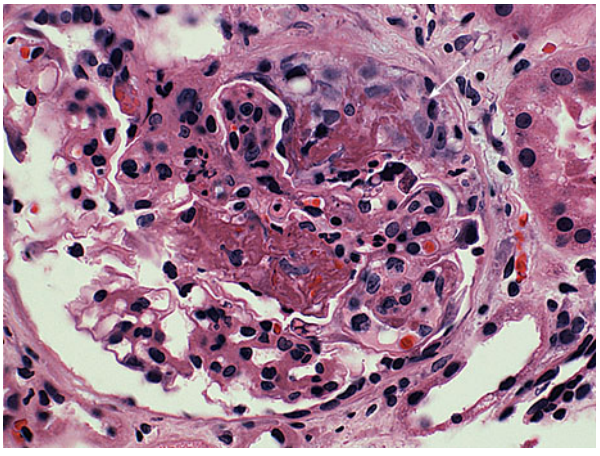

FIGURE 17-13. Crescent (light microscopy). A cellular crescent is seen by the arrow.

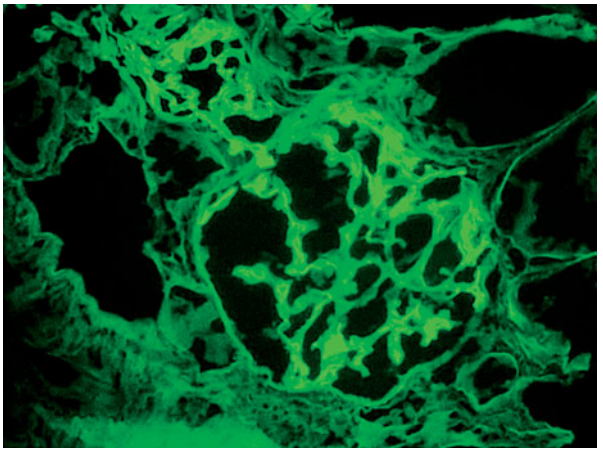

FIGURE 17-14. Goodpasture syndrome (IF microscopy). IF staining in this patient with Goodpasture syndrome shows the classic linear IgG staining pattern. Note that there is no granularity as in Figure 17.7.

when the GBM is severely damaged with breaks observed on EM. This allows fibrin, plasma proteins, macrophages, monocytes, plasma cells, and platelets to gain access to Bowman's space. Patients present with a rising BUN and serum creatinine concentration and may have oliguria. Without adequate treatment irreversible renal failure may develop in weeks. RPGN is subdivided into 3 types based on IF microscopy: (a) anti-GBM antibody disease; (b) pauciimmune glomerulonephritis; and (c) immune complex disease.

Type 1 Anti-GBM Antibody Disease (Goodpasture Syndrome)

Goodpasture syndrome is characterized by circulating antibodies to the GBM in association with glomerulonephritis and pulmonary hemorrhage. Rarely, clinical evidence of an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis may be seen concurrently with anti-GBM disease. Hemoptysis, pulmonary infiltrates, and pulmonary hemorrhage result from cross-reactivity of anti-GBM antibody to the alveolar capillary basement membrane. The autoantibodies recognize an epitope in the α_3 chain of type IV collagen. A small subset of patients have antibodies to the α_5, α_4, or α_1 chains. The binding of antibody to antigen induces an inflammatory response that results in glomerular injury. The initial injury is a focal and segmental necrosis followed by extensive crescent formation. IF microscopy shows linear deposition of IgG in the GBM (Figure 17.14). EM does not reveal dense deposits, excluding immune complex disease.

Anti-GBM disease is uncommon; the annual incidence is 1 to 2 cases per 1 million population/year. It makes up less than 10% of all cases of crescentic glomerulonephritis seen on renal biopsy. The disease incidence has 2 peaks: the first is in the third to sixth decade of life; and the second in the sixth and seventh decades of life. Young males more often present with the pulmonary renal syndrome, whereas elderly females more commonly develop renal-limited disease. Smoking predisposes to the development of pulmonary hemorrhage. Dyspnea, either intermittent or continuous, cough, and hemoptysis are the major symptomatic features of Goodpasture syndrome. Hemoptysis can be massive, minor, or absent. Lack of hemoptysis does not exclude pulmonary disease or hemorrhage. Pulmonary symptoms may develop over hours or slowly over weeks. Tachypnea, cyanosis, and inspiratory rales are signs of pulmonary disease. Arterial blood gas may demonstrate hypoxemia from alveolar hemorrhage. Occasionally, subclinical bleeding in the lungs results in iron-deficiency anemia. Nephritis from anti-GBM disease is associated with hematuria, dysmorphic red cells, and red blood cell casts on urine sediment. Proteinuria and an elevated serum creatinine concentration are often present at the time of diagnosis. Renal function can deteriorate rapidly in the absence of

therapy. Some patients, especially the elderly present with renal manifestations and no pulmonary symptoms. In the absence of pulmonary hemorrhage, patients are considered to have renal-limited anti-GBM disease.

The diagnosis is suspected based on clinical and laboratory findings. The chest radiograph demonstrates patchy or diffuse infiltrates in the central lung fields. The changes are most often symmetric, but rarely can occur asymmetrically. Renal ultrasound typically appears normal. Anti-GBM antibodies may be detected in serum, but this is not a sensitive test (excessive number of false-negative results). False negative serologic assays can occur, therefore, in the absence of a contraindication renal biopsy should be considered if clinical suspicion is high. Circulating anti-GBM antibodies are detected in serum using a specific enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay. The test is based on the principle that purified GBM components are coated on plastic microtiter plates and diluted serum is applied whereby anti-GBM antibodies bind the GBM components. Antibody binding is detected by using a secondary antibody that binds to human IgG. The ANCA test is positive in one-third of patients, with the majority having antibodies reactive to myeloperoxidase. These antibodies appear before the anti-GBM antibody and may play a role in exposing Goodpasture disease epitopes to the immune system. Although rarely performed, lung biopsy is diagnostic when it reveals linear IgG staining along the pulmonary basement membrane. Alveoli are often filled with red blood cells and hemosiderin-laden macrophages. Renal histology is typically obtained in these cases and, as described above, is diagnostic.

Anti-GBM disease is a true autoimmune disease of the kidney and lung. The pathogenesis is thought to be because of both the presence of anti-GBM antibodies and T-cell–mediated immunity to GBM antigens. GBM antigens are expressed in thymus, and autoreactive $CD4^+$ T cells are increased. These T cells provide help to autoreactive B cells in the production of anti-GBM antibodies. These autoantibodies are directed against the noncollagenous 1 domain of the α_3 chain of type IV collagen in kidney and lung. Antibody binding leads to inflammation with complement deposition, leukocyte recruitment, and tissue injury and destruction. Genetic factors may play a role, as HLA-DR2 is associated with the development of anti-GBM disease. Environmental influences, such as smoking, infection, certain geographical locations, and organic solvents or hydrocarbons, are associated with Goodpasture syndrome.

Treatment is directed at removing culprit autoantibodies and suppressing their production. To this end, intensive plasmapheresis, glucocorticoids, and immunosuppressive agents such as cyclophosphamide are employed. Most therapeutic protocols use a combination regimen consisting of prednisolone, cyclophosphamide, and plasmapheresis. Prednisolone is employed at 1 mg/kg/day (maximum 80 mg/day) with a weekly dose reduction to 20 mg/day, followed by a slow taper over the next 1 to 2 years. Oral cyclophosphamide at 2.5 mg/kg/day (maximum 150 mg/day) is given for 4 months (dose adjustment based on white blood cell count) and converted to azathioprine for the next 1 to 2 years. Daily 4-L exchanges with 4.5% albumin for 2 weeks (or until no detectable anti-GBM antibodies) is the plasma exchange regimen. Key to success is initiation of therapy prior to the serum creatinine concentration reaching 5.7 mg/dL. The probability of achieving a 5-year survival without dialysis was 94% in these patients, where it decreased to 50% in patients with higher serum creatinine concentrations not yet requiring dialysis. Dialysis dependence at the time of therapy was associated with a dismal 13% chance of dialysis-free survival. Interestingly, there was no influence of anti-GBM titer on outcome, although 100% glomerular crescents on biopsy portended a poor renal prognosis.

Type 2 Immune Complex Diseases

A variety of immune complex diseases can result in RPGN, including postinfectious glomerulonephritis, lupus nephritis, IgA nephropathy, HSP, MPGN, and membranous glomerulonephritis. Many of these disorders are discussed in other sections of this chapter.

Type 3 Pauciimmune Glomerulonephritis

Pauciimmune glomerulonephritis is characterized by no or very little immunoglobulin deposition on IF. This group of diseases is associated with ANCA. Most patients have evidence of a systemic vasculitis such as granulomatosis with polyangiitis formerly known as Wegener granulomatosis, microscopic polyarteritis, or eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome).

Granulomatosis with Polyangiitis (Wegener Granulomatosis)

Granulomatosis with polyangiitis (GPA) is a necrotizing vasculitis involving small-size vessels. Although GPA can affect any organ system, it classically involves the kidney,

as well as the upper and lower respiratory tract. Pathologic examination of lesions in the nasopharynx and lung reveals a necrotizing granulomatous vasculitis. In kidney, the vasculitis manifests as a necrotizing glomerulonephritis with crescent formation. Granulomas are rarely seen on renal biopsy.

The disease most commonly develops in middle-aged or elderly adults, but can occur at any age. The initial presentation is often nonspecific with a variety of prominent constitutional symptoms, including fever, night sweats, anorexia, weight loss, and fatigue. Upper respiratory and pulmonary symptoms are prominent early on such as rhinorrhea, sinusitis, otitis media, epistaxis, cough, and hemoptysis. A "limited" form of GPA is described that affects the upper and lower respiratory tract and not the kidneys. Renal involvement generally, but not always, follows the development of extrarenal involvement. Microscopic hematuria, red cell casts, proteinuria, and an elevated serum creatinine concentration are often present at the time of diagnosis. Some patients present with the renal lesion and nondiagnostic systemic symptoms. In the absence of upper and lower respiratory involvement these patients are often considered to have microscopic polyarteritis. It is likely that GPA, "limited" GPA, and microscopic polyarteritis are all part of a spectrum of the same disease since patients with "limited" GPA often develop renal involvement, patients with microscopic polyarteritis often subsequently develop pulmonary involvement, and the ANCA test is typically positive in all 3 syndromes. A variety of other organ systems may also be involved including the musculoskeletal system (myalgias, arthralgias), peripheral and CNS (mononeuritis multiplex, cranial nerve abnormalities), cardiovascular (pericarditis, myocarditis), skin (palpable purpura, ulcerative lesions), and eyes (conjunctivitis, episcleritis, uveitis, proptosis).

The diagnosis is suspected based on clinical and laboratory findings. The chest radiograph shows solitary or multiple nodules in the middle or lower lung fields. The nodules are poorly defined and often undergo central necrosis. The ANCA test is frequently positive in a cytoplasmic pattern (cANCA) and has a high sensitivity and specificity in the presence of active classic GPA (>90%), but is not sufficient to either rule in or rule out the diagnosis. In "limited" GPA the ANCA may be negative in as many as 40% of patients.

The ANCA test is performed by incubating the patient's serum with ethanol-fixed human neutrophils. Indirect IF is carried out and 2 patterns are observed. A diffuse cytoplasmic pattern is caused by antibodies directed against proteinase 3 and a perinuclear pattern is caused by antibodies directed against myeloperoxidase. A positive IF should be followed by an ELISA for proteinase 3 and myeloperoxidase. Approximately 70% of patients with microscopic polyarteritis will have a positive perinuclear antineutrophil cytoplasmic antibody (pANCA). The pANCA pattern is, however, nonspecific and is seen in a wide variety of inflammatory diseases. It can also be caused by antibodies against a host of azurophilic granule proteins including: catalase; lysozyme; lactoferrin; and elastase. The pANCA can also be falsely positive in patients with positive antinuclear antibodies (ANA). GPA is an immune-mediated disorder. It likely results from an inciting inflammatory stimulus and a pathologic immune reaction to shielded antigens on neutrophil granule proteins. These ANCAs interact with activated neutrophils and endothelial cells and cause tissue damage. The inciting inflammatory event remains unclear. Given that the initial symptoms often involve the respiratory tract, research has focused on infectious and noninfectious inhaled agents without identifying a causal agent. It is possible that an inflammatory event exposes neoepitopes on granule proteins that generate an immune response that then undergoes epitope spreading. Activated neutrophils have increased surface expression of proteinase 3, are more likely to degranulate and release reactive oxygen species, and have increased binding to endothelial cells resulting in tissue damage.

Confirmation of the diagnosis requires histologic examination of tissue. If lesions are present in the nasopharynx these should be biopsied because of the low morbidity. Granulomatous inflammation is often observed but granulomatous vasculitis is seen in only one-third of patients. If there are no nasopharyngeal lesions the kidney is often biopsied because it is less invasive than an open-lung biopsy (transbronchial biopsy often does not provide sufficient tissue to exclude the diagnosis). A kidney biopsy will not differentiate between GPA and microscopic polyarteritis because granulomas are rarely seen on renal biopsy. This distinction is often not important clinically given that the treatment of both conditions is the same. The characteristic finding in both disorders is a focal necrotizing glomerulonephritis with or without crescent formation. IF studies are negative. Serum complement concentrations are normal.

The mortality rate in untreated GPA is high, 80% within 1 year and 90% within 2 years. Mean survival in

untreated patients is only 5 months. Although corticosteroids alone may yield transient improvement, this is generally only temporary. One-year survival with corticosteroids alone is 33%. Long-term remissions are obtained in those treated with cyclophosphamide. One-year survival with cyclophosphamide is 80% to 95%. Early institution of therapy is paramount. The presence of severe acute kidney injury requiring dialysis during the acute phase of illness does not preclude aggressive therapy. Enough renal function can return to allow the discontinuation of dialysis.

For induction therapy, pulse intravenous cyclophosphamide (15 mg/kg every 2 weeks for 3 doses then every 3 weeks) is associated with a higher relapse rate than daily oral (2 mg/kg) therapy, but there is no difference in morbidity and mortality. Pulse intravenous therapy results in a lower total dose of cyclosporine being administered, less neutropenia and fewer infections. A recent randomized, controlled trial (Rituximab in ANCA-associated Vasculitis [RAVE]) established that rituximab (375 mg/m^2 weekly for 4 weeks) is as effective an agent for induction therapy as oral cyclophosphamide. Patients with severe pulmonary hemorrhage and serum creatinine concentration greater than 4 mg/dL were excluded. Neutropenia and sepsis are potential delayed consequences of therapy and the patient must be closely followed after the drug is stopped. Corticosteroids are continued until the disease is controlled and then tapered to an alternate-day schedule. They should be continued for at least 6 months. Cyclophosphamide is continued until there is no evidence of disease activity. Patients in remission after 3 or 4 months can be switched to oral azathioprine to reduce the incidence of complications providing the ANCA is negative. In this setting azathioprine is superior to MMF. Approximately 80% to 90% of patients can be placed into remission. Maintenance therapy is generally continued for 12 to 24 months after complete remission is induced. Systemic symptoms often improve quickly. The pulmonary and renal abnormalities require 3 to 6 months after cyclophosphamide begins to remit.

Relapses can occur. In this group of patients rituximab may be superior to cyclophosphamide in achieving a complete remission. The relapse rate is higher in patients with an ANCA positive for proteinase 3 and in those with respiratory involvement. Plasmapheresis is of limited benefit, but may be of value in those with pulmonary hemorrhage, patients who require dialysis during the initial phase, and those with anti-GBM antibodies. Seven exchanges are generally done every other day for 2 weeks. Although albumin can generally be used as a replacement, those who are bleeding or have undergone a recent renal biopsy should be replaced with fresh-frozen plasma.

Classical Polyarteritis Nodosa

Classical polyarteritis nodosa (PAN) involves small- and medium-size muscular arteries. Lesions tend to be segmental and commonly occur at arterial bifurcations, with distal spread occasionally involving arterioles. There is prominent neutrophilic infiltration with destruction of the vascular wall. Fibrinoid necrosis occurs with disruption of the internal elastic lamina, ischemia, and infarction. Aneurysm formation develops in the weakened vessel wall, and scarring during the healing process leads to further obliteration of the vascular lumen. The arcuate and interlobular arteries are primarily involved in kidney. The glomerular lesion is a focal, segmental, necrotizing glomerulonephritis. Changes are primarily ischemic, with fibrinoid necrosis and minimal proliferation. IF microscopy is usually negative. In the healing phase, thickening of the vessel wall may resemble that induced by chronic hypertension; however, in hypertension the internal elastic lamina is preserved.

Patients present with systemic symptoms including: fever; weight loss; arthralgia; and loss of appetite. Males are more commonly affected than females with a peak incidence in the sixth decade of life. There is a lack of eosinophilia or significant pulmonary involvement, which differentiates PAN from eosinophilc granulomatosis with polyangiitis. Asymmetric polyneuropathy (mononeuritis multiplex caused by involvement of the vasa vasorum) strongly suggests the diagnosis of PAN. The only other disease causing mononeuritis multiplex is diabetes mellitus. Testicular pain is another common feature. Renal involvement is characterized by azotemia and hypertension. In general, progressive kidney injury is a late manifestation. Urine sediment is variable, and may be relatively benign if only larger vessels are involved, a setting in which there may be glomerular ischemia without significant necrosis. Dysmorphic red blood cells, red blood cell casts, and mild proteinuria are typically seen when there is focal proliferative glomerulonephritis. Nephrotic range proteinuria is unusual. Serum complement concentration is usually normal. Hepatitis B infection is associated with the development of PAN.

The diagnosis is most commonly made by demonstrating typical vascular lesions on angiography of the

celiac and renal arteries. Microaneurysms and irregular segmental constrictions are seen in larger vessels, with tapering and occlusion of smaller intrarenal arteries. Renal biopsy may be required if the angiogram is negative, and if no other easily biopsied affected tissue such as muscle or peripheral nerve can be identified.

The prognosis of untreated PAN is poor with survival rates of only 33% at 1 year and 10% at 5 years. This improved dramatically with the advent of corticosteroids (50% 5-year survival). Mortality remains high secondary to renal failure, congestive heart failure, stroke, and mesenteric infarction. Long-term remissions are induced with cyclophosphamide in doses similar to those used for GPA. Patients with RPGN should also be given pulse corticosteroids. As with GPA improvement in renal function can be seen even in patients with far advanced disease. Maintenance therapy should be continued for 1 to 2 years after remission.

Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss)

Eosinophilic granulomatosis with polyangiitis (EGP) is characterized by extravascular granulomas, eosinophilic infiltration of arteries and venules, and kidney involvement. Clinically, the disease progresses through 3 stages. An allergic diathesis is usually the first clinical manifestation, beginning between ages 20 and 30 years. Asthmatic symptoms are frequent in this stage. This is followed by peripheral eosinophilia. The final stage is systemic vasculitis. The time course required to progress from one stage to another is variable. The shorter the interval, the worse the prognosis. As systemic vasculitis develops, lung involvement becomes more prominent with noncavitating pulmonary infiltrates on chest radiograph. Often allergic and asthmatic symptoms improve as vasculitis develops. Coronary vasculitis is common, and the heart is often the most severely affected organ (resulting in 50% of deaths). Renal involvement is generally mild, with renal failure developing in less than 10% of patients. Despite the paucity of renal findings hypertension is relatively common (75%). The characteristic light microscopy finding on renal biopsy is a focal segmental necrotizing glomerulonephritis. The interstitium is also involved with either a focal or diffuse interstitial nephritis with granuloma formation and eosinophilic infiltration. Patients with EGP often respond to corticosteroids alone and generally are treated for 1 year; relapses are uncommon.

Hypersensitivity Vasculitis

Hypersensitivity vasculitis primarily involves postcapillary venules. Skin lesions (palpable purpura) are the most predominant abnormality observed. Lesions vary in size from a few millimeters to centimeters and in severe cases ulceration may occur. Biopsy of affected skin reveals an intense neutrophilic infiltrate surrounding dermal blood vessels that is associated with hemorrhage and edema (leukocytoclastic vasculitis). Hypersensitivity vasculitis is often confined to skin but other organ systems including kidney may be involved. Vascular involvement in kidney occurs in the distal interlobular arteries and glomerular arterioles. In contrast to pauciimmune forms of glomerulonephritis such as GPA, IF shows diffuse granular deposition of immunoglobulin and complement. When the kidney is affected this is manifested as either HSP, essential mixed cryoglobulinemia (EMC), or serum sickness.

Henoch-Schönlein Purpura

HSP is characterized by IgA-containing immune deposits at sites of involvement. Presenting symptoms include: the characteristic tetrad of abdominal pain; arthritis or arthralgia; purpuric skin lesions; and kidney disease. Its annual incidence is 20 per 100,000 children. Skin lesions are most commonly seen on the extensor surfaces of the arms, legs, and buttocks. They are ultimately seen in all patients, but on occasion are absent at initial presentation. Lesions can begin as urticaria and evolve into purpura. The most common joints involved are the ankles and knees. Gastrointestinal manifestations include: vomiting; abdominal pain; and bleeding. Renal involvement is common and generally evident within days to months after the onset of initial symptoms. The urinalysis reveals microscopic hematuria, red blood cell casts, and mild proteinuria. On presentation the serum creatinine concentration is often normal or slightly elevated. Patients with more severe disease have nephrotic range proteinuria, hypertension, and elevated serum BUN and creatinine concentrations.

IF staining of purpuric skin lesions and occasionally normal skin is positive for IgA in endothelial cells of superficial blood vessels. Immune complexes may be absent from the vessel wall in older lesions. Consequently, the absence of immune complexes does not rule out HSP. Morphologic changes in kidney are identical to those seen in IgA nephropathy. The most common lesion is a mild proliferative glomerulonephritis. In severe cases, crescent

formation and fibrinoid necrosis are observed. IgA and complement containing immune deposits are present on IF.

The diagnosis should be considered in a patient with skin lesions of hypersensitivity vasculitis, particularly in the presence of arthralgias and abdominal pain. Skin biopsy with IF is often diagnostic. IgA deposition is found in dermal vessels in up to 75% of cases, however, early lesions must be biopsied. The absence of IgA in dermal vessels does not rule out HSP. Serum complement concentration is usually normal. Renal biopsy is only performed in patients with progressive increases in serum BUN and creatinine concentrations.

HSP is generally a benign self-limited disorder that resolves spontaneously. Adults tend to have more severe disease than children. Recurrences of purpuric skin lesions or glomerulonephritis can occur and recurrent disease does not imply a worse prognosis. The degree of renal involvement is the most important long-term prognostic factor. Prognosis is excellent in those with asymptomatic hematuria and proteinuria or focal glomerulonephritis. Poor prognostic signs include: nephrotic range proteinuria; and greater than 50% crescents on renal biopsy. This group of patients is less likely to completely recover kidney function. In one study, patients with greater than 50% crescents had a 37% incidence of progressing to ESRD. Progressive kidney disease is uncommon in patients who present initially with mild disease. Skin lesions and kidney disease do not respond to corticosteroids alone. Steroids may reduce the duration of abdominal pain, purpura, arthritis, and the degree of proteinuria, but do not prevent the development of glomerulonephritis. Cyclophosphamide is of no added benefit. The addition of cyclosporine may be of some benefit in those with nephrotic-range proteinuria. The lack of randomized, controlled trials and the high spontaneous remission rate of HSP make therapeutic recommendations difficult.

Essential Mixed Cryoglobulinemia (Type II)

Cryoglobulins are antibodies that precipitate in cold and redissolve on warming. The biochemical characteristics responsible for this are not well understood. There are 3 different types of cryoglobulins. Type I cryoglobulins are monoclonal and are usually the result of multiple myeloma or Waldenström macroglobulinemia. Type II cryoglobulins (EMC) contain a polyclonal IgG and a monoclonal IgM rheumatoid factor directed against the immunoglobulin. Most cases are the result of infection with hepatitis C. Cryoglobulins are abnormally glycosylated and this may play a role in their cryoprecipitation. Type III cryoglobulins are composed of a polyclonal IgG and a polyclonal IgM rheumatoid factor. This may be the result of hepatitis C infection but can also be seen with SLE and lymphoproliferative malignancies.

Hepatitis C virus can bind to B lymphocytes and lower their activation threshold resulting in the production of autoantibodies. Cryoglobulins are also present in other forms of chronic liver disease including infection with hepatitis B and patients with other forms of cirrhosis. Liver disease may contribute to the development or persistence of cryoglobulinemia due to the fact that the liver is the primary clearance site of cryoglobulins.

Patients often present with systemic symptoms, including fatigue and lethargy, as well as arthralgia. Palpable purpura can also be the presenting complaint and commonly involves the lower extremities. Hepatosplenomegaly, lymphadenopathy, peripheral neuropathy, and Raynaud phenomenon may be present. Serum complement concentrations are generally low. Renal involvement is present in approximately half of patients and ranges from asymptomatic hematuria and proteinuria to oliguric acute kidney injury. Azotemia is present at onset of disease in a minority of patients. Hepatic enzymes are often elevated and may reflect underlying hepatitis B or C infection.

EMC should be considered in any patient with palpable purpura, especially if hypocomplementemia is present. The diagnosis is established by the presence of an IgM–IgG cryoglobulin with a monoclonal component by immunofixation electrophoresis. To test for the presence of cryoglobulins, 20 mL of blood must be drawn in the fasting state and collected in a tube without anticoagulants. The tube is then placed in warm water for transportation to the lab. After serum is separated via centrifugation the sample is placed at 4°C (39.2°F) and observed for cryoprecipitation.

The principal pathologic findings are found in skin and kidney. Skin biopsy reveals a leukocytoclastic vasculitis without IgA deposition. In kidney, light microscopy resembles MPGN type I with lobular accentuation, diffuse mesangial and endothelial cell proliferation, and basement membrane thickening. On EM mesangial and subendothelial deposits are seen. The subendothelial

deposits often have a characteristic "fingerprint" appearance. There are numerous intraluminal thrombi composed of precipitated cryoglobulin distinguishing EMC from MPGN type I. IF microscopy reveals the deposition of IgM and C3 in the GBM.

Renal involvement is slowly progressive in most patients, with renal failure developing over months to years. Neither the cryoglobulin or complement concentration predicts those that will develop ESRD. Hypocomplementemia in the presence of renal failure, hypertension, and elevated serum BUN and creatinine concentrations are poor prognostic signs. The efficacy of treatment remains a question. Patients with fulminant disease (acute kidney injury, progressive neuropathy, or distal necrosis requiring amputation) were often treated with plasmapheresis, prednisone, and cyclophosphamide before it became apparent that the majority of cases were related to hepatitis C infection. This regimen was successful in inducing remission in some patients. Reinfused plasma must be warmed or acute kidney injury will be induced. Plasmapheresis is generally done 3 times per week for several weeks. Immunosuppressive therapy carries the risk of worsening viral replication and may further increase the risk of inducing non-Hodgkin lymphoma. More recently, combinations of interferon-α and ribavirin were employed. Although this regimen is effective for the treatment of skin and joint involvement, there is little evidence that it is beneficial for the treatment of the renal lesion. In general, ribavirin should not be used in patients with a GFR below 50 mL/min. There is a high rate of recurrence of EMC in the renal allograft.

KEY POINTS

Rapidly Progressive Glomerulonephritis

1. RPGN is characterized by a rapid decline in renal function and crescent formation on renal biopsy. It is important to recognize since irreversible renal damage can occur over a span of weeks.
2. RPGN is subdivided into 3 types based on IF microscopy: (a) anti-GBM antibody disease; (b) immune complex disease; and (c) pauciimmune glomerulonephritis.
3. Goodpasture syndrome is characterized by circulating antibodies to the GBM, glomerulonephritis, and pulmonary hemorrhage. IF microscopy reveals a linear deposition of IgG.
4. Pauciimmune glomerulonephritis is characterized by no or very little immunoglobulin deposition on IF. This group of diseases is associated with ANCA and includes GPA, microscopic polyarteritis, classic polyarteritis nodosum, and EGP.
5. GPA classically involves the kidney, as well as the upper and lower respiratory tract. Pathologic examination of lesions in the nasopharynx and lung reveals a necrotizing granulomatous vasculitis.
6. Classical PAN is diagnosed by demonstrating typical vascular lesions on angiography of the celiac and renal arteries. Microaneurysms and irregular segmental constrictions are seen in larger vessels, with tapering and occlusion of smaller intrarenal arteries.
7. EGP is characterized by extravascular granulomas, eosinophilic infiltration of arteries and venules, and kidney involvement. Clinically, the disease progresses through 3 stages: an allergic diathesis; peripheral eosinophilia; and systemic vasculitis.
8. HSP presents with the characteristic tetrad of abdominal pain, arthritis or arthralgias, purpuric skin lesions, and kidney disease. Morphologic changes in kidney are identical to those seen in IgA nephropathy.
9. Essential mixed cryoglobulinemia should be considered in any patient with palpable purpura, especially if hypocomplementemia is present. The diagnosis is established by the presence of an IgM–IgG cryoglobulin with a monoclonal component by immunofixation electrophoresis.

ABNORMAL URINALYSIS

Abnormalities on urinalysis, such as microscopic hematuria and proteinuria, may also be the initial presentation of glomerular disease. Microscopic hematuria may result from bleeding anywhere in the urinary tract. The most common causes are nephrolithiasis, urinary tract infection, and malignancies. These disorders do not result in significant proteinuria. Hematuria in association with proteinuria is suggestive of a glomerular disease. Although any glomerular disease can initially present with an abnormal urinalysis, IgA nephropathy, Alport syndrome, and thin basement membrane disease are common glomerular lesions that often present initially with an abnormal urinalysis.

Immunoglobulin A Nephropathy

IgA nephropathy is the most common cause of glomerulonephritis worldwide. It is most common in Asians and whites, and relatively uncommon in African Americans. IgA nephropathy is unique among glomerular diseases in that it is defined not by its light microscopy features, but by the finding of immune deposits containing IgA in the mesangium and occasionally in the GBM on IF microscopy.

Approximately one-third to one-half of patients present prior to the age of 40 years with intermittent macroscopic hematuria after respiratory infection. The majority of the remainder have asymptomatic abnormalities on urinalysis. Nephrotic syndrome and RPGN occur in a small percentage of patients. IgA nephropathy is associated with chronic liver disease, viral infections such as HIV and hepatitis B, rheumatoid arthritis, reactive arthritis (formerly known as Reiter syndrome), dermatitis herpetiformis, and gluten enteropathy. Patients with *S. aureus* infection develop a postinfectious glomerulonephritis with IgA deposits on IF.

Light microscopy findings vary from minimal changes to segmental or diffuse mesangial hypercellularity with an increase in mesangial matrix to segmental sclerosis. On IF microscopy the hallmark is the detection of IgA. Other immunoglobulins, including IgG and IgM, can also be seen, as well as C3. Focal thinning of the GBM is a common feature on electron microscopic examination. The only other glomerular disease associated with extensive glomerular deposition of IgA is lupus nephritis. In lupus nephritis, however, IgG deposition is often more prominent than IgA and C1q is detected because of activation of the classical complement pathway. In IgA nephropathy, immune complexes activate the alternative pathway and do not bind C1. Recently, the Oxford Classification System was adopted for the reporting of renal biopsies in IgA nephropathy. Scoring is based on 4 factors that correlate with outcome: mesangial hypercellularity; segmental glomerulosclerosis; endocapillary hypercellularity; and tubular atrophy/interstitial fibrosis.

The production of a galactose deficient IgA_1 by B cells is the first step in the pathogenesis. Autoantibodies are then produced to newly exposed epitopes on IgA_1. Immune complexes form either in the circulation or GBM and generate an inflammatory reaction.

ESRD develops in 20% of patients by age 20 years. Predictors of a poor outcome include: an elevated serum creatinine concentration; proteinuria greater than 1 g/24 hours; hypertension; male sex; persistent microscopic hematuria; and young age at onset. On renal biopsy the presence of tubulointerstitial disease, low glomerular density, reduced podocyte number, superimposed FSGS, and crescents portends a poor prognosis.

Treatment is generally reserved for patients with an elevated serum creatinine concentration, hypertension, and/or proteinuria greater than 1 g/24 hours. ACE inhibitors are more effective than other antihypertensive agents in slowing the progression of renal failure in patients with IgA nephropathy. Fish oil can be tried but a recent metaanalysis shows it to be of marginal benefit. Corticosteroids may improve outcomes when added to ACE inhibitors. Whether the cytotoxic agents MMF and azathioprine are of benefit requires further study. Those patients with light microscopy features typical of minimal change disease may be especially responsive to corticosteroids. Patients with RPGN are often treated with intravenous pulse methylprednisolone, oral prednisone, and cyclophosphamide with or without plasmapheresis.

Alport Syndrome

Alport syndrome is an inherited disorder that results in the production of defective type IV collagen. Its incidence is approximately 1 in 50,000 in the general population. Type IV collagen is a triple helix of three α chains. Abnormalities in any 1 of the 3 chains results in an abnormal collagen molecule. Six α chains—COL4A1 through COL4A6—have been identified in humans. COL4A3, COL4A4, and COLA5 are expressed in the GBM. Renal involvement (microscopic and gross hematuria, progressive rise in the serum BUN and creatinine concentrations, hypertension, proteinuria) is associated with sensorineural hearing loss and eye abnormalities (perimacular flecks and anterior lenticonus). Retinopathy in males is associated with early onset ESRD. There may be an increased incidence of aortic abnormalities including dissection and aneurysm. The earliest change on renal biopsy is thinning of the GBM. As the disease progresses the GBM splits developing a laminated appearance.

In 85% of cases, the mode of inheritance is X-linked dominant and is caused by mutations in COL4A5 that encodes the α-5 chain. There may be some value in knowing the exact genetic mutation. Splice site and truncating mutations are associated with a 2-fold higher risk of ocular problems. Those with mutations at the 5′ end of the gene have an earlier age of onset of ESRD. Heterozygous females generally have mild disease. In 10% to 15% of cases, inheritance is autosomal recessive and caused by

mutations in COL4A3 and COL4A4. Carriers generally have microscopic hematuria, but rarely progress to renal failure or have hearing loss. In a few cases, an autosomal dominant mode of inheritance is described.

Large deletions and frameshift mutations are associated with a more severe phenotype. Greater than 90% of these patients develop ESRD and deafness by age 30 years. The abnormality of α_5 chain synthesis leads to an abnormal GBM that is also deficient in the α_3 chain (Goodpasture antigen). A deficiency of both α_3 and α_5 results in a higher incidence of ESRD and a higher risk of anti-GBM nephritis after renal transplantation.

Thin Basement Membrane Disease

Thin basement membrane disease or benign familial hematuria is manifested by persistent microscopic hematuria, minimal proteinuria, and the absence of ear or eye involvement. It has been estimated to affect up to 1% of the general population; rarely do patients progress to renal failure. Hypertension and proteinuria may identify a subgroup at increased risk. Inheritance is autosomal dominant. There is diffuse thinning of the lamina densa of the GBM (<250 nm). Up to one-half of these patients are heterozygous for mutations in COLA3 and COLA4, suggesting that thin basement membrane disease may be the heterozygous state of autosomal recessive Alport syndrome.

KEY POINTS

Abnormal Urinalysis

1. IgA nephropathy is the most common cause of glomerulonephritis worldwide.
2. IgA nephropathy is unique among glomerular diseases in that it is defined not by its light microscopy features, but by the finding of immune deposits containing IgA on IF microscopy.
3. Abnormal glycosylation of IgA_1 plays a role in its deposition in the mesangium. IgA binds to mesangial cells, induces proliferation and cytokine production, and binds complement via the alternative pathway.
4. Alport syndrome is an inherited disorder that results in the production of defective type IV collagen. The earliest change on renal biopsy is thinning of the GBM.
5. Thin basement membrane disease or benign familial hematuria is manifested by persistent microscopic hematuria, minimal proteinuria, and the absence of ear or eye involvement.

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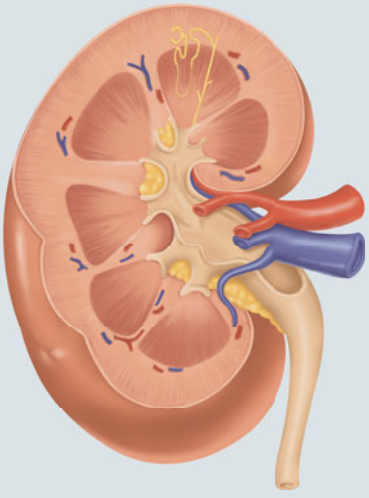
CHAPTER 18

Tubulointerstitial Diseases

• *Mark A. Perazella and Edgar V. Lerma*



Recommended Time to Complete: 1 Day

Guiding Questions

1. How does one diagnose tubulointerstitial disease?
2. What is the basic model of the pathogenesis of tubulointerstitial disease?
3. The development of tubulointerstitial disease is characterized by what 2 circumstances?
4. Tubulointerstitial disease is characterized by what histopathologic findings?
5. What are the common clinical manifestations of tubulointerstitial disease?
6. Are there laboratory tests that suggest a diagnosis of tubulointerstitial disease?
7. What are the common categories of tubulointerstitial disease?

INTRODUCTION

Structural abnormalities of the renal parenchyma that involve primarily the tubules and interstitium are called *tubulointerstitial disease*. In contrast to acute interstitial nephritis (AIN), diseases that cause tubulointerstitial disease, discussed in this section, are more often chronic processes (Table 18.1). Diseases of the tubulointerstitium are best thought of as either primary or secondary processes. Primary causes of tubulointerstitial nephritis typically occur as a result of systemic diseases or following exposure to environmental or therapeutic agents. In this circumstance, the glomeruli and vasculature are typically spared or have only minor structural changes until late in the course of disease. In general, approximately 10% to 20% of end-stage renal disease (ESRD) in the United States occurs from primary chronic tubulointerstitial disease. A secondary form of chronic tubulointerstitial disease may also result from progressive glomerular disease or vascular injury with associated renal parenchymal ischemia. A significant number of disease states cause this form of chronic tubulointerstitial injury, with diabetic nephropathy and hypertensive nephrosclerosis being most common. Tubulointerstitial disease with fibrosis and scarring significantly determine the progressive nature of these lesions and their ultimate outcome, which include chronic kidney disease (CKD) and ESRD requiring renal replacement therapy.

PATHOGENESIS OF TUBULOINTERSTITIAL DISEASE

The tubulointerstitium comprises the majority of renal parenchyma. Approximately 80% of total kidney volume is composed of tubular epithelial cells and cells within the

TABLE 18-1. Etiologies of Tubulointerstitial Disease

Immunologic Causes
Systemic lupus erythematosis
Vasculitis
Amyloidosis
Cryoglobulinemia
Sjögren syndrome
Therapeutic Agents
Analgesics
Nonsteroidal antiinflammatory drugs
Chemotherapy (cisplatin, nitrosoureas)
Immunosuppressive agents (calcineurin inhibitors)
Lithium
Aristolochic acid (Chinese herbs, Balkan nephropathy)
Occupational/Environmental Agents
Heavy metals (lead, cadmium, mercury)
Mycotoxins
Neoplastic/Hematopoietic Diseases
Lymphoma/leukemia
Multiple myeloma
Light-chain deposition disease
Sickle cell disease
Hereditary Diseases
Medullary cystic disease
Polycystic kidney disease
Karyomegalic interstitial nephritis
Vascular Diseases
Renal atheroemboli
Radiation nephritis
Hypertensive nephrosclerosis
Infections
Bacterial pyelonephritis
Xanthogranulomatous pyelonephritis
Malacoplakia
Metabolic Disorders
Hypercalcemia
Hypokalemia
Hyperoxaluria/oxalosis
Hyperuricemia
Cystinosis
Other Conditions
Sarcoidosis
Obstructive uropathy
Immunoglobulin G_4–tubulointerstitial nephritis

interstitial space. The vast majority of nonepithelial cells are associated with the rich vascular network found within the kidney. The rest of the cells consist of a small number of resident mononuclear cells and fibroblasts. Recognizing that the tubulointerstitium is such a large component of the kidney makes it easy to understand why inflammation within this compartment, leading to fibrosis, is a major factor in progressive loss of renal function.

The basic model that underlies the development of chronic tubulointerstitial disease, regardless of the inciting disease or event, is one that involves cellular infiltration, fibroblast differentiation and proliferation, increased extracellular matrix protein deposition, and atrophy of tubular cells. The pathogenesis of tubulointerstitial injury is similar, whether the initiating process is a primary disease or injury to the tubulointerstitium or is secondary to a primary glomerular or vascular disease process. Examples of such secondary causes include primarily glomerular diseases like diabetic nephropathy and vascular diseases such as hypertension and calcineurin inhibitor toxicity. Activation of multiple proliferative pathways within the epithelial cells in an attempt to maintain integrity of this cell type occurs in response to tubular injury. Interplay between homeostatic proliferative and reparative forces and aberrant proinflammatory and overexuberant cell proliferation ensues. If the injurious factors overwhelm the normal cell processes, apoptotic pathways overrun the ability of tubular epithelial cells to survive. This results in tubular atrophy and interstitial fibrosis.

The initiating event that causes either primary or secondary injury to the tubulointerstitium promotes tubular atrophy and interstitial collagen deposition and fibrosis through various intrarenal and systemic factors. These include vasoactive substances such as angiotensin II (AII), endothelin, thromboxane A_2, and vasopressin. These compounds induce reductions in renal blood flow after 24 hours of ureteral obstruction and likely contribute to ischemic injury. In addition to hemodynamic effects, AII has profibrotic effects mediated by binding to the angiotensin type 1 (AT1) receptor. In fact, more than 50% of the fibrosis that develops in a mouse model of obstruction is dependent on expression of the angiotensinogen gene. This same process occurs in other forms of renal injury. AII upregulates the expression of factors such as transforming growth factor (TGF)-β, nuclear factor-κB, basic fibroblast growth factor, vascular cell adhesion molecule-1 (VCAM-1), tumor necrosis factor

(TNF)-α, and platelet-derived growth factor (PDGF). It is important, however, to recognize that increased expression of many of these chemoattractant compounds, adhesion molecules, and cytokines also occur independently of AII.

Other types of renal disease and injury induce these processes through other mechanisms including pressure-associated injury (obstructive uropathy), hyperglycemia (diabetic nephropathy), infiltrative diseases (sarcoidosis), and induction of oxidative stress. Resident nonepithelial cells, such as the fibroblast undergo proliferation/differentiation and produce interstitial fibrosis. Also, it is believed that renal epithelial cells undergo a process of dedifferentiation/redifferentiation into myofibroblastic cells expressing α-smooth muscle actin and collagen following exposure to the various factors noted above. This process has been termed *epithelial-mesenchymal transition* (EMT). Researchers believe that that there are 4 key events that occur in renal tubular EMT in renal fibrogenesis, namely: (a) loss of epithelial adhesion, (b) cytoskeletal reorganization and (c) de novo synthesis of α-SMA (smooth muscle actin), disruption of the tubular basement membrane (TBM), and (d) enhanced cell migration and invasion of the interstitium. It is thought that EMT is primarily an adaptive response of the tubular epithelial cells to an inimical milieu. Ultimately, the balance between homeostatic effects and harmful effects tips the balance in favor of the pathologic consequences, leading to collagen deposition, tubular atrophy, and interstitial fibrosis.

KEY POINTS

Pathogenesis of Tubulointerstitial Disease

1. The tubulointerstitium comprises approximately 80% of total renal mass.
2. The major cells of the tubulointerstitium are tubular and interstitial cells.
3. The basic model of tubulointerstitial disease consists of cellular infiltration, fibroblast differentiation and proliferation, increased extracellular matrix protein deposition, and atrophy of tubular cells.
4. Primary disease of the tubulointerstitium or secondary insults, such as glomerular or vascular disease, causes the same cascade of injury.
5. Vasoactive factors (AII, thromboxane, endothelin, and so on), cytokines (TGF-β, TNF-α, and so on), adhesion molecules (VCAM-1), and chemoattractant compounds (monocyte chemoattractant peptide-1) contribute to tubulointerstitial inflammation and fibrosis.
6. The process known as EMT may underlie the development of tubulointerstitial fibrosis following a pathologic insult.

HISTOPATHOLOGY OF TUBULOINTERSTITIAL DISEASE

In chronic tubulointerstitial disease, a cellular infiltrate and variable amounts of fibrosis are noted within the architecture of the interstitium. The characteristic lesion is an inflammatory cellular infiltrate composed of lymphocytes, usually T cells and, to a lesser degree, plasma cells. Early in the course of disease, the acute cellular infiltrate is accompanied by interstitial edema, tubulitis with TBM disruption, and dissolution of the normal tubulointerstitial architecture. Over time, the acute process transitions to a chronic tubulointerstitial lesion. The chronic histology is characterized by interstitial fibrosis with increased extracellular matrix, tubular ectasia and atrophy, and tubular dropout. The severity of this process typically advances over time until the entire tubulointerstitium is overtaken by fibrosis. In far advanced disease, glomerulosclerosis develops and blood vessels become involved by fibrosis and sclerosis. At this point in time, the patient often manifests clinically advanced CKD.

KEY POINTS

Histopathology of Tubulointerstitial Disease

1. Tubulointerstitial disease is classified as primary or secondary to another disease process.
2. In primary tubulointerstitial disease, the glomeruli and vasculature are normal early in the course of disease.
3. The characteristic lesion is a lymphocytic infiltrate.
4. Early in tubulointerstitial disease, interstitial edema accompanies the cellular infiltrate while tubular injury and interstitial fibrosis develop as the process progresses.

CLINICAL PRESENTATION

More often than not, patients with tubulointerstitial disease have few clinical symptoms suggestive of CKD. In general, symptoms and signs reflect the extent of tubulointerstitial disease. For example, focal areas of injury are minimally symptomatic, whereas diffuse disease causes several tubular defects in electrolyte, acid–base, and mineral handling. Also, the area of the kidney involved by disease leads to disturbances characteristic of the loss of function of injured tubular segment. Injury to the proximal tubule is associated with impaired absorption of sodium, glucose, phosphorus, amino acids, potassium, uric acid, and several low-molecular-weight proteins. In contrast, disease of the loop of Henle and distal convoluted tubule causes sodium and potassium wasting (salt wasting, hypokalemia, and hypotension). Involvement of the cortical and medullary collecting ducts may be associated with hyperkalemia and metabolic acidosis (type 4 renal tubular acidosis) as a consequence of defects in potassium and ammonia (buffers acid) secretion by this segment. Another important determinate of the clinical manifestations of tubulointerstitial disease is the degree of compensation by the remaining normal (or less severely impaired) nephron segments. With mild-to-moderate disease, compensatory hypertrophy may eliminate or substantially reduce symptoms of renal disease.

Often times, chronic tubulointerstitial disease is discovered when blood testing reveals abnormal kidney function (increased blood urea nitrogen [BUN] and serum creatinine concentration) that is otherwise fairly asymptomatic. The presence of certain systemic diseases may also prompt investigation of kidney function and potential kidney disease. As is discussed later, several systemic diseases promote the development of chronic tubulointerstitial disease. The most common symptom associated with disease of the tubulointerstitium is polyuria. Two mechanisms account for this symptom, including salt wasting and the inability to maximally concentrate the urine. Dizziness from low blood pressure (salt wasting), weakness from either severe hypokalemia or hyperkalemia, and bone pain/fractures from osteopenia induced by metabolic acidosis. Advanced chronic tubulointerstitial disease results in the development of usual manifestations of CKD approaching ESRD. These include anorexia, nausea, vomiting, lethargy, somnolence, fatigue, restless legs, and other uremic manifestations.

TABLE 18-2. Laboratory Manifestations of Tubulointerstitial Disease

Proximal Tubular Defects
Type 2 renal tubular acidosis
Fanconi syndrome
Distal Tubular Defects
Type 1 renal tubular acidosis (intercalated cell)
Type 4 renal tubular acidosis (principal cell)
Concentrating defect
Salt-wasting nephropathy
Sterile Pyuria
White blood cells
White blood cell casts
Tubular Proteinuria
Albuminuria (<1 g/day)
β_2-Microglobulinuria
Retinol-binding protein excretion
Enzymuria
N-acetyl-β-glucosaminidase
Alanine aminopeptidase
Intestinal alkaline phosphatasexs

Laboratory Findings

As noted in the previous section, tubulointerstitial disease often manifests with various renal tubular and urinary disorders (Table 18.2). Examination of blood and urine chemistries often provides insight into the disease. Proximal renal tubular acidosis (type 2 renal tubular acidosis [RTA]), as noted by a hypokalemic, nonanion gap metabolic acidosis, may occur in this setting. In this case, the urine is acid (pH ≤5.5) in steady-state acidosis, but becomes alkaline (pH ≥7) when therapy to correct the metabolic acidosis with bicarbonate is attempted. A full-blown Fanconi syndrome can develop with chronic tubulointerstitial disease involving the proximal tubule. This syndrome is characterized by the presence of a type 2 RTA that also demonstrates phosphaturia, aminoaciduria, glycosuria, enzymuria, and uricosuria. Salt wasting (urinary sodium >20 mEq/L) despite hypotension may indicate tubulointerstitial disease of the loop of Henle. Hypokalemia caused by urinary potassium wasting may

also occur with a lesion in this segment. An acidification defect in the distal nephron may cause a type 1 RTA that is characterized by hypokalemia, nonanion gap metabolic acidosis, and alkaline urine (first morning void pH >5.5). A type 4 RTA (hyperkalemia with nonanion gap metabolic acidosis) may be seen with tubulointerstitial disease. Inability to concentrate the urine leads to a low urine osmolality and, if the patient is unable to gain free water access, may cause hypernatremia.

The urinalysis yields variable results in the setting of chronic tubulointerstitial disease. A couple of generalizations, however, can be made. Tubulointerstitial disease rarely has marked proteinuria; most often there is trace to 1+ protein on quantitative examination of the urine. A 24-hour urine collection or spot protein/creatinine usually contains less than 1 g of total protein. Examination of the urinary sediment under the microscope often reveals a preponderance of white blood cells (WBCs), occasionally with some WBC and granular casts. Red blood cells (RBCs) and RBC casts are extremely unusual. Urinary crystals may be present with certain disorders associated with chronic tubulointerstitial disease (calcium oxalate crystals with hyperoxaluria; uric acid crystals with uric acid nephropathy; calcium phosphate with acute/chronic phosphate nephropathy).

Examination of proteinuria (low-molecular-weight proteins) and enzymuria may provide insight into disease limited to the tubulointerstitium; however, they are not widely employed as clinical tools. High-molecular-weight proteins (>40,000 to 50,000 Da) in the urine are typically a marker of glomerular disease. Included in this group is albumin (69,000 Da), transferrin (77,000 Da), and immunoglobulin (Ig) G (146,000 Da). In contrast, small amounts of low-weight-molecular proteins are normally excreted in the urine. They are considered markers of "tubular" proteinuria (vs. glomerular proteinuria). Although there are several low-molecular-weight proteins, β_2-microglobulin (11,800 Da) and retinol-binding protein (21,400 Da) are the markers of tubular injury most commonly employed. Both substances are freely filtered; approximately 99.9% is reabsorbed in the proximal tubule where they are catabolized. When the reabsorptive capacity of the proximal tubular cells is impaired, increased amounts of various low-molecular-weight proteins can be demonstrated in the urine. Thus, levels increase in urine when disease injures proximal tubular cells. Although both β_2-microglobulin and retinol-binding protein are used to evaluate tubulointerstitial disease, the assay employed for retinol-binding protein is more stable in an acid urine and is preferred.

Urinary eosinophils greater than 1% eosinophils in a microscopic sample is a test that is commonly ordered when AIN is considered in the differential diagnosis of acute kidney injury, rather than a chronic tubulointerstitial process. A sensitivity of 63% to 91%, and a specificity of 85% to 93% are noted when using Hansel stain, thereby limiting its diagnostic value. Numerous diseases are associated with eosinophiluria, such as acute pyelonephritis, acute prostatitis, acute complicated cystitis, rapidly progressive glomerulonephritis, atheroembolic kidney disease, parasitic infections, and the presence of intraureteral stents.

Urinary enzymes also reflect tubular dysfunction and act as markers of tubulointerstitial disease. The basis for measuring high-molecular-weight enzymes in urine stems from the knowledge that the only source of enzymes is injured tubular cells. Despite this premise, however, the use of measuring enzymuria is hindered by a lack of correlation with specific disease states and the disconnect between severity of tubular injury and the magnitude of urine enzyme levels. Urinary enzyme activity is also affected by the presence of urinary enzyme inhibitors and activators, as well as urine pH and osmolarity. A few enzymes accepted as useful urinary biomarkers are used in clinical studies to assess tubular damage. They include *N*-acetyl-β-glucosaminidase, alanine aminopeptidase, and intestinal alkaline phosphatase. Enzymuria remains a valuable research tool, but has not gained widespread use in the clinical arena.

Diagnosis of Tubulointerstitial Disease

The clinical diagnosis of chronic tubulointerstitial disease is considered when other possible causes of kidney disease are excluded, in particular intrinsic renal disease such as glomerular lesions, as well as obstructive uropathy. An in-depth history of prescribed or nonprescription medications ingested by the patient and any at-risk occupational or environmental exposures suffered are keys to assess causes of tubulointerstitial disease. Evidence of systemic disease associated with this form of kidney disease helps support the diagnosis. In addition to the history, the laboratory findings described above, point to disease in the tubulointerstitium. In particular, evidence of tubular dysfunction is suggestive of chronic tubulointerstitial disease. These include a RTA, salt wasting, a urinary concentrating defect, and a urinalysis demonstrating pyuria with

little or no protein. Ultrasonography of the kidney reveals normal-to-large-size kidneys with AIN, whereas small echogenic kidneys are present with chronic tubulointerstitial disease. The only exception to this caveat is certain infiltrative diseases. The kidneys are often large and echogenic. Examples include sarcoidosis, lymphomas and leukemias, amyloidosis, and cystic kidney disease. The kidney biopsy helps to establish the diagnosis. The classic lymphocytic infiltrate, the variable degrees of interstitial fibrosis, and tubular ectasia/atrophy characterize chronic tubulointerstitial nephritis. In the absence of a definable cause of chronic tubulointerstitial disease when the kidney biopsy supports this diagnosis, an idiopathic form of disease or presumed substance exposure (drug or toxin) is often implicated as the underlying cause.

KEY POINTS

Clinical Presentation of Tubulointerstitial Disease

1. The clinical manifestations of chronic tubulointerstitial disease depend on the extent and severity of the process, the nephron segments most severely involved, and the compensatory response of the remaining normal nephron segments.
2. RTA, salt wasting, and a urinary concentrating defect are some of the common manifestations of chronic tubulointerstitial disease.
3. The urinalysis in chronic tubulointerstitial disease often reveals pyuria with WBCs and occasional WBC casts in the urine sediment.
4. Measurement of β_2-microglobulin and retinol-binding protein are sometimes helpful to document "tubular" proteinuria and implicate a tubulointerstitial disease process.
5. Eosinophiluria has limited utility in the diagnosis of AIN, and no value in chronic tubulointerstitial disease.
6. Enzymuria reflects disruption of tubular cell integrity, but it has limited clinical use.

TUBULOINTERSTITIAL DISEASES

Analgesics

Chronic tubulointerstitial nephritis, sometimes associated with papillary necrosis, has been considered a complication of high-dose, long-term analgesic ingestion. In particular, combination analgesics containing phenacetin are thought to induce chronic tubulointerstitial damage. It is less clear whether chronic ingestion of analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs) or aspirin alone will cause analgesic nephropathy. The diagnosis of this entity is suggested by a history of chronic headaches and other forms of chronic pain, which promote long-term analgesic ingestion. Also, concomitant anemia may signal peptic ulcer disease from chronic aspirin or NSAID intake. Somatic complaints, such as malaise and weakness, are also present on history. Most patients have no symptoms referable to the urinary tract, although hematuria and flank pain may develop from a sloughed or obstructing papilla. The presence of CKD with minimal or no proteinuria signals tubulointerstitial disease. More prominent proteinuria, however, can occur with advanced CKD, a reflection of hemodynamically mediated glomerular injury and sclerosis. Intravenous pyelography is a highly sensitive radiographic test in the detection of papillary necrosis (Figure 18.1) (total or partial). Partial necrosis is characterized by a cavity extending out from the calyces. Findings in complete papillary necrosis include a ring shadow in the calyx and loss of the entire papillary surface (claw-like appearance). It is not sensitive, however, in the diagnosis of analgesic nephropathy because other diseases may cause papillary necrosis such as diabetes mellitus, obstructive uropathy, sickle cell disease, and renal tuberculosis. Given the limited sensitivity of intravenous pyelography in diagnosing analgesic nephropathy, as well as the associated nephrotoxicity of the large contrast load, other imaging modalities are employed. Renal ultrasound may show small-size kidneys with increased echogenicity. This test is not sensitive enough to reveal subtle medullary calcifications or papillary defects from sloughed papillas. Computed tomography (CT) scan is a better imaging test for analgesic nephropathy. It can demonstrate calcifications in the medulla and papillary areas. Also, it may reveal lobulated or "bumpy" renal contours and decreased kidney size. All of these CT findings are suggestive of analgesic-induced injury. Thus, this imaging modality is recommended to evaluate patients with a history and clinical findings consistent with analgesic nephropathy.

Treatment is supportive. The course of kidney disease is determined by the severity of kidney dysfunction at the time of diagnosis as well as whether the toxic medication is continued or not. Renal decline is expected if analgesic consumption continues, whereas stabilization

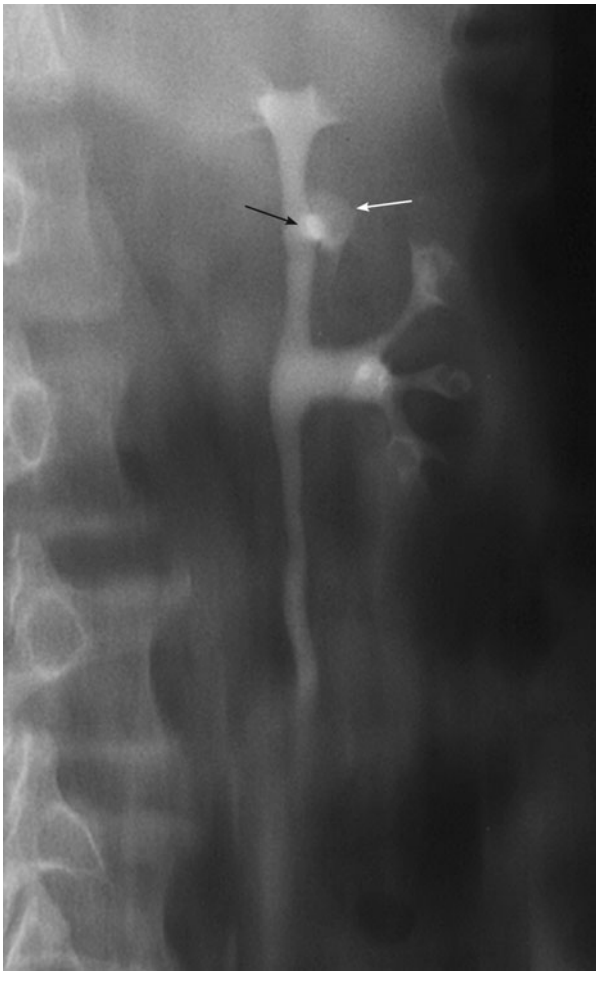


FIGURE 18-1. Papillary necrosis. Intravenous pyelogram of the kidneys reveals a cavity extending out from a renal calyx (shown by the white arrow) consistent with partial sloughing of the papilla. Calcification of several renal papillae is evident (one is shown by the black arrow). (Courtesy of Mark A. Perazella.)

or mild improvement in kidney function can occur with withdrawal of nephrotoxins. In addition to discontinuation of all culprit nephrotoxins, control of blood pressure in those with hypertension is also important. In patients with advanced CKD, progression of kidney failure often occurs despite analgesic discontinuation. In addition to implementation of renal replacement therapy, evaluation for uroepithelial malignancy and diffuse atherosclerotic disease should be undertaken.

Lead Nephropathy

Intoxication with lead is an illness that has plagued mankind since ancient times. Lead toxicity leads to disturbance in multiple organ systems, including the kidneys. Although both acute kidney disease and CKD develop with lead intoxication, the focus of this discussion is lead-associated chronic tubulointerstitial nephritis. Environmental lead exposure was described from ingestion of contaminated foodstuffs (lead in soil) or water (lead pipes, lead pottery). Outbreaks of lead toxicity were reported in the southern states in association with moonshine ingestion, and remain a source of lead exposure to this day. Moonshine, which is homemade corn liquor, is fermented in stills that are often welded with lead solder and use automobile radiators (contaminated with leaded gasoline) as the condenser. Occupational exposure to lead occurs in workers who manufacture storage batteries, pottery, and pewter. Also, lead intoxication can develop in smelters, miners, and plumbers. In children, exposure to lead-based paint chips and dust can cause acute and possibly chronic lead intoxication.

Chronic lead intoxication presents with varying degrees of severity depending on the total amount of cumulative lead burden. Patients may have vague nonspecific symptoms including irritability, anorexia, insomnia, and myalgia. More severe lead exposure generally produces more pronounced neurologic, abdominal, rheumatologic, and renal-related symptoms. Hypertension, gout, and a tubulointerstitial nephropathy are the most common renal effects of lead. Tubulointerstitial nephropathy is often manifested by CKD associated with tubular dysfunction manifested as polyuria (from salt wasting and a urinary concentrating defect), type 4 RTA, absent or low-grade proteinuria, and sterile pyuria. Markers of lead nephropathy include increased urinary β_2-microglobulin, retinol-binding protein, and *N*-acetyl-β-glucosaminidase, and alanine aminopeptidase. Recent data suggest that even chronic low-level lead intoxication can lead to progressive CKD.

The kidney lesion in chronic lead nephropathy consists of tubulointerstitial fibrosis mixed with a lymphocytic cellular infiltrate, tubular atrophy, and arteriolar thickening. Intranuclear inclusions in proximal tubular cells are not present, as they are only found in acute lead nephropathy. The degree of fibrosis varies with the severity and chronicity of lead exposure. Treatment requires discontinuation of lead ingestion; however, reversibility is

limited by lesions formed from previous exposure. Blood pressure control is important in hypertensive patients, although the nephroprotective effect of an antagonist of the renin-angiotensin-aldosterone system (RAAS) is unknown in this disease. Lead chelation with ethylenediaminetetraacetate acid (EDTA) was shown to benefit patients with early CKD. In a study of subjects with chronic low-level lead exposure and kidney dysfunction, chelation therapy stabilized renal function as measured by changes in glomerular filtration rate (GFR).

Autosomal Dominant Polycystic Kidney Disease

The inherited cystic kidney disease, autosomal polycystic kidney disease (ADPKD), is primarily a disease of the tubulointerstitium. It is a relatively common disorder, occurring in approximately 1 in every 400 to 2000 live births. The majority of patients with ADPKD have an abnormality on chromosome 16 (86%) that is linked to the α-globin gene locus (PKD1). Most families have a defect that involves a gene on chromosome 4 (PKD2), and some patients have an abnormality on an entirely different locus. Genes for both polycystic diseases have been identified: PKD1 encodes the protein, polycystin-1 whereas the PKD2 gene product is polycystin-2. Polycystin-1 is localized in renal tubular epithelia, hepatic bile ductules, and pancreatic ducts, and is found in plasma membranes. These sites of expression are also sites of cyst formation. Polycystin-1 is overexpressed in most renal cysts. Poycystin-2 is expressed in distal tubules, collecting duct, and thick ascending limb in normal fetal and adult kidneys and localizes to endoplasmic reticulum. Similarly, it is overexpressed in renal cysts.

Cyst formation is thought to result from a weakening of the TBM or intratubular obstruction from hyperplastic cells. The primary defect, however, may be related to either abnormal cellular differentiation and maturation or altered function of renal cilia. Dilated tubules form early cysts that are filled by glomerular filtrate. Subsequently, cysts enlarge by secretion of fluid by cyst epithelium. Cyst growth is associated with both fluid secretion and hyperplasia of the cyst epithelium. Unidentified growth factors present in the cyst fluid likely contribute to cyst growth and disease progression in ADPKD patients.

Recent studies suggest that ADPKD may also arise from abnormalities in the primary cilium, which is a cellular organelle found on the surface of most cells. Polycystin-1 and polycystin-2 have been localized to the primary cilium or at the basal body at the base of the cilium. It has been suggested that abnormalities in the primary cilium tend to disturb signaling pathways that normally regulate renal tubular epithelial cell growth and differentiation, thereby leading to the formation of cysts.

Diagnosis of ADPKD requires documentation of cysts in kidney. Age determines the criteria. Up until recently, patients younger than age 30 years required at least 2 cysts (unilateral or bilateral), those 30 to 59 years of age at least 2 cysts in each kidney, and patients older than 60 years of age required 4 or more cysts in each kidney. Cysts may also be present in the liver, pancreas, and spleen. This criteria was found to misdiagnose those with milder, such as those with PKD2. In the new ultrasonographic diagnostic criteria for ADPKD (both ADPKD1 and ADPKD2) in families of unknown gene type, the presence of 3 or more kidney cysts is sufficient to establish the diagnosis in those ages 15 to 39 years. In addition, 2 or more cysts in each kidney is sufficient for individuals ages 40 to 59 years, although 4 or more cysts in each kidney is required for diagnosis for subjects 60 years old or older. CT scan also demonstrates cysts within the kidneys (Figure 18.2*A*).

Clinical manifestations of ADPKD include hypertension, hematuria, proteinuria, nephrolithiasis, flank pain, and progressive kidney failure. Hypertension is associated with activation of the RAAS, as well as sodium retention when CKD is present. Hematuria is common (up to 50% of patients), and is caused by renal infection, cyst rupture, and nephrolithiasis. Proteinuria is typically less than 1 g/day. Kidney stones occur in up to 20% of patients. They are composed of both calcium oxalate and uric acid. Acute flank pain is common, most often caused by renal stones, cyst infection or pyelonephritis, or hemorrhage within cysts. Chronic flank pain is troublesome and probably caused by distension of the renal capsule by enlarged cysts (see Figure 18.2*B*). At times, cyst decompression or nephrectomy is required for intractable pain. Development of CKD and progression to ESRD occurs in up to 75% of patients by age 75 years. Factors associated with progression include younger age at diagnosis, male gender, black race, presence of the PKD1 genotype, hypertension, gross hematuria, and rapid renal volume (cyst) growth. It is speculated that kidney disease progresses as a result of vascular sclerosis and tubulointerstitial fibrosis, rather than compression of normal renal tissue by enlarging cysts. This may be partly a result of enhanced apoptosis of glomerular and tubular cells by cysts.

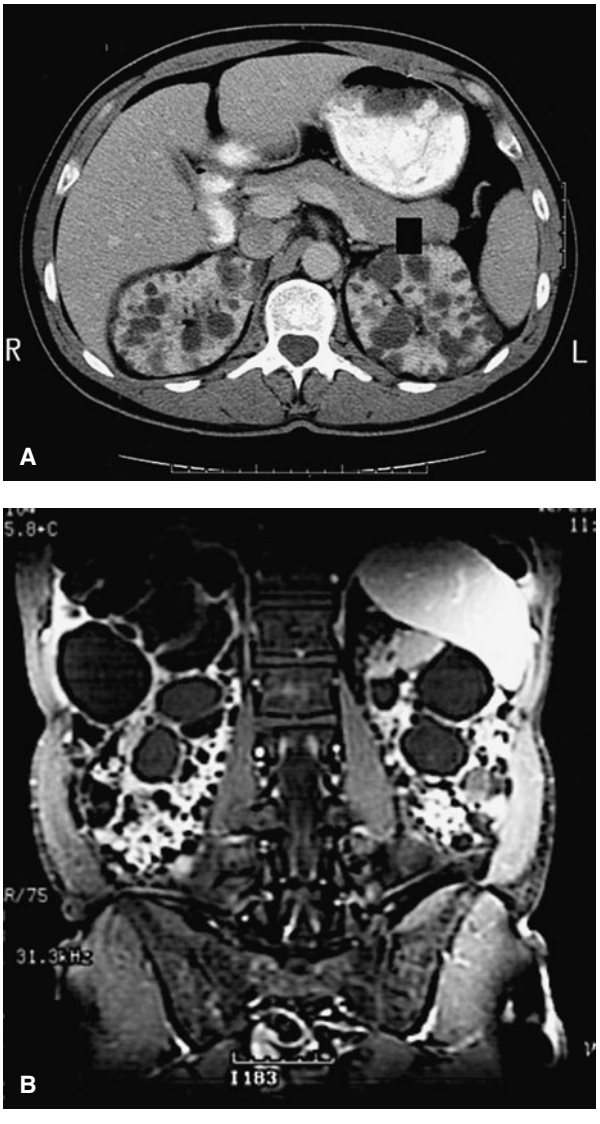


FIGURE 18-2. Adult polycystic kidney disease. A. CT scan of the kidneys demonstrates bilateral renal cysts in a patient with ADPKD. **B.** Magnetic resonance imaging (MRI) of the kidneys also notes large cysts, which can cause pain from capsule distension, rupture, hemorrhage, or infection. (Courtesy of Mark A. Perazella.)

A recent study utilizing magnetic resonance imaging and iothalamate clearances showed a direct correlation between total kidney and total cyst volumes with progression of CKD. Sequential measurements of renal volume may ultimately allow quantification of the rate of disease progression even prior to actual changes in GFR in these patients.

Treatment of ADPKD is directed at slowing progression to ESRD and reducing the morbidity of the other described clinical manifestations. Blood pressure control with drugs that modify the RAAS. Therapy directed at cyst growth is intuitive and supported by animal models, but data in humans are preliminary.

Sirolimus (rapamycin) has received some attention based on its antiproliferative effect, which potentially targets tubular epithelial cells lining cysts that contribute to cyst formation, However, an open-labeled randomized controlled trial (RCT) conducted for 18 months noted that sirolimus did not significantly slow cyst growth. Somatostatin analogs, aimed at SST2 receptors, slow cyclic adenosine monophosphate (cAMP) accumulation in the kidneys. In a small RCT, octreotide administered for 12 months slowed the progressive increase in liver and kidney volume in patients with ADPKD.

Another promising group of agents are the V2 receptor antagonists. Inhibition of V2 receptors in the collecting ducts, may prove beneficial in slowing cyst growth and hence, disease progression. The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) study is a RCT that gave tolvaptan, a selective V2 receptor antagonist, to patients with ADPKD with early disease who were at risk for rapid cyst growth and accelerated outcomes. Cyst growth progressed in a slower fashion with tolvaptan than in historical controls, although adverse effects may limit this therapy.

Appropriate management of CKD (Chapter 16) and preparation for renal replacement therapy is required for these patients. Renal transplantation is recommended; some patients require pretransplantation nephrectomy to accommodate the allograft or remove a potential source of infection. Management of cyst and parenchymal infection requires antimicrobials that penetrate cysts well (quinolones, trimethoprim-sulfamethoxazole) and sometimes percutaneous cyst drainage. Stone therapy is more difficult than in patients with idiopathic nephrolithiasis. Percutaneous nephrostomy is complicated by the presence of large cysts. Extracorporeal shock wave lithotripsy is useful for stones less than 2 cm in diameter, but is associated with a higher frequency of residual stone fragments. Cyst decompression has been used to treat both acute and chronic flank pain and can ameliorate hypertension in some cases.

There is no evidence, however, that this procedure slows progression of kidney disease.

Sarcoidosis

Chronic tubulointerstitial disease may complicate sarcoidosis. This systemic disease involves the tubulointerstitium of the kidneys through nephrocalcinosis from hypercalcemia/hypercalciuria, an effect related to excess 1,25(OH)-vitamin D production by sarcoid granulomata. Diffuse infiltration with noncaseating granulomata and tubulointerstitial nephritis also occurs (Figure 18.3). The presence of disseminated disease, where lung involvement (hilar nodes, interstitial infiltration/fibrosis), uveoparotid disease, skin lesions, and liver lesions are present, allows renal sarcoid to be easily identified. Limited sarcoidosis may require a kidney biopsy to diagnose the cause of kidney disease. The clinical manifestations of renal (tubulointerstitial) sarcoid include absent or mild proteinuria, concentration and/or acidifying defects, and sterile pyuria. Hypercalcemia and hypercalciuria may also be present. A high-serum angiotensin-converting enzyme level supports sarcoidosis in the proper clinical setting. Treatment of tubulointerstitial sarcoidosis includes a course of oral corticosteroids. Corticosteroids similarly correct vitamin D-associated hypercalcemia and hypercalciuria. Ketoconazole is employed to treat hypercalcemia in patients who are unable to tolerate steroid therapy.

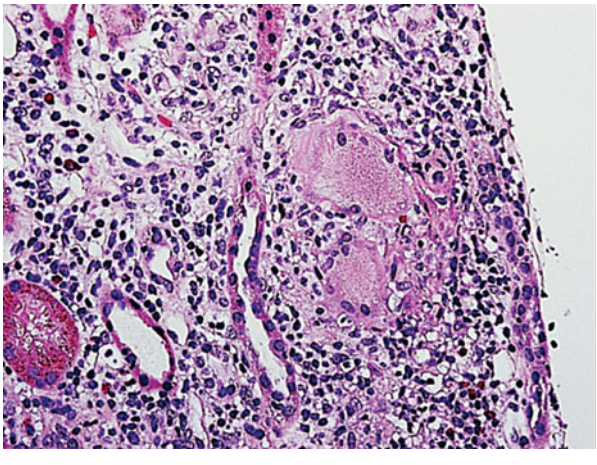


FIGURE 18-3. Renal sarcoidosis. Noncaseating granulomas and interstitial nephritis are seen on light microscopy. (Courtesy of Julio Cabrera, Renal Pathologist.)

Obstructive Uropathy

Obstruction of the urinary system leads to chronic tubulointerstitial injury and fibrosis. As is discussed more fully in the Chapter 19 on obstructive uropathy, uncorrected chronic obstruction promotes irreversible tubulointerstitial disease and CKD. In unrelieved complete obstruction, renal fibrosis evolves fairly rapidly (approximately 2 weeks), whereas partial urinary obstruction may occur insidiously over months. The pathogenesis underlying this process includes a combination of pressure-induced tubular injury and formation of various proinflammatory and profibrotic mediators. The end result of urinary obstruction is tubular atrophy, tubulointerstitial fibrosis, and loss of renal parenchymal mass.

Clinical signals of urinary obstruction include polyuria alternating with oliguria in partial obstruction and anuria with complete urinary obstruction. The presence of associated disease processes also provides clues. A history of kidney stones, prostate disease, and certain types of malignancies (cervical, uterine, prostate, lymphoma, and so on) suggest the possibility of obstructive uropathy. Any patient presenting with renal failure must have obstructive uropathy excluded. Suggestive laboratory tests include a type 4 RTA and bland urine sediment. Renal ultrasound is the preferred test to assess for urinary obstruction. Dilation of the pelvis and calyces (hydronephrosis) signal urinary obstruction. At times, however, CT scan (Figure 18.4) may be required to improve accuracy and provide more information about etiology of the obstructing process. Treatment to relieve the obstructing process depends on the cause. It should be undertaken rapidly to reduce renal injury and preserve kidney function.

Sickle Cell Disease

Sickle cell nephropathy constitutes a number of different renal lesions that affect the glomerulus and tubulointerstitium. The relative hypertonicity and hypoxia of the renal medulla predispose patients to RBC sickling with microcirculatory occlusion and ischemic renal damage. Tubular deposition of heme filtered at the glomerulus contributes to tubulointerstitial injury and fibrosis. Clinical manifestations of sickle-related tubulointerstitial disease include hematuria, urinary concentrating defect, hyperkalemia, an incomplete distal RTA (associated with or without hyperkalemia), and papillary necrosis. Polyuria from the concentrating defect contributes to RBC sickling by increasing plasma tonicity (hypernatremia).

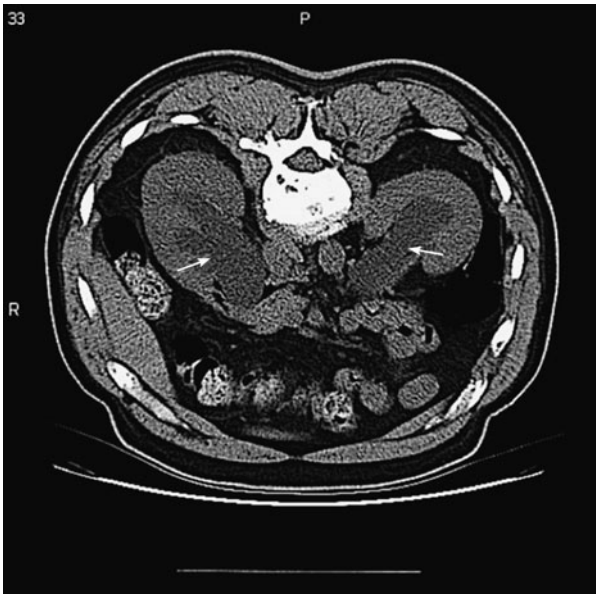


FIGURE 18-4. Obstructive uropathy. CT scan demonstrates dilation of both renal collecting systems (*arrows*) caused by obstruction from bladder cancer. (Courtesy of Mark A. Perazella.)

At times, hematuria is profuse and prolonged. Often no obvious explanation for this type of hematuria is found, but sometimes it is a result of papillary necrosis. Supportive therapy and sometimes bladder lavage to prevent obstructive blood clot formation is undertaken. Obstruction of the urinary tract by necrosed papillary tissue can result and may cause acute kidney injury if bilateral in the ureters or in the urethra.

Limiting the development of sickle-associated tubulointerstitial disease is not an easy task. During childhood, exchange transfusions reversed many of the tubular defects. Over time, however, many of the tubular disturbances become permanent and the patients will need to avoid dehydration from the urinary concentrating defect by drinking large volumes of fluid. This also reduces sickling in the renal medulla. Supportive care for hematuria is the usual treatment, although severe bleeding unrelated to papillary necrosis may require cautious antifibrinolytic therapy with epsilon-aminocaproic acid. Obstruction of the urinary collecting system with sloughed papilla or blood clots necessitates routine urologic therapies, including retrograde cystography with stent placement and irrigation with saline.

Lithium

Lithium is employed widely to manage bipolar (manic-depressive) disorders. Tubular dysfunction clearly occurs with this drug. Nephrogenic diabetes insipidus and an incomplete form of distal RTA are associated with lithium therapy. Treatment with lithium also causes a chronic tubulointerstitial lesion in a small number of patients. It is somewhat controversial, however, whether lithium therapy truly causes chronic tubulointerstitial disease. It is likely that long-term lithium therapy is required to cause this renal lesion. Most cases are associated with mild CKD. Some studies suggest that 15% to 20% of patients develop a slowly progressive reduction in renal function, with the GFR reaching a plateau of approximately 40 mL/min. The kidney lesion is characterized histologically by tubular dropout with dilation of tubular lumens (some forming microcysts), a mononuclear infiltrate in the interstitium, and varying degrees of interstitial fibrosis.

Treatment of CKD associated with lithium requires discontinuation of the drug. In most cases, kidney function improves modestly or stabilizes. The course is often unpredictable, however, and some patients with advanced CKD progress to ESRD. Again, this may reflect secondary hemodynamic glomerular injury, resulting in glomerulosclerosis. Hypercalcemia, caused by lithium-associated upward resetting of the calcium set-point for suppression of parathyroid hormone secretion, may contribute to hemodynamic kidney failure and polyuria in patients with underlying tubulointerstitial disease. Correction of hypercalcemia and any associated intravascular volume depletion reverses these renal disturbances.

Aristolochic Acid Nephropathy

An outbreak of kidney failure was noted in Belgium, which was traced to the ingestion of a Chinese herb (hence the previous designation, *Chinese herb nephropathy*). Contamination of a Chinese herbal slimming (weight loss) regimen with aristolochic acid (or other unknown phytotoxins) promoted the development of a characteristic tubulointerstitial lesion. It turns out that the harmful substance, *Aristolochia fanghi* was used in place of the innocuous herb *Stephania tetranda* in the slimming regimen. Aristolochic acid is metabolized by the CYP450 system to intermediates that form DNA adducts that cause DNA alkylation. Chronic ingestion of these Chinese herbs is associated with CKD and ESRD. More commonly, the loss of kidney function followed a rapidly

progressive course. Many patients required renal replacement therapy with dialysis. The pathology of this renal lesion is characterized by a hypocellular tubulointerstitial fibrosis with marked tubular atrophy. Although aristolochic acid is the offending agent in most cases, other phytoxins may cause a similar lesion. These substances are mutagens (DNA alkylation) and are associated with the development of transitional cell carcinomas. Patients exposed to this mutagen who develop genitourinary tract disease need to be evaluated for the possibility of cancer.

A similar syndrome characterized by chronic tubulointerstitial nephritis, Balkan nephropathy, which is endemic to residents of southeastern Europe, may be linked to aristolochic acid exposure. For many years it was assumed that some food contaminant or environmental exposure caused this nephropathy. It was discovered that Baltic families were unintentionally ingesting *Aristolochia clematitis*, a weed growing in their wheat fields. Breads containing aristolochic acid were causing the chronic tubulointerstitial nephritis.

Treatment requires discontinuation of further aristolochic acid exposure and general supportive care appropriate for patients with CKD. Some patients stabilize kidney function, whereas others have a progressive course to ESRD requiring renal replacement therapy or renal transplantation.

Renal Malacoplakia

Malacoplakia is an unusual chronic granulomatous disorder that can cause disease in the kidney. Although the actual pathogenesis is unknown, it is associated with renal parenchymal infection with Gram-negative organisms. Because of abnormal macrophage function, impaired eradication of infection by organisms such as *Klebsiella*, *Proteus mirabilis*, and *Escherichia coli* leads to chronic tubulointerstitial damage and granuloma formation. Malacoplakia occurs in patients with debilitating diseases marked by an underlying immunologic defect. It is associated with diabetes mellitus, alcoholism, tuberculosis, and treatment with immunosuppressive agents for organ transplantation. Diffuse infiltration or discrete intrarenal masses are seen on gross pathology. Histology reveals tubulointerstitial granulomas with clusters of periodic acid-Schiff–positive histiocytes that contain Michaelis-Gutmann bodies, which are lamellated iron and calcium inclusions (Figure 18.5). These inclusions are believed to result from incomplete digestion of engulfed bacteria (bacterial debris) by abnormal macrophages. Residual intralysosomal debris acts as a nidus for mineralization and leads to the development of complex lysosomal bodies demonstrable by Prussian blue (iron) and von Kossa (calcium) stains. Treatment of genitourinary tract infection is key to preventing malacoplakia in susceptible hosts. At times, nephrectomy is indicated.

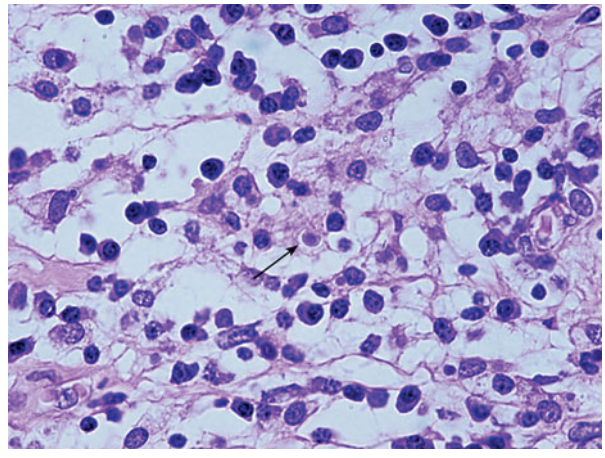


FIGURE 18-5. Renal malacoplakia. Renal histology reveals chronic granulomatous inflammation. The arrow points to a basophilic inclusion (Michaelis-Gutmann body) within a histiocyte. (Courtesy of Julio Cabrera, Renal pathologist.)

Hyperoxaluria/Oxalosis

Deposition of calcium oxalate crystals in the tubules and interstitium can lead to chronic tubulointerstitial nephritis and fibrosis. Hyperoxalosis can be divided into 2 clinical categories. One is the primary hyperoxalurias (types I and II) that are caused by hereditary disorders inherited recessively. Both of these disorders are characterized by tubular calcium oxalate deposition, which often extends into the renal interstitium and is associated with fibrosis and scarring. Type I develops from a deficiency of α-ketoglutarate:glyoxalate carboligase (cytosolic enzyme), leading to the excessive accumulation of oxalate, glyoxalate, and glycolate. Clinical manifestations of type 1 disease are the direct result of end-organ deposition (kidney predominantly) of calcium oxalate crystals. At a young age, patients develop hematuria, nephrolithiasis, renal colic, pyelonephritis, and CKD. ESRD and death often ensue by age 20 years. Type II, which is much less

common, results from a deficiency of leukocyte D-glyceric dehydrogenase. Although formation of calcium oxalate stones is very common, CKD is unusual. Marked urinary excretion of oxalate occurs with both disorders associated with primary hyperoxaluria. As an example, urinary excretion often averages 240 mg/day compared with the normal total of 10 to 50 mg/day. Gross examination of these kidneys reveals dilated urinary systems, nephroliths, and infection while interstitial fibrosis and scarring are present histologically.

Acquired or secondary forms of hyperoxaluria are commonly caused by excessive intake or absorption of oxalate or oxalate precursors. Poisoning with ethylene glycol, found most commonly in antifreeze, is a clinical example of a precursor that ultimately is metabolized to oxalate with tubulointerstitial calcium oxalate deposition. Similarly, anesthesia with methoxyflurane induced calcium oxalate deposition in kidney. Intravenous high-dose vitamin C (ascorbic acid), which is metabolized to oxalate, also induces renal deposition of calcium oxalate. Xylitol and E-ferol can cause tubulointerstitial disease from oxalate deposition (Figure 18.6). Short small bowel syndrome is a well-known gastrointestinal cause of secondary hyperoxaluria. Clinical disorders include small bowel resection or bypass, Crohn disease, celiac sprue, chronic pancreatitis, and Wilson disease. Treatment of obesity with either gastric bypass surgery or the weight loss drug orlistat has both been associated with fat malabsorption and enteric hyperoxaluria. Excessive absorption of oxalate occurs by the following mechanism. There is a high concentration of bile acids in the small intestine and colon. In the small intestine, bile acids saponify calcium, allowing unbound oxalate (which is usually complexed with calcium) to enter the large bowel. In the large bowel, bile acids increase the intestinal permeability to free oxalate entering from the small bowel. An additional mechanism may be reduced active secretion of oxalate into the bowel in the setting of reduced bowel surface area or bowel injury, which would increase plasma oxalate concentrations and subsequent hyperoxaluria. Certainly, volume contraction from associated malabsorption and diarrhea increases renal calcium oxalate crystal formation and deposition.

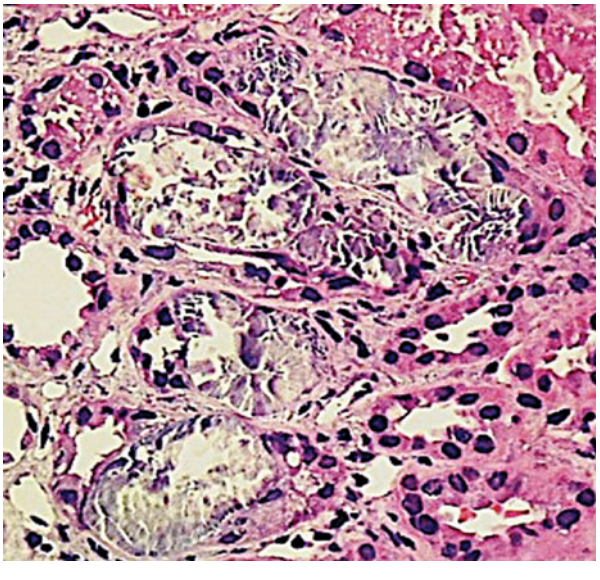


FIGURE 18-6. Acute oxalate nephropathy. Calcium oxalate crystals are noted in the tubular lumens and are associated with interstitial injury and acute kidney injury. (Courtesy of José Antonio Tesser Poloni and Mark A. Perazella.)

Correction of the underlying cause of hyperoxaluria is the most obvious treatment. Liver and/or renal transplantation may be required for the primary forms of hyperoxaluria. Elimination of exogenous sources of oxalate, such as excessive vitamin C, ethylene glycol, and methoxyflurane, is intuitive. General management of all disorders of hyperoxaluria includes generous hydration to maintain high urine flow rate (and reduce calcium oxalate saturation) and reduced ingestion of foods high in oxalate. Oral calcium supplementation may reduce gastrointestinal absorption of oxalate by complexing with oxalate and reducing the amount of free oxalate available for absorption in the large bowel. Oral citrate (potassium or sodium) reduces crystal formation through blocking calcium–oxalate interaction in urine. Routine urologic procedures are required for large and/or obstructive calcium oxalate stones.

Medullary Sponge Kidney

An anatomic malformation in the terminal collecting ducts in the pericalyceal region of the renal pyramids leads to the kidney lesion characteristic of medullary sponge kidney. This relatively common renal disorder is associated with the formation of both small and large medullary cysts. The cortex is always spared. The cysts are most often bilateral and diffuse, but may sometimes only involve 1 kidney and a few calyces. Although medullary sponge

kidney is not considered a genetic kidney disease, some families exhibit an autosomal dominant inheritance.

Most patients are asymptomatic. Medullary sponge kidney is recognized when an intravenous pyelogram (IVP) demonstrates characteristic radiographic findings. The major clinical manifestations are isolated hematuria, urinary tract infection, and nephrolithiasis (flank pain, hematuria). Kidney stones in these patients are composed of calcium phosphate and calcium oxalate. Factors that increase stone formation include hypercalciuria, hyperuricosuria, hypocitraturia, and occasionally, hyperoxaluria. Excessive amounts of calcium in urine are likely a result of impaired reabsorption of calcium by damaged collecting tubules. More importantly, urinary stasis and increased urine pH in cystic terminal collecting ducts contribute to calcium phosphate precipitation. An incomplete distal RTA, which is associated with an alkaline urine pH, may also increase calcium phosphate stone formation. Gross or microscopic hematuria develops from stones or urinary crystals. Episodes can be single or repetitive. Urinary tract infection occurs with increased frequency in medullary sponge kidney. Urinary stasis in collecting duct cysts and obstructing stones enhances infection risk. The diagnosis of this renal disorder is established by IVP. This imaging test demonstrates cystic dilatations of the terminal collecting ducts as a "brush" radiating outward from the calyces (Figure 18.7). Enlargement of the pyramids and intraductal concretions are also seen. When present, calcium stones appear as small clusters in the calyceal regions.

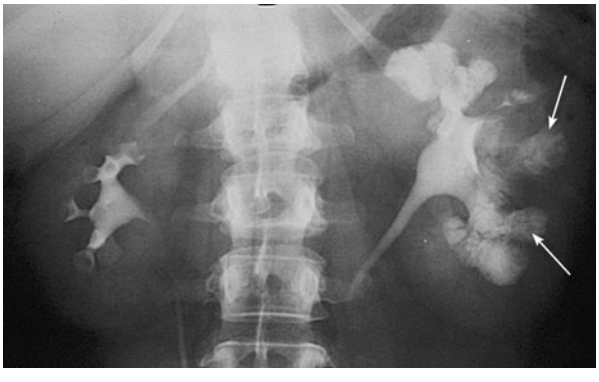


FIGURE 18-7. Medullary sponge kidney. IVP of the kidneys reveals classic finding (cystic dilations of the terminal collecting ducts shown as a *brush* [shown by the *arrows*] radiating outward from the calyces) of medullary sponge kidney. (Courtesy of Mark A. Perazella.)

In general, medullary sponge kidney is a benign condition with an excellent long-term prognosis. Treatment revolves around management of stones and urinary tract infections. Stones that obstruct the urinary system can cause acute kidney injury and need to be appropriately managed by the urologist. Antibiotics that target the infecting organism and penetrate renal tissue (ciprofloxacin, trimethoprim-sulfamethoxazole, chloramphenicol) should be employed during urinary tract infection.

Tubulointerstitial Nephritis Uveitis Syndrome

An idiopathic form of chronic tubulointerstitial disease associated with uveitis (TINU [tubulointerstitial nephritis and uveitis]) represents an autoimmune process. This syndrome is characterized by visual impairment (uveitis), fever, anemia, and tubulointerstitial renal disease (acute kidney injury, minimal proteinuria, pyuria). The kidneys typically are normal or large and highly echogenic when examined by ultrasonography. Renal involvement in TINU is commonly self-limited with the majority having spontaneous resolution. For those with progressive kidney disease, steroid therapy often reverses the renal dysfunction, but the disease process frequently recurs. Because of the relapsing nature of TINU syndrome, chronic therapy with steroids or another immunosuppressive agent may be required.

Immunoglobulin G_4-Related Tubulointerstitial Nephritis

First described in relation to "autoimmune pancreatitis," IgG_4-related tubulointerstitial nephritis is a newly described group of diseases (immune complex-mediated) with multiorgan involvement. It is characterized by elevated serum IgG_4 levels and dense infiltration of IgG_4-positive plasma cells within the renal tubulointerstitium. Predominantly affecting middle-aged to elderly males, there appears to be an association with IgG_4-related diseases involving other organs including aortitis/periaortitis, cholangitis, sialadenitis, and hypophysitis. Obstructive uropathy from IgG_4-related retroperitoneal fibrosis also occurs.

Other features of this disease include elevated serum IgG and IgE levels and hypocomplementemia. Characteristic histopathologic features such as "swirling fibrosis" and a patchy, diffuse distribution pattern are described. Fortunately, treatment with corticosteroids is often associated with a beneficial response.

Chronic Radiation Nephritis

Prolonged exposure to high-dose radiotherapy may result in the development of chronic radiation nephritis. This entity is typically associated with proteinuria and hypertension, as well as progression to CKD and ESRD. High radiation doses can cause endotheliosis (endothelial cell injury and swelling) and are also directly toxic to the tubular epithelial cells. Toxic effects are further potentiated by the concomitant use of other nephrotoxic agents, such as cytotoxic therapy and iodinated radiocontrast.

A pathologic feature seen with this entity is characteristic thickening of the glomerular capillary walls, which may also demonstrate "splitting," as a consequence of the mesangial interposition of fluffy material between the split layers of the glomerular basement membrane (GBM). This material, composed of remnants of platelets, cell debris, and fibrin, leads to widening of the subendothelial space and is usually accompanied by severe tubulointerstitial fibrosis and vascular sclerosis. Such features are also seen in thrombotic microangiopathy, suggesting the common involvement of endothelial injury in these disease states.

Prevention of this form of interstitial nephritis is warranted to prevent future kidney injury and CKD. Proper shielding of the kidneys during performance of radiographic imaging studies is a priority. Similarly, reducing the total radiation dose is recommended. For those who develop hypertension, proteinuria and CKD, angiotensin-converting enzyme (ACE) inhibitor therapy is often effective.

KEY POINTS

Tubulointerstitial Diseases

1. Many diseases through various mechanisms can cause tubulointerstitial disease.
2. Tubulointerstitial disease can develop from medications, toxins, systemic diseases, immune-mediated processes, infection, malignancy, hereditary diseases, and metabolic disorders.
3. The most common causes of tubulointerstitial disease are those induced by therapeutic agents, especially analgesics and vascular disease.
4. Treatment of the various causes of tubulointerstitial disease is directed by the underlying mechanism of injury.

Additional Reading

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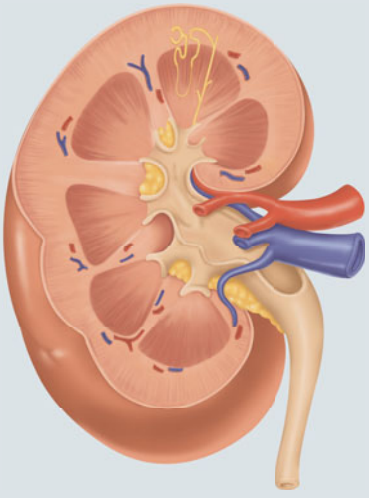
CHAPTER 19

Obstruction of the Genitourinary Tract



• *Richard N. Formica*

Recommended Time to Complete: 1 Day

Guiding Questions

1. How does the bladder empty normally?
2. What are the common causes of urinary tract obstruction?
3. What is the pathophysiology of the acute kidney injury associated with urinary tract obstruction?
4. Which tests are most useful to diagnose urinary tract obstruction?
5. How much time does one have to relieve a urinary tract obstruction before permanent renal damage ensues?

INTRODUCTION

Obstruction of the urinary tract is a common medical condition and an important cause of reversible acute kidney injury. It affects all age groups. The cause of obstruction varies by age. Pediatric patients most commonly have anatomic abnormalities that lead to obstruction, such as stenoses of the ureter at the ureteropelvic or ureterovesicular junction, urethral valves, or strictures. Renal calculi are the most common cause of urinary tract obstruction in young adults, whereas in the elderly population, renal calculi remain a prominent cause, but benign prostatic hyperplasia (BPH) and neoplasm, as well as other pelvic carcinomas, are also important causes.

Urinary tract obstruction can be either unilateral or bilateral, partial or complete. An understanding of this is important because the presence of urine flow does not exclude obstruction. In the case of unilateral obstruction, the unobstructed kidney continues to function normally. With partial obstruction, urine flow can be decreased, normal, or even increased. The increased urine flow from a partially obstructed kidney results from tubular injury and loss of concentrating ability. Anuria most commonly results from profound shock or complete obstruction. Therefore, anuria in a patient who is hemodynamically stable should prompt an immediate search for obstruction.

With partial or unilateral obstruction, the decline in glomerular filtration rate (GFR) may be mild. Therefore,

an elderly patient or a patient with a history compatible with obstruction and unexplained chronic kidney disease should be evaluated for obstruction. Acute kidney injury acquired in the hospital is rarely caused by obstruction; in some studies, however, the incidence is as high as 10%, thus evaluation of these patients should be done on a case-by-case basis.

PHYSIOLOGY OF MICTURITION

Normal Bladder Function

The bladder is a smooth muscle reservoir lined by transitional epithelium. When fully contracted, it is only a potential space. In the absence of obstruction or bladder dysfunction, there is no residual urine after voiding. The bladder fills at a rate of 1 mL/min. This gradual filling allows the bladder to slowly expand and accommodate the increasing volume by progressive relaxation. This allows intravesical pressure to remain between 0 and 10 cm H_2O during filling. When capacity is reached, approximately 400 mL, the ability to accommodate additional volume is exceeded and the intravesical pressure rises rapidly to 30 to 40 cm H_2O. This results in stimulation of pressure receptors in the trigone that send impulses to the micturition center in the spinal cord at S2-S4, which results in detrusor contraction, bladder neck opening, and relaxation of the external sphincter.

Multiple spinal cord levels are involved in bladder function. Nuclei within the sacral spinal cord innervate the bladder and striated sphincter. The micturition center transmits signals to the brain as an urge to void that can be activated or suppressed through facilitator or inhibitor pathways in spinal cord. Parasympathetic fibers at the level of S2 and S3 stimulate contraction of the detrusor muscle and empty the bladder. Contraction is inhibited by α-adrenergic sympathetic fibers. The sphincter controlling continence is composed of voluntary muscles in the perineum innervated by the pudendal nerve (S2, S3) and an inner sleeve of smooth muscle extending from the bladder neck through the prostatic and membranous urethra innervated by α-adrenergic sympathetic nerve fibers. The micturition center coordinates contraction of the detrusor muscle (parasympathetic activation) and relaxation of sphincter muscles (pudendal nerve and sympathetic inhibition). During voiding, intravesicular pressure rises to 40 to 50 cm H_2O, and urine is expelled at a flow rate of 25 mL/s.

KEY POINTS

Physiology of Micturition

1. The bladder is a smooth muscle under both voluntary and involuntary control.
2. Normal micturition involves the coordinated action of many different levels of the central nervous system and disruption of any 1 level can lead to bladder dysfunction and obstruction.

SIGNS AND SYMPTOMS

Symptoms

Signs and symptoms experienced by the patient with urinary tract obstruction depend on the rapidity and degree of obstruction. If obstruction occurs suddenly as in nephrolithiasis, distension of the ureter, kidney, and surrounding fascia causes intense pain. The pain is associated with other visceral symptoms, such as nausea, vomiting, and diaphoresis. This is referred to as *renal colic*. If the onset of obstruction occurs slowly, as with prostate cancer, the patient may be asymptomatic. An important exception to this rule is the patient with partial obstruction. In this setting, a fixed amount of urine can bypass the obstruction without causing back pressure and hence distension of the renal pelvis and ureter. When urine flow increases, ureteral distension can occur proximal to the point of narrowing and result in symptoms similar to acute obstruction. A clinical example is in young adults with asymptomatic partial obstruction through adolescence. During college, beer consumption in large quantities leads to intermittent increases in urine flow and acute episodes of renal colic.

Renal colic is a sharp, pulsatile pain that waxes and wanes. The location of the pain, although not diagnostic of the site of obstruction, can provide clues to its location. Obstruction that occurs at the ureteropelvic junction or in the proximal ureter produces flank pain and tenderness. Obstruction in the distal ureter or at the ureterovesicular junction produces pain that radiates into the ipsilateral groin.

With chronic obstruction such as occurs with BPH symptoms can be either obstructive or irritative. Obstructive symptoms include decreased force of urination, hesitancy, intermittency, and postvoid dribbling. Postvoid dribbling occurs as a result of a loss of pressure at the end of detrusor contraction. Irritative symptoms are the

result of the effects of obstruction on the detrusor muscle. These include frequency, urgency, urge incontinence, and nocturia. Frequency results from a loss of bladder compliance and decreased bladder capacity because of the retention of residual urine. Intravesicular pressure increases at low urine volumes and results in the sensation to void. Urgency is the result of hyperreactivity of the detrusor muscle. There is a sudden increase in the force of contraction that raises intravesicular pressure and an abrupt sensation of having to void ensues.

Signs

Only 2 entities—bilateral obstruction and profound shock—cause anuria. Therefore, anuria in a patient who is hemodynamically stable points almost exclusively to obstruction. The presence of normal to increased urine flow, however, does not rule out obstruction. In the case of unilateral complete obstruction, urine flow remains normal. With partial obstruction, urine flow may increase because of loss of concentrating ability that results in a form of nephrogenic diabetes insipidus. Finally, in some patients with partial obstruction there can be alternation between oligoanuria and polyuria.

Chronic kidney disease can result from obstruction. Renal failure can either be acute with a rapidly rising serum creatinine concentration suggesting near complete loss of renal function or mild suggesting a partial loss of kidney function. The latter is particularly important in the outpatient setting, as this may be the only indication that obstruction is present.

Hypertension may be a presenting sign of urinary tract obstruction. Acute unilateral obstruction can activate the renin-angiotensin-aldosterone system (RAAS) and cause a sudden and acute rise in blood pressure in a fashion similar to that by which renal artery stenosis causes hypertension. Bilateral obstruction does not activate the RAAS. The loss of ability to clear solutes, however, leads to volume overload and results in volume-mediated hypertension. It remains unclear why some patients with obstruction develop hypertension but others do not.

CAUSES OF URINARY TRACT OBSTRUCTION AND ITS DIAGNOSIS

Causes

When considering the causes of urinary tract obstruction it is helpful to distinguish between complete and partial obstruction. Complete obstruction primarily occurs at the level of the bladder and is caused by prostatic enlargement or an atonic bladder. Complete obstruction results from retroperitoneal or pelvic tumors that arise near the bladder and involve both ureters. Complete obstruction may also develop from any cause in the patient with a solitary kidney. Neuropathic or atonic bladder, as in a diabetic or a patient with spinal cord injury, can result in complete obstruction. Proper bladder function requires complex coordination between multiple levels of the spinal cord and the detrusor muscle and sphincters. A defect in any of these results in loss of detrusor contraction, bladder overdistension, and, finally, loss of muscle function. As bladder volume increases, pressure is transferred to the collecting system and causes a decrease in GFR. The most common cause of complete urinary tract obstruction is BPH. Consequently, complete urinary tract obstruction is primarily a problem of men and not women. BPH is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate. Epithelial gland formation is normally seen only in fetal development. This observed increase in cell numbers may be the result of epithelial and stromal proliferation or of impaired programmed cell death leading to cellular accumulation. Possible causes of this process are androgens, estrogens, stromal–epithelial interactions, growth factors, and other neurotransmitters. Hyperplasia of the prostate causes increased urethral resistance and results in compensatory changes in bladder function. The elevated detrusor pressure required to maintain urinary flow in the presence of increased outflow resistance results in decreased bladder storage capacity. Therefore obstruction induces a change in bladder function that results in higher filling pressure and transmission of this pressure back to the renal parenchyma.

Partial obstruction of the urinary tract is caused most commonly by nephrolithiasis. Other causes are ureteral tumors, as well as pelvic tumors that involve 1 ureter. Less commonly, blood clots that result from pathology within the kidney, shed papillae from papillary necrosis, and fungal infections resulting in fungus balls cause unilateral ureteral obstruction. In young male children, congenital urethral strictures and posterior urethral valves are rare forms of obstruction that must be considered. Adult males acquire urethral strictures from infections and trauma from indwelling catheters.

Lastly, retroperitoneal fibrosis in some cases can cause partial obstruction of the urinary tract. This

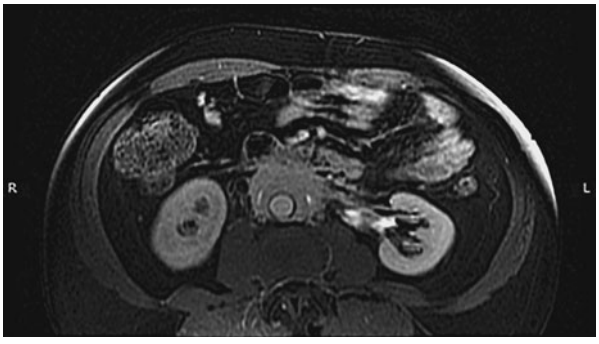


FIGURE 19-1. Magnetic resonance imaging scan of the kidneys showing retroperitoneal fibrosis. Fibrotic tissue is noted surrounding the aorta and the left renal vessels.

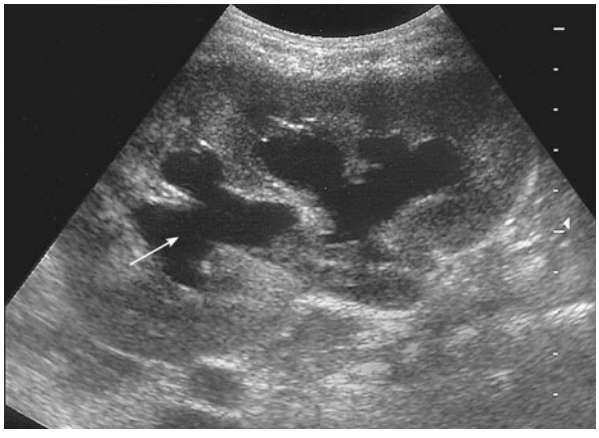


FIGURE 19-2. Renal ultrasound of obstruction. Shown by the arrow is the dilated renal pelvis surrounded by the kidney. This finding is referred to as *hydronephrosis*.

disease process is very rare with an incident rate ranging between 1 per 100,000 and 1 per 1,000,000. Because the disease process is very insidious, manifestations of kidney failure can occur slowly over long periods of time. Recently, this fibrosing disorder has been related to a group of diseases called immunoglobulin (Ig) G_4-related diseases. This disease constellation can present in multiple organs or be isolated to single sites such as the retroperitoneum (Figure 19.1). Discovery of this disease process has changed the landscape somewhat because IgG_4-related retroperitoneal fibrosis may be responsive to glucorticoids; consequently, when it is identified as the cause of acute or chronic kidney disease, a tissue diagnosis will help guide therapy.

Diagnosis

It is important to rapidly diagnose urinary tract obstruction to avoid permanent kidney damage. The initial diagnostic maneuver is bladder catheterization. This should be performed even in the patient who is still producing urine, as an enlarged prostate may cause partial obstruction, resulting in significant transmission of back pressure to the kidney. Urine flow continues because of the increased pressure generated by the overdistended bladder in order to overcome the increased resistance at the bladder neck. Bladder catheterization in this setting is diagnostic and curative. The initial rate of bladder drainage is discussed below.

Renal ultrasound is the test of choice to diagnose urinary tract obstruction because it can be obtained rapidly, is noninvasive, and does not require potentially nephrotoxic agents. Classic findings of obstruction are a dilated ureter and renal pelvis on the affected side (Figure 19.2). These findings may not be present in the setting of acute obstruction before dilation occurs, for patients who are severely volume depleted (prerenal), or in settings where the kidney and collecting system are externally compressed as with retroperitoneal fibrosis or with scarring and fibrosis in a transplanted kidney. In this setting, a Doppler flow study of the kidney is useful because it allows calculation of a resistive index. An elevated resistive index suggests obstruction. The resistive index is calculated by subtracting the rate of diastolic blood flow from the systolic blood flow divided by the systolic blood flow. The resistive index rises as the rate of diastolic blood flow declines because of increased pressure and tissue edema. In extreme cases where diastolic blood flow is absent, the resistive index is 1. An elevated resistive index is a nonspecific finding and occurs in many types of acute kidney injury, such as acute tubular necrosis, renal vein thrombosis, hypotension, external compression of the kidney, and ureteral obstruction. The resistive index is most helpful in the diagnosis of obstruction in the setting of retroperitoneal fibrosis or malignancy. In this circumstance, the classic sonographic findings of obstruction (dilation of the collecting system) are not present and an elevated resistive index may be the only finding. The sensitivity and specificity of ultrasound for obstruction is 90%.

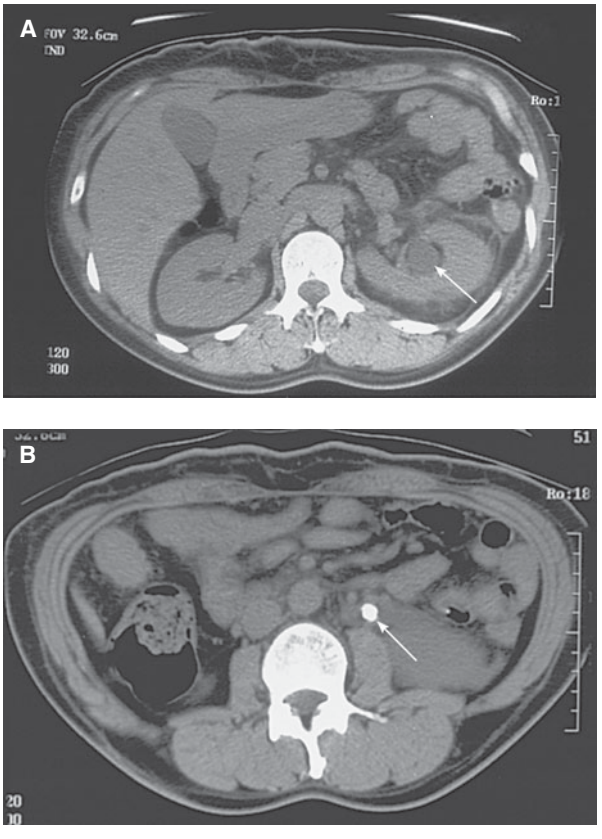


FIGURE 19-3. CT scan of a kidney stone causing obstruction. Shown in panel **A** is the dilated renal pelvis (*arrow*) and in panel **B** the obstructing calculus in the ureter (*arrow*).

Computed tomography (CT) scanning is useful if renal calculi are suspected as the cause of obstruction (Figure 19.3). In this situation not only is the CT diagnostic but it also provides insight as to whether the stone will pass spontaneously because it can demonstrate the stone's size and position. Additionally a CT scan provides information about retroperitoneal processes such as lymphadenopathy, tumor, and hematoma.

Intravenous pyleography provides additional information in settings where papillary necrosis is suspected with staghorn calculi and for patients with multiple renal cysts. Additionally, it is used in association with the CT scan to further define the level of obstruction. Its use is limited, however, because a prolonged period of time is required to visualize the collecting system of the obstructed kidney and a larger dye load.

Diagnosis of partial obstruction secondary to BPH or abnormalities in micturition is accomplished with urodynamic studies. Uroflowmetry is simple to perform and provides useful information. Urine flow rate is determined by measuring the volume of urine expelled over time. Normal urine flow rate is 20 to 25 mL/s for a male and 20 to 30 mL/s for a female. Lower flow rates suggest an outlet obstruction, such as BPH, and higher flow rates indicate bladder spasticity or excessive use of abdominal muscles to overcome outlet resistance. This test is useful to assess the functional state of the lower urinary tract and to monitor therapy.

Cystometry uses gas or water to inflate the bladder while measuring intravesicular pressure. Often electromyographies of the external urethral sphincter and pelvic floor are included to assess synchrony of bladder and sphincter musculature. Cystometric studies provide information about many aspects of bladder function, including total bladder capacity, the ability of the patient to perceive fullness, and the volume at which voiding occurs. Normal bladder capacity is 400 to 500 mL. The first sensation of fullness is usually felt at 150 to 250 mL but the sensation of definite fullness does not occur until 350 to 450 mL. Cystometric studies can also diagnose premature detrusor contraction. Premature detrusor contractions occurring prior to reaching true bladder capacity are the result of a hyperreflexic bladder or uninhibited behavior. Finally, the residual volume in the bladder can be detected. Under normal circumstances complete emptying of the bladder should occur without higher than normal (up to 30 cm H_2O) voiding pressures.

In case of suspected retroperitoneal fibrosis, tissue diagnosis is now potentially helpful. A biopsy showing a dense lymphoplasmacytic infiltrate, with storiform fibrosis and cells staining positive of IgG_4 is very suggestive of IgG_4-related disease.

KEY POINTS

Signs and Symptoms, Causes, and Diagnosis of Urinary Tract Obstruction

1. Symptoms and signs of urinary tract obstruction can vary and a high index of suspicion is necessary to establish the diagnosis.
2. Urinary tract obstruction occurs primarily in men. Benign prostatic hyperplasia is the leading cause.

3. Ultrasonography is the most useful imaging tool to diagnose urinary tract obstruction.
4. Urodynamic studies are used to diagnose functional bladder abnormalities that cause obstruction.
5. Biopsy of retroperitoneal tissue may facilitate a diagnosis of IgG_4-related disease.

PATHOPHYSIOLOGY

Ultrastructural

On the ultrastructural level, acute kidney injury in urinary tract obstruction is the result of increased pressure transmitted from the obstruction retrograde through the collecting system to the glomerulus. As tubular pressure rises the transcapillary pressure gradient decreases. This pressure gradient drives ultrafiltration and, therefore, as it declines so does glomerular filtration. The rise in intratubular pressure leads to reflex vasoconstriction of the intrarenal blood vessels and decreases glomerular blood flow. Thromboxane and angiotensin II (AII) mediate the increase in intrarenal vasoconstriction. This response is physiologic because it shunts blood away from nonfunctioning nephrons. The initial component of renal injury is the result of increased tubular pressure followed by local ischemic injury.

Molecular

The second component of kidney injury in urinary tract obstruction results from inflammatory cells recruited into the obstructed kidney. The obstructed kidney releases chemotactic agents. On a molecular level much is known about the role of cytokines in the molecular pathophysiology of urinary tract obstruction. In most cases of obstructive uropathy AII concentration rises. AII is important in the progression of many renal diseases including urinary tract obstruction. AII is produced both systemically and locally. Tissue concentrations of AII are 1000 times greater in kidney than in plasma. There are 2 types of AII receptors. The type 1 receptor (AT_1) mediates vasoconstriction and myocyte and fibroblast activation and proliferation. The type 2 receptor (AT_2) causes vasodilation and is antiproliferative. Therefore, inhibition of AT_1 receptor signaling is potentially beneficial, whereas AT_2 receptor blockade is potentially detrimental.

It is important to fully understand the mechanism of action of AII-converting enzyme inhibitors (ACEIs). Initially ACEIs cause AII concentrations to fall; however, after 3 months AII levels return to pretreatment values. This "escape" from ACEIs results from local tissue production of AII. Despite this, ACEIs limit and cause regression of fibrosis. In addition to converting angioternsin I to AII, angiotensin-converting enzyme (ACE) degrades bradykinin. Blockade of ACE by ACEI results in increased concentrations of bradykinin that has antifibrotic effects. Furthermore, the affinity of AT_1 and AT_2 receptors for AII is similar, although perhaps there is a greater density of AT_1 receptors. The AII receptor blockers (ARBs), such as losartan, selectively bind AT_1 receptors with 1000-fold greater affinity than AT_2 receptors. It is these differences between ACEI and ARB that underlie the theoretical advantage of using them in combination. ACEI increase bradykinin concentration with its positive effects. ARBs inhibit the detrimental pathway induced via the AT_1 receptor but leave the AT_2 receptor unblocked. Therefore, AII, which returns to normal concentration in the patient treated with ACEI, only signals through the beneficial AT_2 receptor in the patient treated with combination therapy.

Increasing AII concentration in urinary tract obstruction upregulates transforming growth factor-β_1 (TGF-β_1), tumor necrosis factor-α (TNF-α), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1), vascular cell adhesion molecule-1 (VCAM-1), nuclear factor-κB (NF-κB), monocyte chemoattractant peptide-1 (MCP-1), and intercellular adhesion molecule-1 (ICAM-1). These recruit inflammatory cells into the renal parenchyma that perpetuate the damage, repair, and fibrosis process leading to chronic scarring of the kidney.

TGF-β_1 has multiple roles in the pathogenesis of renal disease. It promotes fibrogenesis in kidney by stimulating endothelin production, a potent stimulator of glomerulosclerosis and fibrogenesis, increases the activity of tissue inhibitors of metalloproteinases (TIMPs), and directly decreases the activity of metalloproteinases, which, in concert, result in increased matrix deposition.

THERAPY

The primary goal is rapid diagnosis. Once the level of obstruction is identified, therapy is targeted at the cause. In cases of bladder outlet obstruction, insertion of a Foley catheter is initially curative. There is controversy regarding

how quickly an overdistended bladder should be drained. Two potential consequences of rapid bladder drainage are gross hematuria, which is caused by rapid reexpansion of veins in the bladder wall once pressure is relieved, and the occurrence of reflex hypotension. Because of these concerns, it is advocated that after the first 500 mL of urine is removed, the Foley catheter should be clamped and the remaining urine drained slowly over many hours. This approach is not supported by available data, however, as pressure in a distended bladder falls rapidly with small volume removal. Intravesicular pressure is reduced by 50% when 100 mL is removed and by 75% when 250 mL is removed.

With bilateral obstruction the concentrating gradient in renal medulla is lost. Acute kidney injury causes a retention of osmolytes and fluid. Once obstruction is relieved and renal function begins to recover there is often brisk diuresis. This is referred to as *postobstructive diuresis*. Initially, urine output can be as high as 500 to 1000 mL/h. The diuresis is a result of many factors. During the acute kidney injury phase there is retention of excess fluids and osmoles. As filtration improves these osmotically active molecules are cleared and cause an osmotic diuresis. While obstructed, the kidney loses its medullary concentrating gradient; consequently, when filtration increases there is an inability to reclaim filtered free water. Finally, there is direct tubular injury during obstruction that must recover. Replacement of urinary losses milliliter for milliliter only serves to perpetuate the diuresis. Normal replacement fluids are prescribed and the patient monitored for signs and symptoms of volume depletion. In this setting, daily weights are critical and an admitting weight to which daily weights can be compared is a must. High urine flow rate leads to depletion of potassium and magnesium and their concentrations should be monitored twice daily and replaced as required until urine output slows to 2 to 3 L/day. ACEIs and ARBs interrupt the pathogenic processes that cause kidney injury on a molecular level. Given this, there are theoretical reasons to employ combination therapy in the treatment of obstructive uropathy to prevent scarring and fibrosis. Although data in humans do not exist, animal data show this approach is effective when started up to 3 days after the onset of obstruction.

With BPH outlet obstruction results in hypertrophy of the detrusor muscle and the nonstriated sphincter at the bladder neck. This results in both obstructive and irritative symptoms. Because the inner sphincter is innervated by α_1-adrenergic sympathetic nerves, α_1 blockers may decrease outlet resistance. α_1-Receptors are abundant in the base of the bladder and in the prostate. The density of these receptors is increased in BPH. Terazosin, doxazosin, alfuzosin, and tamsulosin are long-acting α_1 blockers that can decrease bladder outflow resistance. The major side effect of these medications is orthostatic hypotension, which is least with tamsulosin. Drugs that decrease the size of the prostate, such as the α_5-reductase inhibitor finasteride, block the conversion of testosterone to dihydrotestosterone. The prostate shrinks as a result of atrophy of the glandular portion. Fibromuscular hyperplasia is unaffected, but obstructive symptoms may improve because there is less prostate bulk to impinge on the urethra. Combined therapy with an α_1 blocker and a α_5-reductase inhibitor was more effective than either alone in 1 term trial. Invasive therapy should be considered for patients with severe symptoms. The most common surgical intervention is transurethral resection of the prostate (TURP). In the Veterans Cooperative Study, TURP reduced symptom scores and decreased residual urine volume. Reduced and/or retrograde ejaculation is common after TURP. Alternative therapies for patients who are poor surgical candidates include transurethral incision of the prostate and prostatic stents.

In cases of retroperitoneal fibrosis, if IgG_4-related disease is suspected, a trial of glucocorticoids is warranted in patients who are without contraindications. Although there are no studied regimens, 40 mg of prednisone daily is a reasonable dose. Response is variable and depends upon how much permanent fibrosis has occurred. It can take up to 4 weeks to be clinically evident. Once a therapeutic response occurs, the dose of glucocorticoids can be tapered slowly. For patients who do not respond or for those who have recurrent symptoms at lower prednisone doses, more potent immunosuppression can be attempted.

KEY POINTS

Pathophysiology and Therapy

1. Rapid diagnosis is the most important aspect of therapy for obstructive uropathy.
2. After relieving obstruction the patient should be monitored for a postobstructive diuresis, because this may result in volume depletion and further acute kidney injury.

3. Combination therapy with ACEIs and ARBs has a theoretical role in the treatment of obstructive uropathy.
4. Steroid therapy may be beneficial in patients with IgG_4-related retroperitoneal fibrosis.

EXPECTED OUTCOMES

Recovery from urinary tract obstruction is variable and dependent on the duration of obstruction. With total ureteral obstruction, complete recovery of GFR can occur if the obstruction is relieved within 1 week. Little or no recovery occurs if complete obstruction remains for longer than 12 weeks. GFR may overestimate the degree of recovery. In animal models of obstruction, up to 15% of nephrons from the obstructed kidney remain nonfunctional 60 days after the relief of obstruction despite the normalization of GFR. The normal GFR is likely a result of hypertrophy of the uninvolved kidney. With partial obstruction the course is less predictable because obstruction may be present for a prolonged period prior to detection. Most functional recovery occurs within 7 to 10 days after the relief of obstruction. In cases of severe renal failure, dialysis may be necessary to support the patient until sufficient recovery occurs. In these patients, complete recovery is unlikely and they are often left with chronic kidney disease.

KEY POINTS

Expected Outcomes

1. Recovery from urinary tract obstruction is variable and dependent on the duration of obstruction.
2. If obstruction is relieved within 1 week, complete recovery of renal function is expected; however, if the obstruction persists for longer than 12 weeks, no recovery occurs.
3. Most functional recovery occurs within 7 to 10 days after relief of the obstruction.

Additional Reading

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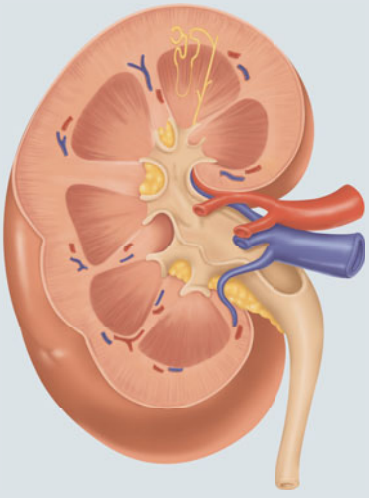

CHAPTER 20

Essential Hypertension

• *Aldo J. Peixoto and Sergio F.F. Santos*

Recommended Time to Complete: 2 Days

Guiding Questions

1. How common is essential hypertension (HTN) and what factors predict its prevalence? How effective are the current degrees of awareness, treatment, and control of HTN in the United States?
2. What are the principal mechanisms of essential HTN?
3. What can we learn from monogenic forms of HTN to explain the origins of essential HTN?
4. What is the general framework of the role of the kidneys and sodium retention in the pathogenesis of HTN?
5. What is pressure natriuresis?
6. What are the goals of the clinical evaluation of the hypertensive patient?
7. What tests are indicated in the initial evaluation of the hypertensive patient?
8. How low should blood pressure (BP) be lowered by antihypertensive therapy?
9. What is the preferred class of drugs to be used in the treatment of the uncomplicated hypertensive patient?
10. How do comorbid conditions affect the choice of antihypertensive agents?
11. What is the difference between hypertensive urgencies and emergencies, and how is management different?
12. What are the appropriate BP-lowering goals in patients with hypertensive emergencies/urgencies?

INTRODUCTION

HTN as defined by current standards afflicts almost 70 million Americans, and is thus—not surprisingly—the most common reason for a physician visit in this country. The magnitude of the problem has generated multiple public health efforts in the past 35 years, leading to the present levels of awareness (81%) and treatment (73%). Although still not optimal, the rates of BP control have improved from 27% to 50% in the last decade. Nevertheless, it is imperative that we focus continued attention on education of the public and medical professionals. The many reports of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure are the most prominent representatives of this educational effort, and its eighth report (*The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* [JNC 8]) is

forthcoming in 2013. We urge everyone interested in HTN to read the full report after its publication. This chapter reviews general aspects of HTN related to epidemiology, mechanisms, diagnostic evaluation, complications, and therapy.

EPIDEMIOLOGY

Current estimates of the worldwide prevalence of HTN are as high as 1 billion individuals (~68 million in the United States). Its prevalence increases with age (Table 20.1), and the BP rise is steeper in men than in premenopausal women. Women show a greater rise in BP following menopause, and the absolute prevalence of HTN is higher in women than men. HTN is a more pervasive problem in the Western world, and there is a relationship between average populational sodium intake and the prevalence of HTN. Other factors associated with a greater prevalence of HTN include ethnicity, lower socioeconomic status, lower dietary potassium intake, higher body mass index, and larger amounts of habitual alcohol use. The prevalence is greater in African Americans and nonblack Hispanics than in whites. These 2 subgroups also have poorer control rates than whites, which further amplify the cardiovascular burden of BP. Another important point is the fact that migration from a rural to an urban setting or from a nonindustrialized to an industrialized country increases the risk of HTN. These effects are primarily mediated by changes in dietary and psychosocial factors.

TABLE 20-1. Prevalence of Hypertension in U.S. Adults According to Age and Gender

	PREVALENCE	
AGE GROUP	MALE	FEMALE
20 to 34 years	11%	7%
35 to 44 years	25%	19%
45 to 54 years	37%	35%
55 to 64 years	54%	53%
65 to 74 years	64%	69%
>75 years	67%	79%

Data compiled from Roger V, Go A, Lloyd-Jones D, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2-e220.

KEY POINTS

Epidemiology of Hypertension

1. The prevalence of HTN in the United States increases with age, female gender, and African American ethnicity.
2. Awareness of HTN is now 81%, and treatment (73%) and control rates (50%) have improved in the last decade.
3. Continued education of the public and medical personnel is necessary to reach optimal rates of BP control.

PATHOPHYSIOLOGY

Essential HTN is the term used to describe elevated BP without a readily detectable cause. The term was coined at a time when high BP was thought to be required or "essential" to surmount the established vascular disease in order to achieve target–organ perfusion. In the past, vascular disease was thought to precede HTN, and not be a result of it. Therefore, most experts discouraged physicians from treating high BP. It was not until the 1960s that it became clear that HTN was itself a major risk factor for vascular disease, and that its treatment resulted in improved outcomes. Only then was it determined that the need for higher BPs was not really "essential."

The operative mechanisms in essential HTN are multiple, intersecting, and represent an attempt at a balance between vasopressor and vasodilator mechanisms. The formula

$$BP = \text{cardiac output} \times \text{vascular resistance}$$

provides a valuable guide to the understanding of the pathophysiology of HTN. Changes in cardiac output usually result only in transient changes in BP, therefore, most of the chronic changes in BP control are dependent on the relationship between 1 of the determinants of cardiac output—blood volume (BV) (the content)—and systemic vascular resistance (SVR, the container). For the sake of this discussion, BV is referred to here as a surrogate for extracellular volume (ECV), even though an increase in ECV does not always result in increased BV, and vice versa. Because the vasculature has a great ability to accommodate BV because of its large capacitance bed (veins and venules), an inappropriate increase in vascular tone is necessary to result in HTN when BV is increased.

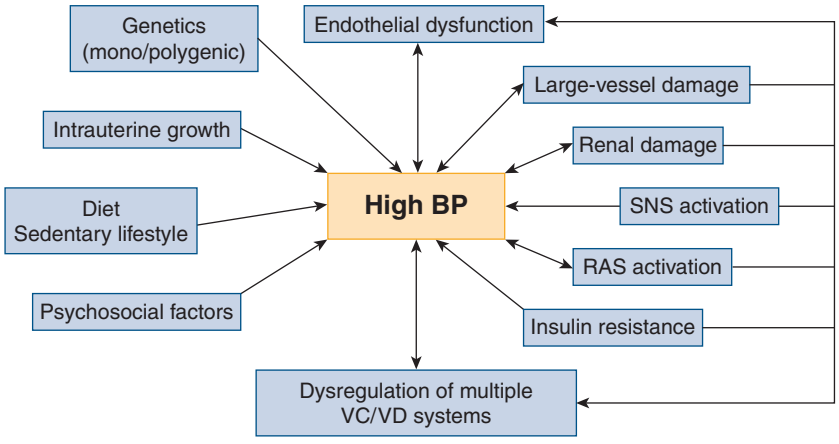

FIGURE 20-1. Relevant mechanisms involved in the genesis of hypertension. *Abbreviations:* RAS, renin-angiotensin system; SNS, sympathetic nervous system; VC, vasoconstrictor; VD, vasodilator.

Therefore, abnormalities in vascular resistance, either as a net increase or an insufficient decrease, are an essential part of HTN in almost all patients. Figure 20.1 is an incomplete list of relevant mechanisms that impact on BP regulation and vascular function. These systems are affected to different degrees in different individuals. Discrepancies are the result of the genetic heterogeneity of the population, and different degrees of exposure to environmental factors (sodium and potassium intake, alcohol use, psychosocial stressors, and so on).

It is estimated that heredity accounts for approximately 20% to 25% of one's BP and the determinants of this effect are polygenic and highly variable. Certain gene polymorphisms affecting the function of certain key mechanisms, especially the renin-angiotensin-aldosterone system (RAAS) (eg, the angiotensinogen, angiotensin-converting enzyme [ACE], aldosterone synthase, and 11β-hydroxysteroid dehydrogenase genes) or salt sensitivity (eg, the α-adducin gene) have been linked with the presence of HTN, but the relative importance of these polymorphisms is small. Recent large genome-wide association studies have identified high-risk loci for the presence of HTN. Some of these involve known pathways related to BP regulation, but not all. Again, the overall effect of each of these loci is quite small (~1 mmHg for systolic blood pressure [SBP] per locus). Perhaps of greater relevance is the approach to monogenic disorders. Although rare, the understanding of the mechanisms related to HTN in these conditions leads to a better understanding of essential HTN in general. Examples of these disorders are listed in Table 20.2, and are discussed in greater detail in Chapter 21. The findings related to their different mechanisms indicate that single-gene mutations altering renal sodium handling are able to produce sustained, severe HTN.

TABLE 20-2. Causes of Monogenic Hypertension and Their Respective Pathophysiologic Mechanisms, All with a Common Link to Increase Sodium Reabsorption

Liddle syndrome (mutation in the epithelial sodium channel gene): decreased rate of removal of the epithelial sodium channel from the apical membrane
Syndrome of HTN exacerbated by pregnancy, or Geller syndrome (mutation in the mineralocorticoid receptor [MR] gene): increased MR activity with increased sensitivity to progesterone
Gordon syndrome (mutations in the CUL3, KLHL3, WNK1 or WNK4 genes): increased Na-Cl cotransporter activity
Glucocorticoid-remediable aldosteronism (chimeric mutation in the aldosterone synthase gene leading to enhanced adrenocorticotropic hormone [ACTH] stimulation of aldosterone synthesis): increased aldosterone and some hybrid steroids (18-oxocortisol, 18-hydroxycortisol)
Apparent mineralocorticoid excess syndrome (mutation in the 11β-hydroxysteroid dehydrogenase type 2 gene): increased glucocorticoid availability for activation of the MR

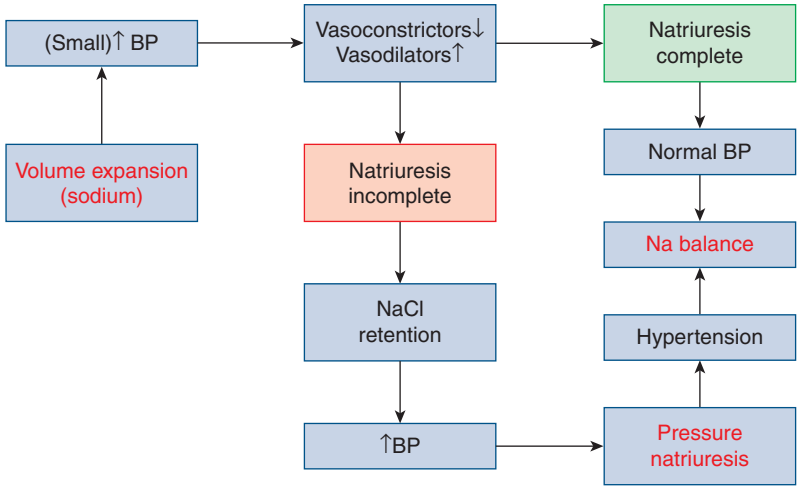

FIGURE 20-2. The concept of pressure natriuresis. If appropriate renal and vascular mechanisms exist, BP increases minimally and the excess volume is excreted completely, rapidly returning BP to normal. If adaptation is not normal, sodium retention occurs resulting in substantially increased BP, which then induces a pressure-natriuresis in order to achieve sodium balance (at the cost of chronic HTN).

The aforementioned genetic diseases lend support to a much older postulate related to the central role of the kidneys in the genesis of HTN. Multiple experimental and clinical models reveal that the development of HTN always depends on an abnormality in renal sodium handling. Even if the primary change is related to increased cardiac output or peripheral resistance, these abnormalities result only in transient increases in BP *unless* a change in the renal pressure–volume relationship occurs, which will result in the need for a higher BP to guarantee sodium balance.

Abnormalities in renal sodium handling commonly result in elevated BP through interactions that were first championed by Guyton (the *Guyton hypothesis*). In this now widely accepted hypothesis, the most relevant mechanism used by the body to regulate BP is to alter renal sodium handling, thereby controlling ECV and cardiac output. In the normal state, increased sodium intake causes an increase in ECV and BP. Because of a steep relationship between volume and pressure, small increases in BP produce natriuresis, which restores sodium balance and returns BP to normal. This response becomes abnormal whenever there is impediment to sodium excretion, such as in states of reduced renal function or high levels of angiotensin II. In such case, the BP rise necessary to restore sodium balance is greater, resulting in a state of increased sensitivity to dietary salt wherein the ability to excrete sodium becomes pressure-dependent. In this situation, sodium balance is only achieved at higher BP levels that are required to excrete the ingested sodium load, a process called *pressure natriuresis* (Figure 20.2). This chronic state of high BP generated by sodium retention is not related to increased BV, which is only minimally increased (if at all) in most hypertensive patients, but to sodium-related increases in SVR. The mechanisms underlying this vascular effect are not completely understood, but we know that sodium overload leads to increased sympathetic outflow and abnormalities in cation flux, especially calcium. Volume expansion decreases extracellular calcium and stimulates the production of parathyroid hormone (PTH), 1,25-dihydroxy vitamin D, and ouabain-like factors that lead to an intracellular calcium shift, increased intracellular calcium, and thus elevated vascular resistance. Thus, abnormalities in pressure–volume relationships lie at the center of essential HTN, and also occur as an important part of the maintenance phase of most other causes of HTN (such as hyperaldosteronism, renal artery stenosis, Cushing syndrome, coarctation of the aorta, and even pheochromocytoma).

The current understanding of the interplay between renal sodium retention and HTN involves changes in sodium handling throughout the nephron. The inciting

event is an increase in arteriolar tone in the renal vasculature (e.g., from increased activity of the RAAS or the sympathetic nervous system), subtle renal injury of any type, aging, or the effects of inherited or environmental factors that lead to a sodium retentive phenotype. An interesting theory with substantial experimental support proposes that this increased renal vasoconstriction leads to a preglomerular (afferent) arteriolopathy that results in impaired sodium filtration. In addition, renal vasoconstriction results in tubular ischemia, which in turn results in increased sodium avidity. The combined result of these processes is salt-sensitive hypertension. The sensitivity of an individual to salt/volume overload and the BP response observed with changes in sodium intake can be improved or corrected by modifying some of the factors that modulate salt sensitivity, especially the RAAS. Obviously, in any individual who has increased sensitivity to salt (30% to 50% of the hypertensive population), sodium restriction can decrease BP effectively.

The sympathetic nervous system is important in BP control, and its activation may be an important early step in the process of increased renovascular resistance (increased arteriolar tone) that leads to sodium retention. Multiple strategies are available to block sympathetic overactivity in HTN, both at the central level, to limit central nervous system (CNS) sympathetic outflow, and at the effector level, with direct α- or β-receptor antagonism. Decreased sympathetic activity can also be achieved clinically by direct electric stimulation of the carotid baroreceptors or by radiofrequency ablation of renal sympathetic afferents.

The balance between vasopressor and vasodilator mechanisms is difficult to interpret in any individual patient. Table 20.3 summarizes the humoral systems that can be abnormally increased or decreased in HTN. Their relative role in the pathogenesis of HTN varies substantially, and a detailed discussion is beyond the scope of this text. The vasculature is not only abnormal in its responses related to vascular tone, but also in its structure. Hypertensive subjects have diffuse capillary rarefaction, as well as a progressive decrease in the lumen of small arteries and arterioles. These structural changes limit organ perfusion (especially important in the kidney), and also impair vascular responses to vasodilatory substances.

An important pathophysiologic mechanism is increased arterial stiffness, a problem that is particularly relevant to older individuals (and isolated systolic HTN [ISH]). Arterial stiffening is caused by loss of elastic fibers of large arteries, and is strongly associated with aging (especially after the sixth decade of life), smoking, diabetes mellitus, and kidney disease. As shown in Figure 20.3, this process leads to increased pulse wave velocity (PWV), which, in turn, results in faster reflection of the incident pulse wave. Faster reflection implies that the reflected wave returns to the heart before the end of systole, resulting in augmentation of central BP

TABLE 20-3. Humoral and Cellular Factors Related to Vascular Function in Hypertension

Catecholamines
Angiotensin II, aldosterone
Sex steroids
Prostaglandins
Endothelin 1
Bradykinin
Natriuretic peptides
Nitric oxide
Reactive oxygen species
Insulin and insulin resistance
Intracellular Na, Cl, K, Ca, Mg
Parathyroid hormone, vitamin D
Adrenomedullin
Renalase

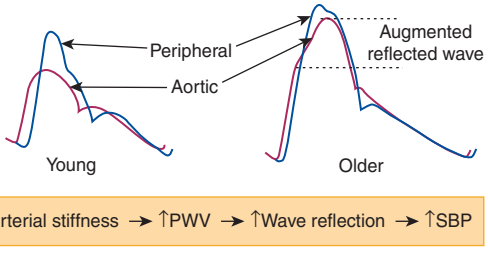

FIGURE 20-3. Effect of age and arterial stiffening on systolic blood pressure. Aging is associated with increased arterial stiffness, which results in faster PWV and wave reflection. Faster wave reflection augments the reflected pulse wave, which returns to the central circulation before the end of systole, thus increasing SBP and decreasing the diastolic BP. The relative magnitude of this effect is greater in the central blood vessels (aorta).

and increased SBP. This abnormality is relevant to left ventricular (LV) performance, as increased impedance to LV ejection is an important factor in generating LV hypertrophy (LVH) and subendocardial myocardial ischemia, 2 common complications of HTN. Abnormalities in arterial structure also alter the shape of decay of the diastolic BP (DBP) curve resulting in a decrease in DBP and wider pulse pressure.

KEY POINTS

Pathophysiology of Hypertension

1. HTN is the result of an imbalance between vasopressor and vasodilatory systems. A multitude of such systems are variably affected in any individual patient.
2. The kidneys have a prominent role in the genesis of HTN as a consequence of its effects on sodium handling. An abnormality in sodium excretion is a part of virtually all types of sustained HTN.
3. Arterial stiffness is an important cause of systolic HTN and widened pulse pressure in older patients.

PATHOPHYSIOLOGY OF THE CLINICAL CONSEQUENCES OF HYPERTENSION

HTN is marked by diffuse vascular injury. If left untreated, elevated BP results in cardiovascular complications in as many as 50% of patients. The risk is directly related to BP levels; in a metaanalysis that included more than 1 million patients, the risk of cardiovascular mortality doubled with each BP increase of 20/10 mmHg, starting with levels above 115/75 mmHg. Progressive damage affects several vascular territories, with a particular predilection for the cerebral vasculature, retinal vessels, coronary arteries, renal circulation, and arteries of the extremities. The heart is not only affected by way of coronary disease, but also from pressure overload that leads to LVH.

Cerebrovascular disease is a frequent complication of HTN. At any given age, the risk of developing a stroke is increased by the presence of HTN, and the magnitude of this risk is directly related to the degree of BP rise. Vessels supplying the basal ganglia, brainstem, and cerebellum are exposed to higher BP levels, and there is a large drop of BP over a short distance in these short resistance vessels. Thus, these vessels sustain most of the damage in HTN, which develop as arterial hyalinosis and/or microaneurysms of the perforating branches. Occlusion of hyalinized vessels results in the small lacunar infarcts due to focal ischemia, and rupture of microaneurysms leads to the classic hypertensive hemorrhagic strokes of any of these sites, particularly the basal ganglia (more than half of all hypertensive cerebral hemorrhages are putaminal). In the neocortex, longer arteries with many branches act as a stepdown transformer, protecting the cortex from more extensive HTN damage.

Damage to retinal vessels is extensive, and examination of these changes with an ophthalmoscope provides valuable information on the state of the microvasculature in HTN (see the section "Diagnostic Evaluation"). Although hypertensive retinopathy is an infrequent cause of visual problems, there is an increased risk of central retinal vein occlusion in HTN, and high BP accelerates the progression of other eye diseases, especially diabetic retinopathy.

Cardiac involvement in HTN is extensive and complex. On the one hand, HTN leads to accelerated coronary atherosclerosis, a process mediated by shear stress, oxidative stress, and the coexistence of the metabolic syndrome (obesity, insulin resistance with or without diabetes mellitus, dyslipidemia, and HTN). This leads to clinical coronary disease and loss of myocardial mass because of ischemia and infarction. Additionally, the pressure overload state results in concentric LVH, which is the most common clinically relevant target-organ complication of HTN, and is associated with worse outcomes in HTN. LVH and changes in the shape of the diastolic decay of the central BP curve (see above) lead to relative subendocardial ischemia, amplifying the effects induced by atherosclerotic changes. Long-term pressure overload and LVH are maladaptive, and chamber dilation and systolic dysfunction ultimately result, especially in patients with associated coronary disease and myocardial infarction. This course is responsible for the increased occurrence of congestive heart failure in HTN.

The kidneys are commonly affected by untreated HTN. Hypertensive nephrosclerosis is the result of progressive parenchymal ischemia as a consequence of narrowing and hyaline sclerosis of arterioles and small arteries. In addition, the larger interlobular arteries develop marked thickening of the media from a reduplication of the elastic lamina (fibroelastic hyperplasia).

This abnormality also results in areas of parenchymal ischemia and interstitial fibrosis. Nephrosclerosis causes a decline of glomerular filtration rate in as many as 5% of patients with HTN, and is most common in patients with long-standing uncontrolled BP, especially in African Americans.

Atherosclerosis of the peripheral vasculature is accelerated by HTN, though other factors seem more relevant, such as smoking, diabetes, and hyperlipidemia. Nevertheless, HTN is a participant in the development of atherosclerotic plaques and its control is associated with small decreases in the incidence of peripheral arterial disease.

In patients who develop "malignant phase HTN," a process in which BP is very high and there is evidence of target-organ dysfunction, diffuse endothelial damage leads to a microangiopathic picture (intravascular hemolysis, consumptive thrombocytopenia) and acute loss of renal function. Endothelial damage is caused by shear trauma as well as toxicity induced by the RAAS (angiotensin II is a major pathogenetic factor). Histologically, there is extensive arteriolar damage and occlusion, a process named *arteriolar fibrinoid necrosis*.

KEY POINTS

Pathophysiology of the Clinical Consequences of Hypertension

1. Chronic hypertensive target-organ damage is mediated by direct injury to the vessel wall resulting in organ hypoperfusion or hemorrhage (retina and brain).
2. LVH is the most common target-organ complication in HTN and it carries a worse prognosis.
3. Malignant HTN presents with signs of diffuse endothelial injury and organ dysfunction.

DIAGNOSTIC EVALUATION

The diagnostic evaluation of patients with high BP has 5 major goals:

1. Confirm the presence of HTN.
2. Stage the severity of the HTN.
3. Assess the extent of HTN-related organ damage.
4. Rule out causes of secondary HTN.
5. Identify factors that may impact therapy.

Confirming the Presence of Hypertension

The diagnosis of HTN is arbitrarily made when BP is higher than 140/90 mmHg on repeated measurements. The expression *repeated measurements* should be emphasized; it is a mistake to label patients as having HTN based on an isolated reading. Therefore, clinicians caring for such patients must obtain repeated measurements of BP on different occasions. This can be done in the office or with the use of home BP measurements. When using office measurements, it is important that the individuals checking the BP observe the necessary techniques to obtain the readings, as these values will ultimately guide therapy. Patients should have at least 5 minutes of rest and no conversation should take place when obtaining the measurements. The arm should be at the level of the heart, with the patient seated comfortably. No tobacco or caffeine intake should occur in the 30 minutes preceding the visit. It is imperative that there is a good fit between arm circumference and cuff size: small cuffs overestimate BP by as much as 20 mmHg. Korotkoff sounds 1 and 5 should be used to define SBP and DBP in all patients, including pregnant women. The presence of an auscultatory gap must be ruled out, especially in older patients. This is easily done by obtaining the SBP by the palpation method before proceeding with the auscultatory technique. At least 2 readings should be obtained and averaged, and the label of HTN should only be applied after high BP readings are obtained on 2 or more occasions.

Recent restrictions on the use of mercury sphygmomanometers have led to the widespread use of electronic oscillometric devices and aneroid manometers. In this respect, 2 cautionary notes apply: one should ascertain that the electronic device in use has been adequately validated according to Association for the Advancement of Medical Instrumentation (AAMI) or European Society of Hypertension standards (this information can be obtained from the manufacturer). An updated list of validated devices can be found at the website of the Dabl Educational Trust (www.dableducational.org). Both aneroid and electronic devices should be calibrated yearly or whenever there are signs of manometer dysfunction, such as inability to zero, erratic deflation rates, or high reading-to-reading variability within the same patient.

Self-measurement of BP is a very useful technique to confirm the presence of HTN. These values provide information on the behavior of BP outside the

physician's office and may represent the overall burden of BP better than office readings. Multiple monitors are available at reasonable prices ($50 to $80), although only a few have been adequately validated (see www.dableducational.org). The attention to technique should be the same as that in the office, thus the physician must spend some time explaining it to patients. Normalcy parameters for home readings are still a matter of debate, although most experts would agree that home readings should be no higher than 135/85 mmHg. Although there are no studies linking the use of home readings to improved cardiovascular outcomes, home monitoring is associated with greater involvement with one's own treatment and improved BP control. Therefore, we encourage most patients to purchase a home BP cuff, if they can afford it. To provide the most accurate measure of BP burden, the patient should monitor the BP twice daily for 4 to 7 days. Each measurement should be obtained in duplicate (and averaged). Patients should check their BP in the morning before taking medications and in the evening before dinner. If a patient is already under antihypertensive treatment, a mid-day measurement may be useful to assess the peak effects of any medications ingested in the morning.

The burden of BP is best assessed by ambulatory BP monitoring (ABPM). In this technique, the patient wears an automated cuff that records BP every 10 to 30 minutes throughout a 24-hour period. ABPM provides readings outside the office and during sleep and wakefulness. This complete assessment affords a stronger ability to stratify risk, and many studies show ABPM to be a much better predictor of cardiovascular complications in HTN than office BP; however, the equipment is expensive ($1500 to $2500 per monitor), and is usually available only at referral practices. Despite the acknowledged value of ABPM in the evaluation of multiple situations in the hypertensive patient (see Table 20.4), current reimbursement schedules approve its use only in the evaluation of white-coat HTN (patients with office readings >140/90 mmHg and out-of-office readings consistently below this level with no evidence of target-organ damage). When the incidence of adverse cardiovascular events and death using ABPM levels was compared to outcomes based on office BP in a large international cohort study, the ABPM values equivalent to an office BP of 140/90 mmHg were 130/80 mmHg (24-hour average), 140/85 mmHg (daytime BP), and 120/70 mmHg (nighttime BP).

TABLE 20-4. Clinical Uses of Ambulatory Blood Pressure Monitoring

To rule out white-coat HTN in patients with high office BP and normal out-of-office BP, or in patients with HTN without target-organ damage
To evaluate patients with borderline office BP values to better define BP averages to help make treatment decisions
To better define prognosis in patients with resistant HTN
To delineate the profile of BP in patients with labile HTN
To evaluate orthostatic symptoms in patients on antihypertensive therapy or in patients with autonomic neuropathy

Staging the Severity of Hypertension

After following the appropriate steps outlined above, we can stage the degree of HTN. The current classification was proposed in JNC7 and consists of 4 categories:

1. Normal	<120/80 mmHg
2. Prehypertension	120 to 139/80 to 89 mmHg
3. Stage 1 hypertension	140 to 159/90 to 99 mmHg
4. Stage 2 hypertension	>160/100 mmHg

Normal BP reflects values that are below the point where BP develops an association with increased risk for cardiovascular events and death. Prehypertension is a widely prevalent condition (up to 40% of the population) and its use remains somewhat controversial. It was created because of observations that cardiovascular risk increases as BP enters this range; however, there are no definitive data showing that treatment alters the outcome of such patients. A recent metaanalysis identified significantly decreased risk of stroke (22%) and marginal decreases in myocardial infarction and death among individuals with prehypertensive BP levels exposed to antihypertensive agents for other reasons. We do not believe these data justify treatment of patients with prehypertension, but it is reasonable to advise these patients to engage in lifestyle practices that decrease their overall cardiovascular risk (see below). The separation of Stages 1 and 2 HTN has few specific ramifications, the most important of which is to raise awareness to the fact that more than 1 drug is likely to be needed to achieve BP control in patients with Stage 2, since a 20/10 mmHg BP fall is seldom achieved with a single agent.

Assessing the Extent of Hypertensive Damage

The initial contact with a patient with suspected or confirmed HTN must provide a good assessment of target-organ damage that has already incurred. The history and physical examination focuses on unraveling signs and symptoms of coronary disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease (including the aorta), and renal disease. The fundoscopic examination is a valuable tool as it provides a direct observation of small blood vessels. It is important to account for 2 separate components of retinal vessel damage: those related to arteriosclerosis and those related to acute BP increases and altered vascular permeability. Chronic arteriosclerotic changes in retinal vessels are a result of long-standing (months to years) pressure-induced damage and include progressive increases in arteriolar wall thickness (copper wiring and the advanced silver wiring appearances), arteriovenous crossings, which are caused by perivascular fibrosis, and arteriolar microaneurysms. Changes related to acute changes in BP are more dramatic and can occur over the course of hours to days. These changes include arteriolar spasm, retinal flame hemorrhages, exudates (from retinal ischemia), and papilledema (from cerebral edema).

Judicious use of laboratory tests (urinalysis, serum creatinine, and electrocardiogram) further adds to the assessment of organ damage in HTN. Some organizations recommend measuring (micro-) albuminuria as an early marker of endothelial injury and dysfunction. In patients with symptoms or abnormal tests, further evaluation is indicated, with a focus on the involved organ system.

Ruling Out Secondary Hypertension

All patients with HTN should receive at least a basic evaluation in search of possible secondary causes of HTN, since these causes may lead to a specific, sometimes curative therapy (see Chapter 21). In the initial visit, the clinician should inquire about a family history of HTN or renal disease, history of established peripheral vascular or coronary artery disease to suggest renal artery stenosis, symptoms possibly related to hyperaldosteronism (muscle weakness, cramps), pheochromocytoma (paroxysms of HTN, headache, sweating, and palpitations), Cushing syndrome (weight gain, new-onset diabetes mellitus or hyperlipidemia, changes in appearance with cushingoid features), sleep apnea (snoring, witnessed apneas during sleep, daytime somnolence), and thyroid disease (hypo- or hyperthyroidism). A detailed evaluation of medications and nonprescription preparations must also be performed in an attempt to identify any hypertensogenic substances (see Chapter 21). Finally, the basic laboratory evaluation advocated for patients with HTN can provide clues to secondary causes, such as the serum creatinine (renal disease, renal artery stenosis), urinalysis (renal disease, glomerulonephritis in particular), serum potassium (hypokalemia of hyperaldosteronism and Cushing syndrome), and hematocrit (polycythemia of sleep apnea). More specific searches for secondary causes are not warranted at the initial evaluation of the hypertensive subject. If any of the above steps are positive, specific screening tests should be ordered targeting the disorders under suspicion.

Identifying Factors That May Alter Therapy

It is essential to approach hypertensive patients not only as it relates to their BP, but from a broad vascular risk perspective. Accordingly, the initial visit must include an assessment of other cardiovascular risk factors, such as diabetes mellitus, obesity, smoking, sedentary lifestyle, hyperlipidemia (a fasting lipid profile is recommended as part of the initial laboratory profile), and the presence of vascular disease in any territory. This stratification of risk is important in designing the aggressiveness of therapy. As discussed under "Treatment," thresholds for initiation of pharmacologic therapy, BP targets, and drug choice vary substantially, according to prevalent comorbid conditions in the individual patient.

Risk stratification is performed objectively using any of the many available risk prediction tables. The European HTN guidelines make stronger statements on risk stratification than JNC 7, and we agree that overall risk assessment is important as an additive to risk estimation based on BP alone. Our personal preference is one of the Framingham risk calculators (calculates the 10-year or 30-year risk of coronary heart disease based on age, sex, SBP, body mass index, total cholesterol, high-density lipoprotein [HDL]-cholesterol, diabetes mellitus, and smoking status). These can be easily estimated using online calculators (http://www.framinghamheartstudy.org/risk/cardiovascular30.html) or smart phone applications.

KEY POINTS

Diagnostic Evaluation

1. HTN should be diagnosed only after high BP levels are reproduced several times.
2. Accurate technique for BP measurement is essential to minimize errors in the assessment of hypertensive patients.
3. Home BP and ABPM are valuable tools in the assessment of BP levels.
4. Evaluation of prevalent comorbidity and overall risk of future cardiovascular disease is an essential part of the initial evaluation of hypertensive patients.
5. The fundoscopic examination provides a direct examination of the structure of small arteries in HTN.
6. Possible secondary causes of HTN should be ruled out in the initial visit through the judicious use of the medical history, physical examination, and basic laboratory studies.

TREATMENT

The primary goal of HTN treatment is to decrease cardiovascular and renal morbidity and mortality. If left untreated, HTN leads to one or multiple cardiovascular complications in as many as 50% of patients, and it is now undisputed that BP lowering leads to an improvement in patient outcomes in all domains of HTN-related injury. Observational data indicate that each 2 mmHg decrease in SBP is associated with a 7% decrease in coronary disease mortality and a 10% decrease in stroke deaths. Estimates based on clinical trial data indicate that, by lowering BP by approximately 10 to 15/5 to 8 mmHg, antihypertensive therapy results in an approximate 40% reduction in the risk of stroke, 20% reduction in coronary disease, and a 50% decrease in heart failure. The progression of chronic kidney disease to end-stage kidney disease is decreased by 50% with better BP control. The end-organ benefits are obviously greater in patients with higher baseline BP and cardiovascular risk categories. Peripheral vascular disease is the least-affected outcome. Lowering BP leads to minimal improvements in symptom scores and no change in objective measures of peripheral vascular disease. Current guidelines do not recommend drug therapy in patients with prehypertension.

The approach to HTN treatment is multifaceted, including risk factor modification, lifestyle changes, and drug therapy if needed. First, one must recognize HTN as a cardiovascular disorder whose morbidity is mediated not only by BP levels, but also by associated risk factors. Because the ultimate therapeutic goal is the prevention of cardiovascular disease, management of other risk factors is imperative regardless of their impact on BP levels per se. Accordingly, aggressive risk factor modification is an integral part of treatment of the hypertensive patient. Counseling and therapy should be provided regarding smoking cessation, weight loss, hyperlipidemia, and diabetes mellitus. All patients should receive low-dose aspirin (75 or 81 mg) daily unless there is a contraindication, as it resulted in fewer cardiovascular events in a large randomized trial of hypertensive patients (Hypertension Optimal Treatment [HOT] trial). Reduction of BP can be achieved with lifestyle changes and antihypertensive medications. We discuss these approaches in detail in the sections that follow.

Lifestyle Modifications

Several lifestyle factors impact BP and are effective in preventing HTN in normotensive persons, as well as in lowering BP in those with HTN (Table 20.5). Weight reduction is an important step in those who are overweight (body mass index [BMI] >25 kg/m^2) or obese (BMI >30 kg/m^2) and should involve a combined effort including caloric restriction and increased physical activity. Unfortunately,

TABLE 20-5. Lifestyle Modifications and Their Effects on Blood Pressure in Patients with Hypertension

MODIFICATION	APPROXIMATE SBP REDUCTION (RANGE)
Weight reduction	5 to 20 mmHg/10 kg weight loss
Adopt DASH eating plan	8 to 14 mmHg
Dietary sodium reduction	2 to 8 mmHg
Physical activity	4 to 9 mmHg
Moderation of alcohol consumption	2 to 4 mmHg

Source: JNC 7. National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program.

significant weight loss is required to reduce BP enough to obviate the need for antihypertensive drugs, and such reductions are often not sustained over time. Pharmacologic adjuncts are of limited value in reducing weight as well as BP, but are worth trying in some patients who have difficulties losing weight despite proven adherence to diet and exercise. Appetite suppressants (phentermine, phendimetrazine, and diethylpropion) are Food and Drug Administration (FDA)-approved for short-term therapy up to 12 weeks in duration. Orlistat, a lipase inhibitor, is approved for long-term use for up to 1 year. Bariatric surgery results in improved BP in a substantial number of morbidly obese patients, but there are questions regarding the long-term durability of the BP effect despite relative weight stability. At this time, bariatric procedures cannot yet be recommended in the management of HTN accompanied by obesity, except in the group of morbidly obese patients (BMI of at least 35 kg/m^2).

The dietary approach to lowering BP should address not only calories (weight reduction), but also other strategies that may improve BP, such as low sodium and high potassium and calcium contents, and a low fat (especially saturated fat) diet to maximize cardiovascular risk reduction. The Dietary Approaches to Stop Hypertension (DASH) diet is the preferred plan, as it produces BP-lowering results (8 to 14 mmHg) that are better than those historically observed with sodium restriction alone (2 to 8 mmHg). The DASH plan is the combination of low sodium, low saturated fats, and large amounts of fruits and vegetables (details of the plan are found at www.dashdiet.org). It is our practice to recommend the DASH diet to all patients with HTN, with the exception of those with hyperkalemia (especially in chronic kidney disease) in whom potassium intake must be curtailed.

Increased physical activity is modestly effective in decreasing BP. It is also an important adjunct to weight loss, and is associated with decreased cardiovascular disease, depression, and osteoporosis. Thus, engagement in frequent aerobic activity for at least 30 minutes on most days of the week is advisable for all patients who are capable of doing so.

Heavy alcohol use is associated with increased BP. The thresholds for this association vary according to population, gender, and type of alcohol, thus making precise recommendations difficult. If one uses a conservative approach however, hypertensive individuals should limit alcohol consumption to no more than 2 drinks (20 to 30 g ethanol) per day for men and 1 to 1.5 drinks (10 to 20 g ethanol) per day for women.

KEY POINTS

Lifestyle Modifications

1. The general approach to treatment of HTN is multifaceted, targeting not only BP values per se, but also other variables that modify cardiovascular risk.
2. Lifestyle modifications should be advised to all patients.
3. The most effective lifestyle interventions are weight loss (in overweight subjects), use of the DASH diet, and increased physical activity.
4. The role of appetite suppressants, other weight-loss drugs, and bariatric surgery for improved BP control remain to be seen and are not recommended at this time.

Antihypertensive Drug Therapy

Multiple large, prospective, randomized clinical trials show that drug treatment of HTN decreases the development of the cardiovascular complications of HTN. Individuals with higher baseline BP derive greater benefit from therapy than those with lower baseline BP. As an example, patients with malignant HTN have a 4-fold decrease in mortality after just 1 year of therapy, a remarkable demonstration of the value of BP control in severe HTN. In subjects with lesser degrees of HTN, results of therapy vary, but overall, there is about a 50% reduction in the incidence of congestive heart failure (CHF), a 30% to 40% decrease in stroke, and a 15% to 25% decrease in coronary artery disease and mortality. These observations justify the use of pharmacologic therapy as needed to bring BP to values under 140/90 mmHg.

How Low Should Blood Pressure Be Lowered?

Several observational studies link low achieved BPs (both SBP and DBP) to worse coronary prognosis and overall mortality, especially in elderly patients. These led to the concept of a "J effect" in the treatment of HTN, and the "J point" would be around DBPs less than 75 mmHg and/or SBP less than 110 to 115 mmHg. Three studies have prospectively examined this question. In the HOT trial,

18,790 subjects were randomly assigned to a target DBP of 90, 85, or 80 mmHg. No significant differences were noted in cardiovascular morbidity and mortality as the BP was lowered below 139/83 mmHg, except in diabetic patients, who benefited from a BP lower than 130/80 mmHg. No J effect reaching statistical significance was observed, but closer scrutiny of the data reveals an increase in most measured events for patients with DBP less than 70 mmHg. This risk pattern was not noted for SBP.

The Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica (CARDIO-SIS) randomized 1111 nondiabetic patients to a target SBP of less than 140 mmHg or less than 130 mmHg. The lower target resulted in 37% less LVH (the primary end point) and 50% fewer cardiovascular events during follow-up. These cardiovascular events were largely represented by coronary revascularization and the development of new atrial fibrillation. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized 4733 diabetic patients to a SBP target of less than 140 mmHg or less than 120 mmHg. There were no differences between the 2 groups for the primary end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, but the lower BP group had significantly lower stroke rates at the cost of more frequent hypotensive complications and episodes of acute kidney injury. Taken together, these results dispel the concept of a J effect within the usual treatment targets. However, they were unable to determine conclusively that lowering BP to levels much lower than 140/90 mmHg resulted in any consistent benefit.

Reflecting the foregoing data, current recommendations are to lower BP to less than 140/90 mmHg in most patients. Some guidelines (eg, the American Diabetes Association, JNC 7) recommend a target of less than 130/80 mmHg in patients with diabetes mellitus, but other organizations (European Society of Hypertension, International Society of Nephrology, British National Institute for Health and Clinical Excellence) have moved away from this lower target in diabetics given the lack of strong supportive data, increased risk of hypotensive complications, and increased costs related to more aggressive therapy. A separate recommendation to lower BP to less than 130/80 mmHg in patients with chronic kidney disease has been made by some guidelines (National Kidney Foundation, JNC 7), but given the lack of supportive data, it is now recommended that only patients with significant proteinuria be treated to lower targets (see Chapter 21). In such patients, the observed benefits are related to kidney disease progression, not cardiovascular outcomes. Finally, there is controversy on the appropriate BP target for elderly patients age 80 years and older. Some (American College of Cardiology/American Heart Association) recommend the same 140/90 mmHg target while accepting 140 to 145/90 mmHg if tolerated, whereas others (National Institute of Health and Clinical Excellence [NICE]) have relaxed the target to less than 150/90 mmHg for the very elderly.

Drug Choice in Uncomplicated Hypertension

The treatment of patients with uncomplicated HTN is based on multiple trials that compare individual antihypertensive drugs with placebo or among each other. Thiazide-type diuretics, ACE inhibitors, calcium channel blockers, and angiotensin receptor blockers (ARBs) are all effective in improving outcomes, and are considered appropriate initial choices. Not all members of each class of drugs were tested in large clinical trials, and many experts argue that interchangeable use of any 1 member of a class is not an acceptable practice. Despite this controversy, current guidelines recommend the use of classes of drugs rather than individual agents. β-Blockers, once considered appropriate initial choices by all consensus guidelines, now no longer have that status. The justification is that these agents are not as protective against stroke when used in older patients. They continue to be considered an appropriate first choice among young patients, patients with coronary artery disease, and those with evidence of sympathetic overactivity (eg, high baseline heart rate).

The initial choice of antihypertensive agent is dictated by the presence of comorbid conditions such as diabetes, coronary artery disease (CAD), CHF, stroke, or chronic kidney disease (CKD). Patients with HTN and no other conditions can be managed with any of the initial choices listed above. This recommendation also includes elderly patients with HTN.

Table 20.6 presents a list of all available drug classes, relevant indications for their use, class-specific side effects, and representative agents from each group. When choosing a thiazide diuretic, our preference is for chlorthalidone, which is longer acting and associated with the best track record among the available options. ACE inhibitors and ARBs are not uniformly interchangeable. For

TABLE 20-6. Antihypertensive Drug Classes

CLASS	SPECIFIC INDICATIONS	RELEVANT SIDE EFFECTS	REPRESENTATIVE AGENTS
Diuretics			
Thiazides	Most patients ISH, poststroke, osteoporosis, hypercalciuria (calcium stones)	Hypokalemia, impotence	Chlorthalidone, hydrochlorothiazide, indapamide, metolazone
Loop	CKD	Hypokalemia	Bumetanide, furosemide, torsemide
Potassium-sparing	Hypokalemia, CHF (spironolactone and eplerenone only)	Hyperkalemia, decreased libido, gynecomastia (spironolactone only)	Aldosterone antagonists: eplerenone, spironolactone Na channel blockers: amiloride, triamterene (should not be used as single agents)
ACE inhibitors	CHF, post-MI, DM, CKD, high cardiovascular risk, poststroke	Common: cough Rare: hyperkalemia, acute kidney injury, angioedema	Captopril, benazepril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Angiotensin 2 receptor blockers	CHF, LVH, DM, CKD, ISH, headache	Best side-effect profile; rare angioedema	Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Renin Inhibiitors	No specific indication. Approved use for hypertension, but enthusiasm decreased due to adverse events in a recent clinical trial.	Hyperkalemia	Aliskiren
Calcium Channel Blockers			
Dihydropyridines	ISH, CAD (angina), Raynaud phenomenon	Flushing, headache, edema, constipation	Amlodipine, felodipine, nifedipine, nisoldipine
Nondihydropyridines	Tachyarrhythmias, proteinuria, migraines (verapamil)		Diltiazem, verapamil
β-Blockers	Post-MI, CAD (angina), tachyarrhythmias Hyperthyroidism, migraines, essential tremor (propranolol)	Bradycardia, sedation, depression, impotence, impaired perception of hypoglycemia	Cardioselective: atenolol, metoprolol, betaxolol Nonselective: propranolol, nadolol Combined α/β-blocker: labetalol, carvedilol
α-Blockers	BPH Should not be used as single agent (not first-line therapy)	Orthostasis (*first-dose reaction*), palpitations, nasal congestion	Terazosin, doxazosin
Central antiadrenergic agents	Fourth-line combination therapy, autonomic diarrhea (clonidine) Intolerance to oral therapy: clonidine is the only agent available in patch form Should not be used as single agent (not first-line therapy)	Sedation, dry mouth, withdrawal syndrome	Clonidine, methyldopa

(*continued*)

TABLE 20-6. Antihypertensive Drug Classes (*Continued*)

CLASS	SPECIFIC INDICATIONS	RELEVANT SIDE EFFECTS	REPRESENTATIVE AGENTS
Direct vasodilators	Fourth-line combination therapy Should not be used as single agent (not first-line therapy)	Edema, tachycardia (should be used in combination with a diuretic and a negative chronotropic agent)	Hydralazine, minoxidil

Abbreviations: BPH, benign prostatic hypertrophy; DM, diabetes mellitus; MI, myocardial infarction.

example, whereas they appear to be equivalent in patients with uncomplicated HTN, diabetes, CKD, and possibly CHF; the efficacy of ACE inhibitors is not matched by ARBs in patients who are at high risk for cardiovascular disease and in patients who have sustained a previous stroke. While all available classes of calcium channel blockers (CCBs) have been well studied in randomized clinical trials, our preference is for agents of the dihydropyridine class, given the strength of their performance in large clinical trials and longer duration of action, in particular amlodipine.

In most trials, a substantial number of patients (up to two-thirds) require more than 1 drug to achieve BP targets, which reminds us of the importance of effective drug combination in the treatment of HTN. This is particularly true for patients with Stage 2 HTN, as a BP fall of more than 20/10 mmHg, which is needed to bring such patients to the 140/90 mmHg target, is unlikely to be achieved with a single drug. Accordingly, combination therapy with 2 drugs from the outset is recommended in patients with Stage 2 HTN.

Results of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial demonstrated fewer cardiovascular events in patients randomized to a regimen combining an ACE inhibitor (benazepril) with a CCB (amlodipine) compared with benazepril and hydrochlorothiazide. These results have led to increased use of ACE inhibitor/CCB combination as the first combination strategy. Adding a thiazide diuretic to other agents, however, still has significant value, especially in patients who are typically salt-sensitive, such as the elderly and patients with underlying kidney disease.

In the process of drug escalation, it is important to note that most drugs display progressive flattening of the dose–response curve within the recommended dose range. In addition, as the dose is increased, the occurrence of side effects is often increased. Thus, it is our preference to add a second drug before reaching the maximal recommended dose of the first. This combination hastens the achievement of BP targets and decreases the likelihood of side effects. Only after the combination is in place do we push the drugs to the maximal recommended doses.

The combination of ACE inhibitors and ARBs, once frequently employed, should not be used routinely. First, because their combination leads to minimal additive BP lowering; second, because combination is associated with increased adverse events, especially episodes of acute kidney injury. The only current role for ACE inhibitor/ARB combination is in the management of patients with nephrotic range proteinuria and patients with severe LV dysfunction.

Patients who do not achieve BP control with 3 intelligently combined drugs at maximal doses, 1 of them being a diuretic, are considered to have resistant HTN and should be referred to a HTN specialist for a more detailed evaluation that includes a thorough search for secondary causes of HTN, aggressive management of salt and volume excess, including maximization of diuretic drugs, and use of less-common antihypertensive agents. Mineralocorticoid receptor antagonists, such as spironolactone or eplerenone, are particularly useful in patients with resistant HTN, and should be used unless there are problems with hyperkalemia. Recent technological developments have brought forth novel nondrug approaches to resistant HTN, such as catheter-based renal sympathetic nerve ablation and chronic baroreceptor activation therapy. These techniques have resulted in large drops in BP in

preliminary trials and represent potentially revolutionary approaches to patients with drug-resistant HTN.

Drug Choice in Patients with Comorbid Conditions

HTN is often accompanied by other conditions that modify cardiovascular risk. In many of these conditions, specific agents were studied and shown to perform better than others. Remarkable examples include the value of ACE inhibitors in heart failure, coronary disease, diabetes mellitus, and proteinuric kidney diseases; ARBs and ACE inhibitors in diabetic nephropathy; ARBs in LVH; β-blockers after myocardial infarction; and combination of ACE inhibitors and thiazides following a stroke. The second column in Table 20.6 presents a summary of these comorbidities and drugs that deserve specific consideration in each case. In these cases, the first choice of antihypertensive agent should be driven by the indication, rather than by general clinical trial results as described previously for the "uncomplicated" patient.

Several other comments apply to drug choice. In some patients, the comorbid condition is not one that alters cardiovascular risk, but may be important enough as to affect choice, either by avoiding or preferring specific agents. For example, patients with reactive airways disease (asthma) should not receive β-blockers, especially those that are not cardioselective, although cardioselective β-blockers are quite safe in stable patients with chronic obstructive pulmonary disease. Patients with diabetes mellitus should have their glucose control monitored more closely when placed on a diuretic. Additionally, because the identification of hypoglycemic symptoms is dependent on adrenergic hyperactivity (tachycardia, diaphoresis, tremors), use of a β-blocker may mask hypoglycemia, and patients and their families should be advised about this potential risk. Gout can be exacerbated by therapy with any type of diuretic. Finally, diuretics and β-blockers may have mild adverse effects on the lipid profile, which should be monitored. Some agents may improve other diseases, such as the favorable effects of α-blockers on prostate hypertrophy; the prophylactic effects of nonselective β-blockers and verapamil on migraines; decrease in vasospasm in Raynaud disease by calcium channel blockers; improvement of autonomic diarrhea by clonidine; or the prevention of calcium-containing stones and improvement in bone mineral density by thiazide diuretics.

KEY POINTS

Drug Therapy

1. Drug therapy is required in a large majority of patients with HTN.
2. Target BP values are less than 140/90 mmHg for most patients.
3. Thiazide-type diuretics, ACE inhibitors, ARBS, and CCBs are all reasonable options for initial therapy of patients with uncomplicated HTN.
4. Comorbid conditions strongly affect drug choice. When present, conditions such as diabetes mellitus, coronary disease, heart failure, LVH, kidney disease, and stroke dictate preferred drug choices.
5. Only 40% of patients achieve BP targets on a single agent. Thus, effective combination therapy is an essential part of antihypertensive drug treatment.

ORGANIZATION OF THE TREATMENT OF HYPERTENSION

Putting it All Together

HTN is a condition that usually demands lifetime therapy. It is most often asymptomatic, thus the clinician needs to work hard with the patient in providing a good understanding of why treatment is needed. It is essential to spend time, explain the clinical consequences of long-standing HTN, and use techniques that are appropriate to the level of education of the patient. The importance of lifestyle changes needs to be emphasized to all patients. Ideally, patients should meet with a dietician to learn about the practical aspects of implementing the DASH diet. Drug therapy should focus not only on the directives on drug choice described above, but also on cost, which is such an important limitation to therapy in uninsured or partly insured patients; using generic drugs may help achieving this goal. To improve adherence to treatment, the use of long-acting drugs with single daily dosing is the best alternative. In addition, patients should be warned of common side effects of therapy so that timely communication can occur in order to minimize patient discomfort and risk. Lastly, choosing drugs with favorable side-effect profiles is essential in improving adherence: HTN is not symptomatic, treatment should not be symptomatic either!

After therapy is commenced, patients should be seen every 2 to 4 weeks until the target BP is achieved. There is

clear evidence that "clinician inactivity" is a common factor in precluding the achievement of target BP values, and we should strive to be proactive in making adjustments in therapy whenever BP is not at target. These changes should consist of either an increase in dose of 1 agent or the addition of another agent. Once at target, it is reasonable to see patients twice a year to review persistence of control, adherence, and tolerance to therapy and to screen for the development of complications.

HYPERTENSIVE URGENCIES AND EMERGENCIES

Whereas most patients with HTN have only mild-to-moderate elevations in BP, and few succumb to the dreaded cardiovascular complications of uncontrolled BP, a small number of patients have acute elevations of BP that demand immediate intervention. These acute events include hypertensive urgencies and emergencies. *Hypertensive urgencies* are those clinical situations in which the BP is severely high (arbitrarily defined here as >180/120 mmHg) in the absence of end-organ dysfunction. If end-organ dysfunction is present, the term *hypertensive emergency* is applied, and emergency therapy is required to limit end-organ damage. Examples of acute end-organ dysfunction include the syndrome of accelerated/malignant HTN, hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction, unstable coronary syndrome, acute heart failure, aortic dissection, and eclampsia. Severe HTN in the immediate postoperative period of major cardiac or aortic surgery, or perioperative HTN in patients with an untreated pheochromocytoma should also be faced as hypertensive emergencies.

In hypertensive urgencies, patients often present without symptoms or with nonspecific symptoms such as headaches, epistaxis, dyspnea, atypical chest pain, palpitations or anxiety. It is important to assure that BP reduction is not brisk, especially in older patients, who may develop an acute ischemic event because of excessive BP reduction. It is our preference to use long-acting drugs to treat acute elevations of BP that are asymptomatic. If the patient is undergoing chronic therapy, we usually resume their previous agent, giving them a dose under our observation. We allow the patient to go home after the patient's BP is safely under 180/110 mmHg, and we see the patient in follow-up in 2 to 7 days. For the previously untreated patients, our practice is to treat them with a short-acting drug (see below) while starting them on a long-acting agent. Patients who are symptomatic deserve the use of faster-acting agents to alleviate symptoms. Many agents were studied with similar results and recommendations were mostly based on opinion and personal preference. Our preference is to use oral clonidine (0.1 mg every 30 minutes up to 3 doses) or oral labetalol (200 mg every 30 minutes up to 600 mg). Short-acting nifedipine, once the most commonly used agent, should be avoided because of its unpredictable, often large reductions in BP that are associated with acute ischemic strokes and coronary events. These patients are best managed in an emergency room or urgent care setting. If improved, they can be discharged on a long-acting drug with early follow-up as described above.

The management of hypertensive emergencies demands placing the patient in an intensive care unit (ICU) setting and treatment should consist of an intravenous agent. Intraarterial continuous BP monitoring is indicated in most patients, particularly in those in whom very tight BP titration is needed, such as patients with aortic dissection, hypertensive encephalopathy, cerebral hemorrhage, or in the postoperative period of cardiovascular procedures. The choice of agent is based on the clinical condition and personal preference. Table 20.7 summarizes drug choices, dose ranges, and key clinical concerns for the most commonly used drugs. Sodium nitroprusside has a long-standing safety record and is our initial choice in most situations, with the exception of patients with increased intracerebral pressure (preferred agent is labetalol), eclampsia (delivery, hydralazine, magnesium sulfate), or acute coronary syndromes (nitroglycerin, β-blockers). In aortic dissection, it is paramount to decrease the heart rate as well as BP, thus, the combination of a β-blocker (metoprolol or esmolol) with nitroprusside is the standard approach.

In tailoring the treatment of hypertensive emergencies, we must understand the importance of autoregulation of blood flow to target organs, especially the brain. The presence of long-standing HTN leads to functional adjustments to blood flow that protect the organ from hypertensive damage. If BP is decreased excessively, organ hypoperfusion may occur despite "normal" systemic BP. Therefore, the goal of therapy in most circumstances is to lower mean arterial pressure by no more than approximately 25% in the first hour of intervention. This is usually well tolerated, and BP can then be further reduced to levels of 160 to 180/100 to 110 mmHg in the ensuing 4 to 6 hours. Normal levels can be safely reached in 24 to

TABLE 20-7. Drugs Commonly Used in the Treatment of Hypertensive Emergencies

	DOSE RANGE	INDICATIONS	CAUTIONS	COMMENTS
Continuous Infusions				
Sodium nitroprusside	0.25 to 10 µg/kg/min IV drip	Most emergencies	Impaired renal function (thiocyanate and cyanide intoxication), high intracranial pressure	Rapid onset and extinction (1 to 2 minutes) of action
Labetalol	20- to 80-mg IV boluses every 10 minutes or 0.5 to 2 mg/min IV drip	Most emergencies Excellent choice in increased intracranial pressure	Heart failure, bradycardia/heart block	Rapid onset but prolonged duration of action (3 to 6 hours)
Esmolol	250 to 500 µg/kg bolus followed by 50 to 100 µg/kg/min IV drip	Aortic dissection (with nitroprusside), perioperative HTN	Heart failure, bradycardia/heart block	Rapid onset and extinction (10 minutes) of action
Fenoldopam	0.1 to 0.3 µg/kg/min IV drip	Most emergencies	Glaucoma	Rapid onset, but extinction may take up to 30 minutes; expensive
Nitroglycerin	5 to 100 µg/min IV drip	Acute coronary syndromes, heart failure	Right ventricular infarction (severe hypotension)	Rapid onset and extinction; tolerance with prolonged use
Nicardipine	5 to 15 mg/h IV drip	Perioperative HTN, stroke, acute coronary syndromes	Slower titration in patients with impaired renal function	Duration of action 1 to 4 hours
Clevidipine	1 to 16 mg/h IV drip	Perioperative hypertension	May increase triglycerides (lipid emulsion); cannot be used in patients allergic to soy or eggs	Rapid onset (2 to 4 minutes) and extinction (5 to 15 minutes) of action
Bolus Dosing				
Hydralazine	10 to 20 mg IV every 15 to 20 minutes, then every 3 to 4 hours	Eclampsia	May worsen coronary ischemia (*steal*)	Duration of action <4 hours
Enalaprilat	1.25 to 5 mg IV every 6 hours	Acute heart failure	Acute kidney injury, acute myocardial infarction	Duration of action 6 to 12 hours
Metoprolol	5 to 10 mg IV every 15 to 30 minutes, then every 4 to 6 hours	Acute coronary syndromes, perioperative HTN	Heart failure, bradycardia/heart block	Duration of action 4 to 6 hours

Abbreviation: IV, intravenously.

48 hours. Similar to hypertensive urgencies, long-acting agents are initiated immediately to shorten the need for intravenous therapy and to provide a bridge to chronic therapy. There are 2 important exceptions to this general rule: in patients with aortic dissection, the lowest BP tolerated should be aggressively sought in order to limit shear stress and further dissection. Conversely, patients with acute stroke call for more conservative treatment, as acute decreases in mean arterial pressure by more than 15% are associated with worsening cerebral ischemia. Thus, current guidelines for ischemic strokes recommend a 10% BP reduction in patients with BP greater than 220/120 mmHg. For patients receiving antihypertensive agents prior to admission in whom the BP is below this value, the drugs should be discontinued for 1 week. Only then can normalization of BP be attempted. In hemorrhagic stroke, intracranial pressure monitoring should be used in patients with impaired sensorium (eg, Glasgow Coma Scale score <9), and careful therapy should take place for patients with BP greater than 160/90 mmHg, aimed at maintaining the cerebral perfusion pressure always above 60 mmHg.

KEY POINTS

Hypertensive Urgencies and Emergencies

1. Hypertensive urgencies are situations in which BP is severely elevated (>180/120 mmHg) without evidence of end-organ dysfunction. Treatment should be started immediately with oral drugs and early outpatient follow-up.
2. Hypertensive emergencies are accompanied by end-organ dysfunction and demand immediate BP lowering with intravenous therapy in the intensive care unit.
3. Nitroprusside is safe and effective in most hypertensive emergencies.
4. BP lowering must take into account the change in cerebral (and other organs) autoregulation. BP should be lowered by 25% in the first hour, except in the setting of stroke where the goal is more conservative (10%).

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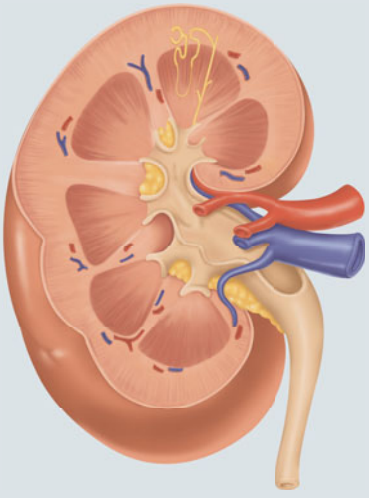

CHAPTER 21

Secondary Causes of Hypertension

• *Sergio F.F. Santos and Aldo J. Peixoto*

Recommended Time to Complete: 1 Day

Guiding Questions

1. What is the prevalence of secondary hypertension?
2. What are the most common causes of secondary hypertension?
3. When should secondary causes of hypertension be investigated?
4. Which drugs/chemicals can cause hypertension and/or impair the effect of antihypertensive agents?
5. What are the clinical findings in a hypertensive patient with obstructive sleep apnea (OSA)?
6. When should renovascular disease be suspected?
7. How should renovascular disease be investigated?
8. Who benefits from interventions in renovascular disease?
9. What are the screening tests used to investigate primary aldosteronism?
10. What are the metabolic tests used for the diagnosis of pheochromocytoma?
11. What are the characteristics of hypertension in thyroid and parathyroid diseases?
12. What is the differential diagnosis of hypertension in pregnancy?
13. What are the major genetic causes of secondary hypertension?

GENERAL APPROACH TO SECONDARY HYPERTENSION

Secondary hypertension (HTN) is defined as HTN that has a known etiology and is potentially reversible by specific treatment. The prevalence of secondary HTN is approximately 5% to 10% of all hypertensive patients, but several factors resulted in a recent increase in these estimates. More aggressive screening and better laboratory methods led to a higher rate of identification of certain conditions, especially primary aldosteronism; advances in the knowledge of mechanisms involved in the pathogenesis of HTN uncovered new causes of secondary HTN; and changes in the characteristics of the hypertensive population increased the prevalence of secondary HTN if the above definition of "potentially

modifiable" HTN is followed. For example, obesity is now "epidemic," is associated with HTN, and its successful treatment improves or normalizes blood pressure (BP). Likewise, essential HTN is a common cause of chronic kidney disease (CKD), and thus both essential and secondary HTN may coexist in the same patient as CKD progresses. The same is true for the aging population where the prevalence of HTN and macrovascular atherosclerotic disease increase concomitantly; making it more likely that renal artery stenosis complicates the evolution of essential HTN. Lastly, secondary causes of HTN are frequently responsible for cases of resistant HTN. It is estimated that up to one-third of patients referred to specialty clinics for the evaluation of resistant HTN have secondary HTN; consequently, a very detailed screening for secondary HTN is imperative in the assessment of these patients. Other clinical circumstances (Table 21.1) also point to the need of more aggressive evaluation for secondary causes of HTN.

The initial evaluation of any hypertensive patient must include enough elements to provide an adequate screen for secondary causes. After all, it is in that initial encounter that the clinician has the unique opportunity of identifying a potentially curable process. The history should include specific inquiry for symptoms of diseases that may cause HTN (Table 21.2), as well as for the use of substances that elevate BP. The physical examination should include a search for differences in BP and pulses between the upper and lower extremities; an evaluation of peripheral vascular disease (auscultation for carotid, abdominal, and femoral bruits, and palpation of the abdomen for aortic aneurysms); palpation of the thyroid gland; and examination of the abdomen for enlarged polycystic kidneys or masses.

TABLE 21-1. Factors Associated with Secondary Hypertension

Hypertension resistant to appropriate therapy
Worsening of previously controlled hypertension
Onset of hypertension in patients younger than 20 or older than 50 years
"Malignant" or accelerated hypertension
No family history of hypertension

TABLE 21-2. Clinical and Laboratory Clues for Relevant Secondary Causes of Hypertension

	SYMPTOMS AND SIGNS	BASIC LABORATORY TESTS
Obstructive sleep apnea	Snoring, obesity, large neck circumference, daytime fatigue	Nonspecific
Renal parenchymal disease	Edema, pallor, hematuria	Elevated creatinine, hematuria, proteinuria, anemia
Renovascular disease	Diffuse atherosclerotic disease, abdominal bruits, unexplained heart failure	Elevated creatinine, hypokalemia
Pregnancy	Pregnancy related	Proteinuria in preeclampsia
Primary aldosteronism	Muscle weakness, cramps	Hypokalemia, hypernatremia, metabolic alkalosis
Pheochromocytoma	Headache, palpitations, diaphoresis	Nonspecific
Cushing syndrome	Truncal obesity, moon facies, purple skin striae	Hyperglycemia, hypokalemia
Thyroid disease	Hyperkinetic or hypokinetic state, enlarged thyroid, thyroid nodules	Nonspecific screening tests, abnormal thyroid function tests
Primary hyperparathyroidism	Constipation, kidney stones	Hypercalcemia with high parathyroid hormone
Coarctation of the aorta	Hypertension in the arms and low BP in the legs	Nonspecific
Drug-induced or drug-related	Nonspecific	Nonspecific

Laboratory tests must include an evaluation of renal function (creatinine and urinalysis), blood glucose, hemoglobin, serum potassium, and calcium. These simple and inexpensive procedures will be enough to raise the suspicion of secondary (identifiable) causes of HTN in most patients. The paragraphs that follow present a more detailed discussion of the most relevant causes of secondary HTN.

KEY POINTS

General Approach to Secondary Hypertension

1. Secondary causes of HTN have been identified more frequently.
2. Primary and secondary HTN may coexist in the same patient.
3. Clinical and laboratory findings in a basic screening in newly diagnosed HTN may suggest secondary causes.

DRUGS AND CHEMICALS

Many chemical substances, used for a variety of reasons, can cause HTN or lessen the effect of antihypertensive agents (Table 21.3). These include prescription and nonprescription medications, as well as abused substances. It is important to remind clinicians to actively inquire about these chemicals when obtaining the history from a hypertensive patient.

Oral Contraceptives

Oral contraceptive drugs commonly raise BP. These effects, however, are mild. No more than 10% to 15% of patients using oral contraceptives fulfill the diagnosis of HTN. The pathophysiology of BP elevation with oral contraceptive use is unknown. The incidence of HTN has decreased with the use of modern, low-estrogen formulations in combination with new synthetic progestogens. It is recommended that every woman taking oral contraceptives have their BP measured regularly. Most cases of HTN related to oral contraceptives are cured with drug withdrawal, although it may take several months until BP normalizes. Therefore, if HTN is diagnosed in a patient who uses oral contraceptives, the pill is discontinued and another type of contraception recommended.

TABLE 21-3. Commonly Used Substances that Can Cause Hypertension and/or Mitigate the Effects of Antihypertensive Drugs

Oral contraceptives
Nonsteroidal antiinflammatory drugs (NSAIDs, selective, and nonselective)
Sympathomimetic/sympathoactivating agents
Pseudoephedrine, phenylpropanolamine
Phentermine
Yohimbine
Cocaine, amphetamines (prescription or illegal)
Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)
Monoamine oxidase inhibitors (MAOIs)
Cyclosporine and tacrolimus
Erythropoietin
Corticosteroids
Anti-vascular endothelial growth factor agents (bevacizumab, tyrosine kinase inhibitors)
Licorice
Ethanol

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are the most commonly prescribed class of drugs in the United States. Because their use is common in the elderly, the population at greatest risk for HTN, it is important to review the effects of these drugs on BP. Decreased prostaglandin synthesis results in decreased renal blood flow and sodium retention, thereby contributing to HTN. Available data demonstrate that NSAIDs cause modest increases in BP, but this effect is primarily noticeable in patients with underlying HTN. Of greater relevance is that NSAIDs antagonize the effects of most antihypertensive drugs, with the exception of calcium channel blockers. Most NSAIDs have similar effects on BP, particularly nonselective agents. Selective cyclooxygenase-2 (COX-2) inhibitors are also associated with BP elevation. There are some nutraceuticals with COX inhibitory actions, such as cherry extract, willow bark, and devil's claw. Therefore, similar BP effects could be observed in patients who consume large amounts of these products.

Substances Enhancing Sympathetic Activity

Remedies to relieve cold symptoms (oral or nasal sprays) often contain sympathomimetic amines such as pseudoephedrine and phenylpropanolamine. All such agents are associated with BP elevation. Other medications containing sympathomimetic activity include amphetamines used in the treatment of attention-deficit hyperactivity disorder or depression (dextroamphetamine, methylphenidate), and sibutramine, which is used for the treatment of obesity. Ephedra was a common component of nutritional supplements and nonprescription weight-loss preparations until its ban from the U.S. market in 2004. There are some nutraceuticals currently available on the market that can result in increased sympathomimetic activity and elevate BP, including bitter orange and Siberian ginseng. The designer drug known as "bath salts" contains several chemicals (methylenedioxopyrrovalerone, mephedrone) that cause HTN and associated end-organ injury.

Other drugs may enhance sympathetic nervous system tone and increase BP without direct sympathomimetic activity. These include several antidepressants such as selective serotonin reuptake inhibitors (SSRIs; eg, fluoxetine, paroxetine, sertraline, citalopram, escitalopram), serotonin-norepinephrine reuptake inhibitors (SNRIs; eg, venlafaxine, desvenlafaxine, duloxetine), the most commonly prescribed antidepressant agents, and monoamine oxidase inhibitors (MAOIs; eg, phenelzine and tranylcypromine). An important nonprescription substance is yohimbine, which has resurged in the market of supplements for improved male sexual performance. Finally, cocaine and ecstasy (methylenedioxymethamphetamine [MDMA]) are 2 illicit drugs that activate the sympathetic nervous system and may precipitate hypertensive crises.

Licorice

Licorice is a bush native to southern Europe and Asia, the roots of which are sweeter than sugar and are used in candies and tobacco flavoring. In this country, the most common source of licorice extract used to be nutritional "energy" supplements, although more recently many of these preparations are "deglycyrrhized," that is, they are devoid of the hypertensogenic ingredient of licorice (glycyrrhizic acid). Glycyrrhizic acid inhibits 11β-hydroxysteroid dehydrogenase, the enzyme that converts cortisol to cortisone, thus increasing the levels of cortisol available to activate the mineralocorticoid receptor. It causes a form of pseudohyperaldosteronism with HTN, sodium retention, and potassium wasting, similar to the syndrome of apparent mineralocorticoid excess (AME). HTN generally reverses with stopping its ingestion.

Cyclosporine and Tacrolimus

Cyclosporine and tacrolimus are calcineurin inhibitor immunosuppressive agents commonly used in transplantation and in the treatment of certain immune-mediated diseases. In kidney transplantation, the prevalence of HTN increased from 50% to 80% after the introduction of cyclosporine. Calcineurin inhibitors induce functional and morphologic changes in kidneys that are directly related to the pathogenesis of HTN. They produce renal vasoconstriction and decreased glomerular filtration rate (GFR) that impair sodium excretion, and long-term use may cause interstitial fibrosis. Nephrotoxicity, however, is not the only mechanism for calcineurin inhibitor-related HTN. Activation of the sympathetic nervous system, impaired nitric oxide production, increased endothelin release, and increased expression of the thiazide-sensitive NaCl cotransporter are other relevant factors. Although some publications suggest that calcium channel blockers are superior in treatment of calcineurin inhibitor HTN, any antihypertensive agent can be used, and it is possible that thiazide diuretics are particularly effective and underused. Importantly, previous concerns about concomitant angiotensin-converting enzyme (ACE) inhibitor use are unfounded, and these drugs can be safely used to treat patients with HTN on a calcineurin inhibitor.

Erythropoietin

Recombinant human erythropoietin (EPO) is used for treatment of anemia in CKD, human immunodeficiency virus (HIV), postchemotherapy, and in certain hematologic disorders. Most patients have a mild BP increase when they initiate EPO therapy, and frank HTN can become manifest or made worse in approximately 30%. The BP rise is attributed to increased blood viscosity and direct EPO effects on vascular resistance, where it causes increased cytosolic calcium, endothelin1 concentration, and resistance to nitric oxide. Because BP elevations are usually mild and benefits of EPO outweigh this side effect in most patients, routine measures to control BP should take place while continuing EPO therapy.

Corticosteroids

Corticosteroids used either for antiinflammatory or immunosuppressive purposes may cause HTN. The proposed mechanism is the same as described for Cushing syndrome (see below), and usually occurs with high-dose therapy or long-term use.

Vascular Endothelial Growth Factor Antagonists

Antagonists of the vascular endothelial growth factor (VEGF) are commonly used in the treatment of several malignancies. These drugs can be either direct antagonists, such as the monoclonal antibodies bevacizumab, or can be tyrosine kinase antagonists that block the kinase activity of the VEGF receptors (eg, sorafenib, sunitinib). Overall, these agents are associated with a 20% to 25% incidence of HTN, which may be severe in as many as 8% of patients. The HTN is mediated by endothelial dysfunction, increased oxidative stress, microvascular rarefaction, and arterial wall injury as a result of loss of vasa vasorum, and typically resolves with removal of the drug. When continued therapy with these agents is needed, HTN can be treated with any drug class. Recent reports have also linked intravitreal administration of VEGF antagonists with endothelial damage and HTN.

KEY POINTS

Drugs and Chemicals

1. A large number of substances, including prescription and nonprescription items, may cause HTN.
2. The mechanism of HTN depends on the substance used.

OBSTRUCTIVE SLEEP APNEA

A good example of "new" causes of secondary HTN is OSA. OSA is a frequent sleep disorder (20% of adults have at least mild OSA), characterized by partial or complete closure of the upper airway during sleep. BP increases not only during apneic episodes, but OSA is also independently linked to daytime HTN. The odds of daytime HTN increase with the number of apneic episodes and the magnitude of nocturnal O_2 desaturation. In patients with drug-resistant HTN, the prevalence of OSA is in the range of 60%.

Pathogenesis

Hypoxemia, CO_2 retention, acute changes in intrathoracic pressure, and arousal from sleep trigger neural and circulatory responses such as sympathetic activation and increased levels of endothelin-1. Other known risk factors for cardiovascular disease, such as oxidative stress, chronic inflammation, hypercoagulability, and aldosterone excess, also coexist in OSA, thus amplifying the cardiovascular risk of these patients.

Diagnosis

Patients with OSA are habitual snorers, have increased neck circumference, are uniformly overweight, and have daytime somnolence. In a hypertensive patient, knowledge of the neck circumference (>17 inches) and 2 features of the medical history (presence of habitual snoring or witnessed nocturnal choking or gasping) can predict polysomnographic abnormalities well and select patients for further investigation. Polysomnography is the best procedure to evaluate OSA, as it provides not only the diagnosis but also information on the severity of the problem. The number of obstructive events (apneas or hypopneas) per hour is commonly used to quantify OSA: mild = 5 to 15 events per hour; moderate = 15 to 30 events per hour; severe = more than 30 events per hour. Patients with more than 15 events per hour are more commonly hypertensive and are more refractory to antihypertensive drug therapy.

Treatment

Weight reduction is essential in obese patients. Avoiding the supine position during sleep also reduces OSA episodes (a tennis ball sewn to the back of pajamas is a useful tool). Nasal continuous positive airway pressure (CPAP) is the best available treatment for OSA. CPAP forces air down the nose and throat under positive pressure, thus keeping the upper airways open, eliminating apneas. Effective CPAP treatment significantly reduces BP. A Cochrane metaanalysis reported an average BP reduction of 7.2/3.0 mmHg. An important caveat is that these estimates are based on studies that also include patients without HTN, thus minimizing the effect. The BP-lowering effect is greater among patients with true drug-resistant HTN and patients who are more adherent with CPAP. The issue of adherence to CPAP is important, as it prevents long-term use in a substantial subgroup of patients. Drug use is usually needed

in these patients. The best available data favor the use of β-blockers, α-blockers, and spironolactone (with or without concomitant use of a loop diuretic).

KEY POINTS

Obstructive Sleep Apnea

1. OSA is a frequent sleep disorder that causes HTN and is associated with other cardiovascular risk factors.
2. Overweight, large neck circumference, snoring or witnessed nocturnal choking or gasping, and daytime somnolence are strong indicators of OSA.
3. Nasal CPAP abolishes OSA and improves BP.
4. Antihypertensive medications are often required to control BP.

RENAL PARENCHYMAL DISEASE

Renal parenchymal disease is the most frequent cause of secondary HTN (5% of all HTN cases). Most patients (80%) with progressive kidney diseases develop HTN, and the prevalence of HTN increases with worsening renal function. Unilateral parenchymal renal disease (cysts, tumors, reflux, hydronephrosis) may infrequently cause HTN.

Pathogenesis

The primary mechanism of HTN in bilateral kidney disease is the impaired fluid and sodium balance, leading to increased plasma volume. A compensatory increase in BP occurs to augment sodium and water excretion (see Chapter 20). Furthermore, complex mechanisms involving activation of the sympathetic nervous system, increased intracellular calcium, inappropriate stimulation of the renin-angiotensin-aldosterone system (RAAS), altered balance of endothelium-derived vasoconstrictor and vasodilating factors (especially endothelin-1 and nitric oxide, respectively), and increased arterial stiffness are also operative in these patients. In unilateral renal disease, activation of the RAAS is often the cause of HTN. The RAAS is also involved in HTN associated with unilateral reflux nephropathy and unilateral hydronephrosis. The presence of proteinuria is associated with worse BP control, partly as a result of induction of sodium avidity, largely through direct activation of the epithelial sodium channel (ENaC).

Diagnosis

Edema, hematuria, and/or foamy urine may be present. Physical examination may disclose abdominal masses representing polycystic kidneys, hydronephrosis, or renal tumors. More importantly, the diagnosis of parenchymal kidney disease in made by laboratory evaluation with elevated concentrations of blood urea nitrogen (BUN) and creatinine and/or abnormalities in the urinalysis (hematuria, proteinuria). Because BUN and creatinine concentration may underestimate the degree of renal dysfunction, formulas that estimate GFR are used to assess renal function more accurately (see Chapter 16). In adults, the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation, Modification of Diet in Renal Disease (MDRD) equation, or the Cockcroft-Gault equation are most often used. They may be complemented by a 24-hour urine collection and the determination of the endogenous creatinine clearance. A more detailed diagnostic evaluation of kidney disease is found in Chapter 16.

Treatment

HTN is the most important factor in the progression of most parenchymal kidney diseases. A decrease in BP is associated with a fall in the rate of loss of glomerular function. Furthermore, BP control to less than 125/75 mmHg leads to substantial protection of renal function in patients with proteinuria. The threshold level of proteinuria that benefits from this low BP target is not certain. It is clear that patients with greater than 3 g proteinuria per day benefit the most. The same is likely true for those with proteinuria above 1 g per day, although lower levels of protein excretion experience less impressive results from aggressive BP lowering. BP targets for patients with nonproteinuric kidney diseases are not well established. The available evidence supports BP lowering to less than 140/90 mmHg, but there is no evidence that lower targets provide any further benefit.

Drugs that act on the RAAS, ACE inhibitors, and angiotensin II receptor blockers (ARBs), are more effective than other agents in renal protection and proteinuria reduction at the same level of BP control. Therefore, patients with CKD should receive an ACE inhibitor or an ARB as the first pharmacologic option for the treatment of HTN. Close follow-up of renal function and potassium must take place after

initiation of any of these drugs. We routinely obtain serum chemistries 1 week after initiation and after each dose titration. It is well established that declines in GFR in the 20% to 30% range can be tolerated, as long as it stabilizes on repeat testing within 30 days. Hyperkalemia in the 5.5 mEq/L range is safe and acceptable. Control of hyperkalemia can be achieved with dietary counseling and diuretics.

To reach low BP targets, a combination of 2 to 3 drugs is often needed. In this decision-making process, the increased cardiovascular risk represented by kidney disease and the frequent cardiovascular comorbidity afflicting these patients must be accounted for. Therefore, a diuretic may be indicated because of its cardiovascular protective effects or as part of the management of volume overload or heart failure. β-Blockers are needed for coronary disease or heart failure. Calcium channel blockers may be helpful in coronary disease, and nondihydropyridine calcium channel blockers (verapamil and diltiazem) have antiproteinuric properties that are additive to ACE inhibitors or ARBs. Combining an ACE inhibitor and ARB may further decrease proteinuria, and may decrease the progression of kidney disease in nondiabetic patients. In the absence of any compelling reason to choose one class over another, the first agent to be added to an ACE inhibitor or ARB is either a calcium channel blocker or a diuretic. A recent trial observed better cardiovascular outcomes when an ACE inhibitor (benazepril) was combined with a calcium channel blocker (amlodipine) than with hydrochlorothiazide. On the other hand, a diuretic is often essential to achieve BP targets in patients with kidney disease. The choice of diuretic type is dependent on GFR: thiazide diuretics can be effectively used with a GFR greater than 30 to 50 mL/min; when below this range, a loop diuretic is usually required, although our anecdotal experience with the thiazide-type diuretic metolazone is quite positive in CKD. Third-line drugs are usually a calcium channel blocker or a β-blocker. The mineralocorticoid receptor antagonists (spironolactone, eplerenone) are effective agents to lower BP and control volume overload; however, their use in combination with an ACE inhibitor or ARB is associated with significant hyperkalemia, thus requiring very close monitoring. The renin inhibitor aliskiren provides additional antiproteinuric and BP-lowering effects when added to an ARB. However, a recent trial demonstrated worse cardiovascular and renal outcomes with this agent. In our opinion, renin inhibitors do not have a role in HTN management at this point.

In the unusual cases of unilateral disease with HTN, nephrectomy is indicated for HTN associated with unilateral renal tumors. In other unilateral parenchymal diseases, nephrectomy must be evaluated carefully, especially in kidneys with residual function. Surgical results are variable and often poor. Most patients can be managed successfully with drug therapy.

KEY POINTS

Renal Parenchymal Disease

1. Strict BP control is recommended for patients with CKD. Patients with proteinuria greater than 1 g/day should be lowered to less than 125/75 mmHg. Those without proteinuria should be decreased to less than 140/90 mmHg.
2. ACE inhibitors and ARBs are preferred for the treatment of HTN in chronic renal disease.
3. The increased cardiovascular risk of CKD must be taken into account when antihypertensive treatment is chosen.

RENOVASCULAR DISEASE

The prevalence of renovascular disease in the hypertensive population is approximately 1% to 5%. Increases in the aging population, however, may lead to an increment in the numbers of renovascular HTN caused by atherosclerosis. The main types of renovascular HTN are atherosclerosis (90%) and fibromuscular dysplasia (FMD) (10%).

Pathogenesis

Two classical animal models demonstrate the role of the RAAS in the pathogenesis of HTN after partial interruption of renal blood flow. In the Goldblatt I model (1 kidney, 1 clip) there is unilateral arterial stenosis and nephrectomy of the contralateral kidney. In the Goldblatt II model (2 kidneys, 1 clip), unilateral arterial stenosis is created, while the other kidney remains intact. Both models demonstrate that the RAAS is activated after constriction of the renal artery resulting in increased BP. In the Goldblatt I model, blood volume expands and there is a "reset" of the RAAS (angiotensin II levels often return

to normal), making chronic HTN primarily dependent on volume. In the Goldblatt II model the nonstenotic kidney promotes salt excretion (pressure natriuresis) and the RAAS remains activated in the underperfused kidney. Thus, chronic HTN is directly related to angiotensin II. In both models, natriuresis induced by diuretics reactivates the RAAS, even if BP is stable at high levels. Goldblatt I is the animal model for human bilateral renal artery stenosis (or unilateral stenosis in a patient with a single kidney). Goldblatt II is the animal model for human unilateral renal artery stenosis.

More recently, a porcine model of renal artery stenosis induced by coiling of the artery has generated important insights into human atherosclerotic disease. Experiments using this model demonstrate that restriction of blood flow to the kidney, when coupled to a proatherosclerotic environment (through a high fat and cholesterol diet), induces a proinflammatory and profibrotic milieu that results in microvascular rarefaction and extensive renal interstitial fibrosis. It is thus not surprising that, once fibrosis is established, restoration of flow does not result in significant improvements in renal function (or BP), as is discussed below.

The cause of FMD is unknown; smoking is a prominent risk factor. FMD has several different subtypes and may affect the arterial intima, media, or adventitia. It occurs predominantly in patients younger than age 30 years and 75% are females. Atherosclerotic renovascular disease increases with age, and affects predominantly males, patients with diabetes mellitus and/or preexisting HTN, individuals who have other vascular disease, and smokers.

Diagnosis

Some clinical features may suggest that renovascular disease is the cause of HTN. Some of these features are those clues to the presence of secondary causes of HTN (see Table 21.1). Others are unexplained azotemia; hypokalemia (caused by secondary hyperaldosteronism in unilateral stenosis); worsening of renal function with use of ACE inhibitors or ARBs (in bilateral disease, unilateral stenosis in a single kidney, or unilateral stenosis accompanied by underlying parenchymal disease); unilateral small kidney; abdominal and/or flank bruits; generalized atherosclerosis; and unexplained pulmonary edema.

Once renovascular disease is suspected, several techniques are used to confirm the diagnosis. Renal arteriography is the gold standard for the diagnosis of renovascular disease, but it is invasive and has risks associated with it, most importantly contrast nephrotoxicity and atheroembolic disease. Therefore, noninvasive techniques are the most commonly used options in the screening of renal artery stenosis. Of the available techniques, 3 can be used as effective screening tools: computed tomography angiography (CTA), magnetic resonance angiography (MRA), and duplex ultrasonography.

MRA (especially when the images are enhanced by gadolinium) and CTA have the highest accuracy (specificity and sensitivity uniformly >90%) and are the most widely used noninvasive methods to detect renovascular disease. MRA is readily available in this country, has excellent sensitivity and specificity, and easy interpretation. Its major limitations are the need for prolonged breathholding to limit image artifacts, and the risk of gadolinium-induced nephrogenic systemic fibrosis in patients with advanced CKD (estimated GFR <15 to 30 mL/min). Newer magnetic resonance imaging (MRI) machines allow for protocols that provide adequate renal artery imaging without need for gadolinium, so this may soon no longer be a problem. CTA provides fantastic resolution and good detail of accessory vessels. It has excellent sensitivity and specificity, but uses a large volume (~150 mL) of iodinated contrast, making it an undesirable option in patients with underlying kidney disease (estimated GFR <60 mL/min). Duplex ultrasonography shows the contour of the renal arteries through its 2-dimensional images and grades the blood flow velocity at different segments of each renal artery via Doppler sampling. The presence of renal artery stenosis is detected by an increase in flow velocity at the stenotic segments. This velocity is compared with the aortic flow velocity at the level of the renal arteries. A renal-to-aortic ratio of the peak systolic velocity greater than 3.5 is associated with the presence of a stenosis greater than 60% on angiography. Duplex ultrasound is easily available, and has good sensitivity and specificity. It is, however, strongly dependent on operator experience, is limited in obese patients, and is not suitable for accessory vessels. Because of these limitations, this test has not fared as well as MRA and CTA in comparative studies. In our opinion, this modality should be used only in places where the radiology service is committed to spending the time and effort required for the acquisition of optimal images. Figure 21.1 displays representative images of renal artery stenosis.

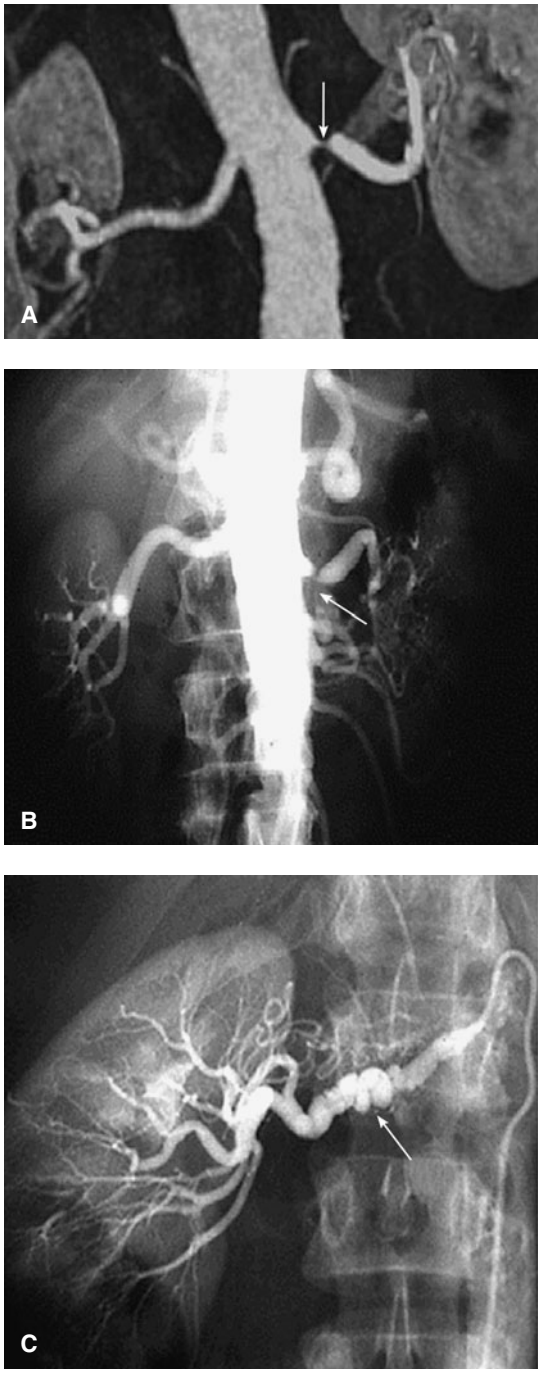

FIGURE 21-1. Representative images of renal artery stenosis. A. Contrast-enhanced MRA with proximal atherosclerotic renal artery stenosis. **B.** Digital subtraction angiography (DSA) with proximal atherosclerotic renal artery stenosis. **C.** DSA showing FMD (medial fibroplasia subtype).

Other techniques used as screening methods for renal artery stenosis include ACE-stimulated peripheral plasma renin activity and ACE-stimulated nuclear scintigraphy. Presently, none of these techniques has a role in the diagnosis of renal artery stenosis in view of their limited sensitivity and specificity, especially in patients with underlying renal dysfunction.

One of the most difficult parts of the evaluation of renal artery stenosis is to establish whether the identified anatomic lesion is physiologically significant. It is generally accepted that a lesion must occlude at least 75% of the arterial lumen to be hemodynamically significant. Measurement of the transstenotic pressure gradient during arteriography is the most consistent determinant of significance, and is considered abnormal when the systolic BP gradient (pre-poststenotic) is greater than 20 mmHg. At present, no clinical or laboratory test is precise enough to predict whether correction of the renal artery stenosis will result in improvement of BP (ie, confirm that renovascular disease translates into renovascular HTN in the individual patient). Although inadequate as screening tests, ACE-scintigrams (using technetium diethylenetriamine pentaacetic acid [DTPA] or mercaptoacetyltriglycine [MAG-3] as the radionuclide) may be useful as functional tests in patients with HTN, renal artery stenosis, and preserved renal function. These tests must be done when the patient is off an ACE inhibitor or ARB for at least 2 weeks. Patients who show lateralization in radionuclide uptake following administration of an ACE inhibitor (usually captopril) tend to have more favorable BP responses to revascularization, whereas those who do not lateralize on the scintigrams usually do not respond. It must be stressed that the literature on the use of these functional tests is not consistent, and personal preference (opinion) still guides most of this decision-making process. An important development has been the use of blood oxygen level dependent MRI (BOLD-MRI) to estimate degree of renal ischemia and renal reserve in renal artery stenosis. Exciting preliminary data indicate that this modality is able to identify viable ischemic renal parenchyma and may thus be a novel predictor of success of revascularization. This has not yet been confirmed in clinical trials. Any patient who has a positive noninvasive test and an indication for intervention (see below) should undergo a renal arteriogram. The arteriogram will provide precise anatomical information (degree of stenosis), as well as some functional data, especially the systolic pressure gradient across the stenosis.

Treatment

The only effective treatment for renal artery stenosis is revascularization to restore the normal blood flow to the kidney, either operatively or percutaneously. However, as mentioned above, renal artery stenosis is often accompanied by extensive renal parenchymal changes that are not reversible by revascularization; thus, not all patients should be revascularized. In patients with HTN and renal artery stenosis, revascularization is indicated in those who have not achieved BP control on a well-designed drug regimen and in those with progressive loss of renal function during follow-up. Patients with bilateral disease benefit more from intervention than those with unilateral renal artery stenosis. One other group found to benefit from intervention consists of patients with renal artery stenosis and recurrent pulmonary edema that cannot be explained by cardiac causes. Results from available randomized clinical trials indicate that patients with well-controlled BP and/or stable renal function do not have any demonstrable benefit from revascularization.

Percutaneous transluminal renal angioplasty (PTRA) with stenting is currently the most commonly used technique for revascularization. In patients with FMD, PTRA alone usually suffices, and is curative in up to 60% of patients. Atherosclerotic disease, which preferentially involves the more proximal segments of the renal artery, uniformly requires the deployment of a stent for optimal results. There are no long-term studies comparing PTRA alone with PTRA plus stenting, but the short-term technical results and restenosis rates are substantially better with stenting than with PTRA alone, thus making the use of stents the current standard of practice. Technical results do not guarantee clinical response, and cures are extremely rare. Nevertheless, most patients do have a decrease in BP levels and/or a decrease in number of antihypertensive drugs. Older studies comparing surgical correction with PTRA indicate that surgery is better in the treatment of bilateral renal artery stenosis, as it affords greater long-term patency. Current practice, however, reserves surgical revascularization for those cases where PTRA is unfeasible or unsuccessful because of the complexity of the lesion. This trend was generated primarily by the improved long-term patency results with the use of stents.

Best medical therapy is a viable option for patients with renal artery stenosis. ACE inhibitors are associated with fewer cardiovascular events and lower death rates in patients with renal artery stenosis, and should be an essential part of therapy. However, patients with bilateral renal artery stenosis may not tolerate these agents, in which case, revascularization is indicated. Additionally, all patients with atherosclerotic disease should be counseled about smoking cessation (if applicable) and should receive aspirin and a statin targeting low-density lipoprotein (LDL)-cholesterol levels below 100 mg/dL.

Medical therapy with antihypertensive drug combinations may achieve BP control in many cases of atherosclerotic renovascular HTN, but renal artery stenosis may progress on the diseased side or develop in the contralateral kidney despite BP control and the use of other strategies to prevent the progression of atherosclerosis. Patients who are managed medically should have their renal function monitored regularly. We also obtain renal ultrasounds every 6 to 12 months to follow changes in renal length as evidence of renal ischemic atrophy, as these changes may occur before a rise in serum creatinine concentration (or decline in estimated GFR). Patients who lose more than 1 cm over the course of 12 months are referred for revascularization.

KEY POINTS

Renovascular Disease

1. The prevalence of atherosclerotic renovascular disease has increased and must be considered in patients with resistant HTN and generalized vascular disease.
2. MRA and CTA are noninvasive methods with the best sensitivity and specificity for the diagnosis of renovascular HTN. Duplex ultrasound is often needed in patients with impaired renal function.
3. Percutaneous transluminal angioplasty with stenting is the most commonly used treatment for renovascular HTN.
4. Medical therapy may achieve BP control in renovascular HTN, but atherosclerotic lesions may progress and renal function may worsen.
5. Interventional therapy must always be considered in patients with refractory HTN, worsening renal function, unexplained congestive heart failure, and in those with bilateral renovascular disease.
6. Revascularization of renal artery stenosis is not indicated in CKD patients with stable kidney function and well-controlled BP.

PRIMARY ALDOSTERONISM

In 1955, Conn published the case of a patient with HTN and hypokalemia cured after the surgical removal of an adrenal adenoma. Since then, laboratory and imaging screening tests have greatly enhanced the identification of cases, and some studies reported an incidence of hyperaldosteronism in as many as 14% of all cases of HTN. Although such a number is likely to be an overestimate, it is clear that hyperaldosteronism is much more common than previously recognized. Furthermore, the appreciation of the toxic effects of excess aldosterone to heart and kidneys suggests that the overproduction of aldosterone is clinically important. Interest in this disease caused by autonomous hypersecretion of aldosterone has increased significantly over the past several years, largely because of the realization of its common occurrence and the observation that these patients have increased burden of all forms of cardiovascular disease.

Pathogenesis

Primary aldosteronism is caused by aldosterone-producing adenomas (APAs), bilateral idiopathic adrenal hyperplasia, unilateral hyperplasia (also called primary adrenal hyperplasia, a form of hyperplasia whose functional behavior is similar to an adenoma), aldosterone-producing adrenal carcinoma, and familial hyperaldosteronism. Excessive aldosterone synthesis causes increased renal sodium reabsorption and potassium excretion. Sodium reabsorption causes plasma volume expansion, which is the primary initiating mechanism of HTN in this disease. Chronically, the hemodynamic profile of patients with hyperaldosteronism varies, and elevated systemic vascular resistance in the absence of volume expansion is common.

The understanding of adrenal proliferation and aldosterone hyperproduction is now better understood. Somatic mutations in the gene coding for the potassium channel KCNJ5 have been demonstrated in adrenal adenomas and in patients with a rare form of hereditary adrenal hyperplasia. These mutant channels expressed in the adrenal zona glomerulosa lose their specificity for potassium and allow inward flow (ie, into the cell) of sodium, resulting in chronic cell depolarization and calcium inflow, which in turn stimulates cell proliferation and aldosterone production.

Diagnosis

Hypokalemia in a hypertensive patient is the most common clinical clue to the presence of primary aldosteronism. Normal serum potassium, however, is present in more than 50% of patients with primary aldosteronism, especially in those with adrenal hyperplasia or familial hyperaldosteronism. In patients with resistant HTN, serum potassium lower than 3.8 mEq/L is very suggestive of primary aldosteronism. Renal potassium wasting is the cause of the hypokalemia.

The plasma aldosterone (ng/dL)-to-plasma renin activity (ng/mL/h) ratio (ARR) is performed as the guiding screening test for aldosteronism (Figure 21.2). This test is performed in random conditions while the patient is on most antihypertensive agents (with the strong exception of spironolactone, eplerenone, and direct renin inhibitors), and is best obtained in a morning blood draw. The diagnosis is made when the aldosterone levels is elevated (at least 15 ng/dL) and the renin plasma activity is suppressed (less than 0.5 ng/mL/h), thus resulting in an elevated ARR. ARR values greater than 20 to 25 are suggestive of primary aldosteronism, and values greater than 60 are highly indicative of this diagnosis. Figure 21.3 lists potential problems in the interpretation of the ARR from drugs or clinical conditions that can result in false-positive or false-negative results. If the clinical suspicion is high and the patient is taking one such drug, the more prudent strategy is to remove the drug for at least 2 weeks and repeat the test.

Because it is the variation in plasma renin activity that accounts for most of the variance in the ARR, other tests are necessary to confirm excessive nonsuppressible aldosterone secretion, the hallmark of primary aldosteronism. The most commonly used confirmatory tests involve the measurement of aldosterone production under salt-loading conditions. Our preference is the oral salt-loading test, wherein 24-hour urinary aldosterone excretion is measured after 3 days of oral sodium loading (at least 200 mmol sodium/day), and a level over 12 μg/24 h is considered evidence of primary aldosteronism. Another technique is to measure plasma aldosterone before and after saline infusion (2 L over 4 hours). A positive test is the failure to lower plasma aldosterone levels to less than 10 ng/dL. Several other techniques are available to confirm the presence of autonomous aldosterone production (fludrocortisone suppression test, captopril, or furosemide-stimulated

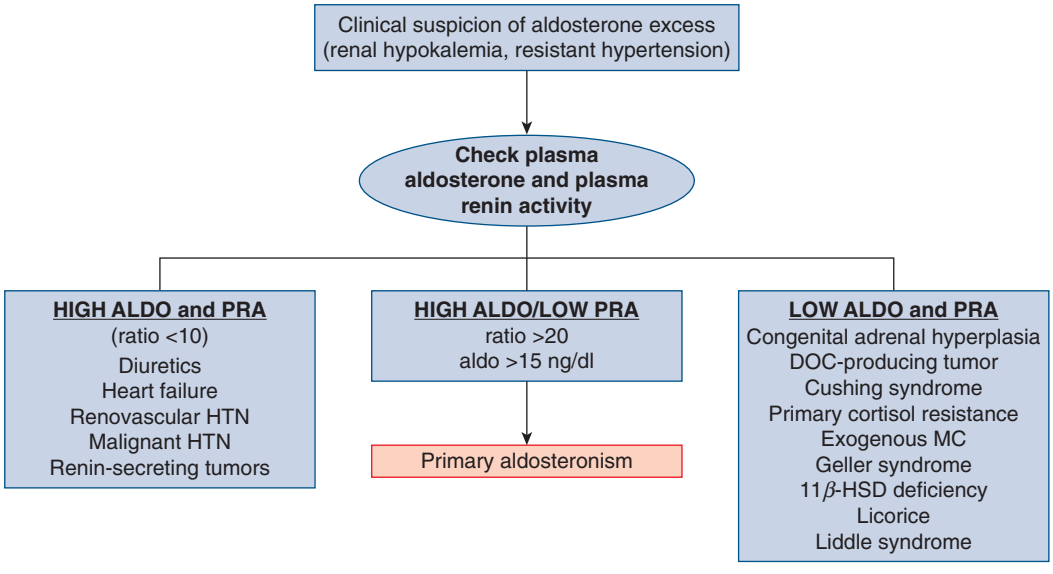

FIGURE 21-2. Evaluation of the patient with suspected hyperaldosteronism. Aldo, aldosterone; DOC, deoxycorticosterone; 11β-HSD, 11β-hydroxysteroid dehydrogenase; MC, mineralocorticoid; PRA, plasma renin activity.

plasma renin and aldosterone), but we find the 2 former tests the easiest and safest to perform in clinical practice.

Once the diagnosis of autonomous production of aldosterone is made, the next step is subtype differentiation. Adenomas were traditionally responsible for 70% of cases, but more recent data reveal a change in prevalence related to the more frequent diagnosis of milder cases, among which idiopathic adrenal hyperplasia (IAH) is the most common cause. Therefore, current trends show IAH being at least as common as APA. Imaging of the adrenal glands with thin-cut adrenal computed tomography (CT) is typically the first step, and its major current value is to rule out a rare but potentially devastating

	False Positives	False Negatives
Aldosterone relatively high	Potassium loading	
Renin relatively low	β-Blockers Central anti-adrenergics Direct renin inhibitors Nonsteroidal drugs Chronic kidney disease Sodium loading	
Aldosterone relatively low		Hypokalemia
Renin relatively high		Diuretics ACE inhibitors Angiotensin receptor blockers Calcium channel blockers Acute sodium depletion

FIGURE 21-3. Factors impacting on the diagnostic accuracy of the aldosterone-to-renin ratio.

adrenal carcinoma. These are large (>4 cm), irregular, heterogenous, and enhancing after contrast administration. This is in contrast to adenomas, which are typically small (<3 cm), regular, homogeneous, nonenhancing, and with low attenuation (<10 Hounsfield units [HU] on noncontrast images). Unfortunately, the prevalence of nonfunctional adrenal adenomas (or "incidentalomas") is as high as 7% among those older than age 70 years. This high prevalence of incidentalomas makes adrenal imaging (CT or MRI) inadequate to distinguish between the 2 main causes of primary aldosteronism, APA, and IAH in patients older than age 40 years. Using lateralization on adrenal venous sampling (AVS; ie, hypersecretion of aldosterone by one of the adrenals, or "lateralization") as the gold standard, a systematic review of 38 published studies showed an overall accuracy of CT or MRI of only 62%. Errors included the identification of an adenoma that does not lateralize, the presence of bilateral adenomas with hypersecretion restricted to 1 side, and lateralization without a lesion. This has led many experts to argue for AVS as an absolute necessity in the differential diagnosis between APA and IAH.

Because AVS is technically difficult in many patients, we take a practical approach in the decision to pursue AVS. First, we estimate the likelihood of cure from adrenalectomy in case of an adenoma or primary (unilateral) adrenal hyperplasia. It is known that most patients have some improvement in BP and all experience resolution of hypokalemia. However, the likelihood of BP response is greatest in women, and in patients who are thin (body mass index <25), have HTN of short duration (≤6 years), and are receiving 2 or fewer antihypertensive drugs. If the patient fits this profile and is willing to undergo adrenalectomy, we advocate proceeding with AVS. An exception is patients younger than the age of 40 years with a clear-cut adenoma on CT. Because the prevalence of incidentalomas is negligible in persons younger than the age of 40 years, the presence of the adenoma with biochemical evidence of aldosterone excess is enough to indicate adrenalectomy without AVS.

There are several "physiologic" methods that can be used in place of AVS to help confirm the subtype. These include iodocholesterol adrenal, and biochemical tests including plasma 18-hydroxycorticosterone levels (high in APA, normal in IAH), and the behavior of plasma aldosterone in response to 2 hours of orthostasis (normal increase in IAH, paradoxical decrease in APA). We find all of these tests of limited reliability and current little use.

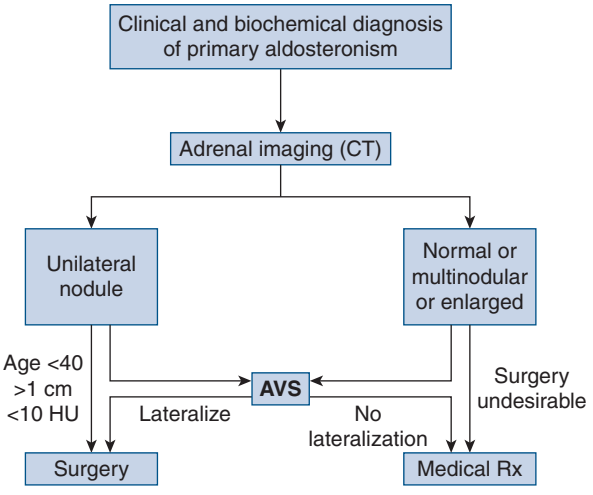

FIGURE 21-4. Summary of the clinical approach to primary hyperaldosteronism.

Figure 21.4 summarizes the sequential approach to the diagnosis and management of primary aldosteronism.

Treatment

Elimination of aldosterone excess is essential to improve the cardiovascular prognosis of patients with primary aldosteronism. This can be achieved by adrenalectomy or mineralocorticoid receptor antagonists. Specific treatment abrogates the excess cardiovascular disease that accompanies hyperaldosteronism.

Unilateral laparoscopic adrenalectomy is the treatment of choice for APA. It cures the HTN in 30% to 60% of cases. As stated above, cures are more common in younger, lean, female patients with shorter duration of HTN and less severe HTN prior to intervention. Hypokalemia uniformly resolves after adrenalectomy.

Mineralocorticoid receptor blockers are the treatment of choice for IAH and for APA patients who are not good surgical candidates or who do not want to undergo surgery. Spironolactone has been used for many years and has an excellent track record in the control of HTN and hypokalemia in patients with IAH. Because of antagonism of androgen and progesterone receptors, however, spironolactone is often poorly tolerated, especially in men, in whom it may cause breast pain, gynecomastia, and decreased libido. Eplerenone is a newer mineralocorticoid receptor antagonist with minimal affinity for androgen and progesterone receptors, and

no sexual or antiandrogenic side effects. It can be used in patients with primary aldosteronism, although a recent head-to-head comparison showed that spironolactone (75 to 225 mg/day) was more effective than eplerenone (100 to 300 mg/day) to lower BP in patients with APA. Therefore, spironolactone should remain as the first option in primary aldosteronism.

KEY POINTS

Primary Aldosteronism

1. HTN and hypokalemia caused by renal potassium wasting suggests hyperaldosteronism.
2. The sequential approach to primary aldosteronism consists of screening (plasma aldosterone-to-renin ratio), confirmation of autonomous production (salt-loading tests), and subtype differentiation (adrenal imaging and AVS).
3. Plasma aldosterone to plasma renin activity ratio over 20 is the best screen for primary aldosteronism.
4. Laparoscopic adrenalectomy is the treatment for APAs.
5. Mineralocorticoid receptor blockers are the treatment for IAH.

PHEOCHROMOCYTOMA

Pheochromocytomas are catecholamine-producing tumors that develop from chromaffin cells of the adrenal medulla or sympathetic ganglia (extraadrenal pheochromocytoma). Pheochromocytoma is a rare cause of secondary HTN, with an estimated incidence of 5 cases in 100,000 hypertensive patients each year. Because they are potentially fatal, however, they should be considered in all hypertensive patients. Approximately 10% of all pheochromocytomas are associated with familial syndromes, which include multiple endocrine neoplasia type 2 (MEN2a: pheochromocytoma, medullary thyroid carcinoma, and parathyroid adenoma; MEN2b: pheochromocytoma, medullary thyroid carcinoma, and mucocutaneous neuromas), von Hippel-Lindau syndrome (retinal and/or cerebellar hemangioblastoma, renal cell carcinoma), and von Recklinghausen disease (neurofibromatosis). Histologically, most pheochromocytomas are benign, although malignancy can occur in 10% of cases, more frequently among extraadrenal pheochromocytomas.

Pathogenesis

Most adrenal pheochromocytomas secrete both norepinephrine and epinephrine, whereas extraadrenal pheochromocytomas secrete predominantly norepinephrine. Most clinical manifestations of pheochromocytomas are caused by activation of adrenergic receptors by circulating catecholamines. In addition, there is a paradoxical elevation of baseline sympathetic tone in this disease, which may explain the poor correlation between catecholamine levels and HTN in pheochromocytoma. Neuropeptide Y concentrations are increased in plasma and tumors of patients with pheochromocytoma. This transmitter has direct and indirect (potentiates norepinephrine) vasoconstricting effect on small arterioles. Lastly, it is important to remember that chronic elevation in sympathetic activity may lead to renal microvascular injury and sodium retention, which is part of the mechanism of HTN in pheochromocytoma.

Diagnosis

Myriad symptoms and signs related to catecholamine release may be present in patients with pheochromocytoma. The most common symptoms are episodes of intense headache, palpitations, and diaphoresis. This triad in a hypertensive patient has a sensitivity of 91% and a specificity of 94% for the diagnosis of pheochromocytoma, with very low positive predictive value (6%) and very high negative predictive value (99%). The presence of orthostatic hypotension adds to the likelihood of the diagnosis of pheochromocytoma. The major differential diagnosis is with anxiety and panic attacks and the use of exogenous sympathomimetic drugs. "Classic" cases have paroxysmal HTN with interspersed periods of normotension. Sustained HTN with or without superimposed paroxysms, however, is the most common presentation (about two-third of all cases). Paroxysms are triggered by a number of stimuli including exercise, smoking, urination, defecation, palpation of the abdomen, induction of anesthesia, or the use of drugs that affect catecholamine metabolism (worsening HTN after initiation of a β-blocker is a classic presentation). Rarely, patients with a predominantly epinephrine-secreting pheochromocytoma may present with paroxysmal hypotension rather than HTN. This does not occur with norepinephrine-secreting tumors.

Biochemical tests are used to demonstrate catecholamine production and metabolism by the tumor. The determination of plasma-free metanephrines, plasma

catecholamines, urine fractionated and total metanephrines, urine catecholamines, and urine vanillylmandelic acid have been used, usually in combination. Plasma-free metanephrines and normetanephrines have excellent sensitivity (but limited specificity) with the convenience of a single blood draw and no specific requirements to stop medications. The most relevant interactions are with acetaminophen, which should not be used for 24 hours prior to testing, tricyclic antidepressants, serotonin and nor-epinephrine reuptake inhibitors, and phenoxybenzamine. Urine tests perform just as well but are more time demanding and affected by drug use (most commonly tricyclic antidepressants, β-blockers, and clonidine). Urine collections are particularly useful in patients with paroxysmal symptoms. It is useful to give these patients a collection bottle to take home with instruction to start a collection immediately following a paroxysm. This approach maximizes the likelihood of identifying excessive catecholamine production. Provocative (glucagon) or suppression (clonidine) tests may be used in patients with borderline levels. The clonidine suppression test is most commonly used, as provocative tests expose the patient to an unwarranted risk of severe HTN and tachycardia. In this test, clonidine 0.3 mg is given orally immediately after measurement of plasma metanephrines, which are measured again 3 hours later. Normally, clonidine lowers catecholamine and metanephrine levels by more than 50%; no such effect occurs in pheochromocytoma.

Once the biochemical diagnosis is made, the next step is localization of the tumor. Both CT and MRI have high sensitivity, but they have low specificity because of the common presence of adrenal tumors. Most (approximately 95%) pheochromocytomas are found within the abdomen, but the possibility of multiple sites justifies the use of extensive scanning. An MRI from the neck to the pelvis (to include the bladder) is the initial imaging of choice; a CT scan is an alternative. Extraadrenal tumors are predominant in patients younger than 20 years old. Bilateral adrenal tumors occur more frequently in patients with familial tumors. A scintigraphy using ^{121}I- or ^{131}I-labeled metaiodobenzylguanidine (MIBG) should be obtained in patients with abnormal hormonal tests but a negative MRI. It will show increased uptake at the site of the tumor (or tumors if multicentric). Patients with a family history of pheochromocytoma or paraganglioma, diagnosis at a young age, multifocal tumors, extraadrenal tumors, and malignant tumors should be considered for genetic screening for possible syndromes, such as MEN2 (RET gene), von Hippel-Lindau (VHL gene), neurofibromatosis (NF-1 gene), and succinate dehydrogenase gene mutations.

Treatment

The treatment of choice is surgical resection. In a hypertensive crisis the nonselective α-adrenergic blocker phentolamine should be used intravenously for BP control. All patients should receive medical therapy with oral phenoxybenzamine (also a nonselective α-blocker) for at least 1 to 2 weeks before surgery to avoid a hypertensive emergency at the time of manipulation of the tumor.

Patients who cannot be treated by surgery receive chronic medical therapy. Long-term therapy with the nonspecific α-adrenergic blocker phenoxybenzamine or with the α_1-receptor blockers prazosin, terazosin, or doxazosin, is the cornerstone of treatment. Tachycardia is a common side effect of phenoxybenzamine that demands the association of a β-blocker. β-Blockers should be started only after α-blockade is established. Patients who are intolerant to antiadrenergic therapy should receive metyrosine, a drug that inhibits catecholamine synthesis.

KEY POINTS

Pheochromocytoma

1. Pheochromocytoma is characterized by episodes of HTN along with intense headache, palpitations, and diaphoresis.
2. Most cases have sustained HTN with or without superimposed paroxysms.
3. Measurements of plasma and/or urinary catecholamines and/or their metabolites are used to confirm the diagnosis of pheochromocytoma.
4. Although most pheochromocytomas are intraabdominal, an extended scanning is recommended to rule out extraabdominal sites.

CUSHING SYNDROME

Cushing syndrome is the result of excessive production of cortisol. The overproduction of adrenocorticotropic hormone (ACTH) by a pituitary adenoma is the most common form of the disease and is called *Cushing disease*. Tumors of diverse origins and locations may secrete ectopic ACTH and cause Cushing syndrome,

most commonly lung carcinomas. ACTH-independent excessive cortisol secretion may be caused by adrenal adenomas and carcinomas. HTN is present in approximately 80% of patients with Cushing syndrome. Because several other clinical features of the syndrome are more prominent, however, HTN rarely is the reason for investigation of the disease.

Pathophysiology

HTN in Cushing syndrome is primarily the result of sodium and fluid retention as a result of the mineralocorticoid action of cortisol, although direct actions on vascular smooth muscle tone have also been observed. When present in high concentrations, cortisol saturates the enzyme 11 β-hydroxysteroid dehydrogenase that converts cortisol to the inactive cortisone. As this enzyme system is saturated, more cortisol becomes available for activation of the mineralocorticoid receptor, which results in sodium avidity and volume expansion.

Diagnosis

Patients with Cushing syndrome may display truncal obesity, the typical moon facies, facial plethora, purple skin striae, hirsutism, muscle weakness and fatigue, and wide mood swings. Glucose intolerance, osteoporosis, hyperlipidemia, amenorrhea, impotence, and decreased libido may also be present. Patients with Cushing syndrome caused by ectopic ACTH secretion may have severe hypokalemia.

The laboratory diagnosis is first made by measurement of 24-hour urine-free cortisol. This test has a high sensitivity, but false-positive results may occur in stress, obesity, alcohol abuse, and psychiatric disorders, especially depression. The overnight suppression test with a single dose of dexamethasone is a useful screening test to augment the specificity of urinary cortisol determination. Low-dose and high-dose dexamethasone tests are confirmatory tests that may also help to distinguish adrenal from pituitary cases. CT scan or MRI of the pituitary and adrenal glands add to the hormonal diagnosis to localize the causative tumor.

Treatment

The treatment of choice is surgical removal of the tumor. For Cushing disease, transsphenoidal adenomectomy is the most used procedure, but in some cases, total hypophysectomy may be necessary. Unilateral or bilateral adrenalectomy is performed for adrenal tumors. Chemotherapy may be necessary for malignant tumors. Drug therapy may be used before surgery, in failure of surgical treatment, and as a palliative treatment for incurable malignant tumors. Drug approaches may target different aspects of the disease, such as decreasing ACTH secretion, suppressing adrenocortical steroid synthesis, or antagonizing glucocorticoids at the receptor level.

KEY POINTS

Cushing Syndrome

1. Increased production of ACTH by a pituitary adenoma is the most common cause of Cushing syndrome.
2. Truncal obesity, moon facies and facial plethora, hirsutism, and purple skin striae are physical signs to suggest Cushing syndrome.
3. Determination of urine-free cortisol is the diagnostic test of choice.
4. Therapy is directed at tumor removal and/or targeting of cortisol production at different levels depending on the cause.

THYROID AND PARATHYROID DISORDERS

Thyroid hormone has effects on the cardiovascular system and BP regulation. HTN may be observed both in hypothyroidism and hyperthyroidism, but the characteristics of the BP profile differ with the metabolic disorder. The prevalence of HTN in hypothyroidism is high (~40%). HTN is predominantly diastolic and is associated with increased systemic vascular resistance and decreased arterial compliance. The decreased cardiac output of hypothyroidism may result in a narrowed pulse pressure. HTN in hyperthyroidism is primarily systolic and is related to an increased cardiac output. Vascular resistance is decreased in hyperthyroidism, which results in a wide pulse pressure. Specific treatments for each thyroid disturbance are sufficient to normalize BP in most patients.

HTN is commonly present in primary hyperparathyroidism (prevalence as high as 70%). Increased cytosolic calcium resulting in increased vascular resistance and

cardiac output would be rational pathogenetic mechanisms for the elevated BP. No correlation between calcium or parathyroid hormone levels and BP, however, are found in these patients. Removal of the adenoma-related gland cures or improves BP in most hypertensive hyperparathyroid patients.

KEY POINTS

Thyroid and Parathyroid Disorders

1. HTN is predominantly diastolic in hypothyroidism, whereas systolic HTN predominates in hyperthyroidism.
2. HTN is frequent in hyperparathyroidism, and is unrelated to serum calcium and parathyroid hormone levels.

COARCTATION OF THE AORTA

Coarctation of the aorta is a constriction of the descending thoracic aorta, most commonly distal to the left subclavian artery. It is a relatively common congenital malformation (~7% of all congenital heart disease), but an unusual cause of HTN in the adult. A bicuspid aortic valve is the most common associated abnormality. The classic findings are HTN in the arms, diminished femoral pulses, and low arterial BP in the lower extremities.

HTN in the upper extremities is a consequence of the mechanical obstruction to blood flow. Furthermore, renal ischemia may cause activation of the RAAS. Headache, chest pain, and pain in the legs with exercise are symptoms of coarctation of the aorta, but many patients may be asymptomatic, particularly when the constriction is small. A systolic murmur may be heard on chest examination.

Chest radiography can show the "3-sign" appearance of the left superior mediastinal border representing the pre- and poststenotic dilation of the aorta separated by the indentation represented by the constriction itself. Notching of the ribs of the posterior lower aspect of the third to eighth ribs as a result of erosion by the large collateral arteries can be observed as well. MRI can define the location and severity of coarctation, which decreases the need for angiography for diagnostic purposes. Echocardiography is an alternative method to make the diagnosis and assess disease severity, though not as precise as magnetic resonance. Surgery is the preferred treatment, although there is growing experience with balloon angioplasty with or without stenting as a viable alternative.

KEY POINTS

Coarctation of the Aorta

1. HTN in the upper extremities along with low BP in the lower extremities are the characteristic findings in coarctation of the aorta.
2. MRI or echocardiography can be used to confirm the diagnosis.

HYPERTENSION ASSOCIATED WITH PREGNANCY

Hypertensive disease of pregnancy is one of most important causes of maternal and perinatal mortality. HTN in pregnancy is also associated with prematurity and intrauterine growth retardation. The incidence of HTN in the first pregnancy is estimated to be 10%. Patients who are hypertensive before pregnancy or develop HTN before the 20th week of gestation are more likely to have HTN from causes other than a hypertensive disorder of pregnancy.

Preeclampsia and Eclampsia

Preeclampsia is a syndrome where HTN (BP ≥140/90 mmHg) is diagnosed for the first time after the 20th week of gestation along with proteinuria of at least 0.3 g/24 h. It occurs in approximately 5% of pregnancies and affects predominantly nulliparas. Eclampsia is the syndrome of HTN and seizures, usually occurring as a progression of preeclampsia, although 20% of eclamptic women do not have proteinuria.

Decreased placental perfusion is the key mechanism of preeclampsia. It is caused by impaired endovascular trophoblastic migration and invasion. Two circulating antiangiogenic molecules, soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) are increased in the placenta and serum of women with preeclampsia. sFlt-1 acts by adhering to the receptor-binding domains of placental growth factor (PlGF) and VEGF, preventing their interaction with endothelial receptors on the cell surface and thereby inducing endothelial dysfunction. sEng, on the other hand, acts

by blocking the binding of transforming growth factor β_1 (TGF-β_1) to its receptor, thus inhibiting TGF-β_1's angiogenic and vasodilatory effects. Differently from normal pregnant women, preeclamptic women are hyperresponsive to vasoactive agents such as angiotensin II and norepinephrine, and there are abnormalities in vasoactive substances such as nitric oxide, relaxin, and endothelin-1. HTN in preeclampsia is marked by increased peripheral resistance. The characteristic renal lesion in preeclampsia is glomerular endotheliosis. The glomeruli are enlarged with hypertrophy and swelling of the glomerular endothelial cells. Intravascular coagulation may be present in severe preeclampsia. HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelet count) is a serious complication of preeclampsia.

The diagnosis of preeclampsia is clinical. HTN in late gestation is defined as BP levels of 140/90 mmHg or greater. Proteinuria of 300 mg or more may be detected in a 24-hour urine collection. The protein-to-creatinine ratio in a random urine sample may estimate proteinuria and substitute for the 24-hour urine collection. Most cases resolve within 6 to 12 weeks following delivery.

Chronic and Transient Hypertension of Pregnancy

HTN diagnosed before the 20th week of pregnancy is usually a preexisting condition and not a specific complication of pregnancy. Preexisting HTN predisposes to preeclampsia. If HTN is diagnosed for the first time after the 20th week of pregnancy, without proteinuria, and the BP normalizes postpartum, the diagnosis is transient HTN of pregnancy. The pathogenesis of this disorder is not well understood, and these patients have higher rates of HTN later in life.

Overview of Hypertension Treatment in Pregnancy

Treatment of HTN in pregnancy requires a tight balance between protection of the mother from elevated BP and preserved perfusion of the fetoplacental unit. In addition, concerns about fetotoxicity of different drugs dictate the use of time-honored therapies and avoidance of certain agents. Methyldopa is the drug of choice for chronic control of BP because of its long track record of safety in pregnancy. Labetalol, calcium channel blockers (especially nifedipine), and hydralazine are reasonable alternatives. β-Blockers (other than labetalol) have a dubious safety record, especially early in pregnancy, and should be avoided. Diuretics are relatively contraindicated because they may induce volume depletion and electrolyte imbalance, but should be used whenever volume overload is present. ACE inhibitors are associated with a specific fetopathy and fetal death because of second and third trimester exposure and their use is contraindicated in pregnancy. Similar concerns apply to angiotensin II receptor blockers. It is important to remember that pregnant women with recent exposure to HTN are more susceptible to target-organ damage at lower BP levels. It is well established that BP levels as low as 170/110 mmHg can be associated with intracerebral hemorrhage in pregnancy, and BPs above this threshold are considered an emergency in the setting of pregnancy. In such situations, intravenous hydralazine is the drug of choice, although intravenous labetalol is a useful alternative. Fetal delivery is the specific treatment for pregnancy-induced HTN. Magnesium sulfate is indicated to control seizure activity in eclampsia; it is not used as a BP-lowering drug.

KEY POINTS

Hypertension Associated with Pregnancy

1. HTN in preeclampsia is diagnosed after the 20th week of gestation.
2. HTN before pregnancy predisposes to preeclampsia.
3. Treatment of HTN in pregnancy requires a tight balance between protection of the mother from elevated BP values and preserved perfusion of the fetoplacental unit.
4. Methyldopa is the time-honored drug of choice in the management of HTN in pregnancy.

INHERITED RENAL TUBULAR DISORDERS

These are rare causes of HTN characterized by increased renal sodium reabsorption as a result of single gene mutations. They are useful to illustrate the role of the kidney in the pathogenesis of HTN (see Chapter 20). Although not actual secondary causes of HTN, they are discussed in this chapter because of the unique nature of their clinical presentations.

Glucocorticoid Remediable Aldosteronism

Glucocorticoid remediable aldosteronism (GRA) is an inherited autosomal-dominant disorder that imitates adrenal hyperplasia. Onset of HTN is in childhood with normal or elevated aldosterone levels along with suppressed plasma renin activity. Marked HTN complicated by cerebral hemorrhage are hallmarks of this condition, whereas hypokalemia is not a prominent finding. GRA is caused by a gene duplication arising by unequal crossing over between 2 genes that lie next to one another on human chromosome 8. The genes encode aldosterone synthase and 11β-hydroxylase. The resulting hybrid gene encodes the ectopic expression of aldosterone synthase in the zona fasciculata. Its activity is thus regulated by ACTH rather than angiotensin II; therefore, administration of a glucocorticoid suppresses ACTH production and results in decreased aldosterone secretion. This is used as a diagnostic and therapeutic test. Specific genetic diagnosis is made by the identification of the chimeric gene. Suppression of ACTH with exogenous glucocorticoid can be used as treatment, although most patients respond well to mineralocorticoid receptor antagonists, and these drugs are the cornerstone of the chronic management of HTN in these patients.

Apparent Mineralocorticoid Excess

AME is a rare autosomal recessive disease. Affected individuals show impaired conversion of cortisol to the inactive cortisone because of the absence of the enzyme 11β-hydroxysteroid dehydrogenase type 2 as a result of mutations of its gene in chromosome 16. In vitro, cortisol activates the mineralocorticoid receptor with potency similar to that of aldosterone. Therefore, normal subjects are protected from the mineralocorticoid effects of cortisol by the action of 11β-hydroxysteroid dehydrogenase. In its absence, there is a marked increase in the availability of cortisol in target epithelia (especially kidney) resulting in "apparent" mineralocorticoid excess. Similar results are produced by licorice (glycyrrhizic acid), which inhibits the enzyme, and Cushing syndrome, which results in overwhelming of the enzyme system. The clinical features are the onset of HTN early in life, hypokalemia, metabolic alkalosis, low plasma renin activity, and suppressed aldosterone. Mineralocorticoid receptor blockers are the best treatment for patients with preserved renal function. Renal transplantation cures the disease.

Liddle Syndrome

Liddle syndrome is an autosomal-dominant disorder. There is a mutation in one of the genes in chromosome 16 coding for the β or γ subunits of the ENaC. These mutations lead to a reduction in the clearance of sodium channels from the cell surface. The result is sodium retention, early onset HTN, hypokalemia, metabolic alkalosis, suppressed plasma renin activity, and low plasma aldosterone levels. It responds well to amiloride.

Hypertension Exacerbated by Pregnancy (Geller Syndrome)

This is a rare autosomal-dominant form of early onset HTN that is exacerbated during pregnancy. It is caused by a mutation of the mineralocorticoid receptor, and compounds that normally bind but do not activate the mineralocorticoid receptor are potent agonists of the mutant receptor, particularly progesterone. As progesterone concentration increases more than 100-fold in pregnancy, patients with this mutation develop accelerated HTN during pregnancy. No specific treatment is available. Spironolactone, however, has an activating effect on the mutant receptor, and may paradoxically result in worsening HTN in these patients.

Pseudohypoaldosteronism Type 2 (Gordon Syndrome)

This is an autosomal-dominant syndrome caused by mutations in the genes coding for the *Kelch-like 3* or *Cullin 3 ligase proteins*, or the serine-threonine kinases WNK1 and WNK4, which result in enhanced sodium and chloride reabsorption via increased activity of the thiazide-sensitive NaCl cotransporter. The syndrome is characterized by HTN, suppression of the RAAS, hyperkalemia, hyperchloremic metabolic acidosis, and hypercalciuria. The molecular mechanisms responsible for the hyperkalemia and acidosis remain unclear. The phenotype is completely corrected by the administration of thiazide diuretics.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) can be caused by mutations in the genes coding for the 17α-hydroxylase or the 11β-hydroxylase enzymes, whose expression is deficient. Both are autosomal recessive disorders that present early in life in females with virilization and HTN. Affected males have signs of hyperandrogenism, such as acne and

premature puberty. Hypokalemia is a rare finding. The underlying pathogenesis of the HTN involves feedback activation of ACTH leading to increased deoxycorticosterone (DOC), which, in turn, stimulates the mineralocorticoid receptor and produces HTN. Because of this DOC effect, CAH patients have suppressed renin and aldosterone levels. Treatment consists of glucocorticoid use to shut down ACTH production and normalize androgen and DOC production. Patients with residual HTN respond well to mineralocorticoid receptor antagonists.

KEY POINT

Inherited Renal Tubular Disorders

1. Mutations of a single gene that provokes increased sodium reabsorption are causes of HTN.

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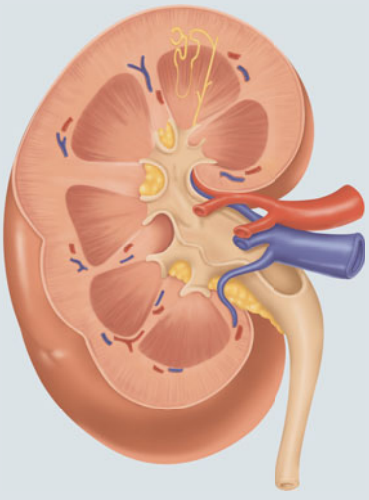

CHAPTER

22

Urinary Tract Infection

• *Richard N. Formica*

Recommended Time to Complete: 1 Day

Guiding Questions

1. How has the epidemiology of urinary tract infections (UTIs) changed?
2. What are the differences between asymptomatic bacteriuria, cystitis, and UTI?
3. What distinguishes an uncomplicated UTI from a complicated UTI and how do treatments vary?
4. Are particular patient populations at increased risk for UTI and are adverse outcomes a concern?
5. What is the pathogenesis of UTI?
6. What impact does bacterial antibiotic resistance have on UTI?
7. What are 2 important types of complicated renal infections?

INTRODUCTION

UTIs are one of the most common bacterial infections in the United States. The clinical presentation ranges from completely asymptomatic to septic shock. All ages are affected and certain subgroups of the population are particularly vulnerable. A national survey in the mid-1990s estimated that UTIs resulted in 7 million office visits, 1 million emergency department visits, and 100,000 hospital admissions per year. It is an illness that primarily affects women. One in 3 women by age 24 years are treated with antibiotics for a UTI, and 50% of women have UTI symptoms at some point in their life. Figure 22.1 shows the incidence of UTI throughout life. Early in life (circle 1 in Figure 22.1) females are at higher risk than males largely as a result of ureteral reflux. During the reproductive years women are at much higher risk than men (circle 2 in Figure 22.1). With advancing age (circle 3 in Figure 22.1) the gap narrows as the incidence of UTI in men increases as a result of benign prostatic hyperplasia. The term *UTI* in this chapter refers generically to an infection in any of the components of the urinary tract—kidney, bladder, prostate, and urethra. Each is discussed individually. Additionally, UTI is referred to as uncomplicated or complicated depending on the presence of risk factors that predispose the patient to an adverse outcome.

Symptoms and Signs

UTI refers to bacterial infection of the urinary tract. Patients, however, present with symptoms referable to the site and nature of infection. They complain of urinary frequency and urgency resulting from spontaneous

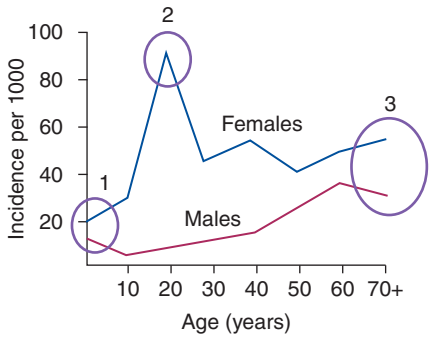

FIGURE 22-1. Incidence of UTI in the general population throughout life. Circles 1, 2, and 3 highlight 3 periods of UTI in life.

bladder contractions due to irritation of the trigone. Dysuria is caused by inflammation of the urethra that causes pain or a burning sensation when further irritated by urine. Flank pain results from stretching and irritation of the renal capsule that causes pain in the area of the costovertebral angle. Irritation of the bladder trigone and pain on defecation results from compression of the inflamed prostate. Finally, patients may report symptoms of systemic infection such as fever, rigors, malaise, nausea, vomiting, general muscle and joint ache, and lassitude. These symptoms suggest a bloodborne bacterial infection. Nausea and vomiting are also the result of increased vagal activity because vagal nerve fibers innervate the renal capsule, as well as the stomach. Stretching of the capsule is sensed as gastric distension and triggers nausea and vomiting.

Site of Infection

The urinary tract is composed of the kidney and ureters; bladder; prostate and epididymis in men; and urethra. Infection in any of these results in the above symptoms and causes the patient to seek medical attention. It is important to accurately diagnose the site of infection, as the type and duration of therapy differs.

The most common form of UTI in both men and women is cystitis. There is a distinction between asymptomatic bacteriuria and a symptomatic infection of the bladder or cystitis. The patient with asymptomatic bacteriuria has a sufficient number of bacteria to be consistent with infection, greater than 10^5 colony forming units (CFU)/mL of a pathogenic bacteria, but no symptoms. Asymptomatic bacteriuria requires therapy only in specific patient populations. However, good practice dictates that all patients should be monitored for progression to symptomatic infection and undergo follow-up urine culture to demonstrate resolution.

Cystitis refers to a symptomatic bladder infection that in addition to having a significant number of urinary bacteria is associated with dysuria, lower abdominal cramping, urinary frequency, and urgency. Cystitis is not associated with fever. If fever is present, an invasive tissue infection exists. This implies infection of the renal parenchyma and is referred to as *pyelonephritis*.

When discussing cystitis or any infection of urinary tract components, it is useful to think in terms of uncomplicated versus complicated infection. Table 22.1 lists criteria that define a complicated UTI. An uncomplicated cystitis is one that occurs in a healthy outpatient. The primary pathogens that cause uncomplicated UTI are *Escherichia coli* (80%) and *Staphylococcus*

TABLE 22-1. Criteria That Define a Complicated Urinary Tract Infection

Documented fever >38°C (100.4°F)
Symptoms of dysuria or urgency present for >7 days
Symptoms of vaginitis present (eg, vaginal discharge or irritation)
Symptoms of abdominal pain, nausea, or vomiting
Gross hematuria in patients older than age 50 years
Presence of immunosuppression (eg, current use of chemotherapy or transplantation immunosuppression)
Diabetes mellitus
Known pregnancy
Chronic renal or urologic abnormalities other than stress incontinence (eg, polycystic kidney disease, neurogenic bladder, chronic kidney disease)
Recent or persistent occurrence of urinary stones
Urinary catheterization or other urologic procedure within 2 weeks
Discharge from hospital or nursing home within 2 weeks
Treatment for UTI within 2 weeks
Recurrent or symptomatic UTI

Source: Modified from Bent S, Saint S. The optimal use of diagnostic testing in women with acute uncomplicated cystitis. *Am J Med*. 2002;113:20S-28S.

saprophyticus (15%). The remaining 5% are composed of non-*E. coli* Gram-negative rods, *Klebsiella, Proteus, Enterobacter, Pseudomonas,* and *Serratia*, and Gram-positive cocci, *Enterococci*, *Staphylococcus aureus,* and group B streptococcus. Complicated cystitis occurs in a patient who is institutionalized, pregnant, diabetic, paralyzed, or a transplantation recipient. Additionally, the presence of an anatomic abnormality of the genitourinary tract or an indwelling urinary catheter makes a UTI complicated. The spectrum of pathogens in these populations is different and is discussed individually.

Pyelonephritis is an infection of the renal parenchyma. Its presentation is varied. If fever is present in a patient with cystitis, by definition the patient has an invasive infection of the kidney. This is one end of the spectrum of pyelonephritis. Often patients have fevers and pain on the affected side. If these symptoms are ignored, a systemic infection ensues with progression to multiple organ dysfunction and shock. Figure 22.2 illustrates the mechanism of renal parenchymal infection. Under most circumstances, bacteria ascend to the renal parenchyma by ureteral reflux from the bladder. One exception to this rule applies. If the causative organism is *S. aureus,* a source of hematogenous infection should be sought.

Factors distinguishing complicated pyelonephritis from uncomplicated pyelonephritis are the same as those for cystitis. The primary pathogens causing uncomplicated pyelonephritis are the same as those for uncomplicated cystitis. If a patient remains febrile for 72 hours on an antibiotic to which the causative organism is sensitive, then evaluation for a parenchymal or perinephric abscess is indicated.

Prostatitis occurs both acutely and chronically. It causes symptoms similar to cystitis. The patient has dysuria and pelvic pain and occasionally discomfort on defecation. Distinct from cystitis, patients with prostatitis are acutely ill with signs and symptoms of systemic infection including fever, rigors, malaise, myalgias, and in extreme cases sepsis. Prostatitis is distinguished from pyelonephritis by its typical history and a tender prostate on rectal examination. The spectrum of bacterial pathogens is similar to that of cystitis and pyelonephritis.

As with cystitis and pyelonephritis, prostatitis can also be complicated. The same populations at risk for complicated cystitis and pyelonephritis are also at risk for complicated prostatitis. Additionally, there are 2 primary anatomic complications that occur in prostatitis, prostatic abscess and chronic prostatitis. The rate of abscess

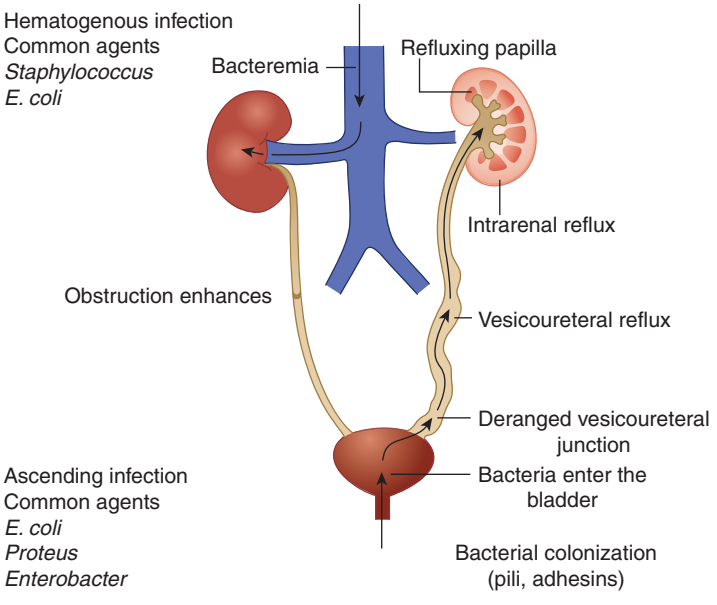

FIGURE 22-2. Pathophysiologic mechanisms of pyelonephritis. Infection of the kidney may arise in 2 ways. Most commonly, the causative organism ascends from the lower urinary tract. Less commonly, bacteria may seed the kidney as a consequence of primary infection elsewhere in the body.

formation has declined significantly since the middle 1970s as a result of antibiotic therapy that allows for better prostatic tissue penetration and higher antibiotic concentration.

Chronic prostatitis results from inappropriate or incomplete therapy of acute prostatitis or without any recognized cause. Symptoms are similar to cystitis without evidence of systemic infection. The diagnosis should be considered with recurrent bouts of cystitis in the absence of bladder catheterization.

In both sexes urethral inflammation causes symptoms of dysuria, urgency, and pelvic pain. Signs of systemic infection are absent. A high index of suspicion is required. In the setting of symptoms consistent with cystitis, a negative urine culture should raise suspicion for urethritis. The patient is carefully questioned regarding new sexual partners and urethral discharge. In both women and men, the most common organism responsible is *Chlamydia trachomatis* followed by *Neisseria gonorrhoeae*. The percentage of episodes of dysuria caused by these pathogens depends on the population studied. It can be as high as 20% in an individual with multiple sexual partners and from the urban indigent populations.

Finally, vaginitis causes symptoms of dysuria and can be mistaken for cystitis. Dysuria occurs when urine comes into contact with inflamed vaginal tissues. The reported symptoms are often perceived by the patient as being more external and sharp. It is common, however, that patients do not mention vaginal symptoms spontaneously and, therefore, should be questioned specifically. As with urethritis, a negative urine for leukocytes and a negative culture should raise suspicion of this diagnosis.

KEY POINTS

Urinary Tract Infection

1. Infections in different locations within the urinary tract present with similar symptoms.
2. Fever in a patient with UTI indicates a tissue invasive infection.
3. The duration of therapy and the pathogens responsible for UTI are different in uncomplicated and complicated UTI.
4. Infection of the urinary tract with *S. aureus* requires evaluation for a hematogenous source of infection.

RISK FACTORS FOR AND PATHOGENESIS OF URINARY TRACT INFECTION

Patient-Specific Factors

For a UTI to occur, bacteria must first gain access to the urogenital system. This happens through introduction of bacteria into the urethra during sexual intercourse or insertion of urinary catheters or other objects. The exception to this rule is infection with *S. aureus* that results from hematogenous spread. Infection of the urinary tract with *S. aureus* should prompt a search for an endovascular infection. Women are at greater risk for UTI because the vaginal introitus can become colonized with fecal bacteria. Use of spermicides and diaphragms increase the risk of UTI by altering the vaginal flora and allowing overgrowth of pathogenic bacteria. Sexual intercourse mechanically introduces bacteria into the bladder. Men are at low risk for UTI compared to women because the periurethral environment is drier and not colonized by bacteria, their urethra is longer, and prostatic fluid contains antibacterial substances. In both men and women, complete bladder emptying following voiding is a primary defence against infection.

Once in the bladder, inadequate emptying of the bladder, as occurs with prostatism or patients with neurogenic bladder allows bacteria to multiply, as illustrated in Figure 22.3. With small residual volumes (1 mL), over time, bacteria are cleared from the bladder. As the residual volume increases (8 mL), this is no longer the case. Anatomic abnormalities or nephrolithiasis provide sites for bacterial adherence and prevent expulsion. Why one individual is susceptible to UTI while another is not is dependent on the genetic, biologic, and behavioral factors shown in Table 22.2. Women who have recurrent UTIs have been found to have higher density, up to 3 times more, *E. coli* adhering to vaginal, buccal and voided uroepithelial cells when compared to women with out recurrent UTIs. Additionally, uropathogenic *E. coli* can colonize the colon. Previous antibiotic use can alter protective vaginal and perineal flora and allow overgrowth of pathogenic organisms.

Pathogen-Specific Factors

Bacteria contain virulence factors that contribute to pathogenicity. The primary virulence factor is the ability of bacteria to adhere to cell surfaces. It is important to note that microbial virulence is not related to antimicrobial resistance. The most adherent bacteria, unless acquired in the hospital setting, are sensitive to antibiotics. Bacteria that

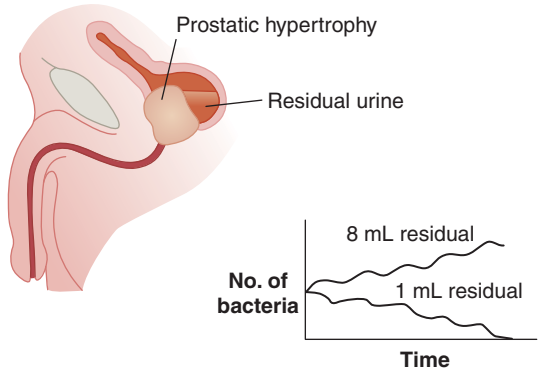

FIGURE 22-3. Urinary retention and UTI. Urinary obstruction results in incomplete emptying of the bladder. The presence of residual urine prevents clearance of organisms from the bladder and allows bacteria to multiply.

do not have an adhesion system do not cause infection. This is because enteric bacteria have negatively charged cell surfaces and are, therefore, repelled by the negatively charged cell membrane. The primary adhesion system used by bacteria is adhesins, which are lectin molecules located on their fimbriae. Adhesins bind oligosaccharides on epithelial cell surfaces and mediate internalization of bacteria into epithelial cells, where they replicate avoiding the host immune system. Other virulence factors include flagella that are necessary for motility and the production of an enzyme, hemolysin, that forms pores in the cell membrane. These pores allow bacteria to gain access to the cytosol of the renal epithelial cell where they multiply in an environment shielded from local defense mechanisms. Finally, the presence of aerobactin, which is necessary for iron acquisition, is an additional virulence factor. Iron is responsible for many processes in bacteria including upregulation of genes that enhance virulence and the formation of superoxides that degrade cell walls.

A virulence factor unique to *Proteus mirabilis* is urease. This enzyme converts urea into ammonia and carbon dioxide. The ammonia buffers hydrogen ions in the urine increasing pH. The alkaline pH results in the precipitation of phosphate, carbonate, and magnesium forming struvite stones. These stones allow *P. mirabilis* to colonize the genitourinary tract and cause obstruction and urinary stasis further promoting bacterial multiplication.

TABLE 22-2. Inherited or Acquired Host Susceptibility Factors for Urinary Tract Infection

GENETIC	BIOLOGIC	BEHAVIORAL	OTHER
Blood group antigen	Congenital abnormalities	Sexual intercourse	Decreased mental status
Nonsecretor status	Urinary obstruction	Use of diaphragm	
Increased adhesion receptors	Calculi	Use of spermicides	
	Diabetes mellitus	Antimicrobial use	
	Anatomy		
	Residual urine		
	Atrophic vaginitis		
	Urinary incontinence		
	Prior history of UTI		
	Maternal history of UTI		
	Childhood history of UTI		
	Catheters/stents/foreign bodies		
	Condom catheters		
	Immunologic abnormalities (human immunodeficiency virus [HIV])		
	Renal transplantation		

Source: Modified from Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Am J Med*. 2002;113:14S-19S.

KEY POINTS

Risk Factors for and Pathogenesis of Urinary Tract Infection

1. Patient-specific risk factors for UTI can be modified to decrease the incidence of infection.
2. Pathogen-specific virulence factors do not change the species of bacteria causing infection.
3. Pathogen-specific virulence factors are not the cause of antibiotic resistance.

DIAGNOSIS OF URINARY TRACT INFECTION

The diagnosis of UTI is based on the history and a few simple laboratory tests. In men, the symptoms of dysuria (pain or difficulty on urinating), frequency (frequent voiding of small amounts of urine), and hematuria (presence of blood in the urine) is relatively diagnostic of UTI. Other diagnoses to consider are prostatitis and urethritis. A diagnosis of acute prostatitis is made when signs and symptoms of UTI are present and there is prostate tenderness on rectal examination.

The physical examination in the evaluation of a patient with UTI is of limited value. As stated above, tenderness on prostate examination aids in differentiating prostatitis from cystitis. Additionally, palpation of the lower abdomen can reproduce symptoms in cystitis helping to confirm the clinical suspicion of cystitis as opposed to urethritis. Finally, eliciting tenderness over the costovertebral angle suggests that if pyelonephritis is present inflammation in the kidney is severe enough to result in significant capsular swelling.

Laboratory Examination

Laboratory examination is usually limited to the urinalysis. In an uncomplicated UTI the presence of pyuria and bacteriuria makes the diagnosis. A urine culture and sensitivity is obtained for any patient with a fever or a patient meeting criteria for complicated UTI. Urine culture is the gold standard for diagnosing UTI. In a patient with symptoms suggesting UTI a quantitative urine culture of equal to or greater than 10^2 CFU/mL is highly sensitive (95%) and specific (85%). In an asymptomatic patient, a quantitative culture of equal to or greater than 10^5 CFU/mL is considered diagnostic of UTI. The diagnosis of UTI is made when the proper signs and symptoms are present and there are leukocytes in the urine and a bacterial colony count of equal to or greater than 10^5 CFU/mL. It should be stressed that in the setting of a history of symptomatic UTI, if the colony count is equal to or less than 10^5 CFU/mL, the patient should still be treated. Other processes such as prostatitis or urethritis should be considered and are discussed below. The importance of the colony count is primarily in the setting of asymptomatic bacteriuria in a patient other than the pregnant woman. In the asymptomatic patient, a risk-to-benefit decision must be made, taking into account the potential for developing true infection versus exposure to unnecessary antibiotic therapy. Additionally, the patient's prior history should be taken into account. Previous progression of asymptomatic bacteruria to symptomatic UTI warrants proactive therapy.

In a woman, the same symptoms are again suggestive of a UTI but the diagnoses of urethritis and vaginitis are more difficult to distinguish. A history of vaginal discharge strongly suggests a vaginal disorder, whereas its absence greatly increases the probability of UTI. The presence of hematuria on urinalysis directs the diagnosis toward UTI. In the nonpregnant woman, leukocyturia and bacteria cultured from the urine at equal to or greater than 10^5 CFU/mL confirms the diagnosis. In pregnancy, asymptomatic bacteriuria of equal to or less than 10^5 CFU/mL is considered to represent an infection.

The diagnosis of chronic prostatitis is more difficult because symptoms are similar to cystitis. Complicating the diagnosis is the fact that bacteria within the bladder may be different than the bacteria causing infection within the prostate. In addition, when cultured bacteria in the bladder often outgrow prostatic bacteria. Therefore, it is necessary to perform a split urine collection. After cleaning the periurethral area, the patient voids an initial amount that is discarded and collects what would be considered a midstream collection. At this point, however, the patient is instructed to stop voiding prior to emptying the bladder and a prostatic massage is performed. Prostatic secretions are collected for culture and leukocyte count and the patient finishes voiding into a separate container. For a test to be positive, the midstream collection must have equal to or less than 10^3 CFU/mL and the postmassage collection must have greater than 12 leukocytes per high power field. Bacterial cultures from prostatic secretions and postmassage urine guide antibiotic therapy.

The diagnosis of urethritis is made by a high index of suspicion and a sample from the urethra. *Chlamydia*

trachomatis is diagnosed using a ligase chain-reaction test performed on urine or urethral discharge. *N. gonorrhoeae* is diagnosed through culture. A urethral swab is performed. The sample is taken several millimeters up the urethra and, therefore, a calcium alginate tip swab is used. The specimen is immediately plated onto room temperature culture medium such as Thayer-Martin agar.

KEY POINTS

Diagnosis of Urinary Tract Infection

1. For an uncomplicated patient, a history consistent with UTI and pyuria on urinalysis establishes the diagnosis.
2. For a complicated patient, a culture and sensitivity must be performed.

ANTIBIOTICS FOR THE TREATMENT OF URINARY TRACT INFECTION

The treatment of uncomplicated UTIs was straightforward until recently. This is because the causative agents, *E. coli* and *S. saprophyticus*, were largely sensitive to trimethoprim-sulfamethoxazole (TMP-SMX). Additionally, antibiotic concentrations in urine greatly exceed those in plasma. This made the concern about in vitro resistance at traditional serum macrophage inhibitory concentrations (MICs) less relevant because a clinical cure could still be achieved. Therefore, empiric therapy with TMP-SMX 160/800 mg twice a day for 3 days resulted in both clinical and biologic cure and was the mainstay of therapy. Since the beginning of the 1990s, resistance to β-lactam antibiotics, principally ampicillin and cephalothin, is too high, up to 40%, to recommend them for empiric therapy. Recently, TMP-SMX resistance is increasing and approaches 20% in some regions of the country. This resulted in a shift in initial therapy.

Resistance to fluoroquinolones remains less than 10% in North America and Europe. However, there is a trend toward increasing resistance and local organism resistance should be monitored. Ciprofloxacin is commonly used in a 3-day course for uncomplicated cystitis and a 7- to 14-day course for complicated cystitis or pyelonephritis. Gatifloxacin, a newer fluoroquinolone, has an advantage in that it has broader Gram-positive organism coverage, can be administered once a day, has a urinary excretion rate of 70%, and it does not affect cytochrome P450-mediated metabolism. Gatifloxacin should be used with caution in diabetic patients as hypo- and hyperglycemic events have been reported.

Resistance to nitrofurantoin remains low. It is used as a suppressive agent to prevent recurrent UTI at dose of 50 to 100 mg/day. It is especially useful in pregnancy because it has not been reported to be teratogenic. It can also be used as treatment for uncomplicated cystitis. Nitrofurantoin, however, does not achieve high enough serum concentrations to be employed for the treatment of acute pyelonephritis. Furthermore, it cannot be used for patients with chronic kidney disease and should be avoided in patients with complicated cystitis.

Recurrent UTIs, which occur commonly in otherwise young, healthy women, can be a source of considerable morbidity. As many as 27% develop a recurrence within 6 months of initial infection. These develop despite normal anatomy and physiology of the urinary system. Typical predisposing factors, such as urinary obstruction, bladder stones, and pregnancy need not be present. Most often, recurrent episodes represent reinfection (new infection after a cure) rather than relapse of a previously treated UTI. Factors associated with recurrent UTI include uropathogenic coliforms (p-fimbriated strains of *E. coli*) that adhere to uroepithelial cells, frequent sexual intercourse and diaphragm–spermicide use, a short urethra, and the postmenopausal state. Once major anatomic problems are excluded, prevention is achieved through behavioral changes (reduced spermicide use, postcoital voiding) and liberal fluid intake. Although cranberry juice ingestion remains a popular home remedy and is harmless, recent studies cast doubt on its effectiveness. Women who experience 2 or more symptomatic UTIs within 6 months or 3 or more over 12 months should receive antibiotic prophylaxis. Postcoital antibiotic prophylaxis or continuous prophylaxis (6 months duration) are effective but run the risk of antibiotic resistance developing over time.

The treatment of acute prostatitis, as distinct from chronic prostatitis, is based on the same principles as treating pyelonephritis. In most cases the patient is hospitalized because of systemic illness and broad-spectrum antibiotics initiated until the causative agent is identified. The same precautions regarding antimicrobial resistance patterns apply as above. The inflamed prostate is freely permeable to antibiotics and in contrast to chronic prostatitis a variety of antimicrobial agents are used. The

duration of therapy is 4 to 6 weeks to ensure that there are no bacterial foci remaining within the prostate.

Chronic prostatitis presents a therapeutic challenge because there is a barrier between the prostatic stroma and the microcirculation. This barrier is analogous to the blood–brain barrier formed by the meninges and makes passive diffusion the only route by which antibiotics can penetrate prostatic tissue. Therefore, only non–protein-bound, lipophilic drugs achieve therapeutic levels within the prostate. The 2 types of antibiotics that are effective in treating chronic prostatitis are the quinolones and TMP-SMX. Both of these antibiotics achieve predictable levels within the prostate and have excellent bioavailability, up to 80%, when administered orally. This is particularly advantageous because the duration of therapy must be 6 to 12 weeks to achieve durable results.

Treatment for urethritis is initiated empirically when the diagnosis is suspected prior to final culture results. Ceftriaxone (250 mg given intramuscularly as a 1-time dose) will treat *N. gonorrhoeae*. Doxycycline (100 mg orally twice a day for 7 days or azithromycin 1 gm given as a single oral dose) is equally effective at treating *C. trachomatis*. Both agents are also effective against *Ureaplasma urealyticum*.

KEY POINTS

Antibiotics for the Treatment of Urinary Tract Infection

1. Antimicrobial-resistant bacteria are more common, therefore, broad-spectrum empiric coverage with a quinolone is appropriate.
2. To avoid inducing further antibiotic resistance, once culture and sensitivity results are available, antibiotic therapy is changed to the narrowest possible spectrum.

SPECIAL POPULATIONS OF PATIENTS

Pregnant Women

UTI in pregnancy, although occurring at only slightly increased frequency compared to similar age nonpregnant women, has a high morbidity. Bacteriuria complicates 6% to 7% of all pregnancies with multiparous women at highest risk. In pregnant women, UTI increases fetal morbidity and mortality. In a large study, bacteriuria and pyuria within 2 weeks of delivery resulted in a significant increase in perinatal mortality. Asymptomatic bacteriuria in pregnant women is associated with preterm deliveries and low birth weight and, therefore, must be treated.

Bacteria isolated from pregnant women with UTI and the virulence factors they possess are the same as those for the general population. This suggests that the mechanism by which bacteria gains access to the urinary tract is the same for pregnant women as for nonpregnant women. The hormonal milieu, however, in pregnancy results in smooth muscle relaxation and ureteral dilation that allows bacteria to reflux into the kidney. Therefore, if untreated up to 40% of patients with asymptomatic bacteria develop pyelonephritis. Because of this, cost-to-benefit analyses demonstrate that it is beneficial to screen pregnant women for asymptomatic bacteriuria.

For asymptomatic bacteriuria a 3-day course of antibiotics is effective. In pregnancy, penicillins and their derivatives are safe. Additionally, sulfonamides are safe with the exception of the last days of pregnancy, and nitrofurantoin can also be used. Trimethoprim should be avoided. Fluoroquinolones and tetracycline are contraindicated.

KEY POINTS

Pregnant Women

1. Bacteriuria and UTI have negative consequences on the outcome of pregnancy.
2. All pregnant women must be treated.

The Spinal Cord Injury Patient

The spinal cord injury (SCI) patient averages 2.5 episodes of UTI and between 10 and 20 episodes of bacteriuria ($>10^5$ CFU/mL) per year. In this circumstance, UTI refers to a true infection. There are many reasons for the increased risk and it is dependent on the level of the SCI and its effects on the normal micturition pattern. SCI patients have impaired or absent micturition and often have chronic indwelling bladder catheters. For patients without catheter drainage, the increase in intravesicular pressure required to void causes reflux of contaminated urine into the renal collecting system and allows

bacteria to seed the parenchyma. For patients with SCI vesicourethral dysfunction may present as high intravesicular pressure, increased residual volume, or both. The increased vesicular pressure is a result of dyssynergy between bladder contraction and the striated sphincter at the bladder neck. The usual response is for sphincter muscles to progressively fire as the bladder fills. This is the guarding reflex that prevents incontinence. Once urination begins the sphincter completely relaxes. In the SCI patient, as the bladder contracts, as a result of distension, the sphincter repetitively contracts forming an obstruction to the free flow of urine. The pressure generated by contraction of the bladder is transmitted backward into the kidney. Stasis is the result of not being able to empty the bladder because of loss of bladder contraction.

The risk of UTI is greatest with indwelling Foley catheters, being many times higher than intermittent catheterization and condom catheters. The risk is equivalent with condom catheters and intermittent catheterization. This reflects the tradeoff between mechanically introducing bacteria from the perineal area into the bladder during each catheter insertion and providing a closed space in which bacteria can proliferate, as is the case with condom catheters.

The bacteria responsible of causing infection in SCI patients vary depending upon which study is cited, however, when compared to non-SCI patients the incidence of *E. coli* and *Klebsiella* species is less common and *Pseudomonas*, *Proteus,* and *Serratia* is more common. Microbial resistance to antibiotics is frequent in these patients because of multiple antibiotic exposures, making culture of the urine necessary. Relapse of infection or recolonization occurs most commonly with *E. coli* and *Klebsiella pneumoniae* because these are 2 common bowel organisms that contaminate the perineal area. If the patient is thought to have a true relapse of infection as opposed to colonization, a source should be sought. Common sources are stasis of urine, urinary calculus, and abscess of the urinary tract.

The treatment of SCI patients with asymptomatic bacteriuria is controversial because, on the one hand, chronic antibiotic exposure leads to antimicrobial resistance, and on the other hand, SCI patients are debilitated and may have less reserve to tolerate systemic infection. The decision to treat an SCI patient must be individualized. The most important factor is the patient's prior clinical course with similar episodes of asymptomatic bacteriuria.

KEY POINTS

The Spinal Cord Injury Patient

1. SCI patients are at high risk for UTI because of chronic indwelling catheters and loss of coordinated micturition.
2. Antimicrobial-resistant organisms are common pathogens because SCI patients have multiple antibiotic exposures.

The Diabetic Patient

Few prospective studies address whether diabetic patients are at increased risk of UTI. Studies in diabetic women suggest that the rates of asymptomatic bacteriuria are higher than their nondiabetic counterparts. In one study, the difference was large with a prevalence of asymptomatic bacteriuria in diabetic women being 26% and 6% in nondiabetic women. This finding suggests a serious health risk because other research showed that asymptomatic bacteriuria in diabetic women is a risk for pyelonephritis and decline in renal function. In healthy, nonpregnant women without structural abnormalities of the urinary tract, diabetes mellitus, or immunosuppression, such serious complications are rare.

Diabetes mellitus is also a risk factor for more serious complications of UTI, as well as infections with unusual pathogens. These serious complications include emphysematous cystitis and pyelonephritis, abscess formation, renal papillary necrosis, and xanthogranulomatous pyelonephritis (XGP). In diabetics, infections with Gram-negative rods other than *E. coli* are more common and the rate of fungal infection is also greatly increased.

There are several reasons postulated as to why patients with diabetes mellitus have a greater incidence of asymptomatic bacteriuria and UTI. The nature of these studies make the hypotheses difficult to prove. Microvascular disease damages bladder function and, therefore, impairs bladder emptying. This results in outflow obstruction, urinary incontinence, and increased residual volume—all of which allow colonization and bacterial overgrowth in urine. Diabetics may have decreased antimicrobial activity of urine and an increased adherence of bacteria to uroepithelium. Hyperglycemia impairs the function of lymphocytes and decreases cytokine production of monocytes.

Whatever the etiology of the increased susceptibility to infection, the presence of diabetes mellitus makes a UTI complicated and it must be treated accordingly.

UTIs in diabetics are more likely to be caused by antibiotic-resistant organisms. There is also a higher rate of complications and a higher rate of infection by unusual organisms. In a prospective surveillance study of hospitalized patients with funguria, diabetes was found to be present in 39% of the cases. Therefore, treatment of a diabetic with UTI should involve initial therapy with a broad-spectrum antibiotic such as a quinolone. Patients need to be monitored carefully, and if there is no improvement in 3 days, alternative pathogens should be sought and imaging studies such as ultrasonography performed to exclude abscess formation. Treatment is employed for a minimum of 7 days, longer as indicated by the progress of an individual patient. Pre- and posttreatment cultures are performed to ensure eradication of the infecting organism.

KEY POINTS

Diabetic Patient

1. Diabetic patients are at high risk for developing complications of UTI.
2. Antimicrobial-resistant pathogens are more common in diabetic patients.
3. Diabetics are at greater risk for atypical pathogens such as fungi.

The Transplantation Patient

In the renal allograft recipient, UTI, specifically pyelonephritis, can cause acute kidney injury. This is because of several factors, including the patient having only 1 kidney; calcineurin inhibitors decreasing afferent arterial blood flow; and interstitial inflammation caused by infection diminishing renal blood flow. Furthermore, in the first 3 months posttransplantation, the incidence of UTI is greater than 30%, and there is a relatively high rate of bacteremia and overt pyelonephritis of the allograft. The reason for this increased risk of infection is the high level of immunosuppression in the first 3 months after transplantation. In addition to decreased immune function in both sexes, there is increased vaginal overgrowth of bacteria and fungi in women. After transplantation a period of time is required for the bladder to stretch back to its normal size and regain adequate contractile function. During this period increased residual volume and incontinence predisposes to bacterial overgrowth. Finally, the transplanted ureter does not have a competent ureterovesical valve; consequently, reflux of urine into the renal collecting system is common.

Rates of UTI in renal transplantation recipients are reduced by the prophylactic use of TMP-SMX and by instructing the patient to void every 2 hours in the initial posttransplantation period. Infections in renal transplantation patients are treated as complicated UTI. Initial antibiotic selection is broad spectrum with the quinolones being first choice. A patient with UTI without fever is treated for cystitis but receives 7 to 10 days of antibiotic. A patient with a fever is treated as having pyelonephritis and receives between 3 and 4 weeks of therapy. Posttreatment urine cultures are required to ensure eradication of the infection and surveillance cultures are recommended if the patient has more than 1 episode of UTI.

Asymptomatic bacteruria presents a management challenge. The risk of excess antibiotic exposure and the development of antibiotic resistance that limits future therapeutic options must be weighed against rapid progression to symptomatic infection in an immunosuppressed patient. In general, asymptomatic bacteruria in the first 3 months following transplantation should be treated. After 3 months, close monitoring and follow-up cultures can replace immediate therapy. As with other patients who fall into the complicated UTI category, prior patient history is the most important factor in determining whether or not to initiate therapy.

KEY POINTS

Transplantation Patient

1. The incidence of UTI during the first 3 posttransplantation months is 30% higher than the normal population.
2. Pyelonephritis in a renal transplantation patient can cause acute kidney injury.
3. Treatment for cystitis is extended to 7 days and treatment for pyelonephritis is extended to 4 weeks.

COMPLICATED RENAL INFECTIONS

Emphysematous Pyelonephritis

This form of pyelonephritis, which occurs most often in patients with diabetes mellitus, is a gas-producing, necrotizing infection involving the renal parenchyma and perirenal tissue. The mechanism of gas formation and pathogenesis of emphysematous pyelonephritis is unclear and is not entirely explained by simple gas production by the involved organisms. The clinical presentation is similar to other forms of severe, acute pyelonephritis. Fevers, chills, flank or abdominal pain, nausea, and vomiting are common. Patients manifest hyperglycemia, leukocytosis, elevated blood urea nitrogen (BUN) and creatinine concentrations, and pyuria. *E. coli* is the most common organism followed by *K. pneumoniae*; bacteremia frequently accompanies this form of pyelonephritis. Diagnosis is made when plain radiograph of the abdomen reveals air in the renal parenchyma or surrounding tissue. Computed tomography (CT) scan is performed in this circumstance to define the extent of infection and evaluate the urinary tract for other lesions.

Treatment of emphysematous pyelonephritis often requires nephrectomy (or open drainage) and intravenous antibiotics. Recently, CT scan was employed to place gas-forming UTIs into 4 prognostic categories:

1. Gas present only in the collecting system.
2. Gas within the renal parenchyma without extension to the extrarenal space.

3a. Extension of gas into the perinephric space.

3b. Extension of gas into the pararenal space.

4. Bilateral or solitary kidney with emphysematous pyelonephritis.

Therapy is based on class of the lesion. Antibiotics plus percutaneous catheter placement are sufficient for patients with Class 1 or 2 disease. Antibiotics plus percutaneous catheter placement is the initial treatment of choice for patients with Class 3 disease without organ dysfunction. Antibiotics plus immediate nephrectomy is needed for patients with Class 3 disease with organ dysfunction (acute kidney injury, disseminated intravascular coagulation, shock). Percutaneous drainage is needed for patients with Class 4 disease. Nephrectomy is employed to treat drainage failures. The overall mortality rate approaches 20%.

KEY POINTS

Emphysematous Pyelonephritis

1. Emphysematous pyelonephritis occurs most commonly in patients with diabetes mellitus.
2. Gas-forming organisms such as *E. coli* and *K. pneumoniae* are associated with this form of pyelonephritis.
3. Treatment is based on class of lesion. Antibiotics and either percutaneous drainage or nephrectomy are available therapeutic options.

Xanthogranulomatous Pyelonephritis

XGP is a relatively unusual form of chronic pyelonephritis characterized by formation of mass-like lesions in the kidney. Destruction and necrosis of the kidney necessitates nephrectomy. Approximately two-thirds of cases are complicated by obstruction of the urinary system with infected nephroliths. Renal cell carcinoma is often a concern on initial evaluation of the enlarged kidney. It is often unilateral, but can be bilateral. XGP frequently develops in middle-aged women with a history of recurrent UTIs. Flank pain, fever, malaise, anorexia, and weight loss are often present at the time of evaluation. A thorough physical examination may reveal a unilateral renal mass. Anemia, liver function abnormalities, and an increased erythrocyte sedimentation rate (ESR) are nonspecific findings. Urinalysis demonstrates pyuria, bacteriuria, and white blood cell casts. Gram-negative organisms (*E. coli*, *Klebsiella*, *Providencia*, and *P. mirabilis*,) are the most common culprits.

Imaging is key to the diagnosis of XGP. CT scan is the preferred diagnostic tool in the evaluation of XGP. Renal carcinoma is excluded by CT scan based on the finding of several rounded, low-density areas within the renal parenchyma that are surrounded by an enhanced rim of contrast medium (dilated calyces lined with necrotic xanthomatous tissue extending into the renal parenchyma). Kidney stones are present in the dilated calyces. Extension of this process into the perirenal area is visualized. Xanthogranulomatous tissue can also invade adjacent gastrointestinal tract and create fistulas into the colon or duodenum.

Grossly, XGP appears as enlarged kidney with multiple mass-like lesions. The kidney is destroyed by inflammation as witnessed by necrotic renal tissue surrounded by

layers of orange-colored material. Staghorn calculi and other nephroliths are often seen within the calyces and renal masses. Perirenal extension into and adherence to surrounding structures develops from the inflamed kidney. Microscopic examination of the renal tissue reveals necrosis, leukocytes, lymphocytes, plasma cells, and macrophages. Vascularized granulation tissue, hemorrhage, and lipid-laden macrophages (xanthoma cells), which give the yellow appearance, are also present.

Surgery combined with antibiotics is the only therapy for XGP. Complete nephrectomy, where kidney and involved surrounding tissue are removed and all fistulas closed, is the mainstay of treatment. Localized disease without extension into surrounding tissue or bilateral XGP can sometimes be successfully treated with partial nephrectomy and antimicrobial agents.

KEY POINTS

Xanthogranulomatous Pyelonephritis

1. XGP can masquerade as a renal malignancy.
2. Gram-negative organisms underlie infection in XGP.
3. CT scan best demonstrates the extent of disease, excludes malignancy, and identifies the presence of renal stones.
4. The histopathology of XGP is characterized by necrotic tissue, cellular infiltration, and lipid-laden macrophages (xanthoma cells).
5. Antibiotics and nephrectomy (complete or partial) are required to treat XGP.

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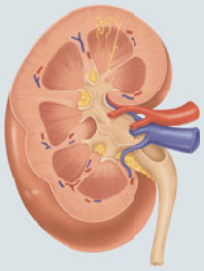

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