MANUAL OF NEPHROLOGY

Eighth Edition

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Edited by

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Preface

The eighth edition of the *Manual of Nephrology* continues to focus on the practical clinical aspects of the diagnosis and management of patients with electrolyte and acid–base disorders, urinary tract infections, kidney stones, glomerulonephritis and vasculitis, acute or chronic renal failure, hypertension, hypertension and renal disease in pregnancy, and drug dosing with renal impairment. Because of the growing number of patients with end-stage renal disease (ESRD), there are separate chapters on treatment by chronic renal replacement therapy with dialysis and kidney transplantation. The *Manual of Nephrology* should continue to be of excellent clinical value for those caregivers encountering patients with the above disorders. This would include house officers, medical students, primary care physicians, nephrology fellows, nurse practitioners, and busy subspecialists outside of nephrology.

I am very appreciative of the outstanding contributions by the authors who have made every effort to update each chapter with recent advances in the diagnosis and management of the spectrum of hypertensive and kidney disorders. There are new lead authors on eight chapters who are outstanding clinician-educators. The *Manual of Nephrology* is dedicated to Professor Hugh de Wardener who just died at age 97. He made enormous contributions to the fields of hypertension and nephrology as a clinician, scientist, and educator for over 60 years.

Robert W. Schrier, MD

Contents

1 The Edematous Patient: Cardiac Failure, Cirrhosis, and Nephrotic Syndrome

Robert W. Schrier and David H. Ellison

I. BODY FLUID DISTRIBUTION. Of the total fluids in the human body, two-thirds reside inside the cell (i.e., intracellular fluid) and one-third resides outside the cells [i.e., extracellular fluid (ECF)]. The patient with generalized edema has an excess of ECF. The ECF resides in two locations: in the vascular compartment (plasma fluid) and between the cells of the body, but outside of the vascular compartment (interstitial fluid). In the vascular compartment, approximately 85% of the fluid resides on the venous side of the circulation and 15% on the arterial side (Table 1-1). An excess of interstitial fluid constitutes edema. On applying digital pressure, the interstitial fluid can generally be moved from the area of pressure, leaving an indentation; this is described as *pitting* edema. This demonstrates that the excess interstitial fluid can move freely within its space between the body's cells. If digital pressure does not cause pitting in the edematous patient, then interstitial fluid cannot move freely. Such nonpitting edema can occur with lymphatic obstruction (i.e., lymphedema) or regional fibrosis of subcutaneous tissue, which may occur with chronic venous stasis.

Although generalized edema always signifies an excess of ECF, specifically in the interstitial compartment, the intravascular volume may be decreased, normal, or increased. For example, because two-thirds of ECF resides in the interstitial space and only one-third in the intravascular compartment, a rise in total ECF volume may occur as a consequence of excess interstitial fluid (i.e., generalized edema) although intravascular volume is decreased.

A. **Starling's law** states that the rate of fluid movement across a capillary wall is proportional to the hydraulic permeability of the capillary, the transcapillary hydrostatic pressure difference, and the transcapillary oncotic pressure difference. As shown in Figure 1-1, under normal conditions, fluid leaves the capillary at the arterial end because the transcapillary hydrostatic pressure difference favoring transudation exceeds the transcapillary oncotic pressure difference, which favors fluid resorption. In contrast, fluid returns to the capillary at the venous end because the transcapillary oncotic pressure difference exceeds the hydrostatic pressure difference. Because serum albumin is the major determinant of capillary oncotic pressure, which acts to maintain fluid in the capillary, hypoalbuminemia can lead to excess transudation of fluid from the vascular to interstitial compartment. Although hypoalbuminemia might be expected to lead commonly to edema, several factors act to buffer the effects of hypoalbuminemia on fluid transudation. First, an

Table 1-1. Body Fluid Distribution		
Compartment	**Amount**	**Volume (L) in 70-kg Man**
Total-body fluid	60% of body weight	42.0
Intracellular fluid	40% of body weight	28.0
Extracellular fluid (ECF)	20% of body weight	14.0
Interstitial fluid	Two-thirds of ECF	9.4
Plasma fluid	One-third of ECF	4.6
Venous fluid	85% of plasma fluid	3.9
Arterial fluid	15% of plasma fluid	0.7

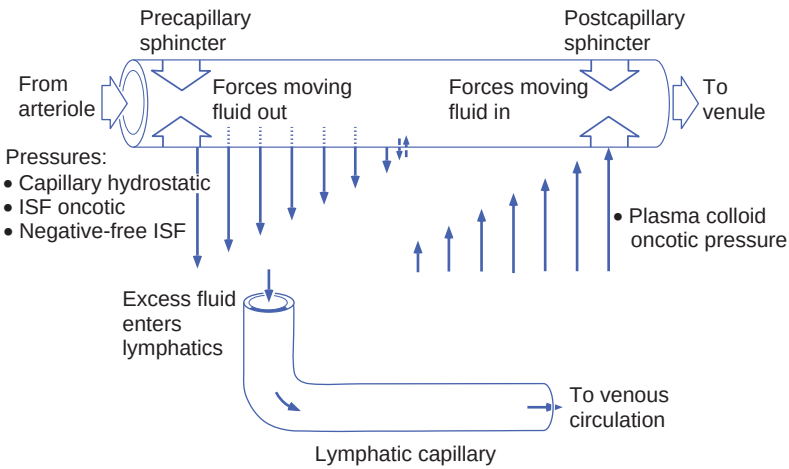

Figure 1-1. Effect of Starling forces on fluid movement across capillary wall. ISF, interstitial fluid.

increase in transudation tends to dilute interstitial fluid, thereby reducing the interstitial protein concentration. Second, increases in interstitial fluid volume increase interstitial hydrostatic pressure. Third, the lymphatic flow into the jugular veins, which returns transudated fluid to the circulation, increases. In fact, in cirrhosis, where hepatic fibrosis causes high capillary hydrostatic pressures in association with hypoalbuminemia, the lymphatic flow can increase 20-fold to 20 L/day, attenuating the tendency to accumulate interstitial fluid. When these buffering factors are overwhelmed,

interstitial fluid accumulation can lead to edema. This generally occurs when serum albumin concentration (<2.0 g/L), and thus oncotic pressure, is quite low. Another factor that must be borne in mind as a cause of edema is an increase in the fluid permeability of the capillary wall (an increase in hydraulic conductivity). This increase is the cause of edema associated with hypersensitivity reactions and angioneurotic edema, and it may be a factor in edema associated with diabetes mellitus and idiopathic cyclic edema.

B. These comments refer to **generalized edema** (i.e., an increase in total-body interstitial fluid), but it should be noted that such edema may still have a **predilection for specific areas** of the body for various reasons. With cirrhosis, edema formation has a predilection for abdominal cavity because of portal hypertension as has already been mentioned. With the normal hours of upright posture, an accumulation of the edema fluid in the lower extremities should be expected, whereas excessive hours of bed rest in the supine position predispose to edema accumulation in the sacral and periorbital areas of the body. The physician must also be aware of the potential presence of localized edema, which must be differentiated from generalized edema.

C. Although generalized edema may have a predilection for certain body sites, it is nevertheless a **total-body phenomenon** of excessive interstitial fluid. Localized edema, on the other hand, is caused by local factors and therefore is not a total-body phenomenon. Venous obstruction, as can occur with thrombophlebitis, may cause localized edema of one lower extremity. Lymphatic obstruction (e.g., from malignancy) can also cause an excessive accumulation of interstitial fluid and, therefore, localized edema. The physical examination of a patient with ankle edema should, therefore, include a search for venous incompetence (e.g., varicose veins) and for evidence of lymphatic disease. It should be recognized, however, that deep venous disease may not be detectable on physical examination and therefore may necessitate other diagnostic approaches (e.g., noninvasive ultrasonography). Therefore, if the venous disease is bilateral, the physician may mistakenly search for causes of generalized edema (e.g., cardiac failure and cirrhosis), when indeed the bilateral ankle edema is due to local factors. Pelvic lymphatic obstruction (e.g., malignancy) can also cause bilateral lower-extremity edema and thereby mimic generalized edema. Trauma, burns, inflammation, and cellulitis are other causes of localized edema.

II. BODY FLUID VOLUME REGULATION.

The edematous patient has long presented a challenge in the understanding of body fluid volume regulation. In the healthy subject, if ECF is expanded by the administration of isotonic saline, the kidney will excrete the excessive amount of sodium and water, thereby returning ECF volume to normal. Such an important role of the kidney in volume regulation has been recognized for many years. What has not been understood, however, is why the kidneys continue to retain sodium and water in the edematous patient. It is understandable that when kidney disease is present and renal function is markedly impaired (i.e., acute or chronic renal failure), the kidney continues to retain sodium and water even to a degree causing hypertension and pulmonary edema. Much more perplexing are those circumstances in which the kidneys are known to be normal and yet continue to retain sodium and water in spite of the expansion of ECF and edema formation (e.g., cirrhosis and

congestive heart failure). For example, if the kidneys from a cirrhotic patient are transplanted to a patient with end-stage renal disease but without liver disease, excessive renal sodium and water retention no longer occur. The conclusion has emerged, therefore, that neither total ECF nor its interstitial component, both of which are expanded in the patient with generalized edema, is the modulator of renal sodium and water excretion. Rather, as Peters suggested in the 1950s, some body fluid compartment other than total ECF or interstitial fluid volume must be the regulator of renal sodium and water excretion.

A. The term *effective blood volume* was coined to describe this undefined, enigmatic body fluid compartment that signals the kidney, through unknown pathways, to retain sodium and water in spite of an expansion of total ECF. That the kidney must be responding to cardiac output was suggested, providing an explanation for sodium and water retention in low-output cardiac failure. This idea, however, did not provide a universal explanation for generalized edema because many patients with decompensated cirrhosis, who were avidly retaining sodium and water, were found to have normal or elevated cardiac output.

B. **Total plasma or blood volume** was then considered as a possible candidate for the effective blood volume modulating renal sodium and water excretion. However, it was soon apparent that expanded plasma and blood volumes were frequently present in the renal sodium- and water-retaining states, such as congestive heart failure and cirrhosis. The venous component of the plasma in the circulation has also been proposed as the modulator of renal sodium and water excretion and thereby of volume regulation, because a rise in the left atrial pressure is known to cause a water diuresis and natriuresis, mediated in part by a suppression of vasopressin and a decrease in neurally mediated renal vascular resistance. A rise in right and left atrial pressure has also been found to cause a rise in atrial natriuretic peptide. However, despite these effects on the low-pressure venous side of the circulation, renal sodium and water retention are hallmarks of congestive heart failure, a situation in which pressures in the atria and venous component of the circulation are routinely increased.

C. The **arterial portion of body fluids** (Table 1-1) is the remaining component that may be pivotal in the regulation of renal sodium and water excretion. More recently, the relationship between cardiac output and systemic arterial resistance [the effective arterial blood volume (EABV)] has been proposed as a predominant regulator of renal sodium and water reabsorption. This relationship establishes the "fullness" of the arterial vascular tree. In this context, a primary decrease in cardiac output or systemic arterial vasodilation, or a combination thereof, may cause arterial underfilling and thereby initiate and sustain a renal sodium- and water-retaining state, which leads to generalized edema. The sodium- and water-retaining states that are initiated by a decline in cardiac output are shown in Figure 1-2 and include (a) ECF volume depletion (e.g., diarrhea, vomiting, and hemorrhage); (b) low-output cardiac failure, pericardial tamponade, and constrictive pericarditis; (c) intravascular volume depletion secondary to protein loss and hypoalbuminemia (e.g., nephrotic syndrome, burns or other protein-losing dermopathies, and protein-losing enteropathy); and (d) increased capillary permeability (capillary leak syndrome). The causes of increased renal sodium

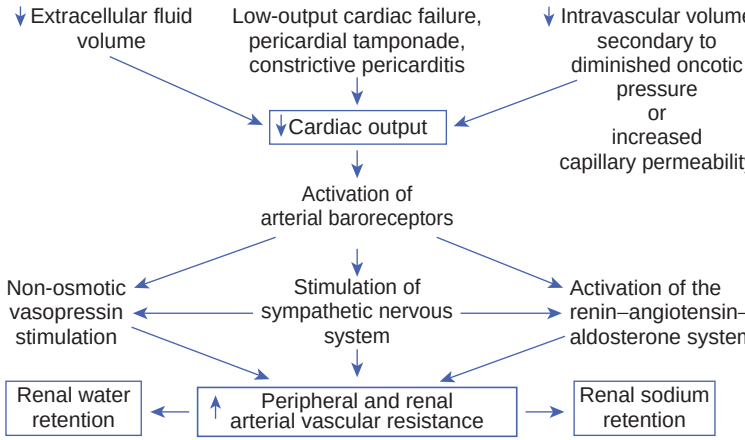

Figure 1-2. Decreased cardiac output as the initiator of arterial underfilling. (Adapted from Schrier RW. A unifying hypothesis of body fluid volume regulation. *J R Coll Physicians Lond* 1992;26:296. Reprinted with permission.)

and water retention leading to generalized edema that are initiated by primary systemic arterial vasodilation are equally numerous and are shown in Figure 1-3. Severe anemia, beriberi, Paget's disease, and thyrotoxicosis are causes of high-output cardiac failure that may lead to sodium and water retention by the normal kidney. A wide-open, large arteriovenous fistula,

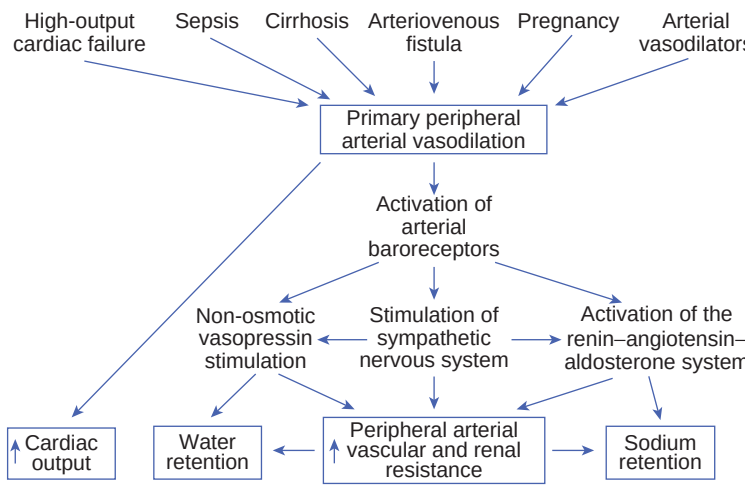

Figure 1-3. Systemic arterial vasodilation as the initiator of arterial underfilling. (Adapted from Schrier RW. A unifying hypothesis of body fluid volume regulation. *J R Coll Physicians Lond* 1992;26:296. Reprinted with permission.)

hepatic cirrhosis, sepsis, pregnancy, and vasodilating drugs (e.g., minoxidil or hydralazine) are other causes of systemic arterial vasodilation that cause arterial underfilling and decrease renal sodium and water excretion.

D. Two major **compensatory processes** protect against arterial underfilling, as defined by the interrelationship of cardiac output and systemic arterial vascular resistance. One compensatory process is very rapid and consists of a neurohumoral and systemic hemodynamic response. The other is slower and involves renal sodium and water retention. In the edematous patient, these compensatory responses have occurred to varying degrees depending on the time point when the patient is seen during the clinical course. Because of the occurrence of the rapid hemodynamic compensatory responses, mean arterial pressure is a poor index of the integrity of the arterial circulation. Whether a primary fall in cardiac output or systemic arterial vasodilation is the initiator of arterial underfilling, the compensatory responses are quite similar. As depicted in Figures 1-2 and 1-3, the common neurohumoral response to a decreased EABV involves the stimulation of three vasoconstrictor pathways, namely the sympathetic nervous system, angiotensin, and vasopressin. In addition to direct effects, the sympathetic nervous system also increases angiotensin and vasopressin because increases in central sympathetic hypothalamic input and β-adrenergic stimulation through the renal nerves are important components of the increased non-osmotic vasopressin release and stimulation of renin secretion, respectively. With a primary fall in cardiac output or primary systemic arterial vasodilation, secondary increases in systemic arterial vascular resistance or cardiac output occur, respectively, to acutely maintain arterial pressure. This rapid compensation allows time for the slower renal sodium and water retention to occur and further attenuate arterial circulatory underfilling. With a decrease in ECF volume, such as occurs with acute gastrointestinal losses, sufficient sodium and water retention can occur to restore cardiac output to normal and therefore terminate renal sodium and water retention before edema forms. Such may not be the case with low-output cardiac failure because even these compensatory responses may not restore cardiac output totally to normal.

1. Therefore, the **neurohumoral** and **renal sodium- and water-retaining mechanisms** persist as important compensatory processes in maintaining EABV. However, neither the acute nor the chronic compensatory mechanisms are successful in restoring cardiac contractility or reversing cardiac tamponade or constrictive pericardial tamponade. Compensatory renal sodium and water retention occurs with an expansion of the venous side of the circulation as arterial vascular filling improves but does not return to normal. The resultant rise in venous pressure enhances capillary hydrostatic pressure and thereby transudation of fluid into the interstitial fluid, with resultant edema formation. In hypoalbuminemia and the capillary leak syndrome, excessive transudation of fluid occurs across the capillary bed and also prevents the restoration of cardiac output; therefore, continuous renal sodium and water retention occurs and causes edema formation.
2. **Systemic arterial vasodilation**, the other major initiator of arterial underfilling, also generally cannot be totally reversed by the compensatory mechanisms and therefore may lead to edema formation.

Systemic arterial vasodilation results in dilation of precapillary arteriolar sphincters, thereby increasing capillary hydrostatic pressure and probably capillary surface area. A larger proportion of retained sodium and water is therefore transudated across the capillary bed into the interstitium in these edematous disorders (Fig. 1-3).

E. Another reason why low cardiac output or systemic arterial vasodilation may lead to edema formation is the inability of patients with these disorders, as compared with healthy subjects, to escape from the **sodium-retaining effect of aldosterone** (Fig. 1-4). In the healthy subject receiving large exogenous doses of aldosterone or another mineralocorticoid hormone, ECF expansion is associated with a rise in the glomerular filtration rate and a decrease in proximal tubular sodium and water reabsorption, which leads to an increase in sodium and water delivery to the distal nephron site of aldosterone action. This increase in distal sodium delivery is the major mediator of escape from the sodium-retaining effect of mineralocorticoids in healthy subjects, thereby avoiding edema formation. In contrast, in patients with cirrhosis or cardiac failure, the renal vasoconstriction that accompanies the

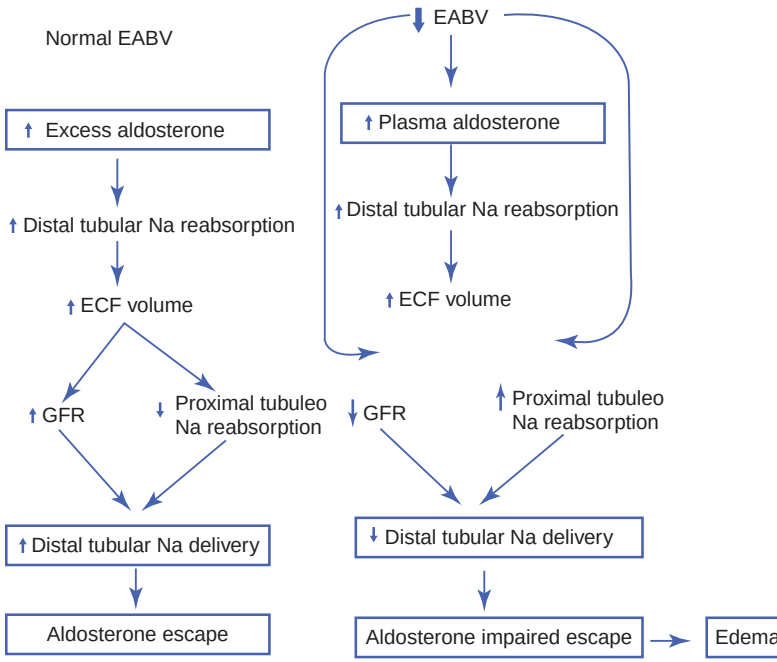

Figure 1-4. Aldosterone escape in a healthy subject (left side) and failure of aldosterone escape in patients with arterial underfilling (right side). (EABV, effective arterial blood volume; ECF, extracellular fluid; GFR, glomerular filtration rate.) (Adapted from Schrier RW. Body fluid regulation in health and disease: a unifying hypothesis. *Ann Intern Med* 1990;113:155–159. Adapted with permission.)

compensatory neurohumoral response to arterial underfilling is associated with a decrease in distal sodium and water delivery to the distal nephron site of aldosterone action. This diminution in distal delivery, which occurs primarily because of a fall in the glomerular filtration rate and an increase in proximal tubular sodium reabsorption, results in a failure to escape from aldosterone and, therefore, causes edema formation. The importance of renal hemodynamics, particularly the glomerular filtration rate, in the aldosterone escape phenomena is emphasized by the observation that in pregnancy, a state of primary arterial vasodilation, aldosterone escape occurs despite arterial underfilling because of an associated 30% to 50% increase in the glomerular filtration rate. It still remains to be determined why pregnancy is associated with this large increase in the glomerular filtration rate, which occurs within 2 to 4 weeks of conception. However, there is evidence that an increase in relaxin may be involved. The increase in the filtration rate cannot be due to plasma volume expansion, because this does not occur until several weeks after conception. The higher filtered load of sodium, and therefore increased distal sodium load in pregnancy, no doubt allows the escape from the sodium-retaining effect of aldosterone which is elevated in normal pregnancy. The occurrence of aldosterone escape in pregnancy attenuates edema formation when compared with other edematous disorders.

III. DIETARY AND DIURETIC TREATMENT OF EDEMA: GENERAL PRINCIPLES. The daily sodium intake in the United States is typically 4 to 6 g [1 g of sodium contains 43 mEq; 1 g of sodium chloride (NaCl) contains 17 mEq of sodium]. By not using added salt at meals, the daily sodium intake can be reduced to 4 g (172 mEq), whereas a typical "low-salt" diet contains 2 g (86 mEq). Diets that are even lower in NaCl content can be prescribed, but many individuals find them unpalatable. If salt substitutes are used, it is important to remember that these contain potassium chloride; therefore potassium-sparing diuretics (i.e., spironolactone, eplerenone, triamterene, and amiloride) should not be used with salt substitutes. Other drugs that increase serum potassium concentration must also be used with caution in the presence of salt substitute intake [i.e., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs)]. When prescribing dietary therapy for an edematous patient, it is important to emphasize that NaCl restriction is required, even if diuretic drugs are employed. The therapeutic potency of diuretic drugs varies inversely with dietary salt intake.

All commonly used **diuretic drugs** act by increasing urinary sodium excretion. They can be divided into five classes based on their predominant site of action along the nephron (Table 1-2). Osmotic diuretics (e.g., mannitol) and proximal diuretics (e.g., acetazolamide) are not employed as primary agents to treat edematous disorders. Loop diuretics (e.g., furosemide), distal convoluted tubule (DCT; e.g., hydrochlorothiazide) diuretics, and collecting duct diuretics (e.g., spironolactone), however, all play important but distinct roles in treating edematous patients. The goal of the diuretic treatment of edema is to reduce ECF volume and to maintain the ECF volume at the reduced level. This requires an initial natriuresis, but, at steady state, urinary NaCl excretion returns close to baseline despite continued diuretic administration. Importantly, an increase in sodium and water excretion does *not* prove therapeutic efficacy if ECF volume does not decline. Conversely, a return to "basal" levels of urinary

Table 1-2.	Physiologic Classification of Diuretic Drugs
Osmotic Diuretics	
Proximal Diuretics	
Carbonic anhydrase inhibitors	
Acetazolamide	
Loop diuretics (Maximal FENa = 30%)	
Na-K-2Cl inhibitors	
Furosemide	
Bumetanide	
Torsemide	
Ethacrynic acid	
DCT Diuretics (Maximal FENa = 9%)	
NaCl inhibitors	
Chlorothiazide	
Hydrochlorothiazide	
Metolazone	
Chlorthalidone	
Indapamide[a]	
Many others	
Collecting Duct Diuretics (Maximal FENa = 3%)	
Na channel blockers	
Amiloride	
Triamterene	
Aldosterone antagonists	
Spironolactone Eplerenone	

DCT, distal convoluted tubule. FENa, fratctional excretion of sodium
[a]Indapamide may have other actions as well.

NaCl excretion does not indicate diuretic resistance. The continued efficacy of a diuretic is documented by the rapid return to ECF volume expansion that occurs if the diuretic is discontinued.

A. When starting a loop diuretic as treatment for edema, it is important to establish a therapeutic goal, usually a target body weight. If a low dose does not lead to natriuresis, it can be doubled repeatedly until the maximum recommended dose is reached (Table 1-3). When a **diuretic drug is administered by mouth**, the magnitude of the natriuretic response is determined by the intrinsic potency of the drug, the dose, the bioavailability, the amount delivered to the kidney, the amount that enters the tubule fluid (most diuretics act from the luminal side), and the physiologic state of the individual. Except for proximal diuretics, the maximal natriuretic potency of a diuretic can be predicted from its site of action. In Table 1-2, it is shown that loop diuretics can maximally increase fractional sodium (Na) excretion to 30%, DCT diuretics can increase it to 9%, and sodium channel blockers can increase it to 3% of the filtered load. The intrinsic diuretic potency of a diuretic is defined by its dose–response curve, which is generally sigmoid. The steep sigmoid relation is the reason that loop diuretic drugs are often described as *threshold drugs*. When starting loop diuretic treatment,

Table 1-3. Ceiling Doses of Loop Diuretics

	Furosemide (mg)		Bumetanide (mg)		Torsemide (mg)	
	IV	PO	IV	PO	IV	PO
Renal Insufficiency						
GFR 20–50 mL/min	80	80–160	2–3	2–3	50	50
GFR <20 mL/min	200	240	8–10	8–10	100	100
Severe acute renal failure	500	NA	12	NA	—	—
Nephrotic syndrome	120	240	3	3	50	50
Cirrhosis	40–80	80–160	1	1–2	10–20	10–20
Congestive heart failure	40–80	160–240	2–3	2–3	20–50	50

GFR, glomerular filtration rate; IV, intravenous; NA, not available.

Ceiling dose indicates the dose that produces the maximal increase in fractional sodium excretion. Larger doses may increase net daily natriuresis by increasing the *duration* of natriuresis without increasing the maximal rate.

ensuring that each dose reaches the steep part of the dose–response curve before the dose frequency is adjusted is important. Because loop diuretics are rapid acting, many patients note an increase in urine output within several hours of taking the drug; this can be helpful in establishing that an adequate dose has been reached. Because loop diuretics are short acting, any increase in urine output more than 6 hours after a dose is unrelated to drug effects. Therefore, most loop diuretic drugs should be administered at least twice daily, when given by mouth.

B. The **bioavailability of diuretic drugs** varies widely among classes of drugs, among different drugs of the same class, and even within the same drug. The bioavailability of loop diuretics varies with furosemide ranging from 10% to 100% (mean, 50% for furosemide; 80% to 100% for bumetanide and torsemide). Limited bioavailability can usually be overcome by appropriate dosing, but some drugs, such as furosemide, are variably absorbed by the same patient on different days, making precise titration difficult. Doubling the furosemide dose when changing from intravenous to oral therapy is customary, but the relation between intravenous and oral dose may vary. For example, the amount of sodium excreted during 24 hours is similar whether furosemide is administered to a healthy individual by mouth or by vein, despite its 50% bioavailability. This paradox results from the fact that oral furosemide absorption is slower than its clearance, leading to "absorption-limited" kinetics. Therefore, effective serum furosemide concentrations persist longer when the drug is given by mouth, because a reservoir in the gastrointestinal tract continues to supply furosemide to the body. This relation holds for a healthy individual. Predicting the precise relation between oral and intravenous doses, therefore, is difficult.

IV. DIURETIC RESISTANCE.

Patients are considered to be **diuretic resistant** when an inadequate reduction in ECF volume is observed despite near-maximal doses of loop diuretics. Several causes of resistance can be determined by considering factors that affect diuretic efficacy, as discussed earlier.

A. Causes of Diuretic Resistance

1. **Excessive Dietary NaCl Intake is One Cause of Diuretic Resistance.** When NaCl intake is high, renal NaCl retention can occur between diuretic-induced natriuretic periods, thereby maintaining the ECF volume expansion. Measuring the sodium excreted during 24 hours can be useful in diagnosing excessive intake. If the patient is at steady state (the weight is stable), then the urinary sodium excreted during 24 hours is equal to dietary NaCl intake. If sodium excretion exceeds 100 to 120 mM (approximately 2 to 3 g sodium/day), then dietary NaCl consumption is too high and dietary counseling should be undertaken.
2. **Impaired diuretic delivery to its active site** in the kidney tubule is another cause of diuretic resistance. Most diuretics, including the loop diuretics, DCT diuretics, and amiloride, act from the luminal surface. Although diuretics are small molecules, most circulate while tightly bound to protein and reach tubule fluid primarily by tubular secretion. Loop and DCT diuretics are organic anions that circulate bound to albumin and reach tubule fluid primarily through the organic anion

secretory pathway in the proximal tubule. Although experimental data suggest that diuretic resistance results when serum albumin concentrations are very low, because the volume of diuretic distribution increases, most studies suggest that this effect is only marginally significant clinically and is observed only when serum albumin concentration declines below 2 g/L. A variety of endogenous and exogenous substances that compete with diuretics for secretion into tubule fluid are more probable causes of diuretic resistance. Uremic anions, NSAIDs, probenecid, and penicillin all inhibit loop and DCT diuretic secretion into tubule fluid. Under some conditions, this may predispose to diuretic resistance, because the concentration of drug achieved in tubule fluid does not exceed the diuretic threshold. For example, chronic renal failure shifts the loop diuretic dose–response curve to the right, therefore requiring a higher dose to achieve maximal effect.

3. **Diuretic binding to protein in tubule fluid** is another factor that may influence diuretic effectiveness. Diuretic drugs are normally bound to proteins in the plasma, but not after they are secreted into tubule fluid. This reflects the normally low protein concentrations in tubule fluid. In contrast, when serum proteins, such as albumin, are filtered in appreciable quantities, as in nephrotic syndrome, diuretic drugs may interact with them and lose effectiveness. Despite experimental support, recent clinical studies have indicated that this phenomenon does not contribute significantly to diuretic resistance in nephrotic syndrome.
4. Figure 1-5 shows how decreased distal sodium delivery and secondary hyperaldosteronism contribute to diuretic resistance.

B. **Treatment of Diuretic Resistance.** Several strategies are available to achieve the effective control of ECF volume in patients who do not respond to full doses of effective loop diuretics.

1. A diuretic of another class may be added to a regimen that includes a loop diuretic (Table 1-4). This strategy produces true synergy; the combination of agents is more effective than the *sum* of the responses to each agent alone. DCT diuretics are most commonly combined with loop diuretics. DCT diuretics inhibit the adaptive changes in the distal nephron that increase the reabsorptive capacity of the tubule and limit the potency of loop diuretics. Because DCT diuretics have longer half-lives than loop diuretics, they prevent or attenuate NaCl retention during the periods between doses of loop diuretics, thereby increasing their net effect. When two diuretics are combined, the DCT diuretic is generally administered some time before the loop diuretic (1 hour is reasonable) to ensure that NaCl transport in the distal nephron is blocked when it is flooded with solute. When intravenous therapy is indicated, chlorothiazide (500 to 1,000 mg) may be employed. Metolazone is the DCT diuretic most frequently combined with loop diuretics, because its half-life is relatively long (as formulated in zaroxylyn) and because it has been reported to be effective even when renal failure is present. Other thiazide and thiazide-like diuretics, however, appear to be equally effective, even in severe renal failure. The dramatic effectiveness of combination diuretic therapy is accompanied by complications in a significant number of patients. Massive fluid and electrolyte losses

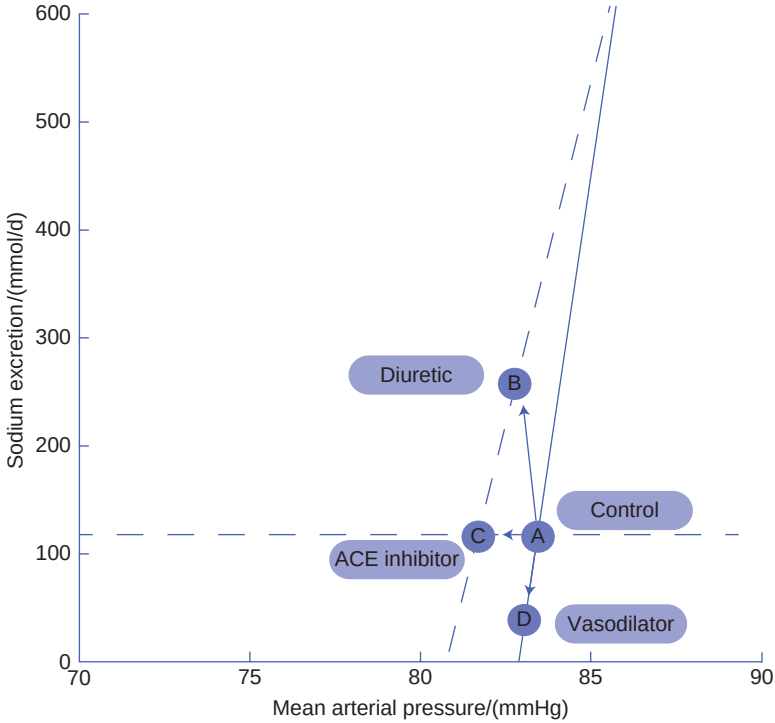

Figure 1-5. Comparison of diuretic, angiotensin-converting enzyme (ACE) inhibitor, and vasodilator effects on mean arterial pressure and natriuresis. The normal renal function curve is shown (*solid line*). Adding a vasodilator reduces mean arterial pressure but also reduces natriuresis because blood pressure declines. A diuretic moves the individual to a new renal function curve (*dashed line*), thereby increasing natriuresis, but has little effect on blood pressure. An ACE inhibitor moves the individual to a new renal function curve, maintaining natriuresis at a lower blood pressure.

(i.e., sodium, potassium, and magnesium) have led to circulatory collapse and arrhythmia during combination therapy, and patients must be followed up carefully. The lowest effective dose of DCT diuretic should be added to the loop diuretic regimen; patients can frequently be treated with combination therapy for only a few days and then must be placed back on a single-drug regimen. When continuous combination therapy is needed, low doses of DCT diuretic (2.5 mg metolazone or 25 mg hydrochlorothiazide) administered only two or three times per week may be sufficient.

2. For hospitalized patients who are resistant to diuretic therapy, the continuous infusion of loop diuretics is an alternative approach. **Continuous diuretic infusions** (Table 1-5) have several advantages over bolus diuretic administration. First, because they avoid peaks and troughs of

Table 1-4.	Combination Diuretic Therapy (to Add to a Ceiling Dose of a Loop Diuretic)
Distal Convoluted Tubule Diuretics	
Metolazone 2.5–10 mg p.o. daily[a]	
Hydrochlorothiazide (or equivalent) 25–100 mg p.o. daily	
Chlorothiazide 500–1,000 mg i.v.	
Proximal Tubule Diuretics	
Acetazolamide 250–375 mg daily or up to 500 mg i.v.	
Collecting Duct Diuretics	
Spironolactone 100–200 mg daily	
Amiloride 5–10 mg daily	

[a]Metolazone is generally best given for a limited period (3 to 5 d) or should be reduced in frequency to three times per week once extracellular fluid volume has declined to the target level. Only in patients who remain volume expanded should full doses be continued indefinitely, based on the target weight.

Table 1-5.	Continuous Infusion of Loop Diuretics			
		Infusion Rate (mg/hr)		
Diuretic	Starting Bolus (mg)	GFR <25 mL/min	GFR 25–75 mL/min	GFR >75 mL/min
Furosemide	40	20, then 40	10, then 20	10
Bumetanide	1	1, then 2	0.5, then 1	05
Torsemide	20	10, then 20	5, then 10	—

GFR, glomerular filtration rate.

diuretic concentration, continuous infusions prevent periods of positive NaCl balance (postdiuretic NaCl retention) from occurring. Second, continuous infusions may be more efficient than bolus therapy (the amount of NaCl excreted per milligram of drug administered is greater). Third, some patients who are resistant to large doses of diuretics given by bolus respond to continuous infusion. Fourth, diuretic response can be titrated; in the intensive care unit, where obligate fluid administration

must be balanced by fluid excretion, excellent control of NaCl and water excretion can be obtained. Finally, complications associated with high doses of loop diuretics, such as ototoxicity, appear to be less common when large doses are administered as a continuous infusion. Total daily furosemide doses exceeding 1 g have been tolerated well when administered over 24 hours. One approach is to administer a loading dose of 20 mg furosemide followed by a continuous infusion at 4 to 60 mg/hour. In patients with preserved renal function, therapy at the lower dosage range should be sufficient. When renal failure is present, higher doses may be used, but patients should be monitored carefully for side effects, such as ECF volume depletion and ototoxicity.

3. The randomized double-blind controlled trial Diuretic Optimization Strategies Evaluation (DOSE) examined the mode and dose of loop diuretics in decompensated heart failure patients. There was no difference in global symptom relief or change in kidney function at 72 hours between intermittent bolus versus continuous infusion of furosemide or between low dose (outpatient dose) and high dose (2.5 times outpatient dose). Later, however, body weight loss was better with the continuous infusion. There was no difference in outcomes between the groups at 60 days follow-up. Nevertheless, the Heart Failure Society of America guidelines recommend switching to continuous infusion of diuretics in patients with decompensated heart failure who are initially unresponsive to bolus diuretics.

Ultrafiltration by a peripheral and central access is another approach for treating fluid overloaded diuretic-resistant patients with decompensated heart failure. The 3-year randomized Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study of 200 patients demonstrated significantly greater weight loss at 48 hours with ultrafiltration and fewer hospital readmissions at 90 days follow-up. There was, however, no formal protocol for diuretic use and the maximal doses used were less than recommended by international guidelines.

A subsequent multicenter trial of Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome (CARRESS-HF) compared stepwise pharmacological treatment versus ultrafiltration in 188 patients with persistent congestion and rising serum creatinine. Both groups had the same weight loss and dyspnea score, but only the ultrafiltration group had an increase in serum creatinine. There was no difference in 60 days follow-up for mortality or rehospitalization.

V. CONGESTIVE HEART FAILURE

A. Early **clinical symptoms** of cardiac failure occur before overt physical findings of pedal edema and pulmonary congestion. These symptoms relate to the compensatory renal sodium and water retention that accompanies arterial underfilling. The patient may present with a history of weight gain, weakness, dyspnea on exertion, decreased exercise tolerance, paroxysmal nocturnal dyspnea, and orthopnea. Nocturia may occur because cardiac output, and therefore renal perfusion, may be enhanced by the supine

position. Patients with congestive heart failure may lose considerable weight during the first few days of hospitalization because of the supine position of bed rest, even without the administration of diuretics. Although overt edema is not detectable early in the course of congestive heart failure, the patient may complain of swollen eyes on awakening and tight rings and shoes, particularly at the end of the day. With incipient edema, as much as 3 to 4 L of fluid can be retained before the occurrence of overt edema.

The period of incipient edema is then followed by more overt symptoms and physical findings: basilar pulmonary rales, ankle edema, distended neck veins at 30 degrees, tachycardia, and a gallop rhythm with a third heart sound. Although the chest x-ray may only show cephalization of pulmonary markings early in cardiac failure, increased hilar markings, Kerley's B lines, and pleural effusions occur later, generally accompanied by an enlarged heart size.

B. Etiology. Two mechanisms that reduce cardiac output are recognized to cause congestive heart failure: systolic dysfunction and diastolic dysfunction. Because specific, life-saving therapy is available for systolic dysfunction, it is essential to determine whether systolic dysfunction is present when a patient presents with the symptoms and signs of heart failure. Although physical examination, chest x-ray, and electrocardiogram are useful in this regard, additional diagnostic tests are usually indicated. An echocardiogram provides information about systolic (the ejection fraction) and diastolic function, and about valvular disease, which may require surgery. Occult hypothyroidism or hyperthyroidism and alcoholic cardiomyopathy may present as congestive heart failure; these entities are treatable. Uncontrolled hypertension may contribute to congestive heart failure, but disease of the coronary arteries is the most common cause. In one study, severe coronary artery disease was found in 9 of 38 patients undergoing cardiac transplantation for presumed idiopathic dilated cardiomyopathy, and in 3 of 4 patients with presumed alcoholic cardiomyopathy. These data suggest that cardiac catheterization may be indicated in virtually all patients who present with new-onset congestive heart failure. In patients with preexisting cardiac disease, a cardiac arrhythmia, pulmonary embolus, cessation of medicines, severe anemia or fever, dietary sodium indiscretion, and worsening of chronic obstructive lung disease with infection and resultant hypoxia are examples of potentially treatable precipitants of worsening congestive heart failure. Drugs with a negative inotropic effect, such as verapamil, may worsen heart failure by decreasing cardiac output. A trial cessation of these drugs is the best means of determining their possible role in worsening congestive heart failure.

C. Treatment. When none of these specific primary or precipitating causes of congestive heart failure are detectable, then general principles of treatment must be considered.

Every patient with symptomatic systolic dysfunction or, if asymptomatic, an ejection fraction of less than 40% should be started on an **angiotensin-converting enzyme (ACE) inhibitor**, unless a specific contraindication exists. ACE inhibitors (and angiotensin receptor inhibitors) are unique agents that reduce blood pressure (reduce afterload), shift the renal function curve to the left (promote continued sodium losses), and

block maladaptive neuroregulatory hormones (Fig. 1-5). Short-acting ACE inhibitors should be started at low doses (enalapril 2.5 mg b.i.d. or captopril 6.25 mg t.i.d.), but increased if tolerated to 10 b.i.d. of enalapril or 50 t.i.d. of captopril, unless side effects occur. Once-daily ACE inhibitor can be used when the patient is stable. If cough or angioedema limits ACE inhibitor use, then an AT_1 angiotensin receptor blocker should be used (although angioedema may develop with AT_1 receptor blockers, the incidence is lower with this class of drugs). If neither class of drug can be employed safely, then therapy with hydralazine and isosorbide dihydrate or monohydrate should be used.

β-Blockers have been shown to improve symptoms and mortality in patients with systolic dysfunction. Both selective β-blockers (metoprolol) and nonselective β-blockers with α-blocking properties (carvedilol) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of congestive heart failure. Because β-blockers can lead to symptomatic exacerbations of heart failure, these drugs are initiated in low doses only when patients are clinically stable and without expansion of the ECF volume.

The role of **digitalis glycosides** has been clarified by recent controlled studies. Digoxin significantly improves symptoms and reduces the incidence of hospitalization in patients with impaired left ventricular function, but it does not appear to prolong life. Therefore, the drug is indicated for symptomatic treatment when combined with ACE inhibitors and diuretics. In certain clinical states of heart failure, however, cardiac glycosides have been shown to be of little therapeutic value, for example, in association with thyrotoxicosis, chronic obstructive pulmonary disease, and cor pulmonale. Cardiac glycosides may actually worsen symptoms in patients with hypertrophic obstructive cardiomyopathy and subaortic stenosis, pericardial tamponade, and constrictive pericarditis. It should also be remembered that digoxin is excreted by the kidneys; therefore, the dosage interval should be increased in the patient with chronic renal disease (see Chapter 16). Also, the elderly patient should receive a decreased dose (e.g., 0.125 mg q.o.d.), even if the serum creatinine level is not increased. Although renal function deteriorates with age, serum creatinine levels may not rise in the elderly because of a concomitant loss of muscle mass. Although potentially useful acute therapy, phosphodiesterase inhibitors, such as milrinone, which also increase cardiac output, have been shown to increase mortality when used chronically. Therefore, the chronic use of these drugs should be avoided.

If symptomatic pulmonary congestion or peripheral edema is present, **diuretic therapy** is indicated (Fig. 1-5). A loop diuretic is usually employed as first-line therapy, although some patients may be managed using a thiazide. In patients with congestive heart failure, diuretic therapy must be instituted with full knowledge of the Starling-Frank curve of myocardial contractility (Fig. 1-6). The patient with congestive heart failure who responds to a diuretic will exhibit improved symptomatology as end-diastolic volume and pulmonary congestion decrease. However, because the Starling-Frank curve is usually either flat or upsloping even in failing hearts, an improvement in cardiac output may not occur. If, during the diuretic treatment of a patient with congestive heart failure, the serum creatinine and blood urea nitrogen levels begin to rise, it is likely that cardiac output has fallen. This situation is especially pronounced in patients who are receiving ACE inhibitor therapy.

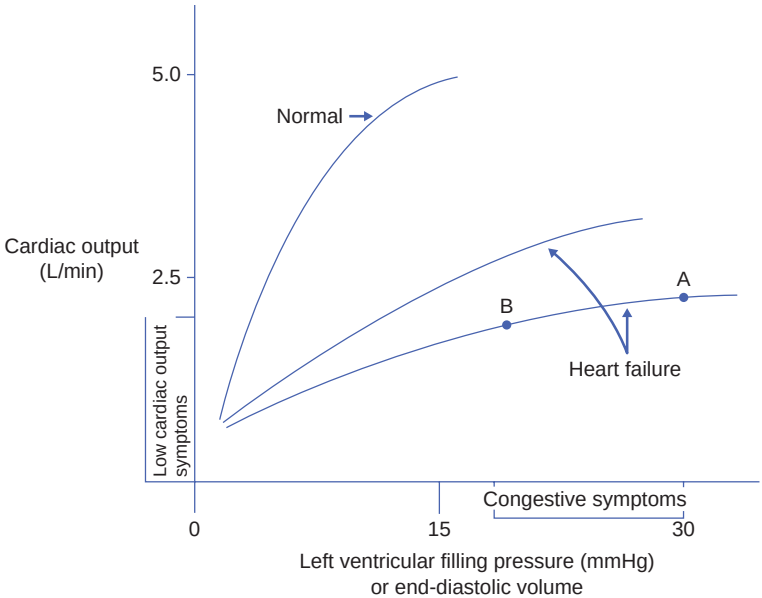

Figure 1-6. Relationship between cardiac output and left ventricular filling pressure under normal circumstances (*upper curve*) and low-output congestive heart failure (*lower curve*). Reduction of afterload [e.g., angiotensin-converting enzyme (ACE) inhibitor or a vasodilator] or improved contractility (inotropic agents) may shift the lower curve to the *middle curve*. Diuretic-induced preload reduction or other causes of volume depletion may decrease cardiac output (e.g., shift from point A to point B on the *lower curve*). (From Schrier RW, ed. *Renal and electrolyte disorders*, 7th ed. Philadelphia, PA: Lippincott Williams and Wilkins, 2010. Reprinted with permission.)

ACE inhibitors impair renal autoregulation and make patients prone to prerenal azotemia. When mild azotemia develops in a patient treated with diuretics and an ACE inhibitor, it is usually advisable to reduce the diuretic dose or liberalize dietary salt intake, provided that pulmonary congestion is not present simultaneously. This approach has been shown to permit the continued administration of ACE inhibitors in many patients. Some pedal edema may be preferable to a diuretic-induced decline in cardiac output as estimated by the occurrence or worsening of prerenal azotemia. Patients with congestive heart failure are especially sensitive to renal functional deterioration if NSAIDs are used together with diuretics and ACE inhibitors. Therefore, NSAIDs should be diligently avoided in this patient population.

Both congestive heart failure and treatment with loop diuretics stimulate the renin–angiotensin–aldosterone axis. Two large studies have provided evidence that **blocking mineralocorticoid (aldosterone) receptors** can improve mortality of such patients. In one trial, adding spironolactone (25 mg/day) to a regimen that included an ACE inhibitor and a diuretic (with or without digoxin) reduced all-cause mortality by 30% and reduced hospitalization for heart failure by 35%. This effect was felt to be independent

of a negative sodium balance, but rather due to inhibition of cardiac fibrosis, inflammation, and apoptosis. Gynecomastia, which is a relatively common side effect of spironolactone owing to its estrogenic side effects, does not appear to occur with a newer more selective inhibitor of mineralocorticoid receptor, eplerenone.

Hyperkalemia is of concern when aldosterone blockade is instituted. It is currently recommended that serum potassium be monitored 1 week after initiating therapy with an aldosterone blocker, after 1 month, and every 3 months thereafter. An increase in serum potassium greater than 5.5 mEq/L should prompt an evaluation of dietary potassium intake and for medications such as potassium supplements or NSAIDs that might be contributing to the hyperkalemia. If such factors are not detected, the dose of aldosterone blocker should be reduced to 25 mg every other day. It is prudent to avoid the use of aldosterone blockers in patients with a creatinine clearance of less than 30 mL/minute and to be cautious in those with a creatinine clearance of between 30 and 50 mL/minute. These patients must be followed up very closely.

Complications of diuretic therapy are shown in Table 1-6. Although hyponatremia may be a complication of diuretic treatment, furosemide,

Table 1-6. Complications of Diuretics

Contraction of the vascular volume
Orthostatic hypotension (from volume depletion)
Hypokalemia (loop and DCT diuretics)
Hyperkalemia (spironolactone, eplerenone, triamterene, and amiloride)
Gynecomastia (spironolactone)
Hyperuricemia
Hypercalcemia (thiazides)
Hypercholesterolemia
Hyponatremia (especially with DCT diuretics)
Metabolic alkalosis
Gastrointestinal upset
Hyperglycemia
Pancreatitis (DCT diuretics)
Allergic interstitial nephritis

DCT, distal convoluted tubule.

when combined with ACE inhibitors, may ameliorate hyponatremia in some patients with congestive heart failure, possibly by improving cardiac output and diminishing urinary concentration. In patients with heart failure, hypokalemia and hypomagnesemia are frequent complications of diuretic treatment because of secondary hyperaldosteronism, which increases sodium delivery to the distal sites at which aldosterone stimulates potassium and hydrogen ion secretion. Severe renal magnesium wasting may also occur in the setting of secondary hyperaldosteronism and loop diuretic administration. Because both magnesium and potassium depletion cause similar deleterious effects on the heart, and potassium repletion is very difficult in the presence of magnesium depletion, supplemental replacement of both these cations is frequently necessary in patients with cardiac failure.

The treatment of patients with congestive heart failure and preserved systolic function is less clearly defined. Hypertension control is clearly paramount in these patients, because hypertension is a frequent cause of cardiac hypertrophy and diastolic dysfunction. Diuretics are usually necessary to improve symptoms of dyspnea and orthopnea. β-Blockers, ACE inhibitors, angiotensin receptor blockers, or nondihydropyridine calcium antagonists may be beneficial in some patients with diastolic dysfunction. Diastolic dysfunction is a very common cause of heart failure in elderly patients.

VI. HEPATIC CIRRHOSIS. The pathogenesis of renal sodium and water retention is similar in all varieties of cirrhosis, including alcoholic, viral, and biliary cirrhosis. Studies in both humans and animals indicate that renal sodium and water retention precedes the formation of ascites in cirrhosis. Therefore, the classic "underfill theory," which attributed the renal sodium and water retention of cirrhosis to ascites formation with resultant hypovolemia, seems untenable as a primary mechanism. Because plasma volume expansion secondary to renal sodium and water excretion occurs before ascites formation, the "overflow theory" of ascites formation was proposed. This postulated that an undefined process, triggered by the diseased liver (e.g., increased intrahepatic pressure), causes renal sodium and water retention that then overflows into the abdomen because of portal hypertension. This overflow theory, however, predicts that renal salt retention and ascites formation would be associated with decreased plasma levels of vasopressin, renin, aldosterone, and norepinephrine. Because these hormones rise progressively as cirrhosis advances from the states of compensation (no ascites) to decompensation (ascites) to hepatorenal syndrome, the overflow hypothesis also does not seem to explain the spectrum of renal sodium and water retention associated with advanced cirrhosis. More recently, the systemic arterial vasodilation theory has been proposed. This theory, summarized in Figure 1-7, is compatible with virtually all known observations in patients during the various stages of cirrhosis. According to this theory, cirrhosis causes systemic arterial vasodilation with activation of the neurohumoral axis. The cause of the primary arterial vasodilation in cirrhosis is not clear, but is known to present early and occur primarily in the splanchnic circulation. Several mediators, including substance P, vasoactive intestinal peptide, endotoxin, and glucagon, have been proposed to play a role in splanchnic arterial vasodilation. Recent information indicates that nitric oxide may be a crucial mediator. The opening of existing splanchnic arteriovenous shunts may account for some early

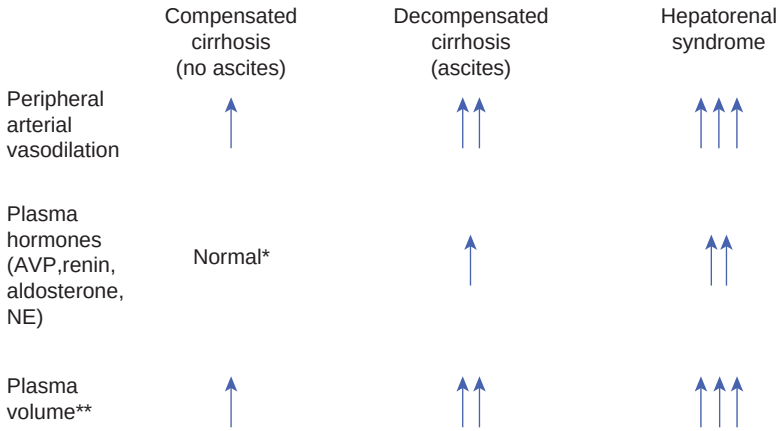

Figure 1-7. Systemic arterial vasodilation hypothesis. Stages of progression of cirrhosis. (AVP, arginine vasopressin; NE, norepinephrine.) *Given the positive sodium and water balance that has occurred, these plasma hormones would be suppressed in healthy subjects without liver disease. **The progressive renal sodium and water retention increases extracellular fluid, interstitial fluid, and plasma volume, but is inadequate to correct the arterial underfilling. The concomitant occurrence of hypoalbuminemia in decompensated cirrhosis and hepatorenal syndrome may attenuate the degree of volume expansion.

arterial vasodilation. Later, anatomically new portosystemic and arteriovenous shunting secondary to the portal hypertension may also occur.

A. **Options for treating cirrhotic ascites and edema** include dietary NaCl restriction, diuretic drugs, large-volume paracentesis, peritoneovenous shunting, portosystemic shunting [usually transjugular intrahepatic portosystemic shunting (TIPS)], and liver transplantation. Each of these approaches has a role in the treatment of cirrhotic ascites, but most patients can be treated successfully with NaCl dietary restriction, diuretics, and intermittent large-volume paracentesis.

The **initial therapy of cirrhotic ascites** is supportive, including dietary sodium restriction and cessation of alcohol. When these measures prove inadequate, diuretic treatment should begin with spironolactone. Spironolactone has several advantages. First, a controlled trial showed that spironolactone is more effective than furosemide alone in reducing ascites in cirrhotic patients. Second, spironolactone is a long-acting diuretic that can be given once per day in doses ranging from 25 to 400 mg. Third, unlike most other diuretics, hypokalemia does not occur when spironolactone is administered. This is important because hypokalemia increases renal ammonia production and can precipitate encephalopathy. The most common side effect of spironolactone is painful gynecomastia. (Gynecomastia appears to be much less common with eplerenone, a more selective antagonist, which may be substituted.) Although amiloride, another K-sparing diuretic, can be used as an alternative, spironolactone is more effective than amiloride in

reducing ascites. In patients who do not respond to a low dose of spironolactone, it can be combined with furosemide, starting at 100 mg spironolactone and 40 mg furosemide (to a daily maximum of 400 mg spironolactone and 160 mg furosemide). This regimen has the advantages of once per day dosing and minimal hypokalemia. Diuretic resistance in cirrhosis has been defined as absence of a natriuretic response to 400 mg spironolactone and 160 mg furosemide.

B. The appropriate **rate of diuresis** depends on the presence or absence of peripheral edema. Because mobilizing ascitic fluid into the vascular compartment is slow (approximately 500 mL/day), the rate of daily diuresis should be limited to 0.5 kg/day if peripheral edema is absent. In the presence of peripheral edema, most patients can tolerate up to 1.0 kg/day of fluid removal. Because ascites in the decompensated cirrhotic patient is associated with substantial complications including (a) spontaneous bacterial peritonitis (50% to 80% mortality), which does not occur in the absence of ascites; (b) impaired ambulation, decreased appetite, and back and abdominal pain; (c) an elevated diaphragm with decreased ventilation predisposing to hypoventilation, atelectasis, and pulmonary infections; and (d) negative cosmetic and psychological effects, the treatment of ascites with diuretics and sodium restriction is appropriate. This approach is successful in approximately 90% of patients, and complications are rare. Earlier studies demonstrating complications with diuretic therapy complications often utilized more aggressive diuretic regimens.

An alternate approach to diuretics is **large-volume paracentesis** in patients with advanced cirrhosis and ascites. Total paracentesis, occurring in increments over 3 days or, more commonly, at one setting, has been shown to have few complications; in some studies, paracentesis appears to have a lower incidence of complications than does diuretic treatment. Albumin 8 g for each liter of ascitic fluid removed should be infused to reduce hemodynamic compromise and the elaboration of vasoregulatory hormones. Patients often favor paracentesis because of the rapid improvement in symptoms and decreased hospitalizations; diuretics and salt restriction are still required between paracentesis. Portosystemic shunting is usually performed as TIPS. In two uncontrolled trials, TIPS led to an increase in urine output, a marked reduction in ascites, and a reduction in diuretic usage. Renal function also improved. Yet in a controlled trial, mortality increased in patients who received TIPS as compared with controls, and TIPS can precipitate hepatic encephalopathy, especially in Child-Pugh class C patients. Contraindications are shown in Figure 1-8. A recent review of the literature confirmed that TIPS can effectively reduce or eliminate ascites, but carries a substantial complication rate. Therefore, it remains best reserved for truly refractory patients who will not receive a liver transplant. Similar considerations apply to peritoneovenous (LeVeen) shunting. In controlled trials, peritoneovenous shunting was shown to reduce ascites more effectively than paracentesis or diuretics, but this was associated with a high rate of complications (e.g., shunt clotting); and there was no survival advantage of the peritoneovenous shunt. Despite reports that the high complication rate can be reduced, most centers reserve this therapy for patients who are truly refractory to more conventional approaches and who are not candidates for liver transplantation.

Child-Pugh score >11
Serum bilirubin >5 mg/dL
Overt or chronic hepatic encephalopathy
Age greater than 70 years
Serum creatinine >3 mg/dL
Cardiac dysfunction
Portal vein thrombosis

Figure 1-8. Contraindications to transjugular intrahepatic portosystemic shunt (TIPS).

The development of ascites in a patient with previously compensated cirrhosis may be an indication for liver transplantation if reversible hepatic insults or sodium-retaining drugs, for example, NSAIDs, have been excluded. In view of the morbidity and mortality associated with diuretic-resistant decompensated cirrhosis, the patient should be considered for placement on the liver transplantation list. Worsening of ascites in a previously stable individual is most often caused by progressive liver disease, but should also compel the search for hepatocellular carcinoma and portal vein thrombosis.

C. **Treatment aimed at the systemic arterial vasodilation** of cirrhosis has previously only been used in the acute setting of the patient with portal hypertension and bleeding esophageal varices. Portal venous hypertension is caused not only by the intrahepatic capillary fibrosis that increases resistance to flow but also by increased splanchnic flow. Therefore, the administration of vasopressin, which selectively constricts the splanchnic vasculature, has been shown to decrease portal venous pressure and thereby diminish esophageal variceal bleeding.

More chronic use of vasoconstrictors in association with albumin administration has emerged as a treatment for hepatorenal syndrome. This therapy has been shown to be effective in some patients with type 1 hepatorenal syndrome. The differences between type 1 and 2 hepatorenal syndromes are shown in Figure 1-9. The V_1 (vascular) vasopressin receptor agonist, terlipressin, has been approved for use with albumin in type 1 hepatorenal syndrome in Europe. However, because the V_2 antidiuretic receptor is already occupied in patients with advanced cirrhosis, vasopressin, a V_1 and V_2 agonist, can be used without worsening water retention. For chronic outpatient use, the α-agonist, midodrine, has been used with albumin to treat type 1 hepatorenal syndrome. The treatment approach with a vasoconstrictor and albumin has been shown to lower serum creatinine below 1.5 mg/dL over a 7- to 10-day period in 60% to 70% of patients with type 1 hepatorenal syndrome. No effect on mortality, however, has been demonstrated. Therefore, the therapeutic advantage of this approach is to allow time for reversibility of any acute hepatic insult or for liver transplantation.

Type I
Rapidly progressive
Serum creatinine double to >2.5 mg/dL or creatinine clearance <20 mL/min in <2 weeks
Prognosis—80% die in 2 weeks without liver transplantation
Frequently precipitating events (e.g., spontaneous bacterial peritonitis)
Type II
Slower deterioration
Serum creatinine >1.5 mg/dL or creatinine clearance <40 mL/min but decline is slow
Most patients die within several weeks without liver transplantation
Most frequent cause of therapy-resistant ascites

Figure 1-9. Two types of hepatorenal syndrome.

Spontaneous bacterial peritonitis is probably the most frequent cause of type 1 hepatorenal syndrome, which frequently occurs on the background of type 2 hepatorenal syndrome. In a prospective, randomized study, the combination of albumin and cefotaxime has been shown to decrease the occurrence of renal failure (33% vs 11%, $p<0.002$) and hospital mortality (18% vs 10%, $p<0.01$) as compared with cefotaxime alone in cirrhotic patients with spontaneous bacterial peritonitis. A diagnostic peritoneal tap, therefore, should be undertaken in all cirrhotic patients with ascites in whom renal function is deteriorating independent of the absence of fever, leukocytosis, or abdominal pain.

VII. NEPHROTIC SYNDROME. Another major cause of edema is nephrotic syndrome, the clinical hallmarks of which include proteinuria (greater than 3.5 g/day), hypoalbuminemia, hypercholesterolemia, and edema. The degree of the edema may range from pedal edema to total-body anasarca, including ascites and pleural effusions. The lower the plasma albumin concentration, the more likely the occurrence of anasarca; the degree of sodium intake is, however, also a determinant of the degree of edema. Nephrotic syndrome has many causes (see Chapter 8). Systemic causes of nephrotic syndrome include diabetes mellitus, lupus erythematosus, drugs (e.g., phenytoin, heavy metals, NSAIDs), carcinomas, and Hodgkin's disease, and primary renal diseases such as minimal-change nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis.

A. The **pathogenesis** of ECF volume expansion in nephrotic syndrome appears to be more variable than the pathogenesis of edema in patients

with congestive heart failure or cirrhotic ascites. Traditionally, ECF volume expansion in nephrotic syndrome was believed to depend on hypoalbuminemia and underfilling of the arterial circulation. Several observations, however, have raised questions about this hypothesis as always accounting for sodium retention in nephrotic patients. First, the interstitial oncotic pressure in healthy individuals is higher than previously appreciated. Transudation of fluid during ECF volume expansion reduces the interstitial oncotic pressure, thereby minimizing the change in transcapillary oncotic pressure. Second, patients recovering from minimal-change nephropathy frequently begin to excrete sodium before their serum albumin concentration rises. Third, the circulating concentrations of volume-regulatory hormones are not as high in many nephrotic patients as in patients with severe cirrhosis or congestive heart failure. These and other observations have **suggested a role for primary renal NaCl retention** (overflow hypothesis) in the pathogenesis of nephrotic edema.

B. Whereas "primary" renal NaCl retention may contribute to nephrotic edema in many patients, it is not often the only mechanism; some component of *underfill* often plays a role, particularly in patients with serum albumin concentrations below 2.0 g/L. Evidence for its role includes the observation that "primary" renal NaCl retention alone may not lead to edema in the absence of a decrease in cardiac output or systemic arterial vasodilation. Chronic aldosterone infusion, for example, leads to hypertension and escape from renal sodium retention in the absence of edema formation. Furthermore, levels of vasoactive hormones, although below the levels commonly seen in cirrhosis and congestive heart failure, are often higher than would be expected on the basis of the level of ECF expansion. It appears, therefore, that nephrotic syndrome may reflect a combination of primary renal NaCl retention and/or relative arterial underfilling. A preponderance of one or the other mechanism may be observed in nephrotic syndrome from different causes. In general, a normal or near-normal glomerular filtration rate is associated with hypovolemic, vasoconstrictor nephrotic syndrome, whereas a diminution in glomerular filtration rate, primary renal sodium retention, and evidence of volume expansion (e.g., decreased plasma renin activity) are characteristic of hypervolemic nephrotic syndrome (Figure 1-10).

C. Treatment. The initial focus of therapy must be aimed at those treatable, systemic causes of nephrotic syndrome such as systemic lupus erythematosus or drugs (e.g., phenytoin, NSAID). The treatment of the primary renal causes of nephrotic syndrome is described in Chapter 8.

The treatment of edema in nephrotic patients involves **dietary sodium restriction and diuretics**. Because these patients may not have as much arterial underfilling as patients with cirrhosis or congestive heart failure, diuretic treatments are often tolerated well. In general, loop diuretics and mineralocorticoid antagonists are used as initial therapy. Some nephrotic patients may be relatively resistant to these drugs. Although low serum albumin concentrations may increase the volume of diuretic distribution, and filtered albumin may bind to diuretics in the tubule lumen, these factors do not appear to be the predominant causes of diuretic resistance. Rather, diuretic resistance may reflect a combination of reduced glomerular

	Overfill	Underfill
GFR <50% of normal	+	–
GFR >75% of normal	–	+
Serum albumin >2 g/dL	+	–
Serum albumin <2 g/dL	–	+
Minimal change histology	–	+
Hypertension	+	–
Postural hypotension	–	+

Figure 1-10. Factors that help to differentiate overfill and underfill edema in nephrotic syndrome. GFR, glomerular filtration rate. (From Schrier RW, Fassett RG. A critique of the overfill hypothesis of sodium and water retention in the nephrotic syndrome. *Kidney Int* 1998;53:1111–1117, with permission.)

filtration rate and intense renal NaCl retention. When the glomerular filtration rate is reduced, endogenous organic anions impair diuretic secretion into the tubule lumen, the site where these drugs act to inhibit NaCl transport. Therefore, higher doses of loop diuretics are often required to achieve natriuresis.

The administration of albumin to patients with nephrotic syndrome can be costly and may cause pulmonary edema. One report, however, suggested that mixing albumin with a loop diuretic (6.25 g albumin per 40 mg furosemide) may induce diuresis in severely hypoalbuminemic patients. Recently, a double-blind, controlled study of nine nephrotic patients compared the effects of (a) 60 mg intravenous furosemide, (b) 60 mg intravenous furosemide plus 200 mL of a 20% solution of albumin, or (c) a sham infusion plus 200 mL of albumin. Coadministration of furosemide and albumin was significantly more effective than either albumin or furosemide alone. The authors noted that although adding albumin did increase natriuresis, the benefit was relatively small. Thus, adding albumin is probably only indicated with diuretic resistance in patients with nephrotic syndrome.

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2 The Patient with Hyponatremia or Hypernatremia

Robert W. Schrier and Tomas Berl

Control of serum sodium and osmolality. Under physiologic conditions, the concentration of sodium in plasma is kept in a very narrow range, between 138 and 142 mEq/L, despite great variations in water intake. Because sodium is the predominant cation in extracellular fluid (ECF), this reflects the equally narrow range in which the tonicity (osmolality) of body fluids is regulated, between 280 and 290 mOsm/kg. Therefore, calculated plasma osmolality can be expressed as follows:

$$P_{OSM} = 2[Na^+] + \frac{\text{blood urea nitrogen (mg/dL)}}{2.8} + \frac{\text{glucose (mg/dL)}}{18}$$

Serum sodium concentration and plasma osmolality are maintained in these normal ranges by the function of arginine vasopressin (AVP) and a very sensitive osmoreceptor that controls the secretion of this antidiuretic hormone. This hormone, in turn, is critical in determining water excretion by allowing urinary dilution in its absence and urinary concentration in its presence. Hyponatremic disorders supervene when water intake exceeds the patient's renal diluting capacity. Conversely, hypernatremia supervenes in settings associated with renal concentrating defects accompanied by inadequate water intake.

Hyponatremia. *Hyponatremia*, defined as a plasma sodium concentration of less than 135 mEq/L, is a frequent occurrence in the hospitalized patient. It has been suggested that approximately 10% to 15% of patients in hospitals have a low plasma sodium concentration at some time during their stay. Hyponatremia in the ambulatory outpatient is a much less frequent occurrence and is usually associated with a chronic disease state.

I. INTERPRETATION OF THE SERUM SODIUM.

Under most clinical circumstances, a decrement in serum sodium reflects a hypo-osmolar state. However, in some settings a low sodium level could be associated with normal or even a high osmolality. The addition to the ECF of osmotically active solutes that do not readily penetrate into cells, such as glucose, mannitol, and glycine, causes water to move from cells to ECF, thereby leading to cellular water loss resulting in a decrement in serum sodium concentration. This *translocational hyponatremia* does not reflect changes in total body water (TBW), but rather the movement of water from the intracellular to the extracellular compartment.

In hyperglycemia, for each 100 mg/dL rise in blood glucose, a 1.6 mEq/L fall in plasma sodium concentration occurs as water moves out of cells into

the ECF. For example, in an untreated diabetic patient, as blood glucose rises from 200 to 1,200 mg/dL, the plasma sodium concentration is expected to fall from 140 to 124 mEq/L (1.6 mEq/L × 10 = 16 mEq) without a change in TBW and electrolytes. Conversely, treatment with insulin and lowering of the blood sugar from 1,200 to 200 mg/dL in this diabetic patient results in a comparable osmotic water movement from the ECF back into cells and a return of plasma sodium concentration to 140 mEq/L without any change in TBW.

Another setting in which hyponatremia can occur without a change in plasma osmolality is termed *pseudohyponatremia*. Pseudohyponatremia occurs when the solid phase of plasma, primarily lipids and proteins (usually 6% to 8%), is greatly increased, as in severe hypertriglyceridemia and paraproteinemic disorders. This falsely low reading is a consequence of the flame photometry methods that measure the concentration of Na^+ in whole plasma and not only in the liquid phase. A measure of the true serum sodium can be obtained in undiluted serum analyzed with an ion-specific electrode that measures the concentration of sodium in serum water.

II. APPROACH TO THE HYPO-OSMOLAR HYPONATREMIC PATIENT.

In the absence of translocational hyponatremia or pseudohyponatremia, the most important initial step in the diagnosis of hyponatremia is an assessment of the ECF volume status.

Sodium is the primary cation in the ECF compartment. Therefore, sodium, with its accompanying anions, dictates ECF osmolality and fluid volume. Hence, ECF volume provides the best index of total body exchangeable sodium. A careful physical examination focused on the evaluation of ECF volume status therefore allows for the classification of the hyponatremic patient into one of three categories: (a) hyponatremia in the presence of an excess of total body sodium (hypervolemic hyponatremia), (b) hyponatremia in the presence of a deficit of total body sodium (hypovolemic hyponatremia), and (c) hyponatremia with a near-normal total body sodium (euvolemic hyponatremia). For example, the edematous patient is classified as having hyponatremia with an excess of total body sodium. The volume-depleted patient with flat neck veins, decreased skin turgor, dry mucous membranes, and orthostatic hypotension and tachycardia is classified as having hyponatremia with a deficit of total body sodium. The patient with neither edema nor evidence of ECF volume depletion is classified as having hyponatremia with near-normal total body sodium (Fig. 2-1).

A. In the **hypervolemic (edematous) hyponatremic patient**, both total body sodium and TBW are increased, water more so than sodium. These patients have cardiac failure, cirrhosis, nephrotic syndrome, or renal failure. When hyponatremia is secondary to cardiac and hepatic disease, the disease is advanced and readily evident on clinical examination. In the absence of the use of diuretics, the urinary sodium concentration in the hyponatremic edematous patient should be quite low (<10 to 20 mEq/L) because of avid tubular sodium reabsorption. The exception occurs in the presence of acute or chronic renal failure, in which, because of tubular dysfunction, the urinary sodium concentration is higher (>20 mEq/L).

B. The diagnostic possibilities in the **hypovolemic hyponatremic patient** are entirely different. Again, a spot urinary sodium concentration is of value. If the volume-depleted hyponatremic patient has a low (<10 to 20 mEq/L)

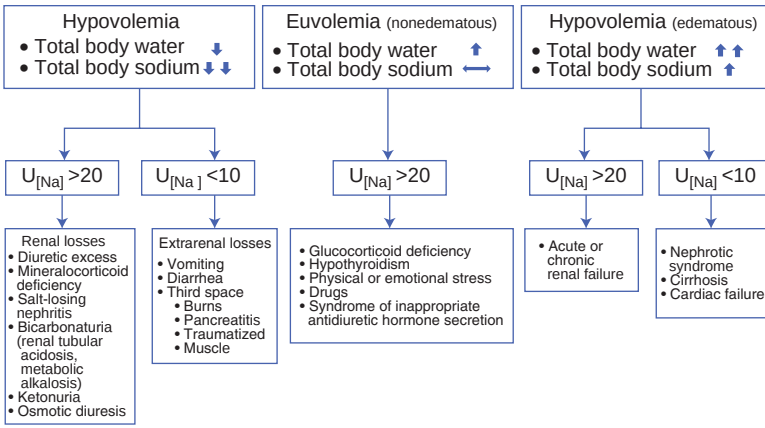

Figure 2-1. Diagnostic approach to hyponatremia. (↑, increased; ↑↑, greatly increased; ↓, decreased; ↓↓, greatly decreased; ↔, not increased or decreased; $U_{[Na]}$, urinary sodium concentration, in mEq/L.)

urine sodium concentration, the kidney is functioning normally by conserving sodium in response to ECF volume depletion. This occurs with extrarenal fluid losses. Conversely, if the urinary sodium concentration is greater than 20 mEq/L in a hypovolemic hyponatremic patient, the kidney is not responding appropriately to the ECF volume depletion, and renal losses of sodium and water must be considered as the likely cause of the hyponatremia.

1. In a hypovolemic hyponatremic patient with a **urinary sodium concentration of less than 10 to 20 mEq/L**, a gastrointestinal (or "third space") source of sodium and water losses must be sought. The source may be readily apparent if the patient presents with a history of vomiting, diarrhea, or both. In the absence of an obvious history of gastrointestinal fluid losses, several other diagnostic possibilities must be considered. Substantial ECF losses may occur into the abdominal cavity with peritonitis or pancreatitis and into the bowel lumen with ileus or pseudomembranous colitis. The surreptitious cathartic abuser may present with evidence of ECF volume depletion and no history of gastrointestinal losses. The presence of hypokalemic metabolic acidosis and phenolphthalein in the urine may be a clue to this diagnosis. Loss of haustra on barium enema and melanosis coli on endoscopy are other clues to cathartic abuse. Burns or muscle damage may also lead to a state of hypovolemia and hyponatremia secondary to substantial fluid and electrolyte losses from skin or into muscle.
2. In a hypovolemic hyponatremic patient with a **urinary sodium level of greater than 20 mEq/L**, renal losses occur, and several different diagnostic possibilities must be considered.
   a. **Excessive use of diuretics** is foremost among these diagnoses. It occurs almost exclusively with thiazide diuretics, because these agents,

unlike loop diuretics, alter only urinary diluting ability, and a urinary concentration remains unimpaired. A fall in plasma sodium concentration in a patient receiving diuretics may be the first clue that a diuretic dosage adjustment is needed. In some patients with diuretic abuse, ECF volume depletion is not readily apparent from clinical examination. An important clue, however, to the diagnosis of diuretic-induced hyponatremia is that virtually all these patients have an associated hypokalemic metabolic alkalosis if they are receiving potassium-losing diuretics. If, however, a potassium-sparing diuretic is involved (e.g., triamterene, amiloride, and spironolactone), neither hypokalemia nor metabolic alkalosis may be present. Cessation of use of the diuretic is the best means of confirming the diagnosis of diuretic-induced hyponatremia. However, it must be remembered that restoration of ECF volume is also necessary to correct the hyponatremia. This will improve renal function and suppress the hypovolemia-mediated nonosmotic release of vasopressin. In the hypokalemic patient, potassium replacement also may be necessary for complete correction of the plasma sodium concentration imbalance.

Surreptitious diuretic abuse occurs among premenopausal women who use diuretics for weight loss or other cosmetic reasons (e.g., thick ankles or calves, "puffy" face). These patients may be difficult to distinguish from patients with surreptitious vomiting, because both may present with evidence of ECF volume depletion and hypokalemic metabolic alkalosis. The presence or absence of hyponatremia depends on the patient's water intake. The pivotal diagnostic test to distinguish between the hypovolemic hyponatremic patient with metabolic alkalosis who is a diuretic abuser and the patient who is a surreptitious vomiter is the urinary chloride concentration. Surreptitious vomiters have low ($<$10 mEq/L) chloride concentrations and surreptitious diuretic abusers have high ($>$20 mEq/L) concentration.

b. **Salt-Losing Nephritis.** Patients with medullary cystic disease, chronic interstitial nephritis, polycystic kidney disease, analgesic nephropathy, partial urinary tract obstruction, and, rarely, chronic glomerulonephritis may present with hypovolemic hyponatremia secondary to salt-losing nephritis. These patients generally have moderately advanced renal impairment with serum creatinine levels greater than 3 to 4 mg/dL. This diagnosis should virtually never be considered in patients with renal disease that is not associated with elevated serum creatinine. Patients with salt-losing nephritis may need supplemental sodium chloride (NaCl) intake to avoid ECF volume depletion, or they may become very susceptible to ECF volume depletion in association with either decreased intake or extrarenal (e.g., gastrointestinal) sodium and water losses. Because these patients may be pigmented secondary to uremic dermatitis and exhibit hyponatremia and volume depletion, their disease was initially described as mimicking Addison disease.

c. **Mineralocorticoid Deficiency.** The patient with Addison disease (i.e., primary adrenal insufficiency) generally has associated hyperkalemia; prerenal azotemia most often does not increase serum

creatinine to concentrations greater than 3 mg/dL. In patients with mineralocorticoid deficiency, ECF volume repletion may correct both the hyponatremia and the hyperkalemia. During periods of stress, the plasma cortisol level may be within the normal range. Therefore, if adrenal insufficiency is suspected, a 2-hour cosyntropin (Cortrosyn) stimulation test should be performed. In addition to a urinary sodium concentration of greater than 20 mEq/L, a urinary potassium concentration of less than 20 mEq/L may be another clue to mineralocorticoid deficiency. If fluid intake has been restricted, the patient with Addison disease may not present with hyponatremia, and hyperkalemia may not be present if the ECF volume depletion is not severe. Therefore, a high index of suspicion is necessary to make the diagnosis of primary adrenal insufficiency. These patients may present with nonspecific symptoms such as weight loss, anorexia, abdominal pain, nausea, vomiting, diarrhea, and fever.

d. Osmotic diuresis obligating anion and cation excretion is another major diagnostic consideration in the hypovolemic hyponatremic patient with a urinary sodium concentration greater than 20 mEq/L.

i. Glucose, urea, or mannitol diuresis. The uncontrolled diabetic patient may have substantial glucosuria, causing water and electrolyte losses and thereby ECF volume depletion. The urea diuresis after the relief of a urinary tract obstruction is another example of an osmotic diuresis that can cause ECF volume depletion. A chronic mannitol infusion without electrolyte replacement can produce a similar situation.

ii. Bicarbonaturia. Increased anion excretion also can obligate renal water and electrolyte losses. The most frequently encountered example of this is metabolic alkalosis with bicarbonaturia. The bicarbonate anion in the urine is accompanied by cations, including sodium and potassium, which maintain electrical neutrality. Bicarbonaturia may accompany the early development of metabolic alkalosis accompanying postoperative nasogastric suction or vomiting. Proximal renal tubular acidosis (e.g., in Fanconi syndrome) is another condition in which bicarbonaturia causes renal electrolyte loss. In the absence of a urinary tract infection with urease-producing organisms, a urinary pH (measured by a pH meter) greater than 6.1 indicates the presence of bicarbonate in the urine.

iii. Ketonuria. Ketoacid anions also can obligate renal electrolyte losses in spite of ECF volume depletion; this may contribute to urinary electrolyte losses in diabetic or alcoholic ketoacidosis or starvation.

e. Cerebral salt wasting is a syndrome, described primarily in patients with subarachnoid bleeds, characterized by renal salt wasting leading to volume contraction and non-osmotic release of vasopressin. It is postulated that a brain hormone leads to the natriuresis. The diagnosis requires the presence of sodium in the urine in the face of substantive evidence for volume contraction. This criterion is rarely fulfilled, suggesting that the entity is quite rare and frequently overdiagnosed.

C. **Euvolemic hyponatremia** is the most commonly encountered form of hyponatremia in hospitalized patients. The urinary sodium concentration in euvolemic hyponatremia is generally greater than 20 mEq/L. However, if the patient is on a sodium-restricted diet or is volume depleted, the urinary sodium concentration may be less than 10 mEq/L. Refeeding with a normal salt intake or expansion of ECF volume with saline increases urinary sodium concentration to more than 20 mEq/L, but hyponatremia will persist in the patient with euvolemic hyponatremia. These patients show no signs of either an increase or decrease in total body sodium. Although the water retention leads to an excess in TBW, no edema is detected because two-thirds of the water is inside the cell. A limited number of diagnostic possibilities are available for hyponatremic patients who exhibit neither edema nor ECF volume depletion (i.e., euvolemic hyponatremic patients) (Fig. 2-1). Two endocrine disorders must be considered: severe hypothyroidism and secondary adrenal insufficiency associated with pituitary or hypothalamic disease.

1. The occurrence of hyponatremia with **hypothyroidism** generally suggests severe disease, including myxedema coma. In some patients, particularly the elderly, the diagnosis may not be readily apparent. Therefore, thyroid function must be assessed in the euvolemic hyponatremic patient.
2. **Glucocorticoid Deficiency.** An intact renin–angiotensin–aldosterone system avoids ECF volume depletion in patients with secondary adrenal insufficiency, but it is clear that glucocorticoid deficiency alone can impair water excretion and cause hyponatremia. Skull films and computed tomographic (CT) scans should always be obtained in the euvolemic hyponatremic patient when the cause of the hyponatremia is not obvious. However, normal skull films or CT scans do not exclude secondary adrenal insufficiency. A low plasma cortisol level associated with a low adrenocorticotropic hormone level supports the diagnosis of secondary adrenal insufficiency. In this setting, both secondary adrenal insufficiency and secondary hypothyroidism may contribute to the hyponatremia accompanying pituitary insufficiency.
3. **Emotional or physical stress** must be considered in the euvolemic hyponatremic patient before invoking the diagnosis of the syndrome of inappropriate antidiuretic hormone (SIADH). Acute pain or severe emotional stress (e.g., decompensated psychosis associated with continued water ingestion) may lead to acute and severe hyponatremia. It is likely that a combination of emotional stress and physical pain accounts for the frequently encountered secretion of vasopressin in the postoperative state, which in turn leads to hyponatremia in the face of hypotonic fluid administration.
4. A number of **pharmacologic agents** either stimulate the release of vasopressin or enhance its action. These include:
   - **a.** Nicotine
   - **b.** Chlorpropamide
   - **c.** Tolbutamide
   - **d.** Clofibrate
   - **e.** Cyclophosphamide

f. Morphine
g. Barbiturates
h. Vincristine
i. Carbamazepine (Tegretol)
j. Acetaminophen
k. Nonsteroidal anti-inflammatory drugs
l. Antipsychotics
m. Antidepressants

Therefore, determining whether the euvolemic hyponatremic patient is receiving such drugs is an important diagnostic step.

5. **SIADH** should be considered after exclusion of other diagnoses in the euvolemic hyponatremic patient. In general, the causes of SIADH include:
   a. **Carcinomas**, most frequently but not exclusively, of the
      i. Lung
      ii. Duodenum
      iii. Pancreas
      iv. Head and neck
   b. **Pulmonary disorders**, including but not limited to,
      i. Viral pneumonia
      ii. Bacterial pneumonia
      iii. Pulmonary abscess
      iv. Tuberculosis
      v. Aspergillosis
   c. **Central Nervous System (CNS) Disorders**
      i. Encephalitis (viral or bacterial)
      ii. Meningitis (viral, bacterial, or tubercular)
      iii. Acute psychosis
      iv. Stroke (cerebral thrombosis or hemorrhage)
      v. Acute intermittent porphyria
      vi. Brain tumor
      vii. Brain abscess
      viii. Subdural or subarachnoid hematoma or hemorrhage
      ix. Guillain–Barré syndrome
      x. Head trauma
   d. **Acquired Immunodeficiency Syndrome.**

   Therefore, SIADH occurs primarily in association with infections and with vascular and neoplastic processes in the CNS or lung.
   e. **Exercise-Induced Hyponatremia**. Hyponatremia has been well described in association with strenuous exercise such as marathons. It appears that a BMI of <20 kg/m^2 and prolonged running times are both risk factors. Most importantly, it has been noted that weight gain during the race is a strong risk factor. This gain is most likely a function of water consumption in excess of insensible losses in the presence of non-osmotic vasopressin release.

III. SIGNS AND SYMPTOMS.

The level of hyponatremia that may cause signs and symptoms varies with the rate of decline in the plasma sodium concentration and the age of the patient. In general, the young adult patient appears to tolerate a specific level of hyponatremia better than does the older patient.

However, the acute (i.e., within a few hours) development of hyponatremia in a previously asymptomatic young patient may cause severe CNS signs and symptoms, such as depressed sensorium, seizures, and even death, when the plasma sodium concentration has reached only a level between 125 and 130 mEq/L. This is because the capacity of brain cells to extrude osmotically active particles, and thereby relieve the brain swelling that accompanies hyponatremia, requires a longer time to be invoked at the beginning of the condition. Conversely, this protective mechanism against brain swelling becomes very effective with the chronic development of hyponatremia over days or weeks, so that an elderly person may present without overt signs or symptoms even with a plasma sodium concentration below 110 mEq/L.

Gastrointestinal symptoms, including anorexia and nausea, may occur early with hyponatremia. The more severe later signs and symptoms relate to the CNS because the cell swelling that occurs with hyponatremia is tolerated worst within the rigid encasement of the skull. Severe hyponatremia of rapid onset may lead to brain edema and herniation and therefore requires rapid treatment. Cheyne-Stokes respiration may be a hallmark of severe acute hyponatremia. In addition to exposure, uremia, and hypothyroidism, hyponatremia also should be considered in the differential diagnosis of the hypothermic patient.

In summary, **symptoms** that may be associated with hyponatremia include:

A. Lethargy, apathy
B. Disorientation
C. Muscle cramps
D. Anorexia, nausea
E. Agitation

Signs that may be associated with hyponatremia include:

F. Abnormal sensorium
G. Depressed deep tendon reflexes
H. Cheyne-Stokes respiration
I. Hypothermia
J. Pathologic reflexes
K. Pseudobulbar palsy
L. Seizures

IV. THERAPY

A. Factors Affecting the Approach to Treatment. The presence or absence of symptoms and the duration of the hyponatremia are the primary guides to treatment strategy. Different time-dependent processes are involved in the adaptation to changes in tonicity, and the presence of cerebral symptoms reflects a failure of the adaptive response. In this regard, hyponatremia developing within 48 hours carries a greater risk of permanent neurologic sequelae from cerebral edema if the plasma sodium concentration is not corrected expeditiously. Conversely, patients with chronic hyponatremia are at risk for osmotic demyelination if the correction is excessive or too rapid.

B. Cerebral Adaptation to Hypotonicity. Decreases in extracellular osmolality cause the movement of water into cells, increasing intracellular volume and causing tissue edema. Edema within the cranium raises intracranial pressure, leading to neurologic syndromes. To prevent this complication, a

volume-regulatory adaptation occurs. Early in the course of hyponatremia, within 1 to 3 hours, cerebral ECF volume decreases through the movement of fluid into the cerebrospinal fluid, which is then shunted into the systemic circulation. Thereafter, the brain adapts by losing cellular potassium and organic solutes, which tend to lower the intracellular osmolality without substantial gain of water. If hyponatremia persists, other organic osmolytes such as phosphocreatine, myoinositol, and amino acids (e.g., glutamine and taurine) are lost. The loss of these solutes greatly decreases cerebral swelling. Patients in whom this adaptive response fails are prone to severe cerebral edema when they develop hyponatremia. Postoperative menstruant females, elderly women on a thiazide diuretic, psychiatric polydipsic patients, and hypoxemic patients are particularly prone to hyponatremia-related encephalopathy. Conversely, as noted earlier, patients who have had the adaptive response are at risk for osmotic demyelination syndrome if the hyponatremia is excessively or too rapidly corrected. For example, a rapid increase in plasma osmolality may cause excessive cerebral water loss in previously adapted brains. Alcoholic and malnourished subjects, burn victims, and patients with severe hypokalemia are at risk for this complication.

C. **Acute symptomatic hyponatremia**, developing in less than 48 hours, is almost inevitable in hospitalized patients receiving hypotonic fluids. Treatment should be prompt because the risk of acute cerebral edema exceeds the risk of osmotic demyelination. The aim should be to raise the serum Na^+ by 2 mmol/L/hour until symptoms resolve. Complete correction is unnecessary, although it is not unsafe. Hypertonic saline (3% NaCl) is infused at the rate of 1 to 2 mL/kg/hour, and a loop diuretic, such as furosemide, enhances solute-free water excretion and hastens the return to a normal serum Na^+. If severe neurologic symptoms (seizures, obtundation, or coma) are present, 3% NaCl may be infused at 4 to 6 mL/kg/hour. Even 24.2% NaCl (50 mL) has been used safely. Serum electrolytes should be carefully monitored.

D. **Chronic Symptomatic Hyponatremia.** If hyponatremia has been present for more than 48 hours or the duration is unknown, correction must be handled carefully. Whether it is the rate of correction of hyponatremia or the magnitude that predisposes to osmotic demyelination is unknown, but in practice dissociating the two is difficult, because a rapid correction rate usually means a greater correction over a given period of time.

The following guidelines are fundamental to successful therapy:

1. Because cerebral water is increased only by approximately 10% in severe chronic hyponatremia, promptly increase the serum Na^+ level by 10%, or by approximately 10 mEq/L.
2. After the initial correction, do not exceed a correction rate of 1.0 to 1.5 mEq/L/hour.
3. The goal of correction should be approximately 8 mEq/L over the first 24 hours.
4. Do not increase the serum Na^+ by more than 12 mEq/L per 24 hours or 18 mEq/L per 48 hours. These are the highest acceptable limits of correction.
5. If the above limits are exceeded, relowering the serum sodium by administration of D5W (5% dextrose in water) with 1-deamino-8-D-arginine vasopressin (DDAVP) may be necessary.

It is important to take into account the rate of infusion and the electrolyte content of infused fluids and the rate of production and electrolyte content of the urine.

Once the desired increment in serum Na^+ concentration is obtained, the treatment should consist of water restriction.

E. The approach to the **chronic asymptomatic patient with hyponatremia** is different. Initial bedside evaluation includes searching for an underlying disorder. Hypothyroidism and adrenal insufficiency should be sought as possible etiologies, and hormones must be replaced if these deficiencies are found. A careful analysis of the patient's medications should be made and necessary adjustments undertaken.

For patients with SIADH, if the etiology is not identifiable or cannot be treated, the approach should be conservative because rapid changes in serum tonicity lead to a greater degree of cerebral water loss and possible osmotic demyelination. Various approaches can be considered.

1. **Fluid restriction** is an easy and usually successful option, if the patient complies. A calculation must be made of the fluid restriction that will maintain a specific serum Na^+. The daily osmolar load ingested divided by the minimal urinary osmolality (a function of the severity of the diluting disorder) determines a patient's maximal urine volume. On a normal North American diet, the daily osmolar load is approximately 10 mOsm/kg of body weight; in a healthy person, the minimum urinary osmolality (given no circulating vasopressin) can be as low as 50 mOsm/kg. Therefore, the daily urine volume in a 70-kg man can be as high as 14 L (700 mOsm per 50 mOsm/L). If the patient has SIADH and the urinary osmolality cannot be lowered below 500 mOsm/kg, the same osmolar load of 700 mOsm/day allows for only 1.4 L of urine. Therefore, if the patient drinks more than 1.4 L/day, the serum Na^+ will fall. A measurement of urinary sodium (U_{Na}) and potassium concentration (U_K) can guide the degree of water restriction that is required. If $U_{Na} + U_K$ is greater than the serum sodium concentration, water restriction alone may not be sufficient to increase serum sodium concentration.

2. **Pharmacologic Agents. Lithium** was the first drug used to antagonize the action of vasopressin in hyponatremic disorders. Lithium may be neurotoxic, and its effects are unpredictable. Therefore, **demeclocycline** became the agent of choice. This drug inhibits the formation and action of cyclic adenosine monophosphate (AMP) in the renal collecting duct. The onset of action is 3 to 6 days after treatment is started. The dose must be decreased to the lowest level that keeps the serum sodium concentration within the desired range with unrestricted water intake; this dose is usually 300 to 900 mg daily. The drug should be given 1 to 2 hours after meals, and calcium-, aluminum-, and magnesium-containing antacids should be avoided. However, polyuria may make patients noncompliant. Skin photosensitivity may occur; in children, tooth or bone abnormalities may result. Nephrotoxicity also limits the drug's use, especially in patients with underlying liver disease or congestive heart failure, in whom the hepatic metabolism of demeclocycline may be impaired.

3. **Vasopressin Antagonists.** The major therapeutic advance that has occurred in hyponatremic patients relates to the development of orally

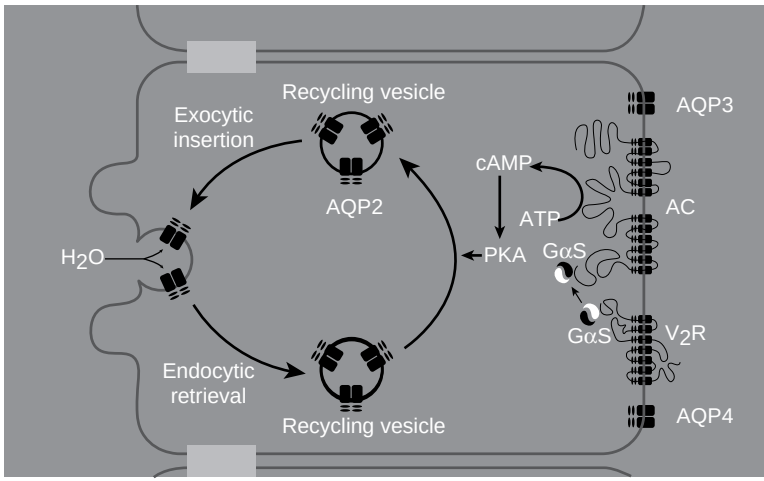

Figure 2-2. Signaling pathways for vasopressin-regulated water absorption. (AQP2, aquaporin-2; ATP, adenosine triphosphate; AC, adenylyl cyclase; PKA, protein kinase A; V_2R, vasopressin receptor.) (Used with permission of Bichet DG. Lithium, cyclic AMP signaling, A-kinase anchoring proteins, and aquaporin-2. *J Am Soc Nephrol* 2006;17:920–922.)

active, nonpeptide antagonists to the V_2 AVP receptor. AVP binds to the basolateral membrane of the principal cells of the renal collecting duct. Activation of this G-protein–linked V_2 receptor stimulates an adenylyl cyclase–cyclic AMP signaling pathway that upregulates the aquaporin-2 (AQP2) water channel expression and trafficking to the apical membrane (Fig. 2-2). The V_2 vasopressin antagonists bind more deeply in the principal cell transmembrane region than AVP. However, these V_2 antagonists do not activate the V_2 receptor, because of a lack of interaction with critical residues on the H_1 helix of the receptor.

The U.S. Food and Drug Administration (FDA) to date has approved two of these antagonists for clinical use, conivaptan and tolvaptan. Table 2-1 compares the two drugs. Conivaptan differs from tolvaptan as it antagonizes both the V_{1a} (vascular) and V_2 receptors, while tolvaptan is a more selective V_2 antagonist. Moreover, conivaptan has only been approved to treat in-hospital hyponatremia by intravenous use for 4 days, while tolvaptan is an oral drug that can be administered long term. Both drugs have been FDA approved to treat euvolemic and hypervolemic hyponatremia. Since a V_{1a} antagonist could theoretically increase splanchnic flow, thereby raising portal pressure in cirrhotic patients, conivaptan may not be advisable to treat hyponatremia associated with cirrhosis. Tolvaptan is effective in increasing serum sodium in patients with cirrhosis. There have been cases of drug-induced liver injury with higher doses of tolvaptan prompting a caution vis-à-vis possible liver toxicity. Polyuria and thirst have been the major observed side effects of these agents. The major benefits of treating hyponatremia

Table 2-1. Nonpeptide Arginine Vasopressin Receptor Antagonists

	Tolvaptan	Conivaptan
Receptor	V_2	V_{1a}/V_2
Route of administration	Oral	IV
Urine volume	↑	↑
Urine osmolality	↓	↓
Na^+ excretion/24 h	↔	↔
Company	Otsuka	Astellas

Used with permission of Lee CR, Watkins ML, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. *Am Heart J* 2003;146:9–18.

appear to relate to CNS function. Correction of hyponatremia with the V_2 receptor antagonists has been shown to improve mental function. Other studies have shown improved gait when raising severe sodium concentrations in "asymptomatic" hyponatremic patients. Because falls and fractures, particularly in the elderly, are more common in hyponatremic patients, there are other clinical implications for using these V_2 receptor antagonists to treat hyponatremia. These relatively safe antagonists, therefore, have potential to more effectively correct acute and chronic hyponatremia when compared with severe fluid restriction, demeclocycline, or urea. They, however, should not be used in hypovolemic hyponatremia, the treatment for which is ECF volume expansion.

4. **Increase in Solute Excretion.** Because urine flow can be significantly increased by obligating the excretion of solutes and thereby allowing a greater intake of water, measures to increase solute excretion have been used. A loop diuretic, when combined with high sodium intake (2 to 3 g additional NaCl), is effective. A single diuretic dose (40 mg furosemide) is usually sufficient. The dose should be doubled if the diuresis induced in the first 8 hours is less than 60% of the total daily urine output. Administration of urea to increase the solute load increases urine flow by causing an osmotic diuresis. This permits a more liberal water intake without worsening the hyponatremia and without altering urinary concentration. The dose is usually 30 to 60 g of urea daily to correct hyponatremia. The major limitations are gastrointestinal distress and unpalatability.

F. Hypovolemic and Hypervolemic Hyponatremia. Symptoms directly related to hyponatremia are unusual in hypovolemic hyponatremia because loss of both sodium and water limits osmotic shifts in the brain. Restoration of ECF volume with crystalloids or colloids interrupts the nonosmotic release of vasopressin. In patients with hypovolemic hyponatremia from diuretics, the drug must be discontinued and potassium repletion ensured. Potassium repletion itself increases serum sodium. The treatment

of hyponatremia in hypervolemic states is more difficult because it requires attention to the underlying disorder of heart failure or chronic liver disease. In congestive heart failure, both sodium and water restriction are critical. Refractory patients may be treated with a combination of an angiotensin-converting enzyme (ACE) inhibitor and a diuretic. The resultant increase in cardiac output with ACE inhibitors may increase solute-free water excretion and improve the hyponatremia. Loop diuretics diminish the action of vasopressin on the collecting tubules, thereby increasing solute-free water excretion. Thiazide diuretics impair urinary dilution and may worsen hyponatremia. Water and salt restriction are also the mainstay of therapy in cirrhotic patients. Vasopressin antagonists increase serum sodium in hypervolemic subjects as well.

Hypernatremia. *Hypernatremia*, defined as a plasma sodium concentration greater than 150 mEq/L, is less common than hyponatremia, probably not because of a more frequent occurrence of disorders of urinary dilution than of urinary concentration, but rather because of drinking behavior. Specifically, if an inability to dilute the urine is present, water intake of 1 to 2 L/day may cause hyponatremia. This amount of fluid intake may be ingested as routine behavior in spite of a hypo-osmolar stimulus to suppress thirst, which may explain the frequency of hyponatremia. Conversely, urinary concentrating defects that cause renal water losses generally do not cause hypernatremia unless a disturbance in thirst is also present or the patient cannot drink or obtain adequate fluid to drink. The very young, the very old, and the very sick are, therefore, those populations that develop hypernatremia most frequently. In the absence of an inability to drink (e.g., with coma, nausea, and vomiting) or to obtain water (e.g., in infants and severely ill adults), the thirst mechanism is very effective in preventing hypernatremia. Whereas hyponatremia does not always reflect a hypotonic state (i.e., pseudohyponatremia or translocation hyponatremia), hypernatremia always denotes a hypertonic state.

I. APPROACH TO THE HYPERNATREMIC PATIENT.

As is the case with hyponatremia, hypernatremic patients may have low, high, or normal total body sodium (Fig. 2-3). Such a classification allows the clinician to focus on the most likely diagnosis in each category.

A. Hypovolemic Hypernatremic Patient.

Hypernatremic patients may have evidence of ECF volume depletion that has occurred secondary to either renal or extrarenal losses. These patients have sustained water losses that are greater than the sodium losses.

1. **Extrarenal Losses.** If the losses have been from an extrarenal site (e.g., diarrhea), then sodium and water conservation by the kidney should be readily apparent. In such patients, the urine sodium concentration is less than 10 mEq/L, and the urine is hypertonic. In fact, losses by hypotonic diarrhea are among the most common causes of hypernatremia in both children and adults, especially in those who are receiving recurring lactulose for underlying severe liver disease with encephalopathy.
2. **Renal Losses.** In contrast, hypotonic electrolyte losses may occur in the urine during osmotic diuresis or use of loop diuretics. In these patients, evidence of renal sodium and water conservation is, of course, not

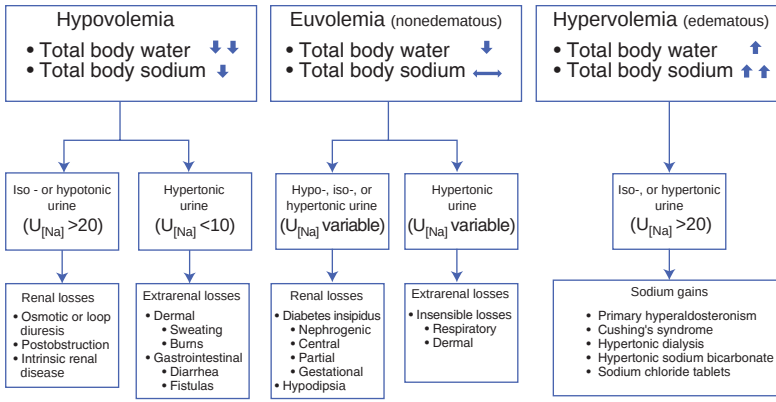

Figure 2-3. Diagnostic approach to hypernatremia. (↑, increased; ↑↑, greatly increased; ↓, decreased; ↓↓, greatly decreased; ↔, not increased or decreased; $U_{[Na]}$, urinary sodium concentration, in mEq/L.)

present, because the urine is the source of the losses. Therefore, the urine is not hypertonic, and urine sodium concentration is generally greater than 20 mEq/L. In the hyperglycemic diabetic patient with good renal function and profound glucosuria, hypernatremia may be a presenting feature because hypotonic renal losses may obscure any effect of hyperglycemia to shift water osmotically from cells to ECF. This is particularly true if the patient does not have access to water or is incapable of ingesting fluids (e.g., a comatose, ketoacidotic diabetic patient). In the setting of high-protein tube feedings, the high rate of urea excretion leads to significant renal water losses.

B. Hypervolemic Hypernatremic Patient. Patients with hypernatremia also may have evidence of ECF volume expansion. Generally, these patients have received excessive amounts of hypertonic NaCl or sodium bicarbonate during cardiac resuscitation. In such an acute setting, the incidence of ECF volume expansion is most likely to be associated with pulmonary congestion, elevated neck veins, or both, rather than with peripheral edema. This variety of hypervolemic hypernatremia is not as infrequent as originally thought as a significant number of acutely ill patients receive sodium-containing solutions without adequate water intake. Hypervolemic hypernatremia can also ensue when NaCl tablets are taken during exercise in a high-temperature, high-humidity environment.

C. Euvolemic Hypernatremia. Most patients with hypernatremia secondary to water loss appear euvolemic with normal total body sodium, because loss of water without sodium does not lead to overt volume contraction. Water loss in and of itself need not culminate in hypernatremia unless it is unaccompanied by water intake. Because such hypodipsia is uncommon, hypernatremia usually supervenes only in those who have no access to water or who have a neurologic deficit that does not allow them to seek it. Extrarenal water loss occurs from the skin and respiratory tract in febrile or other hypermetabolic states. Urine osmolality is very high, reflecting an

intact osmoreceptor–vasopressin–renal response. Therefore, the defense against hyperosmolality requires both stimulation of thirst and the ability to respond by drinking water. The urine sodium concentration varies with sodium intake. The renal losses of water that lead to euvolemic hypernatremia are a consequence of a defect in vasopressin production or release (central diabetes insipidus), a failure of the collecting duct to respond to the hormone (nephrogenic diabetes insipidus), or excessive rapid degradation of vasopressin (gestational diabetes insipidus).

1. Approximately 50% of instances of **central diabetes insipidus** have no detectable underlying cause and therefore are classified as idiopathic. Trauma, surgical procedures in the area of the pituitary or hypothalamus, and brain neoplasms, either primary or secondary (e.g., from metastatic breast cancer), constitute most of the remaining causes of central diabetes insipidus. In addition, encephalitis, sarcoidosis, or eosinophilic granuloma may cause central diabetes insipidus. Central diabetes insipidus can be partial, with some preservation of vasopressin release. When the partial central diabetes insipidus is associated with hypothalamic lesions and hypodipsia, these patients present with hypernatremia and a urine osmolality above plasma. Congenital autosomal dominant and more rarely autosomal recessive (Wolfram syndrome) forms of central diabetes insipidus have also been described.
2. **Nephrogenic Diabetes Insipidus.** This disorder can be **congenital or acquired**. In 85% of congenital diabetes insipidus, the disorder is inherited as an x-linked mutation. The underlying defect resides in the vasopressin receptor that is localized to the x chromosome. The remaining 15% of cases of a rarer autosomal recessive form is related to a mutation in the vasopressin-dependent AQP2 water channel. A number of acquired causes have been described, many of them also associated with decreased AQP2 production:
   a. **Secondary to Renal Diseases.** Medullary or interstitial renal diseases are likely to be accompanied by vasopressin-resistant renal concentrating defects; the most frequent of these diseases are medullary cystic disease, chronic interstitial nephritis (e.g., analgesic nephropathy), polycystic kidney disease, and partial bilateral urinary tract obstruction. Far-advanced renal disease of any cause is uniformly associated with a renal concentrating defect. However, because of the very low glomerular filtration rate, the renal water loss (i.e., polyuria) is modest (2 to 4 L/day).
   b. **Secondary to Hypercalcemia and Hypokalemia.** Hypercalcemia secondary to any cause, including primary hyperparathyroidism, vitamin D intoxication, milk-alkali syndrome, hyperthyroidism, and tumor, may also cause acquired nephrogenic diabetes insipidus. Similarly, hypokalemia secondary to any cause, including primary aldosteronism, diarrhea, and chronic diuretic use, may cause nephrogenic diabetes insipidus. However, some of the polyuria accompanying hypercalcemia or hypokalemia may be due to stimulation of thirst and the resultant increase in water intake.
   c. **Drugs, Dietary Abnormalities, and Other Causes.** Various drugs impair the end-organ response to vasopressin and therefore cause

a renal concentrating defect (see Section II.B.2.d.iii). Excess water intake as well as dietary sodium and protein restriction also have been shown to impair urinary concentration. Other unique causes of nephrogenic diabetes insipidus include multiple myeloma, amyloidosis, Sjögren syndrome, and sarcoidosis.

d. A **summary** of acquired causes of nephrogenic diabetes insipidus includes:

i. Chronic renal disease
- Polycystic kidney disease
- Medullary cystic disease
- Pyelonephritis
- Urinary tract obstruction
- Far-advanced renal failure
- Analgesic nephropathy

ii. Electrolyte disorders
- Hypokalemia
- Hypercalcemia

iii. Drugs
- Vasopressin antagonists
- Lithium
- Demeclocycline
- Acetohexamide
- Tolazamide
- Glyburide
- Propoxyphene
- Amphotericin
- Methoxyflurane
- Vinblastine
- Colchicine

iv. Dietary abnormalities
- Excessive water intake
- Decreased sodium chloride intake
- Decreased protein intake

v. Miscellaneous
- Multiple myeloma
- Amyloidosis
- Sjögren syndrome
- Sarcoidosis
- Sickle cell disease

3. Diabetes Insipidus Secondary to Vasopressinase. Central diabetes insipidus and nephrogenic diabetes are not the only causes of polyuria during pregnancy. Vasopressinase is an enzyme, produced in the placenta, that causes in vivo degradation of AVP during pregnancy. Normally, an increase in vasopressin synthesis and release during pregnancy compensates for the increased degradation of the hormone. In rare cases, however, excessive vasopressinase has been incriminated in causing polyuria during pregnancy. Because vasopressinase cannot degrade DDAVP, this is the treatment of choice for this pregnancy-related polyuria.

Table 2-2.	Procedure and Interpretation of a Water Deprivation Test	
Cause of Polyuria	**Urinary Osmolality with Water Deprivation (mOsm/kg of water)**	**Increase in Urinary Osmolality after Fluid Deprivation with Exogenous Arginine Vasopressin**
Normal	>800	Little or no increase
Complete central diabetes insipidus	<300	Substantially increased above plasma
Partial central diabetes insipidus	300–800	Increase of >10%
Nephrogenic diabetes insipidus	<300–500	Any increase <10%
Primary polydipsia	>500	Any increase <10%

4. **Response to Fluid Deprivation and AVP in the Diagnosis of Polyuric Disorder.** The various forms of diabetes insipidus must be differentiated from primary polydipsia in patients who present with polyuria. The procedure and interpretation of a water deprivation test are summarized in Table 2-2. Patients with compulsive water drinking may present with polyuria and a blunted response to the fluid deprivation test; on cessation of fluid intake, hypernatremia does not develop in these patients and their renal concentration defect is primarily due to a resistance of the kidney to vasopressin. However, because patients with central or nephrogenic diabetes insipidus may present with polyuria and polydipsia in the absence of hypernatremia, awareness of the diagnosis of compulsive (psychogenic) water drinking is quite important. Menopausal women with previous psychiatric problems are particularly prone to compulsive water drinking. Psychoneurosis and psychosis are also frequently associated with increased water intake.

   The differential diagnosis in the polyuric patient between compulsive water drinking and partial central diabetes insipidus is the most difficult. Fluid restriction with 3% to 5% loss of body weight will lead to a urine osmolality above plasma, albeit to a submaximal level in both circumstances. Administration of vasopressin will not increase urine osmolality further (<10%) in the patient with compulsive water drinking because the defect is at the level of the kidney, not inadequate endogenous vasopressin. In contrast, the patient with partial central diabetes insipidus will have a substantial increase in urinary osmolality (>10%) with exogenous vasopressin because the defect is due to inadequate release of vasopressin.

   Last, the patient with nephrogenic diabetes insipidus may occasionally have vasopressin-resistant hypotonic urine (e.g., hypercalcemic or

hypokalemic nephropathy); therefore, the temporary absence of fluid intake because of an intercurrent illness can be associated with hypernatremia. In all hypernatremic patients who primarily have water losses without electrolyte losses, the urine sodium excretion concentration merely reflects sodium intake. During any solute-free water diuresis, the urinary sodium concentration declines so that sodium balance is maintained.

II. SIGNS AND SYMPTOMS.

Polyuria and polydipsia may be prominent symptoms in the patient who subsequently develops hypernatremia in association with inadequate water intake.

A. CNS Dysfunction. Neurologic abnormalities constitute the most prominent manifestations of hypernatremic states. These neurologic manifestations appear to be due primarily to the cellular dehydration and shrinkage of brain cells that are associated with tearing of cerebral vessels. Capillary and venous congestion, subcortical and subarachnoid bleeding, and venous sinus thrombosis all have been described with hypernatremia.

B. Prognosis of Acute versus Chronic Hypernatremia. The signs and symptoms of hypernatremia are more severe in acute than in chronic hypernatremia. Indeed, 75% mortality has been reported in association with acute hypernatremia in adults with acute elevations of plasma sodium concentration above 160 mEq/L. These adults, however, frequently have severe primary diseases associated with their hypernatremia, and these primary diseases may largely account for the high mortality. A 45% mortality has been reported in children with acute hypernatremia, and as many as two-thirds of the surviving children may have neurologic sequelae.

C. Osmolyte Generation in Chronic Hypernatremia. The more benign course of chronic hypernatremia appears to be related to cellular mechanisms that protect against severe brain dehydration. The brain, however, requires some period of time, perhaps days, to adapt. In chronic hypernatremia, brain cells generate organic compounds designated as osmolytes, some of which appear to be amino acids; these osmolytes are osmotically active and restore brain water to near-control levels in spite of persistent hypernatremia. The presence of these osmolytes with chronic hypernatremia, although protective against brain dehydration and shrinkage, may predispose to brain edema if the hypernatremia is corrected too rapidly.

D. Correlation of CNS Dysfunction with Degree of Hyperosmolality. The earliest manifestations of hypernatremia are restlessness, increased irritability, and lethargy. These symptoms may be followed by muscular twitching, hyperreflexia, tremulousness, and ataxia. The level of hyperosmolality at which these signs and symptoms occur depends not only on the rapidity of the change in the plasma sodium concentration but also on the age of the patient; the very young and the very old exhibit the most severe manifestations. In general, however, these signs and symptoms may occur progressively with plasma osmolality in the range of 325 to 375 mOsm/kg of water. At plasma osmolalities above this level, tonic muscular spasticity, focal and grand mal seizures, and death may occur. The elderly patient with dementia or severe cerebrovascular disease may

demonstrate these life-threatening signs and symptoms at a lower level of plasma hyperosmolality.

III. THERAPY. Hypernatremia is frequently a preventable electrolyte disorder if water losses are recognized and appropriately replaced. In most cases, hypernatremia can be treated by the judicious administration of water to patients with water-losing disorders who cannot obtain water. The treatment of hypernatremia depends on two important factors: ECF volume status and the rate of development of the hypernatremia.

A. Correction of ECF Volume Depletion. When hypernatremia is associated with ECF volume depletion, the primary therapeutic goal is to administer isotonic saline until restoration of ECF volume is achieved, as assessed by normal neck veins and absence of orthostatic hypotension and tachycardia. Hypotonic (0.45%) NaCl or 5% glucose solutions can then be used to correct plasma osmolality.

B. Correction of ECF Volume Expansion. In contrast, if hypernatremia is associated with ECF volume expansion, diuretics (e.g., furosemide) with liberal fluid intake can be used to treat the hypernatremia. In the presence of advanced renal failure, the patient with hypernatremia and fluid overload may need to be dialyzed to treat the hypernatremia.

C. Water Replacement Method of Calculation. Last, the patient with euvolemic hypernatremia can be treated primarily with water replacement either orally or parenterally with 5% glucose in water. The method of calculation of the necessary water replacement for a 75-kg man with a plasma sodium of 154 mEq/L is as follows:

$$\text{TBW} = \text{body weight} \times 60\% \text{ or}$$
$$\text{TBW} = 75 \times 0.6 = 45 \text{ L}$$

Then,

$$\frac{\text{Actual plasma sodium}}{\text{Desired plasma sodium}} \times \text{TBW} = \frac{154 \text{ mEq/L}}{145 \text{ mEq/L}} \times 45 \text{ L} = 49.5 \text{ L}$$

Therefore, the repletion of 4.5 L (49.5 – 45 L) positive water balance will correct the plasma sodium concentration. Ongoing water losses should not be overlooked.

D. Rate of Correction. The recommended rate of correction of hypernatremia depends on the rate of development of the hypernatremia and the symptoms. More neurologic signs and symptoms are associated with acute hypernatremia; therefore, this biochemical abnormality should be corrected rapidly, over a few hours.

Conversely, osmolytes appear to accumulate in brain cells during periods of chronic hypernatremia, a mechanism that protects against brain shrinkage. Therefore, the rapid correction of chronic hypernatremia can create an osmotic gradient between the ECF and intracellular compartments, with osmotic water movement into cells and subsequent brain edema. In general, therefore, chronic hypernatremia is best corrected gradually, at a rate not to exceed 2 mOsm/hour. One-half of the correction can be achieved in 24 hours and the other half in the next 24 hours or longer.

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3 The Patient with Hypokalemia or Hyperkalemia

Jie Tang and Stuart L. Linas

Potassium is the most abundant cation in the human body. It regulates intracellular enzyme function and helps determine neuromuscular and cardiovascular tissue excitability. Over 98% of total body potassium is located in the intracellular fluid (ICF; primarily in muscles), less than 2% in the extracellular fluid (ECF). The ratio of extracellular potassium to intracellular potassium determines membrane potential. The acuity of changes in serum potassium concentration and membrane potential determines the severity of clinical symptoms and underlies the clinical findings caused by disorders of potassium metabolism.

I. OVERVIEW OF POTASSIUM PHYSIOLOGY.

The typical Western diet contains 40 to 120 mEq of potassium a day. Tight control of the serum potassium between 3.5 and 5.5 mEq/day is primarily accomplished by the kidney where secretion varies between 40 and 120 mEq/day. Potassium losses in stool and sweat are small (5 to 10 mEq). In addition, the interplay of several hormonal systems and the internal acid–base environment contribute to the exchange of potassium between the ECF and ICF, which helps keep the serum potassium concentration tightly controlled. Although total body potassium declines with aging, and the rate of decline appears to be influenced by sex and race, the clinical significance of these observations is not clear.

A. Internal Balance.

Under certain physiological conditions, potassium is rapidly redistributed between the intracellular and extracellular compartments. Several hormones and physiological factors interact to regulate the transcellular movement of potassium.

1. **Insulin.** High serum potassium increases insulin levels. The binding of the insulin hormone to insulin receptors causes a hyperpolarization of cell membranes that facilitates potassium uptake in liver, fat, cardiac, and skeletal muscle. Insulin also activates Na–K–adenosine triphosphatase (ATPase) pumps and causes the cellular uptake of potassium.
2. **Catecholamines.** Activation of the β_2-adrenoreceptor results in cellular potassium uptake in the liver and muscle. In addition to the activation of inwardly directed Na^+–K^+–Cl_2^- (NKCC) cotransporters, the effect is also transduced by cyclic adenosine monophosphate (cAMP) activation of Na–K–ATPase pumps, causing an influx of potassium in exchange for sodium. Therapeutic agents such as theophylline potentiate β_2-adrenoreceptor–mediated potassium uptake by inhibiting the degradation of cAMP.

3. **Acid–Base.** Inorganic acidosis (e.g., hydrochloric acid) facilitates potassium movement from ICF to ECF. Protons enter cells, whereas impermeant inorganic ions do not. The resulting increases in ICF positive charge favor the outward movement of potassium. Because organic ions (lactate, ketoacids) are less restricted from entering cells, increases in serum potassium may not occur in organic acidosis.
4. **Tonicity.** Hyperglycemia causes potassium-rich fluid to leave the cell, thereby increasing ECF potassium. Under most conditions, increases in insulin modulate and reverse the effect of increased extracellular tonicity. However, when insulin cannot be increased (e.g., type 1 diabetes mellitus) or hyperglycemia occurs rapidly (as with the administration of 50% glucose), hyperkalemia occurs. Rapid infusions of mannitol also may cause hyperkalemia.

B. External Balance

1. Kidney

Urinary potassium excretion is the result of a difference between the potassium secreted and potassium reabsorbed in the distal nephron. Potassium is freely filtered at the glomerulus. More than 50% of filtered potassium is reabsorbed in the proximal convoluted tubule through paracellular pathways. In the descending limb of Henle's loop, especially in deep nephrons, potassium concentration increases. In the medullary thick ascending limb of the loop of Henle, the Na–K–2Cl–cotransporter leads to the reabsorption of potassium. When the tubular fluid reaches the early distal convoluted tubule, only 10% to 15% of filtered potassium remains. Potassium is secreted by the principal cells of the connecting tubule and cortical collecting duct. Potassium is reabsorbed in the outer medullary collecting duct, an effect mediated by intercalated cells. A fall in glomerular filtration rate (GFR) is not generally associated with decreased potassium excretion and hyperkalemia until the GFR is less than 20 mL/min. It is due to an adaptive increase in potassium excretion in the remaining functioning nephrons. The major factors regulating potassium excretion follow.

a. **Distal Nephron Flow Rate and Sodium Delivery.** Under normal conditions, sodium delivered to the cortical collecting tubule is reabsorbed through amiloride-sensitive epithelial sodium channels (ENaCs) in the principal cells. The resulting negative potential in the tubular lumen results in increased potassium excretion through apical potassium channels [renal outer medullary potassium (ROMK) channel]. This system requires sodium delivery to the distal tubule. In addition, increases in tubular flow rate help maintain a low urinary potassium concentration, which favors the movement of potassium from cells into tubular fluid.
b. **Mineralocorticoids.** Aldosterone is the major mineralocorticoid; it increases potassium secretion into the tubular fluid by the following:
   i. Increasing the number and activity of apical amiloride-sensitive ENaCs in the connecting tubule and cortical collecting duct in the distal tubule. This increases sodium reabsorption, thereby creating a negative lumen and driving force for potassium excretion into the tubular lumen.
   ii. Increasing basolateral Na–K–ATPase activity.

c. Increases or decreases in **dietary potassium** increase or decrease urinary potassium, respectively. Renal adaptation to high potassium intake is mediated by a potassium-induced increase in aldosterone secretion and by an increase in distal nephron Na–K–ATPase activity. In response to potassium restriction, mineralocorticoid activity decreases, thereby causing a decline in potassium secretion.

d. Increases in relatively nonresorbable **anions** (e.g., bicarbonate, penicillin) trap secreted potassium in the tubular lumen and limit potassium reabsorption in the medullary collecting duct. The resulting renal potassium losses may lead to severe potassium depletion.

e. WNK kinases are a recently identified series of enzymes found to regulate potassium excretion. WNK4 decreases activity of the NaCl transporter in the distal tubules and decreases the number of potassium channels in the cortical collecting tubule. The net effect of WNK4 is to cause potassium retention.

2. Extrarenal

a. Gastrointestinal Tract

At a lower potassium intake (<55 mmol/day), there appears to be an inverse relationship between renal and gastrointestinal (GI) potassium excretions. However, at a higher intake, both renal and GI potassium excretions increase. It indicates that the GI tract may play a significant role in handling the extra potassium load, especially when the kidney function is compromised. The relative contribution of GI potassium excretion may be different in people with different racial background.

b. Others

Both salivary and sweat glands are involved in potassium excretion regulated by aldosterone. However, its clinical significance in potassium homeostasis is not clear.

II. HYPOKALEMIA

A. Diagnosis. The **initial approach** to hypokalemia is to determine whether it is spurious, secondary to a shift of potassium from the extracellular to intracellular compartments, or a result of a true decrease in total body potassium (Fig. 3-1).

Spurious hypokalemia occurs in the setting of extreme leukocytosis (in vitro white blood cells uptake potassium in the test tube) and is not associated with changes in either internal or external potassium balance.

Potassium shifts into cells may occur acutely in conditions associated with increases in endogenous insulin or catecholamines. For example, catecholamine release associated with shortness of breath (asthma, chronic obstructive pulmonary disease exacerbations, heart failure, and chest pain syndromes including myocardial infarction or angina) or catecholamine release from certain drug withdrawals (alcohol, narcotics, or barbiturates) shifts potassium into cells, thereby decreasing the serum potassium concentration. Hypokalemia may also be caused by insulin administration (correction of diabetic ketoacidosis, postresuscitation for hyperkalemia) or β_2-adrenoreceptor agonist (β_2-agonists, theophylline). Other common causes of decreases in serum potassium without decreases in total body potassium include hypokalemic periodic paralysis (familial

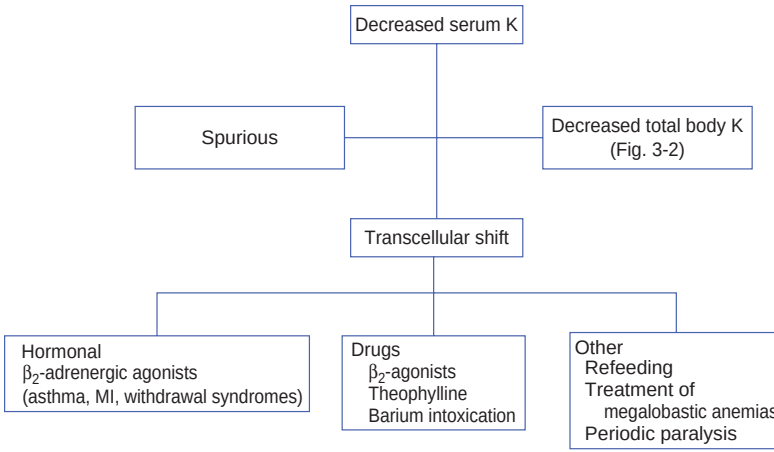

Figure 3-1. Diagnostic approach to hypokalemia. (K, potassium; MI, myocardial infarction.)

and hyperthyroid types), treatment of megaloblastic anemias, and refeeding syndromes (probably insulin mediated). The refeeding syndrome, in which severely malnourished patients are begun on nasogastric feeding, is also seen in older adults in whom the clinical manifestations of malnutrition are less clinically apparent.

Decreases in total body potassium (Fig. 3-2) are caused by either inadequate potassium intake or by excessive renal or extrarenal potassium losses. The measurement of urinary potassium excretion (by 24-hour measurements or "spot" potassium concentrations) is used to distinguish renal versus extrarenal potassium loss. Urinary potassium concentrations less than 20 mEq/L suggest poor potassium intake and/or extrarenal potassium loss. Serum acid–base status is helpful in evaluating hypokalemia with low urinary potassium excretion. Metabolic acidosis may suggest lower GI losses (diarrhea of any cause, e.g., infectious, toxic, and laxative abuse). A normal serum pH is less helpful because hypokalemia can be secondary to both decreases in intake and GI losses. Metabolic alkalosis with urinary potassium of less than 20 mEq/L, although rare, is associated with laxative abuse, villous adenoma, or congenital chloride-losing diarrhea.

Hypokalemia with a urinary potassium excretion of greater than 20 mEq/L suggests renal potassium wasting. The serum pH again is helpful to further evaluate etiologies. Metabolic acidosis suggests renal tubular acidosis (type 1 or type 2), diabetic ketoacidosis (osmotic diuresis), ureterosigmoidostomy, or carbonic anhydrase inhibitor use. More commonly, renal potassium losses are associated with **metabolic alkalosis**. In this clinical setting, the urinary chloride concentration is helpful. A low urinary chloride concentration (less than 20 mEq/L) suggests upper GI potassium losses, recent (but not current) diuretic use, or a posthypercapnic syndrome. Hypokalemia with a high urinary chloride concentration is further distinguished on the basis of the presence

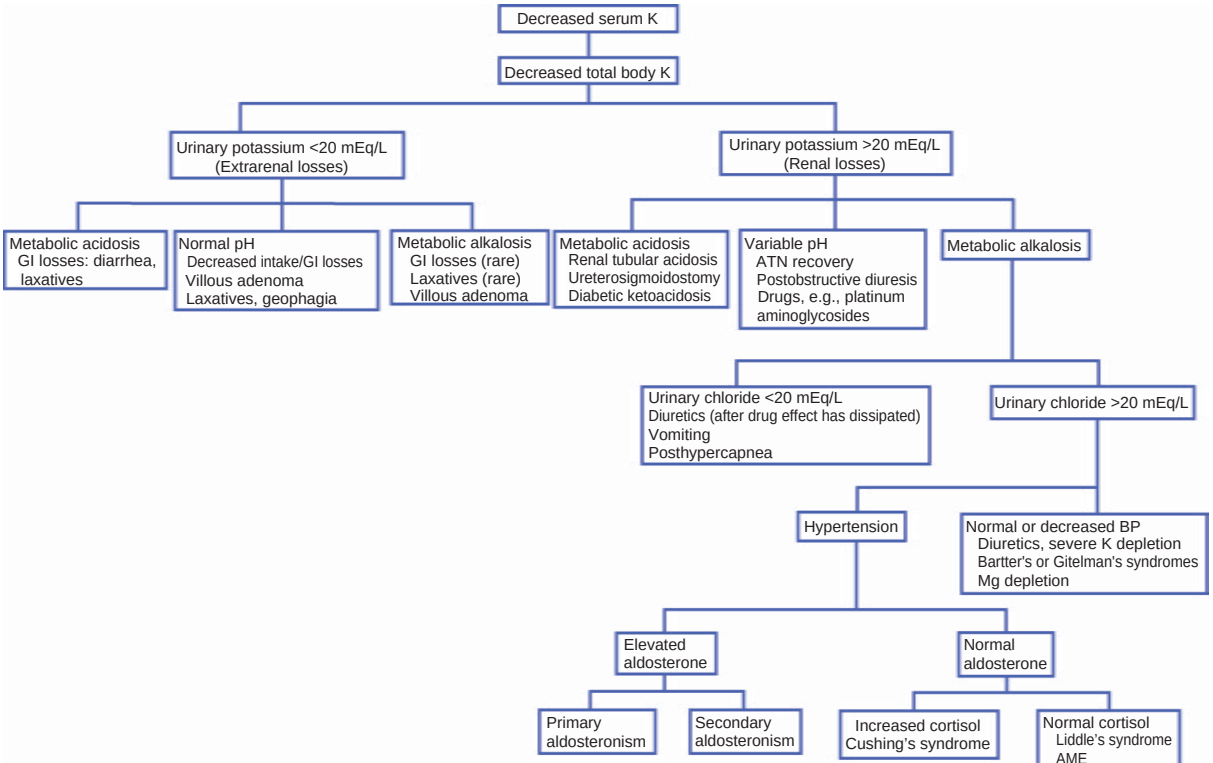

Figure 3-2. Diagnostic approach to hypokalemia. (AME, aseptic meningoencephalitis; ATN, acute tubular necroses; BP, blood pressure; GI, gastrointestinal; K, potassium; Mg, magnesium.)

or absence of hypertension. In normotensive individuals, hypokalemia with metabolic alkalosis and a high urinary chloride occurs with diuretic use (loop or distal convoluted tubule–acting diuretics), in Bartter's and Gitelman's syndrome, and with severe decreases in total body magnesium or potassium. Hypokalemia with renal potassium wasting, renal chloride wasting, and hypertension is further evaluated by urinary aldosterone concentrations. An elevated aldosterone level suggests either primary aldosteronism (adenoma, hyperplasia, glucocorticoid remedial) or secondary aldosteronism (renovascular or accelerated hypertension, diuretic use, renin-secreting tumor). Conversely, normal aldosterone levels with increases in serum cortisol suggest Cushing's syndrome or exogenous steroid use. Normal cortisol and aldosterone levels indicate Liddle's syndrome (caused by increases in the activity of the cortical collecting tubule sodium channel) or apparent mineralocorticoid excess syndrome [decreases in 11-β-hydroxysteroid dehydrogenase activity in kidney tissue (congenital, licorice ingestion) causing the mineralocorticoid receptor to respond to glucocorticoid]. Increases in urinary potassium excretion without a significant acid–base disorder are seen during the recovery phase of acute tubular necrosis, postobstructive diuresis, and magnesium depletion associated with drugs such as aminoglycosides and cisplatinum, or in myelomonocytic leukemia (secondary to lysozymuria).

Finally, hypokalemia is frequently associated with chronic alcoholism. The mechanism behind this electrolyte abnormality is not well defined but is probably multifactorial secondary to poor intake, diarrhea, alcohol withdrawal with respiratory alkalosis, and kaliuresis associated with hypomagnesemia.

1. Genetic Disorders Associated with Hypokalemia

These disorders, mentioned earlier, are characterized by either excess mineralocorticoid production/activity or abnormal renal potassium excretion independent of mineralocorticoid activity. Disorders associated with increased aldosterone production include glucocorticoid-remediable aldosteronism and congenital adrenal hyperplasia.

Bartter's and Gitelman's syndromes are characterized by abnormalities in renal epithelial potassium metabolism. There are five variants of Bartter's syndrome. The phenotypes vary but all are associated with hypokalemia and normotension. Mutations have been identified in the bumetanide-sensitive Na^+–K^+–2Cl–cotransporter gene (*NKCC2*), ROMK channel in the ascending loop of Henle, Barttin gene (β-subunit for CIC-Ka and CIC-Kb chloride channels), CIC-KB, and calcium-ensing receptor. Gitelman's syndrome is a hypokalemia tubulopathy associated with a mutation in the thiazide-sensitive NaCl cotransporter (TSC).

Liddle's syndrome is an autosomal recessive disorder caused by a gain-of-function mutation in the ENaC. As a result, extracellular volume is expanded with hypertension. However, as the ROMK channel is secondarily activated, potassium excretion is increased and hypokalemia results.

Although **cell-shift hypokalemia** and **decreases in total body potassium** do occur as isolated problems, they frequently occur **simultaneously**. Decreases in total body potassium potentiate the effects

of drugs and hormones to shift potassium into cells. For example, small changes in potassium during insulin therapy may not cause hypokalemia if total body potassium is normal, but in the setting of total body potassium depletion (e.g., during the treatment of diabetic ketoacidosis or with diuretic use), cellular shifts of potassium during insulin therapy can result in profound hypokalemia.

B. The **manifestations** of hypokalemia are mainly cardiac and neuromuscular (Table 3-1). The most dramatic neuromuscular symptoms are paresis, paralysis, and respiratory failure. Potassium depletion causes supraventricular and ventricular arrhythmias, especially in patients on digitalis therapy. Although severe hypokalemia is more likely to cause complications, even minimal decreases in serum or total body potassium can be arrhythmogenic in patients with underlying heart disease or who are receiving digitalis therapy.

C. The **treatment** of hypokalemia depends on the underlying cause, the degree of potassium depletion, and the risk of potassium depletion to the patient. In general, hypokalemia secondary to cell shift is managed by treating the underlying conditions. For example, hypokalemia in the setting of catecholamine increases, as in chest pain syndromes, is managed with appropriate treatments for the pain. However, when cell-shift hypokalemia is associated with life-threatening conditions such as paresis, paralysis, or hypokalemia in the setting of myocardial infarction, the administration of potassium is indicated. With potassium depletion, replacement therapy depends on the estimated degree of decreases in total body potassium. For example, decreases in total body potassium accompanied by a fall in serum potassium from 3.5 to 3.0 mEq/L are associated with a potassium deficit of 150 to 200 mEq. Decreases in serum potassium from 3 to 2 mEq/L are associated with 200- to 400-mEq additional decreases in total body potassium. Potassium can be administered intravenously, but in limited quantities (10 mEq/hour into a peripheral vein; 15 to 20 mEq/hour into a central vein). Larger potassium requirements can only be accomplished by oral therapy or with dialysis.

III. HYPERKALEMIA

A. The **approach** to hyperkalemia (Fig. 3-3) is to determine whether increases in serum potassium are spurious, caused by shifts of potassium from cellular to extracellular spaces, or represent a true increase in total body potassium.

Spurious hyperkalemia is caused by red blood cell hemolysis in vitro, ischemic blood draws, extreme thrombocytosis (greater than 1 million mL), or leukocytosis (greater than 50,000 mL). Spurious hyperkalemia is distinguished from true hyperkalemia by the absence of electrocardiographic (ECG) abnormalities. Hyperkalemia caused by **cell shifts** of potassium occurs acutely and results from decreased potassium transfer into cells (with decreases in insulin or β-adrenergic blocker therapy), increased potassium movement from cells to the extracellular space (with metabolic acidosis), hypertonicity (with hyperglycemia or the administration of mannitol), exercise, muscle breakdown (with rhabdomyolysis), or drug intoxications from digitalis or succinylcholine.

Table 3-1.	Clinical Manifestations of Hypokalemia
Cardiovascular	
Electrocardiographic abnormalities: U waves, QT prolongation, ST depression	
Predisposition to digitalis toxicity	
Atrial/ventricular arrhythmias	
Neuromuscular	
Skeletal muscle	
Weakness	
Cramps	
Tetany	
Paralysis—flaccid	
Rhabdomyolysis	
Smooth muscle	
Constipation	
Ileus	
Urinary retention	
Endocrine	
Carbohydrate intolerance	
Diabetes mellitus	
Decreased aldosterone	
Growth retardation	
Renal/electrolyte	
Decreased renal blood flow, glomerular filtration rate	
Nephrogenic diabetes insipidus	
Increased ammoniagenesis (hepatic encephalopathy)	
Chloride wasting/metabolic alkalosis	
Cyst formation	
Interstitial nephritis	
Tubular vacuolization	

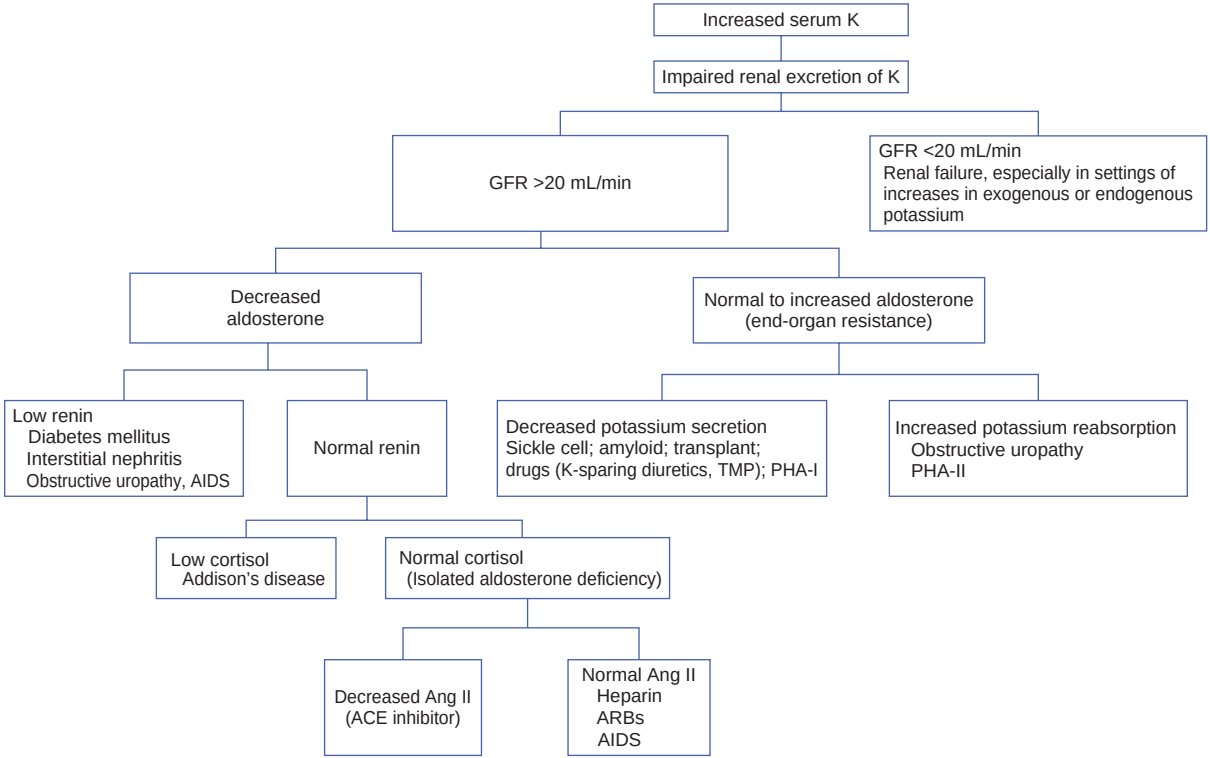

Figure 3-3. Diagnostic approach to hypokalemia. (ACE, angiotensin-converting enzyme; AIDS, acquired immunodeficiency syndrome; Ang, angiotensin; ARBs, adrenergic receptor binders; GFR, glomerular filtration rate; K, potassium; PHA, pseudohypoaldosteronism; TMP, trimethoprim-sulfa.)

Sustained hyperkalemia is caused by decreases in renal potassium excretion. This usually is not seen until the GFR is less than 20 mL/min. However, it may be seen with less severe decreases in GFR when the kidney is challenged with a potassium load from potassium ingestion (e.g., diet, salt substitutes, or drugs, including potassium chloride and potassium citrate) and from increases in endogenous potassium production (e.g., GI bleed, resolving hematoma, rhabdomyolysis, catabolic states, and tumor lysis). Hyperkalemia with less severe decreases in renal function is also associated with reductions in the distal nephron flow rate or low serum aldosterone levels as, for example, with hyporenin hypoaldosteronism. Last, hyperkalemia is also associated with less severe decreases in GFR when drugs that alter potassium physiology are administered. Hyperkalemia occurs in the setting of drugs that inhibit renin secretion (β-adrenergic blockers), renin activity (direct renin inhibition), angiotensin II generation (angiotensin-converting enzyme inhibitors), and the angiotensin receptor (AT_1). Hyperkalemia also occurs when drugs that block activation of the mineralocorticoid receptor (spironolactone, eplerenone) or inhibit the rate-limiting step in aldosterone synthesis (heparin) are administered. Drugs that directly inhibit ENaC such as amiloride, trimethoprim, and pentamidine cause hyperkalemia. The protease inhibitor, nafamostat, indirectly inhibits ENaC through inhibition of membrane-associated proteases. Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause hyperkalemia. NSAIDs block prostaglandin production. As 70% of renin production is prostaglandin dependent, blocking the latter indirectly results in hyporeninemia. Cyclosporine, tacrolimus, and digoxin inhibit Na^+–K^+–ATPase, the enzyme responsible for potassium excretion in the collecting duct and this can cause hyperkalemia. Succinylcholine causes hyperkalemia by depolarizing skeletal muscle.

Clinical studies also suggest that older adults are at increased risk for hyperkalemia. Although no clear explanation exists for this observation, it may be related to an age-associated decline in aldosterone synthesis or possibly a decline in tubular sensitivity to its action. Commonly used medications causing hyperkalemia are shown in Table 3-2.

Hyperkalemia also occurs in the **setting of a relatively well-preserved GFR.** The causes of hyperkalemia in this setting are distinguished on the basis of plasma or urinary aldosterone levels. Decreases in aldosterone occur in the setting of normal, increased, or decreased plasma renin activity. Decreased plasma renin activity (hyporeninemic hypoaldosteronism) tends to occur in older adults and is associated with a number of renal diseases, including diabetes, interstitial nephritis (e.g., sickle cell anemia, analgesic use, and heavy metal toxicity), obstructive uropathy, systemic lupus erythematosus, and amyloidosis. Decreases in plasma renin activity are also associated with acquired immunodeficiency syndrome–associated nephropathy, transplantation, and medications including cyclosporine and NSAIDs. Hyper-reninemic hypoaldosteronism also occurs both with decreases in cortisol production (Addison's disease) and with normal cortisol production when medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and heparin are used. Finally, increases in serum potassium can be associated with normal to high levels of aldosterone and end-organ resistance to aldosterone. Aldosterone resistance is caused by drugs (such as potassium-sparing diuretics,

Table 3-2.	Commonly Used Medications Causing Hyperkalemia
Medication	**Mechanism**
Digitalis overdose	Inhibition of the Na–K–ATPase pump
Angiotensin II inhibitors	Decreased aldosterone excretion
NSAIDs	Blocks prostaglandin stimulation of renin
Trimethoprim	A cationic agent that decreases the number of open sodium channels in the luminal membrane of cortical collecting ducts
Pentamidine	Same mechanism as trimethoprim—blocks distal potassium excretion
Spironolactone	Competes for aldosterone receptor in collecting tubule
Amiloride	Blocks sodium channel
Heparin	Decrease aldosterone
Salt substitutes	Contain potassium
Succinylcholine	Moves potassium from intracellular to extracellular fluid
Cyclosporine	Multifactorial, including hyporenin hypoaldosteronism and interference with aldosterone action in the potassium-secreting cells of the cortical collecting duct
Pentamidine	Blocks distal potassium secretion

ATPase, adenosine triphosphatase; NSAIDs, nonsteroidal anti-inflammatory drugs.

trimethoprim, and pentamidine), interstitial renal diseases (systemic lupus erythematosus, sickle cell anemia), obstructive uropathy, or transplantation. It also occurs in an unusual hereditary disease called *pseudohypoaldosteronism type 1*, in which the etiology is either a decrease in aldosterone receptor number or decreased activity of the ENaC in the distal convoluted tubule. Gordon's syndrome is associated with hyperkalemia in the setting of a normal GFR, decreased renal potassium excretion, and metabolic acidosis. Its mode of heritance is autosomal dominant. It is caused by a *WNK4* gene mutation causing a gain-of-function mutation in TSC with an increase in ECF and as a result, suppression of plasma renin, decreased aldosterone, and hyperkalemia. Hyperkalemia in association with normal potassium secretion and increased potassium reabsorption occurs with obstructive uropathy.

B. Diagnosis. The **urinary potassium excretion rate** or **transtubular potassium gradient (TTKG)** [(urine potassium/serum potassium)/(urine osmolarity/serum osmolarity)] is used to distinguish aldosterone deficiency/resistance from extrarenal causes of hyperkalemia (Table 3-2). This test measures the amount of potassium secreted by the distal tubule corrected by water absorption in the medullary collecting tubules. A normal value for TTKG is 6 to 12. In the setting of hyperkalemia, a value greater than 10 suggests normal aldosterone levels and activity and points to an extrarenal cause of hyperkalemia. In contrast, renal causes of hyperkalemia (hypoaldosteronism) are associated with decreases in urinary potassium excretion (less than 20 mEq/day) and TTKG less than 5 to 7. In this setting, the administration of a mineralocorticoid (0.05 mg fludrocortisone) results in increases in urinary potassium excretion (greater than 40 mEq/day) and TTKG greater than 10 in patients with aldosterone deficiency. However, no increase in urinary potassium excretion or in TTKG suggests aldosterone resistance (e.g., sickle cell anemia).

C. The **clinical manifestations** of hyperkalemia are predominantly cardiac and neuromuscular. It is important to note that patients with hyperkalemia often present with vague GI complaints and nonspecific unwell feelings. ECG abnormalities associated with mild hyperkalemia include peaked T waves. With moderate hyperkalemia there is prolongation of the PR interval, decrease in amplitude of P waves, and widening of the

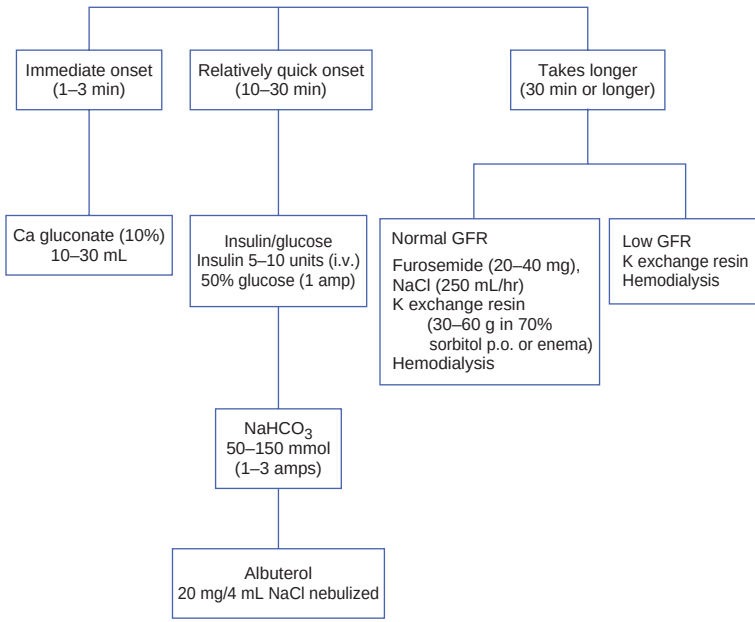

Figure 3-4. Treatment of hyperkalemia. (Ca, calcium; GFR, glomerular filtration rate; K, potassium.)

QRS complex. With severe hyperkalemia, the P wave is absent, there is progressive widening of the QRS complex, and if left untreated, sine waves develop with asystole. Neuromuscular abnormalities include weakness, constipation, and paralysis.

D. The **treatment** of hyperkalemia (Fig. 3-4) depends on the presence or absence of ECG and neuromuscular abnormalities. In the absence of symptoms or ECG abnormalities, hyperkalemia is treated conservatively—for example, by decreasing dietary potassium or withdrawing offending drugs. In the presence of ECG abnormalities or symptoms, the goal of therapy is to stabilize cell membranes. First-line therapy includes calcium gluconate, 10 to 30 mL as a 10% solution (onset of action 1 or 2 minutes). Although the mechanism remains undefined, calcium "stabilizes" the cardiac membranes. Other therapies include sodium bicarbonate, 50 to 150 mEq (onset 15 to 30 minutes) and insulin 5 to 10 units intravenously (onset 5 to 10 minutes). Insulin increases the activity of the Na–K–ATPase pump in skeletal muscle and drives potassium into cells. Glucose, 25 g intravenously, is given simultaneously to prevent hypoglycemia. Blood sugars should be monitored for approximately 6 hours to identify and treat hypoglycemia from the insulin. Albuterol nebulizer, 20 mg in 4 mL normal saline (onset 15 to 30 minutes), also activates the Na–K–ATPase and drives potassium into cells. Potassium driven intracellularly generally begins to move extracellularly again after approximately 6 hours, increasing the serum potassium concentration. Therefore, therapy to remove potassium from the body should be started simultaneously. Reductions in total body potassium may be achieved through a potassium exchange resin. The primary potassium resin used is sodium polystyrene sulfonate. One gram of this medication binds approximately 1 mEq of potassium and releases 1 to 2 mEq of sodium back into the circulation. This medication may be given orally (onset 2 hours) or by enema with sorbitol to induce diarrhea (onset 30 to 60 minutes). Finally, hemodialysis is very effective in removing excess potassium.

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4 The Patient with an Acid–Base Disorder

William D. Kaehny

I. Acid–base disorders are the chest pains of the body fluids. They are important signs of disorders that have deranged physiology. Occasionally, acid–base disorders disrupt homeostasis sufficiently to move the arterial pH into a dangerous range (less than 7.10 or greater than 7.60). Depending on the overall status of the patient and the response of the cardiovascular system, the pH level may require direct attention. After the clinician detects the presence of an acid–base disorder from clinical and laboratory clues, he proceeds logically through a progression of steps to optimal management of the patient.

A. **Step 1.** Measure pH. This identifies **acidemia or alkalemia**. The change in bicarbonate and partial pressure of CO_2 (P_{CO_2}) indicates whether the primary process is metabolic or respiratory.

B. **Step 2.** Check the compensatory or secondary response of the P_{CO_2} or HCO_3^- to see if the disorder is **simple** or **mixed**.

C. **Step 3.** Calculate the serum **anion gap** (AG) to screen for an increase in organic anions such as lactate. Add any increase in AG (ΔAG) that is **potential HCO_3^-** to the serum total carbon dioxide content (tCO_2) to screen for a hidden metabolic alkalosis.

D. **Step 4.** Determine the **cause** of the acid–base disorder from the clinical setting and laboratory tests.

E. **Step 5. Treat** the underlying disorder, unless the pH is dangerous either acutely or chronically (such as acidosis affecting bone).

II. WHEN TO SUSPECT ACID–BASE DISORDERS

A. **Clinical.** The underlying cause of the acid–base disorder is most frequently responsible for a patient's signs and symptoms. Certain clinical settings and findings should alert the clinician to the likelihood of an acid–base disorder. Coma, seizures, congestive heart failure, shock, vomiting, diarrhea, and renal failure generate changes in the P_{CO_2} or HCO_3^- levels. Marked changes in the pH occasionally may cause direct clinical manifestations. Severe alkalemia causes an irritability of heart and skeletal muscle. Severe acidemia causes a depression of heart pump function and vascular tone. Although central nervous system dysfunction appears frequently with acid–base disorders, changes in pH do not appear responsible. Rather, altered plasma osmolality and P_{CO_2} appear to be the causative agents.

B. **Laboratory.** A thoughtful measurement of serum electrolytes in patients with abnormal losses or gains of body fluids is good practice. An abnormal

serum tCO_2 is definite evidence of an acid–base disorder; an abnormal serum AG is very suggestive; an abnormal serum potassium is suspicious.

1. **Serum tCO_2.** The HCO_3^- in blood can be estimated reasonably by measuring the tCO_2 in venous serum. The serum tCO_2 is 1 to 3 mmol/L greater than the arterial HCO_3^- because it is from venous blood, which has more HCO_3^-, and it includes dissolved CO_2 and trivial amounts of other substances. Normal sea level serum tCO_2 levels average 26 to 27 mmol/L. A value below 24 or above 30 likely marks a clinical acid–base disorder. An acid–base disorder of the mixed type may exist with a normal serum tCO_2.
2. The **serum AG** is calculated from the venous serum sodium, chloride, and tCO_2:

$$AG = Na^+ - (Cl^- + tCO_2)$$

The units are in mEq/L, because this calculation estimates the charge difference between the so-called unmeasured anions (serum total anions represented by Cl^- and HCO_3^-) and unmeasured cations (total cations represented by Na^+). The average normal value is 9 ± 3 mEq/L, but varies in different laboratories. Albumin contributes most to the AG. A fall in serum albumin of 1 g/dL from a normal of 4.4 decreases the AG by 2.5 mEq/L. Importantly, the corrected serum AG includes this calculation.

   a. **Metabolic Acidosis** due to an organic acid such as lactic or acetoacetic acid is marked by an increased AG. An increase in the AG of 8 mEq/L to 17 or higher usually indicates the presence of organic acidosis, although at times the exact anion may not be identified. The anion of the organic acid replaces the HCO_3^- lost in the buffering of the hydrogen ion (H^+) part of the acid and therefore increases the unmeasured anions. Importantly, a normal or slightly elevated AG does not rule out the presence of organic metabolic acidosis, such as diabetic ketoacidosis, because a patient with good renal perfusion and ample urine flow may excrete the ketoanions at a rate sufficient to keep the serum AG from rising markedly.
   b. **Metabolic Alkalosis.** At times, a metabolic acidosis that increases the AG and lowers the HCO_3^- may coincide with a process that generates a metabolic alkalosis. For example, vomiting that generates a high HCO_3^- may be caused by diabetic ketoacidosis, which lowers the HCO_3^-. In this case, the serum tCO_2 (and arterial HCO_3^-) may be low or normal despite the elevating action of the metabolic alkalosis. The clue to the presence of such hidden metabolic alkalosis is derived in a Holmesian manner by adding the measured serum tCO_2 and the ΔAG (measured AG − 9). If this sum is greater than 30 mEq/L, a hidden metabolic alkalosis is likely present. The ΔAG is a marker of "lost" or potential HCO_3^-, that which was titrated by the H^+ of an organic acid. Pure metabolic alkalosis may directly increase the AG by up to 5 mEq/L due to effects on the albumin concentration and charge.
3. **Serum Potassium.** Potassium metabolism is linked to acid–base metabolism at the levels of cell shifts, renal tubular functions, and gastrointestinal transport. Therefore, an abnormal serum potassium concentration alerts the clinician to the likelihood that an acid–base disorder is also present.

III. IDENTIFYING THE MAJOR ACID–BASE DISORDERS.

When the clinician suspects that an acid–base disorder might be present and that patient management might be adjusted, a set of acid–base variables should be obtained: pH, P_{CO_2}, and HCO_3^-.

A. Chemistry and Physiology of Acid–Base.

Cellular, tissue, and organ systems apparently function best at an extracellular fluid (ECF) pH of approximately 7.40. Intracellular fluid (ICF) pH is heterogeneous within the cell, depending on organelles and metabolic activity, but averages approximately 7.00. ECF buffer molecules bind or release H^+ to keep pH close to 7.40 in the face of gain or loss of acids or bases.

Current clinical acid–base chemistry is based on the Brønsted–Lowry theory which designates acids as proton donors and bases as proton acceptors. The three key elements are the hydrogen ion activity (pH), carbonic acid (the acid), and bicarbonate (the base). The P_{CO_2} represents the acid in the modified Henderson–Hasselbalch equation. Base excess, used by some, is another concept derived from these elements in an attempt to explain whether alterations in these elements are due to metabolic or respiratory disorders.

Another approach that appears useful in investigative, analytic settings uses the Stewart equations. These calculate the pH from three, so-called independent, variables: P_{CO_2}, the strong ion difference, and total weak acid (mainly protein).

1. **Blood pH** is the mathematical expression of the intensity of acidity or H^+ activity. H^+ concentration usually is expressed in nmol per L. H^+ concentration is 100 nmol/L at pH 7.00 and 40 nmol/L at pH 7.40. The pH is measured at body temperature with a glass, flow-through electrode.
2. The **partial pressure of carbon dioxide in blood, P_{CO_2}**, represents the acid component in blood. The respiratory system determines the level at which the P_{CO_2} is set. P_{CO_2} is measured in whole blood with a pH electrode that detects the change caused by the diffusion of CO_2 from the sample into a buffer solution.
3. **HCO_3^-** is the metabolic component of the acid–base equation, serving as the base in the buffer pair. HCO_3^- concentration is controlled by the buffering state, metabolic processes, and the kidneys. HCO_3^- concentration is calculated from the pH and P_{CO_2} using the Henderson–Hasselbalch equation. The fact that it is calculated makes it no less reliable a value than the serum tCO_2.
4. The **acid–base equation** allows the determination of the state of ECF acid–base balance, the presence of an acid–base disorder, the nature of the disorder, and the presence of a simple or mixed disorder:

$$pH = \text{constant} \times [HCO_3^-]/P_{CO_2}$$

Therefore, the pH level depends on the ratio or mathematical relationship between the HCO_3^- and the P_{CO_2}. An acid–base disorder is generated by an alteration from normal of either of these two factors. The resultant change in pH results in chemical shifts in the buffers, which mitigate the change in pH somewhat. A physiologic compensatory response occurs in the respiratory system for a metabolic disorder and

in the kidneys for a respiratory disorder. A new steady state ensues, with the new pH set by the new values of the HCO_3^- concentration and P_{CO_2}.

B. Measurement of Acid–Base Variables. The determination of the acid–base state is usually based on an analysis of arterial blood, although arterialized venous blood analysis is equally valid. After warming the extremity, blood is drawn without air mixing from an artery or from a forearm vein without tourniquet. Although experimental studies show that ICF pH and mixed venous acid–base measurements correlate better with organ function, arterial blood measurements are more easily available and provide a readily interpretable view of the metabolic state of organs and their function. Keep in mind that tissue hypoperfusion, as in cardiopulmonary arrest or profound shock, makes tissue acidosis worse than that reflected by arterial blood acid–base values.

C. Identification of a Major Acid–Base Disorder. The basis of this approach is to determine the direction (up or down) in which the measured values differ from the arbitrary normal values for pH (7.40), P_{CO_2} (40 mmHg), and HCO_3^- (24 mmol/L). First, determine whether acidemia (pH down) or alkalemia (pH up) is present. Then determine whether the primary generating change was in the HCO_3^- or in the P_{CO_2} (Table 4-1). The compensating factor should change in the same direction as the generating factor to yield a simple acid–base disorder.

1. **Example of a Simple Disorder.** Arterial blood analysis revealed the following values: pH 7.55, HCO_3^- 18 mmol/L, and P_{CO_2} 21 mmHg.
   a. **Step 1.** The pH is up. Therefore, alkalemia is present and must be due to an increased HCO_3^- (as in metabolic alkalosis) or to a decreased P_{CO_2} (as in respiratory alkalosis).
   b. **Step 2.** The HCO_3^- is low and cannot be responsible for an increased pH.
   c. **Step 3.** Because the P_{CO_2} is low, it can account for the increased pH; this is respiratory alkalosis.
   d. **Step 4.** The HCO_3^- change is in the same direction as that of the P_{CO_2}; this is consistent with compensation and a simple respiratory alkalosis.
2. **Example of a Mixed Acid–Base Disorder.** Sampling of arterial blood yielded the following: pH 7.55, HCO_3^- 30 mmol/L, and P_{CO_2} 35 mmHg.

Table 4-1. Simple Acid–Base Disorders

	Metabolic Acidosis	Metabolic Alkalosis	Respiratory Acidosis	Respiratory Alkalosis
Primary change	$\downarrow HCO_3^-$	$\uparrow HCO_3^-$	$\uparrow P_{CO_2}$	$\downarrow P_{CO_2}$
Compensation	$\downarrow P_{CO_2}$	$\uparrow P_{CO_2}$	$\uparrow HCO_3^-$	$\downarrow HCO_3^-$
Effect on pH	↓pH	↑pH	↓pH	↑pH

↓ Decreased; ↑ Increased.

a. **Step 1.** The pH is up. Therefore, alkalemia is present.
b. **Step 2.** The HCO_3^- is increased and may be responsible for the increased pH.
c. **Step 3.** The P_{CO_2} is low and it, too, can account for an increased pH.
d. **Step 4.** The two pH determinants, that is, HCO_3^- and P_{CO_2}, are changed from normal in opposite directions. Therefore, this is mixed metabolic and respiratory alkalosis. The metabolic alkalosis is dominant because the percent change in HCO_3^- is 6/24 or 25% whereas the percent change in P_{CO_2} is 5/40 or 12.5%.

IV. JUDGING WHETHER AN ACID–BASE DISORDER IS SIMPLE OR MIXED.

When an underlying process generates an acid–base disorder by perturbing one member of the HCO_3^- P_{CO_2} buffer pair (remember that P_{CO_2} represents H_2CO_3), the other partner is adjusted to compensate by the physiologic response of the body and changes in the same direction as the primary partner in order to reduce the magnitude of the change in pH. The time-honored term for this physiologic response is *compensation*. However, the physiologic response mechanisms may be activated by stimuli other than pH and actually may contribute to the maintenance of the abnormal pH. Therefore, some have termed these responses *maladaptive* because they are not always truly compensatory. For example, a low P_{CO_2} in response to metabolic acidosis actually causes the kidneys to reduce HCO_3^- reabsorption. Importantly, compensation does not restore the pH exactly to normal, because that would shut off the stimulus for the compensatory mechanism.

A. Steps in Judging Whether an Acid–Base Disorder Is Simple.

After the major disorder is identified, determine whether the compensation for the primary event is appropriate.

1. **Check Directions of Changes from Normal of HCO_3^- and P_{CO_2}.** The acid–base buffer pair changes from normal in the same direction in all simple acid–base disorders. If they change in opposite directions, the disorder must be mixed.
2. **Compare the Magnitude of the Compensation of the P_{CO_2} or HCO_3^- with the Primary Change in the HCO_3^- or P_{CO_2}.** In metabolic disorders, the primary change occurs in the HCO_3^-, with the compensation occurring in the P_{CO_2}. The opposite is true in the respiratory disorders. Table 4-2 contains guidelines or rules that can be used to judge whether compensation is appropriate. The respiratory disorders have two stages of compensation: acute, when only tissue buffering slightly changes the HCO_3^-, and chronic (after 24 hours), when the kidneys cause major changes in the HCO_3^- concentration. If the measured change in the compensating factor does not approximate the change predicted, a mixed disorder is likely. Two methods of predicting compensation appear in Table 4-2. One describes the expected changes in the buffer partner for a given change in the generating partner. For example, a fall in HCO_3^- of 10 mmol/L in metabolic acidosis is expected to result in hyperventilation that drops the P_{CO_2} by 10 to 15 mmHg to 25 to 30 mmHg.
3. **Check the AG for Evidence of a Hidden Metabolic Disorder.** An increase in the AG of more than 8 mEq/L to greater than 17 suggests the

Table 4-2.	Appropriate Compensations in the Acid–Base Disorders	
	Change in P_{CO_2} per Change in HCO_3^-	**Change in pH per Change in HCO_3^-**
Metabolic acidosis	1.0–1.5 per 1	0.010 per 1
Metabolic alkalosis	0.25–1.00 per 1	0.015 per 1
	Change in HCO_3^- per Change in P_{CO_2}	**Change in pH per Change in P_{CO_2}**
Respiratory acidosis		
Acute	1 per 10	0.08 per 10
Chronic	4 per 10	0.03 per 10
Respiratory alkalosis		
Acute	1 per 10	0.08 per 10
Chronic	4 per 10	0.03 per 10

presence of metabolic acidosis due to an organic acid. Also if the ΔAG is added to the measured serum tCO_2, the theoretic maximum serum tCO_2 can be estimated. A value greater than 30 mmol/L suggests metabolic alkalosis.

B. Application of the Rules

1. The **primary event in metabolic acidosis** is a fall in HCO_3^-; the **compensation** is a fall in the P_{CO_2}, due to the stimulation of central nervous system receptors by the low pH. Hyperventilation increases the excretion of CO_2, and P_{CO_2} falls. For example, if the HCO_3^- falls from 24 mmol/L by 10 to 14 mmol/L, the P_{CO_2} should fall by 1.0 to 1.5 times as much, or 10 to 15 mmHg, to a level of 25 to 30 mmHg (40 − 10 = 30; 40 − 15 = 25).
2. The **primary event in metabolic alkalosis** is a rise in HCO_3^-. The respiratory system responds to the rise in pH with hypoventilation, which reduces carbon dioxide excretion and results in a rise in P_{CO_2}. For example, if HCO_3^- rises by 16 mmol/L from 24 to 40 mmol/L, the P_{CO_2} should rise by 0.25 to 1.00 multiplied by the rise in HCO_3^- of 16, or by 4 to 16 mmHg, to a level of 44 to 56 mmHg (40 + 4 = 44; 40 + 16 = 56). This response is tempered by the body's response to the concomitant hypoxemia resulting from hypoventilation.
3. The **primary event in respiratory acidosis** is a rise in P_{CO_2}. During the acute phase (up to 24 hours), only buffering contributes measurably to the response. The HCO_3^- should increase, but not to as high as 30 mmol/L. In contrast, the kidneys respond to chronic elevations

of P_{CO_2} by generating sufficient HCO_3^- to prevent the pH from falling to less than 7.20, even in the most severe cases of chronic respiratory acidosis.

4. The **primary event in respiratory alkalosis** is a fall in P_{CO_2}. Initially, buffering occurs as a result of the release of H^+ from cells; later (hours) the kidneys dump HCO_3^- into the urine, with a resultant fall in blood HCO_3^-, as defined in Table 4-2.

C. Effects of Respiratory Responses to Metabolic Disorders. The kidneys respond to changes in P_{CO_2} regardless of the pH. A fall in P_{CO_2} causes renal HCO_3^- loss; a rise in P_{CO_2} causes renal HCO_3^- generation. Therefore, in chronic metabolic acidosis (lasting days), some of the reduction in bicarbonate actually is due to the compensatory fall in P_{CO_2} and not directly to the process causing the metabolic acidosis. Similarly, the increase in P_{CO_2} in chronic metabolic alkalosis generates some of the hyperbicarbonatemia.

D. Examples of Mixed Acid–Base Disorders. Four combinations of the "double" mixed acid–base disorders are possible. Two are important because they cause drastic changes in pH—metabolic and respiratory acidosis and metabolic and respiratory alkalosis. The other two disorders (metabolic acidosis with respiratory alkalosis and metabolic alkalosis with respiratory acidosis) tend to be associated with pH values close to normal and are not dangerous per se; however, they are important markers of underlying disease. Two other mixed disorders, so-called triple disorders, have also been described. The AG points to both metabolic acidosis and alkalosis developing simultaneously or sequentially in these disorders. The imposition of a respiratory disorder yields the infamous triple acid–base disorder.

1. **Metabolic Acidosis and Respiratory Acidosis.** A patient with emphysema and carbon dioxide retention (chronic respiratory acidosis) develops diarrhea (metabolic acidosis). Note how the reduction in HCO_3^- to normal results in severe acidemia (Table 4-3).

2. **Metabolic Alkalosis and Respiratory Acidosis.** The same emphysematous patient is given a diuretic for cor pulmonale. The bicarbonate level rises from 40 to 48 mmol/L, which, with the P_{CO_2} at 80 mmHg, sets the pH at 7.40. Although this is a normal pH, some believe it is better for carbon dioxide–retaining patients to be mildly acidemic to keep ventilation stimulated.

3. **Triple Acid–Base Disorder.** A more common mixture of disorders involves metabolic acidosis developing in a patient with metabolic

Table 4-3. Example of a Mixed Acid–Base Disorder

	Health	Emphysema	Emphysema and Diarrhea
pH	7.40	7.32	7.10
P_{CO_2}	40	80	80
HCO_3^-	24	40	24

Table 4-4.	Example of a Triple Mixed Acid–Base Disorder			
	Health	Nasogastric Suction	Septic Shock	Endotoxemia
pH	7.40	7.49	7.14	7.44
Pco_2	40	44	24	12
HCO_3^-	24	32	8	8
Anion gap	9	11	33	35
Venous total carbon dioxide	26	35	9	9
Disorder		Metabolic alkalosis	Metabolic alkalosis	Metabolic alkalosis
			Metabolic acidosis	Metabolic acidosis
				Respiratory alkalosis

alkalosis and superimposed respiratory alkalosis. For example, a patient with metabolic alkalosis (HCO_3^- 32) from nasogastric suction becomes septic, which generates both lactic acidosis and pronounced hyperventilation, thereby causing independent respiratory alkalosis due to endotoxin (Table 4-4). Note that both the metabolic and respiratory alkaloses should cause only small increases in the AG. The lactic acidosis of septic shock results in a fall from 32 to 24 mmol/L in the HCO_3^- with a reciprocal increase in AG. The AG of 33 is diagnostic of organic acidosis. The ΔAG of 26 (35 − 9) added to the serum tCO_2 of 9 yields 35 mmol/L, an estimate of the value before acidosis, indicative of metabolic alkalosis. The evidence for the presence of respiratory alkalosis is the high pH and low Pco_2 due to the hyperventilation caused by endotoxemia.

V. IDENTIFY THE UNDERLYING CAUSE OF AN ACID–BASE DISORDER.

Usually, the cause of an acid–base disorder is obvious from the history, examination, and clinical course. However, on occasion, careful review of a thoughtful differential diagnosis is necessary to identify a remote causative disorder.

A. Causes of Metabolic Acidosis. The AG is used to divide the causes of metabolic acidosis into those with influx of organic acid into plasma (increased AG) and those with external losses of bicarbonate (normal AG, hyperchloremic). Some disorders belong to both groups at different stages (diabetic ketoacidosis) or are generated by mechanisms other than those described (renal failure). A list of causes is given in Table 4-5.

Table 4-5.	Causes of Metabolic Acidosis
High Anion Gap Type	
Ketoacidosis	
Diabetic	
Alcoholic	
Starvation	
Lactic acidosis	
Type A	
Type B	
D-Lactic acidosis	
Intoxications	
Ethylene glycol	
Methanol	
Salicylate	
Pyroglutamic acidosis from acetaminophen	
Advanced renal failure	
Normal Anion Gap Type	
Gastrointestinal HCO_3^- loss	
Diarrhea	
External fistulae	
Renal HCO_3^- loss	
Acetazolamide	
Proximal renal tubular acidosis (RTA)	
Distal RTA	
Hyperkalemic RTA	
Miscellaneous	
NH_4Cl ingestion	
Sulfur ingestion	
Toluene inhalation	
Pronounced dilution	

1. **Metabolic Acidosis with Increased AG.** Severe metabolic acidosis is caused by only three broad groups of disorders: ketoacidosis, lactic acidosis, and toxicities. In addition, renal failure may cause mild-to-moderate acidosis.
   a. **Ketoacidosis** arises when glucose is not available to cells because of lack of insulin, cell dysfunction, or glucose depletion, and fatty acids are oxidized to yield energy, acetone (not an acid), and the two ketoacids (acetoacetic and β-hydroxybutyric). The H^+ produced are consumed (buffered) by HCO_3^-, producing carbonic acid, which dehydrates into water and carbon dioxide. The ketoanions accumulate in the serum in place of the HCO_3^-, further increasing the AG. The screening test for ketoacidosis consists of testing the serum with a nitroprusside reagent, which only reacts with the acetoacetate. In diabetic ketoacidosis, the β-hydroxybutyrate–acetoacetate ratio averages 5:2, whereas in alcoholic ketoacidosis, it may reach as high as 20:1. In these cases, measuring the β-hydroxybutyrate, a readily available test, is diagnostic.

      Diabetic ketoacidosis occurs because of insulin deficiency. Hyperglycemia may be corrected by volume re-expansion but insulin is needed to stop ketogenesis. Volume expansion enhances the renal excretion of ketoanions, thereby correcting the increased AG. However, the kidneys take time to generate new HCO_3^- to replace that lost earlier in buffering H^+. Therefore, early in diabetic ketoacidosis, the AG usually is increased; during correction, the AG may return to normal despite a low HCO_3^-. Chloride replaces the ketoanions, and this stage is therefore called *hyperchloremic* or *normal AG metabolic acidosis*. **Alcoholic ketoacidosis** occurs because of volume depletion, which causes the α-adrenergic suppression of insulin release. The patient relates a story of severe vomiting following recently increased alcohol intake. Urine ketones are usually positive. Blood glucose ranges between 50 and 250 mg/dL. **Starvation** ketoacidosis occurs because of the use of fatty acids for energy maintenance. The degree of acidosis is mild, with arterial HCO_3^- not less than 18 mmol/L.
   b. **Lactic acidosis** arises when oxygen delivery to cells is inadequate for the demand (type A) or cell processes cannot use oxygen (type B). In this situation, glucose is metabolized through anaerobic glycolysis to pyruvate and then to the dead-end metabolite lactate. The H^+ produced from nicotinamide adenine dinucleotide (one per lactate) is buffered by HCO_3^-, which is replaced in the blood by lactate. Therefore, the AG is increased. **Type A lactic acidosis** is caused by the primary inadequate delivery of oxygen to tissues. Shock is the most common mechanism. Hypovolemia, heart failure, and sepsis cause shock. Because carbon monoxide binds more avidly to hemoglobin than does oxygen, carbon monoxide poisoning can cause varying degrees of lactic acidosis. **Type B lactic acidosis** occurs when tissue oxygenation is normal but tissues cannot use the oxygen normally or need excessive amounts of oxygen. Causes of type B lactic acidosis include hepatic failure, malignancy, drugs, and seizures. Metformin is a biguanide hypoglycemic agent that when overdosed

causes lactic acidosis. Renal, liver, and heart failure are risk factors. Reverse transcriptase inhibitors for AIDS also cause lactic acidosis due to injury to cell mitochondria. Lactic acidosis has been seen in patients receiving large intravenous doses of lorazepam and diazepam due to the propylene glycol solvent. **D-Lactic acidosis** is generated when colon bacteria metabolize malabsorbs sugars into both L- and D-lactate, which accumulates in the blood. The clinical manifestation is metabolic encephalopathy. At least two dozen inborn errors of metabolism result in pediatric lactic acidosis. The diagnosis is usually established by exclusion of ketoacidosis, toxicities, and advanced renal failure as causes for a high AG metabolic acidosis. L-Lactate can be measured by an automated assay.

c. Four modern **toxicities** cause high AG metabolic acidosis: **ethylene glycol ingestion, methanol ingestion, salicylate intoxication, and pyroglutamic acidosis from acetaminophen**. Methanol and ethylene glycol are low-molecular-weight alcohols that readily enter cells. Metabolism generates H^+ that cause acidosis and formate (with methanol) or glycolate (with ethylene glycol) that causes a high AG. A clue to the presence of early stages of acidosis with elevated alcohol levels is an increased osmolal gap. This gap is the difference between the measured serum osmolality and the calculated osmolality (calc Sosm).

$$\text{Calc Sosm} = 2 \times [Na^+] + \text{glucose}/18 + [\text{urea nitrogen}]/2.8 + [\text{ethanol}]/4.6$$

If this difference between measured and calculated Sosm is greater than 25 mOsm/kg of serum, the presence of a toxic alcohol is probable. Needle-like or envelope-shaped calcium oxalate crystals in the urine suggest ethylene glycol ingestion. The combination of high AG metabolic acidosis and high osmolal gap is an indication for specific analysis for methanol and ethylene glycol. The decision to measure the levels of these alcohols, of course, must be tempered by the clinical setting. **Salicylate** intoxication is an important frequent unintentional chronic or intentional acute overdose that causes metabolic acidosis, respiratory alkalosis, or a mixed disorder. It should be suspected at the extremes of age. Of note salicylate can cause a negative AG when the chloride electrode is months old (designed for 6 months use). Another analgesic, **acetaminophen**, has been linked to pyroglutamic acidosis (5-oxoproline) in malnourished individuals, many with renal disease. Therapeutic doses taken chronically are involved. Most patients are women.

d. Renal Failure. Failure to excrete the daily acid load of 1 mmol/kg of body weight that is generated by metabolism results in metabolic acidosis. Bone buffers take up some hydrogen ions during chronic renal failure, and, therefore, the degree of acidosis is moderated until the end stages of kidney disease. Arterial bicarbonate usually remains above 15 mmol/L. In acute renal failure, venous tCO_2 or arterial HCO_3^- falls by approximately 0.5 mmol/L/day unless hypercatabolism increases daily acid production. The AG increases less than the HCO_3^- falls, resulting in hyperchloremic metabolic acidosis in

early and middle stages of chronic renal failure. In advanced chronic renal failure, the serum AG rises approximately 0.5 mEq/L for each 1.0 mg/dL rise in serum creatinine. Retention of sulfate, phosphate, and organic anions causes the increase in AG.

2. **Metabolic acidosis with normal AG (hyperchloremic)** can be caused by three groups of disorders: gastrointestinal HCO_3^- loss, renal HCO_3^- loss or acid retention, and inorganic acid intake.
   a. **Gastrointestinal Bicarbonate Loss.** The gastrointestinal tract distal to the stomach has the capacity to absorb chloride and secrete bicarbonate. Therefore, diarrhea and external drainage of pancreatic, biliary, or small-bowel juices can cause external losses of bicarbonate-rich fluid. Relatively chloride-rich fluid remains behind. This generates hyperchloremic metabolic acidosis (normal AG). An interesting variety of this disorder occurs when normal urine, rich in sodium chloride (NaCl) from dietary sources, is drained into the gut through ureterosigmoidostomy or ileal loop conduit (both bladder replacement constructions). If contact time with mucosa is excessive, the gut reabsorbs the chloride in exchange for bicarbonate, resulting in hyperchloremic metabolic acidosis.
   b. **Renal Bicarbonate Loss.** The proximal renal tubule reabsorbs the bulk (85%) of filtered HCO_3^-. The carbonic anhydrase inhibitor **acetazolamide** blocks much of this reabsorption, resulting in urinary bicarbonate losses until arterial HCO_3^- falls to 16 to 18 mmol/L. The filtered load of HCO_3^- at this concentration can be completely reabsorbed by the distal nephron. Therefore, the urine becomes bicarbonate free, with an acidic pH, in this new steady state. **Proximal renal tubular acidosis** (old type II RTA), a defect in proximal tubular HCO_3^- reabsorption, has identical features. Proximal RTA is unusual but may occur with Wilson's disease, multiple myeloma, transplant rejection, and in other disease states. **Distal RTA** (old type I) differs in that it is a defect of the collecting duct, in which the daily metabolic acid load is not excreted totally and a small HCO_3^- leak occurs every day. This leads to a mild-to-moderate normal AG, hyperchloremic metabolic acidosis, and hypercalciuria with calcium stones or nephrocalcinosis. Two varieties occur: **hypokalemic distal RTA** and **hyperkalemic distal RTA**. Hypokalemic distal RTA occurs when collecting duct potassium secretion is intact and in fact enhanced by the small amount of bicarbonaturia. Hyperkalemic distal RTA occurs due to two distinct mechanisms when collecting duct hydrogen ion and potassium secretion are impaired: hypoaldosteronism (old type IV RTA) or tubular defect. Hypokalemic distal RTA occurs with Sjögren's syndrome, amphotericin B toxicity, cirrhosis of the liver, medullary sponge kidney, and many other diseases. Chronic obstruction of the kidney, lupus erythematosus, and sickle cell disease can cause the tubular defect type of hyperkalemic distal RTA. Diabetes mellitus, mild chronic renal failure, and old age are associated with the hyporeninemic hypoaldosteronism type of hyperkalemic distal RTA.

Diagnosis of RTA is made by eliminating nonrenal causes for a normal AG metabolic acidosis (e.g., diarrhea). Proximal RTA is

characterized by urinary wasting of more than 5% to 15% of the filtered load of HCO_3^- when serum levels are maintained close to normal. Hypokalemic distal RTA is characterized by the inability to decrease urine pH to less than 5.3 with oral furosemide and fludrocortisone. Hyperkalemic normal ion gap metabolic acidosis almost always is due to distal RTA. The tubular defect type is marked by an inability to acidify maximally (urine pH usually above 6.0), in contrast to the hypoaldosteronism type, in which the intensity of acidification is intact. In both types, renal ammonium excretion is reduced, and the urinary AG is often positive (see Section **V.A.2.d**).

c. Inorganic Acid Intake. The ingestion of ammonium chloride to reduce appetite or acidify urine produces hyperchloremic metabolic acidosis. Inorganic sulfur, such as flowers of sulfur cathartic, is oxidized to form H_2SO_4. The hydrogen ions titrate the HCO_3^- down, and the sulfate is excreted rapidly with sodium. This leaves a low HCO_3^- with a normal AG. A similar process happens with toluene inhalation from paint or glue sniffing. Toluene is metabolized to hippuric acid, and the hippurate is excreted rapidly.

d. Diagnosis of distal RTA is made when urinary ammonium excretion is reduced during hyperchloremic, normal AG metabolic acidosis. A useful screening test for urinary ammonium is the **urinary AG** (UAG):

$$UAG = (Na^+ + K^+) - Cl^-$$

The UAG is an estimate of urinary ammonium that is elevated in gastrointestinal HCO_3^- loss but low in distal RTA. UAG is a negative value if urine ammonium is high (as in diarrhea; average −20 mEq/L), whereas it is positive if urine ammonium is low (as in distal RTA; average +23 mEq/L). Urinary sodium concentration must be ample.

B. Causes of Metabolic Alkalosis. Metabolic alkalosis is generated by three pathophysiological mechanisms: loss of volume, gain of volume due to mineralocorticoids, and miscellaneous factors. Metabolic alkalosis of the volume-depleted type is maintained by Cl^- depletion. The kidney is avid for Cl^-. During the generation phases of metabolic alkalosis, bicarbonaturia may occur and necessitate Na^+ and K^+ excretion. Therefore, urine Cl^- is a better marker than urine Na^+ of the mechanism responsible. During the maintenance stage of metabolic alkalosis, bicarbonaturia is minimal, urine pH is acid, and urine Na^+ is low. Chloride-depletion metabolic alkalosis is due to external losses of hydrogen ion or chloride. Chloride-replete metabolic alkalosis is characterized by spot urine Cl^- concentrations of usually well over 20 mmol/L. The kidney is not avid for salt because of volume expansion (mild) and therefore excretes the daily Na^+ and Cl^- load without difficulty. This group of disorders is due to mineralocorticoid excess or occasionally to profound potassium depletion.

1. Metabolic alkaloses of the chloride-depleted variety have in common the external loss of fluids rich in H^+ and/or Cl^-. The stomach, kidney, or skin may be the culprit (Table 4-6).

Table 4-6.	Causes of Metabolic Alkalosis
Chloride-Depleted Type	
Gastric acid loss	
Vomiting	
Gastric suction	
Renal chloride loss	
Diuretics	
Posthypercapnia	
Cystic fibrosis	
Chloride-Replete Type	
Mineralocorticoid excess	
Hyperaldosteronism	
Gitelman's syndrome	
Bartter's syndrome	
Cushing's syndrome	
Licorice excess	
Profound potassium depletion	

2. **Metabolic alkaloses of the chloride-replete variety** are characterized by enhanced renal H^+ secretion despite normal or increased ECF volume. The stimulus for this sustained H^+ secretion is aldosterone (or a relative) or major cellular potassium depletion (Table 4-6). Gitelman's syndrome is an autosomal recessive disorder usually appearing in adults as hypokalemic, hypomagnesemic metabolic alkalosis. The distal convoluted tubule Na^+Cl^- cotransporter is defective. In contrast, Bartter's syndrome appears in childhood as hypokalemic metabolic alkalosis. In this syndrome, defects in the loop of Henle Na^+Cl^- reabsorption lead to normotensive secondary hyperaldosteronism; loop diuretic abuse resembles these disorders.

C. **Causes of Respiratory Acidosis.** Two ventilatory abnormalities allow CO_2 retention and increased P_{CO_2}: alveolar hypoventilation and severe ventilation–perfusion mismatch. Hypoxemia occurs in both settings. Disorders of respiratory drive, nerve conduction, thoracic cage, pleura,

and lung parenchyma may cause hypercapnia (increased P_{CO_2}). Renal compensation for chronic respiratory acidosis may produce very high HCO_3^- levels. If the P_{CO_2} is reduced by artificial ventilation, the high HCO_3^- may persist if not enough chloride is provided to replace it. This results in posthypercapnic metabolic alkalosis. Acetazolamide may be useful in this setting.

D. Causes of Respiratory Alkalosis. Disorders that drive ventilation independent of P_{CO_2} can cause hyperventilation and hypocapnia. Inflammatory and mass lesions of the brain, psychiatric disorders, and certain central-acting drugs and chemicals increase central respiratory drive and produce hypocapnia. Importantly, salicylates, endotoxin, and progesterone are among this group of drugs and chemicals. Disorders that cause hypoxemia are common causes of the hyperventilation that causes hypocapnia. Disorders that reduce lung or chest compliance such as mild pneumonia or pulmonary edema, vascular disorders such as emboli, and mixed disorders such as hepatic cirrhosis or cardiac failure can cause hypocapnia. Volume depletion is a primary stimulus to hyperventilation and hypocapnia.

VI. TREATING ACID–BASE DISORDERS.

As discussed, acid–base disorders are markers of underlying diseases, and these diseases should be the targets of treatment.

A. Step 1. Correct volume and electrolyte deficiencies.

B. Step 2. Direct specific treatment at the underlying cause.

C. Step 3. Manipulate the bicarbonate or P_{CO_2} in the acute setting only if the pH is adversely affecting organ function or if pH is less than 7.10 or greater than 7.60. Appropriate oxygenation is crucial.

D. Treatment of metabolic acidosis with alkali has not been shown to be efficacious in acute situations, including cardiopulmonary resuscitation, possibly because the HCO_3^- reaction with H^+ generates CO_2 at the tissue level and lowers cell pH. Alkali therapy is not recommended even for severe (pH less than 7.1) acute metabolic acidosis. In chronic distal RTA, alkali therapy reduces bone loss, hypercalciuria, and nephrocalcinosis. In chronic kidney disease, alkali treatment to keep HCO_3^- above 22 mmol/L preserves renal function. Oral alkali can be given as sodium bicarbonate tablets, 500 mg or 6 mmol, or as sodium or potassium citrate solution, 1 mmol/mL. Usually 3 mmol/kg of body weight is the starting dose. Oral HCO_3^- is accompanied by a sodium or potassium load that must be watched for adverse effects.

1. Insulin is the specific **treatment for diabetic ketoacidosis**. HCO_3^- and phosphate administration is unnecessary, but potassium repletion is important. Volume and electrolyte repletion, plus glucose and thiamine, suffice to correct alcoholic ketoacidosis. Starvation requires only calories. Note that metabolism of ketoanions, as with all organic anions, produces HCO_3^-; metabolism corrects approximately half of the HCO_3^- deficit. If alkali is given unwisely, an overshoot metabolic alkalosis may result.
2. In the **treatment of lactic acidosis**, the restoration of tissue perfusion and oxygenation is desirable, but often difficult to attain. Attention to potassium and calcium levels is important.
3. **Treatment of Intoxications.** Ethylene glycol and methanol poisoning require immediate fomepizole infusion to retard metabolism of

the alcohol to toxic products. Hemodialysis is started if renal failure is present. An alternative approach is to infuse ethanol to maintain a blood level of 100 mg/dL to compete for alcohol dehydrogenase activity. The loading dose of ethanol is 0.6 to 1.0 g/kg of body weight followed by a maintenance infusion of 10 to 20 g/hour. Blood alcohol levels must be monitored frequently.

Salicylate intoxication should be treated with urinary alkalinization by infusing a 5% glucose solution containing $NaHCO_3$, 150 mmol added per L, at 375 mL/hour, for 4 or more hours. Hemodialysis should be used to remove salicylate in patients with levels above 100 mg/dL or lower with the following: prominent renal failure, worsening mental status, recalcitrant acidosis, or general deterioration. Discontinuation of acetaminophen corrects pyroglutamic acidosis.

E. Correction of metabolic alkalosis very rarely, if ever, requires the administration of acid. If renal failure prohibits renal excretion of HCO_3^-, the patient usually requires dialysis for other reasons. A low bicarbonate dialysate can be used. If heart failure precludes the use of NaCl, then acetazolamide, 500 mg by mouth or intravenously, consistently reduces the serum tCO_2 by approximately 6 mmol/L. Acid infusion is fraught with the potential complications of hemolysis and vascular necrosis and is best avoided. Ammonium chloride can be given as a source of acid, but it causes gastric distress even when given intravenously and may cause ammonia intoxication.

1. **Chloride-depletion metabolic alkalosis is corrected** by providing ample chloride with sodium or potassium. Prevention, however, is preferable. Proton-pump inhibitors minimize gastric acid loss in patients with nasogastric suction. Use of the potassium-sparing diuretics spironolactone, triamterene, and amiloride reduces the frequency and severity of diuretic-induced alkalosis.
2. **Treatment of Chloride-Replete Metabolic Alkalosis.** If possible, the cause of increased mineralocorticoid production should be removed. For example, a functioning adrenal adenoma should be surgically excised. In the interim, the use of spironolactone in doses up to 400 mg/day with potassium chloride may be effective. Indomethacin may be beneficial in Bartter's syndrome.

F. Respiratory Acidosis Per Se Does Not Require Direct Treatment. Even at chronic P_{CO_2} levels above 100 mmHg, the kidneys generate and maintain HCO_3^- levels sufficient to keep the pH above 7.20. However, adequate oxygenation is the critical issue in both acute and chronic respiratory acidosis.

G. Definitive treatment of respiratory alkalosis again requires the correction of the underlying condition causing hyperventilation. The provision of oxygen is essential for the hypoxemic patient.

H. Treatment of Mixed Acid–Base Disorders

1. **Metabolic Acidosis and Respiratory Acidosis.** The most rapid treatment is to provide assisted or controlled ventilation. The administration of base is not warranted. The correction of the cause of metabolic acidosis is a priority.
2. In **metabolic alkalosis and respiratory acidosis**, the pH is often alkalemic. Acetazolamide given daily or every other day may be used to keep

the pH near 7.35 to 7.40, which is a good level to avoid suppression or excessive stimulation of respiration.

3. **Metabolic alkalosis and respiratory alkalosis** in combination may produce severe alkalemia with dangerous arrhythmias. The most expedient treatment consists of intravenous morphine and a benzodiazepine, with immediate access to airway intubation and mechanical ventilation.

Suggested Readings

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5 The Patient with Disorders of Serum Calcium and Phosphorus

Jeffrey G. Penfield and Robert F. Reilly

DISORDERS OF SERUM CALCIUM

Most calcium in the body is in the form of hydroxyapatite in bone (99%). Although a small fraction of total body calcium is contained in the extracellular fluid (ECF), only the concentration of ionized calcium in the ECF is physiologically active and regulated. Approximately 60% of calcium in the ECF is ultrafilterable and exists either free in solution as ionized calcium (50%) or complexed to anions such as citrate, phosphate, sulfate, and bicarbonate (10%). The remaining 40% is bound to proteins (primarily albumin). Serum or plasma calcium concentration is measured as either total or ionized calcium. Total calcium concentration is measured with a colorimetric assay and includes ionized, complexed, and bound calcium. Ionized calcium concentration is measured with a calcium-specific electrode and represents physiologically regulated calcium. Both total and ionized calcium can be expressed in conventional units of mg per dL or mEq per L or in International System (SI) of units of mmol per L. SI units (mmol per L) can be converted to mg per dL by multiplying by 4. Measuring total calcium levels is inexpensive and convenient. A determination of the ionized calcium concentration requires that the sample be placed on ice and measured within 2 hours making it difficult for routine use, especially in the outpatient setting.

Figure 5-1 illustrates the calcium fluxes between ECF, intestine, kidney, and bone. Net intestinal calcium absorption amounts to approximately 200 mg of the normal dietary intake of 800 to 1,000 mg. In the steady state, this net intestinal absorption is matched by urinary excretion. As a result, 10,600 mg of the approximately 10,800 mg (98%) of calcium that is filtered by the glomerulus daily is reabsorbed by the renal tubules.

I. CALCIUM REGULATION. Plasma-ionized calcium is regulated through a complex and coordinated interplay of parathyroid hormone (PTH) and $1,25(OH)_2$ vitamin D_3 (calcitriol) in the intestine, bone, and kidney. The parathyroid gland senses ECF-ionized calcium concentration through a calcium-sensing receptor. High concentrations of ECF calcium stimulate the receptor and activate second messenger pathways that, in turn, inhibit PTH release. Low ECF calcium concentration stimulates PTH secretion and production and increases parathyroid gland mass. The parathyroid gland responds quickly (within minutes) to alterations in ionized calcium concentration. An inverse sigmoid relationship exists between ECF calcium concentration and PTH secretion, with a nonsuppressible component present even at high plasma calcium concentration. The amount of hormone stored

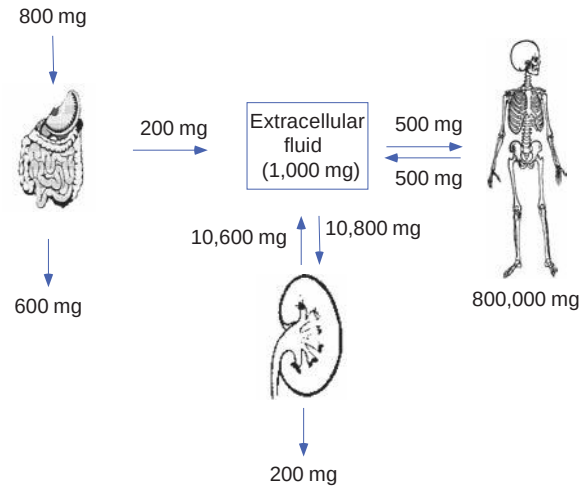


Figure 5-1. Calcium homeostasis.

is enough to support basal secretion for 6 hours and stimulated secretion for 2 hours.

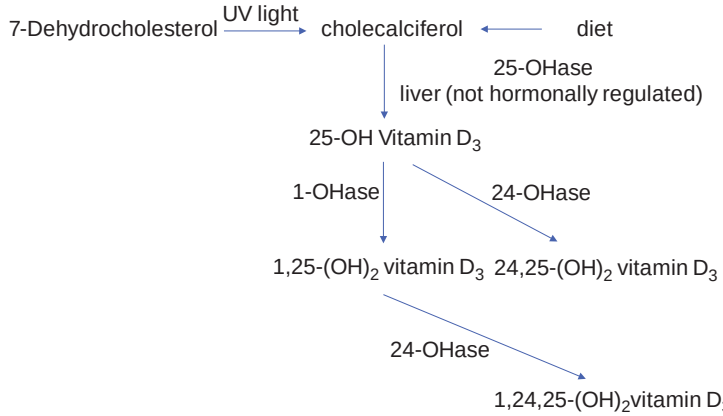
In bone, PTH in the presence of permissive amounts of calcitriol stimulates reabsorption by increasing osteoclast number and activity. In intestine, PTH enhances calcium and phosphate absorption indirectly by promoting the formation of calcitriol. In kidney, PTH augments distal tubular calcium reabsorption, stimulates calcitriol formation in the proximal tubule, and decreases proximal tubular phosphate and bicarbonate reabsorption.

Calcitriol is produced in the proximal tubule through 1α-hydroxylation of 25(OH) vitamin D_3 (calcidiol). The calcitriol biosynthetic pathway is illustrated in Figure 5-2. Principal stimulators of 1α-hydroxylase are PTH and hypophosphatemia. The major function of calcitriol is to enhance calcium and phosphate availability for new bone formation and prevention of symptomatic hypocalcemia and hypophosphatemia. In intestine and kidney, calcitriol increases production of calcium-binding proteins (calbindins) that aid in transcellular calcium movement. In bone, calcitriol potentiates PTH actions, stimulates osteoclastic reabsorption, and induces differentiation of monocytes into osteoclasts.

In parathyroid gland, calcitriol binds to its receptor, leading to a decrease in PTH production. The *PTH* gene promoter contains regions that bind the calcitriol receptor. Binding results in a dramatic decrease in PTH expression. Calcitriol is the most potent suppressor of *PTH* gene transcription.

II. HYPERCALCEMIA

A. **Etiology.** Three basic pathophysiologic mechanisms contribute to hypercalcemia: increased calcium absorption from the gastrointestinal tract, decreased renal calcium excretion, and increased bone calcium resorption. The most common etiologies of hypercalcemia are listed in Table 5-1.



PTH- stimulates 1-OHase, inhibits 24-OHase
1,25-$(OH)_2$ vitamin D3- inhibits 1-OHase, stimulates 24-OHase

Figure 5-2. Vitamin D metabolism. (PTH, parathyroid hormone; UV, ultraviolet.)

Table 5-1.	Etiologies of Hypercalcemia
Hyperparathyroidism	
Malignancy	
Vitamin A and D intoxication	
Milk-alkali syndrome	
Thyrotoxicosis	
Granulomatous disease	
Immobilization	
Paget's disease	
Thiazide diuretic intake	
Addison's disease	
Pheochromocytoma	
Lithium intake	
Chronic kidney disease	
Postrenal transplant	
Familial hypocalciuric hypercalcemia	

1. **Increased calcium absorption from the gastrointestinal tract** plays a primary role in the hypercalcemia of the milk-alkali syndrome, vitamin D intoxication, and granulomatous disorders.
   a. **Milk-alkali syndrome** is the result of ingestion of excess calcium and alkali. In the past, peptic ulcer disease was treated with milk and sodium bicarbonate. This calcium and alkali source used to be the most common cause of the milk-alkali syndrome. This regimen was replaced with histamine antagonists and proton pump inhibitors so that milk and sodium bicarbonate are now rare causes of this syndrome. Currently, this syndrome most often occurs in elderly women consuming excess calcium carbonate or calcium citrate for the treatment of osteoporosis. As a result, many now refer to this as the calcium-alkali syndrome rather than the milk-alkali syndrome. Alkalosis decreases renal calcium excretion and the resultant hypercalcemia, nephrocalcinosis, and subsequent renal dysfunction prevent correction of the alkalosis. Many of these patients are also receiving vitamin D supplements that increase intestinal calcium absorption. Patients present with the classic triad of hypercalcemia, metabolic alkalosis, and elevated serum creatinine concentration. Treatment is volume replacement with normal saline and avoidance of calcium and alkali supplements. The kidney injury may persist and result in chronic kidney disease (CKD). Bisphosphonates should be avoided because these agents prevent bone calcium release, which is not a contributing factor in this syndrome and can also result in hypocalcemia. Treatment of hypercalcemia in these patients is often complicated by hypocalcemia resulting from sustained PTH suppression.
   b. **Hypercalcemia in CKD** is uncommon, except in patients treated with calcium and vitamin D supplements. This disorder and the milk-alkali syndrome illustrate the important concept that hypercalcemia from excessive dietary calcium ingestion alone does not occur in the absence of renal impairment.
   c. **Vitamin D intoxication** also results in hypercalcemia. Calcium is absorbed primarily in the small intestine, and this process is stimulated by calcitriol.
   d. Hypercalcemia may also be secondary to **granulomatous disorders**, such as sarcoidosis. Activated macrophages produce calcitriol, which leads to increased intestinal absorption of dietary calcium. Hypercalciuria is seen more commonly than hypercalcemia. Lymphomas occasionally cause hypercalcemia through the same mechanism.
2. **Increased calcium resorption from bone** plays a primary role in hypercalcemia resulting from primary, secondary, and tertiary hyperparathyroidism, malignancy, hyperthyroidism, immobilization, Paget's disease, and vitamin A toxicity.
   a. **Hyperparathyroidism**
      i. **Primary—**
         Primary hyperparathyroidism is a common cause of hypercalcemia. The estimated incidence ranges from 0.4 to 26 per 100,000 patient years. The incidence declined from the 1970s to 1995 but might now be increasing again. In a large multiracial US study, the

highest incidence was in African Americans followed by whites. Women are more than twice as likely as men to develop primary hyperparathyroidism and the incidence increases with advancing age. The underlying pathology is most often a solitary adenoma (80%). Among the remainder, 15% to 20% have diffuse hyperplasia, and approximately one half of these have a familial syndrome [multiple endocrine neoplasia (MEN) type 1, associated with pituitary adenomas and islet cell tumors, or MEN type II, associated with medullary carcinoma of the thyroid and pheochromocytoma]. Multiple adenomas are uncommon, and parathyroid carcinoma is rare (occurring in less than 1%). Hypercalcemia results from increased calcium resorption from bone, increased intestinal calcium absorption mediated by calcitriol, and increased distal tubular renal calcium reabsorption. In primary hyperparathyroidism, hypercalcemia is often mild, asymptomatic, and identified on routine blood chemistries in the outpatient setting.

ii. **Secondary—**
Secondary hyperparathyroidism is seen in CKD patients or patients with end-stage renal disease on dialysis. Uremia causes PTH resistance and requires a higher PTH level than normal. Decreased production of $1,25(OH)_2$ vitamin D_3 by the kidney results in less PTH suppression, as well as hypocalcemia that increases the half-life of PTH mRNA. Reduced phosphorus excretion by the kidneys results in hyperphosphatemia that also increases the half-life of PTH mRNA.

iii. **Tertiary—**
Tertiary hyperparathyroidism is a result of prolonged stimulation of the parathyroid gland from secondary hyperparathyroidism in end-stage renal disease. The patient will have hypercalcemia instead of hypocalcemia as a result of parathyroid gland hyperplasia. It can also be seen after renal transplantation when plasma phosphorus concentration, vitamin D metabolism, and renal function improve, but PTH secretion remains high secondary to increased parathyroid mass. In most patients, PTH levels drop and hypercalcemia resolves during the first year following transplantation.

b. **Malignancy** is also a common cause of hypercalcemia. Hypercalcemia of malignancy results from several pathophysiologic mechanisms: overproduction of PTH-related peptide (PTHrP), local bone reabsorption around sites of tumor infiltration (mediated through a variety of cytokines and osteolytic prostaglandins), and calcitriol production (e.g., with lymphomas). Patients with squamous cell lung cancer, breast cancer, multiple myeloma, and renal cell carcinoma are at highest risk. Hypercalcemia due to tumoral PTHrP production is often referred to as *humoral hypercalcemia of malignancy* (*HHM*). PTHrP has 70% amino acid identity to the first 13 amino acids of PTH and binds to the PTH receptor. It normally functions as a regulator of chondrocyte growth and differentiation in developing long bones; calcium mobilization from bones and into breast milk during lactation; calcium transport across the placenta to the developing fetus; and uterine blood flow. It is usually

produced in the placenta during pregnancy and by mammary glands during lactation. In certain cancers, the gene for PTHrP is inappropriately activated. HHM often presents with severe hypercalcemia (calcium concentration greater than 14 mg/dL) in a patient with either a known history of malignancy or evidence of malignancy at initial presentation. PTHrP is immunologically distinct from PTH and is not detected by standard PTH assays, but specific assays for PTHrP are commercially available. The normal range for PTHrP is less than 2.0 pmol/L because in normal health its functions are autocrine or paracrine and higher circulating levels are not required. Median survival from the onset of hypercalcemia with HHM is only 3 months. Squamous cell tumors, renal cell carcinomas, and most breast neoplasms produce PTHrP. The diagnoses of primary hyperparathyroidism and malignancy are not mutually exclusive. An increased incidence of primary hyperparathyroidism was reported in patients with malignancy.

Multiple myeloma is associated with hypercalcemia and localized osteolytic skeletal lesions. Approximately 30% of patients with myeloma experience hypercalcemia at some time during the course of their disease. Bone destruction occurs as a consequence of interleukin-6, interleukin-1, and tumor necrosis factor-beta release by malignant plasma cells. Bony lesions demonstrate a marked increase in osteoclastic resorption without manifestations of increased bone formation, in contrast to metastatic lesions of breast and prostate cancer, which generally show some increase in bone formation and radionuclide uptake at sites of increased osteoblastic activity. Because of excessive bone resorption, multiple myeloma can cause severe osteoporosis in addition to hypercalcemia. Bisphosphonates are frequently used to treat these complications. Bisphosphonates can cause acute kidney injury if given at high doses for a prolonged period of time. This risk is higher if the patient has CKD. Unfortunately, patients with multiple myeloma frequently develop CKD and standard- or low-dose bisphosphonates might not be as effective in treating the hypercalcemia and osteoporosis.

c. **Hyperthyroidism** results in mild hypercalcemia in 10% to 20% of patients as a result of increased bone turnover. There is also an increased prevalence of hyperparathyroidism in patients with hyperthyroidism.
d. **Paget's disease** is a disease of bone with focal areas of disrupted bone turnover, disorganized and structurally weak bone, and increased vascularity. There are both hereditary and environmental factors that cause Paget's disease. The most common mode of inheritance is autosomal dominant. Immobilization with Paget's disease can cause hypercalcemia, although this is more likely in children. In adults, hypercalciuria is more common than hypercalcemia.
e. **Miscellaneous causes of hypercalcemia** include lithium use (mild; interferes with the calcium-sensing receptor); thiazide diuretic use (occult primary hyperparathyroidism should be suspected); pheochromocytoma; primary adrenal insufficiency; and a rare genetic disorder, familial hypocalciuric hypercalcemia (FHH).

FHH is an autosomal dominant disorder most commonly caused by a heterozygous mutation in the calcium-sensing receptor. It is rare with a prevalence of 1 in 78,000 in one study. Recently, mutations in two additional genes were reported to cause FHH, the G-protein subunit α_{11} and the S1 subunit of adaptor protein 2. The syndrome presents with mild hypercalcemia early in life, hypocalciuria, and a normal or slightly increased PTH concentration in the absence of signs or symptoms of hypercalcemia. As a result of the mutations, the calcium-sensing receptor is less sensitive to plasma calcium concentration, and a higher than normal calcium concentration is required to suppress PTH. One should be aware of FHH, because this condition is often misdiagnosed as primary hyperparathyroidism, and patients may be inappropriately subjected to neck exploration. FHH may account for a small percentage of patients who undergo surgery for primary hyperparathyroidism in whom no adenoma is found.

B. **Signs and symptoms** of hypercalcemia are related to the severity and rate of rise in plasma-ionized calcium concentration. Mild hypercalcemia is generally asymptomatic and often incidentally discovered on routine blood chemistries, as is the case in many patients with primary hyperparathyroidism. In contrast, severe hypercalcemia is often associated with neurologic and gastrointestinal symptoms. The patient may present with a wide range of central nervous system symptoms, from mild mental status changes to stupor and coma. Gastrointestinal symptoms include constipation, anorexia, nausea, and vomiting. Abdominal pain may result from hypercalcemia-induced peptic ulcer disease or pancreatitis. Hypercalcemia results in polyuria and secondary polydipsia can lead to hypernatremia, ECF volume contraction, a reduction in the glomerular filtration rate (GFR), and an elevation in blood urea nitrogen (BUN) and creatinine concentrations. Hypercalcemia also potentiates the cardiac effects of digitalis toxicity.

C. **Diagnosis.** The most common causes of hypercalcemia are primary hyperparathyroidism and malignancy. These two disorders make up more than 90% of all cases. Initial evaluation includes a history and physical examination. Use of calcium supplements, antacids, vitamin preparations, and over-the-counter medications should be determined. A chest x-ray should be obtained to rule out pulmonary malignancies and granulomatous disorders.

1. **Initial laboratory examination** includes measurement of electrolytes, BUN, creatinine, phosphorus, serum protein electrophoresis, and a 24-hour urine for calcium and creatinine for calculation of the calcium to creatinine clearance ratio. The presence of a high serum chloride concentration and a low serum phosphorus concentration in a ratio greater than 33:1 is suggestive of primary hyperparathyroidism resulting from the effect of PTH decreasing proximal tubular phosphate reabsorption. A low serum chloride concentration, a high serum bicarbonate concentration, and elevated BUN and creatinine concentrations are characteristic of milk-alkali syndrome. A monoclonal spike on either serum protein electrophoresis or urine protein electrophoresis is suggestive of multiple myeloma. A low serum phosphorus concentration is found in primary hyperparathyroidism and HHM. The FE of calcium is low in hypercalcemia caused by the milk-alkali syndrome, thiazide diuretic use,

or FHH. The optimal calcium to creatinine clearance ratio for separation of FHH from primary hyperparathyroidism appears to be a value of 0.0115. This yields a sensitivity of 80% and a specificity of 88%. It can be seen that even at this cutoff there is still overlap between FHH and primary hyperparathyroidism, especially in those with primary hyperparathyroidism that are also vitamin D deficient. The formula for the calcium to creatinine clearance ratio measured in a 24-hour urine is

$$\text{Calcium(urine)} \times \text{Cr(serum)} / \text{Calcium(serum)} \times \text{Cr(urine)}$$

All units are in mg per dL. Creatinine is abbreviated as Cr.

As a general rule, primary hyperparathyroidism is the etiology in asymptomatic outpatients with a serum calcium concentration $\leq$11 mg/dL, whereas malignancy is often the cause in symptomatic patients with an abrupt disease onset and serum calcium concentration $\geq$14 mg/dL.

2. **Intact PTH concentration** is obtained after the initial evaluation is completed. The most common cause of an elevated PTH concentration is primary hyperparathyroidism, although an elevated PTH concentration may also be seen with lithium use and in 15% to 20% of patients with FHH. Occasionally, in primary hyperparathyroidism, PTH concentration will be inappropriately within the normal range compared to the serum calcium concentration. In all other conditions, PTH will be suppressed by hypercalcemia.
3. If no obvious malignancy is present and PTH concentration is not increased, the possibility of vitamin D intoxication or granulomatous disease should be evaluated further with an analysis of **calcidiol and calcitriol** concentration. An increased calcidiol concentration is seen with the ingestion of either vitamin D or calcidiol. An elevated calcitriol concentration is observed with calcitriol ingestion, granulomatous disease, lymphoma, and primary hyperparathyroidism.
4. As a final step, if calcitriol concentration is increased without an apparent cause, occult granulomatous disease can be evaluated with a **hydrocortisone suppression test**. After administration of 40 mg of hydrocortisone every 8 hours for 10 days, the hypercalcemia will resolve if it is the result of granulomatous disease.

D. **Treatment** of hypercalcemia varies depending on the severity of the serum calcium elevation. It is directed at increasing urinary calcium excretion, inhibiting bone resorption, and decreasing intestinal calcium absorption.

1. **Urinary calcium excretion is increased** by first expanding the ECF volume and, subsequently, administering loop diuretics. Calcium reabsorption in the proximal tubule is passive and parallels sodium reabsorption. ECF volume contraction, therefore, increases proximal sodium reabsorption and helps maintain hypercalcemia. Patients with hypercalcemia are often volume contracted. Hypercalcemia decreases sodium reabsorption in the thick ascending limb of the loop of Henle through activation of the calcium-sensing receptor, and it also antagonizes the effects of antidiuretic hormone. In the setting of a reduced GFR, higher doses of loop diuretics may be required. In the presence of little or no renal function and severe hypercalcemia, hemodialysis is indicated.

2. **An agent that inhibits bone resorption** is often required when hypercalcemia is moderate or severe. In the acute setting, calcitonin is often helpful because of its rapid onset of action (2 to 4 hours). Calcitonin inhibits osteoclastic bone reabsorption and increases renal calcium excretion. It reduces serum calcium concentration, however, by only 1 to 2 mg/dL, and tachyphylaxis often develops with repeated use. For these reasons, calcitonin should not be used as the sole agent to inhibit bone resorption.
   a. **Bisphosphonates** are the agents of choice for the management of hypercalcemia due to bone resorption. These analogs of inorganic pyrophosphate are selectively concentrated in bone, where they interfere with osteoclast attachment and function. Bisphosphonates have a slow onset (2 to 3 days) and long duration of action (several weeks). Caution should be exercised in patients with milk-alkali syndrome. These patients do not have a defect in bone turnover and are susceptible to hypocalcemia with treatment, and post treatment hypocalcemia may be exacerbated by bisphosphonates.

      Pamidronate is given at a dose of either 60 or 90 mg intravenously over 4 hours. If serum calcium concentration is ≤13.5 mg/dL, 60 mg is given. If serum calcium concentration is greater than 13.5 mg/dL, 90 mg is administered. Serum calcium concentration gradually falls over the ensuing 2 to 4 days. A single dose is usually effective for 1 to 2 weeks. In most patients, serum calcium concentration normalizes after 7 days.

      Zolendronic acid is now the most commonly used bisphosphonate because it can be given intravenously, which avoids esophageal damage from oral doses, and can be administered over a short interval (4 mg over 15 minutes). It is administered every 3 to 4 weeks if needed and it may be longer lasting than pamidronate. The dose must be adjusted in patients with renal dysfunction as follows given the creatinine clearance: greater than 60 mL/minute—4 mg; 50 to 60 mL/minute—3.5 mg; 40 to 49 mL/minute—3.3 mg; 30 to 39 mL/minute—3.0 mg; less than 30 mL/minute—no data available. The manufacturer recommends that the drug be discontinued if the serum creatinine concentration increases ≥0.5 mg/dL above a normal baseline or greater than 1.0 mg/dL in those with a serum creatinine concentration ≥1.4 mg/dL.

      Bisphosphonates are associated with significant toxicity including focal glomerular sclerosis and acute kidney injury. Most of these cases occurred in patients with preexisting CKD or when recommended doses were exceeded. Multiple myeloma patients are at particular risk because kidney disease is a common complication and management of osteoporosis and/or hypercalcemia may require higher than recommended doses. In addition, when bisphosphonates are used long term in patients with malignancy, especially multiple myeloma and breast cancer, they are associated with osteonecrosis of the jaw. Most of these patients have had recent tooth extraction or surgical tooth removal. Radiation to the jaw also increases the risk of osteonecrosis.
   b. **Gallium nitrate** inhibits bone resorption by decreasing the acid secretion of osteoclasts and also enhancing hydroxyapatite

crystallization of bone. It is an additional agent that can be employed to treat hypercalcemia of malignancy. It is administered as a continuous infusion at a dose of 100 to 200 mg/m^2 for 5 consecutive days. Gallium nitrate has a significant risk of nephrotoxicity and should not be administered to patients with serum creatinine concentrations above 2.5 mg/dL or when other nephrotoxic drugs are also used such as iodinated contrast, aminoglycosides, or cisplatinum. It is probably best reserved for patients who have not responded to more conventional agents. A summary of treatment options is shown in Table 5-2.

c. **Cinacalcet** is a calcimimetic agent with a unique mechanism of action. Though it has no structural similarity with elemental calcium it can bind to the receptor and cause allosteric activation. Calcium-sensing receptors are located in the gastrointestinal tract, kidney, bone, and parathyroid glands. Allosteric activation results in a reduction of PTH release, less calcium release from bone, less intestinal calcium absorption, and an increase in renal calcium excretion. This results in a lowering of calcium and PTH levels. The lower PTH level's effect on serum phosphorus concentration is dependent on renal function. In dialysis patients with no renal function, decreased PTH levels can reduce phosphorus concentration by limiting bone resorption. In patients with significant renal function, such as renal transplant recipients with persistent tertiary hyperparathyroidism, the initial phosphorus concentration can be low because of persistently elevated PTH levels. Treatment with cinacalcet will reduce PTH levels and reduce renal phosphate wasting and increase rather than decrease serum phosphorus levels in these patients. The brain also has calcium-sensing receptors and a significant dose-limiting side effect is nausea. Cinacalcet is approved

Table 5-2. Treatment of Hypercalcemia

Drug	Dosage
Normal saline	2–4 L/d initially
Furosemide	20–160 mg i.v. q8h after volume expansion
Salmon calcitonin	4 IU/kg s.c. q12h
Pamidronate disodium	60–90 mg i.v. over 4 hr
Zolendronic acid	4 mg over 15 min. Dose adjusted for renal function
Plicamycin	25 μg/kg i.v. over 4 hr q.daily for 3–4 d
Corticosteroids	200–300 mg hydrocortisone i.v. q.daily for 3–5 d
Gallium nitrate	100–200 mg/m^2 for 5 d

for use in the United States for treatment of secondary and tertiary hyperparathyroidism and parathyroid carcinoma. In Europe, it is also approved for the medical treatment of primary hyperparathyroidism.

3. **Measures to decrease intestinal calcium absorption** are often employed in outpatients with mild disease. Corticosteroids may be helpful in vitamin D intoxication, granulomatous disease, and certain neoplasms (lymphoma and multiple myeloma). Alternatives to corticosteroids include ketoconazole and hydroxychloroquine. Oral phosphate can be administered, provided the patient does not have an elevated serum phosphorus concentration or advanced CKD. Oral phosphate, however, often causes diarrhea and only lowers the serum calcium concentration by approximately 1 mg/dL.

4. **Treatment of asymptomatic hyperparathyroidism** is controversial. It is generally accepted that symptomatic hyperparathyroidism should be treated with a parathyroidectomy. Symptoms can include bone pain from excessive bone demineralization, kidney stones from hypercalciuria, or symptoms from hypercalcemia such as fatigue, confusion, depression, nausea, polyuria, and polydipsia. In 1991 a consensus conference made recommendations for treatment of asymptomatic hyperparathyroidism. Updated recommendations were made in 2002 and again in 2009. It is recommended that asymptomatic patients with an elevated parathyroid level undergo parathyroidectomy if the calcium is >1.0 mg/dL above the upper limit of normal and they have a bone mineral density T score of less than –2.5 or an estimated GFR of <60 ml/min. Surgery has become less extensive because of the ability to preoperatively scan for parathyroid adenomas with a technetium 99 sestamibi scan and parathyroid ultrasound, as well as being able to measure PTH concentration in the operating room. This allows for a minimally invasive approach that does not require general anesthesia. The surgeon can localize the adenoma preoperatively instead of having to explore both sides of the neck and possibly the mediastinum. Intraoperative PTH levels can confirm that the adenoma was successfully resected because the half-life of PTH is only 4 minutes and should drop very quickly after adequate surgical resection. If the PTH level does not fall greater than 50% in 10 minutes, this suggest that a second adenoma may be present and the patient can then be placed under general anesthesia and the neck explored.

   Asymptomatic patients that do not undergo surgery because of physician/patient preferences should be monitored yearly with serum calcium and creatinine levels and every 1 to 2 years with a bone mineral density and encouraged to proceed with parathyroidectomy if these values worsen. Medical treatment with cinacalcet is approved in Europe for primary hyperparathyroidism but was not recommended by the consensus conference. Cinacalcet increases bone density, lowers calcium levels, increases phosphorus levels, and reduces PTH levels. Bisphosphonates have also been used for medical management. Bisphosphonates improve bone density and reduce hypercalcemia but do not lower PTH levels. Carcinoma of the parathyroid gland is a rare cause of primary hyperparathyroidism. Surgical resection is the

preferred treatment but recurrence is common and may require numerous resections. Cinacalcet is used as medical treatment for hypercalcemia in recurrent disease.

5. **Treatment of Secondary and Tertiary Hyperparathyroidism in Patients with CKD.** Medical management involves regulating PTH levels in the desired range depending on the CKD stage. In CKD stage 3 the desired PTH range is 35 to 70 pg/mL. In CKD stage 4 the desired range is 70 to 120 pg/mL. In CKD stage 5 the desired range is 150 to 300 pg/mL and the range for patients on dialysis is 150 to 600 pg/mL. In patients not yet on dialysis, if the 25(OH) vitamin D_3 level is low it is replaced with ergocalciferol or cholecalciferol. This will give enough precursor to allow the kidney to convert it to $1,25(OH)_2$ vitamin D_3, which will suppress PTH. If correcting 25(OH) vitamin D_3 is not adequate to suppress PTH, then oral calcitriol or paracalcitol is used. Cinacalcet is not used because these patients are often hypocalcemic and a significant side effect of cinacalcet is hypocalcemia.

   Hemodialysis patients are treated with a variety of different $1,25(OH)_2$ vitamin D_3 analogues that can be given intravenously during the hemodialysis treatment. A high PTH level can cause high bone turnover disease with calcification of blood vessels, heart valves, and the lens of the eye, as well as bone fractures and can progress to tertiary hyperparathyroidism. A low PTH level can result in low bone turnover disease with increased fracture rates, as well as calcification of tissues. Once tertiary hyperparathyroidism develops, the use of vitamin D analogues is limited by hypercalcemia. The elevated calcium and PTH levels can be treated medically with cinacalcet. Cinacalcet allows the use of higher doses of vitamin D analogues by lowering calcium levels. Surgical parathyroidectomy is performed when medical treatment with cinacalcet and vitamin D analogues is no longer effective.

III. HYPOCALCEMIA

A. **Etiology.** True hypocalcemia is the result of decreased calcium absorption from the gastrointestinal tract or decreased calcium resorption from bone. Given that 98% of total body calcium is contained within the skeleton, sustained hypocalcemia cannot occur without an abnormality of either PTH or calcitriol action in bone.

As noted earlier, total plasma calcium is composed of three components: ionized calcium (50%); complexed calcium (10%); and protein-bound calcium (40%). True hypocalcemia is present only when ionized calcium concentration is reduced. The reference range for ionized calcium concentration is 4.2 to 5.0 mg/dL (1.05 to 1.25 mmol/L). Therefore, whenever a low total serum calcium concentration is observed, this value must be compared with the serum albumin concentration. For every decrease of 1 g/dL in serum albumin concentration from its normal concentration of 4 g/dL, a decrease of 0.8 mg/dL in total serum calcium concentration can be expected. Therefore, for each fall of 1 g/dL in serum albumin concentration, 0.8 mg/dL must be added to total serum calcium concentration. This correction factor was shown to be unreliable in patients with critical illness. It is also unreliable in patients with CKD due to errors in albumin

measurement using the bromocresol green or bromocresol purple methods. In CKD patients with low serum albumin or decreases in serum bicarbonate concentration, if clinical suspicion warrants, ionized calcium concentration should be measured. Calcium binding to albumin is affected by ECF pH. Acidemia increases and alkalemia decreases ionized calcium concentration. Ionized calcium concentration increases approximately 0.2 mg/dL for each 0.1 decrease in pH. These correction factors are only general guidelines and should not be used as a substitute for the direct measurement of serum-ionized calcium concentration if clinical suspicion warrants.

True hypocalcemia is caused by decreased PTH secretion, end-organ resistance to PTH, or disorders of vitamin D metabolism. Occasionally, hypocalcemia occurs acutely as a result of either extravascular calcium deposition or intravascular calcium binding. The most common etiologies of true hypocalcemia are illustrated in Table 5-3.

3. **Hypoparathyroidism** is caused by a wide variety of acquired and inherited diseases that result from impaired PTH synthesis and release or from peripheral tissue resistance to PTH.
   - **a.** The most common cause of idiopathic hypoparathyroidism is **polyglandular autoimmune syndrome type I**, characterized by chronic mucocutaneous candidiasis and primary adrenal insufficiency. Occasionally, pernicious anemia, diabetes mellitus, vitiligo, and autoimmune thyroid disease are also associated. Mucocutaneous candidiasis often presents first in early childhood and is followed several years later by hypoparathyroidism. Adrenal insufficiency appears in adolescence. The combination of hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis is referred to as the *hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis (HAM) syndrome*. Mutations in the autoimmune regulator (*AIRE*) gene, a transcription factor, were shown to cause the disease.
   - **b.** **Familial hypocalcemia** results from activating mutations in the calcium-sensing receptor that increase its sensitivity to calcium.
   - **c.** **Parathyroid and radical neck surgery** can result in a loss of glandular tissue. Surgical removal of parathyroid tissue in secondary or tertiary hyperparathyroidism in dialysis patients is often complicated by severe hypocalcemia due to remineralization of bone, the so-called hungry bone syndrome. Patients usually require hospitalization for intravenous calcium infusion after the parathyroidectomy. After discharge they may require high doses of calcitriol and oral calcium supplements. Remnant parathyroid tissue is usually left in the neck or autotransplanted in the sternocleidomastoid or a forearm muscle. If not enough tissue is left behind or the transplanted parathyroid tissue does not survive, the patient may be left with permanent hypoparathyroidism and hypocalcemia.
   - **d.** Hypocalcemia also occurs after **thyroid surgery** (5% of cases); in a small percentage of patients hypocalcemia is permanent. Risk factors for the development of permanent hypocalcemia include removal of three or more parathyroid glands; postoperative PTH concentration $\leq$12 pg/mL; total serum calcium concentration $\leq$8 mg/dL after 1 week of oral calcium supplementation; and serum phosphorus concentration $\leq$4 mg/dL after 1 week of calcium supplementation.

Table 5-3.	Etiologies of Hypocalcemia
Hypoparathyroidism	
Idiopathic—HAM syndrome	
Familial	
Post-surgery—hungry bone syndrome	
Infiltrative disorders	
Pseudohypoparathyroidism I and II	
Hypomagnesemia	
Defects in Vitamin D Metabolism	
Nutritional	
Malabsorption	
Drugs	
Liver disease	
Chronic kidney disease	
Vitamin D–dependent rickets	
Miscellaneous	
Tumor lysis syndrome	
Osteoblastic metastases	
Acute pancreatitis	
Toxic shock syndrome	
Sepsis	
HAM, hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis.	

e. Transient hypoparathyroidism may occur after the **removal of a parathyroid adenoma** due to suppression of remaining parathyroid tissue.

f. **Infiltrative disorders** such as hemochromatosis, Wilson's disease, and infection with human immunodeficiency virus can also decrease PTH secretion.

g. **Severe hypomagnesemia** is the most common cause of hypoparathyroidism. Magnesium deficiency results in end-organ resistance to PTH and a decrease in PTH secretion. Patients with hypocalcemia as a result of hypomagnesemia do not respond to calcium or vitamin D replacement until the magnesium deficit is replaced.

2. A variety of rare genetic disorders cause **end-organ resistance to PTH**, including pseudohypoparathyroidism types I and II. Patients with pseudohypoparathyroidism are classified on the basis of the response of nephrogenous cyclic adenosine monophosphate to PTH administration. A decreased response is indicative of type I and a normal response indicative of type II.

3. **Defects in vitamin D metabolism** also cause hypocalcemia. Etiologies include decreased intake of vitamin D, malabsorption, drugs, liver disease, kidney disease, and vitamin D–dependent rickets. Nutritional vitamin D deficiency is uncommon in the United States as a result of the supplementation of milk and other food products. It can occur, however, in poorly nourished patients with little sun exposure. Groups that were shown to be at high risk include the institutionalized elderly, postmenopausal women, and adolescents. Because vitamin D is fat soluble, vitamin D deficiency can be seen in gastrointestinal malabsorption from any cause. Patients with chronic biliary drainage from a cholecystostomy are at risk for developing deficiencies of vitamins D, A, E, and K. Anticonvulsants induce hypocalcemia through a variety of mechanisms including induction of the P-450 system with increased metabolism of vitamin D, inhibition of bone resorption, impaired calcium absorption from the gastrointestinal tract, and peripheral resistance to PTH action. This generally occurs in patients with additional predisposing factors, such as poor nutrition and decreased sun exposure. Phenobarbital enhances hepatic metabolism of vitamin D and calcidiol. Vitamin D deficiency can result from hepatocellular disease if the disease is severe enough to impair 25-hydroxylation of vitamin D to calcidiol. CKD impairs 1α-hydroxylation of calcidiol to calcitriol. Vitamin D–dependent rickets is a result of either impaired hydroxylation of calcidiol to calcitriol (type I) or end-organ resistance to calcitriol (type II). Type I patients respond to physiologic calcitriol doses. Patients with type II disease have dramatically increased calcitriol concentrations, respond poorly to calcitriol therapy, and have mutations in the vitamin D receptor.

4. **Less common causes** of hypocalcemia include tumor lysis syndrome, osteoblastic metastases, acute pancreatitis, toxic shock syndrome, and sepsis. The acute addition or release of phosphate into the extracellular space may cause hypocalcemia through a variety of mechanisms. Calcium and phosphate may precipitate in tissues, although the exact tissue in which the deposition occurs has never been identified. In addition, phosphate infusion increases the rate of bone formation and inhibits PTH-induced bone resorption; both of these processes act to decrease serum calcium concentration.

B. As is the case for hypercalcemia, **signs and symptoms** of hypocalcemia depend not only on the degree of hypocalcemia but also on the rate of

decline of serum calcium concentration. The threshold at which symptoms develop also depends on serum pH and whether concomitant hypomagnesemia, hypokalemia, or hyponatremia is present. Symptoms of neuromuscular excitability predominate. The patient may complain of circumoral and distal extremity paresthesias or of carpopedal spasm. Central nervous system manifestations include mental status changes, irritability, and seizures. On physical examination, hypotension, bradycardia, laryngeal spasm, and bronchospasm may be present. Chvostek's and Trousseau's signs should be checked. Chvostek's sign is a facial twitch elicited by tapping on the facial nerve just below the zygomatic arch with the mouth slightly open. A positive sign is occasionally observed in normal patients. Trousseau's sign is the development of wrist flexion, metacarpophalangeal joint flexion, hyperextended fingers, and thumb flexion after a sphygmomanometer cuff is inflated around the arm to 20 mmHg above systolic pressure for 3 minutes. Hypocalcemia can also prolong the QT interval and cause ventricular and atrial arrhythmias and impair myocardial contractility.

C. Diagnosis. The differential diagnosis of true hypocalcemia is often straightforward, and a diagnostic algorithm is shown in Figure 5-3. The most common causes are magnesium deficiency, CKD, and complications of parathyroid surgery.

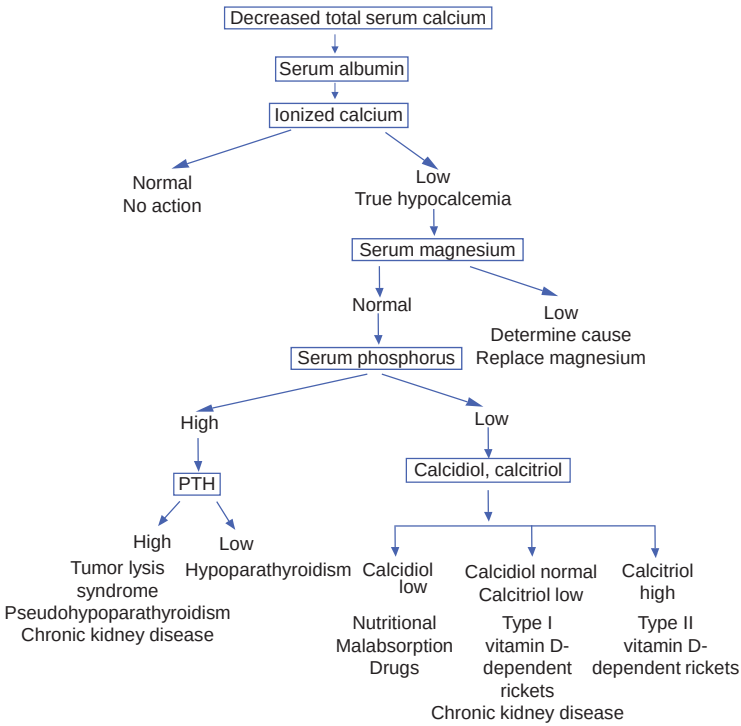


Figure 5-3. Evaluation of hypocalcemia. (PTH, parathyroid hormone.)

1. The first step in the evaluation of the patient with a decreased total serum calcium concentration is to **examine the serum albumin concentration** and, if necessary, measure ionized serum calcium concentration. If true hypocalcemia is documented, then blood analysis should be obtained for BUN, creatinine, magnesium, and phosphorus concentration, and a 24-hour urine sample should be collected to examine phosphorus and creatinine excretion.

   Gadolinium-containing chelates (gadopentetate dimeglumine and gadodiamide) used as contrast agents for magnetic resonance imaging may falsely lower serum calcium concentration. The effect persists for only 3 to 6 hours in those with normal renal function but can result in the spurious lowering of serum calcium concentration by up to 3 mg/dL or more. However, in patients with severe renal dysfunction, serum calcium concentration may remain low for up to 4 days. This is an important entity to be aware of because in many reported cases patients were treated with intravenous calcium for the spuriously low serum calcium concentration.

2. The second step is to **evaluate serum magnesium concentration**. Hypomagnesemia is the most common cause of hypocalcemia in hospitalized patients. A high index of suspicion should be present in patients with a history of steatorrhea, diarrhea, or chronic alcoholism. These patients generally have severe hypomagnesemia, and hypocalcemia will not correct until magnesium losses are replaced. It frequently requires several days for serum calcium concentration to correct after magnesium deficiency is reversed.

3. **Serum and urinary phosphorus concentrations** are evaluated next. Hyperphosphatemia in the absence of CKD suggests a diagnosis of either hypoparathyroidism or pseudohypoparathyroidism. Measuring PTH concentration can differentiate these disorders. In primary hypoparathyroidism, PTH is low; in pseudohypoparathyroidism, PTH is increased. A decrease in serum phosphorus concentration indicates a defect in vitamin D metabolism. Hypocalcemia results in secondary hyperparathyroidism that, in turn, reduces proximal tubular phosphate reabsorption and results in phosphate wasting. Therefore, the fractional excretion (FE) of phosphate is expected to be high (more than 5%). In hypophosphatemia, the kidney has an extraordinary ability to conserve phosphate, and, in extrarenal disorders, the FE of phosphate is below 1%. If phosphaturia is noted, then calcidiol and calcitriol concentration should be measured. Calcidiol concentration is reduced with malabsorption, liver disease, and phenobarbital. Calcitriol concentration is reduced in CKD and increased in type II vitamin D–dependent rickets.

D. Management of hypocalcemia is dependent on its severity and cause.

In an emergency situation in which hypocalcemia is suspected and seizures, tetany, hypotension, or cardiac arrhythmias are present, intravenous calcium should be administered (100 to 300 mg over 10 to 15 minutes) before results of the serum calcium concentration return from the clinical laboratory. Patients with symptomatic hypocalcemia or a total serum calcium concentration corrected for albumin of $\leq$7.5 mg/dL should be initially managed with parenteral calcium. Chronic, mild hypocalcemia, as seen in

the outpatient setting, can be treated with oral calcium supplements, to which a vitamin D preparation may be added if necessary.

1. **Acute symptomatic hypocalcemia** is treated with intravenous calcium. In the absence of seizures, tetany, or cardiac arrhythmias, an infusion of 1.5 mg/kg of elemental calcium given over 4 to 6 hours raises the total serum calcium by 2 to 3 mg/dL. Calcium gluconate (10%) is supplied in 10-mL ampules and contains 94 mg of elemental calcium. The first ampule can be administered over several minutes, followed by a constant infusion begun at a rate of 0.5 to 1.0 mg/kg/hour, with rate adjustments based on serial determinations of serum calcium concentration. Calcium gluceptate (10%) provides 90 mg of elemental calcium in a 5-mL ampule. Calcium chloride has higher bioavailability, and 272 mg of elemental calcium is contained in each 10-mL ampule. Treatment of hypocalcemia is ineffective in the presence of hypomagnesemia. In the setting of metabolic acidosis, hypocalcemia should be corrected before acidosis is reversed because excess protons in acidemia bind albumin in place of calcium, resulting in an increase in ionized calcium concentration.

   Patients with **hypoparathyroidism** are managed with calcium and vitamin D supplements. Serum calcium concentration should be maintained at the lower limit of normal. Oral elemental calcium, 1 to 3 g/day, is usually sufficient. A variety of oral calcium preparations are available, some of which are shown in Table 5-4. Calcium is best absorbed when taken between meals because an acid environment improves calcium absorption. Proton pump inhibitors are associated with decreased calcium absorption and osteoporosis. Calcium citrate is more soluble than calcium carbonate, especially in patients who require H_2 blockers or proton pump inhibitors. In the presence of severe hyperphosphatemia, calcium supplementation should be delayed, if possible, until the serum phosphorus concentration is reduced below 6 mg/dL using non-calcium containing phosphate binders. Severe hypocalcemia, however, may need to be treated despite hyperphosphatemia and clinical judgment must be used.

Table 5-4. Oral Calcium Preparations

Preparation	Formulation (mg)	Elemental Calcium per Tablet (mg)
Calcium carbonate	Tums 500	200
Rolaids 550 mg	220	—
Os-cal 1,250 mg	500	—
Calcium citrate	Citracal 950	200
Calcium lactate	650	85
Calcium gluconate	1,000	90

2. Calcitriol is the most potent of the **vitamin D preparations** and has the fastest onset and shortest duration of action, but is also the most expensive. A dose of 0.5 to 1.0 μg/day is usually required. As one moves back up the metabolic pathway to calcidiol, cholecalciferol, and ergocalciferol, cost decreases and duration of action increases. These agents, however, may be less efficacious in the presence of kidney or liver disease.

   Patients with hypoparathyroidism have decreased distal tubular calcium reabsorption as a result of a lack of PTH. Therefore, the increase in filtered calcium load that results from calcium and vitamin D replacement can lead to hypercalciuria, nephrolithiasis, and nephrocalcinosis. If urinary calcium excretion exceeds 350 mg/day despite a low serum calcium concentration, sodium intake should be restricted; if this is not effective, a thiazide diuretic should be added. The primary goal of treatment should be elimination of symptoms and not necessarily normalization of serum calcium concentration.

DISORDERS OF SERUM PHOSPHORUS

I. OVERVIEW. Approximately two-thirds of total plasma phosphorus is organic phosphorus (phospholipids) and one-third is inorganic. Clinical chemistry laboratories assay only the inorganic fraction. The reference range is 2.8 to 4.5 mg/dL (0.89 to 1.44 mmol/L) in adults. SI units (mmol/L) can be converted to conventional units (mg/dL) by multiplying by 3.1. Approximately 75% of inorganic phosphorus is free and circulates as either $HPO_4(-2)$ or $H_2PO_4(-1)$. The ratio of these two ions depends on ECF pH. At pH 7.4, 80% is $HPO_4(-2)$ and 20% $H_2PO_4(-1)$. Of the remainder, 15% is protein bound, and 10% is complexed with either calcium or magnesium.

As is the case for calcium, most of the total body phosphorus is contained within the skeleton (80-85%). Approximately 14% is within skeletal muscle and viscera. Only a small fraction of the phosphorus pool is inorganic and available for synthesis of adenosine triphosphate. The average Western diet contains 800 to 1,400 mg of phosphorus per day, of which approximately 65% is absorbed in the small intestine. Most of it is absorbed passively, but an active calcitriol-regulated component exists. PTH and calcitriol, through their effects in bone, intestine, and kidney, regulate phosphorus concentration. The major regulator of serum phosphorus concentration is renal phosphate excretion. In kidney, phosphate is reabsorbed primarily in the proximal tubule (80%), where it is cotransported with sodium across the luminal membrane. The sodium–phosphate cotransporter is upregulated in response to phosphate depletion, and, under these circumstances, the kidney is capable of reducing the FE of phosphate to very low levels.

II. PHOSPHATE REGULATION. PTH acts directly in bone to increase phosphate entry into the ECF and indirectly in intestine by stimulating calcitriol production. Most dietary phosphate is reabsorbed in the small intestine, but a component of unregulated secretion is present in colon (100 to 200 mg/day). PTH reduces proximal tubular phosphate reabsorption in kidney. The net effect is to increase plasma calcium concentration while keeping serum phosphorus concentration constant. The major roles of calcitriol are to enhance calcium and phosphate availability for new bone formation and to defend the ECF from hypocalcemia and hypophosphatemia. PTH and hypophosphatemia

stimulate calcitriol production in proximal tubule, although the kidney is the primary regulator of serum phosphorus concentration. Hypophosphatemia causes insertion of sodium–phosphate cotransporters into the luminal membrane of the proximal tubule, whereas PTH results in their removal. The ability of PTH to remove sodium–phosphate cotransporters from apical membrane is blunted in chronic phosphate depletion.

III. HYPERPHOSPHATEMIA

A. **Etiology.** Hyperphosphatemia can result from acute kidney injury, CKD, an acute phosphate load from either exogenous or endogenous sources, or increased proximal tubular phosphate reabsorption. Etiologies are shown in Table 5-5.

1. **CKD and acute kidney injury** are the underlying causes in 90% or more of cases. As GFR begins to decline, the FE of phosphate increases. Once GFR falls below 30 mL/minute, however, phosphorus reabsorption

Table 5-5. Etiologies of Hyperphosphatemia

Decreased Renal Excretion
Acute kidney injury
Chronic kidney disease
Acute Phosphate Load
Tumor lysis syndrome
Rhabdomyolysis
Bowel infarction
Severe hemolysis
Vitamin D Intoxication
Increased Renal Phosphate Reabsorption
Hypoparathyroidism
Acromegaly
Thyrotoxicosis
Drugs—bisphosphonates
Tumoral calcinosis
Pseudohyperphosphatemia

is maximally suppressed, and the FE cannot increase further. As a result, renal excretion can no longer keep pace with dietary intake, and serum phosphorus concentration rises. A new steady state is eventually established, albeit at a higher serum phosphorus concentration. In patients with CKD stage 4 about 15% will be hyperphosphatemic, while 50% of those with CKD stage 5 will have elevated serum phosphorus concentrations. Fibroblast growth factor (FGF)23 levels rise before PTH and serum phosphorus concentration. High FGF23 levels and low calcitriol concentration suppress klotho expression. The decrease in klotho (a coreceptor for FGF23) results in resistance to FGF23 and initiates a vicious cycle of phosphate retention in patients with CKD.

2. **A sudden, massive phosphate load** may result in an increase in serum phosphorus concentration. Phosphate either may be released from the intracellular space, as is the case in tumor lysis syndrome or rhabdomyolysis, or can be ingested and absorbed, as in vitamin D intoxication. Exogenous sources of phosphorus include oral phosphorus-containing laxatives, phosphate-containing enemas, high-dose liposomal amphotericin, and solvent detergent–treated fresh frozen plasma. Tumor lysis syndrome most commonly is seen with treatment of rapidly growing malignancies such as leukemias and lymphomas. It can occur after treatment of solid tumors such as small cell lung carcinoma, breast cancer, and neuroblastoma. Risk factors for tumor lysis syndrome in patients with solid tumors include pretreatment renal impairment, an increased lactate dehydrogenase level, and hyperuricemia. Increased lactate dehydrogenase levels and hyperuricemia are indicators of a large tumor burden.
3. **Primary increases in tubular phosphate reabsorption** are less common. They can occur in hypoparathyroidism; in acromegaly, as a result of direct stimulation of insulin-like growth factor on phosphate transport; with bisphosphonates, through a direct effect on renal phosphate reabsorption; and in tumoral calcinosis. Tumoral calcinosis is an autosomal recessive disorder associated with hyperphosphatemia and soft tissue calcium deposition caused by mutations in three genes. The first is an inactivating mutation in GALNT3 that encodes a glycosyltransferase involved in O-linked glycosylation. It is thought that GALNT3 regulates FGF23 glycosylation and that glycosylation is required for normal FGF23 function. The second mutation was identified in the *FGF23* gene itself. This mutation involves a serine residue that is thought to be involved in FGF23 glycosylation by GALNT3. The third mutation was described in the *Klotho* gene. Klotho binds to several FGF23 receptors and acts as a cofactor that is required for FGF23 signaling. FGF23 and klotho are discussed further in the section on hypophosphatemia.

B. Many of the **signs and symptoms** of an acute rise in serum phosphorus concentration are secondary to concomitant hypocalcemia (mechanism discussed earlier- page 93). Hyperphosphatemia can also cause hypocalcemia by decreasing 1α-hydroxylase activity and calcitriol formation.

C. Diagnosis. Clinically unexplained, persistent hyperphosphatemia should raise the suspicion of pseudohyperphosphatemia, the most common cause of which is paraproteinemia. No consistent relationship of immunoglobulin

type or subclass has been identified. This is a method-dependent artifact, and paraprotein interference may be a general problem in spectrophotometric assays. If paraproteinemia is absent, the cause is generally acute kidney injury or CKD.

D. **Treatment** of hyperphosphatemia is aimed at reducing intestinal phosphate absorption. This is accomplished through the use of oral phosphate-binding drugs such as calcium carbonate, calcium acetate, sevelamer carbonate, lanthanum carbonate, and aluminum hydroxide. These agents should be administered with meals. Aluminum hydroxide may be used in the short term, but chronic use in patients with kidney disease should be avoided because of the potential for aluminum toxicity. Each of the above phosphate binders has strengths and weaknesses. Calcium-containing binders are low in cost but may contribute to vascular calcification, oversuppression of PTH, and adynamic bone disease. The non-calcium containing binders sevelamer and lanthanum carbonate are high in cost. Lanthanum carbonate is frequently associated with nausea and gastrointestinal upset. These newer agents have not been shown to reduce mortality. In patients with coexistent hypocalcemia, it is preferable to lower serum phosphorus below 6 mg/dL, if possible, before treating hypocalcemia to avoid the potential complication of metastatic calcification from calcium phosphate coprecipitation.

IV. HYPOPHOSPHATEMIA

A. **Etiology.** Hypophosphatemia may result from redistribution of phosphorus from the extracellular to the intracellular space, a decrease in intestinal phosphate absorption, a decrease in renal phosphate reabsorption, or extrarenal losses from the gastrointestinal tract or through dialysis. The differential diagnosis is presented in Table 5-6.

1. Respiratory alkalosis and the refeeding syndrome are the most common causes of a **phosphate shift from the ECF to the intracellular fluid (ICF)** in hospitalized patients. Respiratory alkalosis causes a rise in intracellular pH that stimulates phosphofructokinase, the rate-limiting step in glycolysis. This results in severe hypophosphatemia with serum phosphorus concentrations of less than 0.5 to 1.0 mg/dL. Intracellular shifts are also seen with the treatment of diabetic ketoacidosis and in "hungry bone syndrome," which occurs after parathyroidectomy for secondary and tertiary hyperparathyroidism. In "hungry bone syndrome," serum calcium and phosphorus concentration fall dramatically in the postoperative period, although clinically, hypocalcemia is more of a management issue than hypophosphatemia.
2. **Decreased dietary intake** is an unusual cause of hypophosphatemia because oral intake almost always exceeds gastrointestinal losses, and the kidney is capable of reclaiming nearly all the filtered load of phosphate. In general, decreased intake must be combined with increased gastrointestinal losses (e.g., diarrhea) or the use of phosphate binders for hypophosphatemia to result.
3. **Increased urinary phosphate excretion** occurs in primary hyperparathyroidism, secondary hyperparathyroidism due to defects in vitamin D metabolism, Fanconi syndrome, osmotic diuresis, acetazolamide use,

Table 5-6.	Etiologies of Hypophosphatemia
Decreased Dietary Intake	
Alcoholism	
Phosphate-binding agents	
Shift of Phosphate into the Intracellular Fluid	
Respiratory alkalosis	
Refeeding	
Diabetic ketoacidosis	
Hungry bone syndrome	
Increased Renal Excretion	
Hyperparathyroidism	
Vitamin D deficiency	
X-linked hypophosphatemic rickets	
Autosomal dominant hypophosphatemic rickets	
Fanconi syndrome	
Drugs—acetazolamide, sirolimus, and iron carboxymaltose	
Osmotic diuresis	
Oncogenic osteomalacia	
Postrenal transplantation	
Extrarenal Losses	
Intestinal losses	
Dialysis	
Thermal injury	

oncogenic osteomalacia and other disorders of FGF23 homeostasis, imatinib use, and after renal transplantation and with mutations in the sodium–phosphate cotransporter expressed in the proximal tubule. Oncogenic osteomalacia is a rare disorder associated with mesenchymal tumors. It is characterized by hypophosphatemia, phosphaturia, decreased

calcitriol concentration, normal calcidiol concentration, and clinical and histologic evidence of osteomalacia. A considerable delay may occur between the presentation of the syndrome and discovery of the tumor. The tumor produces FGF23 that decreases proximal tubular phosphate reabsorption and calcitriol production. Tumor removal results in resolution of phosphate wasting, osteomalacia, and normalization of FGF23 levels.

FGF23 is produced by osteocytes and osteoblasts and is present in the circulation of healthy individuals, consistent with a physiologic role in regulating serum phosphorus. Animal studies showed that FGF23 is phosphaturic. Dietary phosphorus changes within the physiologic range regulate serum concentrations of FGF23. When administered in vivo, it induces hypophosphatemia, suppresses $1,25(OH)_2$ vitamin D_3 concentration by inhibiting 1α-hydroxylase activity, decreases type II sodium–phosphate cotransporters in proximal tubules, decreases PTH expression, and leads to osteomalacia. $1,25(OH)_2$ vitamin D_3 stimulates FGF23 production, suggesting that it may play a counter-regulatory role in the maintenance of serum phosphorus concentration. $1,25(OH)_2$ vitamin D_3 induces phosphate mobilization from bone and an increase in serum phosphorus concentration. Two inherited renal phosphate wasting disorders, autosomal dominant hypophosphatemic rickets (ADHR) and X-linked hypophosphatemia (XLH), are the result of defects in FGF23 metabolism. Missense mutations in FGF23 cause ADHR.

ADHR is characterized by hypophosphatemia, renal phosphate wasting, short stature, and bony deformities. In ADHR, mutations at a proteolytic cleavage site prevent FGF23 cleavage and inactivation. In vivo studies showed that biologic activity is limited to full-length FGF23 (251 amino acids). The enzyme responsible for the cleavage of FGF23 has not been identified. One report suggested that PHEX, a cell surface metalloprotease, may cleave FGF23, but this has not been confirmed.

XLH is characterized by renal phosphate wasting, hypophosphatemia, growth retardation, defective cartilage and bone calcification, and resistance to phosphate and vitamin D repletion. Inactivating mutations of PHEX (phosphate-regulating gene with homology to endopeptidase) cause XLH. PHEX is a member of a family of zinc-dependent cell surface proteases that cleave small peptides such as endothelin. It is expressed predominantly in cartilage, bone, and teeth. Its physiologically relevant substrate is yet to be identified. Although it has been postulated that PHEX cleaves and inactivates FGF23, the large size of FGF23—251 amino acids—makes this less likely. Other intermediate small molecular weight substrates likely link PHEX function to FGF23.

Fibrous dysplasia of bone is the result of an activating mutation of GNAS1 that encodes the α-subunit of the stimulatory G-protein (G_s). FGF23 is expressed in the abnormal bone tissue and these patients may have renal phosphate wasting and hypophosphatemia. When fibrous dysplasia of bone is associated with precocious puberty and *café au lait* spots, this triad is known as the *McCune–Albright syndrome*.

Hereditary hypophosphatemic rickets with hypercalciuria is inherited as an autosomal recessive disorder manifested by increased renal phosphate excretion, hypophosphatemia, and rickets. It is associated

with increased $1,25(OH)_2$ vitamin D_3 concentration and hypercalciuria. Mutations were identified in SLC34A3, a proximal tubular sodium–phosphate cotransporter.

Post-transplant hypophosphatemia occurs in renal transplant recipients and is related to the use of immunosuppressant drugs, tertiary hyperparathyroidism, or increased FGF23 levels. The effect of tertiary hyperparathyroidism usually resolves after the first year of transplantation, but may persist in some cases. Increasing the sensitivity of the calcium-sensing receptor with cinacalcet results in decreased calcium levels, increased phosphorus concentration, and decreased PTH levels in renal transplant recipients.

Some drugs may also induce phosphate wasting. Iron carboxymaltose stimulates FGF23 release. Klotho expression may be induced by sirolimus.

Fanconi syndrome is associated with glycosuria, aminoaciduria, bicarbonaturia, and phosphaturia. It can be caused by either acquired or inherited disorders. Inherited diseases include Lowe syndrome, Wilson disease, cystinosis, and hereditary fructose intolerance. Acquired disorders include drugs, post-transplant and multiple myeloma. Tenofovir, cidofovir, adefovir, valproic acid, ranitidine, ifosfamide, and tetracyclines have been implicated. The Chinese herb Boui-ougi-tou has also been reported to cause Fanconi syndrome.

4. **Extrarenal losses** may occur through the intestines or through dialysis. Phosphorus is absorbed in the small bowel so high-output ileostomies or cutaneous small bowel fistulas tend to result in hypophosphatemia more frequently than colostomies or diarrhea. Treatment with oral phosphate is difficult because it can exacerbate the diarrhea requiring admission for intravenous phosphate replacement.

   Typically phosphorus is elevated in dialysis patients because dialysate removal is limited and oral phosphorus intake is often high. When oral intake is poor, phosphorus removal through dialysis can result in hypophosphatemia. This is particularly true when continuous dialysis modalities are used in the treatment of acute kidney injury where removal is enhanced and oral intake is reduced.

   Decreases in serum phosphorus concentration can develop several days after a significant thermal injury related to phosphorus losses in the exudate.

B. Signs and Symptoms. Hypophosphatemia results in a variety of clinical sequelae. The correction of moderate hypophosphatemia (serum phosphorus level 1.0 to 2.5 mg/dL) improves diaphragmatic function in patients with acute respiratory failure. In patients with severe hypophosphatemia (serum phosphorus level less than 1.0 mg/dL), failure to wean from mechanical ventilation until phosphate was repleted has been reported. In vitro hypophosphatemia causes a leftward shift in the oxygen dissociation curve. Neuromuscular symptoms include paresthesias, tremor, muscle weakness, and altered mental status; severe hypophosphatemia increases red cell fragility, which can lead to hemolysis, and decreases chemotaxis, phagocytosis, and bacterial killing by white cells, with an increased susceptibility to infection as the possible result. Correction of severe hypophosphatemia

has been reported to increase myocardial contractility by as much as 20%. This effect is highly variable between patients. Rarely does hypophosphatemia result in clinical congestive heart failure.

C. Diagnosis. FE of phosphate or 24-hour urinary phosphate excretion can be used to distinguish among the pathophysiologic mechanisms of hypophosphatemia. If the kidney is responding appropriately to decreased intestinal absorption or phosphate redistribution into cells, FE of phosphate is below 5%, and 24-hour urine phosphate excretion is less than 100 mg/day. When the kidney is the cause of hypophosphatemia, the FE of phosphate is greater than 5% and the 24-hour urine contains more than 100 mg/day of phosphate. In this case, a urinalysis for glycosuria, PTH concentration to rule out hyperparathyroidism, and the measurement of calcidiol and calcitriol concentrations are indicated.

D. Treatment is indicated for severe hypophosphatemia ($\leq$1 mg/dL) or symptoms. It is complicated by the fact that phosphate is largely an intracellular ion, and that serum phosphorus concentration is not a reliable indicator of total body phosphate stores. Hypophosphatemia is often associated with potassium and magnesium depletion. Phosphate repletion should be undertaken with extreme caution in the rare patient with renal dysfunction; the safest mode of therapy is oral, and hypophosphatemia usually can be corrected with 1,000 mg/day of phosphate. Alternative forms of oral phosphate replacement are listed in Table 5-7. Diarrhea is the most common complication.

Intravenous replacement carries the risk of hypocalcemia and hyperphosphatemia and is only warranted in patients with severe symptomatic hypophosphatemia. Sodium–phosphate should be used unless the serum potassium is less than 4 mEq/L. Serum concentrations of phosphorus, calcium, magnesium, potassium, and urine output should be carefully monitored during intravenous replacement. Once serum phosphorus

Table 5-7. Oral Phosphate Preparations

Preparation	Dosage	Contents
K-phos-neutral	2 tablets, b.i.d. or t.i.d.	250 mg phosphate, 12 mEq sodium, 2 mEq potassium per tablet
Fleets Phospho-Soda	5 mL b.i.d.	149 mg phosphate, 6 mEq sodium per mL
Neutra-Phos-K	1–2 capsules, b.i.d. or t.i.d.	250 mg phosphate, 14 mEq potassium per capsule
K-phos	2 tablets, t.i.d. or q.i.d.	114 mg phosphate, 3.68 mEq potassium per tablet

concentration has increased to more than 1 mg/dL, the patient should be switched to an oral preparation. The administration of doses larger than 0.32 mmol/kg over a 12-hour period is rarely warranted.

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6 The Patient with Kidney Stones

Robert F. Reilly

Recent data comparing the prevalence of kidney stone disease in the United States between the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES II (1976–1980) show a 37% increase in new-onset symptomatic kidney stones. Similar studies in the United Kingdom show a 63% increase. In addition, stone disease is increasingly more common in women. In the past, the male:female ratio was 3:1; currently it is 1.3:1. It is estimated that, by the age of 70 years, as many as 20% of all white men and 7% of all white women will suffer from kidney stone disease. African Americans and Asians are affected less often. The peak incidence occurs between the ages of 20 and 30 years. In the United States, calcium-containing stones make up approximately 90% of all stones; they contain calcium oxalate alone, calcium phosphate alone, or a mixture of both. The remaining 10% are composed of uric acid, struvite-carbonate, and cystine.

Kidney stones are a major cause of morbidity due to associated renal colic, urinary tract obstruction, urinary tract infection (UTI), and renal parenchymal damage. It was recognized that nephrolithiasis may be associated with end-stage renal disease (ESRD) and/or a declining glomerular filtration rate (GFR). According to US Renal Data System reports between 1993 and 1997, stone disease was attributed as the cause of ESRD in 1.2% of patients. In Necker Hospital in France between 1989 and 2000, nephrolithiasis was felt to be the primary cause of ESRD in 3.2% of patients. Struvite stones accounted for 42.2% of these cases. In a case–control study of nephrolithiasis, there was a higher incidence of chronic kidney disease (CKD) noted in patients with kidney stones. This was only observed in those patients who did not report a history of hypertension. Finally, although the effect was small, an analysis of NHANES III data revealed an association between history of kidney stones and estimated GFR that was dependent on body mass index (BMI). Stone formers with a BMI greater than 27 kg/m^2 had a mean estimated GFR that was 3.4 mL/minute/1.73 m^2 lower than similar nonstone formers.

A kidney stone can form only when urine is supersaturated with respect to a stone-forming salt. Interestingly, urine in many healthy subjects is often supersaturated with respect to calcium oxalate, calcium phosphate, or uric acid and crystalluria was described in as many as 15% to 20% of healthy subjects. However, urine of recurrent stone formers was noted to contain crystals in first morning voided specimens much more frequently than that of stone formers without subsequent recurrence, suggesting that recurrence may depend on the degree and severity of crystalluria.

Several recent studies provided insight into the crystallization process. Calcium oxalate can crystallize as either calcium oxalate monohydrate (COM) or calcium oxalate dihydrate (COD). COM is the predominant species found in calcium oxalate stones and is the more thermodynamically stable of the two species. Macromolecular inhibitors block COM growth and favor COD formation. Using atomic force

microscopy configured with nanoscale tips, which were modified by biologically relevant functional groups, it was shown that COD crystals do not adhere as well to organic compounds and to the surface of renal epithelia in vitro. This suggests that COD crystals in urine might protect against kidney stone formation given their reduced capacity to form stable aggregates and adhere to epithelial cells.

Urine is also often supersaturated with respect to brushite ($CaHPO_4 \cdot 2H_2O$), a calcium phosphate salt, especially after meals. Brushite can act as a nidus upon which calcium oxalate crystals can form. In vitro studies show that COM crystals once formed grow at the expense of brushite.

Another important factor in the pathogenesis of stone formation that is incompletely understood is the presence of crystallization inhibitors in urine. Normal urine contains a variety of inorganic and organic substances that act as crystallization inhibitors. The most clinically important of these are citrate, magnesium, and pyrophosphate.

Sufficient energy must be generated for a crystal to form in solution. Once a crystal forms, it was once thought that it must either grow to sufficient size to occlude the tubular lumen or anchor itself to the urinary epithelium, which in turn provides a surface upon which it can grow. The typical transit time of a crystal through the nephron is on the order of 3 minutes, and this is too short a period for it to nucleate, grow, and occlude the tubular lumen. However, studies by Evan and Coe have shed additional light on how stones form in the kidney. In patients with idiopathic hypercalciuria, the initial site of crystal formation was in the basement membrane of the thin limb of the loop of Henle. The stone core was made up of calcium phosphate alternating with layers of matrix. The crystal deposit then migrates toward the renal pelvis where it acts as a base upon which a plaque forms, which is then bathed in urine supersaturated with stone-forming constituents upon which calcium oxalate is deposited. Why calcium phosphate precipitates at the basolateral surface of the thin limb of the loop of Henle is unclear. Further studies by Worcester and Coe found a postprandial decrease in proximal tubular calcium reabsorption in these patients. In patients with one type of calcium phosphate stone (brushite), mineral is deposited on the luminal membrane of dilated inner medullary collecting duct cells and grows out into the renal pelvis. The dilated inner medullary collecting ducts are surrounded by areas of interstitial fibrosis.

I. INITIAL PRESENTATION.

A kidney stone most commonly presents with severe flank pain, sudden in onset, and is often associated with nausea and vomiting. The radiation of the pain may provide some clue as to where in the urinary tract the stone is lodged. Stones in the ureteropelvic junction cause flank pain that may radiate to the groin, whereas those lodged in the narrowest portion of the ureter, where it enters the bladder, are associated with signs of bladder irritation (dysuria, frequency, and urgency). Struvite-carbonate stones are, on occasion, incidentally discovered on abdominal radiograph. A careful abdominal examination and, in women, a pelvic examination are important to rule out other potential causes of abdominal pain.

A. Laboratory evaluation should include a complete blood cell count, serum chemistries, and urinalysis. The white blood cell count may be mildly elevated but is generally less than 15,000/mm^3. A white blood cell count greater than 15,000/mm^3 is suggestive of another intra-abdominal cause or an associated infection behind an obstructing calculus. An elevation of the serum blood urea nitrogen (BUN) and creatinine concentrations indicates prerenal azotemia, parenchymal renal disease, or obstruction of

a solitary functioning kidney. A urinalysis should be performed routinely in any patient with abdominal pain. Microscopic hematuria is observed in approximately 90% of patients with renal colic.

B. Once the diagnosis is suspected based on the history, physical examination, and preliminary laboratory studies, **establishing a definitive diagnosis** is the focus of the next stage of the evaluation.

1. A **flat radiographic plate of the abdomen** is often obtained and is capable of identifying radiopaque stones (calcium oxalate, calcium phosphate, struvite-carbonate, and cystine) that are ≥2 mm in size. It will miss radiolucent stones, the most common of which are composed of uric acid, and stones that overlie the bony pelvis. For these reasons, an abdominal flat plate is most valuable in ruling out other intra-abdominal processes.
2. An **ultrasonographic examination of the genitourinary tract** often identifies stones in the renal pelvis; however, most of the stones are lodged in the ureter, and the ultrasonographic examination often misses these.
3. The **intravenous pyelogram** (IVP) was formerly considered the gold standard for the diagnosis of nephrolithiasis and is still of considerable value in the acute setting. Although the stone itself may not be visualized on IVP, the site of obstruction is regularly identified. Structural or anatomic abnormalities that may be present in the urinary tract and renal or ureteral complications can be recognized. Disadvantages of the IVP include the need for intravenous contrast and the prolonged waiting time often required to visualize the collecting system on the side of the obstruction.
4. **Spiral computed tomography** (CT) is the test of choice in the patient with suspected renal colic. The advantages of spiral CT include higher sensitivity, faster scan times, and lack of need for contrast.

C. Management. After the diagnosis is established, subsequent management is determined by (a) the presence or absence of associated pyelonephritis; (b) whether parenteral narcotics are required for pain control; and (c) the likelihood of spontaneous stone passage. Obstructing calculi can be managed with observation alone if pain can be controlled with oral analgesics and spontaneous passage is likely. Extracorporeal shock wave lithotripsy or ureteroscopic lithotripsy may need to be employed for stones lodged in the upper ureter. Calculi in the lower ureter can be removed by cystoscopy and ureteroscopy. Hospital admission is necessary if there is evidence of renal parenchymal infection; when nausea, vomiting, or severe pain precludes oral analgesic use; or the stone is unlikely to pass spontaneously. The likelihood of spontaneous passage is determined by stone size and location in the ureter (Table 6-1). Small stones in the distal ureter will likely pass, whereas large stones in the upper ureter will likely require urologic consultation and intervention. α1-Receptor antagonists, such as tamsulosin, and calcium channel blockers can be used to aid stone passage (medical expulsive therapy).

II. TYPES OF STONES

A. Calcium-containing stones make up 90% of all stones and are generally composed of a mixture of calcium oxalate and calcium phosphate. In mixed stones, calcium oxalate usually predominates, and pure calcium oxalate

Table 6-1. Likelihood of Spontaneous Passage	
	Likelihood of Spontaneous Passage (%)
Size	
>6 mm	25
4–6 mm	60
<4 mm	90
Location	
Upper ureter, >6 mm	1
Upper ureter, <4 mm	81
Lower ureter, <4 mm	93

stones are more common than pure calcium phosphate stones. Calcium phosphate tends to precipitate in alkaline urine, as occurs with renal tubular acidosis (RTA), whereas the precipitation of calcium oxalate does not vary with pH. Because urine is acidic in most patients, calcium oxalate stones are more common. The major risk factors for the formation of calcium-containing stones include hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria, low urine volume, and medullary sponge kidney. These risk factors can occur either alone or in combination. Their relative frequency is shown in Table 6-2.

1. **Hypercalciuria** is often defined as urinary calcium excretion greater than 250 mg/24 hours in women and greater than 300 mg/24 hours in men. Hypercalciuria is present in approximately two-thirds of patients with calcium-containing stones and may result from an increased filtered load, decreased proximal reabsorption, or decreased distal reabsorption. Proximal calcium reabsorption parallels sodium. Any situation that decreases proximal sodium reabsorption such as extracellular fluid (ECF) volume expansion also decreases proximal calcium reabsorption. Distal tubular calcium reabsorption is stimulated by parathyroid hormone (PTH), thiazides, and amiloride and inhibited by acidosis and phosphate depletion.

   Hypercalciuria may be idiopathic or secondary to primary hyperparathyroidism, RTA, sarcoidosis, immobilization, Paget's disease, hyperthyroidism, milk-alkali syndrome, and vitamin D intoxication. The idiopathic group makes up 90% of all hypercalciuria. This category of patients is characterized by increased $1,25(OH)_2$ vitamin D_3 concentration, suppressed PTH, and reduced bone mineral density. Three potential pathophysiologic mechanisms are postulated: increased intestinal calcium absorption; decreased renal calcium or phosphorus reabsorption; and enhanced bone demineralization. On the basis of a fast-and-calcium-load study, some authors advocate subdividing idiopathic hypercalciuria into

Table 6-2.	Risk Factors for Calcium-Containing Kidney Stones	
Risk Factor	**Alone (%)**	**Combined (%)**
Hypercalciuria	60	80
Low urine volume	10	50
Hypocitraturia	10	50
Hyperuricosuria	10	40
Hyperoxaluria	2	15

absorptive hypercalciuria type I (due to primary intestinal calcium hyperabsorption with low-normal PTH), type II (dietary calcium-dependent hypercalciuria), type III (intestinal calcium hyperabsorption induced by elevated calcitriol levels secondary to renal phosphate leak), and renal leak hypercalciuria. Patients with absorptive hypercalciuria have exaggerated intestinal calcium reabsorption, which can be reduced in some by dietary calcium restriction. Some authors have expressed concern over the potential long-term effects of dietary calcium restriction. Patients with idiopathic hypercalciuria often have reduced bone mass and are in negative calcium balance, which may be further exacerbated by a low-calcium diet. In addition, a reciprocal relationship exists between free calcium and free oxalate in the intestinal lumen. Calcium acts to bind oxalate in the intestine and reduce absorption. If oral calcium intake is reduced, oxalate remains free in the intestinal lumen and its absorption increases. However, this may be reduced by concomitant oxalate restriction. Finally, as shown in Table 6-3, most randomized controlled trials demonstrating that a given pharmacologic intervention reduces the risk of calcium-containing stones did not subdivide patients based on results of a calcium load study. Whether patients with recurrent calcium oxalate stone formation should ingest a diet that is either liberal or restricted in calcium remains controversial and will be further discussed in the section on therapy.

In primary hyperparathyroidism, filtered calcium load is increased as a result of bone calcium release and increased intestinal calcium absorption mediated by $1,25(OH)_2$ vitamin D_3. In those patients with hypercalciuria, the increase in filtered calcium load overcomes distal PTH action to increase tubular calcium reabsorption. In RTA, the decreased systemic pH results in increased calcium release from bone. In addition, acidosis directly inhibits distal nephron calcium reabsorption.

Macrophages in sarcoidosis produce $1,25(OH)_2$ vitamin D_3, which leads to increased intestinal calcium absorption. Immobilization, Paget's disease, and hyperthyroidism cause hypercalciuria by releasing calcium from bone and increasing filtered calcium load.

2. **Hypocitraturia.** It is defined as less than 320 mg citrate excretion/day. Citrate combines with calcium in the tubular lumen to form a nondissociable but soluble complex. As a result, less free calcium is available to

Table 6-3. Randomized Trials in Calcium-Containing Nephrolithiasis

Author	Treatment	Dose	Condition	No. of Patients; Length of Follow-Up	Risk Reduction
Borghi	Water	>2 L UO daily	First stone	199; 5 yr	55%
Laerum	Hydrochlorothiazide	25 mg b.i.d.	Noncategorized, recurrent	50; 3 yr	54%
Ettinger	Chlorthalidone	25–50 mg	Noncategorized, recurrent	54; 3 yr	48%
Borghi	Indapamide	2.5 mg	Hypercalciuria, recurrent	75; 3 yr	79%
Ettinger	Allopurinol	100 mg t.i.d.	Hyperuricosuria, recurrent	60; 3 yr	45%
Barcelo	Potassium citrate	30–60 mEq	Hypocitraturia, recurrent	57; 3 yr	65%
Ettinger	Potassium-magnesium citrate	42/21/63 mEq	Noncategorized, recurrent	64; 3 yr	81%
Ettinger	Potassium phosphate	1.4 g	Noncategorized, recurrent	71; 3 yr	None
Ettinger	Magnesium hydroxide	650–1,300 mg	Noncategorized, recurrent	52; 3 yr	None

L, liter; UO, urine output; b.i.d., twice daily; t.i.d., three times daily.

combine with oxalate. Citrate also prevents nucleation and aggregation of calcium oxalate. Chronic metabolic acidosis from any cause enhances proximal tubular citrate reabsorption and decreases urinary citrate concentration; this is the mechanism whereby chronic diarrhea, RTA, and increased dietary protein load result in hypocitraturia. Another important cause of hypocitraturia is hypokalemia, which increases expression of the sodium-citrate cotransporter present in the proximal tubular luminal membrane.

3. **Hyperuricosuria.** It is defined as uric acid excretion greater than 800 mg/day in men and greater than 750 mg/day in women. Uric acid and monosodium urate decrease calcium oxalate solubility in urine. Addition of increasing concentrations of uric acid and sodium urate to normal human urine can induce calcium oxalate precipitation through a poorly understood physiologic phenomenon known as *salting out*.
4. **Hyperoxaluria.** It is defined as urinary oxalate excretion greater than 45 mg/day. The etiologies of hyperoxaluria include enteric hyperoxaluria from inflammatory bowel disease, small bowel resection, jejunoileal bypass, Roux-en-Y gastric bypass, dietary excess (e.g., spinach, Swiss chard, rhubarb), and the rare genetic disorder primary hyperoxaluria. Urinary oxalate is derived from two major sources: 80% to 90% comes from endogenous production in liver and the remainder is obtained from dietary oxalate or ascorbic acid. In enteric hyperoxaluria, intestinal oxalate hyperabsorption occurs through two mechanisms. First, free fatty acids complex calcium and limit the amount of free calcium available to complex oxalate, thereby increasing the oxalate pool available for absorption. Second, bile salts and fatty acids increase colonic oxalate permeability. Additional risk factors for stone formation in these patients include intestinal fluid losses that decrease urine volume; and intestinal bicarbonate and potassium losses that result in hypocitraturia.

   Several studies suggest a correlation between decreased activity of the oxalate-degrading bacteria *Oxalobacter formigenes* and the development of recurrent calcium oxalate–containing kidney stones. *O. formigenes* utilizes oxalate as its sole energy source and has the capacity to degrade 0.5 to 1.0 g of oxalate/day. In this process it converts oxalate to CO_2 and formate. It is unclear why intestinal colonization with *Oxalobacter* decreases with increasing age and in patients who form calcium oxalate stones. One possibility is that antibiotic therapy, especially recurrent courses of fluoroquinolones, act to eradicate the organism. Enteric colonization is much lower in nonstone formers exposed to a recent course of antibiotics when compared with unexposed subjects, 60% versus 17.1%, respectively, and 31% versus 10% in calcium oxalate stone formers. This may explain in part the increased frequency of calcium oxalate stone formation in disease states such as inflammatory bowel disease and cystic fibrosis, although patients with these disorders clearly have multiple other risk factors for stone formation.

   Studies in colons of colonized rats showed that colonization with *Oxalobacter* results in net oxalate secretion across the colonic mucosa and a decrease in urinary oxalate excretion. Control rats showed net oxalate reabsorption. It was postulated that in addition to degrading

luminal oxalate *Oxalobacter* may also stimulate colonic oxalate secretion. Unidirectional flux data, however, seem to indicate that net oxalate secretion occurs as a result of decreased mucosal to serosal flux (absorption) rather than serosal to mucosal flux (secretion).

These exciting recent findings raise the potential for new future therapies in hyperoxaluric calcium oxalate stone formers. Patients could be tested for the absence of fecal *Oxalobacter* and those that lack the organism could undergo replacement with either the bacteria itself or the purified enzymes (formyl coenzyme A transferase and oxalyl-coenzyme A decarboxylase) that metabolize oxalate. To date, however, studies in humans have yielded conflicting results.

5. **Low Urinary Volume.** This is perhaps the most intuitively obvious of risk factors for calcium-containing kidney stones. The lower the volume of solvent, the more likely that a given amount of salt will be supersaturating. This risk factor is particularly prominent in warm climates with low humidity.

6. **Medullary sponge kidney** should be suspected in women, or in men with no other risk factors for calcium-containing stones. Studies showed that as many as 3% to 12% of patients with calcium-containing stones have this disorder. It has a prevalence of approximately 1 in 5,000 and affects males and females equally. The anatomic abnormality is an irregular enlargement of medullary and inner papillary collecting ducts. The diagnosis is usually established in the fourth or fifth decade by an IVP that reveals radial, linear striations in papillae or cystic collections of contrast media in ectatic collecting ducts. Patients present with stones or recurrent UTI, often associated with distal RTA. Malformations of the terminal collecting duct result in urinary stasis that promotes crystal precipitation and attachment to the tubular epithelium.

   Increasingly, obesity is being recognized as a risk factor for calcium oxalate and uric acid stone formation. As body size increases, urinary oxalate and uric acid excretion also increase. In a prospective study of three large cohorts with 4,827 incident stones detected, body weight, BMI, waist circumference, and weight gain after age 21 years were all associated with an increased risk of kidney stone formation. This effect was even more pronounced in women than in men. In another study of 4,883 patients with nephrolithiasis who underwent stone evaluation in two different stone clinics, urinary pH was inversely related to BMI. A persistently low urinary pH is the most important risk factor for uric acid nephrolithiasis. This may in part explain the increasing incidence of stone formation observed over the last several decades in the United States. As the BMI of the population increases, it would be expected that the incidence of stone formation will continue to rise well into the future.

B. **Uric acid stones** represent approximately 5% of all cases of nephrolithiasis in Western countries. The highest incidence was reported from Israel and the Middle East, where as many as 30% of all kidney stones consist solely of uric acid. This may be the result of the arid climate and reduced urinary volume. Uric acid is the major metabolic end product of purine metabolism in humans. Unlike most other mammals, humans do not express uricase,

which degrades uric acid into the much more soluble allantoin. Uric acid stones are the most common radiolucent stone.

1. **Pathophysiology.** The principal determinant of uric acid crystallization is its relative insolubility at acidic pH. Uric acid is a weak organic acid with two dissociable protons. The first has a pK_a of 5.5, and the second a pK_a of 10. As a result, only the first proton is dissociated in urine. At pH less than 5.5, undissociated acid predominates, and it is more likely to crystallize (solubility 80 mg/L). As pH increases, uric acid dissociates into the more soluble sodium urate (solubility 1 g/L). Because of the great increase in solubility with increasing pH, uric acid stones are the only kidney stones that can be completely dissolved with medical therapy. The main determinants of uric acid solubility are pH, concentration, and other cations present in urine. A higher sodium concentration decreases, whereas an increased potassium concentration increases, uric acid solubility. This may explain the complication of calcium-containing stone formation that can develop during sodium alkali therapy but not during treatment with potassium alkali. Sodium-containing alkalis also increase urinary calcium excretion secondary to ECF volume expansion.
2. **Signs and Symptoms.** Patients with uric acid stones exhibit a lower mean urinary pH and ammonium ion excretion rate. As many as 75% demonstrate a mild defect in renal ammoniagenesis in response to an acid load. Urinary buffers other than ammonia are titrated more fully than in unaffected individuals, with a resultant urine pH approximating 4.5.

   Those with defects in ammoniagenesis, such as the elderly and patients with polycystic kidney disease, are at increased risk for uric acid lithiasis. Patients with type 2 diabetes mellitus are also at increased risk for uric acid stone formation, as they have a lower urine pH compared with healthy individuals. In one study, 33% of unselected uric acid stone formers had type 2 diabetes mellitus and 23% had impaired glucose tolerance. The low urine pH in patients with insulin resistance is due to impairment in urinary ammonium excretion. Insulin stimulates ammonia synthesis, as well as the activity of the Na^+/H^+ exchanger in the proximal tubule. Low insulin bioactivity leads to defective ammonia synthesis or transport into the lumen. In addition, insulin deficiency causes an increase in plasma free fatty acid concentration. Ammoniagenesis uses glutamine as substrate; the presence of an alternative nonnitrogen metabolic substrate such as free fatty acids or ketoanions inhibits ammoniagenesis. Uric acid stone formers also have a blunted urinary NH_4^+ response to acute acid load due to low NH_3 availability.

   Patients with type 2 diabetes mellitus also tend to have higher BMI and increasing weight is associated with lower urinary pH. In addition, type 2 diabetic patients also consume more dietary acid and this may contribute to their lower urinary pH. However, neither the increased acid consumption nor body weight alone completely explains the low urinary pH.

   The second most important risk factor is decreased urine volume. Hyperuricosuria is the least important risk factor and is seen in less than 25% of patients with recurrent uric acid stones.

3. A **definitive diagnosis** is established through stone analysis. The diagnosis is suggested by the presence of a radiolucent stone, although xanthine and 2,8-dihydroxyadenine stones can also be radiolucent, or by the presence of uric acid crystals in unusually acidic urine.

C. Struvite-carbonate stones are also known as *infection stones* and are composed of a mixture of magnesium ammonium phosphate (struvite: $MgNH_4PO_4 \cdot 6H_2O$) and carbonate apatite [$Ca_{10}(PO_4)_6CO_3$]. Of all stones, 10% to 15% are estimated to be struvite-carbonate stones. This is likely an overestimate, however, given that these figures are based on reports from chemical stone analyses, and a greater proportion of stones chemically analyzed are obtained from surgical specimens. It is likely that struvite-carbonate stones make up no more than 5% of kidney stones. Their presence is also known as *stone cancer* because, before more recent therapeutic advances, they were the cause of numerous surgeries, renal failure, and death. Struvite-carbonate stones are the most common cause of staghorn calculi, although cystine, calcium oxalate, calcium phosphate and uric acid stones may occasionally form staghorns. Struvite-carbonate becomes supersaturating in urine only in one circumstance: infection by urea-splitting organisms that express urease. The most common urease-producing bacteria include *Proteus*, *Morganella*, *Providencia*, *Pseudomonas*, and *Klebsiella*. *Escherichia coli* and *Citrobacter* do not produce urease.

1. **Risk Factors.** Women with recurrent UTI and patients with spinal cord injury, other forms of neurogenic bladder, or ileal diversions of the ureter are most prone to form struvite-carbonate stones. Men with indwelling bladder catheters and complete spinal cord transection are at highest risk.
2. **Signs and Symptoms.** Struvite stones may present in a variety of ways, including fever, hematuria, flank pain, recurrent UTI, and septicemia. They can grow to a very large size and fill the renal pelvis as a staghorn calculus. The carbonate apatite component makes them radiopaque. Rarely, if ever, do they pass spontaneously, and 25% are discovered incidentally. If untreated, they result in loss of the affected kidney in 50% of cases.
3. **Pathophysiology.** For struvite-carbonate stones to form, urine must be alkaline, with a pH greater than 7.0 and supersaturated with ammonium hydroxide. Bacterial urease hydrolyzes urea to ammonia and carbon dioxide. The ammonia then hydrolyzes spontaneously to form ammonium hydroxide; the carbon dioxide hydrates to form carbonic acid and, subsequently, bicarbonate. At high pH, bicarbonate loses its proton to become carbonate. UTI with a urease-producing organism is the only situation in which urinary pH, ammonium, and carbonate are elevated simultaneously. The bacteria produce supersaturation in their own immediate environment. Crystals form around bacterial clusters, and bacteria permeate every crevice of a struvite-carbonate stone. The stone itself is an infected foreign body.

D. Cystine Stones. Cystinuria is the result of an autosomal recessive defect in proximal tubular and jejunal reabsorption of the dibasic amino acids cysteine, ornithine, lysine, and arginine. Excessive amounts of these amino acids

are excreted in urine, but clinical disease is due solely to the poor urinary cystine solubility. Cystine is a dimer of cysteine. Cystine stones make up less than 1% of all calculi in adults but may constitute as many as 5% to 8% of kidney stones in children. The prevalence of cystinuria is approximately 1 per 15,000 individuals in the United States. Pure cystine stones form only in homozygotes. A healthy adult excretes less than 19 mg of cystine per g of creatinine in 24 hours. Excretion of greater than 250 mg/g of creatinine is almost always indicative of homozygous cystinuria. Cystine stones are radiopaque due to the sulfhydryl moiety of cysteine.

1. **Pathophysiology.** Cystine solubility is approximately 250 mg/L, and this rises with increasing urinary pH. The pK_a of cysteine is 6.5; therefore, a gradual increase in solubility occurs as urinary pH rises from 6.5 to 7.5. Supersaturation occurs at cystine concentrations greater than 250 mg/L. If the cystine concentration can be maintained below 200 mg/L, cystine stones should not form. In patients with severe cystinuria (greater than 500 mg/day) as much as 4 L of urine is required at normal urinary pH to keep cystine concentration within the soluble range.
2. **Signs and Symptoms.** Cystine stones begin to form in the first to fourth decade. Patients tend to have bilateral obstructive staghorn calculi with associated renal failure. Characteristic hexagonal crystals may be identified, particularly in first morning urine, which is usually acidic. Heterozygotes can form stones either with no cystine or with cystine as only a minor component, given that cystine can act as a nidus for crystallization of both calcium oxalate and calcium phosphate.

E. Drug-Related Stones. A variety of drugs can precipitate in urine, including sulfonamides, triamterene, acyclovir, and the antiretroviral agent indinavir. Microscopic hematuria occurs in up to 20% of patients on indinavir. Nephrolithiasis develops in 3%, and 5% experience either dysuria or flank pain that resolves when the drug is discontinued. Reports show that patients with flank pain may have abnormal CT scans with a decrease in contrast excretion in the medullary rays.

Topiramate is often used in the treatment of migraines and seizure disorders and is associated with an increased risk of kidney stone formation. It is an inhibitor of carbonic anhydrases II and IV, which are expressed in proximal and distal tubules. As a result, topiramate is associated with metabolic acidosis, hypercalciuria, and increased urinary pH, factors which result in urinary brushite supersaturation that can subsequently lead to calcium phosphate stone formation.

III. EVALUATION OF THE PATIENT

A. Calcium-Containing Stones. The first question to be addressed in the patient with calcium-containing stones is whether the stone disease is simple or complicated. Simple disease is defined as a single stone in the absence of an associated systemic disorder. Complicated calcium-containing stone disease is present if the patient has multiple stones, evidence of new stone formation, enlargement of old stones, or passage of gravel. This distinction is made based on the initial evaluation. A history should be obtained, looking for a family history of stone disease, skeletal disease, inflammatory

bowel disease, and UTI. Environmental risk factors are evaluated, such as fluid intake, urine volume, immobilization, diet, medications, and vitamin ingestion. A physical examination is performed. Initial laboratory evaluation includes blood chemistries, urinalysis, and a renal ultrasound and flat radiographic plate of the abdomen to assess stone burden. Stone analysis should always be carried out if the patient has saved the stone. Stone analysis is inexpensive. It is also the only way to establish the diagnosis of a specific disorder and often helps to direct therapy. In addition, it was shown that in 15% of cases, analyses of 24-hour urine would not have predicted the chemical composition of the stone.

In the patient with complicated disease, two to three measurements of serum calcium concentration should be performed. If any serum calcium level is above 10 mg/dL, PTH concentration should be evaluated. Blood chemistries are examined. An IVP may be indicated to rule out structural abnormalities that predispose to stone formation. First morning void urine should be examined for cystine crystals. One or two 24-hour urine collections should be obtained on the patient's usual diet for calcium, citrate, uric acid, oxalate, sodium, phosphate, volume, pH, and creatinine. Further therapeutic intervention depends on the results of these collections. Normal values for 24-hour urine collection are shown in Table 6-4. If a therapeutic intervention is undertaken, a 24-hour urine collection should be repeated in 6 to 8 weeks to verify its expected effect and then repeated yearly.

B. Uric Acid Stones. The etiologies of **uric acid stones** can be subdivided into three pathophysiologic groups based on risk factors. Low urine volume contributes to uric acid stones in gastrointestinal disorders such as Crohn's disease, ulcerative colitis, diarrhea, ileostomies, and dehydration. Acidic urinary pH plays an important role in primary gout and gastrointestinal disorders. Hyperuricosuria is divided into those with hyperuricemia (primary gout, enzyme disorders, myeloproliferative diseases, hemolytic anemia, and drugs) and those without hyperuricemia (dietary excess).

Primary gout is an inherited disorder most likely transmitted in an autosomal dominant manner with variable penetrance. It is associated with hyperuricemia, hyperuricosuria, and persistently acid urine. In affected patients, 10% to 20% have uric acid stones, and in 40% kidney stones precede the first articular gout attack. Because urine is always acidic, risk of uric acid lithiasis varies directly with serum and uric acid concentration.

Table 6-4. Normal Values for 24-Hour Urine Collection

Substance	Male (mg/24 h)	Female (mg/24 h)
Calcium	<300	<250
Uric acid	<800	<750
Citrate	>320	>320
Oxalate	<45	<45

Uric acid stones are typically round and smooth and are more likely to pass spontaneously than calcium-containing stones, which are often jagged. They are also radiolucent, as are xanthine, hypoxanthine, and 2,8-dihydroxyadenine stones. Xanthine, hypoxanthine, and 2,8-dihydroxyadenine stones should be suspected if a radiolucent stone fails to dissolve with alkali therapy.

C. **Struvite-Carbonate Stones.** Seventy-five percent of all staghorn calculi are composed of struvite-carbonate. Struvite-carbonate stones are large and less radiopaque than calcium-containing stones. As with any kidney stone, the definitive diagnosis is only established on chemical analysis, but a diagnosis of struvite-carbonate stones should be strongly suspected in any patient with an infected alkaline urine. In the presence of an infected acidic urine and a staghorn calculus, one should consider the possibility that the two are unrelated and that the calculus may be either calcium containing or uric acid. Stone analysis and culture should be carried out in all patients after either percutaneous nephrolithotomy or extracorporeal shock wave lithotripsy. Some patients, especially ambulatory men, have stones that contain a mixture of struvite-carbonate and calcium oxalate. These patients should always undergo complete metabolic evaluation, because virtually all have an underlying metabolic defect, and they are probably at higher risk for stone recurrence, even with complete stone removal.

Proteus mirabilis accounts for more than one-half of all urease-producing infections. Stone culture, when possible, is important, because urine culture is not always completely representative of the organisms present in the stone. If no organisms are cultured, then the possibility of infection with *Ureaplasma urealyticum*, which is often difficult to culture, should be considered.

D. **Cystine Stones.** The presence of characteristic hexagonal crystals in first morning void urine is diagnostic of cystinuria, although this is a very infrequent finding. The simplest and most rapid screening test for cystinuria is the sodium-nitroprusside test, which has a lower limit of detection of 75 mg/g of creatinine. The nitroprusside complex binds to sulfide groups and may yield a false-positive result in patients taking sulfur-containing drugs. Phosphotungstic acid has also been used as an alternative screening test. Patients with a positive screening test result should undergo 24-hour urine cystine quantitation. Cystine stones are usually less radiodense on radiography than calcium-containing or struvite-carbonate stones. They typically have a homogeneous structure without striation.

IV. TREATMENT

A. **Calcium-Containing Stones.** Treatment of calcium-containing stones is determined by whether the patient has simple or complicated disease. The American College of Physicians advises that the patient with a single, isolated stone and no associated systemic disease be managed with nonspecific forms of therapy alone, including increased fluid intake. This approach is appropriate in patients at low risk of recurrence. One may consider, however, performing more extensive studies in patients at high risk for recurrence (white males; 63% will form a second stone within 8 years) or in those

who may experience substantial morbidity with a recurrence (patients who have undergone transplantation or patients with a solitary kidney).

The patient with complicated disease is managed with both nonspecific and specific treatment. Specific therapy varies depending on assessment of risk factors derived from analysis of 24-hour urines.

Although conventional upper limits of daily calciuria (95th percentiles) are defined as 250 mg/day for women and 300 mg/day for men, stone formers in the 70th percentiles (170 mg/day for women and 210 mg/day for men) or lower may benefit from even lower calcium excretion rates. Data linking calcium excretion to stone risk are supportive of the idea that quantity of calciuria is a graded risk factor for development of calcium-containing kidney stones.

1. **Nonspecific therapeutic options** include manipulation of fluid intake and diet. Increasing fluid intake is the cheapest way to reduce urinary supersaturation with calcium oxalate and phosphate. In a prospective randomized trial of 199 first-time stone formers followed up for a 5-year period, the risk of recurrent stone formation was reduced from 27% to 12% by raising urinary volume to more than 2 L/day with water ingestion. The average increase in urine volume in patients advised to increase fluid intake is approximately 300 mL/day.

   Before 1993, most patients with calcium-containing stones were advised to restrict dietary calcium. Three large prospective cohort studies, however, in both men and women suggest that a low-calcium diet may increase the risk of forming calcium-containing stones. The postulated mechanism is that ingested calcium aids in complexing dietary oxalate, and a reduction in dietary calcium results in a reciprocal increase in intestinal oxalate absorption. As a result, urinary supersaturation of calcium oxalate increases. Therefore, these authors recommend a liberal calcium intake in patients with calcium-containing stones. In these studies, however, ingestion of a high-calcium diet was also associated with increased magnesium, potassium, and phosphate intake, which may have acted as confounding variables in reducing stone risk. A recent prospective, randomized controlled trial compared patients on a low-calcium diet to those on a normal calcium, low-sodium, low-protein diet. The relative risk for kidney stone formation was reduced by 51% in those on the normal calcium diet. As predicted, urinary oxalate increased in the low-calcium group, compatible with the reciprocal relationship hypothesis. However, there was no low-calcium, low-sodium, low-protein control group to directly assess the effects of decreasing dietary calcium intake alone. Observational studies showed an association between increased sodium intake and elevated risk of stone formation in women, whereas increased animal protein intake increases the risk of stone formation in men.

   Pak et al. conducted a retrospective analysis of their stone registry to examine the potential effects of dietary calcium restriction on urinary stone risk as assessed by 24-hour urine analysis. It should be stressed that this was an analysis of a surrogate rather than a hard end point (rate of new stone formation). Patients were subdivided into three groups: group 1 (urinary calcium excretion greater than 275 mg/day); group 2

(urinary calcium excretion 200 to 275 mg/day); and group 3 (urinary calcium excretion less than 200 mg/day). Patients were then placed on a diet restricted in calcium, oxalate, and sodium. Urinary calcium excretion declined by 29% in group 1, 19% in group 2, and 10% in group 3. Relative supersaturation of calcium oxalate fell by 12% in group 1 and 6% in group 2, an effect that was statistically significant but less than the fall in urinary calcium. Calcium phosphate relative supersaturation fell in all three groups: 31% in group 1; 22% in group 2; and 17% in group 3. Urinary oxalate excretion did not increase.

These authors recommend that intake of oxalate, sodium, and meat products be limited in all patients with calcium-containing kidney stones. They also recommend that patients with urinary calcium excretion greater than 275 mg/day be treated with dietary calcium restriction (400 mg/day), thiazide diuretics, and potassium citrate. Patients with urinary calcium excretion between 200 and 275 mg/day are treated with mild calcium restriction (800 mg/day) and potassium citrate. Those with calcium excretion less than 200 mg/day are treated with a liberal calcium intake and potassium citrate. Based on studies discussed earlier, the role of dietary calcium in the prevention of calcium-containing stones remains controversial.

Another study examined the effects of the Atkins diet on risk factors for calcium-containing stone disease. Net acid excretion increased by 56 mEq/day, urinary citrate decreased from an average of 763 to 449 mg/day, urinary pH fell from 6.09 to 5.67, and urinary calcium increased from 160 to 248 mg/day. Patients with a history of kidney stones should avoid this highly lithogenic diet.

The question of whether supplemental calcium increases risk of nephrolithiasis in women is controversial. One report suggested that any use of supplemental calcium raises the relative risk of stone disease by approximately 20%. Risk in this study, however, did not increase with increasing dose. Although the relative risk of kidney stone formation is increased by supplemental calcium, one should bear in mind that women, in general, are at lower risk for stone formation. In patients with a history of calcium-containing stones, urinary calcium excretion, as well as calcium oxalate and phosphate saturation, should be monitored closely. If saturation increases, consideration should be given to discontinuing the supplements.

2. **Specific forms of treatment** are directed by results of the 24-hour urine studies. Therapy is focused on agents shown to reduce the relative risk of stone formation in randomized placebo-controlled clinical trials with more than 1 year of follow-up (results shown in Table 6-3). This is important because of the "stone clinic effect." After patients present for evaluation of nephrolithiasis, the subsequent period is often associated with a reduced risk of new stone formation (the "stone clinic effect"). This is the result of at least two factors: (a) regression to the mean and (b) increased adherence to nonspecific forms of treatment. Trials with less than 12 to 24 months of follow-up should be viewed with skepticism if no effect is detected. At the start of treatment, patients at high risk for recurrence may have stones too small to be detected radiographically

that grow and subsequently are identified as new stones. Because calcium-containing stones are often difficult to prevent from increasing in size once a nidus is established, this could minimize the treatment effect in high-risk patients. Agents that were shown to be effective in randomized placebo-controlled trials with a long duration of follow-up include thiazide diuretics, allopurinol, potassium citrate, and potassium-magnesium citrate.

a. **Hypercalciuria** is managed initially with thiazide diuretics. Thiazides act directly to increase distal calcium reabsorption and indirectly to increase calcium reabsorption in the proximal tubule by inducing a state of mild volume contraction. Volume contraction must be maintained and hypokalemia avoided for thiazide diuretics to remain maximally effective. Thiazides generally reduce urinary calcium by approximately 50%. The doses used in studies that show an effect are high (25 mg of hydrochlorothiazide twice a day, 25 to 50 mg of chlorthalidone once a day, or 2.5 mg of indapamide per day). If they are ineffective, noncompliance with the low-sodium diet is usually the reason. This can be monitored with a 24-hour urine for sodium. Amiloride acts independently of thiazides at a more distal site and can be added if required. Four randomized controlled trials in recurrent calcium oxalate stone formers demonstrated a reduction in new stone formation risk with thiazide diuretics. Although all patients in these trials were calcium oxalate stone formers, the minority were actually hypercalciuric. This suggests that thiazides may have additional effects beyond reducing urinary calcium or that the reduction of urinary calcium, even in the absence of hypercalciuria, may reduce the risk of recurrent kidney stone formation. Some have argued that the effect of thiazide diuretics may diminish with time, but this does not appear to be the case.

   In patients who cannot tolerate thiazide diuretics, other potential therapies include sodium cellulose phosphate and orthophosphate. These are often poorly tolerated. Slow-release neutral phosphate appears to be better tolerated and may become the second-line agent of choice. Randomized controlled trials of potassium acid phosphate and magnesium hydroxide showed no benefit when compared with placebo.

b. **Hypocitraturia** is managed with potassium citrate or potassium-magnesium citrate. Each of these agents reduced the relative risk of stone formation in randomized controlled trials. Potassium-magnesium citrate may be especially beneficial in patients receiving thiazide diuretics, because potassium and magnesium losses induced by the diuretic are repleted. Patients with struvite-carbonate stones should not be given citrate, because it may increase deposition of magnesium ammonium phosphate and carbonate apatite. Citrate may also increase intestinal aluminum absorption in patients with CKD. Currently, potassium-magnesium citrate is not clinically available. Citrate preparations are often difficult for patients to tolerate secondary to diarrhea. Slow-release preparations such as Urocit-K are well tolerated but are relatively expensive. In patients with urinary citrate levels less than 150 mg/24 hours, 60 mEq of citrate should be

administered daily in divided doses with meals. If urinary citrate is greater than 150 mg/24 hours, the dose is 30 mEq/day.

c. **Hyperuricosuria** is probably best managed with allopurinol. Whether alkalinization is of benefit is unclear, because "salting out" can also be initiated by sodium urate. Citrate may reduce calcium oxalate precipitation in this setting, but this remains to be proved.

d. **Hyperoxaluria** is managed with a low-oxalate diet. Enteric hyperoxaluria should be initially treated with a low-fat, low-oxalate diet. If this is unsuccessful, calcium carbonate, cholestyramine, or both can be added. It remains to be determined if enteral administration of oxalate-degrading bacterium *O. formigenes* is safe and effective in reducing urinary oxalate excretion.

e. **Urinary volume** should be increased to at least 2 L/day. This is best accomplished by drinking water, which is the only liquid shown to reduce stone formation rate in randomized controlled clinical trials. A recent study suggests that even in patients with a substantial genetic susceptibility for developing nephrolithiasis, coffee, milk, and perhaps tea might also be protective against stone formation.

This approach, directed at both specific and nonspecific risk factor reduction, was shown to decrease frequency of recurrent stone formation and reduce the number of cystoscopies, surgeries, and hospitalizations.

f. **Calcium phosphate stones** remain a controversial area with respect to therapy. All randomized controlled trials to date have enrolled patients with either pure calcium oxalate stones or those containing calcium oxalate and a small percentage of calcium phosphate ($<$20%). Thus, there is little evidence to guide therapy. Stones that are predominantly calcium phosphate ($\geq$60% calcium phosphate salt—usually either brushite or apatite) may be increasing in frequency over the last several decades. Lowering urinary calcium and increasing fluid ingestion seem prudent and are likely beneficial. However, use of potassium citrate which can raise urinary pH may be harmful, given that rises in urinary pH are associated with increases in calcium phosphate supersaturation. Whether the deleterious effects of rising urinary pH on supersaturation would win out over the benefits of increased urinary citrate concentration on reducing calcium phosphate supersaturation, as well as crystal aggregation and agglomeration, is difficult to predict. In this situation, it may be prudent to employ citric acid, which can raise urinary citrate concentration without increasing urinary pH (citric acid is acid–base neutral while metabolism of potassium citrate generates three bicarbonates).

B. **Uric Acid Stones.** Therapy for uric acid stones is directed at the three major risk factors (decreased urine pH, decreased urine volume, and hyperuricosuria). First, urine volume should be increased to 2 to 3 L/day. Second, urine should be alkalinized to a pH of 6.5 using potassium citrate. The starting dose is 20 to 30 mEq twice daily to be titrated upward according to urinary pH. More than 80 to 100 mEq is rarely required. Sodium alkali therapy should be avoided, because it may result in hypercalciuria. In one study of 12 patients, alkali therapy resulted in a dissolution of stones

within a period of 3 weeks to 5 months. Increases in urinary pH above 6.5 should be avoided because of the increased risk of calcium phosphate stone formation at high urinary pH. If first morning void urine remains acidic, acetazolamide (250 mg) can be added at bedtime.

If hyperuricosuria is present, dietary purine consumption should be reduced. Allopurinol should only be used when stones recur despite fluid and alkali administration, or if uric acid excretion is above 1,000 mg/day. When allopurinol is administered for massive uric acid overproduction, adequate hydration must be maintained to avoid the precipitation of xanthine crystals.

C. Struvite-Carbonate Stones. Open surgical removal was formerly the treatment of choice for staghorn struvite-carbonate calculi. The recurrence rate, however, 6 years after surgery is 27%, and UTI persists in 41%. A second pyelolithotomy carries substantial morbidity. More recently, the combination of percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy has decreased morbidity substantially and is now the treatment modality of choice. Total stone elimination remains a challenge, because of the inability to remove small, bacteria-containing particles that act as nidi for further crystal growth. After complete removal, chronic culture-specific antimicrobial agents are indicated as prophylaxis against recurrent infection. If a struvite-carbonate stone is not removed in its entirety, the patient will continue to have recurrent UTI, and the stone will regrow. Stone growth in most patients with residual fragments progresses despite antibiotic treatment. It can be slowed by reducing the bacterial population, but cure with antibiotics alone is remote. Urease inhibitors, such as acetohydroxamic acid, reduce urinary saturation of struvite-carbonate and prevent stone growth and may, on occasion, cause dissolution of existing stones. These agents, however, are associated with a variety of severe complications including hemolytic anemia, thrombophlebitis, and nonspecific neurologic symptoms (e.g., disorientation, tremor, and headache) and are best avoided if possible. Acetohydroxamic acid is also renally excreted and should not be used in those with a creatinine clearance less than 40 mL/min.

D. Cystine Stones. Water is the hallmark of cystinuria treatment. The required dose is based on the patient's urinary cystine excretion. A urine output of at least 4 L/day is often required to reduce recurrent stone formation in patients with severe cystinuria. Two 8-oz glasses of water should be ingested every 4 hours. When patients void during the night, they should drink two glasses of water. Urine can be periodically examined for cystine crystals to assess adequacy of fluid intake. Caution should be exercised in interpreting urinary cystine concentrations in treated patients. Cystine excretion may be underestimated due to precipitation in the sample. In addition, many cystine assays employ steps that disrupt cysteine–thiol bonds releasing cysteine bound to therapeutic agents, discussed further in the following text, such as D-penicillamine or α-mercaptopropionylglycine (tiopronin). The released cysteine can dimerize and form cystine, overestimating the amount of free cystine in the urine. These therapeutic agents can also interfere with cystine assays because they contain an active thiol group. Cystine excretion is related to sodium intake and some advocate salt restriction to reduce

urinary cystine excretion. In addition, methionine is a substrate for cystine production and fish, red meat, poultry, and dairy products are rich sources of methionine.

Urinary alkalinization may be of some benefit. The dissociation constant of cystine is 6.5. As a result, a pH of 7.5 is required for 90% of cystine to exist in the ionized form. At this pH, calcium phosphate stone formation risk is increased. As a result, alkalinization should be viewed as an ancillary measure. The goal should be to keep monitored urinary pH in the 6.5 to 7.0 range. Potassium citrate is the agent of choice and is preferable to sodium-containing alkali because ECF volume expansion increases cystine excretion.

If these measures are ineffective, then either D-penicillamine or tiopronin can be tried. These compounds are thiols that bind preferentially to cysteine, forming compounds that are more soluble than cysteine–cysteine dimers (cystine). Tiopronin causes fewer complications than D-penicillamine and is preferred. D-Penicillamine also binds pyridoxine, and therefore pyridoxine (50 mg/day) should be administered to prevent deficiency. Zinc supplements can usually prevent the anosmia and loss of taste that often occurs with D-penicillamine. Captopril although initially reported to be of benefit has more recently fallen out of favor.

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7 The Patient with Urinary Tract Infection

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Urinary tract infections (UTIs) are some of the most common infections experienced by humans, exceeded in frequency among ambulatory patients only by respiratory and gastrointestinal infections. Over 8 million episodes of acute cystitis occur annually in the United States. Bacterial infections of the urinary tract are the most common cause of both community-acquired and nosocomial infections for patients admitted to hospitals in the United States.

The prognosis and management of UTIs depend on the site of infection and any predisposing factors.

I. DEFINITIONS.

Some definitions are necessary because infection of the urinary tract may result from microbial invasion of any of the tissues extending from the urethral orifice to the renal cortex. Although the infection and resultant symptoms may be localized at one site, the presence of bacteria in the urine (bacteriuria) places the entire urinary system at risk for invasion by bacteria.

A. **Significant bacteriuria** is defined as the presence of 100,000 or more colony-forming units (CFUs) of bacteria per milliliter of urine, although smaller colony counts can be of diagnostic importance, particularly in young women, where 1,000 bacteria per CFU may be associated with cystitis or acute urethral syndrome.

B. **Anatomic Location.** The first useful distinction is between upper (kidney) and lower (bladder, prostate, and urethra) UTIs. Infections confined to the bladder (cystitis), the urethra (urethritis), and the prostate (prostatitis) commonly cause dysuria, frequency, and urgency. Pyelonephritis is the nonspecific inflammation of the renal parenchyma; acute bacterial pyelonephritis is a clinical syndrome characterized by chills and fever, flank pain, and constitutional symptoms caused by the bacterial invasion of the kidney. Chronic pyelonephritis has a histopathology that is similar to tubulointerstitial nephritis, a renal disease caused by a variety of disorders such as chronic obstructive uropathy, vesical ureteral reflux (reflux nephropathy), renal medullary disease, drugs and toxins, and possibly chronic or recurring renal bacteriuria.

C. **Recurrence of UTI** is the result of either relapse or reinfection; making this distinction is clinically important. Recurrent UTI is defined as two uncomplicated infections within 6 months or three infections within a year and are often considered reinfections. Most recurring episodes of cystourethritis are due to reinfection. While the pathogenesis of recurrent UTIs is classically attributed to different pathogens, recent studies indicate that over 50% of recurrent infections occur with genetically identical pathogens and is usually drug susceptible. Relapse is a return of infection due to the same

microorganism, is often drug resistant, and may require further urologic evaluation, longer treatment courses, and potential surgical intervention. Most relapses occur after treatment of acute pyelonephritis or prostatitis. Finally, asymptomatic bacteriuria is an important clue to the presence of parenchymal infection somewhere in the urinary tract; however, the importance of the infection and the need for treatment depend on the age, sex, and underlying condition of the patient.

D. Complicated and Uncomplicated UTIs. For the clinician, another important distinction is made between uncomplicated and complicated infections. An uncomplicated infection is an episode of cystourethritis following bacterial colonization of the urethral and bladder mucosae in the absence of upper tract disease. This type of infection is considered *uncomplicated* because sequelae are rare and exclusively due to the morbidity associated with reinfections in a subset of women. Complicated UTIs increase the risk of potentially life-threatening infectious sequelae such as bacteremia and sepsis or treatment failure. Complicated UTIs may occur with pregnancy, diabetes, immunosuppression, structural abnormalities of the urinary tract, symptoms lasting for more than 2 weeks, and previous pyelonephritis. Young women constitute a subset of patients with pyelonephritis (acute uncomplicated pyelonephritis) who often respond well to therapy and may also have a low incidence of sequelae. In contrast, complicated infections include those involving parenchyma (pyelonephritis or prostatitis) and frequently occur in the setting of obstructive uropathy or after instrumentation. Episodes may be refractory to therapy, often resulting in relapses, and occasionally leading to significant sequelae such as sepsis, metastatic abscesses, and, rarely, acute renal failure.

E. Several authors have proposed a **clinical classification** for the practicing clinician.

1. **Asymptomatic Bacteriuria**
2. **Acute Uncomplicated Cystitis in Women**
3. **Recurrent Infections in Women**
4. **Acute Uncomplicated Pyelonephritis in Women**
5. **Complicated UTIs in Both Sexes**
6. **Catheter-Associated UTIs**

II. RISK FACTORS AND PATHOGENESIS.

Early recognition and possible prevention depend on an understanding of the pathogenesis and epidemiology of UTIs. Figure 7-1 shows the major risk periods of life for symptomatic UTIs; the increasing prevalence of asymptomatic bacteriuria that accompanies aging is apparent. Much has been learned about the risk factors for UTIs. Associations have been established between UTI and age; pregnancy; sexual intercourse; use of diaphragms, condoms, and spermicides, particularly Nonoxynol-9; delayed postcoital micturition; menopause; and a history of recent UTI. Factors that do not seem to increase the risk include diet, use of tampons, clothing, and personal hygiene, including directions of cleansing after defecation and bathing practices. Studies on pathogenesis have elucidated specific interactions between the host and microbes that are causally related to bacteriuria. Bacteria in the

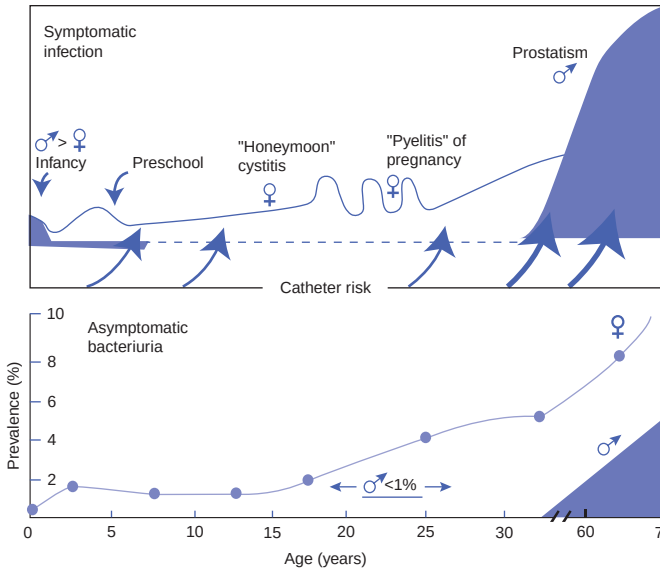

Figure 7-1. Frequency distribution of symptomatic urinary tract infections and prevalence of asymptomatic bacteriuria by age and sex (male, *shaded area;* female, *line*). (Modified from Jawetz's original concept. From Kunin CM. *Detection, prevention and management of urinary tract infections,* 4th ed. Philadelphia, PA: Lea & Febiger, 1987. Reprinted with permission.)

enteric flora periodically gain access to the genitourinary tract. How such bacteria actually migrate from the gastrointestinal tract to the periurethra is not known; close proximity of the anus in women is a likely factor. The subsequent bacterial colonization of uroepithelial cells is the biological phenomenon that sets the stage for persistent bacteriuria. The colonization of the periurethra often precedes the onset of bladder bacteriuria. P-fimbriated strains of *Escherichia coli* adhere to uroepithelial cells, in which glycolipids function as receptors in women who secrete blood group antigens. *E. coli* that encode for the type 1 pilus, which contains the adhesin FimH, recognizes multiple cell types associated with cystitis, sepsis, and meningitis. Immunocompromised patients may become infected with less virulent *E. coli* strains. Opposing colonization are several host factors, most notably acid pH, normal vaginal flora, and type-specific cervicovaginal antibodies.

After periurethral colonization, uropathogens gain access to the bladder through the urethra, to the kidneys through the ureters, and to the prostate through the ejaculatory ducts. The urethra and ureterovesical junction are mechanical barriers that prevent ascension. Besides instrumentation and mechanical obstruction, however, factors promoting ascent of bacteria are not as well understood. In the bladder, organisms multiply, colonize the bladder mucosa, and invade the mucosal surface. Although urine adequately supports the growth of most uropathogens, the bladder has several mechanisms that prevent bacteriuria: (a) a mucopolysaccharide (urine slime) layer covers the bladder

epithelium and prevents colonization; (b) Tamm–Horsfall protein, which is a component of uromucoid, adheres to P fimbriae and prevents colonization; and (c) urine flow and bladder contraction serve to prevent stasis and colonization. Bladder bacteriuria sets the stage for subsequent migration to the kidneys, where organisms such as P-fimbriated *E. coli* adhere to renal tubular cells. In fact, outside the setting of obstructive nephropathy, this strain of *E. coli* is the most common cause of pyelonephritis. With obstruction, however, bacterial adherence is ostensibly unimportant. Other host factors that prevent a renal infection are a high urine osmolality, high ammonium concentration, phagocytes, and increased urine flow rate.

In the presence of a urethral catheter, defense mechanisms against bacterial–epithelial cell interactions are impaired both by disruption of the protective glycosaminoglycan layer of the bladder and by the formation of biofilm on the catheter. Microorganisms in the biofilm are protected from antibiotics, host defenses, and mechanical flushing. Effective therapy ultimately requires removal of the catheter.

Pathogens colonizing indwelling urinary catheters often have reduced virulence, for example, *E. coli* strains lacking P fimbriation, which accounts for the low incidence of febrile UTIs and bacteremia.

Chronic urinary catheters are associated with lower tract obstruction due to catheter blockage with encrustation and urinary tract stones and may be complicated by scrotal abscesses, epididymitis, and prostatitis. The incidence of bladder cancer may be increased with prolonged catheter use that exceeds 10 years as in patients with spinal cord injuries.

III. CLINICAL SETTING

A. **Asymptomatic bacteriuria** is especially common in women, as evidenced by a minimum prevalence of 2% to 4% in young and 10% in elderly women and a three to four times higher prevalence of asymptomatic bacteriuria in diabetic women compared with their nondiabetic counterparts. The higher incidence of asymptomatic bacteriuria in diabetic women is attributed to lower urinary cytokine and leukocyte concentrations and enhanced adherence to uroepithelial cells of *E. coli* that express type 1 fimbriae.

The cumulative prevalence of asymptomatic bacteriuria in women increases approximately 1% per decade throughout life. Of note, this phenomenon has been observed in different ethnic groups and geographic locations. In contrast to women, the occurrence of asymptomatic bacteriuria in men is rare until after the age of 60 years, at which time the prevalence increases per decade and often approaches the rate in elderly women. For example, in noncatheterized, institutionalized elderly men, the prevalence of bacteriuria exceeds 20%. Prostatic hypertrophy and increased likelihood of instrumentation are thought to account for the bacteriuria of older men. Moreover, differences between men and women in the rates of bacteriuria have been attributed to the shorter female urethra and its proximity to the vaginal and rectal mucosae and the abundant microbial flora of these areas. Screening for and treatment of asymptomatic bacteriuria is not warranted unless the patient is at high risk for serious complications (e.g., pregnant women and patients undergoing urologic surgery).

Patients in long-term care facilities have an increased risk of asymptomatic bacteriuria as do patients with spinal cord injuries owing to

intermittent catheters, sphincterotomies, or condom catheters. Bacteriuria related to indwelling catheters increases at a rate of 3% to 10% per day and is predominantly asymptomatic. In the absence of UTI symptoms, a positive urine culture for 10^5 CFU/mL of bacteria is consistent with asymptomatic catheter-associated bacteriuria. Asymptomatic catheter-associated candiduria is defined as 10^3 per mL of yeast. The incidence of significant morbidity with asymptomatic bacteriuria and candiduria is low, and antimicrobial therapy is not recommended while the catheter is present.

B. **Symptomatic UTIs** occur in all age groups. Among newborns and infants, boys are affected more often than girls. When the urinary tract is the source of neonatal sepsis, serious underlying congenital anomalies are frequently present. During childhood, persistent bacteriuria, with or without repeated symptomatic episodes, occurs in a small group (less than 2%) of school-aged girls. Such girls, and also school-aged boys with bacteriuria, should have a urologic evaluation to detect correctable structural abnormalities when UTIs are documented. Sexually active women have a markedly increased risk of episodes of cystitis. *E. coli* is the predominant organism in 75% to 90% of cases, whereas *Staphylococcus saprophyticus* is found in 5% to 15%, primarily in young women. The remainder of cases are due to *enterococci* and aerobic gram-negative rods, such as *Klebsiella* species and *Proteus mirabilis*.

In the absence of prostatitis, bacteriuria and symptomatic UTIs are unusual in men. In fact, asymptomatic prostatitis is very common in men presenting with febrile UTIs. More recently, uropathogenic strains of *E. coli* have been recognized as causes of cystitis in young men at risk because of homosexuality and anal intercourse, lack of circumcision, or having a partner with vaginal colonization with such P-fimbriated *E. coli*. At any age, both sexes may develop symptomatic infections in the presence of risk factors that alter urinary flow. *Mycoplasma hominis* has been well recognized as a sexually transmitted infection and cause of bacterial vaginosis in females and nongonococcal urethritis in males. *Ureaplasma urealyticum* is a cause of nongonococcal urethritis and chronic prostatitis and can be isolated from expressed prostatic secretions and urine voided after prostatic massage.

1. **Obstruction to Urine Flow**
   a. **Congenital Anomalies**
   b. **Renal Calculi**
   c. **Ureteral Occlusion (Partial or Total)**
2. **Vesicoureteral Reflux**
3. **Residual Urine in Bladder**
   a. **Neurogenic Bladder**
   b. **Urethral Stricture**
   c. **Prostatic Hypertrophy**
4. **Instrumentation of Urinary Tract**
   a. **Indwelling Urinary Catheter**
   b. **Catheterization**
   c. **Urethral Dilation**
   d. **Cystoscopy**

IV. CLINICAL FEATURES

A. Acute Urethral Syndrome. The cardinal symptoms of frequency and dysuria occur in more than 90% of ambulatory patients with acute genitourinary tract infections. One-third to one-half of all patients with frequency and dysuria, however, do not have significant bacteriuria, although most have pyuria. These patients have acute urethral syndrome, which can mimic both bladder and renal infections. Vaginitis, urethritis, and prostatitis are common causes of acute urethral syndrome. Although certain signs and symptoms help to differentiate these clinical entities, a classic UTI can be definitively diagnosed only by quantitative cultures of urine.

1. **Vaginitis.** Approximately 20% of women in the United States have an episode of dysuria each year, and one-half of these seek medical care. The presence of an abnormal vaginal discharge (leukorrhea) and irritation make vaginitis the likely cause of dysuria, unless a concomitant UTI can be confirmed by culture. *Candida albicans*, the most common specific cause of vaginitis, can be demonstrated readily by culture or by finding yeast cells in a Gram-stained smear of vaginal secretions or in a saline preparation with potassium hydroxide added. Trichomoniasis can be documented with a saline preparation that shows the motile protozoa of *Trichomonas vaginalis*. Nonspecific vaginitis most often is associated with *Gardnerella vaginalis*. A clue to this diagnosis is the presence of many small gram-negative bacilli that adhere to vaginal epithelial cells.
2. **Urethritis.** Acute urinary frequency, dysuria, and pyuria in the absence of vaginal symptoms favor a diagnosis of urethritis or UTI rather than vaginitis. *Chlamydia trachomatis* is a common cause of the acute urethral syndrome in women, as well as nonspecific urethritis in men. *Neisseria gonorrhoeae* is also a widespread cause of urethritis and dysuria. The diagnosis and treatment of gonorrhea are now well standardized. Low colony count (100 to 1,000 CFU) infections with coliforms are now a recognized cause of urethritis in symptomatic young women with pyuria. Herpes simplex virus, usually type 2, is another sexually transmitted agent that can cause severe dysuria through ulcerations in close proximity to the urethral orifice. The diagnosis of herpes progenitalis can be confirmed by finding giant multinucleated transformed cells in epidermal scrapings stained with Wright's stain (Tzanck smear), by isolating the virus in tissue culture, or by direct fluorescent antibody test.
3. **Prostatitis**. Prostatitis is a common affliction in men that causes dysuria and urinary frequency in middle-aged and younger men more frequently than UTIs do. In addition, more than 90% of men with febrile UTIs have asymptomatic prostatitis manifested by elevated prostate-specific antigens (PSAs) and prostate volume. The PSA may remain elevated for up to 12 months. Prostate syndromes have classically been divided into four clinical entities: (a) acute bacterial prostatitis, (b) chronic bacterial prostatitis, (c) nonbacterial prostatitis, and (d) prostatodynia.
   a. **Acute bacterial prostatitis** is easily distinguished from the other prostatitis syndromes by its acute characteristics. The patient often appears acutely ill, with the sudden onset of chills and fever, urinary frequency and urgency, dysuria, perineal and low back pain, and constitutional symptoms. Rectal examination should not be performed

because of the risk of precipitating sepsis, but it may disclose an exquisitely tender, hot, and swollen prostate gland. Microscopic examination of the urine usually displays numerous white blood cells. Urine culture is usually positive for enteric gram-negative bacteria (especially *E. coli*); gram-positive bacteria (*staphylococci* and *enterococci*) are less frequently isolated.

b. Chronic Bacterial Prostatitis. A hallmark of chronic prostatitis is relapsing UTIs. Urinary frequency, dysuria, nocturia, and low back and perineal pain are the usual symptoms, although patients may have a minimum of symptoms between UTIs. The patient is often afebrile, does not appear acutely ill, and may have an unremarkable prostate examination. A proposed mechanism to explain the migration of bacteria into the prostate is by reflux of urine and bacteria into the prostatic ducts from the urethra. This syndrome is distinguished from other forms of chronic prostatitis by displaying an initial negative midstream urine examination and culture; after prostate massage, however, the urine displays a positive microscopic examination for white blood cells, and a uropathogen can be cultured (see Section V). Nonbacterial prostatitis is the most common form of chronic prostatitis. It mimics chronic bacterial prostatitis clinically and displays inflammatory cells on post-prostate massage specimens. However, bacteriologic cultures of urine and prostatic secretions are sterile. The etiology is unknown, but some evidence exists for an infectious etiology involving organisms that are difficult to culture.

c. Prostatodynia has also been referred to as *chronic noninflammatory prostatitis*. Clinically, it presents with symptoms similar to other forms of chronic prostatitis. It is distinguished by the absence of inflammatory cells or uropathogens from all specimens.

B. UTIs. Despite the mimicking syndromes, a presumptive diagnosis of infections of the urinary tract can be established economically by analyzing urine in patients with characteristic, albeit nonspecific, signs and symptoms. Acute uncomplicated UTIs occur mainly in women of childbearing age. The presenting features are only suggestive of the site of infection. Patients with bacterial cystourethritis, as distinct from urethritis caused by a sexually transmitted disease (STD) pathogen, will have had prior episodes, will have experienced symptoms for less than 1 week, and will experience suprapubic pain.

V. LABORATORY DIAGNOSIS

A. Urine Specimens for Culture

1. Indications. The diagnosis of UTI, from simple cystitis to complicated pyelonephritis with sepsis, can be established with absolute certainty only by quantitative cultures of urine. The major indications for urine cultures are as follows:

a. Patients with Symptoms or Signs of UTIs
b. Follow-Up of Recently Treated UTI
c. Removal of Indwelling Urinary Catheter
d. Screening for Asymptomatic Bacteriuria during Pregnancy
e. Patients with Obstructive Uropathy and Stasis Before Instrumentation

2. When universally applied, the first two indications may not be the most cost-effective approach to diagnosing UTIs in nonpregnant, young adult women. These individuals present with dysuria, urgency, and pyuria due to an uncomplicated episode of cystourethritis, with organisms usually susceptible to a variety of antimicrobial agents, or due to an STD pathogen such as *gonococcus* or *chlamydia*. Moreover, because the beneficial outcome of therapy is to minimize morbidity rather than prevent life-threatening complications, laboratory costs and use of resources can be minimized if pretreatment cultures are not ordered in this clinical setting. Therefore, women with symptoms consistent with simple uncomplicated lower tract disease and a positive urine dipstick can be treated without obtaining a urine culture. Additionally, if symptoms completely resolve, posttreatment cultures are also unnecessary for patients with uncomplicated infections.
3. **Methods.** Urine specimens must be cultured promptly within 2 hours or be preserved by refrigeration or a suitable chemical additive (e.g., boric acid sodium formate preservative). Acceptable methods of collection are the following:
   a. **Midstream urine voided into a sterile container after careful washing (water or saline) of external genitalia (any soap must be rinsed away)**
   b. **Urine obtained by single catheterization or suprapubic needle aspiration of the bladder**
   c. **Sterile needle aspiration of urine from the tube of a closed catheter drainage system (do not disconnect tubing to get specimen)**
4. Not acceptable, because of constant contamination and the impossibility of quantitative counts, are tips from indwelling urinary catheters and urine obtained randomly, without adequate patient preparation. The clean-voided, midstream technique of collection is preferred whenever possible to avoid the risk of introducing infection at the time of catheterization, a hazard in elderly patients confined to bed, in men with condom catheters, and in diabetic patients with dysfunctional bladders. Because contamination is exceedingly rare in circumcised men, a clean-catch, midstream specimen is unnecessary in such patients. Occasionally, suprapubic aspiration of the bladder is necessary to verify infection. This technique has been most helpful in obtaining specimens from possibly septic infants and from adults in whom repeated clean-voided specimens have yielded equivocal colony counts on culture.
5. **The usual microbial pathogens** isolated from patients with UTIs are listed in Table 7-1. Results of cultures highly depend, however, on the clinical setting in which bacteriuria occurs. For example, *E. coli* is found in the urine of 80% to 90% of patients with acute uncomplicated cystitis and acute uncomplicated pyelonephritis. *S. saprophyticus* is another common cause of UTI, but rarely causes acute pyelonephritis. Many patients with staghorn calculi of the kidneys harbor urea-splitting *Proteus* organisms in their urine. *Klebsiella*, *Pseudomonas aeruginosa*, and *Enterobacter* infections are commonly acquired in the hospital. The presence of *Staphylococcus aureus* in the urine most often is a clue to concomitant staphylococcal bacteremia, unless an underlying risk factor exists.

Table 7-1. Microbial Pathogens of Kidney and Bladder

Organism	Uncomplicated Cystitis: Young Women[a] (%)	Pyelonephritis: Outpatient, Women[b] (%)	UTI: Men[c] (%)	Bacteremic UTIs[d] (%)	Nosocomial UTIs[e] (%)
Gram-Negative Bacteria					
Escherichia coli	79	86	41	54	29
Klebsiella pneumoniae	3	4	3	9	8
Proteus	2	3	6	8	4
Enterobacter	0	0	1	2	4
Pseudomonas aeruginosa	0	0	NS	3	9
Gram-Positive Bacteria					
Staphylococcus saprophyticus	11	3	NS	0	0
Staphylococcus aureus	0	1	1	13	
Staphylococcus nonaureus	0	0	5	1	5
Enterococci	2	0	5	6	13
Other Bacteria	0	4	19	4	15
Mixed Infections	3	3	18	2	NS
Yeast	0	0	0	3	13

NS, not stated; UTI, urinary tract infection.
[a]Data from 607 episodes of cystitis; from Stamm WE. Urinary tract infections. In: Root RK, ed. *Clinical infectious diseases: a practical approach*, 1st ed. New York: Oxford University Press, 1999.
[b]Eighty-four episodes from Stamm 1992 and 54 nonhospitalized women; from Pinson AG, Philbrock JT, Lindbeck GH, Schorling JB, eds. Management of acute pyelonephritis in women: a cohort study. *Am J Emerg Med* 1994;12:271–278.
[c]Data from 223 outpatient males with symptoms; from Pead L, Maskell R. Urinary tract infections in adult men. *J Infect* 1981;3:71–78.
[d]185 cases (excluding five cases of *Candida albicans*); from Ackermann RJ, Monroe PW. Bacteremic urinary tract infections in older people. *J Am Geriatr Soc* 1996;44:927–933.
[e]90% catheter-associated infections, 1991 experience at the University of Iowa (900-bed hospital); from Bronsema DA, Adams JR, Pallares R, Wenzel RP. Secular trends in rates and etiology of nosocomial urinary tract infections at a university hospital. *J Urol* 1993;150:414–416.

Microorganisms in young men are similar to the organisms that cause uncomplicated infections in women. *Enterococci* and coagulase-negative *staphylococci* are more common in elderly men, most likely representing recent instrumentation or catheterization. *C. albicans* is rarely encountered, except in patients with indwelling catheters, nosocomial UTIs, or relapsing infections after multiple courses of antibiotic therapy. Most urinary catheter-related infections originate from the patient's colonic flora with long-term catheterization exceeding 28 days. Multidrug-resistant organisms such as *Providencia stuartii*, *Pseudomonas* spp., *Proteus* spp., *Morganella* spp., and *Acinetobacter* spp. are found more frequently owing to antibiotic exposure. In addition, polymicrobial bacteriuria is found in up to 95% of urine cultures from patients with long-term catheter use. Although the likely microorganism and usual susceptibility patterns are sufficient to guide the initial empiric therapy of uncomplicated cystitis, adequate treatment of acute bacterial pyelonephritis and complicated UTIs necessitates precise therapy based on isolation of the causative bacterium and standardized antimicrobial susceptibility testing using the disk-diffusion or the broth-dilution or agar-dilution methods.

B. Interpretation of Urine Cultures. Organisms residing in the distal urethra and on pubic hairs contaminate voided, clean-catch specimens. This bacterial contamination must be distinguished from "true infection" or "significant bacteriuria" in urine cultures. Quantitative bacteriology makes this distinction. Because quantitation of bacteriuria is so important clinically, methods for culture of urine must enable the CFU number of a potential pathogen per milliliter of urine to be assessed. The standard procedure involves the use of calibrated bacteriologic loops that deliver a known volume of urine to the surface of agar plates. Proper plating techniques achieve isolated colonies that can be enumerated accurately. A satisfactory alternative for the diagnosis of uncomplicated UTIs is the dip slide method, which is particularly well suited to quantitative urine cultures in smaller clinics. Rapid methods based on filtration and colorimetry, bioluminescence, growth kinetics, and biochemical reactions are used increasingly to screen urine specimens for the presence of bacteria. The sensitivities of these rapid assays are in the range of 10^4 to 10^5 CFU/mL. The simplest screen is the paper-strip test for detection of leukocyte esterase and nitrite in first morning urine specimens. However, these methods are not a substitute for standard cultures in symptomatic patients with complicated UTIs.

1. **Colony Counts.** Figure 7-2 shows a basic guide to the interpretation of quantitative cultures of urine. Colony counts greater than 10^5 CFU/mL in properly collected and transported specimens usually indicate infection. Colony counts of 10^3 or fewer CFU/mL from untreated patients are uncommon with true UTIs, except in symptomatic young women with pyuria and urethritis, in whom colony counts of *E. coli* as low as 10^3 may be interpretable if the urine was obtained by single catheterization. Intermediate counts, especially with mixed flora, usually imply poor collection or delayed transport and culture. Brisk diuresis may transiently reduce an otherwise high colony count.
2. **Suprapubic Needle Aspiration.** Any growth from urine obtained by suprapubic needle aspiration may be important. Use of a 0.01 mL

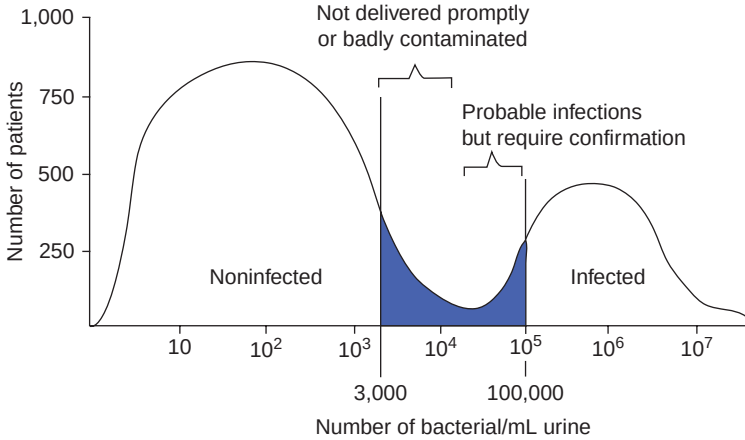

Figure 7-2. Results of quantitative bacterial counts from cultures of urine specimens. (From Brumfitt W, Percival A. Pathogenesis and laboratory diagnosis of nontuberculous urinary tract infection: a review. *J Clin Pathol* 1964;17:482. Reprinted with permission.)

quantitative loop for culturing aspirated urine permits the detection of as few as 100 CFU/mL. Two or more colonies (≤200 CFU/mL) of the same microorganism ensure the purity of growth from such specimens and permit standardized antimicrobial susceptibility testing. Similar criteria should be used for patients who are receiving antimicrobials at the time of culture. Except in unusual circumstances, the isolation of diphtheroids, α-hemolytic *streptococci*, and *lactobacilli* indicates contamination of the urine specimen with vaginal or periurethral flora.

3. **Prostatic Secretions.** In men, the distinction between a urinary source and a prostatic focus of infection must be made. The procedure for obtaining voided urine and expressed prostatic secretions in partitioned segments that enable proper interpretation is diagrammed in Figure 7-3. Leukocytes (greater than 10 to 15 white blood cells per high-power field) and lipid-laden macrophages are seldom observed in the expressed prostatic secretion of healthy men. These agents signify prostatic inflammation. Therefore, a prostatic focus of infection should be considered when a significant step-up of pyuria or colony counts occurs in the prostate specimens. A UTI of prostatic origin is indicated by colony counts of 10^5 or more CFU/mL of the same microorganism in all four specimens. Both urologists and primary care physicians underuse this procedure. In one study, a two-step procedure involving microscopic examination and culture of pre- and post-prostate massage urine specimens compared favorably to this four-step procedure. This simplified approach was able to arrive at a similar diagnosis in 91% of patients. Further trials are needed to evaluate this approach, which may improve physician use.

C. Microscopic Examination of Urine. Procedures for the microscopic examination of urine are poorly standardized; nonetheless, visualization of

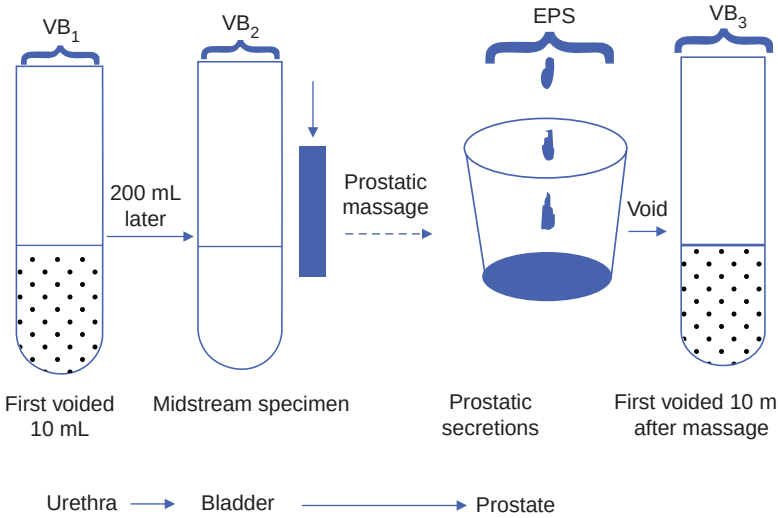

Figure 7-3. Localization of infection with segmented cultures of the lower urinary tract in men. VB_1 is the first 10 mL of voided urine, and VB_2 is the midstream specimen of urine obtained before prostatic massage. Subsequently, the expressed prostatic secretions (EPS) are collected before the final voided urine specimen (VB_3). When the bacterial colony counts in the urethral culture exceed by 10-fold or more those of the midstream and prostatic cultures, the urethra is the source of the infection. The diagnosis is bacterial prostatitis if the quantitative counts of the prostatic specimens exceed those of the urethral and midstream samples. (From Meares EM, Stamey TA. Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol* 1968;5:492. Reprinted with permission.)

bacteria, leukocytes, and epithelial cells in urine can provide some useful information and enable the clinician to make a presumptive diagnosis of UTI. The advantages of microscopic analysis are immediate availability and low cost. The disadvantages, depending on the method, are lack of sensitivity, specificity, or both. Only properly collected and processed specimens for quantitative urine cultures can provide definitive diagnosis. The microscopic examination can be done on either unspun urine or the centrifuged sediment. A critical comparison of these two techniques is not available. The presence of squamous epithelial cells and mixed bacterial flora indicates contamination and the need for a repeat specimen.

1. **Unspun Urine.** When fresh, unspun urine from patients with significant bacteriuria (greater than 10^5 CFU/mL) is examined microscopically (×1,000), 90% of specimens show one or more bacteria, and 75% of specimens show one or more white blood cells per oil-immersion field. The best assessment of pyuria is the finding of approximately 10 white blood cells per mm^3 of unspun urine examined in a counting chamber.
2. **Centrifuged Sediment.** After 10 mL of urine is centrifuged in a standard 15-mL conical tube for 5 minutes at 2,500 revolutions/minute in a clinical centrifuge, three or four drops of the sediment are examined

under a coverslip at high power (×400) in diminished light. Patients with significant bacteriuria usually show bacilli in the urinary sediment, whereas only approximately 10% of patients with fewer than 10^5 CFU/mL show bacteria. Approximately 60% to 85% of patients with significant bacteriuria have 10 or more white blood cells per high-power field in the sediment of midstream voided urine; however, approximately 25% of patients with negative urine cultures also have pyuria (10 or more white blood cells per high-power field), and only approximately 40% of patients with pyuria have 10^5 or more bacteria per mL of urine by quantitative culture. The principal pitfall is false-positive pyuria owing to leukocytes from a contaminating vaginal discharge.

3. **Gram's Stain.** A simple Gram-stained smear of unspun urine or spun sediment can enhance the specificity of the test, because morphology and stain characteristics aid in identifying the likely pathogen and in targeting empiric therapy.
4. **Pyuria.** Although the presence of pyuria in a midstream specimen has low predictive value for significant bacteriuria, pyuria is a sensitive indicator of inflammation. Therefore, pyuria may be more accurate than bacteriuria in distinguishing a "true infection" from contamination: 95% of patients with pyuria have a genitourinary tract infection; however, pyuria cannot distinguish a bacterial UTI from acute urethral syndrome. In addition to a UTI, any of the causes of acute urethral syndrome (see Section IV.A) can result in pyuria. For example, tuberculosis is a cause of pyuria with negative routine urine cultures, although mycobacterial cultures are positive in 90% of instances. Analgesic nephropathy, interstitial nephritis, perinephric abscess, renal cortical abscess, disseminated fungal infection, and appendicitis may also result in pyuria.

D. Biochemical Tests for Bacteriuria. Two metabolic capabilities shared by most bacterial pathogens of the urinary tract are use of glucose and reduction of nitrate to nitrite; these are properties of all Enterobacteriaceae. Because small amounts of glucose and nitrate are normally present in urine, the presence of significant numbers of bacteria in urine results in the absence of glucose and presence of nitrite. Dipstick devices are commercially available for both types of testing. Studies with nitrite-indicator strips show that 85% of women and children with culture-confirmed significant bacteriuria show positive results if three consecutive morning urine specimens are tested. A morning urine specimen is preferred for the nitrite test because most bacteria take 4 to 6 hours to convert nitrate to nitrite. A negative nitrite test may be observed in patients taking diuretics or with organisms that do not produce nitrate reductase (*Staphylococcus* species, *Enterococcus* species, and *P. aeruginosa*). The sensitivity of the glucose-use test is approximately 90% to 95% in patients without diabetes mellitus. Both biochemical tests have fewer than 5% false-positive results. Therefore, these biochemical tests can be used by patients or parents, after proper instruction, to determine when quantitative cultures are needed in the management of recurrent episodes of UTI. Spectrum bias in the use of dipsticks must be avoided. Dipsticks should only be used for patients with symptoms suggestive of UTI (i.e., high pretest probability of UTI) and not for asymptomatic screening, as in pregnancy.

E. Localization of the Site of Infection. The site of infection within the urinary tract has great therapeutic and prognostic importance. Upper UTI (pyelonephritis) indicates a much greater likelihood of underlying uropathy (e.g., congenital anomalies, renal stones, ureteral occlusion, vesicoureteral reflux, neurogenic bladder, or prostatic hypertrophy) or previous instrumentation (see Section III.B). Relapses with the same, often multiple, antibiotic-resistant bacteria are common with pyelonephritis or chronic bacterial prostatitis. Treatment is long (minimum 10 to 14 days) and may be arduous. On the other hand, cystitis rarely is complicated, and treatment can be short (single dose or 3 days) and usually is easy. No ready way exists to distinguish between upper and lower UTIs by simple laboratory tests. The difficulty in making this distinction reliably on clinical grounds alone has been discussed (see Section IV.B). Older, indirect methods (e.g., serum antibodies, urine concentration test, and urinary β-glucuronidase activity) are neither sensitive nor specific. Direct methods for localization (e.g., ureteral catheterization, renal biopsy, and the bladder washout technique) are hazardous, expensive, or both. Eradication of bacteriuria with single-dose or short-course (3-day) antibiotic therapy in symptomatic patients with uncomplicated disease is a practical method for presumptive localization of infection to the bladder or urethra.

F. Radiography and Other Diagnostic Procedures: Indications. The principal role of radiographic and urologic studies for patients with UTIs is to detect vesicoureteral reflux, renal calculi, and potentially correctable lesions that obstruct urine flow and cause stasis. Uncomplicated reinfections (cystitis and urethritis) in women who respond to short-course antimicrobial therapy are not an indication for radiographic and cystoscopic investigation of the urinary tract. Radiologic and urologic evaluation should be considered in all children with a first episode of UTIs (except for school-aged girls). Special emphasis should be on the early detection of urologic abnormalities in all young children and boys with a first infection, as well as any child with pyelonephritis or a complicated course. A review of studies evaluating diagnostic imaging in children with UTIs expressed the need for better outcome-based research in this area. Radiologic and urologic evaluation should be considered in adults with UTIs. In the past, all UTIs in males were considered complicated. The conventional recommendation that all males presenting with initial UTIs undergo urologic evaluation to identify predisposing anatomic or functional abnormalities is still followed. However, several studies have indicated that only approximately 20% of men have previously unidentified abnormalities. Some sexually active males are at a higher risk for cystitis (homosexual males, males with a partner who harbors a uropathogen, and uncircumcised males). The value of urologic evaluation in this high-risk group, with a single episode of cystitis and an uncomplicated course, is not known. In general, urologic evaluations are recommended in the following situations: (a) males with first episode, (b) all patients with a complicated infection or bacteremia, (c) suspected obstruction or renal stones, (d) hematuria following infection, (e) failure to respond to appropriate antibiotic therapy, and (f) patients with recurrent infections.

Some experts recommend the evaluation of all patients with pyelonephritis. The radiologic evaluation of a subgroup of patients with pyelonephritis (young and otherwise healthy women who respond well to therapy)

may have a low diagnostic yield. In one study, only 1 of 25 young women with uncomplicated pyelonephritis had a surgically correctable etiology, and 2 of 25 had focal abnormalities that resolved on a follow-up ultrasonography. This has led others to recommend a diagnostic evaluation in young women with uncomplicated pyelonephritis after the second recurrence, or at any time, if a complicating course is present. The ease in obtaining a noninvasive test (ultrasonography) has increased radiologic evaluations for most patients admitted with pyelonephritis.

Ultrasonography with a plain film of the abdomen has replaced intravenous pyelogram (IVP) as the initial radiologic study for most adults. For a detailed evaluation of the ureterovesical junction, bladder, and urethra, a voiding cystourethrogram and measurement of the residual urine after voiding may be necessary. If vesicoureteral reflux is present after acute infection has been treated, a urologist should be consulted. Cystoscopy may be warranted. Contrast-enhanced computed tomography (CT) of the kidneys is the most effective imaging modality in adult patients with pyelonephritis. CT has high sensitivity in detecting renal abnormalities and perirenal fluid collections. Noncontrast spiral CT is the most sensitive test to detect renal calculi as many are not seen on plain radiograph of the abdomen or ultrasound. Radionuclide imaging procedures are not used in the evaluation of adult patients with UTI, but they are useful in children with pyelonephritis. Ordinarily, radiographic studies should not be performed within 6 weeks of acute infections.

Gram-negative bacilli have the ability to impede ureteral peristalsis, and transient abnormalities of the IVP are common with acute pyelonephritis. These include hydroureter, vesicoureteral reflux, diminished pyelogram, loss of renal outline, and renal enlargement. Acute pyelonephritis with an obstructed ureter is a surgical emergency, and a perinephric abscess also requires surgical drainage. These complications, however, are best detected initially by ultrasonography and by CT, respectively. To avoid radiocontrast-induced acute renal failure, excretory urography and other radiocontrast studies should be avoided whenever possible in patients with a serum creatinine above 1.5 mg/dL, diabetes mellitus, dehydration, or advanced age.

VI. TREATMENT OF UTI

A. Principles of Underlying Therapy and Follow-Up. To successfully treat a UTI, the clinician must have knowledge of microbial susceptibility and mechanisms of resistance, pharmacokinetics and pharmacodynamics, and status of host defenses. First, most uropathogens are susceptible to a wide range of antibiotics; however, resistant gram-negative bacteria frequently are seen with indwelling catheters, in immunocompromised patients, and in patients with relapsing bacteriuria. Second, most antibiotics are filtered by the kidney and therefore achieve a urinary concentration that is many times higher than the minimum inhibitory concentration. Third, although most antibiotics achieve adequate concentration in renal tissue, only tetracyclines, trimethoprim-sulfamethoxazole, and fluoroquinolones achieve any reasonable concentration in the prostate. Finally, patients with systemic or local abnormalities in host defenses usually develop a renal

infection that is refractory to therapy. In this case, antibiotics that achieve adequate serum concentrations and are bactericidal are preferable to bacterial static agents. The basic caveats for the effective management of UTIs are outlined here.

1. **Asymptomatic patients** should have colony counts ≥100,000/mL on at least two occasions before treatment is considered.
2. Unless symptoms are present, **no attempt should be made to eradicate bacteriuria** until catheters, stones, or obstructions are removed.
3. Selected patients with chronic bacteriuria may benefit from suppressive therapy.
4. A patient who develops **bacteriuria as a result of catheterization** should have treatment to reestablish a sterile urine after the removal of catheter.
5. **Antimicrobial agents used for treatment** should be the safest and least expensive agents to which the causative microorganisms are susceptible.
6. **Efficacy of treatment** should be evaluated by urine culture 1 week after completion of therapy, except in nonpregnant adult women who respond to therapy for uncomplicated cystitis and uncomplicated pyelonephritis.

B. Antimicrobial Agents

1. **β-Lactams.** The increasing antimicrobial resistance observed in *E. coli* makes amoxicillin and ampicillin less attractive choices for empiric therapy in the patient with a complicated UTI, unless *enterococcus* is strongly considered to be the etiologic agent. Amoxicillin has replaced oral ampicillin due to improved bioavailability and less frequent dosing. Amoxicillin is effective for uncomplicated cystitis, but short-course therapy (single-dose and 3-day regimens) has generally been less effective than trimethoprim-sulfamethoxazole or fluoroquinolones given for a similar duration. Cefixime and cefpodoxime are oral third-generation cephalosporins with enhanced activity against enteric gram-negative bacteria, longer serum half-life, and less frequent dosing than first-generation cephalosporins. Parenteral β-lactams are generally reserved for more complicated infections. Ceftriaxone is a third-generation cephalosporin with good activity against most community-acquired gram-negative enteric bacteria (except *P. aeruginosa*). Ceftazidime and cefepime are examples of cephalosporins with good activity against many gram-negative bacteria, including *P. aeruginosa*.
2. **Nitrofurantoin** is active against many uropathogens, including *Escherichia coli*, *S. saprophyticus*, and *Enterococcus faecalis*. Some gram-negative bacteria are resistant to nitrofurantoin (*Klebsiella*, *Enterobacter*, and *Pseudomonas* species), making it a less than ideal agent for the empiric therapy of complicated UTIs. No clinically significant increase in resistance has been observed. However, this drug is significantly less active than fluoroquinolones and trimethoprim-sulfamethoxazole against non-*Escherichia coli* aerobic gram-negative rods and is inactive against *Proteus* and *Pseudomonas* species. The major role of nitrofurantoin in

therapy includes the treatment of uncomplicated cystitis and as an alternative agent for cystitis caused by *Enterococcus faecalis*. The oral adult dose for both crystalline and macrocrystalline preparations is 50 to 100 mg every 6 hours for 7 days. Although a 3-day regimen is successful in many patients with uncomplicated cystitis, one clinical trial found nitrofurantoin to be less effective than a 3-day regimen of trimethoprim-sulfamethoxazole. Patients with renal insufficiency (creatinine clearance less than 60 mL/minute) should not receive this agent. Nitrofurantoin has been used in pregnancy [U.S. Food and Drug Administration (FDA) category B], although it is contraindicated in nursing mothers, pregnant women near term, and newborns (in whom it is associated with hemolytic anemia). Suppressive therapy has been successful in some patients, although concern for less common reactions (e.g., peripheral neuropathy, pneumonitis, and hepatitis) may limit long-term use.

3. **Trimethoprim-sulfamethoxazole and Trimethoprim.** Trimethoprim-sulfamethoxazole has a wide spectrum of activity against many uropathogens. However, lack of clinical activity against *enterococci* and *P. aeruginosa*, as well as increased resistance by some enteric gram-negative bacteria (*Klebsiella* species, *Enterobacter* species), makes trimethoprim-sulfamethoxazole a less than ideal agent for the treatment of complicated UTIs. In addition, resistance patterns tabulated by microbiology laboratories show trimethoprim-sulfamethoxazole resistance variability depending on locale; an 18% incidence of resistance is present in the southeastern and western United States for women with acute cystitis who have had a UTI in the last 6 months. Therefore, some authorities recommend the use of trimethoprim-sulfamethoxazole only if (a) the local resistance pattern is less than 20%, (b) no sulfa allergy exists, and (c) no recent antibiotic use is present. Of interest, despite a 30% resistance prevalence in some locales, at least half of the women treated with trimethoprim-sulfamethoxazole have 80% to 85% clinical and microbiologic cures.

   Trimethoprim-sulfamethoxazole is well tolerated in most patients. Adverse effects due to sulfonamides are well described and include gastrointestinal symptoms, transient elevation in the serum creatinine, and hematologic and dermatologic reactions. Sulfonamides displace warfarin and hypoglycemic agents from albumin, thereby potentiating these drug effects. Trimethoprim-sulfamethoxazole is highly effective for the prophylaxis and therapy for uncomplicated cystitis and for therapy of uncomplicated pyelonephritis. A randomized trial with four different 3-day drug regimens in women with uncomplicated acute cystitis found that a 3-day regimen of trimethoprim-sulfamethoxazole was the most cost effective. Trimethoprim-sulfamethoxazole should be used with caution in patients with kidney disease (creatinine clearance $<$30 mL/min) due to the risk of worsening renal failure and hyperkalemia. Complicated UTIs, especially catheter-associated infections and nosocomial UTIs, should have in vitro susceptibility testing performed. Trimethoprim-sulfamethoxazole has been used in pregnancy, but it is not FDA-approved for pregnant women. Other agents such as amoxicillin, nitrofurantoin, and cephalosporins are preferred.

Trimethoprim alone is preferred over trimethoprim-sulfamethoxazole by some experts for the prophylaxis and treatment of uncomplicated cystitis because its efficacy is similar and the side effects fewer (because of the absence of sulfamethoxazole). This agent should not be used alone for the therapy of complicated UTIs.

Trimethoprim monotherapy also achieves good prostate concentrations and is an alternative to fluoroquinolones depending on the susceptibility pattern of the bacteria.

4. Multiple **fluoroquinolones** are now available for clinical use (Tables 7-2 and 7-3). These agents achieve very high concentrations in the urine and renal tissue, easily exceeding the minimal inhibitory concentration of most uropathogens. Fluoroquinolones should not be used as first-line agents for the therapy of uncomplicated cystitis because of concern for the development of resistance and because of the cost. However, their antimicrobial spectrum and generally low side-effect profile make them excellent choices for empiric therapy of complicated UTIs. Among current agents within this antimicrobial class, no particular drug has demonstrated superior clinical efficacy for the therapy of patients with UTIs. An exception is moxifloxacin, which does not achieve adequate urinary concentrations and should be avoided in the treatment of UTIs. Fluoroquinolones should not be used for enterococcal UTIs (only 60% to 70% susceptible) during pregnancy or in children (until further information is available). Aluminum- and magnesium-containing antacids and iron-, calcium-, and zinc-containing preparations should not be administered with oral fluoroquinolones due to a significant decrease in absorption. In general, these agents are well tolerated by most patients. The most common adverse effects are gastrointestinal and on the central nervous system, but these infrequently lead to drug discontinuation. Photosensitivity may limit the use of some of these agents (e.g., lomefloxacin, sparfloxacin). Many of these agents are available for both parenteral and oral administration. Conversion from parenteral to oral therapy (step-down therapy) should be considered for patients who are clinically stable and tolerating oral medications. The excellent bioavailability of these drugs, good clinical success with oral therapy, and the high cost of parenteral therapy due to intravenous catheter–related complications and cost of intravenous preparations are all good reasons for considering oral therapy.

5. Macrolides—Erythromycin, clarithromycin, and azithromycin may be considered for the treatment of *Mycoplasma* sp and *U. urealyticum.*

6. Tetracyclines—May be used for *Chlamydia* sp and *Mycoplasma* sp

C. Treatment of Asymptomatic Bacteriuria

1. **Pregnancy** increases the risk of UTI complications. The rate of premature children born to women who have bacteriuria during pregnancy is increased, and 20% to 40% of these patients develop pyelonephritis. Successful therapy in these patients with bacteriuria decreases the risk of symptomatic infection by 80% to 90%. Therefore, all women should be screened twice during gestation for asymptomatic bacteriuria. Pregnant women with a history of recurrent UTI should have monthly urine

Table 7-2. Oral Antimicrobial Agents Commonly Used for the Treatment of Urinary Tract Infections

	Adult Dose	Comment
Miscellaneous Agents		
Trimethoprim	100 mg every 12 h	Prophylaxis, uncomplicated cystitis
Trimethoprim-sulfamethoxazole	160 mg/800 mg every 12 h	Uncomplicated cystitis; cost effective
Nitrofurantoin	50–100 mg every 6 h	Prophylaxis, uncomplicated cystitis
Tetracycline	250–500 mg every 6 h	Prophylaxis
β-Lactams[a]		
Amoxicillin	250–500 mg every 8 h	During pregnancy, enterococcal infections
Cephalexin or cephradine	250 mg every 6 h	During pregnancy, uncomplicated cystitis
Cefixime	200 mg every 12 h/400 mg every 24 h	Step-down therapy[a]
Cefpodoxime	100–200 mg every 12 h	Step-down therapy[a]
Fluoroquinolones		
Norfloxacin	400 mg every 12 h	Low-serum drug levels
Ciprofloxacin	250–500 mg every 12 h	First "systemic" fluoroquinolone
Lomefloxacin	400 mg every 24 h	Skin photosensitivity reactions
Enoxacin	400 mg every 12 h	P-450 drug interactions[b]
Ofloxacin	200–400 mg every 12 h	Generally replaced by levofloxacin
Levofloxacin	250–500 mg every 24 h	L-isomer of ofloxacin

Comments for miscellaneous agents and β-lactams relate to role in therapy. The role of fluoroquinolones has been for treatment of complicated urinary tract infections and as an alternative agent for uncomplicated cystitis. Because these agents have not been rigorously compared, comments are related to general spectrum of activity, side-effect profile, and drug interactions.

[a]Short-course therapy for uncomplicated cystitis has generally been less effective than the use of trimethoprim-sulfamethoxazole or fluoroquinolones for a similar duration. The general role of extended-spectrum oral cephalosporins (cefixime, cefpodoxime) has been for the treatment of complicated urinary tract infections (alternative agent) and for intravenous to oral step-down therapy.

[b]Enoxacin is a potent inhibitor of P-450 hepatic isoenzymes. (Inhibition of hepatic isoenzymes causes an elevation of serum levels of theophylline and caffeine.)

Table 7-3. Intravenous Antimicrobial Agents Commonly Used for the Treatment of Urinary Tract Infections (UTIs)

	Adult Dose	Comment
β-Lactams		
Ampicillin	1–2 g every 4 h	*Enterococcus faecalis*; usually combined with gentamicin
Ceftriaxone	1 g every 12–24 h	Pyelonephritis
Ceftazidime	1–2 g every 8–12 h	Complicated UTI, including *Pseudomonas aeruginosa*
Cefepime	1–2 g every 12 h	Complicated UTI, including *Pseudomonas aeruginosa*
Aztreonam	1 g every 8–12 h	Penicillin-allergic patient
Fluoroquinolones[a]		
Ciprofloxacin	200–400 mg every 12 h	—
Ofloxacin	200–400 mg every 12 h	Generally changed to levofloxacin
Levofloxacin	500 mg every 24 h	—
Miscellaneous Agents		
Trimethoprim-sulfamethoxazole	160 mg/800 mg every 12 h	Prophylaxis, uncomplicated cystitis
Vancomycin	1 g every 12 h	Methicillin-resistant *Staphylococcus aureus*; serious enterococcal infection in the penicillin-allergic patient
Gentamicin	4–7 mg/kg every 24 h	Serious gram-negative infection
	1.5–2.0 mg/kg every 8 h	Older dosing schedule; for enterococcus combined with ampicillin

[a]Because oral fluoroquinolones have excellent bioavailability and cost approximately 20% as much as parenteral fluoroquinolones, conversion from intravenous to oral therapy should be done when the patient is clinically stable.

cultures and should undergo imaging of the urinary tract before conception or early in pregnancy to evaluate for structural disease. All patients with bacteriuria should be treated, with follow-up cultures to identify relapses. Long-term prophylaxis offers no advantage over close surveillance. In selecting therapy, the risk to the fetus should be considered. Amoxicillin, amoxicillin-clavulanate, nitrofurantoin, or cephalexin for 3 to 7 days usually suffices, because almost all these infections are caused by susceptible *Escherichia coli*. Tetracyclines (FDA category D), trimethoprim (FDA category C), and fluoroquinolones (FDA category C) should be avoided.

2. **Children.** Asymptomatic bacteriuria in preschool- and school-aged girls may signify underlying vesicoureteral reflux. Moreover, vesicoureteral reflux, when combined with recurring bacteriuria, can result in progressive renal scarring. Therefore, in this at-risk population, asymptomatic bacteriuria should routinely be detected and treated, with follow-up urologic evaluations after 6 weeks.
3. **General Population.** Asymptomatic bacteriuria in men and nonpregnant women, a common condition in the elderly, does not appear to cause renal damage in the absence of obstructive uropathy or vesical ureteral reflux. Prospective randomized studies of therapy for asymptomatic bacteriuria in the elderly have been recently reviewed. Of five clinical trials reviewed, three studies had very small sample sizes, and one nonblinded study displayed a nonstatistical significant decrease in symptomatic infections. The largest randomized trial failed to demonstrate any significant difference in mortality between treated and untreated patients. Therefore, repeated attempts to clear the bacteriuria with antimicrobial agents seem unwarranted; they may only select for more resistant microorganisms and create a need for more toxic and costly antibiotics should the patient subsequently develop symptoms. Treatment of asymptomatic catheter-associated UTIs should be avoided due to the risk of developing a reservoir of resistant organisms. Patients with diabetes also have a high incidence of asymptomatic bacteriuria. The bacteriuria does not need to be treated as it is not associated with adverse renal outcomes, and studies have found treatment does not reduce symptomatic infection.
4. **Miscellaneous.** Instrumentation of the genitourinary tract should be avoided in patients with asymptomatic bacteriuria or, if necessary, done under the cover of prophylactic antimicrobial therapy. Treatment of asymptomatic catheter-associated bacteriuria is recommended only for (a) patients undergoing urologic surgery or implantation of a prosthesis, (b) part of a treatment plan to control a virulent organism predominant in a treatment unit, (c) patients at risk for serious infectious complications, such as immunosuppressed individuals, and (d) treatment of pathogens associated with a high risk of bacteremia, such as *Serratia marcescens*.

D. **Treatment of Uncomplicated Cystitis.** Acute cystitis and low colony count coliform urethritis are almost exclusively diseases of women, mostly sexually active women between the ages of 15 and 45 years. Although reinfection is common, complications are rare.

1. **Short-Course Therapy.** Appreciable evidence exists that infections truly confined to the bladder or urethra respond as well to single-dose or short-course (3-day) therapy as to conventional therapy for 10 to 14 days. Indeed, response to single-dose or short-course therapy implies a lower UTI. Reviews of short-course therapy have concluded that 3-day regimens are more effective than single-dose therapy. One randomized trial evaluated four different 3-day drug regimens in women with uncomplicated acute cystitis. A 3-day regimen of trimethoprim-sulfamethoxazole was more effective than a 3-day regimen of nitrofurantoin. Cure rates for cefadroxil (66%) and amoxicillin (67%) were not statistically different from the cure rate for trimethoprim-sulfamethoxazole (82%). The 3-day regimen of trimethoprim-sulfamethoxazole was the most cost-effective regimen. Infectious Diseases Society of America (IDSA) guidelines recommend the use of oral 3-day regimens including trimethoprim-sulfamethoxazole or a fluoroquinolone. This variety of treatments is an important breakthrough in the management of uncomplicated cystitis and coliform urethritis, because all patients were treated formerly with the standard 10 to 14 days of therapy. Diabetic women with uncomplicated infections (i.e., with normal urinary tracts) may also be treated with a 3-day course of antibiotic therapy. Posttreatment urine cultures are not required unless symptoms persist. Formal urologic imaging, such as ultrasonography, IVP, and CT, is not needed in most cases because correctable abnormalities are rarely found.
2. **Seven-Day Regimen.** A longer course of therapy for cystitis should be considered in patients with complicating factors that lead to a lower success rate and a higher risk of relapse. These complicating factors include a history of prolonged symptoms (more than 7 days), recent UTI, diabetic patients with abnormal urinary tracts, age older than 65 years, and use of a diaphragm. Importantly, the elderly frequently have concurrent renal bacteriuria; therefore, short-course therapy should not be used.
3. **Symptomatic pyuria without bacteriuria** in an otherwise healthy young person suggests chlamydial or gonococcal urethritis. The importance of documenting these infections as well as screening for other STDs (e.g., human immunodeficiency virus infection, syphilis), and the necessity of counseling about STD risk reduction cannot be understated. Recent guidelines suggest that either a single dose of azithromycin or a 7-day course of doxycycline is effective for chlamydial urethritis. Therapy for gonococcal urethritis includes a single dose of ceftriaxone or cefixime, or a fluoroquinolone combined with therapy for chlamydial infection.

E. **Management of Recurrent Cystitis (Reinfections).** Ten percent to 20% of women develop recurrent UTIs within several months. Some infections are related to inadequate antimicrobial therapy. It is common, however, for women whose periurethral and vaginal epithelial cells avidly support attachment of coliform bacteria to have recurrent episodes of cystitis in the absence of recognized structural abnormalities of the urinary tract. A recent prospective study of UTIs in young women identified recent use of a diaphragm and spermicide such as Nonoxynol-9, recent sexual intercourse, and a history of recurrent infection as risk factors for infection.

1. **Antimicrobial Strategies.** Strategies for managing the disease of women with frequent episodes of cystitis include (a) postcoital prophylaxis, (b) continuous low-dose prophylaxis, (c) patient self-administered therapy, and (d) consideration of contraception or barrier methods against STDs without the use of vaginal spermicides. Postcoital prophylaxis is most helpful for patients who associate recurrent UTIs with sexual intercourse. In these women, a single dose of an antimicrobial after sexual intercourse or thrice weekly at bedtime has been shown to significantly reduce the frequency of episodes of cystitis from an average of 3 per patient-year to 0.1 per patient-year. Women with frequent recurrent infections (more than three UTIs per year) are offered these prophylactic regimens. Women with fewer than three UTIs per year can be offered self-administered treatment. Multiple antimicrobial agents have demonstrated efficacy in prophylaxis and self-administered therapy. Some of these regimens include nitrofurantoin, 100 mg; trimethoprim, 100 mg; trimethoprim-sulfamethoxazole, 40 mg/200 mg; and cephalexin, 250 mg. Fluoroquinolones and cephalosporins are also effective but are more expensive. Although antimicrobial prophylaxis is effective and usually safely tolerated for months to years, single-dose therapy for acute cystitis makes prophylaxis more expensive and possibly more hazardous for most patients because of alterations in fecal and vaginal bacterial flora. Indeed, self-administration of a single-dose regimen at the onset of symptoms has proved to be as cost effective as prophylaxis.

2. **Nonantimicrobial Prophylaxis Issues.** Encouraging women to practice regular and complete emptying of the bladder may help prevent recurrent cystitis. Postcoital emptying of the bladder has also been widely recommended, although one prospective study failed to demonstrate any relationship with recurrent infections. Moreover, several theoretic preventive measures relate to the use of an alternative contraceptive method: to use a properly fitted diaphragm, to void frequently when wearing a diaphragm, and to limit diaphragm use to the recommended 6 to 8 hours after intercourse. Women should also increase fluid intake to increase the frequency of micturition. In postmenopausal women, intravaginal administration of estriol can reduce recurrent UTIs by modifying the milieu for vaginal flora. Cranberry juice (300 mL/day) was effective in decreasing asymptomatic bacteriuria with pyuria in postmenopausal women. The small difference in symptomatic UTIs was not statistically significant.

3. **Emerging Therapies**. Many recurrent UTIs arise from the ability of bacteria to attach and invade the bladder mucosa. Pillicides are small synthetic molecules that interfere with pilus assembly, thereby blocking bacterial adhesion and subsequent reservoir formation. Pillicides have potential as a therapy for recurrent UTIs but their efficacy in animal models has not yet been reported. Mannoside, a soluble receptor analogue, is also an antiadhesive that binds to FimH. FimH allows bacteria to bind to and invade host bladder cells and mannoside prevents FimH from interacting with host receptors. Mannosides have shown great promise as a therapy, both prophylactically and for established infections. In a murine UTI model, mannoside prevented bacterial invasion into bladder tissue. These agents also act synergistically with antibiotics to reduce bacteria

titers within the urinary tract of infected mice. Vaccination approaches have also been explored but to date, none have been shown to protect against cystitis.

F. Treatment of Acute Bacterial Pyelonephritis. The occurrence of flank pain, costovertebral angle tenderness, chills, fever, and nausea and vomiting with or without dysuria suggests acute bacterial pyelonephritis. In this clinical setting, blood cultures and quantitative cultures of urine should be obtained. Whether ambulatory patients should be admitted to the hospital for treatment depends in part on a subjective assessment of toxicity, likely compliance with therapy, and the home situation. When the assessment is doubtful, the patient should be treated in the hospital, at least until a clear response to therapy has occurred. This policy also applies to patients with known underlying uropathies because complications are more common in these patients.

1. **Outpatient Therapy.** Recommendations for therapy of uncomplicated pyelonephritis are outlined in Table 7-4. Fluoroquinolone or trimethoprim-sulfamethoxazole is the drug of choice for initial therapy of pyelonephritis in outpatients. Local susceptibility patterns will influence the choice for initial therapy. After culture results and susceptibility tests are available, a full 10- to 14-day course of antimicrobial therapy may be completed with the least expensive drug to which the patient's microorganism is susceptible.
2. **Inpatient Therapy.** Patients who require admission to the hospital should be treated initially with a third-generation cephalosporin or a fluoroquinolone (intramuscular or intravenous), or gentamicin or tobramycin (1.5 to 2.0 mg/kg every 8 hours or 4.0 to 7.0 mg/kg every 24 hours, with appropriate alteration of the dose interval if the serum creatinine exceeds 1 mg/dL) if the urine shows gram-negative bacilli on microscopic examination. If gram-positive cocci are seen in the urine, intravenous ampicillin (l g every 4 hours) should be given in addition to the aminoglycoside, to cover the possibility of enterococcal infection while the results of urine and blood cultures and antimicrobial susceptibility tests are pending. If no complications ensue and the patient becomes afebrile, the remaining days of a 10- to 14-day course can be completed with oral therapy. However, persistent fever, persistent bacteriuria in 48 to 72 hours, or continual signs of toxicity beyond 3 days of therapy suggest the need for an evaluation to exclude obstruction, metastatic focus, or the formation of a perinephric abscess. The urinary tract is a common source of sepsis and bacteremic shock in patients with underlying uropathies. As with other patients in septic shock, intravenous fluids must be given to maintain adequate arterial perfusion, which usually results in a urinary output in excess of 50 mL/hour. Failure to respond to seemingly appropriate therapy suggests the possibility of undrained pus. Examination by ultrasonography or CT may disclose an obstructed ureter or perinephric abscess, both of which require surgical drainage.

G. Management of Recurrent Renal Infections (Relapses). Chronic bacterial pyelonephritis is one of the most refractory problems in clinical medicine; relapse rates are as high as 90%. The entity is a heterogeneous one with multiple underlying factors.

Table 7-4.	Recommendations for Therapy for UTIs		
Infection	**Group**	**Medication**	**Duration**
Uncomplicated cystitis	Young women	Trimethoprim-sulfamethoxazole, trimethoprim, fluoroquinolone[a]	3 d
Cystitis	Women with risk factors including recent UTI, symptoms >7 d, diaphragm use, age older than 65 yr, diabetic patients with abnormal GU structures	Trimethoprim-sulfamethoxazole, trimethoprim, fluoroquinolone, nitrofurantoin, cephalosporins	7 d
	Pregnant women	Amoxicillin, cephalosporins[b], nitrofurantoin, sulfonamides, trimethoprim-sulfamethoxazole[c]	7 d
Acute uncomplicated pyelonephritis	Women (outpatient)	Fluoroquinolone, trimethoprim-sulfamethoxazole, oral cephalosporin[d]	10–14 d
	Women (inpatient)	Fluoroquinolone[e], ceftriaxone, ampicillin plus gentamicin[f], trimethoprim-sulfamethoxazole	14 d
Complicated infection	Outpatient	Fluoroquinolone	10–14 d
	Inpatient	Fluoroquinolone[e], cephalosporins[g], ampicillin plus gentamicin[f]	14 d

(*Continued*)

Table 7-4. Recommendations for Therapy for UTIs (Continued)

GU, genitourinary; UTI, urinary tract infection.

[a]Oral fluoroquinolones are listed in Table 7-2; they offer no significant advantage over trimethoprim-sulfamethoxazole in women with uncomplicated cystitis.

[b]Oral cephalosporins: cephradine, cephalexin.

[c]Trimethoprim-sulfamethoxazole has been used in pregnancy, but it has not been approved by the U.S. Food and Drug Administration for pregnant patients.

[d]Oral cephalosporins with an extended spectrum: cefpodoxime, loracarbef.

[e]Fluoroquinolones available for intravenous administration are listed in Table 7-3.

[f]Increasing ampicillin resistance among many enteric bacteria, including *Escherichia coli*, limits ampicillin as a single agent for complicated UTIs. If enterococcus is not likely, then a fluoroquinolone or a parenteral third- or fourth-generation cephalosporin is recommended.

[g]Some examples of parenteral cephalosporins are listed in Table 7-3.

(Adapted from Falagas ME. Practice guidelines: urinary tract infections. *Infect Dis Clin Pract* 1995;4:241–257; Kunin CM. *Detection, prevention, and management of urinary tract infections*, 5th ed. Philadelphia, PA: Lea & Febiger, 1997; Stamm WE. Urinary tract infections. In: Root RK, ed. *Clinical infectious diseases: a practical approach*, 1st ed. New York: Oxford University Press, 1999.)

1. **Risk Factors.** To improve the success rate, it is of utmost importance that any correctable lesion be repaired, that obstructions to urine flow be relieved, and that foreign bodies (e.g., indwelling urinary catheters or renal staghorn calculi) be removed if possible. If the risk factors cannot be corrected, long-term eradication of bacteriuria is almost impossible. Attempting eradication in such instances leads only to the emergence of more resistant strains of bacteria or fungi; consequently, the physician must be resigned to treating symptomatic episodes of infection and suppressing bacteriuria in selected patients.
2. **Acute Symptomatic Infection.** The treatment of acute symptoms and signs of UTI in a patient with chronic renal bacteriuria is the same as for patients with acute bacterial pyelonephritis. Urine cultures to detect a possible change in antimicrobial susceptibility of the infecting microorganism are important. Toxic patients should also have blood cultures.
3. **Prolonged Treatment.** Some patients with relapsing bacteriuria after 2 weeks of therapy respond to 6 weeks of antimicrobial therapy. This is especially true of patients with no underlying structural abnormalities. Men may require 6 to 12 weeks of antibiotic therapy for febrile UTIs because more than 90% have associated asymptomatic prostatitis. Patients who fail the longer therapy, who have repeated episodes of symptomatic infection, or who have progressive renal disease despite corrective measures are candidates for suppressive chemotherapy.
4. **Suppressive Therapy.** To reduce the colony counts in their urine, patients selected for suppressive therapy should have 2 to 3 days of specific high-dose antimicrobial therapy, to which their infecting bacteria are susceptible. The preferred agent for long-term suppression is methenamine mandelate, 1 g four times daily in adults. To be most effective, the pH of the urine should be maintained below 5.5; this can be accomplished with ascorbic acid, 500 mg two to four times daily. Alternatively, the dosage of methenamine mandelate alone can be increased to 8 g or even 12 g/day. The dosage should be adjusted to the minimum amount required to keep the urine free of bacteria. To avoid metabolic acidosis, the dosage of methenamine mandelate must be reduced in patients with renal insufficiency, in whom 2 g/day may suffice. In these patients, methenamine mandelate should not be used at all unless the creatinine clearance exceeds 10 mL/minute. Alternative therapy is trimethoprim-sulfamethoxazole (160 mg/800 mg tablets twice daily) or nitrofurantoin (50 to 100 mg once or twice daily).
5. **Prognosis.** Although a common cause of appreciable morbidity, UTIs do not play a major role in the pathogenesis of end-stage renal disease. Patients who come to renal dialysis or transplantation because of chronic bacterial pyelonephritis almost always have an underlying structural defect. Most often, the lesion is chronic atrophic pyelonephritis associated with vesicoureteral reflux that started in infancy. The role of surgical correction of vesicoureteral reflux is not clear despite years of debate; what is certain, however, is the importance of meticulous control of infection in children to prevent progressive renal scarring and renal failure by early adulthood.

H. Treatment of Prostatitis

1. **Acute bacterial prostatitis** is commonly accompanied by acute cystitis, which enables the recovery of its causative pathogen by culture of voided urine. Massage of an acutely inflamed prostate gland often results in bacteremia; therefore, this procedure should be avoided unless the patient is already receiving effective antibiotic therapy. Antimicrobial selection depends on the susceptibility pattern of the causative bacteria and the ability of the drug to achieve concentrations in the prostate that exceed the minimum inhibitory concentrations of the bacteria. The drug of choice most commonly is either the combination of trimethoprim-sulfamethoxazole (cotrimoxazole) or a fluoroquinolone; treatment, however, must be based ultimately on an accurate microbiological diagnosis. β-Lactam antibiotics should be avoided because of the low concentrations achieved in prostatic tissue and lower cure rates. Treatment should be given for 30 days to prevent chronic bacterial prostatitis. After acute symptoms subside, a suitable oral antibiotic can be given in full dose for at least 30 days. Urethral catheterization should be avoided. If acute urinary retention develops, drainage should be by suprapubic needle aspiration or, if prolonged bladder drainage is required, by a suprapubic cystostomy tube, placed while the patient is under local anesthesia.
2. **Chronic Bacterial Prostatitis.** The hallmark of chronic bacterial prostatitis is relapsing UTI. It is most refractory to treatment. Although erythromycin with alkalinization of the urine has been effective against susceptible gram-positive pathogens, most instances of chronic bacterial prostatitis are caused by gram-negative enteric bacilli. Cotrimoxazole or a fluoroquinolone is the drug of choice. Approximately 75% of patients improve, and 33% are cured with 12 weeks of cotrimoxazole therapy (160 mg/800 mg twice daily). For patients who cannot tolerate cotrimoxazole or a fluoroquinolone, nitrofurantoin, 50 or 100 mg once or twice daily, can be used for long-term (6 to 12 months) suppressive therapy.
3. The therapy for **nonbacterial chronic prostatitis** is difficult because an exact etiology has not been identified. Owing to a concern for *C. trachomatis*, *U. urealyticum*, and other fastidious and difficult to culture organisms, many experts recommend a 6-week trial of a tetracycline or erythromycin. Symptomatic therapy with nonsteroidal anti-inflammatory drugs and α-receptor blockers has also been used.

I. Recommendations for the Care of Urinary Catheters.

Urinary catheters are valuable devices for enabling drainage of the bladder and while they may be associated with asymptomatic bacteriuria, their use is also associated with an appreciable risk of infection in the urinary tract, specifically pyelonephritis. In addition, bacteremia and sepsis are recognized complications.

On August 1, 2007, the Centers for Medicare and Medicaid Services issued a decision to implement a modification to the Inpatient Prospective Payment System whereby additional payment for the complication or comorbidity of a catheter-related UTI will not be reimbursed. Therefore, it

is imperative that guidelines for the prevention and expeditious treatment of catheter-related UTIs be enforced. In addition, documentation of an existing UTI at the time of admission is recommended.

For a single (in-and-out) catheterization, the risk is small (12%), although this prevalence is much higher in diabetic and elderly women. Intermittent catheterization is a safe alternative for patients in four situations: (a) children with neurogenic bladders (such as spina bifida), (b) uncontrolled reflex detrusor contraction resulting in incontinence in women, (c) chronic urinary retention due to ineffective or absent detrusor contraction, and (d) bladder outlet obstruction in men who are not surgical candidates.

In the absence of outlet obstruction, condom catheters are an alternative method of urinary drainage that has a lower incidence of bacteriuria.

Bacteriuria occurs in virtually all patients with indwelling urinary catheters within 3 to 4 days unless placement is done under sterile conditions and a sterile, closed drainage system is maintained (Fig. 7-4). The use of a neomycin–polymyxin irrigant does not prevent catheter-associated infections. To decrease the incidence of catheter-associated UTIs, use of suprapubic catheters, condom drainage systems, or intermittent catheters may be preferable in appropriate patients. Explicit recommendations for the prevention of catheter-associated UTIs, formulated by the Centers for Disease Control and Prevention, are as follows:

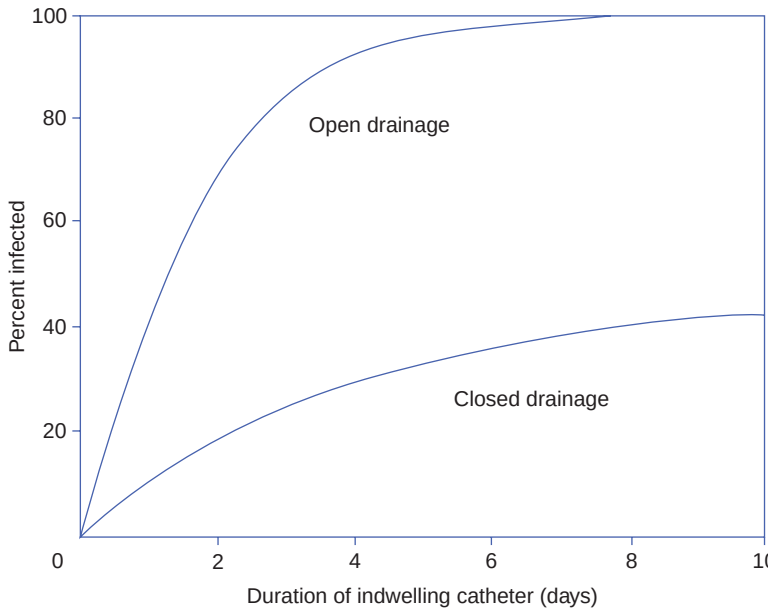

Figure 7-4. Prevalence of bacteriuria in catheterized patients according to duration of catheterization and type of drainage system. (From Fass RJ, Klainer AS, Perkins RL. Urinary tract infection: practical aspects of diagnosis and treatment. *JAMA* 1973;225:1509. Reprinted with permission.)

1. **Indwelling Urinary Catheters Should Be Used Only When Absolutely Necessary.** They should never be used solely for nurse or physician convenience and be removed as soon as possible. Duration of catheter use is the most important risk factor for the development of bacteriuria.
2. **Catheters Should Be Inserted Only by Adequately Trained Personnel.** If practical, a team of individuals should be given responsibility for catheter insertion and maintenance.
3. **Urinary Catheters Should Be Aseptically Inserted Using Proper Sterile Technique and the Following Sterile Equipment:** gloves, a fenestrated drape, sterile sponges and an iodophor solution for periurethral cleansing, a lubricant jelly, and an appropriately sized urinary catheter. After insertion, catheters should be properly secured to prevent movement and urethral traction.
4. **Once- or twice-daily perineal care for catheterized patients** should include cleansing of the meatal-catheter junction with an antiseptic soap; subsequently, an antimicrobial ointment may be applied.
5. **A Sterile Closed Drainage System Should Always Be Used.** The urinary catheter and the proximal portion of the drainage tube should not be disconnected (thereby opening the closed system) unless it is required for irrigation of an obstructed catheter. Sterile technique must be observed whenever the collecting system is opened and catheter irrigation is done. A large-volume sterile syringe and sterile irrigant fluid should be used and then discarded. If frequent irrigations are necessary to ensure catheter patency, a triple-lumen catheter that permits continuous irrigation within a closed system is preferable.
6. **Small volumes of urine for culture can** be aspirated from the distal end of the catheter with a sterile syringe and 21-gauge needle. The catheter must first be prepared with tincture of iodine or alcohol. Urine for chemical analyses can be obtained from the drainage bag in a sterile manner.
7. **Nonobstructed Gravity Flow Must Be Maintained at All Times.** This requires emptying the collecting bag regularly, replacing poorly functioning or obstructed catheters, and ensuring that collection bags always remain below the level of the bladder.
8. **All closed collecting systems contaminated by inappropriate technique, accidental disconnection, leaks, or other means should be immediately replaced.**
9. **Routine catheter change is not necessary** in patients with urinary catheterization of less than 2 weeks' duration, except when obstruction, contamination, or other malfunction occurs. In patients with chronic indwelling catheters, replacement is necessary when concretions can be palpated in the catheter or when malfunction or obstruction occurs.
10. **Catheterized patients should be separated from each other whenever possible** and should not share the same room or adjacent beds if other arrangements are available. Separation of patients with bacteriuria and those without it is particularly important.

These guidelines should be adhered to meticulously, and the use of indwelling urinary catheters should be kept to a responsible minimum.

J. Catheter-Associated Infections. Catheter-associated bacteriuria should only be treated in the symptomatic patient. When the decision to treat a patient with a catheter-associated infection is made, removal of the catheter is an important aspect of therapy. If an infected catheter remains in place, relapsing infection is very common. The interaction between the organisms and catheter (foreign body) causes the organism to form a biofilm or area in which antibiotics are unable to completely eradicate these organisms. Recommendations for empiric therapy are similar to recommendations for complicated UTIs (Table 7-4). The choice of empiric therapy is based on an initial Gram's stain of the urine, local susceptibility patterns, host factors, and the patient's recent antibiotic use. The final choice of an antibiotic and duration of therapy should be based on the identification and susceptibility of the etiologic agent and the host's response to therapy. Patients who respond rapidly to therapy may be treated for 7 days, although making firm conclusions about duration of therapy is very difficult.

Patients with candiduria may fall into several different clinical categories. Otherwise healthy patients with asymptomatic candiduria often require only a urinary catheter change and may not require antifungal therapy. On the other end of the spectrum is the immunocompromised host, in whom candiduria may represent disseminated infection. The patient with disseminated candidiasis requires systemic therapy with either fluconazole or amphotericin B or a liposomal preparation of amphotericin. General recommendations for treating patients with candiduria and without evidence of disseminated infection include the removal of the urinary catheter and discontinuation of antibiotics. Antifungal options include fluconazole (200 mg the first day, then 100 mg for 4 days), continuous bladder irrigation with amphotericin B (50 mg/1,000 mL of sterile water through a three-way catheter for 5 days), or low-dose intravenous therapy with amphotericin (0.3 mg/kg in a single dose). Occasionally, longer systemic therapy with oral 5-fluorocytosine, intravenous amphotericin B, or both is required.

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8 The Patient with Hematuria, Proteinuria, or Both, and Abnormal Findings on Urinary Microscopy

Godela M. Brosnahan

I. URINE ANALYSIS

A urine sample is usually easy to obtain, and it can provide important information in the evaluation of patients with hypertension (underlying kidney disease), edema (nephrotic syndrome), and elevated serum creatinine (acute kidney injury and/or chronic kidney disease). It is also useful in patients with symptoms such as dysuria, flank pain, or gross hematuria, because it may point to a specific diagnosis. However, it must always be interpreted in conjunction with the patient's history, physical examination, and other laboratory findings. Correct interpretation requires practice and experience from the clinician. Urinalysis must be performed in patients with systemic diseases such as systemic lupus erythematosus (SLE) or vasculitis to detect asymptomatic kidney involvement early so that appropriate therapy can be instituted.

A complete urinalysis consists of gross inspection, dipstick evaluation, and microscopic examination by a trained clinician. Proper collection and prompt examination of the urine sample are essential for obtaining reliable results.

A. Method of Collection of Urine Specimens: Ambulatory patients usually are asked to provide a **midstream urine sample** after thorough cleaning of the external genitalia with moist wipes (see Table 8-1). Unless these procedures are followed, contamination of the urine with bacteria, squamous cells, and leukocytes from vagina, vulva, or foreskin is common and leads to misinterpretation.

In hospitalized patients who are unable to void, a catheter may be inserted to obtain a urine sample. If possible, at least 200 mL urine should pass through the catheter to flush out contaminating urethral contents before the specimen is collected.

In patients with indwelling urinary catheters, the sample should be obtained directly from the catheter tubing, to collect recently produced urine, as opposed to urine from the drainage bag which is often contaminated with debris.

Suprapubic aspiration is rarely performed if accurate evaluation for infection is required. A fine lumbar puncture needle with stylet in place is passed through sterilized suprapubic skin directly into a full bladder. Uncontaminated urine can then be aspirated.

Table 8-1.	Guidelines for Collecting a Midstream Urine Sample
Women	
When possible use a vaginal tampon	
Hold labia well separated during collection of the specimen	
Gently cleanse the periurethral area from anterior to posterior with several moistened gauze squares	
Men	
Hold the retracted foreskin back throughout the collection	
Clean the urethral meatus with moist gauze	
In both sexes, at least 200 mL should be passed before a midstream urine specimen is collected, without interruption of the flow of urine.	

B. Gross Inspection: Normal urine is clear and light yellow. Urine that contains an abundance of cells or crystals may look turbid. The most common abnormal color is **red to brown urine** which is often due to blood (hematuria) but may have other causes. The first step in the evaluation is **centrifugation of the urine** to determine whether the red color is in the sediment or in the supernatant. If the sediment is red but not the supernatant, the patient has hematuria. If the supernatant is red, it should be tested for heme with a dipstick. If the supernatant is heme positive, the patient has either hemoglobinuria due to massive hemolysis or myoglobinuria due to rhabdomyolysis.

A red supernatant that is negative for heme can be due to medications (rifampin, phenytoin, phenazopyridine) or food dyes. Ingestion of beets or rhubarb and acute intermittent porphyria are also in the differential diagnosis.

White urine may be due to pyuria, chyluria, or propofol (often used as a sedative in the intensive care unit), whereas **green urine** can be seen after administration of methylene blue, propofol, or amitriptyline. **Black urine** can occur with hemoglobinuria or myoglobinuria. Urine that turns black after standing for some time is a sign of alkaptonuria ("black urine disease"), an inborn disorder of tyrosine metabolism; the black color is due to oxidation of urinary homogentisic acid. **Purple urine** can be due to bacteriuria in patients with urinary catheters (purple urine bag syndrome).

C. Dipstick Testing: Dipstick testing of urine provides a rapid determination of urine pH, specific gravity, and the presence of protein, blood (hemoglobin), leukocytes, nitrites, glucose, and bile. It is important that the sample is tested promptly, because urine pH may change with time after collection, and contaminating bacteria multiply, converting nitrate to nitrite and causing a false-positive test result for bacteriuria. For confirmation of infection, a urine culture is required (see Chapter 7).

Increasing concentrations of **protein** in the urine cause a color change of the dipstick indicator from yellow to deepening shades of green. Because this is dependent on the concentration of the urine, very dilute urine will

result in underestimation of the amount of proteinuria (excreted over 24 hours) and very concentrated urine leads to overestimation. Therefore, a positive dipstick test for protein needs to be followed by a quantitative determination of protein excretion (see below). False-positive dipstick results for proteinuria are seen when urine pH is 8 or greater and when the patient is excreting metabolites of penicillins, aspirin, or oral hypoglycemic agents. It is important to bear in mind that **standard dipsticks detect mainly albumin**, but not light chains or immunoglobulins. Therefore, patients with multiple myeloma may have a negative result for protein on dipstick testing but large amounts of protein in a 24-hour urine collection. The dipstick also **cannot detect** very small quantities of albumin (e.g., **microalbuminuria**, see below).

Dipstick testing is very sensitive for **heme** in the urine, but it cannot differentiate between hemoglobin in red blood cells (RBCs; hematuria) and free hemoglobin or myoglobin, which are present in urine from patients with intravascular hemolysis or rhabdomyolysis. Ascorbic acid, a strong reducing agent, prevents the chemical reaction in dipsticks that detects hemoglobin and may be a cause of false-negative test results in subjects who ingest large amounts of vitamin C. False-positive results are even more common and may be due to the presence of semen in the urine, to a very alkaline urine pH or contamination with oxidizing agents used to clean the perineum. Therefore, **a positive dipstick result for heme does not equal a diagnosis of hematuria**; this must be established by microscopic examination.

Dipsticks can also detect **leukocyte esterase** which is released by lysed neutrophils and macrophages in urine. A positive test is a surrogate for pyuria (white blood cells in the urine); however, there are several causes for false-positive (e.g., very dilute urine) and false-negative (e.g., concentrated urine or the presence of proteinuria and glucosuria) test results. Moreover, **many conditions can cause pyuria**, and therefore microscopic examination of the urine and urine culture are still required to confirm or rule out urinary tract infection.

D. Microscopic Analysis: As stated above, microscopic analysis of the urine is essential because dipstick testing alone can be misleading and cannot identify the presence of renal epithelial cells (a marker of acute kidney injury, see Chapter 10), casts, or crystals. In the United States, urine is usually examined using a standard light microscope, after 10 mL of urine is centrifuged at 400–450 g for 5 minutes. The supernatant is then poured out, the pellet is resuspended, and a small drop is placed on a glass slide and covered with a coverslip. The specimen is then examined at low power (10×) to look for casts and at high power (40×) to count the number of RBCs, white blood cells, and epithelial cells per high-power field. This yields a semiquantitative estimate of the frequency of these cells in the urine.

More quantitative measures can be obtained by examining the urine in a counting chamber rather than on a plain glass slide, but this is usually not available for routine use in the United States. Phase-contrast microscopy is more sensitive for the observation of morphologic detail such as dysmorphic RBCs and should be used when available.

Most large clinical laboratories now perform the microscopic examination of the urine with automated analyzers utilizing flow cytometry. These accurately quantify urine elements such as epithelial cells, RBCs,

and white blood cells, but a qualitative morphologic assessment is not performed. Therefore, a distinction between dysmorphic glomerular hematuria and eumorphic hematuria of lower tract origin (see below) still requires manual examination. In addition, cellular and noncellular casts, crystalluria, and budding yeast are still better evaluated manually than by automated analyzers.

1. **Hematuria:** Abnormal hematuria is commonly defined as three or more RBCs per high-power field. Microscopic hematuria is only detected by examining the urine under the microscope, whereas macroscopic hematuria means visibly red to brown urine. Both can be due to glomerulonephritis or arise from an extraglomerular source, including the collecting system, ureter and bladder. Microscopic urinalysis may be useful in distinguishing between the two. **Glomerular hematuria** is likely if hematuria is accompanied by significant proteinuria, if the red cells have a dysmorphic appearance (i.e., red cells with blebs, budding, vesicle-shaped protrusions, and marked variability in shape and size, see Fig. 8-1), and if there are red cell casts (see below). In patients with macroscopic hematuria, a glomerular source is suggested

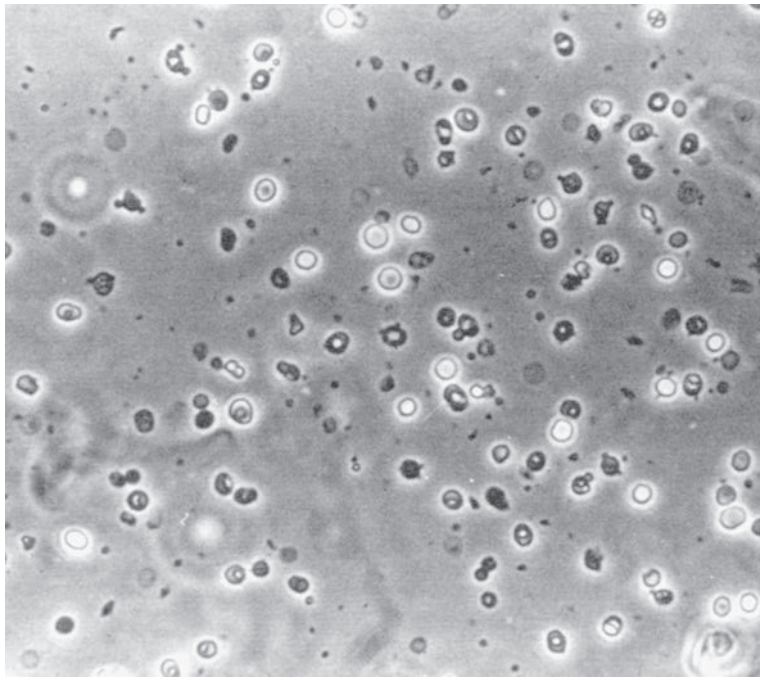


Figure 8-1. Erythrocytes, showing the wide variation in size, shape, and hemoglobin content, in the urine of a patient with glomerulonephritis (phase-contrast microscopy). (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston, MA: Little, Brown and Company, 1988. Reprinted with permission.)

by a dark, cola-like color of the urine. This color arises from the formation of methemoglobin during prolonged passage of the red cells through the nephron in an acidic environment. If the urine is alkaline, glomerular bleeding may result in red urine. **Nonglomerular bleeding** is characterized by red to pink urine and microscopically by red cells that are round and uniform in size and shape, but there may be some "ghost cells," that is, cells that are losing their hemoglobin (Fig. 8-2), which can occur in acid urine. Hematuria with passage of clots almost always arises from a lower urinary tract source (collecting system and/or bladder).

2. **Urinary Leukocytes (Pyuria):** Normal midstream urine contains up to 2,000 nucleated cells/mL, mostly leukocytes, whereas normal bladder urine obtained by needle aspiration contains very low numbers of leukocytes (mean, 283/mL). The higher counts in midstream urine are likely due to contamination from the urethra or in women from the vagina.

   An increase in urinary leukocyte count (>20,000 leukocytes/mL or >5 leukocytes per high-power field) may be due to **infection** (see Chapter 7), but it also occurs in **other conditions**. When pyuria is present without bacteriuria, three-fourths of patients show an

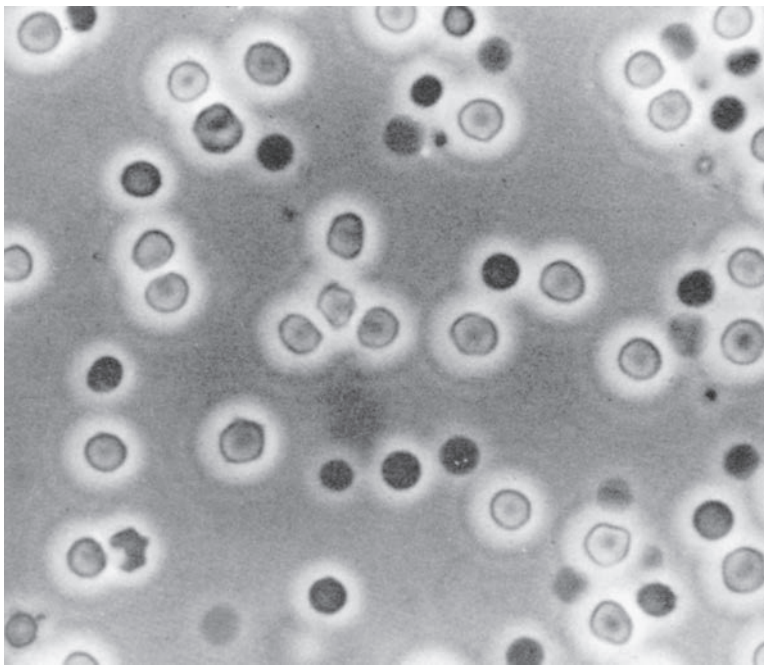


Figure 8-2. Nonglomerular bleeding, showing two populations of cells (phase-contrast microscopy). (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston, MA: Little, Brown and Company, 1988. Reprinted with permission.)

underlying urinary tract abnormality such as acute or chronic interstitial nephritis, renal papillary necrosis and analgesic nephropathy, nephrolithiasis, glomerulonephritis, and polycystic kidney disease. In these conditions, the urine often contains red cells as well. If it is difficult to distinguish leukocytes from renal tubular epithelial cells, a drop of acetic acid makes it easier to recognize the lobed nuclei of polymorphonuclear leukocytes.

3. **Renal Tubular Cells:** Large numbers of renal tubular cells in the urine can be found in **acute tubular necrosis** and **acute interstitial nephritis**. Acute interstitial nephritis can be distinguished from acute tubular necrosis if concomitant pyuria, microhematuria, and eosinophiluria are present. Eosinophils in the urine are best seen with Hansel's stain, which, unlike Wright's stain, is not pH dependent. However, acute interstitial nephritis can be present even in patients with few or no urinary abnormalities. Therefore, if clinical suspicion is high, renal biopsy should be performed.

   Nucleated cells in the urine may also be found in patients with glomerulonephritis, particularly crescentic glomerulonephritis, in which red cells, white cells, and renal tubular cells are present in higher numbers than in noncrescentic glomerulonephritis. Glomerular epithelial cells (podocytes) may also appear in urine from patients with crescentic glomerulonephritis. These cells can be identified by monoclonal antibody staining for podocyte-specific proteins such as nephrin, but this is available only in research settings.

4. **Urinary Casts:** Casts are cylindrical structures that are formed in the tubular lumen from an organic matrix and may contain red or white blood cells, renal tubular cells, crystals, lipid, or bile. The major component of the matrix is Tamm–Horsfall glycoprotein, which is synthesized and secreted in the ascending limb of the loop of Henle and in distal convoluted tubules. Some casts are physiologic, that is, seen in the urine of healthy subjects. These are **hyaline** casts, which are transparent and consist of the protein matrix only, and occasional **granular** casts, which contain granules (likely cellular debris) embedded in the matrix. The number of hyaline and granular casts in the urine may be increased by fever, exercise, and volume depletion. A large number of muddy-brown granular casts are characteristic of acute tubular necrosis (see Chapter 10).

   Pathologic casts are those that have tightly packed RBCs or white blood cells or renal tubular epithelial cells embedded in their matrix. The finding of cellular casts indicates an intrarenal origin of these cells. **Red cell casts** (Fig. 8-3) are most commonly seen in patients with glomerulonephritis, but may also occur with acute interstitial nephritis. **White cell casts** can be seen in patients with pyelonephritis or with noninfectious interstitial nephritis, but sometimes also with proliferative glomerulonephritis. **Renal tubular epithelial cell casts** are indicative of acute tubular necrosis or acute interstitial nephritis.

   In nephrotic syndrome, casts usually contain fat particles of varying sizes and some contain oval fat bodies **(fatty casts)**. Oval fat bodies are tubular cells laden with fat droplets. Because the fat bodies consist of cholesterol esters, they can be easily identified under polarized light by

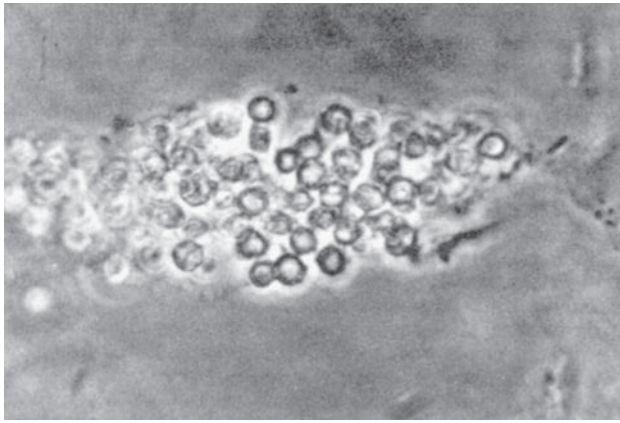


Figure 8-3. An erythrocyte cast in an acid urine, composed of red cells from which much of the hemoglobin has disappeared. (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston, MA: Little, Brown and Company, 1988. Reprinted with permission.)

their "Maltese cross" birefringence (Figs. 8-4 and 8-5). If fat particles are too small to show crosses, they appear as a faint glow in polarized light.

Broad casts form in dilated tubules with little flow and usually signify advanced chronic kidney disease.

5. **Crystals:** Although crystals of calcium oxalate and uric acid may be seen in normal urine samples, large, bizarre crystals of any type, including calcium oxalate and uric acid, usually signify increased urinary excretion of these substances and may indicate calculous disease. Cystine crystals are always abnormal and indicate cystinuria (see Chapter 6). Massive calcium oxalate crystalluria suggests ethylene glycol overdose.

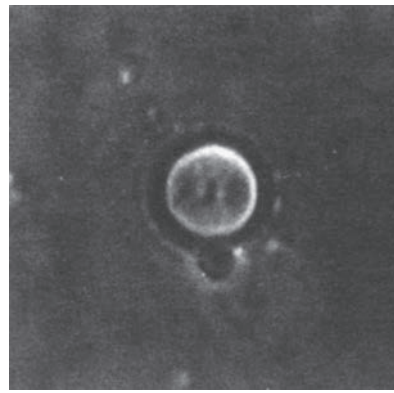


Figure 8-4. A cholesterol ester spherulite approximately the same size as an erythrocyte. (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston, MA: Little, Brown and Company, 1988. Reprinted with permission.)

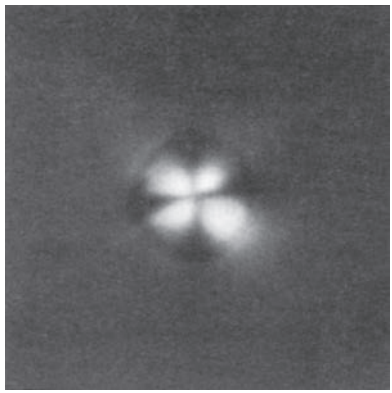


Figure 8-5. The particle in Figure 8-4, when viewed with polarized light, shows the classic "Maltese cross." (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston, MA: Little, Brown and Company, 1988. Reprinted with permission.)

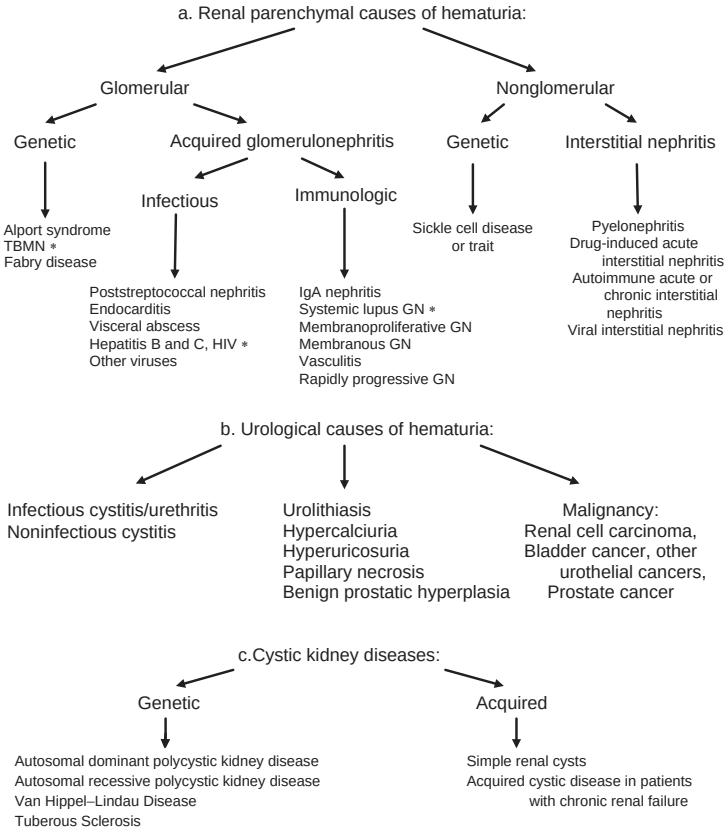
II. CAUSES OF HEMATURIA

Hematuria can arise from any part of the kidneys or urogenital tract and may be due to a transient problem or to serious and progressive disease. It may be useful to distinguish between renal parenchymal causes of hematuria, which are best evaluated by a nephrologist, and urological causes, which may need surgical intervention. In cystic kidney diseases, hematuria is thought to be due to cyst ruptures. Figure 8-6 may be helpful for the differential diagnosis of hematuria.

III. APPROACH TO THE PATIENT WITH HEMATURIA

A. General Principles: The approach to the evaluation of gross and microscopic hematuria depends on the age of the patient and the likelihood of an underlying serious disease. For instance, **malignancy** is a much greater possibility in individuals who are older than 40 years than in younger people, particularly if they have other risk factors such as smoking or a history of chemotherapy, particularly with cyclophosphamide which can cause bladder cancer. Other risk factors for malignancy are occupational exposure to chemicals or dyes, history of pelvic irradiation, and analgesic or Chinese herb nephropathy. The latter is due to the contaminant aristolochic acid, which also appears to be the cause of Balkan nephropathy, a chronic interstitial nephritis leading to end-stage renal disease (ESRD) and an increased risk of urothelial cancer.

Evaluation of hematuria also depends on associated signs and symptoms. For instance, a patient with acute onset of dysuria and gross hematuria most likely has an infection, that is, **acute cystitis**, whereas the patient with colicky unilateral flank pain and microscopic or macroscopic hematuria most likely has a **ureteral stone**. However, if these symptoms occur in an older patient, they may be a manifestation of bladder or renal cancer, and therefore the evaluation needs to rule out malignancy. In patients with renal transplants, gross hematuria can be due to infection with **adenovirus or cytomegalovirus**.



*TBMN: Thin Basement Membrane Nephropathy; HIV: Human immunodeficiency virus; GN: Glomerulonephritis; IgA: Immunoglobulin A.

Figure 8-6. Differential diagnosis of hematuria. GN, glomerulonephritis; HIV, human immunodeficiency virus; IgA, immunoglobulin A.

If the hematuria is clearly of glomerular origin, that is, if the urine contains mostly dysmorphic RBCs and/or red cell casts, an acute or chronic **glomerulonephritis** is likely, and this directs the diagnostic tests, including renal biopsy. If the family history is positive for **Alport syndrome, autosomal dominant polycystic kidney disease, or sickle cell disease,** the finding of microscopic or macroscopic hematuria indicates that the proband likely also has the disease. In these cases (glomerular and genetic hematuria), a workup for malignancy is not necessary, particularly if the patient is young and has no other risk factors.

Other historical clues pointing to the diagnosis are a recent upper respiratory or gastrointestinal infection. Onset of gross hematuria 2 to 3 days later suggests

a diagnosis of **immunoglobulin A (IgA) nephropathy**, particularly in young adults. In children, Alport syndrome and sickle cell disease or sickle cell trait are also diagnostic considerations. If the hematuria appears 2 to 3 weeks after a pharyngitis (or impetigo in children), **acute poststreptococcal glomerulonephritis** is a possibility. Younger subjects with a purpuric rash, arthralgias, and gross or microscopic hematuria may have Henoch–Schönlein purpura, whereas older patients with hematuria, proteinuria, profound constitutional symptoms, arthralgias, or respiratory symptoms may have vasculitis such as **Wegener's granulomatosis** (granulomatosis with polyangiitis) or **microscopic polyangiitis** (see Chapter 9). Patients with known **SLE** should be screened regularly for the development of hematuria and/or proteinuria, because these findings indicate renal involvement and the need for a kidney biopsy and further treatment.

Gross or microscopic hematuria can occur after **strenuous exercise**. This includes contact sports with direct trauma to the kidneys and noncontact sports, such as marathon running, bicycling, rowing, and even swimming. The hematuria has been attributed to trauma to the bladder due to up and down movement with running and biking; however, other studies using phase-contrast microscopy have found significant numbers of dysmorphic RBCs and even red cell casts in the urine after running, indicating that exercise-induced hematuria may be of glomerular origin. Purely exercise-induced hematuria disappears within 2 to 7 days after vigorous exercise and is benign; however, it is a **diagnosis of exclusion**. Hematuria that occurs after exercise may also uncover an underlying condition, such as autosomal dominant polycystic kidney disease. Another cause of exercise-induced hematuria is the **nutcracker syndrome**, which describes the compression of the left renal vein between the aorta and superior mesenteric artery; this may be accompanied by left flank pain.

Hematuria (microscopic or macroscopic) that occurs in an anticoagulated patient should not be attributed to the anticoagulation per se unless bleeding is observed from multiple sites and there is clear evidence for overanticoagulation. Prospective studies in anticoagulated patients have shown that hematuria is not significantly more common than in the general population, and when it occurs, an underlying urological condition, including malignancy, is found in a high percentage of subjects. Therefore, **hematuria in anticoagulated patients should be evaluated as in other individuals**.

B. Specific diagnostic recommendations:

1. All patients with hematuria should have a **urine culture, microscopic urinalysis** by a trained clinician, and **quantitation of proteinuria**. The urine culture will detect infection as a cause of hematuria, particularly if associated with dysuria and pyuria. It will also rule out infection before any invasive procedures such as cystoscopy are undertaken (contraindicated during active infection). Infection, if present, should be treated appropriately and urinalysis should be repeated in 4 to 6 weeks. If the hematuria has resolved completely and there are no other risk factors, further tests are not necessary.

Microscopic examination of the urine and quantitation of proteinuria help to determine whether hematuria is of glomerular origin (see above). Dysmorphic red cells, red cell casts, and proteinuria of more than 1 to 2 g/day point to glomerulonephritis, and referral to a nephrologist for kidney biopsy is indicated. Serum chemistries to assess renal function and specific serologic tests to look for immunologic or infectious disease should be ordered as well (for details, see Chapter 9). If there is clear evidence for a glomerular source of hematuria and the patient has no risk factors for malignancy, imaging of the urinary tract and cystoscopy are not necessary.

Isolated dysmorphic hematuria without proteinuria can be due to Alport syndrome, thin basement membrane nephropathy, or mild IgA nephropathy. **Alport syndrome** is a genetic disorder of glomerular basement membrane (GBM) collagen chains and leads to end-stage renal failure, often in young adults. In 50% to 80% of patients, it is associated with sensorineural hearing loss and ophthalmologic abnormalities. Inheritance is x-linked in 80% to 85% of families and autosomal recessive in about 15%. The diagnosis can be made by renal biopsy and/or genetic testing. **Thin basement membrane nephropathy** has also been called benign familial hematuria. It affects about 1% of the population, is an autosomal dominant trait, is characterized by very thin GBMs, and has usually a benign course. Subjects with isolated glomerular hematuria are often not biopsied because the prognosis is good, unless Alport syndrome is a possibility and cannot be diagnosed otherwise. However, patients with isolated glomerular hematuria should be followed for the development of proteinuria, elevated blood pressure, or decreased renal function.

2. **Imaging** is usually performed in the evaluation of hematuria. The choice of test depends on the patient's age and history. In children, adolescents, and pregnant women a renal ultrasound should be ordered first to avoid the significant radiation associated with computed tomography (CT). **Renal ultrasound** will detect polycystic kidney disease, other congenital abnormalities of the kidneys and urinary tract, kidney stones, particularly if associated with obstruction, and Wilms tumor in children. Renal ultrasound is also helpful in patients with suspected glomerular hematuria, to determine kidney size. If both kidneys are small, renal biopsy may not be indicated because of limited diagnostic utility (scarred kidneys) and increased risk of bleeding. If the patient's history or symptoms suggest nephrolithiasis, a computed tomography scan of kidneys, ureters and bladder (CT-KUB) should be ordered, which does not need the administration of intravenous contrast.

   Most patients with unexplained hematuria, particularly if over age 40 years, or with risk factors for malignancy should undergo multidetector CT urography with and without contrast. This is currently the most sensitive imaging modality for the detection of cancers of the urogenital tract, as well as calculi. However, the radiation dose is significant, and intravenous contrast can precipitate acute kidney injury, particularly in patients with underlying renal disease. In such cases, magnetic resonance imaging without gadolinium contrast can be done.

3. **Cystoscopy**: Cystoscopy should be performed in patients with hematuria and dysuria or other bladder/urethral symptoms, **after infection has been ruled out**. It should be performed in most patients with unexplained gross hematuria, unless the patient is young (less than 35 to 40 years for men and less than 45 years for women) and has no risk factors for bladder cancer. Cystoscopy is not necessary in young patients with a known diagnosis of autosomal dominant polycystic kidney disease, Alport syndrome, sickle cell disease, or IgA nephropathy; these disorders are typically associated with episodes of gross hematuria. However, cystoscopy is mandatory in older patients, smokers, patients who had been treated with cyclophosphamide, or with other risk factors for bladder cancer (see above). Cystoscopy also allows visualization of the prostate and urethra. Prostate cancer and benign prostatic hyperplasia can give rise to hematuria, due to increased vascularity and fragile blood vessels. However, other causes should be ruled out before attributing hematuria to benign prostatic hyperplasia.
4. **Urine cytology** has been reported to be 90% sensitive for bladder cancer but much less sensitive for upper tract malignancies. It is usually performed as an ancillary test before cystoscopy, but may be ordered instead of cystoscopy in patients at low risk for bladder cancer, such as individuals younger than 40 years, particularly if female and nonsmoker.

   A **24-hour urine** collection should be ordered in children and young adults with unexplained nonglomerular hematuria to look for **hypercalciuria and hyperuricosuria**. These conditions have been reported as a cause of hematuria in up to 35% of children with an otherwise negative evaluation, as well as in young adults. Decreasing urinary calcium excretion with a thiazide diuretic or urinary urate excretion with allopurinol usually leads to resolution of the hematuria. These treatments also reduce the risk of stone formation in these patients (see Chapter 6).
5. Rarely **arteriography** may be needed to diagnose arteriovenous fistulas or malformations, which may be congenital or acquired, or aneurysms of the renal arterial branches in **polyarteritis nodosa** or **microscopic polyangiitis**. Renal venography or Doppler ultrasound can establish a diagnosis of nutcracker syndrome. Other rare conditions are hereditary hemorrhagic telangiectasia, radiation cystitis, and schistosomiasis in endemic areas.

   Despite extensive testing, hematuria may remain **unexplained**. These patients should be followed with repeat urinalysis, cytology, monitoring of blood pressure and renal function, and in some cases repeat imaging, depending on the clinical situation and risk for malignancy.

IV. EVALUATION OF PROTEINURIA

A. **Physiologic Considerations:** Healthy adults excrete less than 150 mg protein/day. Less than 20 mg of that is albumin, which is normally filtered by the glomerulus in higher amounts (the exact amount is still controversial)

and then reabsorbed and broken down by proximal tubular epithelial cells. About half of the normally excreted protein consists of **Tamm–Horsfall protein**, also called **uromodulin**, which is secreted by tubular cells lining the loop of Henle and distal tubules. The other half of the normal protein excretion consists of filtered plasma proteins and polypeptides, including albumin (about 15% of total urinary protein), immunoglobulins (about 5%), light chains (also about 5%), beta-2 microglobulin, and others. The normal protein excretion rate in children is less than 100 mg/m^2/day.

Increased urinary protein excretion is often a sign of kidney disease. **Abnormal proteinuria** can be due to increased glomerular filtration of proteins, decreased tubular reabsorption, or both. Increased glomerular filtration occurs with overproduction of filterable proteins, usually immunoglobulin light chains due to multiple myeloma, or due to increased permeability of the glomerular filtration barrier, indicating glomerular disease. Therefore, based on physiology, abnormal proteinuria can be classified as follows:

1. **Overflow Proteinuria**: Overflow proteinuria is due to the filtration of an abnormally large amount of small molecular weight proteins that exceed the capacity of the tubules for reabsorption. Causes of overflow proteinuria include intravascular hemolysis (hemoglobinuria), rhabdomyolysis (myoglobinuria), and multiple myeloma (light chains). These proteins and light chains are not detected by the urine dipstick test (see above) but are detected in a 24-hour urine collection, or by determination of a urine protein–creatinine ratio (UPCR). Evaluation of overflow proteinuria is guided by the clinical context. Hemoglobinuria and myoglobinuria are usually recognized by the presence of red urine, with red, heme-positive supernatant after centrifugation (see above). Urinary light chains are detected by urine immunofixation (IFE).

2. **Tubular Proteinuria:** In contrast to overflow proteinuria, in which normal tubular reabsorption is overwhelmed by the large amount of filtered proteins, tubular proteinuria is caused by damage to the renal tubulointerstitium leading to a failure to reabsorb normally filtered small molecular weight proteins, mostly beta-2 microglobulin, light chains, retinol-binding protein, and breakdown products of albumin. In addition, brush border and cellular enzymes (such as *N*-acetylglucosamine and lysozyme) may appear in the urine when proximal tubular epithelia are injured, and uromodulin may be secreted in increased amounts with injury to epithelial cells of the loop of Henle and distal nephron. As in overflow proteinuria, these tubular proteins are not detected by the urine dipstick test and may therefore remain undiagnosed. However, they will be measured if a 24-hour urine collection is ordered for evaluation of an elevated serum creatinine or hematuria. Proteinuria due to tubulointerstitial disease is no more than 1 to 2 g/day. Higher amounts of proteinuria (>3 g/day) are due to glomerular disease or overflow of filtered light chains. If the source of proteinuria is unclear, urine protein electrophoresis (UPEP) and IFE should be used to aid in diagnosis. In glomerular proteinuria, UPEP demonstrates primarily albumin, whereas tubular proteinuria demonstrates a predominance of small molecular weight proteins. UPEP and IFE will

detect abnormal light chains. Tubular and glomerular proteinuria are not mutually exclusive as most glomerular diseases are accompanied by tubulointerstitial injury and inflammation, and tubulointerstitial diseases eventually lead to focal segmental or global glomerulosclerosis.

3. **Glomerular Proteinuria:** Glomerular proteinuria results from injury to the glomerular filtration barrier, which consists of the fenestrated endothelial cells, the GBM, and the visceral glomerular epithelial cells or podocytes. Damage to any one of these barriers may be responsible for increased glomerular permeability to macromolecules. For instance, the **endothelial cell layer** is disrupted in **preeclampsia**, the **GBM** is defective in **Alport** syndrome, and the **podocytes** are injured in **focal segmental glomerulosclerosis**, all diseases characterized by proteinuria. In the last decade, the importance of the slit-diaphragm between the foot processes of podocytes has been recognized through the discovery of **genetic mutations in slit-diaphragm proteins** in infants and children with heavy glomerular proteinuria. Other genetic mutations of podocyte enzymes or of protein constituents of the GBM also lead to glomerular proteinuria. Injury to the filtration barrier may change its *size*-selective properties, allowing the passage of higher molecular weight proteins or even of cells (as in crescentic glomerulonephritis), or may change its *charge*-selective properties, permitting the ultrafiltration of negatively charged albumin (as in minimal change nephropathy), or both. Finally, mesangial injury may also contribute to proteinuria by interfering with normal mesangial clearance functions. Glomerular proteinuria can be mild, with albumin excretion rates of 30 to 300 mg/day (high albuminuria), moderate, in the range of 1 to 3 g/day, or heavy (nephrotic), more than 3 g/day and up to over 20 g/day (see below). In general, the heavier the proteinuria, the worse is the prognosis of the underlying kidney disease.
4. **"Postrenal" Proteinuria** occurs with inflammation in the urinary tract, that is, with infection, nephrolithiasis, gross hematuria, and tumors. The amounts are small to moderate.

B. Definitions used clinically to classify proteinuria:

1. **High Albuminuria** (formerly called microalbuminuria because dipstick tests are usually negative due to low urine albumin concentrations): albumin excretion 30 to 300 mg/day, or spot urine albumin to creatinine ratio >30 mg/g.
2. **Overt Proteinuria** (also called macroalbuminuria, dipstick positive): Albumin excretion >300 mg/day, or spot urine albumin to creatinine ratio >300 mg/g.
3. **Nephrotic Range Proteinuria**: Protein excretion >3 to 3.5 g/day, or spot UPCR >3 g/g.
4. **Nephrotic Syndrome**: Nephrotic range proteinuria, hypoalbuminemia (<3.0 g/dL), edema, and hyperlipidemia (elevated serum cholesterol and/or triglyceride levels) (see below).
5. **Nephritic Syndrome**: Glomerular proteinuria (any degree) and micro- or macrohematuria of glomerular origin, indicating glomerular

inflammation (glomerulonephritis). Red cell casts may be present, as well as elevated serum creatinine and hypertension.

6. **Isolated Proteinuria**: Nonnephrotic proteinuria (usually <2 g/day) without hematuria or decreased GFR, bland urine sediment, and no underlying diabetes, hypertension, or systemic disease. This presentation is often benign, but patients do need follow-up to detect any changes.
7. **Transient Proteinuria**: Transient proteinuria is common in children, adolescents, and young adults. It can occur with fever, exercise, upright position (orthostatic proteinuria), or symptomatic urinary tract infection. It is usually low grade (<1 to 2 g/day) and benign if repeat testing is negative for protein. **Orthostatic proteinuria** is diagnosed if the first morning urine (or an overnight collection) is negative for protein, and proteinuria is only present during a daytime collection. These individuals do not need any further testing and do not have kidney disease. **Heavy exercise** can occasionally cause proteinuria of more than 2 g/day as well as hematuria. If these findings resolve completely within a few days of rest, the patient can be reassured, after polycystic kidney disease has been excluded. Other causes of transient proteinuria are uncontrolled diabetes with hyperglycemia, severe hypertension, and heart failure.

C. **Detection and Quantification of Proteinuria:** Although the urinary dipstick test is used frequently as a screening test for proteinuria, it is important to recognize its limitations. It is neither very sensitive nor quantitative. **A negative dipstick result does not rule out clinically significant proteinuria** (because it mainly detects albumin and is concentration dependent). This limitation can be overcome by the **sulfosalicylic acid (SSA) test**: One part urine supernatant is mixed with 3 parts of 3% SSA, which results in increasing turbidity with increasing urinary protein concentrations. The SSA test detects the presence of all proteins including light chains. A positive SSA test with a negative dipstick result indicates the presence of nonalbumin proteins in the urine, most often light chains due to multiple myeloma.

A **positive dipstick** result needs to be followed by a **quantitative assessment of proteinuria**, because prognosis and treatment often depend on the degree of proteinuria. Quantification of proteinuria can be achieved with two methods, a 24-hour urine collection and a spot urine protein (or albumin) to creatinine ratio. Both methods have limitations.

1. **The 24-hour Urine Collection:** When done properly, the 24-hour urine collection provides the most accurate measure of urinary protein excretion. This method involves emptying the bladder and discarding the first morning urine, then collecting all urine for the subsequent 24 hours, including the first morning void the following day. The urine should be refrigerated during the collection period. This is cumbersome for the patient, and collections are often done incorrectly, so that over- and undercollections are common. To assess the adequacy of a collection, the **total creatinine excretion should always be measured simultaneously with the 24-hour urine protein excretion**. If the measured amount of creatinine is significantly outside the expected range, the collection is inaccurate. In healthy adults under age 50 years, 24-hour urinary excretion of creatinine should be 15 to 20 mg/kg of ideal body weight for females and 18 to

25 mg/kg for males. In older adults, there is a progressive decrease in daily creatinine excretion due to progressive decline in muscle mass.

2. **Urine Protein–Creatinine Ratio:** A urinary protein–creatinine concentration ratio on the first voided morning urine can be used as a quick assessment of proteinuria. In clinical practice, however, it is often a random daytime sample that is obtained during an office visit. Assuming that the average individual excretes approximately 1 g of creatinine per day, **normal spot UPCR** on random samples generally falls **below 0.2** (gram protein per gram creatinine), whereas values **greater than 3** suggest the presence of **nephrotic range proteinuria**. Measuring the protein–creatinine ratio in a spot urine sample is useful for a quick and easy determination whether proteinuria is mild or in the nephrotic range. This distinction is important for two reasons: First, nephrotic proteinuria is always due to glomerular disease (unless there is overflow of light chains), whereas lesser degrees can be of either tubular or glomerular origin. Second, primary glomerular diseases with nephrotic range proteinuria have a worse prognosis and are treated differently than the same diseases with milder degrees of proteinuria. The spot UPCR is also useful as a substitute for repeated 24-hour urine collections during treatment and follow-up, but it should not be used alone if it is in an equivocal range (2 to 3) or in patients whose creatinine generation and excretion is significantly greater or less than 1 g/day (e.g., in individuals with very large or very low muscle mass).

3. **Urinary Albumin–Creatinine Ratio (UACR):** This ratio is usually obtained in diabetic patients to screen for diabetic nephropathy, or in research studies. **Healthy** adults have a ratio of **5 to 15** (mg albumin per gram creatinine). An albumin–creatinine ratio **greater than 30** in repeated spot urine samples is considered abnormal and can be a sign of **incipient diabetic nephropathy**, but is also seen with hyperglycemia in uncontrolled diabetes, in patients with hypertension, and in patients with cardiovascular disease. An elevated UACR serves as a biomarker for **increased cardiovascular disease risk**.

   Another limitation to using spot UPCR and UACR is the variability of protein excretion throughout the day as well as day to day. Therefore, only large (such as halving) and sustained changes in the UPCR during follow-up are indicative of a response to treatment.

V. APPROACH TO THE PATIENT WITH PROTEINURIA.

When evaluating a patient with persistent proteinuria, the main questions to be considered are as follows:

1. What is the etiology of the proteinuria, and are further tests needed, including a kidney biopsy?
2. What is the risk of progression to ESRD, and are there specific therapies available to prevent ESRD?

A. Causes of Proteinuria: The most common cause of proteinuria and the nephrotic syndrome in the US adult population is **diabetes**, usually type 2. This highlights the fact that proteinuria is often due to underlying systemic diseases that also involve the kidneys. Therefore, a thorough medical history

and physical examination, together with targeted laboratory testing, will often reveal the diagnosis and a kidney biopsy may not be necessary, particularly if the proteinuria is mild (nonnephrotic).

Other systemic diseases that may cause proteinuria, mild to moderate or nephrotic, with or without glomerular hematuria, are **rheumatological disorders** such as SLE, sarcoidosis, and systemic vasculitis; **infections** such as human immunodeficiency virus (HIV) disease, hepatitis B and C, endocarditis, and visceral abscess; **genetic diseases** such as Alport syndrome and others; and **neoplasms** including multiple myeloma and solid tumors. Chapter 9 discusses glomerulonephritis due to these diseases in more detail. Moreover, a variety of **medications** can induce proteinuria by immunologic or toxic mechanisms, calling for a thorough medication history when evaluating proteinuria. The most common causes of "secondary" proteinuria, that is, proteinuria due to renal (glomerular) involvement with an underlying systemic disease or medications, are listed in Table 8-2.

Table 8-2.	Causes of Secondary Proteinuria (Due to a Systemic Disorder or Medication)
Metabolic	
Diabetes mellitus, morbid obesity	
Hereditary/Genetic	
Alport's syndrome, Fabry's disease, nail–patella syndrome, polycystic kidney disease, congenital nephrotic syndrome	
Infectious	
Hepatitis B and C, human immunodeficiency virus–associated nephropathy, malaria, secondary syphilis, amyloidosis due to chronic infection	
Immunologic	
Systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, postrenal transplantation, post-bone marrow transplantation, rheumatoid arthritis	
Medications	
Penicillamine, lithium, nonsteroidal anti-inflammatory drugs, bisphosphonates, tyrosine kinase inhibitors, VEGF (vascular endothelial growth factor) antagonists, sirolimus	
Neoplasms	
Multiple myeloma; colon, lung, or breast carcinoma; lymphoma; leukemia; immunoglobulin light chain (AL) amyloidosis	
Miscellaneous	
Reflux nephropathy, sickle cell disease, and other disorders associated with nephron loss and secondary glomerulosclerosis	

Table 8-3.	Causes of Nephritic (Glomerular) Proteinuria and Hematuria
Hereditary	
Alport syndrome; hereditary IgA nephropathy, and focal segmental glomerulosclerosis	
Infectious	
Hepatitis B and C, human immunodeficiency virus–induced immunocomplex-mediated glomerulonephritis, endocarditis, ventriculoperitoneal shunt infection, visceral abscess, poststreptococcal glomerulonephritis	
Immunologic	
Systemic lupus erythematosus, Henoch–Schönlein purpura and IgA nephropathy, Wegener granulomatosis, microscopic polyarteritis, Goodpasture's syndrome, cryoglobulinemia; membranoproliferative glomerulonephritis	
Neoplasms	
Chronic lymphocytic leukemia (membranoproliferative glomerulonephritis), multiple myeloma (membranoproliferative glomerulonephritis), rapidly progressive glomerulonephritis associated with cancer (rare)	
Miscellaneous	
Liver cirrhosis (IgA nephropathy)	

IgA, immunoglobulin A.

Some of these disorders can also be associated with significant glomerular hematuria, that is, a nephritic sediment, and these are listed in Table 8-3.

If no systemic condition is present, the patient likely has a **primary or idiopathic glomerulopathy**, which can only be diagnosed by kidney biopsy. Primary glomerular disorders are minimal change nephropathy, IgA nephropathy, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, necrotizing and crescentic glomerulonephritis, and focal and segmental glomerulosclerosis (see Chapter 9).

B. **Risk Assessment:** The risk of progression to ESRD is not only determined by the underlying disease, but mostly by the degree of proteinuria, the presence of decreased renal function at baseline, and the degree of control of hypertension. In general, **the higher the amount of proteinuria, the higher the risk for progression to ESRD**, particularly if blood pressure is not controlled. Nephrotic range proteinuria carries a much higher risk than nonnephrotic proteinuria even if the underlying renal disease is the same, for

example, membranous nephropathy or focal segmental glomerulosclerosis. Patients with **renal insufficiency** or concurrent **hematuria** also have a **higher risk** of progression. This risk assessment guides the need for further testing and treatment. Specifically, if renal function is normal, no red cells are present, and proteinuria is less than 500 mg/day, the risk of future renal injury is low in the absence of diabetes and/or hypertension, and the patient can be observed. Proteinuria in the range of 1 to 2 g/day with no hematuria and normal renal function may be caused by glomerular lesions or tubular abnormalities; the prognosis is still good if blood pressure is adequately controlled, but the patient requires closer follow-up to detect any changes in his/her condition which would call for further testing or treatment. Proteinuria greater than 3 g/day is due to glomerular disease (if mostly albumin and not overflow of light chains) and needs further evaluation, usually by kidney biopsy, unless it is clearly due to diabetic nephropathy. Any degree of proteinuria accompanied by urinary RBC casts or dysmorphic RBCs (**nephritic** picture) must be further evaluated for the presence of **glomerulonephritis or vasculitis**.

C. **Specific Recommendations for Therapy:** Because the risk of rapid progression in proteinuric kidney diseases is potentiated by uncontrolled hypertension, **adequate blood pressure control** is a cornerstone for treatment. Multiple intervention trials have demonstrated the benefits of blood pressure control to less than 130/80 mmHg if proteinuria is 1 g/day or more, and less than 125/75 mmHg if proteinuria is more than 3 g/day (in patients younger than 65 years; older patients may be treated to slightly higher blood pressure goals). In addition, **blockers of the renin–angiotensin system (RAS)**, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, can preserve kidney function better than other antihypertensive agents in patients with proteinuria, provided that the blood pressure goal is reached. Patients with heavy proteinuria benefit the most from RAS blocking drugs. Renal function and potassium levels need to be monitored during this therapy, particularly in patients with diabetes who are prone to developing hyperkalemia. Combination with a diuretic can help to prevent hyperkalemia. Most patients with underlying kidney disease need two or more drugs to adequately control their blood pressure, and the **antiproteinuric effect of RAS blocking drugs** can be **enhanced** by combination with **diuretics**, as well as a **low-salt diet**. Calcium channel blockers such as nifedipine should not be used alone for patients with proteinuria because they dilate the afferent arteriole and therefore increase glomerular pressure and proteinuria, but they can be used in combination with RAS blocking drugs if the blood pressure goal cannot be attained with RAS blockers (with or without diuretic) alone.

In patients with proteinuria due to diabetes, **adequate blood sugar control** is also important; however, overly aggressive control to achieve a hemoglobin A1c level of 6% carries more risk (frequent episodes of hypoglycemia) than benefit for most patients with type 2 diabetes who already have end-organ damage. Three large intervention trials have shown that the risk–benefit ratio is best when aiming at a hemoglobin A1c level between 7% and 8%. Strict blood pressure control using RAS blocking drugs is the mainstay of treating proteinuria in diabetic subjects.

Dietary protein restriction in the range of 0.6 to 0.8 g/kg/day has been suggested, both to reduce proteinuria and to slow the rate of loss of renal function in proteinuric kidney diseases. The efficacy of RAS blockade to reduce proteinuria, the conflicting supporting data for the efficacy of low-protein diets, and concerns regarding nutritional safety in patients with heavy proteinuria (i.e., more than 10 g/day) have led to an abandonment of stringent dietary protein restriction. Nevertheless, patients with proteinuria, even if heavy, should probably be advised to **avoid high-protein diets** and eat a diet close to the recommended daily allowance of protein, which is 0.8 g protein/kg body weight. Moderate **salt restriction** to 2 to 3 g/day should be recommended to facilitate blood pressure control and reduce proteinuria and edema if present.

Immunosuppressive therapy with corticosteroids either alone or in combination with cytotoxic drugs (e.g., cyclophosphamide) or calcineurin inhibitors (cyclosporine A or tacrolimus) is used for treatment of proteinuria and/or hematuria if an underlying glomerulonephritis or vasculitis is documented by renal biopsy. These specific therapies are discussed in Chapter 9.

The **nephrotic syndrome,** defined by proteinuria of more than 3.5 g/1.73 m^2 (body surface area)/day, hypoalbuminemia, hyperlipidemia, and edema, is always due to glomerular disease with disruption of the filtration barrier. Not all patients with a given amount of nephrotic range proteinuria develop the full nephrotic syndrome; the reasons for this are not completely understood. **Hypoalbuminemia** develops when hepatic albumin synthesis is insufficient to compensate for heavy urinary albumin losses. **Sodium and water retention** with resultant edema occur in many patients as a direct result of glomerular and tubular injury; the exact mechanism is not entirely clear. Fluid overload can be massive, with anasarca, pleural effusions, and ascites, requiring high-dose diuretic therapy (see Chapter 1). **Hyperlipidemia** may be caused by increased apolipoprotein synthesis in the liver, which is stimulated by hypoproteinemia and an associated decrement in plasma oncotic pressure. Diminished clearance of plasma cholesterol and triglycerides also plays a role. Lipids are filtered in nephrotic syndrome, leading to **lipiduria**, either as free lipids or enclosed in casts (fatty cast) or in degenerating tubular cells (oval fat bodies). If hyperlipidemia due to nephrotic disorders persists for years, it likely contributes to accelerated atherosclerosis, and therefore these patients are usually treated with 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins) or fibrates to reduce their cardiovascular risk. However, statins and fibrates should not be used together because of the increased risk of rhabdomyolysis in patients with kidney disease. Heavy proteinuria also predisposes to **hypercoagulability**. Variable losses of antithrombin III, protein S, and protein C have been described in some but not all nephrotic patients. Deep vein thrombosis, renal vein thrombosis, and pulmonary emboli are well-known complications of the nephrotic syndrome and require anticoagulation as long as the nephrotic syndrome persists. Urinary losses of immunoglobulins and complement factors contribute to an increased susceptibility to infections, particularly in children with the nephrotic syndrome. Other urinary losses include thyroid-binding globulin (low total thyroxine, normal thyroid-stimulating hormone, and

Table 8-4. Treatment of Signs and Complications of the Nephrotic Syndrome

Sign or Complication	Treatment
Proteinuria >3.5 g/d	1. Blood pressure reduction to less than 125/75–130/80 mmHg, using drugs that block the renin–angiotensin–aldosterone system 2. Low-salt diet 3. Avoidance of large dietary protein loads; daily protein intake 0.8 g/kg recommended
Edema and fluid overload	Diuretics, usually loop diuretics, and salt restriction; may be combined with aldosterone antagonist (e.g., spironolactone)
Hypercholesterolemia	Statin drug
Hypertriglyceridemia >1,000 mg/dL	Fibrate drug
Thromboembolism	Anticoagulation
Secondary hyperparathyroidism, vitamin D deficiency	Vitamin D replacement

normal free thyroxine), transferrin, and vitamin D, resulting in vitamin D deficiency, hypocalcemia, and secondary hyperparathyroidism.

As described above (causes of proteinuria), the nephrotic syndrome is often a manifestation of an underlying systemic disease or may be induced by medications. Therefore, a thorough evaluation for underlying diseases and medication use is mandatory. Usually a kidney biopsy is performed to define the exact histopathology and prognostic features, except in patients with diabetes who have other microvascular complications such as retinopathy and/or neuropathy and no atypical features. Such patients most likely have diabetic nephropathy and are treated with RAS blocking drugs, not immunosuppressants. **Treatment of the nephrotic syndrome** is directed at the underlying disease if present (e.g., hepatitis, HIV, malignancy) and at complications of the nephrotic syndrome, such as edema or venous thrombosis, and also includes the general recommendations for proteinuria reduction described above (Table 8-4).

Suggested Readings

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9 The Patient with Glomerular Disease or Vasculitis

Sarah E. Panzer and Joshua M. Thurman

I. OVERVIEW. The glomerular diseases are defined by their clinical presentations and the histologic findings associated with the diseases. Glomerular diseases can also be categorized as primary processes in which the disease is confined to the kidney or as secondary processes in which a systemic disease impacts the kidney. Many glomerular diseases are autoimmune in nature. Injury to the kidney may be caused by the deposition of immune complexes within the glomeruli or by autoantibodies directed against antigens present within the kidney. The small vessels of the kidney and the glomerular capillaries are also frequently the target of small vessel vasculitides.

Clinically, the presence of a glomerular disease should be considered when proteinuria is present. Glomerulonephritis (GN) and vasculitis should be considered when hematuria and/or proteinuria is present. Therefore, the approach to the patient with possible glomerular disease should begin with an assessment of the protein excretion in the urine and a microscopic analysis of the urine for dysmorphic red blood cells and/or red blood cell casts.

When hematuria and/or proteinuria has been identified and glomerular disease is determined to be the most likely etiology, further clinical information and serologic testing can assist in the classification of the renal disorder before invasive testing. Although it is often difficult to predict the histologic pattern of injury in a patient with glomerular disease, patients frequently fall into two general clinical presentations—the nephritic syndrome and the nephrotic syndrome. The recognition of these syndromes can guide further serologic testing.

II. CLINICAL PATTERNS OF GLOMERULAR DISEASE

A. The Nephritic Syndrome. Patients with the nephritic syndrome typically present with hematuria, dysmorphic red blood cells and/or red blood cell casts, and proteinuria. The proteinuria can range from 200 mg/day to heavy proteinuria (greater than 10 g/day). Clinically, it is accompanied by hypertension and edema. Renal insufficiency is common and typically progressive. The term *rapidly progressive glomerulonephritis* (RPGN) refers to diseases with a nephritic syndrome that lead to a rapid deterioration in renal function, defined as a doubling of serum creatinine or a 50% decrease in glomerular filtration rate (GFR) over 3 months or less.

B. The Nephrotic Syndrome. Patients with the nephrotic syndrome present with proteinuria, hypoalbuminemia (serum albumin less than 3.0 mg/dL), and edema. Nephrotic range proteinuria (often defined as greater than 3.5 g

of proteinuria per day) is usually the most prominent renal abnormality. Dysmorphic red blood cells and casts are typically absent, but exceptions do exist. Focal segmental glomerulosclerosis (FSGS), for example, usually presents with nephrotic range proteinuria but can be associated with low-grade hematuria. Additional complications of the nephrotic syndrome include hyperlipidemia, thrombosis, and infection. The diseases that cause the nephrotic syndrome can lead to chronic, progressive renal injury, but typically are more slowly progressive than diseases presenting as the nephritic syndrome.

C. **Clinicopathologic Correlation.** The pathologic diagnosis of glomerular diseases incorporates the histologic pattern defined by light microscopy, immunofluorescence staining for immunoglobulins (Igs) and complement proteins, and examination of the glomerular ultrastructure by electron microscopy. The primary glomerular diseases are listed in Table 9-1, with the prominent histologic findings on biopsy that define the disorder. There is a general correlation between the pattern of histologic injury and the clinical presentation. Thus, the clinical findings can suggest the underlying pathologic process, although definitive diagnosis requires a biopsy. The clinician must also consider if there is a systemic process that may be causing the proteinuria. Primary glomerular diseases can often not be distinguished histologically from the injury pattern seen in systemic diseases, so this distinction is usually made clinically.

The nephritic syndrome is usually caused by glomerular inflammation and manifests with an "active" urine sediment (e.g., cells and/or casts). Immune complexes which deposit in the mesangium or in the subendothelial space [membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, and many forms of lupus nephritis] generate inflammatory mediators that have access to the circulation and can cause an influx of inflammatory cells. Glomerular endothelial injury is also caused by autoantibodies to the glomerular basement membrane (anti-GBM), and with necrotizing injury of the glomerular capillaries as occurs in the antineutrophil cytoplasmic antibody (ANCA)–mediated vasculitides. These two diseases frequently present with glomerular crescents and RPGN (Table 9-2).

Diseases that present with the nephrotic syndrome disrupt the size and charge-selective barriers that ordinarily prevent the ultrafiltration of macromolecules across the glomerular capillary wall. In general, these diseases disrupt the glomerular capillary wall without causing overt inflammation (FSGS, diabetic nephropathy, and amyloidosis), or they affect the epithelial cells without causing endovascular inflammation [membranous nephropathy (MN) and minimal change disease (MCD)].

III. CLINICAL ASSESSMENT OF GLOMERULAR DISEASE

A. **The Nephritic Syndrome.** In cases in which the nephritic syndrome is the predominant clinical presentation, a search for systemic diseases is warranted (Table 9-3). The history and physical examination should particularly focus on the assessment of rashes, lung disease, neurologic abnormalities, evidence of viral or bacterial infections, and musculoskeletal and hematologic abnormalities. Laboratory assessment should be tailored to the clinical findings in the history and physical examination. A complete blood count (CBC), electrolyte panel, 24-hour urine collection for protein and creatinine clearance, and liver function tests should be obtained initially. Serum complement (C3) levels are often

Table 9-1. Primary Glomerular Diseases, Defined by Histology

Nephritic	Histologic Findings	Nephrotic	Histologic Findings
Renal limited vasculitis/ microscopic polyangiitis	Necrotizing capillary lesions, crescents; negative IF, EM	Minimal change disease	Normal light microscopy, effaced foot processes on EM
Antiglomerular basement membrane disease	Linear IgG staining along glomerular basement membrane	Membranous nephropathy	Thickened GBM on light, subepithelial "spikes" on light, IF, EM, granular IgG and C3
Membranoproliferative glomerulonephritis	Thickened mesangial matrix, splitting ("double contour") of the glomerular basement membrane, C3 granular staining on IF	Focal segmental glomerulosclerosis	Sclerosis in portions of glomeruli, C3 in areas of sclerosis on IF
		Fibrillary glomerulonephritis	Fibrillar deposits in mesangium, negative Congo red staining on IF
IgA nephropathy	IgA in mesangium on IF		

EM, electron microscopy; GBM, glomerular basement membrane; IF, immunofluorescence; Ig, immunoglobulin.

Table 9-2. Histologic Classification of Crescentic (or Rapidly Progressive) Glomerulonephritis

Linear Immunofluorescence	Granular Immunofluorescence	Absent (Pauci-immune) Immunofluorescence
Goodpasture's disease Anti-GBM disease	Lupus nephritis IgA nephropathy Cryoglobulinemia Henoch–Schönlein purpura	ANCA-associated vasculitis (GPA, Churg–Strauss syndrome, microscopic polyangiitis)

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GPA, granulomatosis with polyangiitis; Ig, immunoglobulin.

clinically helpful to assist in the diagnosis of a specific renal disease (Table 9-4). Further laboratory assessment may be performed based on these findings, and may include an antistreptolysin titer, antinuclear antibody (ANA), ANCA, cryoglobulins, and/or an anti-GBM antibody (Table 9-3). These early assessments may provide a presumptive diagnosis and should lead the clinician to an appropriate therapeutic intervention while awaiting renal biopsy results, but they are not a substitute for renal biopsy. Proper management of the glomerular diseases requires a tissue diagnosis to confirm the clinical findings and provide information regarding the acuity and chronicity of the disease process.

B. The Nephrotic Syndrome. With the identification of significant proteinuria, with or without other features of the nephrotic syndrome, secondary causes of proteinuria should be considered (Table 9-5). History and physical examination should evaluate for the presence of viral and bacterial infections, malignancies (particularly lung, breast, and lymphomas), and chronic diseases (such as diabetes), and medications should be reviewed for their potential to cause glomerular proteinuria. Laboratory assessment initially includes CBC, electrolyte panel, 24-hour urine collection for protein and creatinine clearance, liver function tests, and a cholesterol panel. Further assessment may include hepatitis and human immunodeficiency virus (HIV) serologies, ANA, rapid plasma reagin, and serum and urine electrophoresis (Table 9-5). Renal biopsy should be performed in all cases in which no cause is evident, or to determine the extent of renal disease to guide therapy or prognosis.

IV. THERAPY FOR GLOMERULAR DISEASE.

Treatment of glomerular disorders can be approached by management of the nephrotic syndrome and immunomodulatory therapies for specific glomerular diseases and vasculitides. The management of systemic diseases that cause secondary glomerular injury is rapidly changing (e.g., new antiviral therapies for HIV and hepatitis B and C, and clinical trials using chemotherapeutic regimens for malignancies and vasculitides). Therefore, the reader is encouraged to refer to recent disease-specific reviews of the literature for current management strategies for these systemic diseases.

A. General Management of Proteinuric Glomerular Disease. Untreated nephrotic syndrome is associated with significant morbidity due to

Table 9-3. Systemic Diseases That Cause Glomerular Injury and a Nephritic Clinical Presentation

Disease	Specific Examples	Laboratory Findings
Infections	Hepatitis C (Hepatitis B less commonly)	Low C3, hepatitis C Ab, hepatitis C viral PCR, cryoglobulins
	Poststreptococcal GN	Low C3, antistreptolysin Ab
	Bacterial endocarditis	Low C3, positive blood cultures
	Methicillin-resistant *Staphylococcus aureus* infection	Low C3, positive blood cultures
Autoimmune diseases	Lupus nephritis	Low C3, ANA, anti-dsDNA Ab
	Goodpasture's syndrome	Anti-GBM Ab
Vasculitides	Granulomatosis with polyangiitis	c-ANCA
	Microscopic polyangiitis	p-ANCA
	Churg–Strauss syndrome	p-ANCA
	Henoch–Schönlein purpura	IgA in skin biopsy
	Polyarteritis nodosa	ANCA in 20% (c- or p-ANCA)
	Mixed cryoglobulinemia	Rheumatoid factor, low C4
Thrombotic microangiopathy	Scleroderma renal crisis	Anti-Scl-70
	Thrombotic thrombocytopenic purpura	Low platelets, hemolysis, low ADAMS13 activity
	Hemolytic uremic syndrome	Low platelets, hemolysis, *Escherichia coli* enteritis, low C3 or other evidence of complement activation
	Malignant hypertension	

Ab, antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-dsDNA, antidouble-stranded DNA; GN, glomerulonephritis; Ig, immunoglobulin; PCR, polymerase chain reaction.

accelerated atherosclerosis, dyslipidemia, thromboembolic events, and infections. Often treatment requires both general management and disease-specific treatment to achieve remission and lessen morbidity. The general treatment strategies that should be considered in the patient with nephrotic syndrome include management of proteinuria, hypertension, edema, hyperlipidemia, and hypercoagulability.

Table 9-4. Clinical Approach to Glomerulonephritis Based upon Serum Complement

Low Serum Complement Level		Normal Serum Complement Level	
Systemic diseases	**Primary renal diseases**	**Systemic diseases**	**Primary renal diseases**
SLE Subacute bacterial endocarditis "Shunt" nephritis Cryoglobulinemia Atypical hemolytic uremic syndrome	Poststreptococcal glomerulonephritis Membranoproliferative glomerulonephritis Dense deposit disease	Polyarteritis nodosa Hypersensitivity vasculitis Granulomatosis with polyangiitis Henoch–Schönlein purpura Goodpasture's syndrome Visceral abscess	IgA nephropathy Idiopathic rapidly progressive glomerulonephritis (antiglomerular basement membrane disease, pauci-immune glomerulonephritis, immune complex disease)

Ig, immunoglobulin; SLE, systemic lupus erythematosus.

(Adapted from Madaio MP, Harrington JT. Current concepts. The diagnosis of acute glomerulonephritis. *N Engl J Med* 1983;309:1299, with permission.)

Table 9-5. Systemic Diseases That Cause Glomerular Injury and a Nephrotic Clinical Presentation

Disease State	Common Etiologies	Laboratory Findings
Infections	Hepatitis B (hepatitis C less common) HIV Syphilis	Hepatitis B sAg, hepatitis B eAg HIV Ab RPR
Chronic diseases	Diabetes Amyloidosis Sickle cell disease Obesity	Elevated $HgbA_{1c}$, blood glucose UPEP/IEP (when associated with light chains) Hemoglobin electrophoresis
Malignancies	Multiple myeloma Adenocarcinoma (lung, breast, colon most common) Lymphoma	SPEP, UPEP Abnormal cancer screening studies (usually clinically evident tumor burden)
Rheumatologic	Systemic lupus erythematosus Rheumatoid arthritis Mixed connective tissue disease	ANA, anti-dsDNA Ab Rheumatoid factor Anti-RNP (ribonuclear protein) Ab
Medications	NSAIDs Lithium Bucillamine Penicillamine Ampicillin Captopril	—

Ab, antibody; ANA, antinuclear antibody; anti-dsDNA Ab, antidouble-stranded DNA antibody; HIV, human immunodeficiency virus; IEP, immunoelectrophoresis; NSAID, nonsteroidal anti-inflammatory drug; RPR, rapid plasma reagin; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

1. **Proteinuria.** In nephrotic syndrome, treatment to reduce the degree of proteinuria to the nonnephrotic range will often result in an elevation or normalization of serum proteins (such as albumin). This is associated with a reduction in the symptoms of nephrotic syndrome, thus improving patients' quality of life. The cornerstone to management of proteinuria is the inhibition of the renin–angiotensin system using either

angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). The ACE inhibitor and ARB classes of drugs are particularly effective at reducing proteinuria when compared with other antihypertensive agents. Treatment with an ACE inhibitor or an ARB has been shown to reduce proteinuria by up to 30% to 50% in a dose-dependent manner. The reduction in proteinuria is more pronounced if the patient complies with dietary salt restriction. Likewise, studies have demonstrated that the antiproteinuric efficacy of ACE inhibitors and ARB can be reversed in the setting of a high-salt diet.

The benefit of ACE inhibitors in diabetic kidney disease is well established. ACE inhibitor and ARB therapy have been shown to slow the development of overt diabetic nephropathy and reduce the incidence of end-stage renal disease (ESRD) and overall mortality in patients with type 1 or type 2 diabetes. Recent studies have demonstrated that the renoprotective benefits of ACE inhibitor or ARB therapy extend to chronic kidney disease (CKD) patients with nondiabetic proteinuria as well. Therapy with ACE inhibitors or ARBs in this patient population reduces progression to ESRD. The benefits of ACE inhibitors and ARBs are likely mediated through a reduction in glomerular pressure due to efferent arteriolar vasodilation, thereby resulting in a reduced amount of protein filtration. This is likely accompanied by a reduction in podocyte damage. Filtered proteins may also be directly toxic to the tubulointerstitium. Additionally, ACE inhibitors and ARBs may have direct antifibrotic effects.

2. **Hypertension.** According to the 2012 International Kidney Disease Improving Global Outcomes (KDIGO) guidelines, the recommended goal blood pressure in patients with proteinuric nondiabetic CKD is less than 130/80 mmHg. For reasons described above, the first-line antihypertensive therapy should be with an ACE inhibitor or ARB. Treatment to achieve goal blood pressure should include lifestyle modification (salt restriction, weight normalization, regular exercise, and smoking cessation). In addition, in a large study in which proteinuric nondiabetic CKD patients had their blood pressure lowered below 130/80 mmHg, there was a significantly lower rate of both renal failure (defined as dialysis or renal transplantation) and the combined endpoint of renal failure or all-cause mortality at long-term follow-up for both patients excreting more than 3 g of proteinuria/day and those excreting 1 to 3 g/day.

3. **Edema.** Edema associated with nephrotic syndrome should be treated with dietary sodium restriction (1.5 to 2 g of sodium/24 hours) and diuretics. Thiazides are a reasonable treatment choice for patients with mild edema and normal renal function. However, most patients, particularly those with impaired renal function, will require a loop diuretic such as furosemide for adequate sodium balance. Nephrotic patients are often diuretic-resistant even if the patient's GFR is normal. Oftentimes combining a loop diuretic with a thiazide diuretic or with metolazone is required to overcome diuretic resistance. The use of intravenous albumin infusions with diuretics to treat diuretic resistance has not been shown to be effective. Occasionally, mechanical ultrafiltration is required for resistant edema with severely impaired renal function.

4. **Hyperlipidemia.** Treatment of hyperlipidemia in nephrotic syndrome should follow the guidelines for those patients at high risk for the development of cardiovascular disease. For the treatment of hyperlipidemia, statins [3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors] or agents such as gemfibrozil are well tolerated and effective in correcting the lipid profile. However, treatment with these agents has not been proven to reduce cardiovascular events in patients with nephrotic syndrome. Some studies have associated statin therapy in nephrotic syndrome to slow the decline in GFR, although conflicting studies exist. In patients undergoing treatment for nephrotic syndrome, be aware there is an increased risk of myositis and rhabdomyolysis when statins are combined with calcineurin inhibitors.
5. **Hypercoagulability.** Patients with nephrotic syndrome have an increased incidence of arterial and venous thrombosis, particularly episodes of deep vein thrombosis or renal vein thrombosis. The development of a hypercoagulable state in nephrotic syndrome is not entirely understood; however, some of the predisposition is attributed to loss of anticoagulant proteins. Urinary protein losses include the loss of antithrombotic factors such as antithrombin III and plasminogen. Additionally, some studies have demonstrated increased platelet activation and high fibrinogen levels. The risk of thrombotic events increases as serum albumin values fall below 2.5 g/dL (25 g/L). Full-dose anticoagulation with low-molecular-weight heparin or warfarin is required in patients with a diagnosed arterial or venous thrombosis or pulmonary embolism. Evidence for the use of prophylactic anticoagulation in nephrotic syndrome is not well established.
6. **Infection.** Historically infection was a major cause of morbidity and mortality in children with nephrotic syndrome prior to the antibiotic era. The increased risk of infection may be due to increased urinary losses of Ig. Studies show that patients with GN and nephrotic syndrome are at increased risk of invasive pneumococcal infection. These patients should receive pneumococcal vaccination as well as annual influenza vaccination. Vaccination with live vaccines is contraindicated for those patients receiving treatment with immunosuppressive or cytotoxic agents for nephrotic syndrome. It is generally recommended that patients on immunosuppressive therapy for nephrotic syndrome receive prophylactic antibiotics to minimize opportunistic infection.

V. TREATMENT OF SPECIFIC GLOMERULAR DISEASES.

The specific management of glomerular diseases requires the information obtained by renal biopsy, but is also influenced by the patient's clinical presentation. For example, more aggressive treatment may be undertaken in patients with a faster rate of progression or a greater degree of proteinuria.

1. Nephritic Syndrome

A. Renal Limited Disease.

1. **IgA Nephropathy.** IgA nephropathy is the most common form of primary glomerular disease in the world. It is particularly prevalent in Asia and Australia (perhaps due to sampling bias resulting from the

screening of school-aged children and a more frequent rate of biopsy in these regions), and it is rare in African Americans. Although generally considered to be a slowly progressive renal disease, ESRD occurs in 20% to 40% of patients by 20 years. A minority of patients may experience RPGN with crescent formation on biopsy, and approximately 10% of patients present with the nephrotic syndrome.

a. **Diagnosis.** Patients with IgA nephropathy usually present with hematuria and subnephrotic proteinuria, which is often an incidental finding on urinalysis. Some patients develop gross hematuria, which classically develops in the setting of an upper respiratory tract infection ("synpharyngitic"). The definitive diagnosis of IgA nephropathy requires a renal biopsy, and the hallmark of IgA nephropathy is the detection of IgA within the mesangium of affected patients. By light microscopy, mesangial expansion and mesangial proliferation are usually seen. IgA is also present in the capillary loops of some patients, a finding that is associated with endocapillary proliferation. In autopsy series, some patients without clinical disease also have glomerular IgA deposits.

b. **Pathophysiology.** IgA nephropathy has been linked with the aberrant glycosylation of IgA1 molecules. Affected patients develop IgG and IgA autoantibodies that recognize the abnormally glycosylated IgA1 and form immune complexes that deposit in the mesangium. Genome-wide association studies have linked some major histocompatibility complex loci with IgA nephropathy, further supporting an immunologic basis of the disease.

c. **Treatment.** ACE inhibitors have been shown to slow the progression of IgA nephropathy, and all patients should be treated with either ACE inhibitors or ARBs. Several clinical trials have demonstrated that corticosteroids are effective at slowing the progression of IgA nephropathy. Although further studies are needed, patients with proteinuria greater than 1 g/day may benefit from treatment with a 6-month course of prednisone (0.5 mg/kg on alternate days). Some studies support the use of fish oil in slowing the progression of renal insufficiency, although not all studies showed a benefit. For crescentic disease, short-term, high-dose prednisone may be of benefit. The use of cytotoxic agents, such as cyclophosphamide, remains investigational at this time, but these agents are sometimes employed in patients with rapidly progressive disease.

2. **Membranoproliferative GN.** MPGN is a form of glomerulonephritis defined by the histologic appearance of the glomeruli by light microscopy. The MPGN pattern of glomerular injury is associated with a variety of systemic conditions. The MPGN pattern can be seen in patients with autoimmune diseases (e.g., in patients with lupus nephritis), in infection-associated glomerular disease (e.g., with hepatitis C), and in patients with thrombotic microangiopathy. Patients with an identified autoimmune or infectious cause of their disease are categorized according to the primary disease, and idiopathic MPGN refers to those patients in whom an associated systemic disease is not identified.

a. **Diagnosis.** The clinical presentation of idiopathic MPGN is variable. Patients can present with mild nephritic findings, a rapid decline in renal function, or with the nephrotic syndrome. On biopsy, the

glomeruli demonstrate mesangial expansion and hypercellularity; endocapillary proliferation, duplication, or splitting of the GBM (referred to as "double contours" or "tram tracks"); and lobulation of the glomerular tuft. Ultrastructural examination of the glomeruli led to subclassification of MPGN into MPGN I (subendothelial immune deposits), MPGN II (dense appearing deposits in the GBM), and MPGN III (subendothelial and subepithelial deposits). MPGN II is now understood to be caused by uncontrolled activation of the alternative pathway of complement. The pathognomonic electron-dense deposits seen in MPGN II can also be seen in association with other histologic patterns of glomerular injury and this disease is now referred to as "dense deposit disease" rather than MPGN II.

b. **Pathophysiology.** Immune complexes and complement proteins are frequently detected in the capillary wall and mesangium of patients with MPGN I and III. In these cases, the deposition of the immune complexes likely causes glomerular inflammation and injury. The target antigen is unknown in idiopathic MPGN. In some cases of MPGN I and III, complement proteins deposit within the glomeruli with little or no evidence of Ig. This finding has been recently termed "C3 glomerulopathy" and is caused by uncontrolled activation of the alternative pathway of complement. This disease classification includes dense deposit disease. As with dense deposit disease, not all patients with C3 glomerulopathy have a MPGN pattern of injury by light microscopy.

c. **Treatment.** In any case of MPGN, secondary causes must be fully evaluated, because diseases such as chronic bacterial infection, hepatitis C infection, and cryoglobulinemia, as well as leukemias and lymphomas, all have therapies that may lead to remission of the renal disease. The blood pressure should be controlled in all patients, and treatment should include an ACE inhibitor. Unfortunately, at this time there is no established specific treatment for any of the forms of MPGN. A randomized controlled trial did demonstrate a benefit to treating children and teenagers with alternate-day corticosteroids, although this study included patients with all forms of MPGN (types I, III, and dense deposit disease). Our understanding of the underlying processes that cause MPGN has improved in recent years. It is logical that immunosuppressive drugs may be beneficial in patients with immune complex–associated disease and complement inhibition may be beneficial in patients with C3 glomerulopathy. At this time, however, there are no data to support specific treatments.

B. Nephritic Syndrome with Systemic Manifestations.

1. **Anti-GBM Disease and Goodpasture's Syndrome.** Anti-GBM disease is a severe and rapidly progressive form of GN caused by antibodies to targets expressed within the GBM. The same epitopes are expressed within the basement membranes of other tissues, and patients can present with isolated renal dysfunction (anti-GBM disease) or with renal disease in conjunction with pulmonary involvement (Goodpasture's syndrome).

   a. **Diagnosis.** Anti-GBM disease causes a nephritic pattern of injury, and the loss of renal function can be rapid. Patients with Goodpasture's syndrome can have pulmonary hemorrhage at the

time of presentation, and this diagnosis should be considered in all patients who present with a pulmonary-renal syndrome. The anti-GBM antibodies can be detected in patient serum using an enzyme-linked immunosorbent assay (ELISA) test. Renal biopsy typically reveals fibrinoid necrosis and crescents. Immunofluorescence microscopy is central to the diagnosis of the disease, and is characterized by linear deposition of Ig (usually IgG) along the glomerular capillaries.

b. **Pathophysiology.** Strong evidence indicates that anti-GBM antibodies cause glomerular inflammation and are pathogenic. Passive transfer of the antibodies into rodents causes glomerular disease. The disease-inducing antibodies bind to specific epitopes in type IV collagen.

c. **Treatment.** Treatment for anti-GBM disease and Goodpasture's syndrome includes high-dose steroids, cyclophosphamide, and plasmapheresis to remove the anti-GBM antibody. Patients who present with oliguria have a poor renal prognosis, but occasionally may avoid chronic dialysis with aggressive and early therapy.

2. **Pauci-immune Renal Vasculitis.** Small vessel vasculitis frequently involves the kidneys. Several diseases can cause immune complex–mediated renal vasculitis (e.g., cryoglobulinemia, lupus, and anti-GBM disease). Patients with small vessel vasculitis of the kidneys who do not have evidence of immune complex deposition in vessels are considered to have *pauci-immune* vasculitis. Approximately 90% of patients with pauci-immune small vessel vasculitis have detectable ANCA. ANCAs recognize several different antigens, including myeloperoxidase (MPO) and proteinase-3 (PR-3). Antibody to MPO results in perinuclear staining of neutrophils (p-ANCA), whereas antibody to PR-3 results in cytoplasmic staining of neutrophils (c-ANCA). ANCA-associated small vessel vasculitis of the kidney typically presents as one of three different syndromes: granulomatosis with polyangiitis (GPA; formerly called Wegener's granulomatosis), Churg–Strauss syndrome, and microscopic polyangiitis.

a. **Diagnosis.** All forms of pauci-immune small vessel vasculitis can affect multiple organ systems, including the skin, lungs, and gastrointestinal system. Churg–Strauss syndrome is associated with asthma and eosinophilia. The clinical presentation of small vessel pauci-immune vasculitis is variable, but patients generally present with a nephritic pattern of renal disease. The renal disease can progress rapidly, making it very important to diagnose the disease promptly. Because the lungs are frequently involved in all forms of ANCA-associated vasculitis, patients can present with alveolar capillaritis and pulmonary hemorrhage ("pulmonary-renal syndrome"). GPA is most commonly associated with c-ANCA (anti-PR-3). Churg–Strauss syndrome and microscopic polyangiitis are more commonly associated with p-ANCA (anti-MPO). However, there is overlap in the clinical presentation and ANCA specificity among all three diseases. Histologically, the glomeruli in patients with renal involvement in all forms of pauci-immune small vessel vasculitis typically demonstrate fibrinoid necrosis and crescents. GPA is associated with granulomas on tissue biopsy, whereas granulomas are not seen in patients with microscopic polyangiitis and Churg–Strauss

syndrome. Immune complexes must be sparse or absent in order to make the diagnosis of pauci-immune vasculitis.

b. **Pathophysiology.** There is evidence that ANCA are pathogenic in small vessel vasculitis. Experiments in rodents have demonstrated that injection of the antibodies can cause glomerular disease. The ANCA titer does not always correlate with disease severity, however, and ANCA are not detected in some patients.

c. **Treatment.** Whether systemic or renal limited, patients with pauci-immune small vessel vasculitis are treated with immunosuppressive drugs. The most commonly used protocols include high-dose steroids and cyclophosphamide (either oral or intravenous). Approximately 80% of patients respond to therapy, although patients with a serum creatinine greater than 6 mg/dL at presentation are less likely to respond than patients with a lower serum creatinine. Plasma exchange may be beneficial in patients with pulmonary hemorrhage and in patients with renal failure severe enough to require dialysis. Recent studies have demonstrated that rituximab is as effective as cyclophosphamide for inducing remission in patients with severe disease.

3. **Lupus Nephritis.** More than half of the patients with lupus develop clinically evident renal involvement. Renal disease is an important cause of morbidity in these patients, and mortality is higher in patients with lupus who have renal involvement than in those who do not.

a. **Diagnosis.** The manifestations of lupus nephritis are variable among patients, and in individual patients the nature of the disease can change over time and in response to therapy. Renal involvement is usually discovered by the detection of proteinuria and hematuria, but patients can present with either nephritic or nephrotic patterns of injury. Because the histologic pattern of injury in lupus nephritis is variable, different classifications have been developed in order to better predict the prognosis. In patients with lupus, immune complexes may be seen within the mesangium, the subendothelial space, and the subepithelial space. The location of the immune deposits often correlates with the clinical presentation. Subepithelial deposits, for example, cause injury that is clinically and histologically similar to MN. Patients with this pattern of injury often present with the nephrotic syndrome. Mesangial and subendothelial deposits, on the other hand, can cause glomerular inflammation and a nephritic syndrome. Immunofluorescence may demonstrate C3, IgG, IgM, IgA, and C1q, all within the same kidney. These deposits appear as "lumps and bumps" and are distinguishable from the linear pattern seen in anti-GBM disease.

b. **Pathophysiology.** Lupus is caused by the loss of tolerance to self-antigens and the generation of autoantibodies. Most of the autoantibodies react with antigens present in the cell nucleus, such as DNA, RNA, and histone. Preformed immune complexes may deposit in the kidney, or the antibodies and antigen may deposit separately. There is also evidence that some autoantibodies cross-react with proteins expressed within the kidney. Antibodies that deposit within the kidney or that bind to glomerular structures can cause injury to nearby cells through activation of the complement system or via signaling through Fc receptors.

c. **Treatment.** In general, therapy for lupus nephritis includes high-dose corticosteroids in combination with either mycophenolate mofetil or cyclophosphamide, particularly for the treatment of diffuse proliferative lupus nephritis. Patients with severe disease are usually treated with high doses of these drugs for an induction period, typically about 6 months. In patients who respond well, the dose of immunosuppression can be reduced, but patients are usually continued on some form of maintenance regimen for another 18 months or longer.

4. **Cryoglobulinemia (MPGN and/or Cryoglobulinemia).** Cryoglobulins are antibodies that precipitate in the cold. In vivo, they can form immune complexes that precipitate in small vessels, causing vasculitis. Cryoglobulins are most frequently associated with hepatitis C infection, although they are also seen in other conditions.
   a. **Diagnosis.** Cryoglobulinemia can affect numerous different tissues throughout the body. Most patients with symptomatic disease develop palpable purpura, arthralgias, and generalized weakness. In the kidney, cryoglobulinemia causes an immune complex GN. Patients typically have proteinuria, hematuria, and slowly progressive disease. Some patients have nephrotic range proteinuria, however, and patients can have a rapid loss of renal function. Cryoglobulinemic GN should be suspected in any patient with known hepatitis C infection who develops renal disease. Labs that support the diagnosis of cryoglobulinemia include a low C4 level and the cryoglobulins often have rheumatoid factor activity. On renal biopsy, affected patients usually have a membranoproliferative pattern of injury and subendothelial immune deposits. Microtubular structures are seen on electron microscopy, and the deposits can form a characteristic "fingerprint" appearance.
   b. **Pathophysiology.** Three categories of cryoglobulins have been identified. They can be composed of monoclonal antibodies (type I), a monoclonal IgM that binds to polyclonal IgG (type II, "mixed"), and polyclonal IgM that binds to polyclonal IgG (type III; "mixed"). Cryoglobulinemia is associated with lymphoproliferative disorders, autoimmune disease (particularly Sjögren's syndrome), and infections (particularly hepatitis C). Cooling of blood in the extremities may favor precipitation of cryoglobulins in blood vessels. In organs such as the kidneys, immune complexes formed by IgM with rheumatoid activity may favor precipitation.
   c. **Treatment.** For patients with hepatitis C and symptomatic cryoglobulinemia, antiviral therapy with peginterferon alpha and ribavirin is associated with clinical improvement. B-cell–depleting therapies, such as rituximab, are beneficial in patients with an underlying B-cell lymphoproliferative disease and in those with rapidly progressive or resistant disease. Plasmapheresis removes the cryoglobulins and can be beneficial in patients with rapidly progressive disease.

5. **Infection-Related GN.** Various forms of infection-related GN can develop in patients with bacterial, viral, fungal, and helminthic infections. Some pathogens are associated with specific patterns of renal disease, and there is a range of clinical presentations among different

organisms. Chronic hepatitis B is associated with MN and nephrotic syndrome, for example, and HIV infection is associated with FSGS. The most common form of infection-related GN is poststreptococcal GN, although the incidence of this disease is declining due to improved recognition and treatment of these infections. Bacterial endocarditis and infected atrioventricular shunts are also associated with the development of immune complex GN, and the incidence of *Staphylococcus aureus*–related GN is growing due to an increase in the prevalence of resistant organisms.

a. **Diagnosis.** Most patients with bacterial infection–related GN present with a nephritic pattern of injury. Streptococcal infections have often resolved by the time that GN develops ("poststreptococcal"). Patients with endocarditis or infected shunts may have fevers and arthralgias. Levels of C3 in plasma are often low (Table 9-4). Light microscopy in patients with postinfectious disease typically reveals proliferative glomerular changes, and is often described as "exudative" (abundant neutrophils). By immunofluorescence microscopy, large granular deposits of IgG, IgM, and C3 are seen in the mesangium and capillary loops of patients with poststreptococcal disease, and electron-dense deposits are seen in the subendothelial, mesangial, and subepithelial spaces by electron microscopy. Large subepithelial deposits ("humps") are characteristic of poststreptococcal GN.

b. **Pathophysiology.** Immune complexes formed by antibodies bound to bacterial antigens may deposit in the kidneys, triggering local inflammation. Although C3 is consistently seen within the glomeruli of patients with poststreptococcal GN, C4 is often absent. One possible explanation is that bacterial antigens may directly activate the alternative pathway of complement.

c. **Treatment.** In general, eradication of the underlying infection is the best treatment for infection-related GN. Although steroids have been used in patients with rapidly progressive poststreptococcal GN, there is no evidence that it improves outcomes.

2. **Nephrotic Syndrome**

A. Renal Limited Disease

1. **Primary MN.** Approximately 30% to 40% of cases of idiopathic nephrotic syndrome in adults are due to MN.

a. **Diagnosis.** MN typically presents in the 4th or 5th decade with a 2:1 male predominance. MN is often slowly progressive; however, some patients have spontaneous remission of disease. The hallmark of MN is the thickened glomerular capillary basement membrane visible on light microscopy. Specialized staining performed with silver stain will reveal the characteristic "spike-and-dome" feature of the capillary basement membrane. Electron microscopy demonstrates subepithelial deposits within the capillary basement membrane. Immunofluorescence microscopy demonstrates IgG and C3 along the glomerular capillary walls.

b. **Pathophysiology.** Recent research has revealed that the M-type phospholipase A2 receptor (PLA2R) is the target antigen in 70% to

80% of cases of primary MN. Circulating antibodies to PLA2R in the serum of patients with MN parallel the clinical disease course, but these autoantibodies are much less common in cases of secondary MN. Studies are underway to determine the usefulness of detecting anti-PLA2R antibodies for diagnosing MN, differentiating primary and secondary MN, and monitoring the response to treatment.

c. **Treatment.** All patients with MN should be treated with ACE inhibitor or ARB therapy. Treatment with immunosuppressive agents is indicated for those patients at high risk for progressive loss of renal function. Risk factors include heavy proteinuria (greater than 8 g/day), hypertension, diminished GFR (creatinine greater than 1.2 mg/dL for women, greater than 1.4 mg/dL for men), male gender, and greater than 20% tubulointerstitial fibrosis on renal biopsy. Immunosuppressive therapy is indicated for patients with persistent nephrotic range proteinuria after antiproteinuric therapy with an ACE inhibitor or ARB over an observation period of 6 months, development of severe symptoms due to the nephrotic syndrome, or progressive renal impairment. Provided there is no absolute contraindication to immunosuppressive therapy (active untreated infection, malignancy, preexisting leukopenia, or an inability to comply with treatment), initial therapy consists of steroids alternating monthly with a cytotoxic agent (intravenous or oral cyclophosphamide or chlorambucil) for a total duration of 6 months. Kidney function, white blood cell count, and urinary protein excretion should be monitored during treatment. Calcineurin inhibitors (tacrolimus or cyclosporine) are also capable of inducing remission, although patients frequently relapse after discontinuation of treatment. Mycophenolate mofetil may also be effective in the management of low- to moderate-risk patients as shown in short-term studies.

2. **Primary FSGS.** Approximately 20% of cases of idiopathic nephrotic syndrome in adults are due to FSGS.
   a. **Diagnosis.** Patients with FSGS present with features of the nephrotic syndrome and often have hypertension. Light microscopy in FSGS demonstrates focal areas of segmental glomerular sclerosis and electron microscopy demonstrates foot process effacement.
   b. **Pathophysiology.** Segmental areas of sclerosis occur as a result of damaged podocytes or as a repair process after segmental glomerular inflammation. It has long been suspected that primary FSGS can be caused by circulating factors. Recent research has identified a circulating podocyte toxin called soluble urokinase receptor (suPAR) as a pathogenic factor in a portion of cases of primary FSGS. suPAR is elevated in the serum of some patients with primary FSGS and in patients who develop a recurrence of FSGS after kidney transplant.
   c. **Treatment.** The natural history of primary FSGS is variable, but spontaneous remission in primary FSGS associated with nephrotic syndrome is low (<10%). The strongest predictor of progression to ESRD is resistance to corticosteroids. In patients who do not achieve remission of disease, the 5-year kidney survival is poor (on average 65%) and the 10-year kidney survival is 30%. Even

in patients who achieve remission, relapse rates can be as high as 40%. Treatment for the initial presentation of primary FSGS with nephrotic syndrome consists of prednisone at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg). High dose of corticosteroids should be continued for 12 to 16 weeks before tapering. Calcineurin inhibitors (cyclosporine, tacrolimus) can be considered as first-line therapy for patients with contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, and severe osteoporosis). However, while calcineurin inhibitors have been successful at inducing remission they are associated with a high relapse rate and difficulty discontinuing the medication.

3. **Minimal Change Disease.** Approximately 10% to 15% of cases of idiopathic nephrotic syndrome in adults and 85% in children are due to MCD.
   a. **Diagnosis.** Patients with MCD may have a sudden onset of edema and signs of the nephrotic syndrome. On kidney biopsy glomeruli appear normal by light microscopy and immunofluorescence is typically negative. However, histologic variants with immunofluorescence demonstrating IgM deposits within the mesangium may be seen, which may portend a poorer prognosis. Electron microscopy shows the characteristic effacement of the podocyte foot processes but no electron-dense deposits.
   b. **Pathophysiology.** The etiology of MCD is not well understood. Some studies suggest that T-cell dysfunction or podocyte-related factors are involved.
   c. **Treatment.** For a first episode, treatment consists of high-dose prednisone [1 mg/kg daily (maximum 80 mg) or alternate-day single-dose 2 mg/kg (maximum 120 mg)], for a minimum of 4 weeks and up to 16 weeks. After achieving complete remission, prednisone can be slowly tapered over a total period of up to 6 months. Whereas greater than 90% of children with MCD will have a complete remission of proteinuria within 2 months of starting steroid therapy, in adults this figure is approximately 50% to 75%. Extending the duration of high-dose prednisone to 5 to 6 months increases the rate of complete remission to 80%. Prednisone should then be slowly tapered over approximately 4 months. In adults relapses are common, with relapse rates as high as 60% to 70%. For relapsed disease, the corticosteroid regimen is to be repeated as if it is the first episode. In cases where steroids cannot be tapered (steroid dependence or frequently relapsing), second-line agents (cyclophosphamide, cyclosporine, tacrolimus, or mycophenolate mofetil) may be effective.

B. Nephrotic Syndrome Due to Systemic Illness.

1. **Secondary MN.** Approximately 20% of MN cases can be secondary in etiology. Factors on biopsy that favor a secondary form of MN include subendothelial and/or mesangial deposits, a "full house" of Igs and complement (suggestive of lupus nephropathy), tubuloreticular inclusions in endothelial cells, and mesangial or endocapillary

proliferation. MN can be caused by secondary factors such as malignancy (colon, lung, or prostate cancer), autoimmune disease (systemic lupus erythematosus), infectious disease (hepatitis B virus, hepatitis C virus), drugs [nonsteroidal anti-inflammatory drugs (NSAIDs), gold, penicillamine], and others. Secondary MN due to malignancy is more prominent in patients greater than 65 years old. In cases of malignancy-related MN, a clinical remission of cancer is associated with a reduction in proteinuria.

2. **Secondary FSGS.** Secondary causes of FSGS include genetic mutations, in key podocyte structural proteins, viral nephropathies (HIV-associated nephropathy and parvovirus B19), drug-induced nephropathy (pamidronate, interferon alpha, heroin), and adaptive hemodynamic changes (unilateral renal agenesis, reflux nephropathy, obesity). Secondary causes of FSGS typically have patchy foot process effacement instead of global effacement on biopsy. Patients with secondary FSGS are not treated with immunosuppressive therapy. Instead treatment should be focused on treatment of the underlying disorder.
3. **Secondary MCD.** Systemic conditions associated with secondary MCD include Hodgkin's disease and medications, such as lithium and NSAIDs.
4. **Diabetic Nephropathy.** Diabetes is the leading cause of ESRD in dialysis patients in the United States. The earliest clinical manifestation of diabetic nephropathy is microalbuminuria. Risk factors for progression of diabetic nephropathy to ESRD include nephrotic range proteinuria and renal impairment at diagnosis.
   a. **Diagnosis.** Diabetic nephropathy is characterized by persistent proteinuria. It is recommended that diabetic patients are screened regularly with a urine albumin/creatinine ratio. Diabetes affects the microvascular circulation, and it has been shown that the presence of diabetic retinopathy correlates well with overt diabetic nephropathy. Diagnosis can typically be made on clinical history. If renal biopsy is performed, it classically shows mesangial and matrix expansion, GBM thickening, and nodular glomerulosclerosis with the characteristic nodular Kimmelstiel–Wilson lesions.
   b. **Pathophysiology.** The renal disease associated with diabetes progresses over the span of years. Glomerular hyperfiltration develops in most patients with an initial increase in GFR. Renal hypertrophy develops, which can be seen as large kidneys on ultrasound imaging. Glomerular hypertension occurs with subsequent development of clinical abnormalities such as microalbuminuria, glomerular lesions, macroalbuminuria, and a progressive loss of GFR.
   c. **Treatment.** Hypertension is a modifiable risk factor of the GFR decline in diabetic nephropathy. The antihypertensive agent of choice in diabetes is an ACE inhibitor or ARB. Treatment with ACE inhibitors or ARB has been shown to reduce the rate of decline in GFR in patients with hypertension and diabetes.
5. **Amyloid Deposition Disease.** Amyloidosis is a disorder defined by deposition of an insoluble extracellular protein in a variety of tissue sites.

Renal involvement is common, and patients present with proteinuria and renal impairment. Primary amyloidosis is often associated with B-cell lymphoproliferative disorders (as seen in multiple myeloma). Less commonly secondary amyloidosis can be secondary to a chronic inflammatory state, such as rheumatoid arthritis or chronic infections.

a. **Diagnosis.** Congo red staining of tissue with amyloid deposits, such as a fat pad biopsy or kidney biopsy, demonstrates green birefringence under polarized light. Electron microscopy of the amyloid deposits displays nonbranching fibrils. Serum and urine protein electrophoresis with immunofixation electrophoresis reveals the presence of a monoclonal protein in primary amyloid.

b. **Treatment.** Treatment is aimed at reducing the concentration of serum Ig free light chains. In patients with plasma cell dyscrasia, treatment often involves the use of high-dose chemotherapy with melphalan/dexamethasone, lenalidomide, or bortezomib with or without autologous stem-cell transplantation.

VI. THE THROMBOTIC MICROANGIOPATHIES.

Systemic disorders that may produce a nephritic clinical presentation include a number of diseases that are not classical inflammatory diseases or vasculidities. Systemic diseases such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), scleroderma, malignant hypertension, and antiphospholipid antibody syndrome (APS) can present with hematuria, hypertension, and proteinuria (although usually less than 1 to 1.5 g/day). Common histologic findings on renal biopsy in HUS, TTP, and APS include glomerular capillary thrombi and afferent arterioles with fibrinoid necrosis from endothelial injury. These diseases can cause a MPGN pattern of injury by light microscopy, but immunofluorescence is typically negative, with the exception of the presence of fibrinogen. Electron microscopy is also usually unremarkable, with no deposits noted. Additionally, malignant hypertension and scleroderma can cause subintimal proliferation within blood vessels, leading to an "onion skin" appearance of arterioles. Microthrombi may be present as well.

The specific management of the thrombotic microangiopathies differs significantly from other disorders that lead to a nephritic clinical presentation; therefore, a correct diagnosis rather than empiric therapy is critical under circumstances of a nephritic presentation. For treatment of malignant hypertension and scleroderma renal crisis, blood pressure control is paramount. ACE inhibitor therapy is the first-line therapy in the setting of scleroderma, because data demonstrate improved patient survival and renal outcomes using this form of therapy.

A. **Hemolytic Uremic Syndrome.** In HUS, the clinical picture is predominantly one of acute renal failure, thrombocytopenia, and hemolysis resulting from verotoxin (from *Escherichia coli* 0157:H7 gastrointestinal infection). Therapy is primarily supportive and 90% of cases of diarrhea-associated HUS will completely recover, although 5% die within the acute phase and 5% may have persistent renal and extrarenal complications. Patients who develop HUS in the absence of a verotoxin-producing infection are regarded as having atypical HUS, a disease that is usually caused by dysregulated activation of the alternative pathway of complement. These patients have a worse prognosis than those with diarrhea-associated HUS.

Plasma exchange is beneficial in some patients with atypical HUS, and eculizumab (a therapeutic complement inhibitor) has been approved for treatment of this disease.

B. Thrombotic Thrombocytopenic Purpura. The "classic pentad" of signs of TTP includes thrombocytopenia, hemolytic anemia, neurologic abnormalities, fever, and renal failure. Most patients do not have all five of these symptoms, however, and these findings can wax and wane. Secondary forms of TTP exist, and include pregnancy-, malignancy-, and HIV-associated causes. Primary TTP is believed to be triggered by endothelial injury in patients who have abnormally large von Willebrand factor (vWF) multimers. This leads to platelet aggregation and thrombi formation. The failure to cleave large vWF multimers is usually caused by a functional deficiency of the metalloproteinase ADAMTS13. ADAMTS13 activity can be tested clinically. A very low ADAMTS13 level supports the diagnosis of TTP, but it may take several days to get these results and the decision to treat TTP is usually made on clinical grounds. Plasma exchange or infusion is the most effective therapeutic intervention for TTP. It is felt that plasma exchange may remove autoantibody when it is present and replace ADAMTS13 when there is a deficiency of this protein. Plasma exchange should be continued until the platelet count has normalized and the serum lactate dehydrogenase enzyme level returns to normal range. Additional therapies that have been described include high-dose prednisone therapy, rituximab, vincristine, and other chemotherapeutic agents. The benefit of these therapies is not clear.

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10 The Patient with Acute Kidney Injury

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I. DEFINITION AND RECOGNITION OF ACUTE KIDNEY INJURY (AKI).

AKI, formerly known as acute renal failure, is a sudden decrease in kidney function characterized by a reduction in the glomerular filtration rate (GFR). AKI may occur in patients with previously normal renal function or patients with chronic kidney disease (CKD); in either case, the clinical approach to find and treat the cause remains similar. Criteria to diagnose AKI have been established by the Acute Kidney Injury Network (AKIN) and the *R*isk, *I*njury, *F*ailure, *L*oss, *E*nd-stage kidney disease (RIFLE) criteria (Table 10-1). The AKIN and RIFLE classifications convey the concept that AKI is not only significant when it requires renal replacement therapy (RRT), but that it is a spectrum ranging from early disease to long-term failure. Based on the AKIN and RIFLE criteria, the definition of AKI is as follows: 1) an increase in serum creatinine from baseline by $\geq$0.3 mg/dL within 48 hours, or 2) an increase in serum creatinine $\geq$1.5 times baseline which is known or presumed to have occurred within the prior 7 days, or 3) urine volume $<$0.5 mL/kg/hour for 6 hours (as summarized in Table 10-2). For example, an increase in serum creatinine from 2.0 to 2.3 mg/dL within 48 hours is diagnostic of AKI; similarly, an increase from 1.0 to 1.3 within 48 hours is diagnostic of AKI. The AKIN and RIFLE criteria have been validated in multiple studies. Furthermore, an increase in serum creatinine by 0.3 mg/dL is associated with an independent increased risk of mortality. The recent Kidney Disease/Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI definition is in agreement with this definition (Table 10-2).

A. Serum Creatinine as a Marker of AKI and GFR.

Normal serum creatinine is 0.6 to 1.2 mg/dL and is the most commonly used parameter to assess kidney function. Unfortunately, the correlation between serum creatinine concentration and GFR may be confounded by several factors.

1. **Creatinine Excretion is Dependent on Renal Factors Independent of Function.** Certain medications such as trimethoprim or cimetidine interfere with proximal tubular creatinine secretion and may cause a rise in serum creatinine without a fall in GFR (Table 10-3). Once filtered, creatinine cannot be reabsorbed.

2. **Serum Creatinine is Dependent on Nonrenal Factors Independent of Kidney Function.** For example, creatinine production is dependent on muscle mass. Muscle mass declines with age and illness. Therefore, a serum creatinine of 1.2 mg/dL in an elderly, 40-kg patient with cancer and wasted muscles may represent a severely impaired GFR, whereas a serum creatinine of 1.2 mg/dL in a 100-kg weightlifter with large muscle mass may represent a normal GFR. Serum creatinine is also

Table 10-1. AKIN and RIFLE Criteria for Diagnosis and Classification of AKI

AKIN Criteria			RIFLE Criteria		
Stage	SCr	Urine Output	Class	SCr	GFR
1	Increase of ≥0.3 mg/dL or increased ≥1.5- to 2-fold from baseline	<0.5 mL/kg/h for >6 h	Risk	Increased × 1.5	Decreased >25%
2	Increased >2- to 3-fold from baseline	<0.5 mL/kg/h for >12 h	Injury	Increased × 2	Decreased >50%
3	Increased >3-fold from baseline, or baseline ≥4.0 mg/dL with an acute rise of ≥0.5 mg/dL or on RRT	<0.5 mL/kg/h for >24 h or anuria for 12 h	Failure	Increased × 3 or baseline >4 mg/dL with an acute rise >0.5 mg/dL	Decreased >75%
			Loss		Persistent AKI=complete loss of kidney function >4 wk
			ESRD		ESRD >3 months
Time	<48 h			1–7 d	
				Sustained >24 h	

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RIFLE, *R*isk, *I*njury, *F*ailure, *L*oss, *E*nd-stage kidney disease; RRT, renal replacement therapy; SCr, serum creatinine.

dependent on other factors such as nutritional status, infection, volume of distribution, age, gender, race, body habitus, presence of amputations, malnutrition, and diet.

3. **Creatinine Production and Excretion Must Be in a Steady State Before Creatinine Levels Accurately Reflect the Decline in**

Table 10-2.	KI DGO Definition of AKI
Increase in SCr by ≥0.3 mg/dL within 48 h;	
or	
Increase in SCr to ≥1.5 times baseline, which	
is known or presumed to have occurred within	
the prior 7 d;	
or	
Urine volume <0.5 mL/kg/h for 6 h	

AKI, acute kidney injury; SCr, serum creatinine.

Table 10-3.	Medications and other Conditions That Affect Serum Creatinine without Actually Affecting Renal Function
Mechanism and Medication	
Increased serum creatinine by the inhibition of creatinine secretion	
Trimethoprim	
Cimetidine	
Increased serum creatinine due to interference with creatinine measurement	
Ascorbic acid	
Cephalosporins	
Flucytosine	
Plasma ketosis	
Falsely low serum creatinine due to interference with creatinine measurement	
Very high serum bilirubin levels (usually 5.85 mg/dL)	
Enhanced creatinine production	
Cooked meat (creatine is converted to creatinine by cooking)	

Kidney Function. The most commonly used formulae to estimate GFR, *in a steady state*, are the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), the modified MDRD, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. In a steady state, the CKD-EPI equation is the most reliable estimate of kidney function. However, all of these formulae need to be used with caution in estimating kidney function in patients with AKI. For example, after an acute insult, it takes several days for creatinine excretion and production to reach a steady state and kidney function will be worse than what the formulae suggest. For example, if a 60 kg, 30-year-old woman with a serum creatinine of 1.0 mg/dL suddenly loses all renal function, her serum creatinine may only rise to 1.8 mg/dL after 1 day. By CKD-EPI, her GFR is 37 mL/minute; by Cockcroft-Gault it is 43 mL/minute, but it is actually 0 mL/minute. For reference, the formulae for Cockcroft-Gault, MDRD, modified MDRD, and CKD-EPI are listed below.

a. Cockcroft-Gault Formula

$$\text{GFR} = [([140 - \text{age (years)}] \times \text{lean body weight in kg})/(\text{serum Cr} \times 72)] \times (0.85 \text{ if female})$$

b. MDRD Formula

$$\text{GFR, in mL/minute/1.73 m}^2 = 170 \times (\text{serum Cr}^{-0.999}) \times (\text{age}^{-0.176}) \times (\text{BUN}^{-0.170}) \times (\text{serum albumin}^{+0.318}) \times (0.762 \text{ if female}) \times (1.180 \text{ if black})$$

where serum Cr (creatinine) and blood urea nitrogen (BUN) are in mg/dL; serum albumin is in g/dL.

c. Modified MDRD Formula

$$\text{GFR, in mL/minute/1.73 m}^2 = 186.3 \times (\text{serum Cr}^{-1.154}) \times (\text{age}^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

d. CKD-EPI

$$\text{GFR, in mL/minute} = 141 \times \min(\text{SerumCreat/kappa}, 1)^{\text{alpha}} \times \max(\text{SerumCreat/kappa}, 1)^{-1.209} \times 0.993^{\text{Age}} \times \text{Sex} \times \text{Race}$$

For females, the following values are used: Sex = 1.018; alpha = −0.329; kappa = 0.7. For males, the following values are used: Sex = 1; alpha = −0.411; kappa = 0.9.

e. Creatinine clearance (CrCl) may be measured in the acute setting to give an estimate of kidney function; more reliable results will be obtained when creatinine production and excretion are in a steady state. Steady state may be suggested when the creatinine reaches its peak and then stabilizes (e.g., if creatinine (mg/dL) is 1.0 at baseline, 2.0 on day 2, 4.0 on day 3, and 4.0 on the subsequent days, one may reasonably conclude that a steady state has been achieved at a creatinine of 4.0). Normal ranges for CrCl are 120 ± 25 mL/minute

for men and 95 ± 20 mL/minute for women. The formula for CrCl performed on a 24-hour urine collection is as follows:

$$\text{CrCl} = [\text{urine creatinine (mg/dL)} \times \text{urine volume (mL/24 hours)}] / [\text{serum Cr (mg/dL)} \times 1{,}440 \text{ minutes}]$$

When the reduction in kidney function is severe, both CrCl and urea clearance may be determined on the same 24-hour urine collection; the average of CrCl and urea clearance may be a more accurate assessment of kidney function than CrCl alone (due to the increase in creatinine secretion that may occur with kidney dysfunction which will increase the amount of creatinine in the urine not related to GFR).

B. BUN as a Marker of AKI and GFR. Normal BUN is 8 to 18 mg/dL. An increase in BUN typically accompanies a rise in serum creatinine in the setting of AKI. Urea is filtered, but not secreted. Increased reabsorption of urea by the proximal tubule and arginine vasopressin (AVP)–sensitive urea transporters in the collecting duct occurs in states of volume depletion. In this setting, BUN can rise without a rise in creatinine, resulting in a BUN to serum creatinine ratio that is greater than 20.

BUN levels are affected by multiple factors not related to GFR. Because BUN production is related to protein metabolism, an increase in BUN without a decline in GFR may occur with hypercatabolic states, protein loading, upper gastrointestinal (GI) bleeding, and high-dose steroid administration. Conversely, a low BUN may be present in the setting of reduced GFR in patients who are on a low-protein diet, are severely malnourished, or have severe liver disease.

C. Cystatin C as a Marker of AKI and GFR. Cystatin C is a protein produced by all nucleated cells. It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubules, and is not secreted by the renal tubules. Therefore, some of the limitations of serum creatinine, for example, effect of muscle mass, are not a problem with cystatin C. In AKI, changes in cystatin C occur sooner after changes in kidney function than serum creatinine. In studies, serum cystatin C correlated better with GFR than did serum creatinine and was diagnostically superior to creatinine especially in patients with liver cirrhosis. Cystatin C is best measured by an immunonephelometric assay, but is not yet routinely measured except in patients in whom serum creatinine is judged to be a poor marker of renal function, for example, liver cirrhosis, and in patients with reduced muscle mass.

D. Biomarkers of AKI. A biomarker that is released into the blood or urine by the injured kidney (analogous to troponin release by injured myocardial cells after myocardial ischemia) is a more sensitive and specific marker of AKI than BUN and serum creatinine. Urinary interleukin-18 (IL-18), neutrophil gelatinase–associated lipocalin (NGAL), kidney injury molecule-1 (Kim-1), and tubular enzymes have been found to increase 1 to 2 days before serum creatinine in patients with ischemic AKI. Higher levels of IL-18, NGAL, KIM-1, and liver fatty acid binding protein (L-FABP) also predict worsening AKI and death. Many studies are in progress to develop biomarkers of AKI that are superior to BUN and serum creatinine and will allow the early detection of AKI.

E. Distinguishing AKI from CKD. Distinguishing AKI from CKD may be challenging. Laboratory findings such as hyperphosphatemia, hypoalbuminemia, and hyperkalemia are unreliable factors to distinguish AKI from CKD and may be present in either case. Symptoms such as nausea, vomiting, and malaise may also occur in AKI or CKD. Potential methods to distinguish between the two include the following:

1. **Old Records.** The most reliable way to distinguish AKI from CKD is an evaluation of old records. Increased BUN or serum creatinine documented months earlier and/or a history of kidney disease suggests that the renal failure is chronic.
2. **Renal Ultrasonography.** As summarized in Table 10-4, ultrasound may be a useful technique to distinguish AKI from CKD. Increased echogenicity (i.e., the kidney appears brighter than the normal liver) may occur in either AKI or CKD (echogenicity may also be normal in AKI or CKD); however, decreased kidney length or cortical thinning do not occur in AKI. Therefore, decreased kidney length and/or cortical thinning suggests that CKD is present. It is important to note that since AKI is common in patients with CKD, the presence of small kidneys or a thin cortex does not necessarily exclude the possibility that AKI is also present. For reference, "normal" kidney size is dependent on age. For example, at age 55, normal kidney length is approximately 11 cm; at age 75, normal kidney length is approximately 10 cm (although it is currently unknown whether the decrease in kidney length that is observed in aging is "normal" or represents undetected CKD). Normal cortex is approximately 1 cm.
3. **Anemia.** Normochromic normocytic anemia is common in patients with CKD and a GFR less than 30 mL/minute; in patients with a GFR of 30 to 44 mL/minute, only approximately 20% of patients have anemia. Therefore, with a GFR of 30 mL/minute or below, the absence of anemia suggests that the decline in renal function may be acute. In some etiologies of CKD (e.g., autosomal dominant polycystic kidney disease), however, anemia may be absent. In some etiologies of AKI, anemia may be present, for example, hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP). Thus, the presence or absence of anemia must be interpreted in context with other clinical indicators when considering the diagnosis of AKI versus CKD.

Table 10-4. Use of Ultrasonography to Distinguish Acute from Chronic Kidney Diseases

Ultrasound Finding	Acute	Chronic
Increased echogenicity	Yes	Yes
Cortical thinning	No	Yes
Decrease in renal size	No	Yes

F. Urine Output in AKI. AKI is typically described as either oliguric or nonoliguric. **Oliguria** is defined as a urine output of less than 400 mL/day; 400 mL is the minimum amount of urine that a person in a normal metabolic state must excrete to get rid of the daily solute production. For example, a person with a daily solute production of 500 mOsm who concentrates urine to a maximum of 1,200 mOsm/L would need to pass approximately 400 mL of urine per day to excrete the daily solute production (i.e., 500 mOsm/1,200 mOsm/L = 417 mL of urine per day).

Anuria is defined as a lack of urine obtained from a bladder catheter; it has a short list of potential causes. It is most often caused by complete bilateral urinary tract obstruction, urinary tract obstruction in a solitary kidney, and shock. Less common causes are HUS and rapidly progressive glomerulonephritis (RPGN), particularly anti-glomerular basement membrane (GBM) antibody disease; bilateral renal arterial or venous occlusion can also cause anuria.

II. CLASSIFICATIONS OF AKI: DEFINITIONS AND CAUSES.

AKI is classified as either intrinsic renal or postrenal. Prerenal azotemia may also cause a decline in GFR, which is reflected by increased serum creatinine and BUN.

A. Prerenal Azotemia (Fig. 10-1). Prerenal azotemia is a fall in the GFR due to reduced renal perfusion in which minimal cellular damage to the kidney has occurred. Urine sediment is typically bland and hyaline casts may be present. Essential to this diagnosis is that renal function returns to normal within

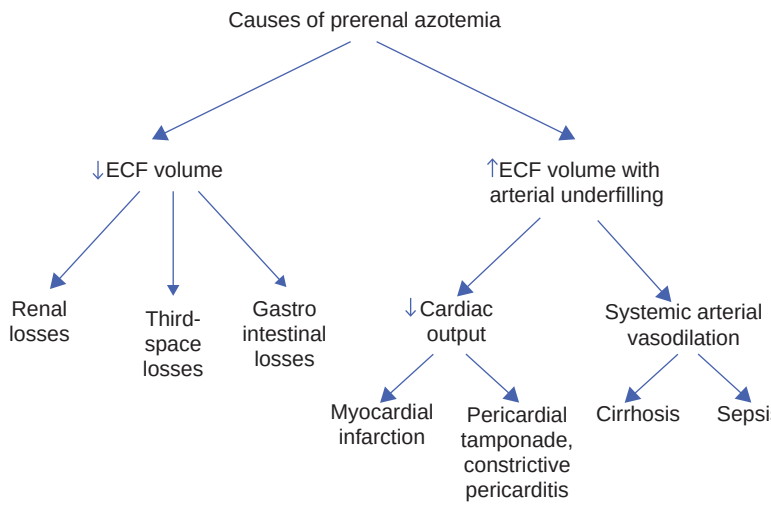

Figure 10-1. Causes of prerenal azotemia. Prerenal azotemia may be secondary to true intravascular volume depletion or arterial underfilling from a decrease in cardiac output or arterial vasodilatation. The extracellular fluid (ECF) volume comprises the intravascular and the interstitial body water compartments.

24 to 72 hours of correction of the hypoperfused state. Prerenal azotemia occurs in the following situations:

1. **Total Intravascular Volume Depletion.** This condition can occur in a number of settings where intravascular volume is reduced and may be secondary to
   - **a.** Hemorrhage
   - **b.** Renal fluid loss
     - Excessive diuresis (e.g., diuretics)
     - Osmotic diuresis (e.g., glucosuria, mannitol administration)
     - Primary adrenal insufficiency (i.e., hypoaldosteronism)
     - Salt-wasting nephritis
     - Diabetes insipidus
   - **c.** GI fluid loss
     - Vomiting
     - Diarrhea
     - Nasogastric tube drainage
   - **d.** Skin fluid loss
     - Burns
     - Excessive sweating
     - Hyperthermia
   - **e.** Third-space fluid loss
     - Peritonitis
     - Pancreatitis
     - Systemic inflammatory response syndrome
     - Profound hypoalbuminemia
2. **Effective Volume Depletion from Arterial Underfilling.** Arterial underfilling is a state in which intravascular volume is actually normal (or even increased) but circulatory factors are inadequate to maintain renal perfusion pressure. Underfilling may be due to either a decrease in cardiac output or arterial vasodilatation and may occur in a number of clinical settings:
   - **a.** Reduced cardiac output
     - Acute decompensated heart failure (ADHF) (previously referred to as congestive heart failure)
     - Cardiogenic shock (e.g., acute myocardial infarction)
     - Pericardial effusion with tamponade
     - Massive pulmonary embolism
   - **b.** Peripheral vasodilatation
     - Sepsis
     - Antihypertensive medications
     - Anaphylaxis
     - Anesthesia
     - Cirrhosis and other liver diseases
3. **Intrarenal Hemodynamic Changes**
   - **a.** Glomerular afferent arteriole vasoconstriction (preglomerular effect)
     - Nonsteroidal anti-inflammatory drugs (NSAIDs) (prostaglandin inhibition)
     - Cyclooxygenase 2 (Cox-2) inhibitors (prostaglandin inhibition)
     - Cyclosporine

- Tacrolimus
- Radiocontrast dye
- Hypercalcemia

b. Glomerular efferent arteriole vasodilatation (postglomerular effect)

- Angiotensin-converting enzyme inhibitors (ACEIs)
- Angiotensin II receptor blockers (ARBs)

B. Postrenal AKI. Postrenal AKI is caused by the acute obstruction of the flow of urine. Urinary obstruction of both ureters, the bladder, or the urethra may cause postrenal AKI. Patients most at risk for postrenal AKI are elderly men, in whom prostatic hypertrophy or prostatic cancer may lead to complete or partial obstruction of urine flow. In women, complete urinary tract obstruction is relatively uncommon in the absence of pelvic surgery, pelvic malignancy, or previous pelvic irradiation. The causes of postrenal AKI include the following:

1. Bilateral Ureteral Obstruction or Unilateral Obstruction in a Solitary Kidney (Upper Urinary Tract Obstruction)

a. Intraureteral

- Stones
- Blood clots
- Pyogenic debris or sloughed papillae
- Edema following retrograde pyelography
- Transitional cell carcinoma

b. Extraureteral

- Pelvic or abdominal malignancy
- Retroperitoneal fibrosis
- Accidental ureteral ligation or trauma during pelvic surgery

c. Bladder neck/urethral obstruction (lower urinary tract obstruction)

- Prostatic hypertrophy
- Prostatic and bladder carcinoma
- Autonomic neuropathy or anticholinergic agents causing urinary retention
- Urethral stricture
- Bladder stones
- Fungal infection (e.g., fungus balls)
- Blood clots

C. Intrarenal or Intrinsic AKI. In contrast to prerenal azotemia and postrenal AKI, the disorders listed here represent problems that originate within the kidney itself. These problems may be vascular, glomerular, interstitial, or tubular. The diseases may be primary renal or part of a systemic disease. The course of AKI in these situations cannot be changed by manipulating factors outside the kidney (e.g., performing volume repletion, improving cardiac function, correcting hypotension, or removing obstruction).

1. Vascular. Vascular disorders causing AKI are classified based on the size of the vessels involved.

a. Large- and medium-sized vessels

- Renal artery thrombosis or embolism
- Operative arterial cross-clamping
- Bilateral renal vein thrombosis
- Polyarteritis nodosa

b. Small vessels
- Atheroembolic disease
- TTP-HUS
- Scleroderma renal crisis
- Malignant hypertension
- *H*emolysis, *E*levated *L*iver enzymes, and *L*ow *P*latelets (HELLP) syndrome
- Postpartum AKI

2. Glomerular. Glomerular diseases are typically categorized based on urine findings as either nephrotic or nephritic.

a. Nephrotic glomerular disorders are characterized by large proteinuria (greater than 3 g in 24 hours) and minimal hematuria. Nephrotic glomerular disorders are uncommonly associated with AKI, but may occur in minimal-change disease or focal segmental glomerulosclerosis (FSGS), particularly collapsing FSGS.

b. Nephritic glomerular disorders (glomerulonephritis) are characterized by hematuria and proteinuria (typically 1 to 2 g in 24 hours). Patients with known glomerulonephritis may develop AKI; alternatively, glomerulonephritis may present as AKI. Rapidly progressing Glomerulo Nephritis (RPGN), also called *crescentic nephritis*, should be suspected in a patient with a rising creatinine, hematuria, and proteinuria. RPGN is caused by injury to the glomerular capillary wall, which results in subsequent inflammation, fibrosis, and crescent formation. Urgency is required to make the diagnosis of RPGN, because crescent formation can rapidly destroy the glomeruli; response to therapy is directly correlated with the percentage of glomeruli having crescents. If RPGN is suspected, a biopsy should be performed as soon as possible as waiting even a few days can result in irreversible loss of kidney function. Because the diagnosis is typically made by renal biopsy, the causes of glomerulonephritis and RPGN are classified according to immunofluorescence staining on renal biopsy.

i. Diseases with Linear (anti-GBM) Immune Complex Deposition
- Goodpasture's syndrome (renal and pulmonary complications are present)
- Renal-limited Goodpasture's syndrome

ii. Diseases with Granular Immune Complex Deposition
- Acute postinfectious glomerulonephritis
- Lupus nephritis
- Infective endocarditis
- Immunoglobulin (Ig) A glomerulonephritis
- Henoch–Schönlein purpura
- Membranoproliferative glomerulonephritis
- Cryoglobulinemia

iii. Diseases with No Immune Deposits (Pauci-immune)
- Granulomatosis with polyangiitis (GPA), (formerly known as Wegener's granulomatosis)
- Microscopic polyangiitis (MPA)
- Churg–Strauss syndrome (CSS)
- Idiopathic crescentic glomerulonephritis

3. **Interstitium.** AKI from an interstitial cause is known as *acute interstitial nephritis* (*AIN*). The primary histologic lesion of AIN is marked edema of the interstitial space with a focal or diffuse infiltration of the renal interstitium with inflammatory cells (lymphocytes and/or eosinophils). AIN (also called *acute tubulointerstitial nephritis*) is most commonly due to drug hypersensitivity, but may also be a consequence of infections or systemic disease (e.g., systemic lupus erythematosus).
   a. **Drug-Induced AIN.** More than 100 drugs have been implicated in drug-induced AIN. Some of the drugs most commonly associated with AIN are as follows:
      - **Antibiotics** (e.g., methicillin, cephalosporins, rifampicin, sulfonamides, erythromycin, and ciprofloxacin)
      - **Diuretics** (e.g., furosemide, thiazides, chlorthalidone)
      - **NSAIDs**
      - **Anticonvulsant drugs** (e.g., phenytoin, carbamazepine)
      - **Allopurinol**
   b. **Infection-Associated AIN**
      - **Bacterial** (e.g., *Staphylococcus*, *Streptococcus*)
      - **Viral** (e.g., cytomegalovirus, Epstein–Barr virus)
      - **Tuberculosis**

4. **Tubular.** Acute tubular necrosis (ATN) is characterized by an abrupt decrease in GFR due to proximal tubular dysfunction most commonly caused by ischemic AKI or nephrotoxic AKI. Although this type of renal injury has long been designated ATN, the term is a misnomer because, in many cases, true necrosis of tubular cells is not present on histologic examination. Most of the renal biopsies are, however, late and therefore could miss early tubular necrosis. The tubules may demonstrate morphologic changes of sublethal injury (e.g., swelling, vacuolization, loss of brush border, apical blebbing, and loss of basolateral infoldings). Loss of viable and nonviable tubular epithelial cells into the urine also occurs. The continued presence of renal blood flow and reversibility of tubular dysfunction is compatible with the recovery of renal function that is seen in some patients with ischemic or nephrotoxic AKI.

   Ischemic AKI is a consequence of reduced blood flow to the kidneys, which results from a decreased total blood volume or arterial underfilling with a redistribution of blood away from the kidney. Ischemic AKI is seen most commonly after septic or hemorrhagic shock. **Nephrotoxic AKI** is most commonly caused by aminoglycoside antibiotics and radiocontrast dye. In most cases, the insults are multifactorial.

   Causes of ischemic or nephrotoxic AKI include the following:
   a. **Renal Ischemia**
      - Shock
      - Hemorrhage
      - Trauma
      - Gram-negative sepsis
      - Pancreatitis
      - Hypotension from any cause

b. Nephrotoxic Drugs

- Aminoglycoside antibiotics
- Amphotericin B
- Pentamidine
- Foscarnet
- Acyclovir
- Indinavir
- Antineoplastic agents (e.g., cisplatin)
- Radiocontrast dye
- Organic solvents (e.g., carbon tetrachloride)
- Ethylene glycol (antifreeze)
- Anesthetics (enflurane)
- Oral sodium phosphosoda used for bowel preparation for colonoscopy can cause acute phosphate nephropathy resulting in acute nephrocalcinosis

c. Endogenous Toxins

- Myoglobin (e.g., rhabdomyolysis)
- Hemoglobin (e.g., incompatible blood transfusion, acute falciparum malaria)
- Uric acid (e.g., acute uric acid nephropathy)

5. **Sepsis**. Sepsis is the most common cause of AKI in the intensive care unit (ICU). The pathophysiology of AKI in sepsis is complex, and many aspects of the cause of renal function decline in sepsis remain controversial. Although previously thought to be similar to ischemic AKI, it is now understood that septic AKI is a separate entity from ischemic AKI—although ischemic AKI may ultimately occur in severe sepsis or shock from reduced renal blood flow. Renal function decline in sepsis is likely due to a combination of vascular factors (affecting autoregulation and resulting in decreased GFR) as well as intrinsic tubular damage.

III. EPIDEMIOLOGY OF AKI (Table 10-5)

A. Community-Acquired AKI. AKI is present on admission in approximately 1% of hospitalized patients. Half of the cases occur in patients with CKD. The most common causes of community-acquired AKI include prerenal (70%) and postrenal (17%). The overall mortality of patients presenting with community-acquired AKI is 15%.

B. Hospital-Acquired AKI. The development of AKI in hospitalized patients is common and carries with it a significant independent risk of mortality. Using the RIFLE criteria, up to 20% of hospitalized patients may develop AKI. The most common causes of AKI in hospitalized patients include ischemia, sepsis, medications, and radiocontrast dye. Prerenal azotemia is a common cause of an increase in creatinine in ward patients; however, ATN or sepsis accounts for the majority of causes of AKI in ICU patients. AKI in the ICU is typically multifactorial and may be part of multiple organ dysfunction syndrome.

C. Prevention of AKI. Numerous factors predispose hospitalized patients to the development of AKI: sepsis, volume depletion, drugs that affect renal blood flow (e.g., NSAIDs and Cox-2 inhibitors), and the use of nephrotoxic medications and contrast dye.

Table 10-5. Characteristics of AKI in Regard to the Location of Its Development

History/Symptoms	Predisposing Factor(s)	Type of AKI
Community-Acquired AKI		
Acute systemic illness (e.g., viral influenza, gastroenteritis)	Volume depletion	Prerenal azotemia or ATN
Streptococcal pharyngitis or pyoderma (vesicular skin lesions, typically located on the extremities, which become pustular and then crust)	Immune complex deposition in the glomeruli	Acute poststreptococcal glomerulonephritis
Trauma, crush injury, prolonged immobilization, "found down"	Extensive muscle damage and tissue breakdown	Rhabdomyolysis
Urinary tract symptoms such as difficulty voiding, incontinence, dribbling	Obstruction to urine flow or neurogenic bladder	Postrenal
Fever and/or rash in a patient recently prescribed a new medication	NSAIDs, antibiotics, and diuretics are frequently prescribed on an outpatient basis	Allergic interstitial nephritis
Accidental or intentional overdose of a nephrotoxin (altered mental status may be a frequent accompaniment)	Heavy metal compounds, solvents, ethylene glycol, salicylates, and acetaminophen	Nephrotoxic AKI
AKI Occurring Inside the Hospital		
Excessive fluid loss from aggressive diuresis, nasogastric suction, surgical drains, diarrhea, etc.	Volume depletion	Prerenal azotemia or ischemic AKI
Surgery with or without concomitant volume depletion	Anesthesia causes renal vasoconstriction, which reduces renal blood flow	Prerenal azotemia or ischemic AKI
Radiologic (contrast CT) or other procedures (e.g., coronary angiography)	Intravenous contrast dye	Nephrotoxic AKI
Sepsis	Infection, volume depletion, hypotension, nephrotoxic antibiotics (e.g., aminoglycosides)	Ischemic or nephrotoxic AKI

AKI, acute kidney injury; ATN, acute tubular necrosis; CT, computed tomography; NSAID, nonsteroidal anti-inflammatory drug.

Although data are limited on treatments to prevent AKI, it is prudent to carefully follow volume status and maintain adequate hydration; discontinue (when possible) medications that are potentially nephrotoxic; choose alternate nonradiocontrast imaging techniques (e.g., magnetic resonance imaging without gadolinium); and use nonnephrotoxic antibiotics.

D. Morbidity and Mortality Associated with AKI. It was previously thought that AKI is a completely reversible disorder. Recent data suggest that of patients who develop AKI in the ICU and require dialysis, 10% to 30% may require maintenance dialysis after discharge from the hospital.

Another previously held belief is that patients die with AKI, not from AKI. Numerous well-controlled studies have found that after adjusting for comorbidities, the development of AKI in hospitalized patients is an independent and significant predictor of in-hospital mortality, regardless of whether the AKI is mild or requires renal replacement therapy (RRT). Clinical and animal data suggest that AKI is a multisystem disease that affects the lung, brain, liver, metabolic function, and immune function. These multisystem effects likely contribute to the increased mortality observed in patients with AKI.

IV. EVALUATION OF THE PATIENT WITH AKI.

A stepwise evaluation approach to the patient with AKI is recommended. A comprehensive **history** and thorough **physical examination** suggest the diagnosis in most patients.

Whether the patient is seen for the first time in the office, emergency room, hospital, or ICU, careful tabulation and recording of data are the first steps in determining the diagnosis. Vital signs, daily weights, records of intake and output, past and current laboratory data, and the fluid and medication list should be recorded on a flow sheet and included in the patient's chart. When the patient has been hospitalized for several days or weeks with a complicated course before developing AKI, a carefully prepared flow sheet may often be the only way to comprehend the problem and guide the selection of proper therapy.

Urinalysis by dipstick and the evaluation of **urine sediment** by microscopy should always be performed in patients with AKI. **Urine chemistries** that may be helpful in the diagnosis of AKI include sodium, creatinine, urea, osmolality, and protein content.

Clinical features of the common causes of AKI are described in the following sections.

A. Prerenal Azotemia. This may occur in patients who are clinically hypovolemic (total intravascular volume depletion) or hypervolemic (arterial underfilling).

1. **History.** The following history is suggestive of prerenal azotemia from true volume depletion or hypovolemia: thirst, decreased fluid intake, fever, nausea, vomiting, diarrhea, burns, peritonitis, and pancreatitis. Prerenal azotemia from arterial underfilling occurs most commonly in patients with ADHF or liver disease. Features of the history that are suggestive of ADHF include recent myocardial infarction, orthopnea, paroxysmal nocturnal dyspnea, or dyspnea on exertion. Features suggesting liver disease and cirrhosis include a history of alcohol abuse or hepatitis. A complete documentation of medications (prescribed and over-the-counter) is important in the evaluation of prerenal azotemia.

Medications that affect intrarenal hemodynamics include cyclosporine, tacrolimus, NSAIDs, Cox-2 inhibitors, ACEIs, and ARBs.

2. **Physical Examination.** Assessment of volume status and the adequacy of the extracellular fluid (ECF) volume are critical to the diagnosis of prerenal azotemia.
   a. **Physical findings that suggest a reduction in intravascular volume** include the following:
      - Absence of axillary sweat
      - A recent reduction in body weight
      - Orthostatic hypotension. Defined as a fall in systolic blood pressure of more than 20 mmHg or a rise in pulse rate of more than 10 beats/minute after standing
      - Tachycardia
      - Dry mucous membranes
      - "Tenting" of upper thorax skin when pinched between the fingers
      - Jugular venous pressure not visible when supine
   b. **Physical examination findings generally found in arterial underfilling states with an excess of ECF** include the following:
      - Elevated jugular venous pressure
      - Ascites
      - Lower extremity pitting edema
      - Anasarca

        ADHF in particular may be identified by
      - Pulmonary crackles
      - S3 gallop

        Liver failure may be identified by
      - Jaundice
      - Decreased liver size
      - Palmar erythema
      - Spider angiomas

3. **Urinary Findings.** Regardless of the cause of prerenal azotemia (hypovolemic, arterial underfilling, or medication induced) the urine dipstick, sediment, and chemistries will be the same (see Table 10-6 for a comparison of urinary findings in various types of AKI).
   a. The urine **dipstick** should be normal with negative protein, heme, leukocyte esterase, and nitrate. The specific gravity is increased (greater than 1.020).
   b. The **urine sediment** may be bland and hyaline casts may be present.
   c. **Urine Chemistry and Indices.** Frequently it is difficult to distinguish between prerenal azotemia and ATN. Laboratory tests and indices characteristic of prerenal azotemia versus other causes of AKI are summarized in Table 10-7. The pathophysiologic basis of these tests is discussed below.

4. **Specific Disorders of Prerenal Azotemia**
   a. **Hepatorenal syndrome (HRS)** occurs in patients with severe liver failure. It is characterized by peripheral vasodilatation (low systemic vascular resistance) accompanied by intense renal vasoconstriction that causes a fall in GFR. Two forms of HRS are recognized. **Type I HRS** is the more severe form and is characterized by an abrupt decline

Table 10-6. Urinary Findings in Various Causes of AKI

Dipstick	Prerenal Azotemia[a]	Postrenal[b]	Small Vessel Vascular	Nephrotic Glomerular	Nephritic Glomerular	AIN	ATN[c]
Leukocyte esterase	(−)	(−)	(−)	(−)	(−)	(+)	(−)
Heme	(−)	(−)	(+)	(−) or trace	(+)	(+)	(−)
Protein	(−)	(−)	(+)	(+)	(+)	(+)	(−) or trace
Specific gravity	>1.020	1.010	Variable	Variable	Variable	1.010	1.010
Microscopy							
RBCs	(−)	(−)	(+)	(−) or few	(+)	(+)	(−)
WBCs	(−)	(−)	(−)	(−)	(−)	(+)	(−)
RBC casts	(−)	(−)	(+)	(−)	(+)	(−)	(−)
WBC casts	(−)	(−)	(−)	(−)	(−)	(+)	(−)
Granular casts	(−)	(−)	(−)	(−)	(−)	(−)	(+)
Renal tubular epithelial cells	(−)	(−)	(−)	(−)	(−)	(−)	(+)
Tests							
Osmolality (mOsm/L)	>500	≤350	Variable	Variable	Variable	≤350	≤350
Protein (g/d)	(−)	(−)	1–2	>3	1–2	1–2	≤1

AKI, acute kidney injury; AIN, acute interstitial nephritis; ATN, acute tubular Necrosis; RBCs, red blood cells; WBCs, white blood cells.
[a]Although classically associated with a bland urinary sediment, a few granular casts may occasionally be present.
[b]If a superimposed infection is present due to urine stasis, the leukocyte esterase, heme, protein, RBCs, and WBCs may be positive.
[c]If ATN is secondary to rhabdomyolysis, heme will be positive on dipstick and RBCs will be absent on microscopy.

Table 10-7. Urinary Diagnostic Indices

Index	Prerenal Azotemia	ATN
Urine sodium (UNa), mEq/L	<20	>40
Urine osmolality, mOsm/kg H_2O	>500	<350
UCr to PCr	>40	<20
BUN/serum creatinine	>20	≤10
Fractional excretion of sodium (FENa):		
FENa = [(UNa/PNa)/(UCr/PCr)] × 100	<1	>1
Fractional excretion of urea (FEUN):		
FEUN = [(UUN/BUN)/(UCr/PCr)] × 100	<35	>50

ATN, acute tubular necrosis; BUN, blood urea nitrogen (mg/dL); PCr, plasma creatinine (mg/dL); PNa, plasma sodium (mEq/L); UCr, urine creatinine; UUN, urine urea nitrogen (mg/dL).

of renal function, defined as a doubling of serum creatinine to greater than 2.5 mg/dL within 2 weeks. Without liver transplantation, the mortality of this condition is very high. **Type II HRS** is characterized by slowly progressing renal insufficiency (serum creatinine greater than 1.5 mg/dL) in a patient with refractory ascites; it has a much better prognosis. Patients with type II HRS may convert to type I in the setting of certain insults such as the development of infections (e.g., spontaneous bacterial peritonitis) or the use of NSAIDs. HRS is typical of other forms of prerenal azotemia, and the kidney functions normally if transplanted into a person with a normal liver. The only permanent cure for HRS is liver transplantation unless there is substantial recovery of an acute liver insult.

The **diagnostic criteria for HRS** have recently been revised. To diagnose HRS, each of the criteria must be present.

Diagnostic Criteria for HRS

- Cirrhosis with ascites
- Serum creatinine greater than 1.5 mg/dL
- Absence of another cause to fully explain AKI
- No current or recent treatment with nephrotoxic drugs
- Absence of shock
- Absence of a sustained improvement in renal function following at least 2 days of diuretic withdrawal and volume expansion with albumin. Recommended dose of albumin is 1 g/kg/day up to a maximum of 100 g/day.

b. **Vasomotor Prerenal Azotemia Due to NSAIDs.** A history of NSAID use in all patients with prerenal azotemia or AKI should be aggressively sought. Under euvolemic conditions with normal kidney, liver, and cardiac function, the administration of NSAIDs does not cause an increase in serum creatinine. In the presence of clinical conditions with increased renal vasoconstrictor activity (e.g., ADHF, cirrhosis, nephrotic syndrome, hypertension, sepsis, volume depletion, anesthesia), NSAIDs can cause prerenal azotemia. Patients with CKD (e.g., diabetic nephropathy) are also at risk for acute vasomotor decline in renal function with NSAIDs. Typical clinical features include the presence of risk factors, decreased urinary output, usually bland urine sediment, low (less than 1%) fractional excretion of sodium (FENa), and prompt improvement in renal function after discontinuation of NSAIDs. NSAIDs may cause AIN and contribute to ischemic AKI.

c. **Cyclosporine and Tacrolimus** are calcineurin inhibitors that may cause a dose-dependent, hemodynamically mediated prerenal azotemia in patients who have undergone solid-organ and bone marrow transplantation. A large increase in renal vascular resistance occurs. The loss of renal function is generally reversible when the dosage of the drug is reduced. The urine sediment is bland. Animal and human data suggest that concurrent administration of calcium channel blockers may protect against calcineurin inhibitor toxicity.

d. **ACEIs and ARBs** are widely used for the treatment of hypertension, heart failure, and diabetic nephropathy. Prerenal azotemia may occur in conditions where angiotensin plays a crucial protective role in maintaining GFR by constricting the glomerular efferent arteriole, such as volume depletion, bilateral renal artery stenosis, autosomal dominant polycystic kidney disease, cardiac failure, cirrhosis, and diabetic nephropathy. Diuretic-induced sodium depletion and underlying chronic renal insufficiency are other major predisposing factors. The decline in renal function is usually asymptomatic, nonoliguric, and associated with hyperkalemia; renal function returns to baseline in most cases after discontinuation of the ACEI or ARB. Prerenal azotemia from ACEI or ARB can usually be managed in the outpatient setting by discontinuation of the ACEI or ARB and discontinuation of diuretics if present. An increase in BUN and serum creatinine in a patient on an ACEI or ARB should raise the possibility of renal artery stenosis.

B. Postrenal AKI

1. **History.** Symptoms that suggest urinary tract obstruction are anuria or intermittent anuria and polyuria, prostatic symptoms (urinary frequency and urgency, dysuria, straining upon urination), pelvic malignancy or previous radiotherapy, and recurrent renal stones. Patients may complain of pain over a distended bladder; severe pain (renal colic) may be present if obstruction is due to renal calculi. Patients with diabetes mellitus, sickle cell anemia, analgesic nephropathy, and benign prostatic hypertrophy are predisposed to papillary necrosis that causes obstruction.

2. **Physical Examination.** The physical examination is important in diagnosing postrenal AKI, especially in the unconscious patient or in the confused patient in whom otherwise unexplained agitation may be the only clue to acute urinary retention. Careful abdominal examination may uncover a distended, tender bladder or bilaterally hydronephrotic kidneys. A digital examination of the prostate should be performed routinely in any male patient with AKI. Although it is tempting to place a Foley catheter immediately to assess urine volume and relieve obstruction, we recommend obtaining an ultrasound first, if it is possible to be done in a timely fashion (within an hour or two) and if complications such as infection and sepsis are absent. As discussed below, ultrasound is the modality of choice to evaluate for obstruction; however, if the obstruction is relieved by catheterization, then the diagnostic utility of ultrasound is lost. Furthermore, catheter placement may significantly alter the diagnostic utility of urinalysis [i.e., red blood cells (RBCs) may be present from catheter placement rather than signifying glomerular diseases]. If urine output does not occur, catheter placement is a reasonable and important procedure. The patient should be asked to attempt to void, and urine output after catheterization should be recorded. The normal postvoid residual volume should be less than 50 mL.
3. **Urine Findings.** The typical urinalysis and sediment finding in postrenal AKI compared with other causes of AKI is presented in Table 10-6.
   a. **Urinalysis.** The urine dipstick should be normal with negative protein, heme, leukocyte esterase, and nitrite. The specific gravity is typically isosmotic (1.010). Heme test for RBCs may be positive if obstruction is due to renal calculi. A secondary infection may be present due to urine stasis; in this setting, the dipstick may be positive for leukocyte esterase, nitrite, heme, and trace protein.
   b. **Urine sediment** is typically bland without cells or casts. As noted, hematuria may be present if obstruction is due to renal calculi. Prostatitis and some cases of benign prostatic hypertrophy may also be associated with hematuria. In the setting of a secondary urinary tract infection, the sediment may contain white blood cells (WBCs), RBCs, and/or bacteria.
4. **Radiologic Tests.** Renal ultrasonography is sufficient to diagnose urinary obstruction in most patients.
   a. **Renal ultrasonography** is the radiologic test of choice to evaluate for obstruction, characterized by dilatation of the urinary tract (hydronephrosis). The absence of hydronephrosis virtually excludes important urinary tract obstruction; hydronephrosis may be absent, however, in the following settings: early obstruction (before the urinary tract has been able to dilate) and obstruction due to the encasement of the urinary system by retroperitoneal fibrosis or tumor.

      Hydronephrosis that is not functionally significant may occur in pregnancy and in people with anatomic variants of the collecting system. If the functional importance of hydronephrosis is in doubt, a furosemide isotope renogram can evaluate the functional significance of the obstruction.

b. **Isotope renography** is performed by the intravenous injection of a radionucleotide and furosemide. Furosemide increases urinary flow and normally causes a rapid washout of the radionucleotide. Persistence of the isotope in the renal parenchyma suggests obstruction. Poor renal function limits the usefulness of this test because the diuretic response may be blunted, thereby making interpretation of the test difficult.

c. **Noncontrast computed tomography (CT)** of the kidneys, ureters, and abdomen is often done following renal ultrasonography to identify the cause and location of urinary obstruction.

d. **Cystoscopy and Retrograde Pyelography.** In instances of AKI with a high clinical suspicion of urinary tract obstruction (e.g., calculi, pyogenic debris, blood clots, bladder cancer), cystoscopy and retrograde or anterograde pyelography should be performed, even if ultrasonographic findings are negative for obstruction.

C. Intrinsic Renal Disease—Large Vessel Disease

1. **History.** Renal artery thrombosis or embolism, or bilateral renal vein thrombosis may present with flank pain. Predisposing disorders such as membranous nephropathy or antiphospholipid antibody syndrome may be present.

2. **Urine Findings**
   a. **Urinalysis.** The urine dipstick is positive for heme.
   b. **Urine Sediment.** RBCs.

3. **Laboratory Findings and Radiology.** An elevated serum lactic dehydrogenase (LDH) may be present. Doppler ultrasonography may be used to assess renal blood flow and to evaluate for renal vein thrombosis. CT or MR angiography is useful for detecting clots in the renal vein or inferior vena cava. Angiography may be required in emergent cases (e.g., acute anuria due to acute renal embolization).

D. Intrinsic Renal Disease—Small Vessel Disease. Intrinsic renal disease due to small vessel disease is caused by either atheroembolic disease or thrombotic microangiopathy. The clinical and laboratory features of these disorders are as follows:

1. **Atheroembolic disease** is caused by the detachment of atheromatous plaques from the intimal surface of large vessels. These plaques travel distally and occlude small arteries or large arterioles of the kidney. Showers of cholesterol crystals or microemboli from the surface of ulcerated plaques may also occur, traveling distally to occlude small arterioles throughout the body (e.g., kidney, gut, or skin). The presentation and clinical findings of atheroembolic disease can be confused with those of polyarteritis nodosa, allergic vasculitis, subacute bacterial endocarditis, or left atrial myxoma.

   The usual course is progressive renal insufficiency. However, milder forms of kidney injury with some recovery of function have been described. No treatment is known. Prevention of the disease involves avoiding unnecessary invasive procedures (e.g., renal arteriogram in patients with clinical evidence of widespread atherosclerosis).

a. **History.** A history of AKI occurring after cardiovascular surgery, angiography, or administration of intravenous thrombolytics should raise a suspicion of atheroembolic disease as the cause of AKI, particularly in a patient with known atherosclerosis. Occasionally, the disease occurs spontaneously.
b. **Physical Examination.** Skin manifestations of cholesterol emboli include discrete peripheral necrotic areas, blue toe syndrome, and livedo reticularis. Small cholesterol emboli to the gut and pancreas may cause abdominal pain.
c. **Laboratory investigation** may reveal an increased erythrocyte sedimentation rate, eosinophilia, and hypocomplementemia (C3 is reduced whereas C4 remains normal). Biopsy of the skin, muscle, or kidney reveals intravascular cholesterol crystals.
d. **Urinary Evaluation**
   i. **Urinalysis.** Dipstick is frequently negative although heme or protein or both may be positive. Specific gravity is variable.
   ii. **Urine Sediment.** Sediment is often bland, although RBCs, granular casts, RBC casts, or all may be present.
   iii. **Urine Tests.** Proteinuria is typically less than 1 g in 24 hours.

2. **Thrombotic microangiopathies** are characterized by a microangiopathic hemolytic anemia, thrombocytopenia, and variable renal and neurologic manifestations. These disorders begin with endothelial injury followed by secondary platelet thrombi formation in renal arterioles; renal cortical necrosis may result from the arterial lesions. The primary site of injury is the glomerulus or the vascular supply of the glomerulus; the proximal tubule and interstitium are relatively uninvolved.
   a. **History and Physical Examination.** HUS-TTP should be suspected in patients with anemia, AKI, and thrombocytopenia. Malignant hypertension causing a thrombotic microangiopathy is characterized by high blood pressure associated with papilledema and/or retinal hemorrhages; other organ involvement may manifest as chest pain, shortness of breath from pulmonary edema, and confusion from brain involvement. Scleroderma renal crisis should be considered in patients with scleroderma and an abrupt rise in serum creatinine associated with hypertension.
   b. **Laboratory Findings.** Peripheral blood smear demonstrates increased RBC fragmentation (schistocytes) and thrombocytopenia. Indices of hemolysis (e.g., LDH) are elevated.
   c. **Urine Findings**
      i. **On Dipstick.** Variable specific gravity; heme positive, protein positive, or both.
      ii. **Urine Sediment** is characterized by granular casts, RBC casts, or both.

E. **Intrinsic Renal Disease—Glomerular Disease from a Nephrotic Cause.** Nephrotic glomerular disorders are characterized by a urine protein excretion of greater than 3 g in 24 hours. Nephrotic glomerular disorders are uncommonly associated with AKI, but it may occur in patients with minimal-change disease (especially in the elderly) and FSGS (especially from

collapsing FSGS). This generally occurs when the serum albumin concentration is less than 2.0 g/dL.

1. **History and Physical Examination.** Clinical symptoms and signs characteristic of a nephrotic disorder include pitting peripheral edema, hypertension, periorbital edema, and anasarca.
2. **Laboratory Findings**. Typically hypoalbuminemia and hypercholesterolemia are present.
3. **Urine Findings.** In cases of minimal-change–induced AKI, urine dipstick and sediment may also include features of ATN.
   a. **Dipstick** is strongly positive for protein. Heme is negative or trace.
   b. **Urine sediment** is typically bland, possibly with few RBCs. Oval fat bodies reflecting lipiduria may be present.
   c. **Urine tests** show proteinuria greater than 3 g in 24 hours.

F. Intrinsic Renal Disease—Glomerular Disease from a Nephritic Cause. Nephritic glomerular disorders (glomerulonephritis) frequently cause AKI. Nephritic glomerular disorders are characterized by hematuria and proteinuria (typically 1 to 2 g in 24 hours). RPGN should be suspected in a patient with an increase in serum creatinine associated with hematuria and proteinuria.

1. **History and Physical Examination.** Clinical symptoms and signs that suggest that the glomerulonephritis is part of a systemic disease include palpable purpura, skin rash, arthralgias, arthritis, fever, cardiac murmurs, sinusitis, hemoptysis, abdominal pain, and acute neuropathy. Hemoptysis is an ominous symptom in a patient with AKI and may indicate a life-threatening vasculitis, such as Goodpasture's syndrome or GPA (formerly known as Wegener's granulomatosis).
2. **Urine Findings.** Glomerulonephritis is characterized by hematuria and proteinuria. The identification of RBC casts confirms the presence of glomerular disease.
3. **Laboratory Findings.** ANCAs are helpful in determining the cause of glomerulonephritis. ANCA staining by immunofluorescence is either cytoplasmic (c-ANCA) or perinuclear (p-ANCA). Although c-ANCA and p-ANCA are sensitive screening tests, numerous conditions other than vasculitis and glomerulonephritis may result in c-ANCA or p-ANCA positivity. Therefore, all positive results must be confirmed with enzyme-linked immunosorbent assay (ELISA) tests for the more specific antigen targets proteinase 3 (PR3) and myeloperoxidase (MPO). The PR3-ANCA antibody is typically responsible for c-ANCA staining and the MPO-ANCA antibody for the p-ANCA staining.

   Of patients with active GPA (formerly known as Wegener's granulomatosis), up to 90% are ANCA positive (the majority are PR3-ANCA positive). Of patients with MPA, 70% are ANCA positive (the majority are MPO-ANCA positive). Of patients with CSS, 50% are ANCA positive (PR3- and MPO-ANCA detected with about equal frequency). More than 90% of patients with renal-limited, idiopathic pauci-immune vasculitis are ANCA positive (the majority are MPO-ANCA positive).

4. **Anti-GBM antibodies** are useful for the diagnosis of Goodpasture's disease, although false-negative results may occur.
5. Evaluation of **serum complement** (C3 and C4) may be helpful in the evaluation of patients with AKI and glomerulonephritis. Hypocomplementemia is common in postinfectious glomerulonephritis, lupus nephritis, membranoproliferative glomerulonephritis, and mixed cryoglobulinemia. Another cause of AKI associated with hypocomplementemia includes atheroembolic renal disease. It is important to recognize that other nonrenal conditions may lower serum complement levels (e.g., sepsis, acute pancreatitis, and advanced liver disease).

G. **Intrinsic Renal Disease—AIN.** Intrinsic renal disease due to AIN may be secondary to medications, infections, or a systemic illness such as lupus. Drug-induced AIN may be divided into three categories: AIN from methicillin, AIN from a medication other than methicillin, and NSAID-induced AIN. Interstitial nephritis from methicillin is no longer seen because this drug is no longer clinically available; however, methicillin-induced AIN remains the prototype for the classification of AIN. The clinical presentation and findings of these three major forms of drug-induced AIN are described in Table 10-8. Renal insufficiency typically persists for a mean of 1.5 months; however, complete recovery of renal function occurs in most patients.

1. **History.** In NSAID-induced AIN, symptoms and findings do not occur until several months after initiation of drug therapy (average 6 months). AIN from other medications typically occurs within a few weeks of drug therapy. Patients may complain of fever, rash, or flank pain.
2. **Physical Examination.** Physical findings with acute drug-induced interstitial nephritis may be lacking, although fever and a maculopapular or petechial skin eruption may occur with any of the agents, particularly the penicillin derivatives and allopurinol.
3. **Laboratory Findings.** Eosinophilia was common in methicillin-induced AIN, but is present in less than 50% of cases of AIN from NSAIDs and other drugs.
4. **Urine Findings.** When AIN is caused by methicillin and other drugs, RBCs and WBCs are present in most cases; also present are WBC casts. The urine is typically isotonic, and 20% of cases are oliguric. In NSAID-induced AIN, nephrotic-range proteinuria is present in 80% of cases (greater than 3 g in 24 hours); WBCs, RBCs, and eosinophils are present in less than 50% of cases.

   Urinary eosinophils have long been considered useful in the evaluation of patients with suspected AIN. However, data have mounted that the presence of urinary eosinophils is neither sensitive nor specific for the diagnosis of AIN. Indeed, urinary eosinophils are present in many other kidney diseases such as ATN and glomerulonephritis and may commonly be absent in patients with AIN. Thus, due to the failure of urinary eosinophils to either rule in or rule out AIN, urinary eosinophils should NO LONGER be examined in the evaluation of AKI with or without suspected AIN.

Table 10-8. Three Types of Drug-Induced Interstitial Nephritis

Drug Group	Age	Duration of Therapy	Fever	Rash	Hematuria and Pyuria	Eosinophilia	Nephrotic Syndrome
Methicillin	Any age	2 wk	80%	25%	90%	80%	No
Nonmethicillin	Any age	3 wk	<50%	<50%	50%	<50%	No
NSAIDs	>50 yr	Mo	10%	10%	<50%	20%	70%

NSAIDs, nonsteroidal anti-inflammatory drugs.

H. Intrinsic Renal Disease—ATN. ATN typically occurs in hospitalized patients as a consequence of ischemia or nephrotoxins.

1. **History.** The evaluation of a patient with suspected ischemic or nephrotoxic ATN must focus on identifying a predisposing cause. The chart should be reviewed for a history of sepsis, hypotensive episodes, fluid losses, aminoglycoside use, NSAID administration, or radiologic procedures associated with contrast administration.
2. **Physical Examination.** Signs of sepsis or ongoing infection should be evaluated. Volume status should be determined (see Section IV.A.2.a).
3. **Laboratory Findings and Urinalysis.** Distinguishing ischemic or nephrotoxic ATN from prerenal azotemia is often very difficult; this is an important clinical problem because a decline in GFR in hospitalized patients is most commonly due to either ATN or prerenal azotemia. In addition, prolonged prerenal azotemia often predisposes to the development of ATN. Because the causative factors for prerenal azotemia and ATN overlap, distinguishing between the two may become possible only by the outcome of therapy (e.g., if volume repletion improves renal function, then prerenal azotemia was present).

   In general, a urine sediment with muddy brown granular casts is characteristic of ischemic or nephrotoxic ATN. However, this finding may be lacking, and other clinical clues will be necessary to make the diagnosis. To distinguish between the two, numerous diagnostic indices and formulae have been developed based on their pathophysiologic differences.

   Prerenal azotemia is a hemodynamic condition in which tubular function is normal, whereas ATN is characterized by tubular dysfunction. This distinction is the basis for the following tests (Table 10-5):

   - Urine specific gravity
   - Urine osmolality
   - Urine creatinine/plasma creatinine
   - Urine sodium concentration
   - FENa
   - BUN to plasma creatinine ratio

   Prerenal azotemia is characterized by the increased reabsorption of water and sodium by the nephron. The increased reabsorption of water increases urine specific gravity and osmolality. Tubular reabsorption of urea increases, thereby increasing the BUN to plasma creatinine ratio; creatinine, however, is not reabsorbed, and its concentration increases in the urine and increases the urine to plasma creatinine ratio. Sodium reabsorption increases, resulting in a low urine sodium concentration and FENa. In ATN, these processes typically cannot occur. Therefore, urine specific gravity and osmolality are isotonic, the urine creatinine to plasma creatinine ratio does not increase above a 20:1 ratio, the serum BUN to creatinine ratio does not increase, and urine sodium and FENa are higher than in prerenal azotemia. FENa is not always increased in ATN; the causes of ATN that are associated with a low urine sodium concentration and low FENa include radiocontrast nephropathy and rhabdomyolysis.

The use of loop diuretics in AKI is a confounding factor in the use of FENa to distinguish prerenal azotemia and ATN. Distal acting diuretics (e.g., furosemide) increase urinary sodium excretion and increase FENa even if the patient is prerenal. A study evaluated the use of the fractional excretion of urea nitrogen (FEUN) to distinguish prerenal azotemia in the setting of diuretic use from ATN (both of which are typically associated with a FENa of greater than 2%). The basis of this test is that urea absorption increases in the proximal tubule in prerenal azotemia and would not be affected by the use of diuretics, which act on the distal tubule. In the setting of loop diuretic use, FEUN was an excellent test to distinguish between these conditions. In prerenal azotemia, the FEUN is less than 35% and in ATN it is greater than 50%. The use of FEUN in cases of ATN associated with a low FENa could not be assessed in this study because of the lack of patients with this condition. Keep in mind that FEUN cannot be used in the setting of osmotic diuretic use (e.g., mannitol), because these agents affect proximal tubular reabsorption.

4. **Specific Causes of Nephrotoxic AKI**
   a. **Aminoglycoside Nephrotoxicity.** AKI occurs in up to 20% of patients on aminoglycosides, even with careful dosing and therapeutic plasma levels. The incidence of nephrotoxicity correlates better with total cumulative dose than with plasma levels. Predisposing factors are old age, preexisting renal disease, volume depletion, and combination with other agents (e.g., diuretics, cephalosporins, vancomycin). Nephrotoxicity is usually clinically apparent after 5 to 10 days of therapy; early findings are isosthenuria caused by nephrogenic diabetes insipidus, and magnesium and potassium wasting. An increase in serum creatinine and BUN may not develop for the first time until after the drug has been discontinued; conversely, recovery of renal function after discontinuation of the nephrotoxic aminoglycoside is often delayed and may require weeks or months to be complete. AKI from aminoglycosides is typically nonoliguric. It is suggested that, in patients with normal kidney function in steady state, aminoglycosides are administered as a single dose daily rather than multiple-dose daily treatment regimens. It is also suggested that aminoglycoside drug levels are monitored when treatment with single daily dosing is used for more than 48 hours.
   b. **Contrast-Induced AKI (**also known as **Contrast Nephropathy).** Radiocontrast agents cause AKI through a direct nephrotoxic effect and by causing renal vasoconstriction. Risk factors include old age, high-contrast dose, preexisting renal disease (especially diabetes mellitus), volume depletion, and recent exposure to other agents, such as NSAIDs. AKI typically develops 1 to 2 days after exposure and is typically nonoliguric and associated with a high urine specific gravity, bland urine sediment, and low FENa. Serum creatinine typically peaks at 3 to 4 days and returns to baseline after about a week.
      i. **Prevention.** Either iso-osmolar or low-osmolar contrast media, rather than high-osmolar iodinated contrast media is recommended in patients at increased risk for contrast-induced AKI. Drugs that affect renal hemodynamics (e.g., NSAIDs) and diuretics should be discontinued before the procedure if possible.

Although numerous agents have been studied to prevent contrast nephropathy, the only therapies that have been shown to be beneficial are intravenous hydration with either isotonic saline or isotonic sodium bicarbonate before and after the contrast load.

N-acetylcysteine (NAC) may be beneficial in the prevention of contrast nephropathy, and its administration before contrast is reasonable but not mandatory. The benefit of NAC in the prevention of contrast nephropathy is uncertain as some studies have shown a benefit, while others have not. In general, the studies of NAC have been underpowered. The PRESERVE trial (clinicaltrials.gov: NCT01467466), which plans to enroll 8,680 patients, should definitively determine whether NAC is indeed beneficial in the prevention of contrast-induced AKI. The recommended procedure for NAC administration is that 1,200 mg of NAC be given orally twice a day on the day of the procedure and the day after. It was previously thought that NAC may artificially lower serum creatinine measurement; however, the very small lowering of serum creatinine seen with NAC administration does not explain the magnitude of the potential benefit seen in clinical trials.

Prophylactic hemofiltration or hemodialysis (HD) is probably harmful and is not a recommended measure to prevent contrast-induced AKI.

The clinical significance of contrast-induced AKI should not be underestimated. It has been demonstrated that the development of AKI after contrast administration is associated with an adjusted odds ratio of death of 5.5 versus patients who do not develop AKI.

Agents tested and demonstrated to be ineffective in the prevention of contrast-induced AKI include furosemide, mannitol, theophylline, dopamine, fenoldopam, and atrial natriuretic peptide.

c. Rhabdomyolysis is caused by muscle injury (traumatic or atraumatic) that leads to the systemic release of muscle contents including myoglobin. Myoglobin is a heme pigment that is directly nephrotoxic; the intratubular precipitation of myoglobin causes obstruction and also contributes to the development of AKI. Rhabdomyolysis should be considered in patients with trauma, muscle pain, and dark brown urine. However, rhabdomyolysis is frequently atraumatic, and up to 50% of patients have no muscular complaints. In Table 10-9 predisposing factors for rhabdomyolysis are listed.

The characteristic **urine finding** is a heme-positive urine with absence of RBCs. Pigmented granular casts are typically present on urine sediment. Laboratory clues to the diagnosis include a rapid rise of serum creatinine, massively increased creatine phosphokinase, hyperphosphatemia, hyperuricemia, hypocalcemia, increased anion gap, and disproportionate hyperkalemia. Serum calcium is reduced due to the sequestration of calcium into injured muscle; this calcium is released from the tissue during the recovery phase and may cause hypercalcemia. Therefore, replacement of serum calcium should be avoided unless symptoms of hypocalcemia are present.

The only proven **therapy** in the treatment of rhabdomyolysis is early and vigorous infusion of intravenous isotonic saline. In crush

Table 10-9.	Causes of Rhabdomyolysis
Direct muscle damage (e.g., crush injuries, polymyositis, prolonged immobilization associated with unconsciousness)	
Muscle ischemia (e.g., arterial occlusion or embolism)	
Excess energy consumption (e.g., seizures, hyperthermia, delirium tremens)	
Decreased energy production (e.g., severe hypophosphatemia, hypokalemia, myxedema, genetic defect)	
Drugs and toxins (e.g., alcohol, heroin, cocaine, amphetamines, poisonous insect, and snake bites)	
Severe infections (e.g., tetanus, Legionnaire's disease, influenza)	

injury, it is recommended that intravenous saline be administered even before extrication. Mannitol administration and urinary alkalinization are often attempted in the treatment of rhabdomyolysis, although their efficacy may not be superior to vigorous hydration with saline alone. Theoretically, forced diuresis with mannitol may aid in the washout of obstructing myoglobin pigment. Mannitol administration may be attempted only after the correction of volume deficits; saline and mannitol should be administered together with a goal urine output of 300 mL/hour. Urinary alkalinization may inhibit myoglobin precipitation; however, urinary alkalinization is difficult to achieve in practice and requires the administration of a large quantity of bicarbonate. Bicarbonate administration in rhabdomyolysis carries the risk of worsening hypocalcemia due to increased calcium and phosphorus precipitation into injured muscle. Thus, mannitol and urinary alkalinization should be utilized cautiously, if at all, in the management of rhabdomyolysis.

d. Acute uric acid nephropathy causes AKI due to the intratubular deposition of uric acid crystals. A very high serum uric acid concentration is present (e.g., $\geq$15 mg/dL). The condition typically occurs during induction chemotherapy for malignancies with high cell turnover (e.g., leukemias and lymphoproliferative malignancies). Acute uric acid nephropathy and AKI occur in tumor lysis syndrome, but may occur spontaneously in patients with high tumor burden. Clinical features of acute uric acid nephropathy are hyperuricemia, hyperkalemia, hyperphosphatemia, and a urine urate to creatinine ratio higher than 1. Preventive measures include allopurinol administration (300 to 600 mg/day) and vigorous hydration and forced diuresis with mannitol. Alkalinization of the urine has been traditionally recommended, but has not been proved more beneficial than saline administration alone; additionally, bicarbonate therapy carries the risk of increased calcium precipitation. Rasburicase, a recombinant urate oxidase, can lower uric acid levels rapidly allowing earlier

institution of chemotherapy, and may reduce the risk of acute uric acid nephropathy. Patients at high risk for tumor lysis syndrome, for example, Burkitt's lymphoma, should receive rasburicase 0.2 mg/kg daily for 5 to 7 days.

V. AKI IN SPECIAL CLINICAL CIRCUMSTANCES

A. Crystal-Associated AKI. A number of important causes of AKI may be due to the formation of urinary crystals. In Table 10-10 the causes of AKI associated with crystal formation are listed.

B. Acute Phosphate Nephropathy. A number of case reports and case series have described a potential association between use of oral sodium phosphosoda (used as a bowel preparation for colonoscopy) resulting in hyperphosphatemia, hypocalcemia, and the development of acute nephrocalcinosis, AKI, and CKD. Oral or enema sodium phosphosoda therefore is contraindicated in patients with kidney disease.

C. AKI in Patients with HIV Infection (Table 10-11). The approach to the causes of AKI in patients with HIV infection is the same as that for other patients (i.e., classification into prerenal, intrinsic renal, and postrenal causes), although patients with HIV are at an increased risk for AKI. Hypovolemia is common in HIV-infected patients, and prerenal azotemia is the most common cause of a rise in creatinine. Numerous other factors predispose patients with HIV to AKI including nephrotoxic medications, nephrotoxicity of highly active antiretroviral therapy (HAART), collapsing FSGS, and others. Although AKI is a major cause of morbidity and

Table 10-10. Urinary Crystals Associated with AKI

Type of AKI	Crystal	Shape/Appearance
AKI from ethylene glycol	Calcium oxalate monohydrate or	Needle shaped
	Calcium oxalate dihydrate	Envelope shaped
AKI from uric acid nephropathy	Uric acid	Diamond shaped, yellow or brown
AKI from sulfadiazine (intratubular obstruction)	Sulfadiazine	Needle shaped or shocks of wheat
AKI from acyclovir (intratubular obstruction)	Acyclovir	Needle shaped, birefringent
AKI from indinavir, atazanavir (intratubular obstruction)	Indinavir sulfate or atazanavir	Needle shaped, occasionally forming rosettes

AKI, acute kidney injury.

Table 10-11. AKI in Patients with HIV Infection
Prerenal Azotemia
Hypovolemia (diarrhea)
Hypotension (sepsis, bleeding)
Decreased effective arterial blood volume (hypoalbuminemia, cachexia, HIV nephropathy)
Vasoconstriction (radiocontrast agents)
Postrenal AKI
Tubular obstruction due to crystalluria (intravenous acyclovir, sulfadiazine, indinavir, saquinavir, ritonavir)
Extrinsic ureteral compression (lymph nodes, tumors)
Intrinsic ureteral obstruction (fungus balls)
Bladder obstruction (tumors, fungus balls)
Renal AKI
Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura
Postinfectious glomerulonephritis
Collapsing focal segmental glomerular sclerosis
Acute allergic interstitial nephritis (penicillins, sulfonamides)
Plasmacytic interstitial nephritis
Acute tubular necrosis (shock, sepsis, aminoglycosides, amphotericin)
Rhabdomyolysis (pentamidine, zidovudine)

AKI, acute kidney injury; HIV, human immunodeficiency virus.

mortality in patients with HIV infection, it is also potentially reversible and treatable. All supportive measures, including dialysis, should be used as warranted by the clinical situation. Importantly, AKI is avoidable in some cases when preventative measures are used (e.g., maintaining adequate hydration before use of radiocontrast agents and during use of antibiotics and antiretroviral therapy that precipitates crystalluria).

D. AKI in Hematopoietic Cell Transplant (HCT) Patients. Approximately 90% of patients have a doubling of serum creatinine after allogeneic HCT.

This incidence of AKI is higher in patients who receive allogeneic as opposed to autologous transplantation and myeloablative as opposed to nonmyeloablative transplants. The incidence of AKI is high in HCT because of the life-threatening nature of the underlying diseases and the toxicity of the cancer drugs, immunosuppressive regimens, and antibiotics. Patients who have undergone autologous HCT do not receive immunosuppressive drugs and have less AKI than allogeneic HCT. Patients with AKI after HCT who require dialysis have a greater than 90% incidence of mortality.

Factors that predispose to ATN are vomiting and diarrhea due to radiochemotherapy or acute graft-versus-host disease; nephrotoxic drugs such as aminoglycosides and amphotericin B; and hemorrhagic and septic shock. **Hepatic sinusoidal obstruction syndrome** also known as hepatic veno-occlusive disease, which is more common in allogeneic than in autologous bone marrow transplants, is a syndrome that may resemble HRS. A sodium retention state occurs and leads to weight gain, edema, and a low FENa of less than 1%, despite the use of diuretics. Progressive hyperbilirubinemia and nonoliguric AKI occur.

By far, the most common time for development of AKI is 7 to 21 days after the transplant. The renal syndromes unique to HCT recipients are classified according to the time of presentation:

- **Immediate (first few days)**
  Tumor lysis syndrome
  Stored marrow toxicity
- **Early (7 to 21 days)**
  Hepatic veno-occlusive disease
  Sepsis-induced, ischemic or nephrotoxic AKI
  Cyclosporin or FK506 toxicity
- **Late (6 weeks to 1 year)**
  Bone marrow transplant–associated HUS
  Chronic cyclosporine nephrotoxicity
  Nephrotic syndrome (membranous glomerulonephritis related to graft-versus-host disease)

E. AKI in the Setting of Liver Disease. In addition to HRS, AKI in patients with liver disease may also occur in other clinical settings. Jaundice and AKI may be due to HUS, leptospirosis, mismatched blood transfusion, acute hemorrhage, or falciparum malaria. Simultaneous AKI and acute liver failure suggests acetaminophen overdose, bacteremia, or carbon tetrachloride exposure. Glomerulonephritis and liver cirrhosis are associated with cryoglobulinemia, IgA nephropathy, membranous glomerulonephritis (associated with hepatitis B), and membranoproliferative glomerulonephritis (associated with hepatitis C).

F. Indications for Renal Biopsy. Renal biopsy may be considered in the following settings.

1. **AKI of Unknown Etiology.** In most cases, a stepwise approach reveals a cause of the AKI. However, in some patients with AKI, the diagnosis is not clear.
2. **Suspicion of glomerulonephritis** or systemic disease (e.g., vasculitis) as the cause of AKI. A renal biopsy in such circumstances may provide the

basis and justification for aggressive and life-saving therapy (e.g., high-dose steroids, cytotoxic agents, plasmapheresis).

3. **Suspicion of AIN**. Early initiation of steroids, in addition to discontinuation of offending medications, may facilitate renal recovery in patients with AIN. Although not always possible, it is generally advisable to perform a renal biopsy to confirm the diagnosis if steroids are being considered for suspicion of AIN.

VI. MANAGEMENT

A. Prerenal Azotemia

1. **True Volume Depletion or Hypovolemia.** Therapy in this setting is directed toward correcting volume deficits. If volume depletion is due to hemorrhage, then the administration of packed RBCs is indicated; otherwise, the administration of an isotonic crystalloid fluid such as 0.9% saline (also known as normal Saline) or lactated Ringer's is appropriate. When 1 L of isotonic crystalloid is given, approximately 250 mL remains in the plasma compartment, whereas 750 mL enters the interstitial compartment. The Saline vs. Albumin Fluid Evaluation (SAFE) study, a randomized controlled trial comparing 4% human albumin in 0.9% saline with isotonic saline in ICU patients, demonstrated that albumin is no more effective than isotonic saline for fluid resuscitation.

   The most appropriate choice of isotonic crystalloid (normal saline versus lactated Ringer's) for volume resuscitation remains uncertain. Normal saline is composed of 154 mEq/L of sodium and 154 mEq/L chloride. Since normal plasma sodium is approximately 140 mEq/L and normal chloride concentration is approximately 110 mEq/L, it has been argued that normal saline is not normal. Studies clearly demonstrate that normal saline administration increases the risk of hyperchloremic metabolic acidosis; other complications—including AKI—may also occur. Lactated Ringer's is composed of 130 mEq/L of sodium, 109 mEq/L of chloride, 28 mEq/L of lactate, 4 mEq/L of potassium, and 3 mEq of calcium. Clearly, lactated Ringer's should be avoided in patients with hyperkalemia and those who cannot metabolize lactate.

   The amount of intravenous fluid (IVF) and the rapidity of administration depend on the clinical situation. In a young, stable patient, IVF should be given in one-time boluses (e.g., 500 to 1,000 mL over 1 hour). Smaller boluses (e.g., 250 mL over 1 hour) may be prudent in elderly patients in whom cardiac status is unknown. After a bolus, the patient should be evaluated clinically for signs of hypovolemia or volume overload. Bedside evaluation includes monitoring of orthostatic changes in blood pressure and pulse and jugular venous pulsation (JVP). JVP is a gross indicator of pressure in the central venous area of the right heart. In a normovolemic patient, JVPs are visible when the patient is supine but disappear when the patient assumes the sitting position. JVPs are not visible in the volume-depleted patient; therefore, their reappearance following fluid administration suggests that the central venous pressure has returned to normal. The presence of basilar crackles or a third heart sound implies too vigorous fluid replacement,

with resultant cardiopulmonary congestion. Intravenous boluses of fluid should continue until euvolemia is achieved. Electrolyte deficits (e.g., potassium) should be monitored and replaced if necessary.

2. **Arterial Underfilling with an ECF Excess.** Prerenal azotemia in this setting is usually a secondary problem overshadowed by primary cardiac or liver disease. The management goal, therefore, is to treat the underlying cause; if the primary disease cannot be treated, then conservative management of symptoms is desirable.
   a. **Heart Failure.** Numerous medications may be employed to improve cardiac output in patients with cardiac disease including diuretics, betablockers, ACEIs, ARBs, nitrates, and hydralazine. Improved cardiac output may improve renal blood flow and improve kidney function. However, with advanced heart failure that is refractory or only partially responsive to these agents, the physician may be forced to accept mild to moderate prerenal azotemia as a trade-off. Such azotemia rarely leads to symptomatic uremia.

      In hospitalized patients with ADHF who are diuretic resistant, fluid may be removed with continuous venovenous hemofiltration (CVVH), slow continuous ultrafiltration (SCUF), or intermittent ultrafiltration, without dialysis.
   b. **Liver Disease.** Prerenal azotemia associated with advanced hepatic cirrhosis and patients with type II HRS are often refractory to attempts to improve intravascular volume. Ordinarily, however, the management goal is to reduce symptoms and treat ascites and edema with a sodium-restricted diet (1 to 2 g of salt per day), an aldosterone antagonist (e.g., spironolactone 200 to 400 mg/day), and a loop diuretic (e.g., furosemide) while the usually mild prerenal state may persist. Diuretic-resistant patients can be treated with intermittent large volume paracentesis, transjugular intrahepatic portosystemic stent shunt (TIPS), or liver transplantation. Treatment of hospitalized patients with type I HRS may include vasopressin analogs with albumin, or TIPS (see Chapter 2) in an attempt to improve renal blood flow. In reports from Europe, the antidiuretic hormone analogs, specifically terlipressin, with albumin infusion, have shown some promise in the treatment of HRS; however, these agents may have significant ischemic side effects. It remains to be determined if the benefits of these agents will outweigh the risk of use (terlipressin is currently available in the United States, but AVP can be used). To date, liver transplant is the only definitive cure for HRS.

B. Postrenal Failure. Foley catheter drainage is usually successful for acute obstruction secondary to prostatic hypertrophy. The decision regarding further therapy must be made in consultation with a urologist. Medical therapy with finasteride or an α-blocker, or surgical removal of prostatic tissue may be recommended.

With ureteral obstruction, cystoscopy and the placement of ureteral drainage catheters or stents may allow passage of obstructing stones, sludge, or pus, but if this fails, surgical intervention is required. With ureteral

obstruction due to more chronic conditions like tumor infiltration, prograde stents and nephrostomies are often placed by interventional radiology.

C. **Primary Renal Disease: Vasculitis and Glomerulonephritis.** When kidney injury develops in the course of a systemic or vascular disorder, it is usually a grave sign. A comprehensive discussion of the treatment of these systemic and vascular disorders is beyond the scope of this chapter. Obtaining a renal biopsy early after presentation is essential to make the diagnosis and to guide appropriate therapy. Therapeutic options include immunosuppressive therapy with steroids and/or cyclophosphamide. A subset of patients may benefit from plasmapheresis (e.g., Goodpasture's syndrome).

D. **AIN**. When a therapeutic agent is identified as the cause of AIN, removal of the agent is the obvious first step in therapy. If renal function does not improve within a week, initiation of steroids is recommended as early treatment with steroids has been shown in retrospective analysis to be beneficial in terms of improvement of kidney function and reduction in renal fibrosis versus late (after 2 weeks) initiation of steroids. Although a prospective randomized trial has not been done, the weight of evidence favors early initiation of prednisone for drug-induced AIN. Treatment regimens are varied; however, initiation therapy with 1 mg/kg of prednisone (up to 60 mg/day) for 2 to 4 weeks with a taper for 2 to 3 months is a commonly used approach. Although it is preferred to perform a renal biopsy to confirm the diagnosis, a biopsy is not always feasible. In all cases, the approach to care needs to be individualized, with the risk and benefits of steroid therapy and kidney biopsy carefully considered.

E. **Intrinsic Renal Disease, ATN.** No specific therapy exists for the treatment of ATN, although this is a widely investigated area of interest.

F. Management Principles for AKI, in general

1. **What to Avoid in AKI**
   a. **High-Dose Diuretics.** No data support the use of high-dose diuretic therapy in established ATN. Furosemide and other loop diuretics are frequently used in oliguric AKI in an effort to convert it to nonoliguric AKI. Although the conversion of oliguric to nonoliguric kidney injury may simplify fluid management, clinical trials have failed to demonstrate that the use of diuretics is associated with improved outcome in patients with AKI.
   b. **Renal Dose Dopamine.** Dopamine is a selective renal vasodilator. It elicits profound natriuresis and increases urine output in patients with normal kidney function. The renal selective dose is 1 to 3 μg/kg/minute. No evidence suggests that renal dose dopamine is beneficial in AKI. In fact, several studies have identified deleterious effects, such as bowel ischemia and arrhythmias, and thus, dopamine is not to be used as specific therapy for AKI.
   c. **Nephrotoxic Drugs.** Potentially nephrotoxic drugs and agents should be avoided in AKI, because they may perpetuate the renal injury. These agents and drugs include NSAIDs, cyclosporine, tacrolimus, aminoglycosides, radiocontrast agents, and amphotericin B.

d. **Gadolinium-Based Contrast Agents (GBCAs).** Nephrogenic systemic fibrosis (NSF) is a rare but devastating disorder that can occur in patients with kidney failure who are given GBCA. NSF is characterized by sclerosis of the skin, muscle, and internal organs and can be debilitating or even fatal. Most cases have been identified in patients with end-stage kidney disease on dialysis; however, cases in patients with chronic renal failure (stage IV), not requiring dialysis, have been reported. The latest boxed warning from the U.S. Food and Drug Administration (FDA) states that exposure to GBCA increases the risk of NSF in patients with AKI or CKD with GFR less than 30 mL/minute/1.73 m^2, AKI in general, or AKI of any severity due to HRS or in perioperative liver transplantation. Because of the risk of NSF, GBCA should be avoided in AKI. Although the risk of NSF appears to be greatest with a low GFR (less than 30 mL/minute), accurate assessment of GFR in patients with AKI is very difficult because serum creatinine is typically not in a steady state.

e. **Volume Overload.** The amount of IVF necessary for critically ill patients is unknown, and IVFs must be given judiciously in the setting of AKI, especially if the patient is oliguric. In patients with acute lung injury, conservative fluid management improves outcomes without increasing the development of nonpulmonary organ failures such as the kidney. In general, IVFs should not contain potassium. It is now well documented that the development of fluid overload in patients with AKI is associated with increased mortality. Although it is currently unknown whether excess fluid administration itself is harmful, or whether fluid overload is a marker of severity of illness, a fluid conservative strategy is a reasonable approach to patients with AKI.

2. **Supportive Therapy in AKI**

a. **Drug Dosages.** Drug dosages should be adjusted based on the measured or best estimate of CrCl, not merely on serum creatinine. Certain medication doses also must be adjusted if the patient with AKI is receiving dialysis [intermittent hemodialysis (IHD) or continuous RRT (CRRT)].

b. **Nutritional Support.** AKI is a hypercatabolic state associated with increased protein breakdown. Nitrogen balance is extremely negative, especially in AKI associated with sepsis, postsurgery, and multiorgan dysfunction syndrome. Renal factors contributing to the negative nitrogen balance include uremia, acidosis, parathyroid hormone abnormalities, inadequate protein intake, and protein losses. If supplemental nutrition is provided, enteral feeding is the preferred method of nutritional support, although it is not always possible. The use of parenteral nutrition remains controversial, and randomized controlled clinical trials have yet to demonstrate a benefit in acutely ill patients with AKI. A total energy intake of 20 to 30 kcal/kg/day is recommended in any stage of AKI. The following protein intake is recommended: 0.8 to 1.0 g/kg/day of protein in noncatabolic AKI patients without need for dialysis, 1.0 to 1.5 g/kg/day in patients with AKI on RRT, and up to a maximum of 1.7 g/kg/day in patients on CRRT and in hypercatabolic patients.

c. Renal Replacement Therapy.

The main modalities of RRT are IHD and CRRT.

i. IHD is the same form of dialysis used in patients with end-stage kidney disease. IHD is typically used in otherwise stable patients who can tolerate rapid fluid removal (e.g., 1 L/hour). IHD is mandatory in ambulatory patients.

In this form of dialysis, the patient is connected to a dialysis machine for 4 hours at a time, daily or every second day. Fluid removal and urea clearance for the day is achieved during the period of a few hours. Rapid removal of solutes and fluids may cause hemodynamic instability. The technique requires a double-lumen catheter, tubing, a HD machine (blood pump, dialysate generation system, dialysate pump, and alarms and safety monitoring devices), a dialysis membrane, and a dialysis nurse. It is strongly recommended that delivered dialysis dose be assessed in patients with AKI, and that the target level of clearance per session range between a Kt/V of 1.2 to 1.4. It is well described that delivered doses of dialysis may not match prescribed dose and that underdosing of dialysis is associated with worse outcomes.

ii. CRRT. Currently, four main types of **CRRT** are used: SCUF, CVVH, continuous venovenous hemodialysis, and continuous venovenous hemodiafiltration (CVVHDF). In Table 10-12 the

Table 10-12. Comparison of IHD and Various Types of CRRT

Type of Renal Replacement	Amount of Ultrafiltrate Formed/Hour (mL)[a]	Use of Replacement Fluid[b]	Use of Dialysate	Urea Clearance (L/d)
IHD	500–1,000	No	Yes	40–60
SCUF	50–100	No	No	2–5
CVVH	1,000–2,000	Yes	No	20–50
CVVHD	50–100	No	Yes	20–55
CVVHDF	1,000–2,000	Yes	Yes	25–75

CVVHDF, continuous venovenous hemodiafiltration; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; GI, gastrointestinal; IHD, intermittent hemodialysis; SCUF, slow continuous ultrafiltration

[a]The ultrafiltrate formed has the same electrolyte composition as plasma; therefore, with high ultrafiltrate formation, increased losses of potassium, phosphorous, calcium, and magnesium may occur. These electrolytes may need to be replaced intravenously.

[b]Replacement fluid typically contains sodium, chloride, and calcium and replaces fluid lost in the ultrafiltrate and other sources (GI, etc.) to achieve the desired hourly net fluid loss. In IHD, net fluid loss is typically 500–1,000 mL/h, whereas in CRRT net fluid loss is typically 50–100 mL/h.

different characteristics of each CRRT are summarized. The type of CRRT is individualized.

In CRRT, the goal is for the patient to undergo continuous dialysis for 24 hours a day. In practice, interruptions in dialysis for patient procedures, radiologic testing, and dialysis membrane clotting are frequent and reduce the amount of time the patient is actually receiving dialysis. CRRT is the mandatory form of dialysis for patients who are hemodynamically unstable. Because the removal of solutes and fluid is slow and continuous, hemodynamic instability and hypotensive episodes are reduced. Minimization of hypotension theoretically avoids the perpetuation of renal injury. CRRT requires a double-lumen catheter (the same catheter that is used for IHD), tubing, a simple blood pump with safety devices, sterile replacement fluid, volumetric pumps to control replacement and ultrafiltration rate, continuous anticoagulation, and a high-flux dialysis membrane. ICU nurses typically monitor therapy.

iii. Sustained low-efficiency dialysis (SLED). SLED is a "hybrid" form of RRT between IHD and continuous CRRT. In SLED, a regular IHD machine is used but the blood flow rate and dialysate flow rates are halved and the treatment is usually performed for 8 to 12 hours either daily or every second day. SLED is a safe, cheap, and convenient modality of RRT, providing excellent control of electrolytes and fluid balance. As SLED uses a regular IHD machine, a dialysis nurse is required for part of the therapy.

iv. **Peritoneal dialysis** is uncommonly used as a mode of acute dialysis therapy for AKI in the United States despite the fact that it is not technically difficult and can be used with minimally trained staff. It may be an option in locations where IHD or CRRT is not available. It can be used in patients with minimally increased catabolism without an immediate or life-threatening indication for dialysis. It is ideal for patients who are hemodynamically unstable. For short-term dialysis, a rigid dialysis catheter is inserted into the peritoneum, through the anterior abdominal wall, 5 to 10 cm below the umbilicus. Exchanges of 1.5 to 2.0 L of standard peritoneal dialysis solutions are infused into the peritoneum. The major risks are bowel perforation during insertion of the catheter and peritonitis. Acute peritoneal dialysis offers the same potential advantages to the pediatric patient that CRRT offers to the adult with AKI.

d. **Starting a Patient on RRT.** When starting a patient on RRT, the following questions need to be considered: When to start RRT? What modality of RRT to use? What type of temporary dialysis access to use? What type of dialysis membrane to use? What dose of RRT to give?

i. When to start RRT? In general, the indications to start RRT in AKI are not specific and should be individualized by nephrology consultation. Accepted indications to start RRT are as follows: 1) refractory fluid overload not responding to diuretics, 2) hyperkalemia (plasma potassium concentration >6.5 mEq/L) or rapidly

rising potassium levels, 3) signs of uremia, such as pericarditis, neuropathy, or an otherwise unexplained decline in mental status, 4) metabolic acidosis (pH less than 7.1), 5) certain alcohol and drug intoxications. However, we suggest initiating RRT prior to the development of the symptoms and signs of AKI listed above. The initiation of RRT depends on the entire clinical picture, not just the presence or absence of certain factors. In the absence of other specific indications, RRT is often initiated when the BUN reaches 80 to 100 mg/dL and is expected to continue to rise.

ii. What modality of RRT to use? Many nonrandomized studies have compared IHD and CRRT. Prospective randomized studies comparing IHD with CRRT are difficult to carry out, because patients who are hemodynamically unstable and cannot tolerate IHD are almost always started on CRRT. Alternatively, confining a mobile patient to bed to receive CRRT may be unethical. Therefore, any randomization may be biased. CRRT is believed to be the modality of choice in very ill patients, and IHD is used in less ill patients. At present, IHD and CRRT are regarded as equivalent methods for the treatment of AKI. The choice of IHD or CRRT should be made in consultation with a nephrologist and tailored for the individual patient. The decision may also depend on facility-specific issues, such as experience, nursing resources, and technical proficiency. The cost of CRRT is greater than that of IHD and SLED. In Table 10-13 a comparison of IHD and CRRT is listed. CRRT is similar in solute clearance to a GFR of 15 to 20 mL/minute. A day of CRRT is roughly equivalent to one HD treatment. Therefore, drug-dosing adjustments must be made in CRRT. At present, indications for CRRT in AKI include hemodynamic instability, brain injury, raised intracranial pressure, cerebral edema, hypercatabolism, and severe fluid overload (Table 10-14).

iii. What type of temporary vascular access to use? The primary vascular sites used for insertion of temporary dialysis catheters are the internal jugular or femoral vein. The internal jugular access is required in patients who are mobile, and the right internal jugular vein is preferred over the left due to a lower rate of central stenosis. Femoral access is indicated when the cardiopulmonary condition of the patient limits attempts at thoracic catheterization; it is useful in bedridden patients. The subclavian vein may be used if other access sites are unavailable; however, use of subclavian catheters entails a major risk of stenosis or thrombosis of the subclavian vein or its branches.

iv. What type of dialysis membrane to use? Some studies have demonstrated that the dialysis of patients with AKI having biocompatible membranes is associated with improved mortality; therefore, biocompatible membranes are used for dialysis in AKI. Biocompatible membranes are made of synthetic polymers and include polyamides, polycarbonate, and polysulfone. The adverse effects of bioincompatible cellulosic membranes (e.g., cellulose, cuprophane, hemophane, cellulose acetate) include activation of complement, increased production of cytokines, and hypotension.

Table 10-13.	Analysis of CRRT Versus Intermittent Hemodialysis
Advantages	
Hemodynamic stability (may relate in part to decreased body temperature)	
Minimizes shifts in intracranial pressure	
Unlimited alimentation	
Avoidance of rapid fluid and electrolyte shifts	
Aggressive correction of acid–base status	
Massive fluid removal	
Steady state of BUN and serum creatinine	
Simple to perform, no complex machinery	
Disadvantages	
Immobilization	
Lactate load[a]	
Continuous anticoagulation[b]	

BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy.
[a]Lactate should be avoided in patients with severe liver disease who cannot metabolize lactate. The lactate load may be avoided by making a custom dialysate that contains bicarbonate instead of lactate or using premixed replacement fluid solutions that contain bicarbonate instead of lactate.
[b]CRRT may be performed without anticoagulation; however, frequent clotting of the membrane may occur.

Table 10-14.	Indications for CRRT in AKI
Hemodynamic instability	
Brain injury	
Raised intracranial pressure	
Cerebral edema	
Hypercatabolism	
Severe fluid overload	

AKI, acute kidney injury; CRRT, continuous renal replacement therapy.

v. What dose of RRT to give? Two large randomized studies, the Acute Renal Failure Trial Network (ATN) and the RENAL study, have demonstrated that intensive dialysis does not improve mortality compared with conventional dialysis. In the ATN study no mortality benefit was observed for intensive dialysis [IHD hemodialysis or sustained low-efficiency (daily) dialysis (SLEDD) six days a week, or CVVHDF at 35 mL/kg/hour] versus conventional dialysis (IHD thrice weekly or CVVHDF at 20 mL/kg/hour). In the ATN study, achieved target clearance goals for IHD were 1.2 to 1.4 *Kt/V* urea per treatment, suggesting that this level of clearance be maintained in patients receiving IHD. In the RENAL study, CVVH at a dose of 40 mL/kg/hour did not have a mortality benefit compared with CVVH at a dose of 25 mL/kg/hour. Thus, the recommended effluent volume for CVVH is 20 to 25 mL/kg/hour; however, it should be noted that CVVH is often interrupted in ICU patients (e.g., for procedures) and that higher effluent volumes may need to be prescribed for adequate clearance to be achieved.

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11 The Patient with Chronic Kidney Disease

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Patients with end-stage renal disease (ESRD) have decreased quality of life and high morbidity and mortality. In 2007, the adjusted annual mortality of dialysis patients in the United States was 19%. Although still unacceptably high, there has been a progressive decline in the mortality rate of dialysis patients, particularly since 1999, when the annual mortality rate was >22%. The rate of growth of the ESRD population has slowed. The incidence of treated ESRD decreased between 2006 and 2007; however, the absolute number of new dialysis patients continues to increase every year, albeit at a slower rate. The prevalence of ESRD continues to increase, as does the size of the total dialysis population in the United States. It is estimated that in the year 2020, 142,858 patients will be given a new diagnosis of ESRD, and by the end of that year, more than 750,000 Americans will have ESRD.

This chapter presents an overview of the current recommendations designed to retard the progression of chronic kidney disease (CKD); to optimize the medical management of comorbid medical conditions, such as cardiovascular disease (CVD), diabetes, and lipid disorders; and to decrease the complications secondary to progression of kidney disease including hypertension, anemia, secondary hyperparathyroidism, and malnutrition. These recommendations are derived from the clinical practice guidelines published by the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF).

I. DEFINITION AND STAGING OF CKD.

The definition of CKD is as follows:

A. Kidney damage for 3 months or longer, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifest by either

1. Pathological abnormalities; or

2. Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests

B. GFR of less than 60 mL/minute/1.73 m^2 for 3 months or longer, with or without kidney damage.

In an NKF report, CKD was divided into stages of severity (Table 11-1). Importantly, the staging system is based on estimated GFR (eGFR) and not on the measurement of serum creatinine. Stage 1 CKD is recognized by the presence of kidney damage at a time when GFR is conserved; this includes patients with albuminuria or abnormal imaging studies. For example, a patient with type 2 diabetes and normal GFR, but with microalbuminuria, is classified as stage 1 CKD. The definition for microalbuminuria is 30 to 300 mg/day (24-hour excretion) and for clinical proteinuria more than 300 mg/day (24-hour excretion). Stage 2 CKD takes into account patients

Table 11-1. National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification, Prevalence, and Action Plan for Stages of Chronic Kidney Disease

Stage	Description	GFR, mL/min/1.73 m^3	Prevalence, *n* (%)	Action
—	At increased risk	≥60 (with chronic kidney disease risk factors)	—	Screening: chronic kidney disease risk reduction
1	Kidney damage with normal or increased GFR	≥90	5,900,000 (3.3)	Diagnosis and treatment; treatment of comorbid conditions; slowing progression; CVD risk reduction
2	Kidney damage with slightly decreased GFR	60–89	5,300,000 (3.0)	Estimating progression
3	Moderately decreased GFR	30–59	7,600,000 (4.3)	Evaluating and treating complications
4	Severely decreased GFR	15–29	400,000 (0.2)	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	300,000 (0.1)	Kidney replacement (if uremia present)

CVD, cardiovascular disease; GFR, glomerular filtration rate.
National Kidney Foundation-K/DOQI. Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(Suppl 1):S1–S266.

with evidence of kidney damage with decreased GFR (60 to 89 mL/minute/1.73 m^2). Lastly, all patients with a GFR of less than 60 mL/minute/1.73 m^2 are classified as having CKD irrespective of whether kidney damage is present.

The staging of CKD is useful because it endorses a model in which primary physicians and specialists share responsibility for the care of patients with CKD. This classification also offers a common language for patients

and the practitioners involved in the treatment of CKD. For each stage of CKD, K/DOQI provides recommendations for a clinical action plan (Table 11-1).

An essential requirement for the classification and monitoring of CKD is the measurement or estimation of GFR. Serum creatinine is not an ideal marker of GFR, because it is both filtered at the glomerulus and secreted by the proximal tubule. Creatinine clearance (CrCl) is known to overestimate GFR by as much as 20% in healthy individuals and by even more in patients with CKD. Estimates of GFR based on 24-hour CrCl require timed urine collections, which are difficult to obtain and often involve errors in collection. Classic methods for measurements of GFR, including the gold standard inulin clearance, are cumbersome, require an intravenous infusion and timed urine collections, and are not clinically feasible. In adults, the normal GFR based on inulin clearance and adjusted to a standard body surface area of 1.73 m^2 is 127 mL/minute/1.73 m^2 for men and 118 mL/minute/1.73 m^2 for women, with a standard deviation of approximately 20 mL/minute/1.73 m^2. After age 30, the average decrease in GFR is 1 mL/minute/1.73 m^2/year.

Equations based on serum creatinine but factored for gender, age, and ethnicity are the best alternative for estimation of GFR. The most commonly used formula is the Cockcroft-Gault equation. This equation was developed to predict CrCl, but has been used to estimate GFR:

$$\text{CrCl} = \frac{(140 - \text{age})\ (\text{weight in kg})}{(\text{Serum creatinine})\ (72)} \times\ 0.85 \text{ if female} \qquad (11.1)$$

The Modification of Diet in Renal Disease (MDRD) study equation was derived on the basis of data from a large number of patients with a wide variety of kidney diseases and GFRs up to 90 mL/minute/1.73 m^2. Therefore, the abbreviated MDRD equation is recommended for routine use and requires only serum creatinine, age, gender, and race:

$$\begin{aligned}\text{GFR (mL/minute/1.73 m}^2) = {} & 186 \times \text{serum creatinine (SCR)}^{-1.154} \times (\text{age})^{-0.203} \\ & \times (0.742 \text{ if female}) \\ & \times (1.210 \text{ if African American}) \qquad (11.2)\end{aligned}$$

The calculations can be made using available web-based and downloadable medical calculators (www.kidney.org/professionals/KDOQI/gfr_calculator.cfm).

The MDRD study equation has many advantages. It is more accurate and precise than the Cockcroft-Gault equation for persons with a GFR of less than approximately 90 mL/minute/1.73 m^2. This equation predicts GFR as measured by using an accepted method [urinary clearance of iodine 125 (^{125}I)-iothalamate]. It does not require height or weight and has been validated in kidney transplant recipients and African Americans with nephrosclerosis. It has not been validated in diabetic kidney disease, in patients with serious comorbid conditions, in healthy persons, or in individuals older than 70 years.

Creatinine-based measurements are currently used to calculate eGFR, but this measurement has limitations in risk assessment due to non-GFR determinants of serum creatinine. For this reason, cystatin C has received attention as an alternative marker for estimating GFR. A recent meta-analysis

examined whether the addition of cystatin C measurements to creatinine measurements in calculating eGFR improved the risk classification for death, CVD, and ESRD. Sixteen studies (11 general population studies and 5 CKD cohort studies) were included in the analysis. Cystatin C–based eGFR detected increased risks of all-cause and cardiovascular deaths that were not detected with creatinine-based calculations of eGFR. Cystatin C–based eGFR and eGFR based on combined measurements of creatinine and cystatin C had a constant linear relationship with adverse outcomes for all eGFR levels below 85 mL/minute/1.73 m^2. Forty-two percent of patients with a creatinine-based eGFR of 45 to 59 mL/minute had a cystatin C–based eGFR of 60 mL/minute or more, and the reclassified eGFR resulted in a 34% reduction in the risk of death and an 80% reduction in the risk of ESRD. This study provides evidence that cystatin C improves the role of eGFR in risk categorization of patients with CKD.

II. PREVALENCE OF CKD. The Third National Health and Nutrition Examination Survey (NHANES III) included 15,625 participants aged 20 years or older and was conducted, between 1988 and 1994, by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. The goal of this survey was to provide nationally representative data on the health and nutritional status of the civilian, noninstitutionalized US population. The results, when extrapolated to the US population of adults older than 20 years (n = 177 million), revealed the following findings relevant to CKD:

A. A total of 6.2 million individuals had a serum creatinine ≥1.5 mg/dL, which is a 30-fold higher prevalence of reduced kidney function compared with the prevalence of treated ESRD during the same time interval.

B. A total of 2.5 million individuals had a serum creatinine ≥1.7 mg/dL.

C. A total of 800,000 individuals had a serum creatinine ≥2.0 mg/dL.

D. Of individuals with elevated serum creatinine, 70% have hypertension.

E. Only 75% of patients with hypertension and elevated serum creatinine received treatment, with only 27% having a blood pressure (BP) reading lower than 140/90 mmHg and 11% having their BP reduced to lower than 130/85 mmHg.

In a further analysis of NHANES III data, eGFR was calculated from serum creatinine using the MDRD study equation. The prevalence of the different stages of CKD clearly shows that the CKD population is several times larger than the ESRD population. The challenge for the medical community is to identify earlier stages of CKD and institute correct treatment strategies to decrease complications and slow the progression to ESRD.

More recently it was noticed that the prevalence of CKD stages 1 to 4 increased from 10.0% in 1988 to 1994 to 13.1% in 1999 to 2004 in the US population. This increase was partly explained by the increasing prevalence of diabetes and hypertension. However, compared with 1995, the death rate in Medicare patients with CKD has fallen 40.3% and the adjusted death rate from CKD was 74.9/1,000 patient years in 2010.

III. MECHANISM OF KIDNEY DISEASE PROGRESSION. Diabetes and hypertension are responsible for the largest proportion of ESRD. Glomerulonephritis

represents the third most common cause of ESRD. Despite the many diseases that can initiate kidney injury, a limited number of common pathways are available for kidney disease progression. A general theme of many of these pathways is that adaptive changes in the nephron lead to maladaptive consequences. One of the best developed of these themes is the hyperfiltration that occurs in remaining nephrons after loss of renal mass. Elevated glomerular pressures drive this hyperfiltration. Glomerular hyperfiltration has initial adaptive effects by maintaining GFR, but later may lead to glomerular injury. Abnormal glomerular permeability is common in glomerular disorders, with proteinuria being the clinical consequence. Evidence has accumulated that this proteinuria might be a factor inciting tubulointerstitial disease. The extent of tubulointerstitial damage is a prime risk factor for subsequent renal disease progression in all forms of glomerular diseases studied. In experimental models and in human trials, an association has been consistently demonstrated between the reduction of proteinuria and renoprotection.

IV. RISK FACTORS FOR PROGRESSION TO ESRD.

The quantity of protein excreted in the urine is one of the strongest predictors of kidney disease progression and response to antihypertensive therapy in almost all studies of CKD. Therefore, the greater the proteinuria the higher the risk for progression.

As described in the previous section, an important risk factor for most glomerular diseases is the extent of tubulointerstitial disease on renal biopsy.

A. **Ethnicity** is a risk factor for many kidney diseases. For example, African American patients with diabetes have a twofold to threefold higher risk of developing ESRD compared with white patients. Some of this increased risk is attributable to such modifiable factors as suboptimal health behaviors, suboptimal glucose and BP control, and lower socioeconomic status. Human immunodeficiency virus–associated nephropathy is also more common in African American patients compared with white patients.

B. **Gender** is an additional risk factor for the development and progression of certain types of kidney disease. Overall, the incidence of ESRD is greater in males than in females.

C. **Smoking** has been associated with proteinuria and kidney disease progression in both type 1 and 2 diabetes, as well as in immunoglobulin (Ig) A nephropathy, lupus nephritis, and polycystic kidney disease. Smoking cessation has been associated with a slower rate of progression of kidney disease in type 1 diabetic patients.

D. **Finally**, heavy consumption of nonnarcotic analgesics, particularly phenacetin, has been associated with an increased risk of CKD.

V. RETARDING PROGRESSION TO ESRD

A. **Antihypertensive Therapy.** Hypertension is a risk factor for the progression of kidney disease, and it is the second most common cause of ESRD. The seventh report of the Joint National Committee (JNC VII) recommended that BP be lowered to levels below 130/80 mmHg in patients with diabetes or CKD.

An increasing amount of evidence has demonstrated that the inhibition of the renin–angiotensin system by either inhibiting angiotensin II generation with angiotensin-converting enzyme (ACE) inhibitors or blocking the

angiotensin type 1A receptor with angiotensin receptor blockers (ARBs) has renoprotective effects above and beyond the effects of these therapies on reducing BP.

1. **Studies in Patients with Diabetic Kidney Disease with Established Nephropathy**
   a. **Type 1 Diabetic Patients with Established Nephropathy**
      A pronounced benefit of ACE inhibitors in type 1 diabetic patients who already had overt nephropathy has been demonstrated in the largest study to date. Four hundred and nine patients with overt proteinuria and a plasma creatinine concentration ≥2.5 mg/dL were randomized to therapy with either captopril or placebo. Further antihypertensive drugs were then added as necessary, although calcium channel blockers and other ACE inhibitors were excluded. At approximately 4 years of nearly equivalent BP control, patients treated with captopril had a slower rate of increase in the plasma creatinine concentration and a lesser likelihood of progressing to ESRD or death.
   b. **Type 2 Diabetic Patients with Established Nephropathy**
      i. **The Reduction of Endpoints in type 2 diabetes with the Angiotensin II Antagonist Losartan (RENAAL)** study examined the effects of losartan versus non-ACE inhibitors or ARB antihypertensive therapy in 1,513 patients with type 2 diabetes and nephropathy, followed for a mean of 3.4 years. The results of this study demonstrated a beneficial effect of losartan, beyond its effects on lowering BP, on the time to doubling of serum creatinine concentration and onset of ESRD.
      ii. **In the Irbesartan Diabetic Nephropathy Trial (IDNT)**, 1,715 patients with nephropathy secondary to type 2 diabetes were randomly assigned to receive irbesartan, amlodipine, or placebo. The mean duration of follow-up was 2.6 years. This study revealed that patients assigned to irbesartan had a 33% reduction of risk for the doubling of serum creatinine compared with placebo and a 37% decrease compared with patients on amlodipine.
   c. **Studies in Patients with Diabetic Kidney Disease with Microalbuminuria**
      i. **Meta-analysis of Published Trials.** Diabetic nephropathy trialists have examined 12 selected studies involving 698 patients to compare the effects of ACE inhibitors versus placebo in type 1 diabetic patients with microalbuminuria and normal BP. Results showed that ACE inhibitors were more likely associated with regression of microalbuminuria. This effect persisted despite adjustment for any changes in BP.
      ii. **The United Kingdom Prospective Diabetes Study (UKPDS)** examined the efficacy of atenolol and captopril in reducing the risk of both macrovascular and microvascular complications in type 2 diabetic patients with hypertension. This study found that both captopril and atenolol were equivalent in reducing the renal endpoints of progression of albuminuria, overt nephropathy, a twofold increase in serum creatinine, and the development of ESRD.

iii. The Appropriate Blood Pressure Control in Diabetics **(ABCD)** trial was a prospective randomized trial of 950 type 2 diabetic patients examining whether intensive versus moderate BP control affected the incidence of progression of type 2 diabetic complications. The hypertensive patients ($n = 470$) were randomized to intensive BP control [diastolic blood pressure (DBP) goal of 75 mmHg] versus moderate BP control (DBP goal of 80 to 89 mmHg) and to either nisoldipine or enalapril as the initial antihypertensive medication. BP control of 138/86 or 132/78 mmHg with either nisoldipine or enalapril as the initial antihypertensive medication appeared to stabilize kidney function in hypertensive type 2 diabetic patients without overt albuminuria over a 5-year period. The enalapril-treated patients had significantly fewer heart attacks than the nisoldipine-treated patients. The more intensive BP control decreased all-cause mortality. The effects of intensive versus moderate DBP control were also studied in 480 normotensive type 2 diabetic patients. Over a 5-year follow-up period, intensive (approximately 128/75 mmHg) BP control in normotensive type 2 diabetic patients (a) slowed the progression to incipient and overt diabetic nephropathy, (b) decreased the progression of diabetic retinopathy, and (c) diminished the incidence of stroke. Cardiovascular events occurred more commonly in the nisoldipine group.

iv. The **Heart Outcomes Prevention Evaluation (HOPE)** study included 3,577 people with diabetes. Of the patients recruited in the study, 1,120 had microalbuminuria. Patients were randomized to the ACE inhibitor ramipril or placebo. Patients treated with ramipril had a 25% reduction in myocardial infarction, stroke, or cardiovascular death. In the ramipril group, the risk of developing overt nephropathy decreased by 24%.

v. **Irbesartan Microalbuminuria Study.** The effects of the ARB irbesartan were examined in 590 hypertensive patients with type 2 diabetes and microalbuminuria. The primary endpoint was time from baseline visit to the first detection of overt nephropathy. This study revealed that irbesartan had a renoprotective effect independent of its BP lowering effect.

d. Studies in Patients with Nondiabetic Kidney Disease

i. **The African-American Study of Kidney Disease and Hypertension (AASK)** was designed to study the effect on progression of hypertensive kidney disease of (a) two different mean arterial pressure (MAP) goals—usual (MAP: 102 to 107 mmHg) and lower (MAP: equal to below 92 mmHg)—and (b) treatment with three different antihypertensive drug classes: an ACE inhibitor (ramipril), a dihydropyridine calcium channel blocker (amlodipine), and a β-blocker (metoprolol). This study concluded that lowering BP below the achieved 141/85 mmHg was not associated with added beneficial effects and that ACE inhibitors are more effective antihypertensives in slowing the progression of hypertensive nephrosclerosis.

ii. In the **Ramipril Efficacy in Nephropathy (REIN)** study, patients were stratified before randomization by the level

of 24-hour urinary protein, with stratum 1 having less than 3 g/24-hour proteinuria, and stratum 2 having 3 or more g/24-hour proteinuria. The patients were then randomized to receive ramipril or placebo, with other medications added to achieve a target DBP of lower than 90 mmHg. An analysis of the results of this study demonstrated a beneficial effect of ramipril on slowing GFR decline that was more than expected from the reduction in BP.

The care of diabetic and nondiabetic kidney disease has been significantly advanced by this series of controlled trials. The results of these studies clearly demonstrate the renoprotective effects of ACE inhibitors and ARBs in both reducing proteinuria and slowing the progression of kidney disease. The effects of these medications may be related to decreases in glomerular capillary pressure or other effects of angiotensin II on fibrosis and growth. These agents should be considered the drugs of first choice in patients with CKD, and the BP goal should be lower than 130/80 mmHg.

e. Combined Therapy with ACE Inhibitors and ARBs in Diabetic Renal Disease

i. In the **Candesartan and Lisinopril Microalbuminuria (CALM)** study, the effects of candesartan or lisinopril or both on BP or urinary albumin excretion were examined in patients with microalbuminuria, hypertension, and type 2 diabetes.

Combination therapy reduced BP and albumin excretion more than either agent alone.

This study provided some evidence that combining an ACE inhibitor with an ARB may be more effective than either agent alone in reducing proteinuria and improving BP control.

ii. Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy (VA NEPHRON D). In this study, investigators provided losartan (100 mg/day) to patients with established nephropathy, secondary type 2 diabetes, and eGFR of 30.0 to 89.9 mL/min/1.73 m^2 and then randomly assigned them to receive lisinopril (at a dose of 10 to 40 mg/day) or placebo. The study was stopped early owing to safety concerns. Among 1,448 patients with a median follow-up of 2.2 years, there were 152 primary endpoint events (i.e., first occurrence of a change in eGFR) in the monotherapy group and 132 in the combination therapy ($p = 0.30$). There was no benefit respect to all-cause mortality or cardiovascular events. Combination therapy increased the risk of hyperkalemia and acute kidney injury.

VI. MANAGING COMPLICATIONS OF CKD

A. Anemia. Anemia secondary to kidney disease develops during the course of CKD. The degree of anemia is better evaluated using hemoglobin values rather than hematocrit. A direct correlation exists between the level of hemoglobin and GFR. In the NHANES III data, this association exists at GFR levels of less than 90 mL/minute/1.73 m^2, but was most marked when the GFR was

less than 60 mL/minute/1.73 m^2. The etiology of the anemia of CKD is multifactorial, with the major factor being a decline in erythropoietin synthesis by the kidneys. Anemia is a common complication of CKD, and recently there has been considerable interest in the relationship between hemoglobin targets and major cardiovascular outcomes in patients with stage 3 and 4 CKD. The publication of two large randomized controlled trials of recombinant human erythropoietin in CKD patients—Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)—has received intense attention and discussion by the nephrology community. Both studies tested the hypothesis that early and complete correction of anemia with the use of recombinant human erythropoietin would result in improvements of major cardiovascular outcomes; however, both studies resulted in negative findings. More recently, a post hoc analysis of the CHOIR study reported achieved and targeted hemoglobin levels and epoetin dosages. A greater proportion of patients in the high hemoglobin (target 13.5 g/dL) compared with the low hemoglobin (target 11.3 g/dL) group were unable to achieve their target. In both groups, patients who did not achieve their target hemoglobin within 4 and 9 months experienced the composite endpoint of death, congestive heart failure, stroke, and myocardial infarction at a higher rate than those who did achieve their target hemoglobin level. Those who received high-dosage epoetin (>20,000 IU) also experienced events at a higher rate in both groups. These observations, albeit from a secondary analysis, suggest that patients who have CKD and achieve their target hemoglobin level have better outcomes than those who do not, regardless of target level. High-dosage epoetin treatment may contribute to the worse outcomes observed in patients with CKD and with higher hemoglobin targets, particularly among those who are not able to achieve their target hemoglobin level. K/DOQI guidelines recommend that patients with CKD be evaluated for anemia when the GFR is less than 60 mL/minute/1.73 m^2. Erythropoietin levels are not helpful in assessing the anemia of kidney disease. The iron status of patients should be assessed, including measurements of serum ferritin, iron, and transferrin saturation. Transferrin saturations and ferritin levels should exceed 20% and 100 ng/mL, respectively, to optimize erythropoiesis. The ideal hemoglobin level for CKD patients has not been definitively determined. NKF-DOQI guidelines recommend a target hemoglobin level. In the opinion of the work group, in nondialysis patients with CKD receiving erythropoiesis- stimulating agents (ESA) therapy, the selected hemoglobin target should generally be in the range of 11.0 to 12.0 g/dL.

B. Phosphate Control. Phosphate control in CKD is important to preserve the bone mineral content and avoid hyperparathyroidism. Phosphate binders can be instituted when the GFR falls below 30 to 50 mL/minute. Vitamin D analogs can clearly help suppress parathyroid gland overactivity, but often at the expense of higher serum phosphate levels and the risk of hypercalcemia, both of which can worsen extraskeletal calcifications. Recommendations for patients with CKD include the following:

1. Maintain serum phosphorus between 3.0 and 4.6 mg/dL.
2. Restrict dietary phosphorus to 800 to 1,000 mg/day when serum phosphorus is greater than 4.6 mg/dL.

3. Restrict dietary phosphorus to 800 to 1,000 mg/day when serum levels of intact parathyroid hormone are greater than 65 pg/mL.
4. Monitor serum phosphorus every 3 months if patients are on a phosphorus-restricted diet.
5. The target range for corrected serum calcium (for every 1 g decrease in serum albumin, the serum calcium should be corrected by 0.8 mg) is 8.8 to 9.5 mg/dL.
6. If serum calcium is greater than 10.2 mg/dL, reduce or discontinue vitamin D analogs, and/or switch to a noncalcium-based phosphate binder.

C. **Acid–Base Control.** Acidosis is common in almost all forms of CKD. The main mechanism responsible for the acidosis is a decrease in total ammonia excretion, leading to a decrease in net hydrogen secretion and a fall in serum bicarbonate. This net positive acid balance results in dissolution of bone, ultimately worsening uremic osteodystrophy. Other adverse consequences of metabolic acidosis include protein malnutrition and the suppression of albumin synthesis. Early treatment of acidosis with oral bicarbonate therapy may help prevent some of the bone disease of chronic uremia and may slow down kidney disease progression. K/DOQI recommends maintaining a serum bicarbonate level of greater than 22 mEq/L.

VII. MANAGING CARDIOVASCULAR COMORBIDITY.

CVD remains the most common cause of death in patients with ESRD, and CKD patients are more likely to die from CVD than are expected to progress to ESRD. The CKD population has a higher incidence of traditional cardiovascular risk factors, including diabetes, hypertension, and dyslipidemias. In addition, overwhelming scientific evidence has shown that decreased GFR and proteinuria are independent risk factors for CVD. Consensus exists in the nephrology community that the CKD population should undergo aggressive risk factor management. This includes strict control of BP and lipids, as well as smoking cessation. K/DOQI clinical practice guidelines on the management of dyslipidemias in CKD have recommended drug therapy for patients with a low-density lipoprotein (LDL) cholesterol level $\geq$100 mg/dL after 3 months of therapeutic lifestyle changes. Statins are recommended as initial drug therapy for high LDL, and fibrates (e.g., gemfibrozil) are recommended for an elevated fasting triglyceride.

VIII. WHEN TO REFER TO A NEPHROLOGIST.

Several studies have shown that delayed referral to a nephrologist is common and is associated with adverse consequences, including greater morbidity and mortality, more severe uremia, increased use of percutaneous vascular access with associated morbidity, reduced use of the preferred arteriovenous fistula for vascular access, restricted patient choice of treatment modality, prolonged and more costly hospitalization at initiation of dialysis, and higher rates of emotional and socioeconomic problems. An early referral allows the patient to develop an effective relationship with a multidisciplinary team consisting of a nephrologist, vascular surgeon, nurse, dietitian, social worker, and mental health professional. This relationship allows for a more informed consideration by patients of renal replacement options including transplantation, initiation of renal replacement therapy to

maintain optimal patient health, timely placement of a dialysis access, supervision of dietary modification, and support services regarding unmet psychological, social, and financial needs. A nephrologist should participate in the care of patients with a GFR of less than 30 mL/minute/1.73 m^2.

Suggested Readings

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12 The Patient Receiving Chronic Renal Replacement with Dialysis

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Maintenance dialysis is a treatment for patients with advanced chronic kidney disease (CKD). While dialysis cannot duplicate many functions of a normal kidney, the goals of dialysis are to remove toxins that are normally cleared by the kidney and to maintain euvolemia in the patient. Ideally, chronic dialysis will improve signs and symptoms of uremia and allow patients to return to predialysis functional status. There are two major types of dialysis: hemodialysis (HD; performed in a dialysis unit or at home) and peritoneal dialysis (PD; almost always done at home). There are no well-performed prospective clinical trials comparing the two modalities, so the choice of modality depends on patient preferences, treatment availability, or possible contraindications to either modality.

In the United States, there has been a steady increase in the incidence and prevalence of end-stage renal disease (ESRD) over the last 30 years (Fig. 12-1). Although the utilization of PD is reported to be increasing, at present approximately 93% of patients in the United States use hemodialysis as their initial modality. Worldwide, approximately 89% of patients with ESRD are treated with hemodialysis.

I. INDICATIONS FOR INITIATING DIALYSIS

Starting a patient on dialysis is associated with dramatic changes in the patient's lifestyle and is frequently associated with medical complications. It is therefore important to thoroughly assess the benefits of initiating dialysis in patients with CKD. In general, life-threatening conditions, such as severe hyperkalemia, severe volume overload, or uremic pericarditis, will mandate prompt initiation of dialysis. Less severe symptoms, such as mild cognitive changes associated with uremia, would warrant dialysis initiation if the patient has appropriate dialysis access [e.g., arteriovenous fistula (AVF) for hemodialysis or catheter for PD]. If the patient does not have access, the benefits of dialysis must be weighed against the risk of a temporary hemodialysis catheter infection.

Ideally, dialysis should be initiated before life-threatening symptoms develop. Possible indications for initiating dialysis are listed in Table 12-1. The most recent guideline recommendations for dialysis initiation come from Kidney Disease: Improving Global Outcomes (K-DIGO). The K-DIGO recommendations suggest initiating dialysis when symptoms or signs of kidney disease develop, blood pressure or volume status is uncontrolled, nutritional status deteriorates, or cognitive dysfunction is present.

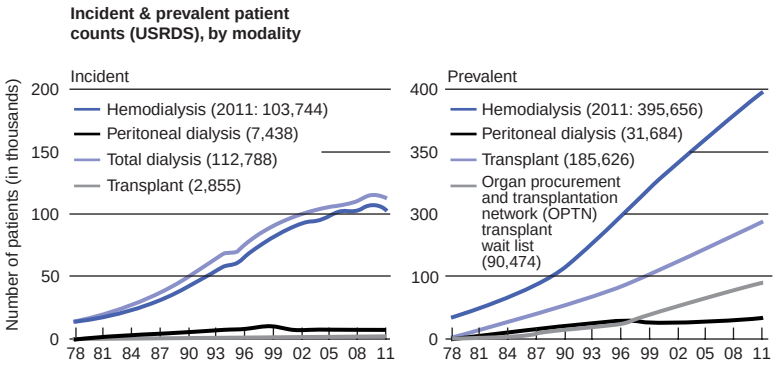

Figure 12-1. Incident and prevalent dialysis counts in the United States. (From Atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 2013; 61(1):e149–e164.) Reprinted with permission.

Table 12-1.	Potential Indications for Dialysis Initiation
Volume overload refractory to diuretics	
Hyperkalemia	
Pleuritis or pericarditis	
Peripheral neuropathy	
Encephalopathy	
Malnutrition	
Nausea/vomiting	
Uremic bleeding	
Metabolic acidosis	
Resistant hypertension	
Severe hyperphosphatemia	
Severe hypocalcemia	

Although most patients with a severely depressed glomerular filtration rate (GFR; <10 mL/min) will have some complication of renal failure, there is no specific GFR that mandates dialysis initiation. Possible benefits to starting dialysis earlier (GFR >10 mL/min) include preventing malnutrition and improving volume status. While observational studies have had conflicting results regarding the benefit of starting dialysis early, there has only been one

controlled study to test the timing of dialysis initiation. The Initiating Dialysis Early and Late (IDEAL) study randomized 828 patients to "early start" dialysis (GFR 10 to 15 mL/min) or "late start" dialysis (GFR 5 to 7 mL/min). The primary outcome was death from any cause. In the intention-to-treat analysis, there was no difference in the primary end point between the two groups. After a follow-up of 3.6 years, both groups had a mortality rate over 35%. There was also no difference in secondary outcomes (cardiovascular events, infections) between the groups. In the study, the treating physician was given discretion to initiate dialysis with a GFR above 7 mL/min if dialysis was felt to be warranted. Consequently, most patients in the late start group needed to start dialysis before the GFR reached 7 mL/min. It should also be noted that estimated GFR measurements [by the Modification of Diet in Renal Disease (MDRD) equation] between the two groups were small; 9 mL/min in the early group versus 7.2 mL/min in the late group. While the IDEAL study does not support routinely starting dialysis in patients with a GFR between 10 and 15 mL/min, it also showed that most patients develop a need for dialysis soon after their GFR falls below 10 mL/min.

Education regarding dialysis is an essential part of predialysis care. Therefore, patients should be well informed regarding all possible options (including palliative care). Some patients with significantly reduced life expectancy (severe comorbidity or elderly patients) may not live longer with dialysis and may have a reduction in quality of life with dialysis. For instance, one study found that elderly nursing home patients starting dialysis have a 58% mortality rate at 1 year while only having a 13% chance of maintaining their predialysis functional status. The decision to initiate dialysis in these patients should be a collaborative one between the patient, nephrologist, and family members.

II. HEMODIALYSIS

A. Hemodialysis Procedure.

Hemodialysis is the most common dialysis modality in the United States; it can be performed either at an outpatient dialysis unit or at home. Most patients in the United States receive hemodialysis at a dialysis center. Hemodialysis at dialysis units is usually performed thrice weekly, with each treatment lasting close to 4 hours. Some patients receive longer, nocturnal sessions at dialysis units. Home dialysis patients do shorter treatments more frequently (five or six times weekly, known as short daily dialysis) or nocturnal treatments.

During the hemodialysis procedure, blood is rapidly moved through an extracorporeal circuit. Blood is removed by a needle or through a catheter port and enters the dialysis filter (Fig. 12-2). The dialysis filter contains thousands of hollow tubes with a semipermeable membrane. On the outside of the tube is the dialysate moving in a countercurrent fashion. Solutes in the blood (high concentration) move into the dialysate (low concentration) by diffusion. Blood is then returned via a separate venous needle or port. In a process known as ultrafiltration, fluid is removed by changing hydrostatic pressure across the dialysis membrane.

Conventional hemodialysis has many advantages. With modern filters, the treatment provides for rapid and effective removal of small molecular

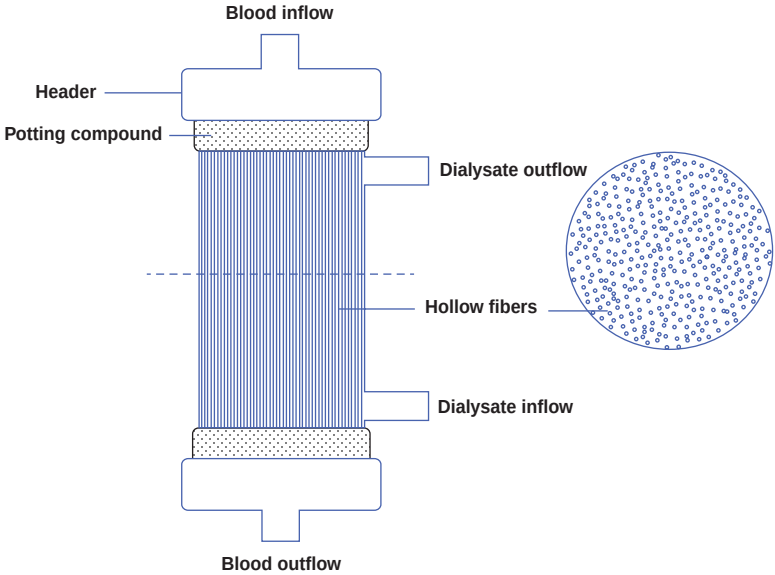

Figure 12-2. Schematic of a dialysis filter. (From Bieber SD, Himmelfarb J. Hemodialysis. In: Coffman TM, Falk RJ, Molitoris BA, Neilson EG, Schrier RW, eds. *Schrier's diseases of the kidney.* Vol II, 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2013:2473–2505.)

weight solutes, over a 4-hour treatment. Also, hemodialysis machines allow for precise control of ultrafiltration, allowing providers to prescribe a specific amount of fluid removal. In dialysis centers, patients can have trained health care professionals perform the treatment and the total treatment time is roughly 12 hours/week. However, in-center hemodialysis does have some limitations as well. Since it is not a continuous treatment, fluid removal is not physiologic and often necessitates removing large volumes of fluid during a 4-hour treatment. Hemodialysis is also not very effective at removing larger molecules or solutes that are protein bound.

B. Hemodialysis Access.

To perform hemodialysis regularly, it is necessary to have a dialysis access through which blood can be removed at a fast flow rate. The preferred access for hemodialysis is an AVF. AVFs are created by surgical anastomoses of an artery to a vein, usually in the arm. AVFs have the lowest rate of both infectious and noninfectious complications and, on average, can be used longer than other types of accesses. However, AVFs take time to mature (at least 6 to 8 weeks but up to 6 to 9 months) and sometimes fail to ever become suitable for dialysis. Prior to creation of an AVF, mapping of the upper extremity veins is usually done with ultrasound. Vein mapping can detect central stenosis and measure vein diameter. As recommended in the Kidney Dialysis Outcomes Quality Initiative (K-DOQI) guidelines, the AVF should ideally be placed distally in the nondominant arm. However,

since the success of an AVF depends on the size of the vein, if the forearm veins are less than 3 mm, then a nondominant upper arm fistula would be the second choice.

Arteriovenous grafts (AVGs) are synthetic grafts that are connected to the artery and vein. AVGs can be used more quickly, sometimes as early as 2 to 3 weeks after placement. AVGs also have a higher primary success rate. However, AVGs fail sooner than AVFs due to neointimal hyperplasia, require frequent interventions to maintain patency, and have a higher infection risk. AVGs should ideally be placed in the arms but can be placed in the thigh if there are no suitable arm veins.

Finally, dual lumen catheters can be used for dialysis. Catheters are most often placed in the internal jugular vein and can be used immediately for dialysis. Catheters should be placed in the internal jugular vein as subclavian catheters are associated with a high risk of subclavian stenosis, a complication that causes morbidity and usually will prevent future dialysis access in the ipsilateral arm. Catheters intended for use for more than a few days are tunneled under the skin to decrease the rate of infection. However, catheters have a much higher infection rate than AVFs or AVGs and also have a high rate of dysfunction.

Since AVFs are the preferred access yet take time to mature, patients with stage 4 CKD should be referred for fistula placement prior to starting dialysis. Accesses are preferably placed in the nondominant arm; therefore, preserving the nondominant arm from needle sticks, peripheral intravenous (IV) lines, and peripherally inserted central catheters is important in patients with CKD.

C. Hemodialysis Complications.

Hemodialysis may also be associated with numerous complications. There are both infectious and noninfectious complications of the vascular access. Infectious complications are relatively common in HD patients and lead to significant morbidity. Most commonly, HD patients develop bloodstream infections with gram-positive bacteria, such as *Staphylococcus aureus* and coagulase-negative staphylococci. In addition to appropriate antibiotic therapy, the dialysis catheter needs to be removed in patients with *S. aureus* bacteremia. AVFs and AVGs can develop stenosis near the venous anastomoses or in central veins. Venous stenosis can lead to arm swelling, difficulty with cannulation, and prolonged bleeding after dialysis. Stenoses are usually treated with percutaneous angioplasty.

During the first few dialysis treatments, patients starting dialysis may develop the disequilibrium syndrome, characterized by headache, somnolence, and rarely seizures or coma. It is thought that disequilibrium syndrome is due to cerebral edema after a rapid decrease in plasma osmolality; it is rarely seen if the initial dialysis treatments are short and done with low blood flows. The dialysis procedure commonly also causes hypotension. Hypotension is associated with fast ultrafiltration rates and/or autonomic dysfunction and is relatively common. A newly appreciated complication of dialysis is the development of silent myocardial ischemia during the treatment, but the long-term consequences of transient ischemia are not well understood. Very rare but potentially fatal complications of the dialysis procedure are air emboli and anaphylaxis.

III. PERITONEAL DIALYSIS

A. PD Procedure.

PD is usually done by the patient or caregiver at home and is designed to be a continuous therapy. To perform PD, a catheter is tunneled through the subcutaneous portion of the abdominal wall into the peritoneal cavity. The location at which the catheter penetrates the skin of the anterior abdominal wall is known as the exit site. Prepackaged sterile dialysate is infused into the peritoneal cavity and allowed to dwell there for a period of several hours. Peritoneal dialysate has a high osmotic (or oncotic) pressure due to the presence of dextrose or icodextrin (a starch). Therefore, fluid moves from the bloodstream to the peritoneal cavity by osmosis. Solutes move down their concentration gradient by diffusion and are also removed with fluid by convection. The dialysate and ultrafiltrate are then drained from the peritoneal cavity and fresh dialysate is instilled. There are two main types of PD. Continuous ambulatory PD is a manual therapy. The patient generally does three to four manual exchanges of dialysate daily. Automated PD uses a cycler machine to instill and drain dialysate many times throughout the night. When a dwell of dialysate is left in the peritoneum during the day, this is known as continuous cycling PD (CCPD). Less commonly, patients perform nocturnal intermittent PD; the cycler performs the exchanges at night but no fluid is left in the peritoneal cavity during the day.

PD is the preferred dialysis method in some countries due to lower cost. PD often provides the patient with more freedom and autonomy than does HD. The patient is responsible for performing the exchanges, taking vital signs, weighing themselves, and using their judgment to determine the proper dextrose concentrations for their dwells (thereby affecting their fluid removal). Although many patients on HD also continue their employment, PD may make it easier to continue one's job due to an uninterrupted day when one performs CCPD. Fluid removal is also more gradual and continuous than with HD, potentially making it more tolerable from a hemodynamic standpoint. As it does not require vascular access, PD may be easier to perform than HD in a patient without adequate veins.

B. Complications of PD.

PD is usually not associated with bloodstream infections. However, patients can develop exit site infections or infectious peritonitis. Exit site infections present with pain at the exit site, erythema, and purulent drainage. The most common organisms associated with exit site infections are coagulase-negative Staphylococcus, *S. aureus*, and *Pseudomonas aeruginosa*. Unless the patient has a history of *Pseudomonas* exit site infection, initial treatment can be directed against gram-positive organisms and tailored depending on culture data. Peritonitis is diagnosed if the patient meets two out of three diagnostic criteria: abdominal pain, cloudy PD fluid with white blood cells >100 cells/L and $>50\%$ neutrophils, or positive gram stain/culture of PD fluid. Empiric antibiotic treatment of peritonitis requires coverage for both gram-positive and gram-negative bacteria. Subsequent treatment of peritonitis depends on the pathogen. Most cases of bacterial peritonitis resolve with antibiotic therapy. Peritoneal catheters may need to be removed if there is a concurrent exit site infection or relapsing peritonitis (repeat

episode with same bacteria). Patients with fungal peritonitis should always have the catheter removed.

Due to increased intra-abdominal pressure, PD can cause hernias in the inguinal region or abdominal wall. As a result, patients who have a hernia will need to have the hernia repaired prior to initiating PD. Patients with diaphragmatic disruption may have PD fluid enter the pleural space leading to pleural effusions. Since PD contains hypertonic dextrose, patients typically receive a moderate carbohydrate load daily with therapy. Finally, catheter problems, such as kinking or malposition, can lead to problems with dialysis and may require surgical correction.

IV. GENERAL ISSUES RELATED TO CARE OF CHRONIC DIALYSIS PATIENTS

A. Dialysis Dose.

A major goal of dialysis is to eliminate uremic signs and symptoms. If patients continue to have uremic symptoms on dialysis, the dose should be increased. On hemodialysis, the dose can be increased by increasing the dialysis time, blood flow rate, or the surface area of the dialysis filter. On PD, the major modifications that will increase dialysis dose are increasing dwell volumes or adding exchanges. In the absence of uremic symptoms, measuring urea clearance with dialysis offers a way to monitor dialysis dose. Urea is used as the primary measurement since it is an easily measured small molecule. The two most common equations measuring dialysis dose for hemodialysis are urea reduction ratio (URR), shown in Table 12-2, and Kt/V urea, a unitless value that represents urea clearance over time normalized to the volume of distribution. Kt/V can be estimated from many different equations and URR can be easily calculated at the bedside. However, the URR measurement does not consider changes in body volume that occur with hemodialysis. PD adequacy is typically measured by calculating the weekly standardized Kt/V urea.

Though observational studies have suggested that higher urea clearance is associated with improved mortality, these findings have not been borne out in the few randomized controlled trials testing two or more different doses of dialysis. The hemodialysis (HEMO) study randomized 1,848 patients on thrice-weekly dialysis to standard or high-dose dialysis. The standard dose group received, on average, 190 minute dialysis treatments three times a week, while the high-dose group received 219 minutes per treatment. After a follow-up of over 2 years, there was no difference in mortality between the two groups; both groups had an average yearly

Table 12-2. Calculation of Urea Reduction Ratio

$$\frac{\text{Predialysis BUN} - \text{postdialysis BUN}}{\text{Predialysis BUN}} \times 100\%$$

BUN, blood urea nitrogen.

mortality over 16%. The adequacy of PD in Mexico (ADEMEX) trial randomized 965 patients to continue their PD prescription or increase the dose of PD. At 2 years, there was no survival advantage with high-dose PD as both groups had mortality rate greater than 30%. Although there was no survival advantage with the high-dose group, fewer patients with high-dose PD developed uremic symptoms. Based on the observational data and the interventional studies, it is recommended for hemodialysis patients to have a minimum single-pool *Kt/V* of 1.4 for each treatment and for PD patients to have a minimum standardized weekly *Kt/V* of 1.7.

B. Cardiovascular Health.

In the United States, the majority of the patients on dialysis die from cardiovascular causes, such as acute myocardial infarction, sudden cardiac death, and congestive heart failure. Unfortunately, reducing cardiovascular mortality has been hampered by the lack of evidence-based therapies. Two large studies randomizing dialysis patients to statins or placebo have not shown a mortality benefit. Since left ventricular hypertrophy (LVH) and volume overload are present in the majority of incident patients, it is possible that improved fluid control can prevent worsening heart function. Achieving euvolemia requires both fluid removal with dialysis and patient adherence to a low-salt diet. Recent studies have also shown that more frequent hemodialysis and nocturnal hemodialysis may lead to regression of LVH.

As there are no interventional studies supporting a specific goal blood pressure in dialysis patients, the ideal blood pressure for a dialysis patient is not known. Clinical practice is dictated by extrapolating results from the general and CKD populations. Data from observational studies in dialysis patients can be helpful but, unfortunately, observational studies have shown conflicting results regarding blood pressure levels and cardiovascular mortality. This is partly due to high variability of blood pressure readings in hemodialysis patients depending on the timing of the measurement. In fact, ambulatory blood pressure monitors predict mortality better in dialysis patients than blood pressure measurements during dialysis. K-DOQI suggests a predialysis blood pressure of 140/90, although the strength of that recommendation is tempered by the above observations. To achieve blood pressure control, maintaining euvolemia is crucial; however, despite achieving euvolemia, many patients will require antihypertensive medications.

C. Mineral Bone Disorder.

Abnormalities in mineral metabolism begin before the patient starts dialysis. Increases in circulating parathyroid hormone (PTH) and the phosphaturic hormone fibroblast growth factor 23 (FGF-23) often occur in patients with CKD stages 2 and 3. Serum phosphorous rises and serum calcium decreases later in the course of CKD. These biochemical changes are associated with changes in bone metabolism. Elevated PTH is usually associated with high-turnover bone disease (osteitis fibrosa cystica). Dialysis patients can also have a form of bone disease known as osteomalacia, a disease of defective bone mineralization sometimes associated with aluminum toxicity. Finally, low-turnover bone disease is associated with low PTH levels and high serum calcium levels. Although blood markers can help distinguish forms of bone disease, a bone biopsy is the only definitive way to diagnose the specific

abnormality in bone metabolism. It is generally accepted that maintaining a normal serum phosphorous and reducing severely elevated PTH levels will improve overall bone health.

D. Nutrition.

Preventing malnutrition improves the quality of life for dialysis patients and likely improves mortality. Dialysis patients are at risk for malnutrition due to enhanced muscle breakdown, inadequate caloric intake, and protein losses due to dialysis itself. A comprehensive assessment of nutritional status includes serial weight measurements, serum markers (albumin, prealbumin, or creatinine), questionnaires (Subjective Global Assessment), dietary interviews, anthropomorphic measurements, and possibly urine collections to measure nitrogen excretion (an estimate of daily protein intake). Low serum albumin measurements do correlate with mortality; however, serum albumin alone is not sufficiently sensitive or specific enough to diagnose protein energy malnutrition.

K-DOQI guidelines recommend that dialysis patients consume 35 kcal/kg/day. The recommendations also state that hemodialysis patients eat protein more than 1.2 g/kg/day and PD patients eat more than 1.3 g/kg/day. The latter recommendation is due to enhanced protein losses with PD. There is a significant body of data demonstrating that treatment of metabolic acidosis improves nutritional status. Therefore, it is crucial to ensure that dialysis patients maintain normal serum bicarbonate levels.

E. Anemia.

Anemia occurs in most patients on dialysis. In observational studies, anemia was associated with a decrease in quality of life, impairment in cardiac function, and mortality. In the past, anemia was treated with red blood cell transfusions, a treatment that could cause iron overload or sensitization to future transplants and which conferred risks of infections such as hepatitis B and C. Recombinant erythropoietic agents (ESAs), such as erythropoietin and darbepoetin, are now used to treat anemia and prevent blood transfusions. However, there are no data from randomized trials that ESAs improve mortality in dialysis patients. Because high doses of ESAs can cause hypertension, vascular access problems, and strokes, it is recommended that they not be used to increase the hemoglobin above 11.5 g/dL. A variety of IV iron formulations are also commonly used in dialysis patients. The newer formulations are well tolerated and help improve responsiveness to ESAs. To date, there are no long-term data concerning IV iron formulations and mortality. There are many treatment strategies for using these agents, including some that rely more heavily on IV iron. Since there have been no direct comparisons of the two treatment classes, treatment of anemia varies significantly depending on patient characteristics and provider preferences.

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13 The Patient with a Kidney Transplant

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I. INTRODUCTION AND EPIDEMIOLOGY. The prevalence of end-stage renal disease (ESRD) in the United States and developed nations is alarmingly high. In 2011, there were 115,643 new ESRD patients and more than 615,899 total patients with ESRD in the United States. These are dramatic increases from previous decades. Currently, hemodialysis, peritoneal dialysis, and kidney transplantation are the only available therapies for ESRD.

Comparisons of kidney transplant recipients to patients on dialysis awaiting transplantation have shown that kidney transplantation, in most cases, is the ideal treatment for ESRD. Advantages include longer patient survival, less morbidity, cost savings, and improved quality of life compared with dialysis. Living kidney donation remains the most effective therapy, with average graft survival of approximately 12 to 15 years, with longer survival for well-matched sibling transplants. This good news is tempered by the reality that demand for transplant kidneys far exceeds the supply of available organs. Although modest increases in deceased donor transplants have occurred owing to efforts to improve recovery from expanded donors, donors with cardiac death, and donors with brain death, these increases have not kept pace with demands. With more than 119,900 patients on the kidney waiting list in September 2013, the unfortunate result is that many patients will die on the waiting list before receiving a transplant.

II. PATIENT SELECTION. There are few contraindications to receiving a kidney transplant. However, patients should not receive a transplant if they have an active infection, ongoing active immunologic disease which led to kidney failure, metastatic malignancy, are unable to follow a medical regimen due to medical or psychological reasons, or are at high operative risk due to other conditions. Although there is no definite age limit to receive a kidney transplant, elderly patients (age >70) with comorbid conditions have less demonstrable survival benefit compared with dialysis and should be screened thoroughly and counseled regarding expected benefits and potential risks of transplantation.

A. Recipient Evaluation

The goals of evaluating a potential recipient should be to identify potential barriers to transplantation, identify treatable conditions that would attenuate the risk of the surgery or immunosuppression, and explain the benefits and risks. Attention is given to the cause of ESRD and its tendency to recur in kidney transplants. Comorbid conditions and the effects of immunosuppression on these conditions are considered. Patient age older than 50 years,

diabetes, abnormal electrocardiogram, angina, or congestive heart failure have been demonstrated as predictors of cardiac death and nonfatal cardiac events with kidney transplantation. Noninvasive strategies such as thallium perfusion imaging and dobutamine stress echo have demonstrated the ability to predict cardiac events and may prevent high-risk patients from requiring angiography. Screening for malignancy should follow age-appropriate guidelines. In patients with malignancies, a 2- to 5-year remission may be required before transplantation depending on tumor type, invasiveness, and prior treatment. Although obesity is a risk for wound-related complications, long-term outcomes are similar to nonobese patients unless cardiovascular disease exists. Psychosocial screening is usually performed. Testing generally includes evaluation for human immunodeficiency virus (HIV) and hepatitis B and C. Imaging or functional evaluation of the kidneys and lower urinary tract may be necessary in certain patients. ABO and human leukocyte antigen (HLA) typing is performed, along with determination of serologic status for cytomegalovirus (CMV) and varicella. After a patient has been accepted as a candidate, he or she is added to the transplant waiting list, at which time initial medical screening of potential living kidney donors can take place. A patient on the waiting list for more than 1 year should be seen periodically to update his or her condition.

The candidate's blood is screened for anti-HLA antibodies using single antigen beads (SABs) while on the transplant waiting list at various intervals depending on individual program protocols. Antibodies against another individual's HLA antigen(s) are produced as a result of prior transfusion, pregnancy, and/or organ transplant. Anti-HLA antibodies detected as a result of this screening process are used to calculate the overall degree of HLA sensitization, or calculated panel reactive antibody (cPRA). If the antibodies are deemed clinically significant by the transplant center, the corresponding HLA antigen is listed as "unacceptable" for that recipient, and donor kidneys containing that antigen will not be offered. Thus, higher values of cPRA equate to fewer potential compatible donors, resulting in significantly longer expected waiting times for the recipient. This process is known as "virtual cross-matching." See Section IV.A for more details regarding donor/recipient cross-matching.

B. Organ Donors

1. **Living Donors.** Although the risks of kidney donation are small, these risks need to be carefully explained to a potential **living donor**. Mortality is uncommon, but has occurred in 0.02% of donors (2 per 10,000). Infection, bleeding, and other postoperative complications occur in up to 15% of patients. Progression to ESRD has occurred and may be slightly more common than in the general population, however remains an infrequent consequence. Mild blood pressure elevation and proteinuria after donation has been reported in some studies but not all, and the long-term consequences are currently unclear. After ABO compatibility and a negative cross-match are assured, the donor evaluation process can begin. If there are multiple candidates, the donor with fewer HLA mismatches is usually selected. Donors are carefully screened for kidney disease to prevent the possibility of loss of function in the remaining kidney. Hypertension, proteinuria, obesity, kidney stones, and structural

or functional kidney disease are all relative contraindications to donation depending on severity. Testing for latent diabetes mellitus with a glucose tolerance test may be performed if there is a family history or perceived risk of future diabetes. When recipients are affected by hereditary disorders such as polycystic kidney disease or hereditary nephritis, the condition must be ruled out in related donors either clinically or with genetic testing. If a donor is thought to be acceptable, imaging of the kidneys is performed with computed tomographic (CT) angiography or other modalities, allowing the team to assess for structural or vascular anomalies and suitability for laparoscopic donation.

2. **Deceased Donors**
   A deceased donor must also be evaluated. The presence of metastasis, unknown cause of death, HIV, or widespread infection precludes donation. Donors with hepatitis C are sometimes accepted for hepatitis C–positive recipients. A combination of factors such as hypertension, advanced age, elevated serum creatinine, oliguria, or dependence on pressor support may exclude a donor. Preimplantation biopsies can be performed on an individual basis when there is concern about the function of a donor kidney. **Standard criteria donors (SCDs)** typically experienced primary brain death while cardiac and respiratory function remained intact, and do not meet expanded donor criteria. **Expanded criteria donors (ECDs)** are defined by any donor older than 60 years, or any donor older than 50 years with at least two of the following: terminal serum creatinine greater than 1.5, cerebrovascular accident as a cause of death, or preexisting hypertension. ECD kidneys have a 1.7 relative risk of graft failure compared with SCD kidneys but still provide survival benefit compared with dialysis in selected populations. They are commonly used in recipients with characteristics associated with poor dialysis survival such as advanced age or diabetes. In **donation after cardiac death (DCD)**, organs are recovered from a donor who has undergone cardiac death after a period of circulatory arrest, usually in the setting of a withdrawal of care in the hospital. Although longer warm ischemia times lead to an increase in delayed graft function (DGF), DCD kidneys have similar long-term survival and function when compared with SCD kidneys.

C. Predictors of Outcome

Recipient factors, donor factors, and donor/recipient compatibility all influence long-term graft survival. Recipients who are younger, have low levels of PRA, have spent less time on dialysis, and who are employed or college educated have superior graft survival. Race and ethnicity may affect graft survival for both donors and recipients, with nonblack donor kidneys and nonblack, non-Hispanic recipients of grafts having the longest graft survival. Kidneys from living related or unrelated donors survive longer on average than deceased donor kidneys, as do kidneys from younger compared with older donors. As described above, deceased donor kidneys meeting ECD have a shorter expected survival versus standard criteria kidneys. Finally, factors of donor and recipient compatibility also affect outcomes: better HLA matching, negative immunologic cross-matching, CMV serologic status matching, and equivalent donor/recipient body mass index all have positive effects on long-term graft survival.

III. IMMUNOLOGY AND PHARMACOTHERAPY

A. Immunology

A basic review of the mechanisms of immune recognition and response to an allograft is helpful to better understand the patient who has undergone kidney transplantation as well as the pharmacologic agents used to prevent allograft rejection.

1. Major Histocompatibility Complex

Cells in the tissues of mammals, birds, and bony fish express major histocompatibility complex (MHC) surface molecules, which are crucial for the immune system to be able to recognize and respond to a foreign antigen. In humans, these MHC molecules are located on the short arm of chromosome 6 and encode for proteins termed the *HLAs*. MHC molecules serve two basic functions: they identify self from nonself and coordinate the T-cell receptor (TCR) recognition of the antigen–MHC complex. The MHC molecules are divided into two groups: class I and class II. MHC class I molecules appear on the surface of all nucleated cells and are known as *HLA-A*, *B*, and *C*. MHC class II molecules appear on antigen-presenting cells (APCs) and are termed *HLA-DR*, *DP*, and *DQ*. One MHC *haplotype* is inherited from each parent as a locus containing each of the six genetically linked HLA molecules. In kidney transplantation, only the HLA-A, -B, and -DR are determined due to their immunogenicity. A "zero-antigen mismatched kidney" has no mismatches in either locus for HLA-A, -B, and -DR, although mismatches may be present at HLA-C, -DP, -DQ, or at other minor antigens. Although advances in immunosuppression have narrowed advantages for well-matched transplants, a two-haplotype identical transplant from a family member or a zero-antigen mismatched deceased donor transplant confers a graft survival benefit compared with transplants with lesser degrees of matching.

2. Antigen-Presenting Cells

APCs are distributed in a ubiquitous manner in body tissues and allow T cells to recognize foreign antigens. Monocytes, macrophages, dendritic cells, and activated B cells can all serve as APCs. Either by phagocytosis or through surface immunoglobulin (Ig) (B cells), APCs capture foreign antigens, degrade and process them into peptides, and express these foreign peptides on MHC class II surface molecules. Through TCR interactions and various downstream events, the T cell is then able to coordinate an immune response to this foreign antigen.

3. T cells

T cells are processed in the thymus and are central to cellular immunity and allograft recognition and rejection. These properties make them a common target of drugs designed to prevent rejection. Central to the immune response is the ability of the T cell to recognize foreign antigens through a surface TCR. These receptors recognize antigens through either indirect or direct pathways. The *indirect pathway* involves TCR recognition of a foreign (nonself) MHC antigen that has been shed from the graft and is presented by a self-MHC molecule located on an APC surface. The *direct pathway* involves TCR recognition of an intact foreign MHC antigen present on the surface of a *donor* APC that has been shed from the

graft. This latter phenomenon occurs only in alloimmune responses and is responsible for the majority of TCR recognition in acute graft rejection at a frequency of 100:1 compared with indirect recognition.

There are two major classes of T cells: T-helper cells which express CD4 surface molecules ($CD4^+$), and cytotoxic T cells which express CD8 ($CD8^+$). $CD4^+$ cells recognize MHC class II molecules on the surface of APCs, whereas $CD8^+$ cells are restricted to recognition of MHC class I. $CD4^+$ cells are activated after recognition of a foreign antigen (e.g., foreign MHC from a kidney transplant). They then initiate an immune response to foreign peptides by secreting cytokines important in B-cell proliferation and activation and cytotoxic T-cell activation. $CD8^+$ T cells kill cells bearing foreign antigen through the use of cytotoxic molecules such as perforins, granzymes, and Fas, which triggers apoptosis in the targeted cell. Regulatory T cells (Treg) are a recently described T-helper cell subset that suppress the activation and proliferation of $CD4^+$ and $CD8^+$ T cells and have been implicated in allograft tolerance.

4. **T-Cell and APC Interactions**
   T cells and APCs have a number of important interactions central to allograft recognition and rejection. *Signal 1* is the term for initial binding of the T cell to the APC through interactions between the TCR/CD3 complex and foreign peptide expressed in MHC. Signal 1 is a calcium-dependent process and results in calcineurin activation. Although signal 1 alone will cause anergy, the addition of **signal 2**, also known as *costimulation*, will lead to an immune response. The best understood costimulation signal is between CD28 on the T-cell surface and B7 on the APC surface. CD28/B7 activation leads to intracellular signaling, interleukin 2 (IL-2) production, and T-cell activation. While CD28 is expressed on resting T cells, the T-cell surface molecule cytotoxic T lymphocyte antigen-4 (CTLA-4) Ig is expressed only on activated T cells. CTLA-4 binds preferentially to B7 and eventually inactivates the immune response, thereby providing potent negative feedback. Another costimulatory molecule, CD40, is found on APCs and activated B cells, and binds to CD40 ligand (CD40L) on T cells. The CD40/CD40L pathway is important in Ig production and class switching by B cells.

5. **B Cells**
   B cells develop at multiple sites of the body, including the liver, spleen, and lymph nodes. In response to T-cell allorecognition-induced activation and proliferation signaling, B cells produce antibodies that are specific to foreign MHC antigens. When these antibodies are specific to donor antigens they are termed donor-specific antibodies (DSA). Antibody-mediated cellular cytotoxicity occurs via complement fixation and subsequent cell lysis. B cells and antibodies are important in allograft rejection, with the potential to cause hyperacute rejection (immediate allograft destruction due to preformed antibodies), as well as acute and chronic antibody-mediated rejection (due to either preformed or de novo DSA).

B. Pharmacotherapy

In the 1960s and 1970s the first transplant immunosuppressive agents consisted of steroids and azathioprine. Since that time the number of available

immunosuppressive agents has increased greatly. Agents can be used for *desensitization* therapy prior to transplant, *induction* therapy at the time of transplant, *maintenance* therapy to prevent rejection of the allograft, or the treatment of *acute rejection*. There is a large degree of overlap between indications, and many agents are used "off-label." Commonly used agents, their mechanism of action, and common toxicities appear in Table 13-1. Desensitization is discussed separately (see Section IV.A).

1. **Agents Used for Induction**
   a. **Basiliximab:** Chimeric murine/human monoclonal antibody that binds to the IL-2 receptor on activated T cells, inhibiting IL-2-induced T-cell activation and proliferation without depleting T-cell populations. It is given as 20 mg intravenous (IV) infusions at the time of transplant and 4 days later, and is 75% humanized with minimal side effects.
   b. **Antithymocyte Globulin (ATG, thymoglobulin):** Polyclonal Ig preparations developed by injecting human thymic extracts into rabbits (rATG) or, less commonly, horses (Atgam) and purifying the antibodies produced. These preparations neutralize lymphocytes by multiple antibody-mediated mechanisms, with a sustained effect on proliferation, and are more effective than basiliximab in preventing acute rejection. Toxicities are related to immunosuppression, heterogeneity of preparations, allergic or anaphylactoid responses to nonhuman preparations, and cytopenias. Dosing schedules are commonly 1.5 mg/kg IV daily for 3 to 5 days but vary by center.
   c. **Alemtuzumab (Campath):** Humanized monoclonal anti-CD-52 antibody that depletes both B and T cells. Due to its potent immunosuppressive properties it is often used with steroid avoidance and immunosuppression-reduction protocols; however, it is also associated with profound lymphopenia, susceptibility to infection, and autoimmune syndromes. Furthermore, a change in type and timing of rejection may be seen, including monocyte-induced and humoral rejections occurring past the early posttransplant months. It is used off-label for kidney transplant induction and standard dosing has not been defined; however, 30 mg IV at the time of transplant is common.
2. **Agents Used for Maintenance**
   a. **Calcineurin Inhibitors**: Cyclosporine A (CsA) and tacrolimus (FK506) are the mainstay of maintenance immunosuppression. Both agents bind intracellular calcineurin, inhibiting translocation of transcription factor nuclear factor of activated T-cells (NFAT) to the nucleus and subsequent cytokine-induced cell proliferation. Cyclosporine and tacrolimus have similar side effects, but hyperlipidemia, hypertension, hirsutism, and gingival hyperplasia are more common with cyclosporine, and posttransplant diabetes mellitus (PTDM) and neurotoxicity may be more common with tacrolimus. They both have potential to cause nephrotoxicity. Dosing is adjusted according to trough or peak blood levels and varies depending on immunosuppressive regimen (see Section V.C.1).
   b. **Mammalian Target of Rapamycin Inhibitors (mTOR-Is):** Sirolimus and everolimus downregulate mTOR, inhibiting IL-2-mediated signal transduction and cell proliferation. Important toxicities include

Table 13-1. Commonly Used Drugs in Renal Transplantation			
Class and Drugs	**Mechanism**	**Toxicity**	**Indication**
Calcineurin Inhibitors			
Cyclosporin	Binds cyclophilin and blocks action of calcineurin	Hypertension, hyperlipidemia nephrotoxicity, neurotoxicity, hirsutism, gingival hyperplasia	M
Tacrolimus	Binds to FKBP, inhibiting action of calcineurin	PTDM, neurotoxicity side effects similar to cyclosporine	M
TOR Inhibitors			
Sirolimus Everolimus	Binds to FKBP and inhibits mTOR effects, cytokine signaling, cell cycling, and CD28-mediated costimulation	Elevated cholesterol and triglycerides, cytopenias, acne, wound healing, pneumonitis	M, CIM
Antimetabolites			
Azathioprine	6-MP release in vivo, interferes with DNA synthesis, cell cycling	Cytopenias, diarrhea, hepatotoxic, neoplasias	M
Mycophenolate mofetil Mycophenolic acid	Inosine monophosphate dehydrogenase inhibitors, blocks de novo purine synthesis	Diarrhea, GI discomfort, cytopenias, invasive CMV	M M
Corticosteroids	Multiple sites of action; cytokine production, T-cell proliferation, leukocyte traffic, others	HTN, PTDM, hyperlipidemia, obesity, infection, osteoporosis, AVN	I, M, CR

(*continued*)

Table 13-1. Commonly Used Drugs in Renal Transplantation (Continued)

Class and Drugs	Mechanism	Toxicity	Indication
Belatacept	Fusion protein of human IgG and CTLA-4, inhibits CD28-mediated costimulation	PTLD: only for use in EBV-seropositive patients	M, CIM
Antibody Therapies			
Antithymocyte globulin	Rabbit polyclonal Ab against thymocytes	Allergic reaction, leukopenia	I, CR
Basiliximab	Partially humanized (75%) monoclonal Ab, same target as daclizumab		I
Alemtuzumab	Humanized monoclonal Ab against CD52 on lymphocytes and monocytes	Lymphopenia, autoimmune syndromes, infection, delayed rejection	I
IVIG	Immune modulation, multiple sites of action	Infusion reactions, headache, acute kidney injury when sucrose based	AMR, D
Rituximab	B-cell-depleting anti-CD20 monoclonal antibody	Infusion and dermatologic reactions, cytopenias	AMR, D

Ab, antibody; AMR, antibody-mediated rejection; AVN, avascular necrosis; CIM, calcineurin inhibitor minimization; CMV, cytomegalovirus; CR, cellular rejection; D, desensitization; EBV, Epstein-Barr virus; FKBP, FK binding protein; GI, gastrointestinal; HTN, hypertension; I, induction; IgG, immunoglobulin G; IL-2, interleukin 2; IVIG, intravenous immunoglobulin; M, maintenance; 6-MP: 6-mercaptopurine; PTDM, posttransplant diabetes mellitus; PTLD, posttransplant lymphoproliferative disorder; TCR, T-cell receptor; TOR, target of rapamycin.

hypertriglyceridemia, hypercholesterolemia, cytopenias, pneumonitis, delayed wound healing, lymphoceles, diarrhea, and proteinuria, as well as potentiation of calcineurin inhibitor toxicity. As with calcineurin inhibitors, dosing is adjusted according to trough or peak blood levels and varies depending on immunosuppressive regimen (see Section V.C.1).

c. **Antimetabolites:** Mycophenolate mofetil (MMF), mycophenolic acid (MPA), and azathioprine can be used in combination with calcineurin inhibitors and corticosteroids for maintenance immunosuppression. They inhibit purine synthesis and subsequent lymphocyte proliferation. MMF and MPA often cause diarrhea and gastrointestinal discomfort, can be associated with cytopenias, and may be associated with an increased risk of tissue-invasive CMV. They are dosed at 1 g (MMF) or 720 mg (MPA) twice daily. Azathioprine provides less selective lymphocyte inhibition and can be associated with cytopenias and neoplasias. It is commonly dosed at 1.5 mg/kg daily.

d. **Corticosteroids** are used during induction, as maintenance therapy, and for the treatment of acute rejection. They inhibit the immune response via a broad effect on inflammatory mediators. Their effectiveness is complicated by a variety of well-known side effects, including hypertension, glucose intolerance, weight gain, cataracts, poor wound healing, osteoporosis, and osteonecrosis. Although corticosteroid withdrawal and avoidance have been explored (see Section V.C.2), they remain a mainstay of current immunosuppression in ~70% of US transplant centers.

e. **Belatacept** is a fusion protein consisting of the Fc portion of human IgG and the extracellular domain of CTLA-4 that was approved in the United States for use in kidney transplant recipients in 2011. It binds with high affinity to B7 on the APC, inhibiting CD28-mediated T-cell costimulation (signal 2, see Section III.A.4). It is used in calcineurin inhibitor–sparing protocols (see Section V.C.2) and is generally well tolerated; however, it has been associated with higher rates of posttransplant lymphoproliferative disorder (PTLD) and therefore is only indicated in patients who are seropositive for Epstein-Barr virus (EBV; who have a lower risk of PTLD). It is only available in IV formulation, and is infused once monthly during the maintenance phase (more frequently during initiation).

3. **Agents Used for Treatment of Rejection**

The pharmacologic treatment of rejection depends on the type of immune response as determined by histology from an allograft biopsy (see Section VI.B). Corticosteroids and antithymoctye globulin (described in the previous sections) are used in cell-mediated (T-cell) rejection. Intravenous immunoglobulin (IVIG), rituximab, bortezomib, and eculizumab have been used to treat antibody-mediated (B-cell) rejection, often in combination with plasma exchange therapy. IVIG exerts immunomodulatory action via numerous mechanisms, including inhibition of cytokine activity, inhibition of T-cell activation and functionality, and inhibition of complement activation. Rituximab is a chimeric murine/human monoclonal anti-CD20 antibody that reduces populations of pre-B and mature B lymphocytes. Bortezomib is a proteasome inhibitor that reduces

numbers of antibody-secreting plasma cells. Eculizumab is a monoclonal antibody that inhibits terminal C5 complement activation, thereby limiting antibody-mediated cell toxicity, and is approved for treatment of atypical hemolytic uremic syndrome. These agents, while often very effective, are all considered off-label for the indication of kidney transplant rejection, and dosing has not been standardized. Common side effects of these agents are listed in Table 13-1.

4. **Drug Interactions**
Although it is not possible to list all potential drug interactions, it is important for the clinician to be aware of general types of interactions when initiating new therapies or witnessing unexpected toxicities. In general, interactions can result from changes in absorption, metabolism, excretion, or through additive or synergistic toxicity with agents that have similar side effects. Agents that can decrease the absorption of immunosuppressive agents include antacids, cholestyramine, and food, whereas promotility agents can increase absorption. Metabolism of tacrolimus and cyclosporine occurs through cytochrome P-450-3A4; therefore, agents that affect this system can alter calcineurin inhibitor levels or altered metabolism of the interacting agent, leading to toxicity or inadequate levels. Examples include calcium channel blockers, azole antifungals, macrolide antibiotics, and grapefruit juice, which can increase calcineurin inhibitor levels, and anticonvulsants and rifampin, which can decrease levels. Simvastatin and atorvastatin should not be used with cyclosporine due to decreased clearance and risk of myopathy and rhabdomyolysis. Allopurinol can cause severe myelosuppression when used with azathioprine and should be avoided. Cyclosporine reduces MMF exposure, and mTOR-Is can potentiate calcineurin inhibitor nephrotoxicity. Also, nonsteroidal anti-inflammatory drugs and ACE inhibitors may have additive effects on glomerular hemodynamics with calcineurin inhibitors. Although this summary is not exhaustive, cautious attention to these possibilities can prevent morbidity from drug interactions.

IV. TRANSPLANTATION

A. Cross-Matching and Desensitization

Cross-matching between the recipient and donor is usually performed immediately prior to transplantation in order to minimize the risk of hyperacute and acute antibody-mediated rejection. This is accomplished using complement-dependent cytotoxicity, cell-based flow cytometry, solid-phase SAB assays, or a combination of these methods. If a cross-match assay is positive, a decision is made to either cancel the procedure or proceed with some form of desensitization depending on the perceived rejection risk, transplant center experience, and available resources. Desensitization protocols aim to reduce the risk of rejection by mitigating the impact of preexisting recipient DSA. They vary depending on donor organ source and degree of cross-match positivity, and generally consist of therapies that are used to treat antibody-mediated rejection (Sections III.B.3 and VI.B). Examples include plasma exchange treatments followed by low-dose (100 to 200 mg/kg) IVIG until the cross-match assay is negative (useful for patients with living

donors and surgery dates that can be planned or postponed), and high-dose (1 to 2 g/kg) IVIG with or without rituximab immediately before and/or after surgery (for recipients of deceased donor kidneys). Transplantation across a positive cross-match generally increases the risk of rejection and graft loss even with desensitization, but likely improves patient outcomes compared with remaining on dialysis.

B. Induction

With few exceptions, kidney transplant recipients will receive a brief course of high-dose steroids at the time of transplantation, followed by a taper to the initial maintenance dose. Either for perceived increased risk of rejection or by local protocol, antibody therapy may be given during induction. Increased risks of rejection may be seen in those with high PRA, previous transplants, and African Americans. Available antibody-based therapies include ATG, IL-2 receptor antagonists, and alemtuzumab. ATG and alemtuzumab deplete the lymphocyte pool and provide more potent immunosuppression compared with IL-2 receptor antagonists, but also have more potential for toxicity (see Section III.B.1).

C. Donor Nephrectomy

Living donor kidneys can be recovered in either an open or laparoscopic approach, each with its own advantages and disadvantages. The left kidney is most often selected due to its longer renal vein and accessibility. Laparoscopic donation rates have increased due to technical advancement and donor preferences. In general, laparoscopic donation has advantages of a shorter hospital stay, quicker return to work, and less pain, but can come with higher costs, longer operative time, and a learning curve to decrease rates of morbidity to equal that of open nephrectomy. Deceased donor kidneys are removed together with a patch of aorta and inferior vena cava as part of a multiorgan recovery. The organs are then separated and stored in hypothermic preservation solution until implantation. Pulsatile perfusion may be used, especially in ECD or DCD kidneys.

D. Transplant Surgery

The transplanted kidney is placed in either the right or left iliac fossa. The renal vein and artery are both connected through an end-to-side anastomosis, the donor vein usually being connected to the external iliac vein and the donor artery to the external iliac artery. The ureter is implanted into the bladder, and the bladder mucosa is pulled over the ureter to create a tunnel which prevents reflux and urine leak. A ureteral stent is often placed at the time of surgery to ensure patency and prevent urine leak. Lymphatics are ligated to prevent postoperative lymphocele formation. A Foley catheter is placed at the time of surgery and maintained for up to 5 days postoperatively. Kidney transplantation in the absence of donor ischemia or technical complications is usually accompanied by prompt urine formation.

V. POSTOPERATIVE MANAGEMENT

A. **Immediate postoperative care** of the transplant recipient involves close monitoring of urine output, fluid administration, and vital signs. Many

centers use algorithms, which replace the urine output with half normal saline or similar solution. The brisk diuresis that can ensue in a transplant recipient can cause disturbances in potassium, magnesium, calcium, and phosphorus. The effect of elevated parathyroid hormone along with a suddenly functioning kidney also contributes to these abnormalities. Insulin requirements may increase in diabetic patients or those without prior diabetes due to the presence of steroids, calcineurin inhibitors, and improved clearance of insulin by the transplanted kidney. An uncomplicated patient with a functioning kidney can usually ambulate by postoperative day 1 or 2, and the diet can be advanced as tolerated. By postoperative day 3 or 4, the Foley catheter can be removed and the patient can be discharged if he or she is free of other complications.

B. **Surgical complications** include problems with each of the aspects of the transplant: the vascular anastomoses, urologic complications, lymphocele, and wound complications.

1. Urologic complications include urine leak, obstruction, and reflux. Routine stenting at many centers may be responsible for a decrease in the incidence of urologic complications. *Urine leak* can occur in approximately 2% of transplants. It is usually due to ureteral necrosis caused by interruption of distal ureteral blood supply but can be at the site of bladder implantation or the calyces. The clinical presentation is one of decreased urine output, pain, fever, abdominal tenderness, swelling, and a perinephric fluid collection by ultrasonography. Fluid aspiration reveals a high creatinine that far exceeds the plasma creatinine. The diagnosis can be confirmed by nuclear scan or CT urography demonstrating extravasation into local tissues. Temporary Foley catheterization and ureteral stenting followed by surgical repair are the usual management. *Ureteric obstruction* can be secondary to ureteral ischemia as well as fluid collections or masses. Imaging by ultrasonography, cystogram, or other studies usually leads to a diagnosis; the obstruction can be relieved by ureteral repair, stenting, or nephrostomy. *Vesicoureteral reflux* into the transplanted ureter is less common since the introduction of submucosal tunneling of the ureter through the bladder.
2. **Arterial or venous thrombosis** is uncommon but may occur as a result of preexisting hypercoagulability or technical difficulty, and should be suspected when sudden deterioration develops in a previously functioning transplant. While venous thromboses can occasionally be reversed by surgery or thrombolysis, vascular thromboses most often lead to graft loss.
3. **Lymphocele** presents as an asymptomatic cystic fluid collection. It may, however, cause graft obstruction and reduced kidney function, pain, or lower extremity edema and deep vein thrombosis due to compression of the iliofemoral vessels. Lymphoceles are distinguished from urine leaks as fluid aspiration yields a fluid creatinine equal to serum creatinine. The aspirated fluid should also be sent for cell count and Gram stain to rule out hematoma or abscess. Lymphoceles can be aspirated but may require surgical repair (marsupialization) if they are recurrent.
4. **Wound complications** may stem from the problems detailed earlier, or due to infection. Clinical suspicion is necessary, as immunosuppression

masks the symptoms and increases the risk of wound infections. Prompt drainage and antibiotic administration are central to treatment.

5. **Infections** in the first postoperative month are similar to those in other postoperative patients but occur more frequently in immunosuppressed patients. Lung, urine, and wound infections and infections related to dialysis catheters are common culprits. Infections of fluid collections (lymphocele, urinoma, and hematoma) may also occur. Opportunistic and other infections are discussed in Section VI.

C. Maintenance Immunosuppression

1. Conventional Therapy

Since 1995, the available options for maintenance immunosuppression have been expanded with the introduction of MMF, tacrolimus, cyclosporine microemulsion, and sirolimus. Standard therapy in the United States consists of a calcineurin inhibitor, an antimetabolite, and corticosteroids. The calcineurin inhibitors, tacrolimus and cyclosporine, have similar efficacy in patient and graft survival, but with slightly different toxicity profiles. Tacrolimus has also lowered both the incidence and severity of acute rejection in head-to-head comparisons. One approach is to maintain target trough levels of cyclosporine that are highest (300 ng/mL) in the first month, with gradual tapering to 150 to 250 ng/mL by 6 months and 50 to 200 ng/mL after 12 months. Similarly, target tacrolimus levels are 6 to 12 ng/mL in the first month, 5 to 8 ng/mL for months 1 to 5, and 4 to 7 ng/mL after 6 months. Target levels may need to be lower in patients receiving sirolimus, and are often individualized based on age, PRA, matching, rejection history, and the presence of infection. MMF and sirolimus have largely supplanted azathioprine in clinical use, as both result in less acute rejection. The third agent used in combination regimens is corticosteroids; they are usually tapered rapidly to 20 mg daily by 1 to 2 weeks posttransplant. They are then gradually tapered to 5 to 10 mg daily by month 6. The availability of multiple agents has allowed clinicians to choose a regimen that best fits a patient's profile of immunologic risk and perceived susceptibility to side effects. For example, patients with second transplants or poor matching who are at greater risk for rejection may be placed on tacrolimus. However, an obese patient with a family history of diabetes but with low immunologic risk may be placed on cyclosporine or chosen for a steroid withdrawal protocol in an attempt to reduce the risk of PTDM.

2. Alternative Regimens

The toxicities of corticosteroids and calcineurin inhibitors have led to multiple clinical trials of withdrawal and avoidance strategies. Meta-analysis of late steroid withdrawal has been associated with acute rejection and graft loss, particularly in African Americans. In contrast, trials of early withdrawal or avoidance of steroids in low-risk patients have shown promise; however, they are associated with higher rates of rejection with limited benefit in metabolic complications, and lack long-term results. Calcineurin inhibitor withdrawal/avoidance is another goal due to nephrotoxicity and other side effects. Clinical trials of belatacept, a costimulation blocker, in combination with steroids and MMF, show improved

3-year graft function despite increased acute rejection rates compared with cyclosporine-containing regimens; however, long-term graft and patient survival data are not yet available and there is a higher risk of PTLD (Section VII.C). The mTOR-Is sirolimus and everolimus have been studied in several calcineurin inhibitor avoidance strategies including avoidance, withdrawal, and conversion protocols. While results from the ELITE-Symphony study show calcineurin inhibitor avoidance using mTOR-I is associated with worse graft outcomes, studies of early (1 to 6 months) or late (>6 months) conversion or withdrawal have been more promising. However, as with belatacept, most trials of calcineurin inhibitor minimization using mTOR-Is have shown increased rates of acute rejection, and long-term improvements in patient or graft survival have not been published.

VI. MEDICAL COMPLICATIONS.

In addition to DGF, acute or chronic rejection, and recurrent disease, patients who have undergone kidney transplantation are susceptible to kidney failure from all the causes that affect the general population. In the initial 48 hours after transplantation, technical causes related to surgery or DGF are most common. After 48 hours, the approach to a patient with kidney dysfunction should rule out hypovolemia, medication toxicity, and urinary tract obstruction, and should attempt to uncover causes of acute tubular necrosis (ATN) such as hypotension, sepsis, or radiocontrast. Evaluation for acute rejection should take place if clear causes are not found.

A. Delayed Graft Function

DGF is commonly defined as the requirement for dialysis in the first 7 days after transplantation. It occurs in 20% to 30% of deceased donor transplants but is uncommon in living donor transplants. Although technical factors or other events that affect kidney function can cause DGF, it is most commonly a result of postischemic ATN, caused by donor hypovolemia or hypotension, or prolonged cold or warm ischemia during recovery and preservation. DGF adds to the cost and length of hospitalization and is associated with decreased short- and long-term graft survival. To determine the cause of graft dysfunction in the early postoperative period, a kidney ultrasonography should be performed to rule out technical causes, and the timing of kidney biopsy to rule out acute rejection should be guided by the patient's immunologic risk.

B. Acute Rejection

Rejection refers to an immunologic response by the recipient to the transplanted organ. There are several types of acute rejection. *Hyperacute rejection* is rare and is caused by preformed antibodies against donor antigen, leading to immediate graft destruction after perfusion. *Accelerated acute rejection* usually occurs 2 to 3 days after transplant, and often is an antibody-mediated process that takes place in presensitized patients with prior transplants, transfusions, or pregnancies. Acute cellular rejection is either a T-cell or antibody-mediated response, or a combination of both, that may occur at any time, but is most common from 5 to 7 days posttransplant until 4 weeks after transplant, with a gradual lessening of risk in the first 6 months. Clinically, symptoms such as low-grade fever;

a swollen, tender allograft; and oliguria are not seen commonly with modern immunosuppression. Therefore, frequent laboratory monitoring and a high index of suspicion are necessary to diagnose acute rejection. Acute rejection typically presents as a decrease in kidney function, as measured by the serum creatinine. However, rejection can occur without discernable changes in kidney function, a process referred to as *subclinical rejection*. Some centers perform routine "protocol biopsies" to evaluate for subclinical rejection and other graft abnormalities. Current regimens incorporating newer agents have lowered the incidence of acute rejection in the first year to 15% or lower, have improved 1-year deceased donor allograft survival to approximately 90%, and may be responsible for some of the improvement in long-term outcomes. The diagnosis of acute rejection requires an ultrasound-guided kidney biopsy, with application of the Banff criteria to grade the severity of rejection or disclose other pathology. Pathologic features of interstitial infiltration with lymphocytes, tubulitis, and endarteritis are seen in T-cell rejection, whereas peritubular capillary inflammation and C4d staining, circulating DSA, and tissue injury are diagnostic for antibody-mediated processes. Treatment of acute T-cell rejection is usually a 3- to 5-day course of high-dose IV steroids and/or a 5- to 10-day course of ATG for more severe rejection. Treatment of antibody-mediated rejection usually involves five or more sessions of plasma exchange followed by IVIG, and occasionally rituximab or bortezomib for more severe cases. Although most acute rejection can be reversed, its occurrence remains a powerful predictor of long-term graft survival, most notably antibody-mediated rejection or T-cell rejection involving the large vessels.

C. Recurrent Disease

The diagnosis of recurrent disease is guided by the clinical scenario and knowledge of which diseases tend to recur in kidney transplants. Recurrent nephritis may present as proteinuria, nephrotic syndrome, microscopic hematuria, and loss of function. It can be differentiated from other causes (chronic allograft dysfunction, *de novo* glomerular disease) by kidney biopsy. In the patient who has undergone transplantation, the important variables are the frequency of recurrence and frequency of graft loss due to recurrence. For example, type II membranoproliferative glomerulonephritis (MPGN) recurs in close to 100% of the cases and commonly leads to graft loss. Primary focal and segmental glomerulosclerosis and type I MPGN recur in 20% to 60% of patients, and also commonly may lead to graft loss. Alternatively, IgA nephropathy recurs in approximately 50% of recipients, but uncommonly causes graft loss. Systemic lupus erythematosus may also recur microscopically in kidney allografts but rarely is clinically important. Glomerular disease was the cause of 30% of all graft loss in one study, half of which was due to recurrent disease.

D. Chronic Allograft Damage

Despite a significant reduction in the incidence of acute rejection over the last several decades, long-term graft survival has improved only marginally. The most common cause of graft loss is patient death with a functioning graft, the majority of which is due to cardiovascular disease, and accounts for

close to half of all cases. The remaining cases of graft loss are due to a range of both immunologic (chronic rejection) and nonimmunologic (e.g., donor organ quality, hypertension, drug toxicity) allograft injuries, the epidemiology of which has changed over time. Protocol biopsy studies of patients transplanted in the 1980s and 1990s described interstitial fibrosis/tubular atrophy (IFTA) due to calcineurin inhibitor toxicity as the dominant cause for late graft dysfunction. More recent studies have shown a much lower rate of IFTA in failed grafts, placing more emphasis on glomerular pathology and chronic antibody-mediated graft damage. Glomerular pathology can consist of recurrent primary or de novo disease, the latter often in the form of transplant glomerulopathy. This lesion is characterized by double contouring of the glomerular basement membrane with proteinuria, is often associated with glomerular C4d staining and circulating DSA, and portends a particularly poor prognosis for the graft. Chronic antibody-mediated graft damage, occasionally in the form of transplant glomerulopathy, is often due to medication nonadherence and has been reported as responsible for over 60% of graft failures. IFTA is still a pathologic finding in up to 30% of graft failures, the cause of which is usually multifactorial and can include chronic infection, rejection, drug toxicity, or glomerular disease. Chronic allograft damage is not typically a reversible disease, and treatment is patient specific. For example, a patient with suspected calcineurin inhibitor toxicity may benefit from a reduction or withdrawal of the offending agent, whereas a patient with circulating DSA and chronic antibody-mediated rejection may benefit from increasing immunosuppressive exposure.

VII. MEDICAL CARE OF THE TRANSPLANTED PATIENT.

The success of kidney transplantation and the growing population of transplant recipients are unfortunately accompanied by the complications from comorbid diseases and side effects of long-term immunosuppression. Patients often die with functioning grafts due to cardiovascular disease, infections, and malignancy, and these and other conditions contribute to a spectrum of common disorders in transplantation.

A. Infectious Diseases

In the patient who has undergone transplantation, typical signs and symptoms of infection may be absent, and coinfections are common, necessitating increased scrutiny. Infections after kidney transplantation occur in patterns that are important to recognize. Immediately after transplant, patients are at risk for common postoperative infections: wound infections, pneumonia, line, and urinary infections. The first 6 months after transplant is marked by a risk of opportunistic infections due to more intense immunosuppression, especially after antibody induction. For this reason, patients usually receive prophylaxis against *Pneumocystis carinii pneumonia* for at least 6 months, and for CMV for 3 to 6 months if they are at risk (see next section). Some centers provide prophylaxis for fungal infections. After 6 months, the risk of opportunistic infections is lower but remains present, and patients remain at risk for more frequent and severe infections with community-acquired pathogens. Some common pathogens and principles specific to kidney transplantation will be reviewed.

1. **Immunosuppression during Infection**
   There are no clear guidelines for decreasing immunosuppression during infection. Furthermore, many infections carry an increased risk of acute rejection due to upregulation of immune surveillance and activity. In general, mild infections treated with appropriate antimicrobials can be managed without a change in immunosuppression. However, more severe infections may require decreasing or stopping antiproliferative medications (sirolimus, MMF, azathioprine) and reductions in calcineurin inhibitor dosing. Severe or life-threatening infections should include attention to the requirement for stress doses of corticosteroids, which are often adequate to decrease the risk of rejection during an illness. Reduction of immunosuppression is best done with careful monitoring of graft function along with the consultation of transplant physicians.
2. **Cytomegalovirus**
   CMV is a human herpes virus that is common in the general population but usually does not lead to serious morbidity without immunosuppression. The risk of CMV infection is tied to serologic status of the donor and recipient. A potential organ recipient who has not been exposed to CMV is at risk for a primary infection if transplanted with a CMV-positive organ, a recipient who has been exposed before transplant is at risk for reactivation or superinfection, especially if receiving antibody induction, and CMV disease is uncommon in donor-negative/recipient-negative transplants. Therefore, donor-positive/recipient-negative patients and recipient-positive patients generally receive prophylaxis for CMV for 3 to 6 months, usually with valganciclovir. CMV infection leads to morbidity related directly to infection, but also increases the risk of acute rejection, graft loss, and death. Clinically, the disease often presents as low-grade fever, leukopenia and/or thrombocytopenia, and malaise. Tissue invasion can occur in 5% to 15% of infections, with syndromes of pneumonitis, hepatitis, esophagitis, and diarrhea being most common. Polymerase chain reaction (PCR)–based testing is the most sensitive diagnostic technique, but other options exist, including biopsy of affected tissues. Standard therapy is IV ganciclovir, a nucleoside analog, although ganciclovir resistance can develop.
3. **BK Virus Nephropathy (Polyomavirus)**
   Human BK virus (BKV) is a polyoma virus that is present as a latent infection in most of the population and has tropism for the genitourinary tract. During immunosuppression, the virus can reactivate. In patients who have undergone kidney transplantation, BKV most commonly causes a syndrome of decreased kidney function and interstitial nephritis, which appears clinically and pathologically similar to acute rejection. Because discovery at the time of nephropathy may be too late to prevent graft loss, current practices emphasize screening for BK viruria and viremia using PCR-based testing. Immunohistochemical techniques and the presence of viral inclusions can be used to confirm the diagnosis through kidney biopsy. It is important to suspect BKV nephropathy when presumed acute rejection does not respond to steroids or occurs after 6 months, as increasing the intensity of immunosuppression may lead to graft loss. The mainstay of management is

decreasing the intensity of immunosuppression, which may stabilize BKV-related kidney dysfunction but increase the risk of acute rejection. IVIG, cidofovir, and leflunomide have been used anecdotally with varying success in subjects with ongoing viremia or declining kidney function despite immunosuppression reduction.

4. **Hepatitis B and C**
   Although the incidence of hepatitis B in patients with ESRD has been declining due to immunization, isolation techniques, and screening of transfused blood, hepatitis C infections are relatively common, affecting up to 7% of recent US deceased donor transplant recipients. There is no consensus on management or outcome of either disease in respect to kidney transplantation. For hepatitis B, patients with antigenemia usually receive evaluation and liver biopsy before transplant, as antiviral therapies may be more effective before transplantation. For hepatitis C, the effects on outcomes and management are somewhat controversial. Data suggest that hepatitis C infection increases the risk of graft loss, death, and PTDM. Although many patients have mild, indolent disease, there are reports of rapid progression to cirrhosis and liver failure after kidney transplantation. A complicating factor is that interferon therapy increases the risk of acute rejection. Most patients with hepatitis C should receive liver biopsy to exclude cirrhosis and should have consideration of interferon therapy before transplantation.
5. **Human Immunodeficiency Virus**: HIV infection was historically a contraindication to transplantation, but successful kidney transplantation is now more common in patients free of opportunistic infections with undetectable viral replication and sustained CD4 counts greater than 200. For reasons that are not completely understood, HIV+ kidney recipients experience acute rejection at rates up to fourfold higher compared with HIV-negative patients. Protease inhibitors can significantly increase calcineurin inhibitor exposure, and frequent monitoring for appropriate dose titration is essential when used together.
6. **Other Infections**
   Urinary infections are common after kidney transplantation, and pyelonephritis of the transplanted kidney can lead to decreased kidney function. Pulmonary infections from both common and uncommon pathogens are the most common cause of tissue-invasive infection. Although the list of pathogens affecting patients is too long to mention, differential diagnosis should include fungal diseases such as *Cryptococcus*, *Candida*, and endemic fungi, mycobacterial disease, nocardia, *Pneumocystis carinii*, viral pathogens, and others.
7. **Immunization**
   Potential transplant recipients should receive immunization against influenza, pneumococcus, hepatitis B, and varicella if they are seronegative. After transplant, many centers wait 6 months before any immunizations because of theoretic risks of stimulating the immune system and increasing the risk of rejection. Also, the vaccines may be less effective in this time period. The oral polio, typhoid, varicella, yellow fever, and Bacillus Calmette-Guérin (BCG) vaccines are live vaccines that are contraindicated

after kidney transplant due to their ability to cause disease in immunocompromised hosts. However, the live measles-mumps-rubella (MMR) vaccine can be given after 6 months if indicated. Vaccination for influenza, pneumococcus, hepatitis A and B, and tetanus/diphtheria should be given as indicated. The role of human papilloma virus (HPV) vaccine in transplant candidates requires elucidation.

B. Cardiovascular Disease. Cardiovascular disease is the most common cause of death in patients with a functioning allograft. Ischemic coronary artery disease, congestive heart failure, and left ventricular hypertrophy are all more common in patients with kidney disease, and cerebrovascular disease is another important cause of morbidity and mortality. Therefore, efforts at improving outcomes after kidney transplantation have been appropriately shifted to focus on cardiovascular risks. Efforts at preventing cardiovascular events begin with pretransplant evaluation, risk stratification, and intervention when necessary. After transplantation, attention is given to modification of existing risk factors and careful evaluation and treatment of new symptoms or disease.

1. Hypertension

Since the introduction of calcineurin inhibitors, hypertension has been present in 70% to 90% of patients after kidney transplant. Hypertension not only represents a modifiable cardiovascular risk factor but also is correlated with graft loss. Clinicians should aim for a target blood pressure below 130/80 mmHg as indicated by current recommendations for patients with chronic kidney disease. The choice of agents after kidney transplantation is controversial and complicated by interpretation of fluctuations in kidney function that occur with diuretics, ACE inhibitors, and angiotensin receptor blockers (ARBs). In general, β-blockers and dihydropyridine calcium channel blockers are used in the early posttransplant period due to their lack of drug interactions and effects on kidney function. Many patients require diuretics because of salt retention due to corticosteroids, calcineurin inhibitors, and other blood pressure medication. ACE inhibitors and ARBs are often avoided early after transplantation due to effects on renal hemodynamics and serum creatinine.

2. Hyperlipidemia

Lipid abnormalities occur in at least 50% of transplant recipients and represent an important modifiable cardiovascular risk factor. Hypertriglyceridemia, high low-density lipoprotein, and low high-density lipoprotein often occur as part of a metabolic syndrome which is common after transplantation. Corticosteroids, calcineurin inhibitors, and sirolimus may all play important roles in worsening lipid profiles. Despite concerns about rhabdomyolysis due to drug interactions, there is now prospective data from randomized controlled trials indicating that statins (specifically, fluvastatin) may prevent cardiac death and nonfatal myocardial infarction after kidney transplantation without effects on graft survival. Other therapies such as niacin, fibrates, and binding resins have been used as well. As always, attention to drug interactions must be given, especially regarding the risk of rhabdomyolysis (statins, fibrates, and calcineurin inhibitors) and decreased or enhanced absorption (binding resins and ezetimibe).

3. Diabetes Mellitus

a. Background

Diabetes is a major independent risk factor for cardiovascular disease, is present in 30% to 40% of patients before transplant, and develops after transplant in 2.5% to 35% of nondiabetic patients depending on pretransplant risk factors and the immunosuppressive regimen. Complications from diabetes have important effects on patient outcomes, leading to cardiovascular and infectious morbidity, renal allograft loss and decreased function, as well as decreased patient survival. In patients with diabetes preceding transplant, control may be worsened by corticosteroids, calcineurin inhibitors, and the decreased half-life of endogenous and exogenous insulin due to improved kidney function. Rigorous control of diabetes is likely to decrease diabetic complications, based on accumulated evidence in other populations. A glycosylated hemoglobin target of 6.5 to 7.0 is likely to be associated with improved outcomes.

b. Posttransplant Diabetes Mellitus

PTDM, also called *new-onset diabetes after transplantation*, complicates a substantial percentage of kidney transplants, and is associated with poorer patient outcomes. Risks for PTDM include increasing age, obesity, family history of diabetes, African American or Hispanic race/ethnicity, hepatitis C infection, and abnormal glucose tolerance. Corticosteroids have well-known adverse effects on insulin resistance, and calcineurin inhibitors are diabetogenic, likely due to a combination of β-cell toxicity and promotion of insulin resistance. Fasting plasma glucose should be routinely monitored after transplant because the incidence of PTDM is high. Prevention of diabetes through weight loss and exercise in patients at risk should be attempted, and treatment of new-onset diabetes should follow established guidelines.

4. Other Cardiovascular Risk Factors

Smoking is obviously an important modifiable cardiovascular risk factor, and evidence is accumulating that smoking also influences deterioration of kidney function and is a risk for graft loss. At any stage in the transplant process, counseling, formal smoking cessation programs, and pharmacologic agents should be offered to encourage smoking cessation. Anemia is present in many patients both before and after transplant, and may be underrecognized and undertreated. Anemia is correlated with left ventricular hypertrophy and cardiovascular disease; therefore, diagnosis and treatment based on cause is probably appropriate.

C. Malignancy

Malignancy is an important complication of immunosuppression, probably due to effects on immune surveillance of abnormal tumor cell populations and viral-mediated cancers. The intensity of immunosuppression, including exposure to antilymphocyte antibodies, is an important factor determining risk of malignancy. Nonmelanoma skin cancers, especially squamous cell carcinomas, have a particularly high incidence and aggressiveness in transplant patients compared with the general population. mTOR-Is have

recently been shown to decrease subsequent squamous cell carcinomas in patients with at least one prior event, and conversion from calcineurin inhibitor–based therapy to an mTOR-I may be warranted in this population. Transplant recipients are counseled to avoid the sun, use protective sunscreens and clothing, and to see a dermatologist at least once yearly. After skin cancers, PTLDs are the next most common malignancy. These lymphomas are associated with EBV infection and usually contain EBV DNA. Risks are increased after T-cell-depleting antibody therapies. These malignancies are often managed with reduction in immunosuppression, but aggressive tumors, particularly when monoclonal, may require systemic chemotherapy. Similarly, women are at increased risk for cervical squamous cell carcinomas related to HPV infection and require yearly Pap smears with increased frequency of surveillance and attention if there are any abnormalities. Vulvar, perineal, and anogenital cancers are also more frequent after transplantation. Hepatitis B and C may lead to hepatocellular carcinoma, and Kaposi's sarcoma, caused by human herpes virus 8, is another viral-mediated cancer that affects transplant recipients. Renal cell carcinoma occurs in 4% of transplant candidates, perhaps due to acquired cystic kidney disease. Screening native kidneys for disease has been advocated. Other solid tumors, such as breast, lung, and colon cancer, show modest elevation in risk compared with the general population. Given the risks of malignancy in transplantation, age-appropriate screening should occur before placement on the waiting list, and should continue for the patient's lifetime.

D. Bone Disease

1. Preexisting Bone Disease

The clinical picture after kidney transplantation is often complicated by the presence of preexisting bone disease. Most commonly, secondary hyperparathyroidism leads to osteitis fibrosa, imparting a risk of bone loss and fracture. Other causes of preexisting bone disease include adynamic (low turnover) bone disease, aluminum-related osteomalacia, and β_2-microglobulin-associated arthropathy. Furthermore, diabetic patients have decreased bone mineral density compared with other populations.

2. Posttransplant Bone Disease

It is well established that up to 9% of bone density is lost in the first 6 to 12 months after transplantation. Furthermore, osteopenia and osteoporosis are present in a substantial number of patients who have undergone transplantation after long-term follow-up. Kidney transplant recipients carry an increased risk of fracture of 3% to 4% per year for the first 3 years after transplant, declining somewhat after that time. Fracture risk is increased in both males and females and is particularly increased in older females. There are many contributing factors to the milieu that supports bone loss. Steroids are known to induce osteopenia and osteoporosis through effects on calcium absorption and excretion, aggravation of secondary hyperparathyroidism, hypogonadism, and effects on bone turnover. Cyclosporine, secondary hyperparathyroidism, renal phosphate wasting, uremia, and gonadal hormones are other contributing factors to bone loss. Another syndrome affecting transplant recipients is avascular osteonecrosis, especially of the femoral head, which is

associated with steroid use. Patients present with bone pain but may be asymptomatic. Often patients require operative intervention including replacement of the affected joint.

3. Management

The timing and frequency of measuring bone mineral density is not well defined, but should be performed at some established interval due to the risk of fractures. Control of secondary hyperparathyroidism before transplant is important. After transplant, calcium and vitamin D supplements are recommended unless hypercalcemia is present. Parathyroidectomy is usually reserved for patients with symptomatic or persistent hypercalcemia or with persistent (greater than 1 to 2 years) hyperparathyroidism. Cinacalcet has been used with some success in posttransplant hyperparathyroidism. Trials of bisphosphonates have been shown to reduce bone loss especially when given immediately after transplant, but indications are not defined and concerns remain regarding promotion of adynamic bone disease. Weight-bearing exercise is a low-cost intervention that should be recommended for all patients.

E. Hematologic Disease

Hematologic disorders are common after transplantation and have multifactorial origins. Anemia and posttransplant erythrocytosis (PTE) are common and are covered in the subsequent text. Leukopenia and thrombocytopenia are often seen as complications of antiproliferative medication, CMV or other viral infections, or any of a number of primary diseases.

1. Anemia

Anemia is common after kidney transplantation, occurring in 30% to 40% of patients in some series. Furthermore, it has been correlated with an increased risk of cardiovascular events and death and therefore may be an important prognostic factor. It is more common in the early posttransplant period but is also present in high frequency in patients with decreased kidney function. An obvious factor involved in the presence of anemia is decreased production of erythropoietin, especially when graft function is impaired. Iron deficiency, ACE inhibitors, ARBs, MMF, and azathioprine have also been associated with anemia after transplantation. Recurrent or de novo hemolytic uremic syndrome can be a dramatic cause of anemia and graft loss and may be associated with calcineurin inhibitors and other medications. Although prospective data are needed, it seems prudent to correct anemia depending on the underlying etiology, including administration of erythropoietin to those with chronic kidney disease stages III–V.

2. Posttransplant Erythrocytosis

PTE, a hematocrit above 51%, occurs in 5% to 15% of kidney transplant recipients. The etiology of the disorder is not clear, but erythropoietin- and nonerythropoietin-dependent mechanisms have been implicated. It is more common in smokers, those without acute rejection episodes, and patients with diabetes. This condition can usually be managed by treatment with ACE inhibitors or ARBs. Occasionally, phlebotomy may be necessary if the hematocrit cannot be lowered below 56%.

F. Pregnancy

Years of experience in kidney transplantation have allowed some understanding of pregnancy after transplantation. Most women are counseled to avoid pregnancy for some time after the transplant, usually 6 months to 2 years. Fertility is improved after transplantation, and attention should be given to contraception. In mothers at high risk for primary CMV infection, pregnancy should probably be delayed until an antibody response has occurred and viremia has cleared. Kidney function, if normal at the time of conception, is probably not adversely affected during pregnancy. However, the risk of a pregnancy-related deterioration in kidney function is increased when renal insufficiency is present. Glucose intolerance may also complicate pregnancy, leading to gestational diabetes or increased insulin requirements in those with diabetes. Immunosuppression should be maintained at levels similar to nonpregnant women, but levels should be checked frequently as changes in pharmacokinetics are unpredictable. Prednisone is unlikely to be teratogenic, and calcineurin inhibitors and azathioprine have minimal to small risks. MMF is teratogenic and contraindicated in pregnancy, and women planning for pregnancy should be converted to azathioprine. mTOR-Is have limited experience in pregnancy. Fetal outcomes after kidney transplantation include a significant risk of preterm delivery (50%) and growth restriction (40%), but these outcomes may be more closely related to decreased kidney function than the transplant per se. After delivery, breast-feeding may not be recommended in patients taking calcineurin inhibitors, but discussion of the risks and benefits should occur on an individual basis.

Suggested Readings

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14 The Patient with Kidney Disease and Hypertension in Pregnancy

Phyllis August, Diana I. Jalal, and Judy Blaine

In most instances, pregnancy in women with renal disorders is successful, provided kidney function is well preserved and hypertension absent.

I. THE KIDNEY FUNCTION AND BLOOD PRESSURE IN NORMAL PREGNANCY. The anatomy and function of the kidneys and lower urinary tract are altered during gestation. Physiologic alterations in volume homeostasis and blood pressure (BP) control also occur, and recognizing this is a prerequisite for the appropriate interpretation of data from pregnant patients with renal disease or hypertension (Table 14-1).

A. Anatomic and Functional Changes in Urinary Tract. Kidney length increases approximately 1 cm during normal gestation. The major anatomic alterations of the urinary tract during pregnancy, however, are seen in the collecting system, where calyces, renal pelves, and ureters dilate often giving the erroneous impression of obstructive uropathy. The dilation is accompanied by hypertrophy of ureteral smooth muscle and hyperplasia of its connective tissue, but whether bladder reflux is more common in gravidas is unclear. The cause of the ureteral dilation is disputed. Some researchers favor hormonal mechanisms, whereas other researchers believe that it is obstructive in origin. Clearly, as pregnancy progresses, assumption of a supine or upright posture may cause ureteral obstruction when the enlarged uterus entraps the ureters at the pelvic brim (Fig. 14-1). These morphologic changes result in stasis in the urinary tract and a propensity of pregnant women with asymptomatic bacteriuria to develop pyelonephritis, especially in women with a history of prior urinary tract infection (UTI).

Acceptable norms of kidney size increase should be by 1 cm if estimated during pregnancy or the immediate puerperium, and reductions of renal length noted several months postpartum need not be attributed to renal disease. Rarely, ureteral dilation is of sufficient magnitude to cause a "distension" syndrome (characterized by abdominal pain, and on occasion small increments in serum creatinine levels presenting in late gestation; these resolve with the placement of ureteral stents). Also, because dilation of the ureters may persist until the 12th postpartum week, elective ultrasonographic or radiologic examination of the urinary tract should be deferred, if possible, until after this time.

Table 14-1. Renal Changes in Normal Pregnancy

Alteration	Manifestation	Clinical Relevance
Increased renal size	Renal length approximately 1 cm greater on radiographs	Postpartum decreases in size should not be mistaken for parenchymal loss
Dilation of pelves, calyces, and ureters	Resembles hydronephrosis on renal ultrasonography or intravenous pyelography (more marked on right)	Not to be mistaken for obstructive uropathy; elective evaluation should be deferred to the 12th postpartum wk; upper urinary tract infections are more virulent; retained urine leads to collection errors
Increased renal vasodilation	Glomerular filtration rate and renal plasma flow increase 35–50%	Serum creatinine and urea nitrogen values decrease during normal gestations; >0.8 mg/dL creatinine already suspect; protein, amino acid, and glucose urinary excretion all increase
Changes in acid–base metabolism	Renal bicarbonate threshold decreases	Serum bicarbonate is 4–5 μmol/L lower in normal gestation
Renal water handling	Osmoregulation altered	Serum osmolality decreases 10 mOsm/L (serum sodium decreases 5 mEq/L) during normal gestation
—	Osmotic thresholds for thirst and AVP decrease; the metabolic clearance of AVP increases markedly; high levels of vasopressinase circulating	Increased metabolism of AVP may cause transient diabetes insipidus in pregnancy

AVP, arginine vasopressin.

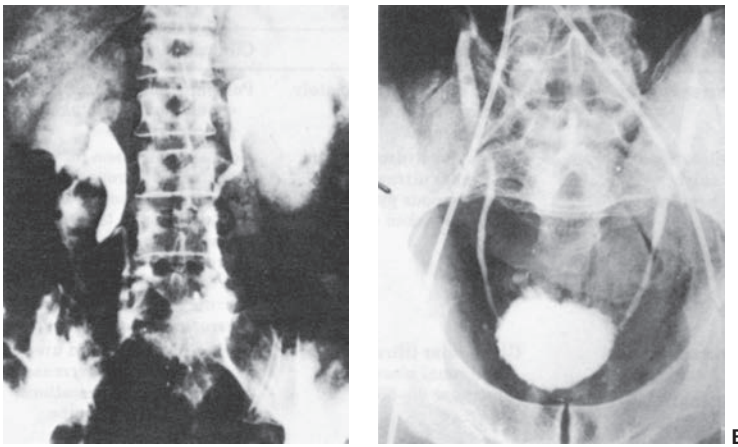

Figure 14-1. Intravenous pyelogram. **A:** Ureteral dilation of pregnancy. The right ureter is sharply cut off at the pelvic brim where it crosses the iliac artery (the iliac sign). **B:** Relationship between the ureters and iliac arteries can be demonstrated in postmortem studies. Note the iliac sign at the pelvic brim on the right. (From Dure-Smith P. Pregnancy dilation of the urinary tract. *Radiology* 1970;96:545. Reprinted with permission.)

B. Renal Hemodynamics. The changes in renal hemodynamics in gestation are the most striking and clinically significant of all the urinary tract alterations of pregnancy.

1. **Glomerular filtration rate (GFR) and renal plasma flow (RPF)** increase to levels 30% and 50%, respectively, above nongravid values during pregnancy. Increments in GFR that are already present during the early days after conception reach a maximum during the first trimester. The basis for the increase in GFR and RPF is unknown. Animal studies suggest that renal vasodilation [mediated by nitric oxide (NO)] leading to increased glomerular plasma flow is a contributing, but not the sole, factor. RPF is greatest at midgestation, declining somewhat in the third trimester. Although increments in GFR measured by the infusion of inulin appear to be sustained until term, 24-hour creatinine clearance declines during the last 4 weeks of pregnancy, accompanied by increases in serum creatinine levels of 15% to 20%.

   The increase in GFR has important clinical implications. Because creatinine production is unchanged during pregnancy, increments in its clearance result in decreased serum levels. Using the Hare method, one group of investigators observed that true serum creatinine, which averaged 0.67 mg/dL in nongravid women, decreased to 0.46 mg/dL during gestation [to convert to SI units (μmol/L), multiply serum creatinine (mg/dL) by 88.4]. In studies that also measured creatinine chromogen (which yielded results resembling those reported in most clinical laboratories), values were 0.83 mg/dL in nonpregnant women and decreased to 0.74, 0.58, and 0.53 mg/dL in the first, second, and third trimester

of pregnancy, respectively. Therefore, values considered normal in nongravid women may reflect decreased renal function during pregnancy. For example, in gravid women, concentrations of serum creatinine exceeding 0.8 mg/dL or of serum urea nitrogen that are greater than 13 mg/dL suggest the need for additional evaluation of renal function.

2. **Other Consequences of the Increased Renal Hemodynamics.** Increased GFR and RPF also alter urinary solute content. For example, excretion of glucose, most amino acids, and several water-soluble vitamins increases, and these increments in the nutrient content of urine may be a factor in the enhanced susceptibility of gravidas to UTIs. Urinary protein excretion also increases during gestation, but the fate of albumin excretion is more complex and disputed.

C. Acid–Base Regulation in Pregnancy. Renal acid–base regulation is altered during gestation. The bicarbonate threshold decreases, and early morning urines are often more alkaline than those in the nongravid state. In addition, plasma bicarbonate concentrations decrease approximately 4 μmol/L, averaging 22 μmol/L. This change most likely represents a compensatory renal response to hypocapnia, because pregnant women hyperventilate and their P_{CO_2} averages only 30 mmHg. The mild alkalosis (arterial pH averages 7.44) found in pregnancy is in accord with this view. Because steady-state P_{CO_2} and HCO_3 levels are already diminished, pregnant women are, in theory, at a disadvantage when threatened by sudden metabolic acidosis [e.g., lactic acidosis in preeclampsia, diabetic ketoacidosis, or acute kidney injury (AKI)]; however, they respond with appropriate increments in urinary titratable acid and ammonia after an acid load, and proton regeneration is already evident at blood pH levels higher than those in similarly tested nonpregnant women. Finally, when managing gravidas with pulmonary disorders, it should be noted that a P_{CO_2} of 40 mmHg, normal in nonpregnant women, signifies considerable carbon dioxide retention in pregnancy.

D. Water Excretion. After conception, a rapid decrease in plasma osmolality levels of 5 to 10 mOsm/kg below that of nongravid subjects occurs. If this decrease occurred in a nonpregnant woman, she would cease secreting antidiuretic hormone and enter a state of water diuresis; however, gravidas maintain this new osmolality, diluting and concentrating urine appropriately when the woman is subjected to water loading or dehydration. This suggests a resetting of the osmoreceptor system, and, indeed, clinical studies demonstrate that the osmotic thresholds for both thirst and arginine vasopressin (AVP) release are decreased in pregnant women. Furthermore, the plasma of pregnant women contains large quantities of a placental enzyme (vasopressinase) capable of destroying substantial quantities of AVP in vitro; moreover, the in vivo production and metabolic clearance of AVP hormone are increased fourfold after midgestation.

The changes in osmoregulation and AVP metabolism may be responsible for two unusual syndromes of transient diabetes insipidus that complicate pregnancy. One, in which polyuria is responsive to both AVP and deamino-8-D-arginine vasopressin (dDAVP), probably occurs in women with unapparent partial central diabetes insipidus whose disease is brought to the fore by the increment in hormonal disposal rates during late gestation. The other disorder, in which the marked polyuria continues despite large doses of AVP, is responsive to dDAVP, an analog resistant to inactivation by

vasopressinase. These gravidas may have excessively high circulating levels of this aminopeptidase enzyme due to increased activation.

E. Volume Regulation. Most healthy women gain approximately 12.5 kg during the first pregnancy and 1 kg less during subsequent pregnancies. Most of the increment is fluid, with total body water increasing 6 to 8 L, 4 to 6 L of which is extracellular. Plasma volume increases 50% during gestation, the largest rate of increment occurring during midpregnancy, whereas increments in the interstitial space are greatest in the third trimester. A gradual cumulative retention of approximately 900 mEq of sodium occurs in pregnancy; this is distributed between the products of conception and the maternal extracellular space. These alterations in maternal intravascular and interstitial compartments produce apparent hypervolemia, yet the gravida's volume receptors sense these changes as normal. Therefore, when salt restriction or diuretic therapy limits this physiologic expansion, maternal responses resemble those in salt-depleted nonpregnant women. This is one compelling reason for the reluctance to recommend sodium restriction or diuretics during pregnancy. Pregnant women are now advised to salt their food to taste, and some researchers believe that a liberal sodium intake is beneficial during gestation. Another physiologic adaptation that appears to influence sodium balance during pregnancy is the marked stimulation of the renin–angiotensin–aldosterone system. Aldosterone levels are markedly increased during pregnancy, despite normal BP and normal potassium balance. It is likely that the increased aldosterone secretion is a compensatory mechanism to counteract the increase in sodium excretion that would be expected as a result of the large increase in GFR and RPF. Arterial vasodilation that causes relative arterial underfilling, as occurs in pregnancy, is known to stimulate the renin–angiotensin–aldosterone system. Moreover, increases in aldosterone balance the natriuretic effects of the large increases in progesterone during pregnancy.

F. BP Regulation. Mean BP starts to decrease early in gestation, with diastolic levels in midpregnancy averaging 10 mmHg less than measurements postpartum. In later pregnancy, BP increases, gradually approaching nonpregnancy values near term. Because cardiac output rises quickly in the first trimester and remains relatively constant thereafter, the decrease in pressure is due to a marked decrement in systemic vascular resistance. The slow rise toward nonpregnant levels after a midtrimester nadir is interesting, because it demonstrates that increasing vasoconstrictor tone is a feature of late gestation in healthy women as well as in women in whom preeclampsia is developing. The cause of the decrease in systemic vascular resistance during pregnancy is obscure. Studies of arterial compliance in pregnancy demonstrate early rises, perhaps due to alterations in vessel ground substance. Elevations of plasma estrogen and progesterone to concentrations that may relax smooth muscle occur, and increments in vasodilating prostaglandins and relaxin are also present during gestation. Hormonally mediated increases in endothelial NO production may also contribute to the vasodilation in pregnancy. With the lower BP, the levels of all components of the renin–angiotensin system are increased during pregnancy. Exaggerated hypotensive responses to converting enzyme inhibition in normal gravidas suggest that the increased renin–angiotensin system in pregnancy is a normal physiologic response to decreased BP and increased sodium excretion.

Lack of awareness of the fluctuation in BP during normal gestation may lead to diagnostic errors. For example, women with mild essential hypertension often experience a decrease in BP during early pregnancy, and BP may even approach normal levels. They may then be erroneously labeled preeclamptic in the last trimester, when frankly elevated pressures occur.

G. Mineral Metabolism. Serum calcium levels decrease in pregnancy, in conjunction with a decrement in circulating albumin concentrations. Ionized calcium levels, however, remain in the normal nonpregnant range. Striking changes relating to calcium regulatory hormones also occur during normal pregnancy. Production of 1,25-dihydroxyvitamin D_3 increases as early as the first trimester, reaching circulating levels that are approximately twice the nonpregnant values. Gastrointestinal absorption of calcium increases, resulting in an "absorptive hypercalciuria," with 24-hour urine excretion often exceeding 300 mg/day (in appropriately nourished individuals). Intact parathyroid hormone levels are lower during normal pregnancy.

II. CLINICAL EVALUATION OF RENAL FUNCTION IN PREGNANCY

A. Examination of the Urine. The association of proteinuria with eclampsia was first noted in the 1840s, and the science of prenatal care advanced dramatically when physicians began to systematically examine the urine of gravidas, primarily for albuminuria. In certain instances, latent renal disease is first uncovered by the detection of excessive protein excretion or microscopic hematuria during a routine prenatal evaluation.

Healthy nonpregnant women excrete considerably less than 100 mg of protein in the urine daily, but due to the relative imprecision and variability of testing methods used in hospital laboratories, proteinuria is not considered abnormal until it exceeds 150 mg/day. During pregnancy, protein excretion increases, and excretion up to 300 mg/day may still be normal. On occasion, a healthy gravida can excrete more than that amount. In pregnancy, the gold standard for evaluation of abnormal proteinuria is the 24-hour urine protein measurement. A 24-hour protein excretion of greater than 300 mg is abnormal in pregnancy and correlates with a urine dipstick 1+ protein measurement. Although commonly used to detect proteinuria, urine dipstick testing is susceptible to error due to variations in urine concentration; therefore, if the level of suspicion is high, 24-hour urine testing should be performed. Total protein/creatinine ratio has been shown to accurately estimate 24-hour urine protein excretion in nonpregnant patients. In pregnancy, however, the urine protein/creatinine ratio does not adequately exclude the equivalent of 0.3 g per 24-hour proteinuria and underestimates severe proteinuria.

Few attempts have been made to quantitate the urine sediment in pregnancy. The excretion of both red and white blood cells may increase during normal gestation, and one to two red blood cells per high-power field is acceptable in a urinalysis.

B. Renal Function Tests. The clearance of endogenous creatinine, the most satisfactory approximation of GFR in nongravid subjects, is equally useful for assessing renal function in gravidas. Gravidas, as well as nonpregnant women, show little variation (approximately 10% per day) in urinary

creatinine excretion and, presumably, in creatinine production, which in a given woman is similar both during and after gestation. The lower limit of normal creatinine clearance during gestation should be 30% greater than the average of 110 to 115 mL/minute for nongravid women. Calculation of GFR by serum creatinine–based formulae is confounded by increasing maternal weight which is not muscle weight, and neither Modification of Diet in Renal Disease (MDRD) nor Cockroft-Gault GFR estimates have been validated in pregnancy.

Acid excretion and urinary concentration and dilution are similar in gravid and nonpregnant women. Therefore, tests such as ammonium loading (rarely indicated in gestation) give values similar to those in nongravid women. When examining urinary diluting ability, the clinician should be aware that supine posture can interfere with this test. Therefore, studies to detect minimal urinary osmolal concentrations should be performed with the patient lying on her side. However, although lateral recumbency is the required position for prenatal measurement of most renal function parameters, this posture interferes with tests of concentration. For example, a urine osmolality that was 800 mOsm/kg after overnight dehydration may decrease to 400 mOsm/kg within 1 hour through fluid mobilization from the extremities during bed rest, thereby resulting in volume-induced inhibition of AVP secretion, a mild osmotic diuresis, or both. These observations demonstrate the importance of upright posture, such as quiet sitting, when maximum urinary concentration is measured in pregnancy.

C. Role of Renal Biopsy in Pregnancy. Percutaneous renal biopsy is performed infrequently during gestation. In fact, pregnancy was once considered a relative contraindication to the procedure because of early reports of excessive bleeding and other complications in gravid women. It is now evident that if the renal biopsy is performed in women with well-controlled BP and normal coagulation indices, morbidity is similar to that of nonpregnant patients. Renal biopsy should be considered only when renal function suddenly deteriorates remote from term and no obvious cause is present. This is because certain forms of rapidly progressive glomerulonephritis, when diagnosed early, may respond to aggressive treatment such as steroid pulses and, perhaps, plasma exchange. Another situation in which biopsy may be recommended is symptomatic nephrotic syndrome. Although some might consider a therapeutic trial of steroids in such cases, it may be prudent to determine beforehand whether the lesion is likely to respond to steroids, because pregnancy is itself a hypercoagulable state prone to worsening by such treatment. Biopsy can usually be deferred when proteinuria alone develops in a normotensive woman with well-preserved renal function who has neither marked hypoalbuminemia nor intolerable edema. These women can usually be evaluated at more frequent intervals, and monitored for signs of either deterioration in renal function or development of superimposed preeclampsia, and renal biopsy deferred to the postpartum period. Similarly, there is rarely a need for renal biopsy during pregnancy in women with normal renal function and asymptomatic microscopic hematuria, when neither stone nor tumor is suggested by ultrasonography. Later in pregnancy (after 30 weeks) biopsy is rarely indicated and almost always should be deferred until after delivery.

III. RENAL DISEASE IN PREGNANCY

A. Asymptomatic Bacteriuria. UTI is the most common renal problem occurring in pregnancy. The urine of gravidas supports bacterial growth better than that of nonpregnant women because of its increased nutrient content. This, as well as ureteral dilation, stasis, and occasional obstruction, would be expected to increase the susceptibility of pregnant women to UTI. Surprisingly, this is not the case and, with the exception of certain high-risk groups (diabetic patients and gravidas with sickle cell trait), the prevalence of asymptomatic bacteriuria during gestation varies between 4% and 7%, a value similar to that in sexually active nonpregnant women. The natural history of asymptomatic UTIs is, however, quite different in pregnancy.

Although in the nonpregnant state asymptomatic bacteriuria is quite benign, progression to overt cystitis or pyelonephritis occurs in up to 40% of affected gravidas. Therefore, screening all pregnant women for the presence of asymptomatic bacteriuria and treating those with positive urine cultures are important.

1. **Method of Urine Collection.** Pregnant women contaminate midstream urine specimens more frequently. The incidence can be reduced by the use of multiple vulval washings combined with carefully supervised collection procedures. In some women, suprapubic aspiration is required to differentiate contamination from true infection. Pregnancy is not a contraindication to this procedure.

   If the urine is sterile at the beginning of pregnancy, it usually remains so until term. Still, a small number (1% to 2%) of gravidas whose original urine cultures are negative subsequently have bacteriuria. Abnormal urinalysis and the presence of dysuria do not differentiate between contamination and true infection. For example, dysuria occurs in 30% of gravidas whose urines are sterile, and the urine may be infected and still contain fewer than two leukocytes per high-power field.

2. **Method of Treatment.** The optimum way to manage asymptomatic UTI in pregnancy has not been precisely defined. In the earlier literature, some authors recommended continuous antibiotic treatment from the time the bacteriuria was detected until delivery. This was based on the belief that the relapse rate was high, and that most bacteriuric women have renal parenchymal involvement as opposed to bladder infection. However, it is now apparent that one-half of these infections involve only the bladder, and most of these patients are cured by standard short-course (or even single-dose) therapy. More than 90% of the uropathogens involved are aerobic gram-negative rods, usually *Escherichia coli*, and the physicians recommend a 4- to 7-day course of the antibiotic to which the cultured organism is sensitive, preferably a short-acting sulfa drug, nitrofurantoin, amoxicillin, a cephalosporin, or a single dose of fosfomycin. This approach, when combined with surveillance for recurrent bacteriuria, has been shown to be quite effective.

3. **Importance of Postpartum Evaluation.** Asymptomatic UTI has been linked to premature labor, hypertension, and anemia during gestation, but these assertions have not been proved. On the other hand, an

increased incidence of occult urinary tract pathology is present in these gravidas. Therefore, women with bacteriuria during pregnancy may benefit from evaluation of their urinary tract postpartum, especially those in whom the infection is resistant to therapy.

B. Symptomatic Bacteriuria. The clinical approach to symptomatic UTI during gestation differs from that for asymptomatic bacteriuria.

1. **Acute Pyelonephritis.** Pyelonephritis was a cause of maternal death in the preantibiotic era, and 3% of pregnant patients in a more recently reported series developed septic shock. At one time, symptomatic UTIs complicated almost 2% of all gestations, but prenatal screening combined with rapid treatment of asymptomatic bacteriuria has reduced this incidence to approximately 0.5%. The bacteriology of these infections resembles that in asymptomatic patients (predominantly *E. coli*), and most cases present after midpregnancy. The clinical presentation of pyelonephritis in pregnancy can be dramatic. As noted in the preceding text, the disease caused maternal deaths in the preantibiotic era, and upper UTIs in gravidas are associated with exaggerated effects of endotoxemia, including shock, respiratory distress syndrome, marked renal dysfunction, and hematologic and liver abnormalities. Symptomatic UTIs have also been implicated in the etiology of intrauterine growth restriction, prematurity, congenital anomalies, and fetal demise; however, most studies reporting these associations were not adequately controlled for potential confounders. The treatment of pyelonephritis should be aggressive and is best performed in the hospital.

   Most patients with pyelonephritis respond quickly, with defervescence within 48 to 72 hours. Once afebrile for 48 hours, oral therapy may be started and continued to complete 10 to 14 days of treatment. Continuous low-dose suppressive therapy during the remainder of pregnancy is recommended because of the high rate of recurrence. An alternative approach, frequent surveillance for recurrent infection with prompt treatment when significant bacteriuria is identified, has been claimed to be as effective as suppressive therapy.

2. **Perirenal abscess and renal abscess formation or carbuncle**, although infrequent complications of gestation, should be considered in the differential diagnosis of postpartum fever. It is important to recognize that a high incidence of positive urine cultures occurs in the postpartum period—perhaps 17% to 20% in the first few days after delivery, decreasing to 4% after the third postpartum day. These cases, which resolve spontaneously, may reflect a temporary breakdown in the normal host antibacterial mechanisms in the immediate postpartum period rather than true infection.

3. **Antibiotic Use in Pregnancy.** The first-choice antibiotic for symptomatic infections changes from decade to decade because of the rapid emergence of resistant strains, thereby resulting in the use of drugs that have not yet withstood the test of time for safety in pregnancy. The physicians continue to recommend starting treatment with cephalosporins, because a significant percentage of community-acquired *E. coli* infections are resistant to ampicillin. For routine cystitis, nitrofurantoin is often effective and is acceptable during pregnancy.

The physician should also be aware of problems specific to the use of antibiotics in obstetrics and anticipate the potential fetal toxicity of agents that cross the placental barrier. (Information concerning drug safety during pregnancy is listed in the *Physicians' Desk Reference*, which is updated annually.) In brief, sulfa drugs should not be used near term, because they may precipitate kernicterus in the newborn. The anti–folic acid activity of trimethoprim has been associated with anomalies such as cleft palate in animals, and this combination drug should also be avoided, at least before midpregnancy.

Aminoglycosides such as gentamicin may be used in pregnancy. Fluoroquinolones cross the placenta and should be avoided if possible. Tetracyclines are contraindicated because they deposit in fetal bones and teeth and may cause severe reactions in the mother, including hepatic failure. Nitrofurantoin is contraindicated at term because of risk of hemolytic disease in the newborn.

C. Acute Kidney Injury

1. **Incidence.** Before 1970, the incidence of AKI in pregnancy severe enough to require dialytic therapy was estimated at between 1 in 2,000 and 1 in 5,000 gestations, and it represented a considerable proportion of cases reported in large series. Since then, the number of patients with AKI from obstetric causes has declined markedly, and the incidence is now estimated to be less than 1 in 20,000 pregnancies. This trend, attributed to the liberalization of abortion laws and improvement of prenatal care, has not been shared by the poorer and less industrialized nations. In the developing world, the incidence of AKI in pregnancy has been estimated to be as high as 20% and is a significant cause of fetal and maternal morbidity and mortality.

   The frequency distribution of AKI during gestation was bimodal, with one peak early in pregnancy (12 to 18 weeks) comprising most of the cases associated with septic abortion, and a second peak between gestational week 35 and the puerperium, primarily due to preeclampsia, sepsis, and bleeding complications, especially placental abruption.

2. **Causes.** AKI in pregnancy can be induced by any of the disorders leading to renal failure in the general population, such as acute tubular necrosis (ATN). Early in pregnancy, the most common problems are prerenal disease due to hyperemesis gravidarum, and ATN resulting from a septic abortion. Several different uncommon disorders can lead to AKI later in pregnancy. Mild to moderately severe preeclampsia is not usually associated with renal failure, because renal function is generally maintained in the normal or near-normal range for a nonpregnant woman. A variant of preeclampsia, the *H*emolysis, *E*levated *L*iver *E*nzymes, and *L*ow *P*latelet count (HELLP) syndrome (see Section VI.B), may be associated with significant renal dysfunction, especially if not treated promptly.
   a. **Thrombotic Microangiopathy (TMA).** TMA is characterized by fibrin and platelet aggregates in the microvasculature, particularly in the kidney and the brain. Histologic features include endothelial cell swelling, accumulation of protein in the endothelial cell layer, and sometimes splitting of the glomerular basement membrane.

TMA affecting primarily the kidney is termed hemolytic uremic syndrome (HUS), whereas TMA characterized by profound thrombocytopenia and neurologic disturbances is called thrombotic thrombocytopenic purpura (TTP). TTP is caused by an acquired or inherited disorder of a metalloproteinase ADAMTS13 that cleaves ultralarge multimers of von Willebrand factor, whereas HUS is caused by dysregulation and uncontrolled activation of the complement system.

An important and difficult differential diagnosis is that of AKI in late pregnancy in association with microangiopathic hemolytic anemia and thrombocytopenia. Pregnancy is considered to be a risk factor for TTP/HUS. However, whether the pathogenesis of these disorders in pregnancy is similar to that in nonpregnant individuals is unclear. TTP/HUS is rare in pregnancy, and must be distinguished from the HELLP variant of preeclampsia, a much more common condition. The distinction of these syndromes is important for therapeutic and prognostic reasons, but considerable overlap exists in their clinical and laboratory features. Features that may be helpful in making the diagnosis include timing of onset and the pattern of laboratory abnormalities, which in TTP may include decreased levels of a von Willebrand cleaving protease. Preeclampsia typically develops in the third trimester, with only a few cases developing in the postpartum period, usually within a few days of delivery. TTP usually occurs antepartum, with many cases developing in the second trimester, as well as the third. HUS is usually a postpartum disease. Symptoms may begin antepartum, but most cases are diagnosed postpartum.

Preeclampsia is much more common than TTP/HUS, and it is usually preceded by hypertension and proteinuria. Renal failure is unusual even with severe cases, unless significant bleeding or hemodynamic instability, or marked disseminated intravascular coagulation (DIC) occurs. In some cases, preeclampsia develops in the immediate postpartum period, and when thrombocytopenia is severe, it may be indistinguishable from HUS. However, preeclampsia spontaneously recovers, whereas HUS only infrequently improves.

In contrast to TTP/HUS, preeclampsia may be associated with mild DIC and prolongation of prothrombin and partial thromboplastin time. Another laboratory feature of preeclampsia/HELLP syndrome that is not usually associated with TTP/HUS is marked elevations in liver enzymes. The presence of fever is more consistent with a diagnosis of TTP than preeclampsia or HUS. The main distinctive features of HUS are its tendency to occur in the postpartum period and the severity of the associated renal failure. Treatment of preeclampsia/HELLP syndrome is delivery and supportive care. More aggressive treatment is rarely indicated. Treatment of TTP/HUS includes plasma infusion or exchange and other modalities used in nonpregnant patients with these disorders, although clinical trials of these modalities in pregnancy have not been performed.

b. Renal Cortical Necrosis. Renal cortical necrosis (RCN) occurs in 1.5% to 2% of all causes of AKI in developed countries and in 3% to 7% of all causes of AKI in developing countries. The primary

inciting events for RCN are obstetric complications (septic abortions, abruptio placenta, and DIC). Affected patients typically present with oliguria or anuria, hematuria, and flank pain. Ultrasonography or computed tomographic scanning may demonstrate hypoechoic or hypodense areas in the renal cortex. Most patients require chronic dialysis, but 20% to 40% have partial recovery of renal function.

c. **Acute Pyelonephritis.** Some pregnant women may develop AKI in association with pyelonephritis.

d. **Acute fatty liver of pregnancy** (fatty infiltration of hepatocytes without inflammation or necrosis) is a rare complication of pregnancy that is associated with significant azotemia. Women with this disorder often complain of anorexia and occasionally of abdominal pain in the third trimester. Clinical features suggesting preeclampsia, including hypertension and proteinuria, are not uncommon. Laboratory test results reveal elevations in liver enzymes, hypoglycemia, hypofibrinogenemia, and prolonged partial thromboplastin time. Delivery is indicated, and most patients improve shortly afterward.

e. **Urinary Tract Obstruction.** Pregnancy is associated with dilation of the collecting system, which is not usually associated with renal dysfunction. Rarely, complications such as large uterine fibroids, which may enlarge in the setting of pregnancy, can lead to obstructive uropathy. Uncommonly, acute urinary tract obstruction in pregnancy is induced by a kidney stone. Diagnosis can usually be made by ultrasonography. Often the stones pass spontaneously, but occasionally cystoscopy is necessary for insertion of a stent to remove a fragment of stone and relieve obstruction, particularly if there is sepsis or a solitary kidney.

3. The **management** of AKI occurring in gestation or immediately postpartum is similar to that in nongravid subjects (see Chapter 11), but several points peculiar to pregnancy deserve emphasis. Because uterine hemorrhage near term may be concealed and blood loss underestimated, any overt blood loss should be replaced early. Gravidas should be slightly overtransfused to forestall the development of acute tubular or cortical necrosis. Both peritoneal dialysis and hemodialysis have been successfully used in patients with obstetric-related AKI. Neither pelvic peritonitis nor the enlarged uterus is a contraindication to the former method. In fact, this form of treatment is more gradual than hemodialysis and therefore less likely to precipitate labor. Because urea, creatinine, and other metabolites that accumulate in uremia traverse the placenta, dialysis should be undertaken early, with the aim of maintaining the blood urea nitrogen at approximately 50 mg/dL. In essence, the advantages of early dialysis in nongravid patients are even more important for the pregnant patient, making arguments for prophylactic dialysis quite compelling. Excessive fluid removal should be avoided, because it may contribute to hemodynamic compromise, reduction of uteroplacental perfusion, and premature labor. Some obstetricians and perinatologists recommend continuous fetal monitoring during hemodialysis treatments, starting at midpregnancy. Finally, the physician should be aware of potential dehydration in the neonate, because the newborn usually undergoes a brisk urea-induced diuresis.

D. Pregnancy in Women with Preexisting Renal Disease. The current approach to management of pregnancy in women with chronic kidney disease (CKD) is primarily based on retrospective studies. Nevertheless, several generalizations can be made and some guidelines presented regarding gestation in women with chronic kidney dysfunction (Table 14-2).

1. **Prognosis.** Counseling and managing women with CKD is based on the following general approach: Fertility and ability to sustain an uncomplicated pregnancy relate to the degree of functional impairment, and whether hypertension is present, and not to the underlying disorder.
   a. **Degree of Impairment.** Patients are arbitrarily considered in three categories: preserved or mildly impaired renal function (serum creatinine less than or at 1.5 mg/dL), moderate renal insufficiency (creatinine 1.5 to 3.0 mg/dL), and severe renal insufficiency (creatinine higher than or equal to 3 mg/dL).

      In Table 14-3 the maternal and fetal prognosis in each category is summarized. Pregnancy is hazardous in the presence of moderate or severe renal dysfunction, because up to 40% of pregnancies in the former category are complicated by either difficult to control hypertension or sudden declines in GFR, which may not reverse after delivery. An even higher incidence of serious maternal problems occurs when renal insufficiency is severe. This is especially true for women receiving dialytic therapy, in whom fewer than 50% of the gestations succeed, and problems of extreme prematurity plague many of those that do. Notably, although prognosis is based primarily on the degree of functional impairment, the underlying disease may also play a role. Therefore, all authorities recommend against pregnancy in women with scleroderma and periarteritis nodosa.
   b. **Level of BP.** The BP level at the time of gestation is an important prognostic index. In the absence of hypertension, the natural history of most established renal parenchymal disease is unaffected by gestation (although preeclampsia may occur more readily). In contrast, when renal disease and hypertension coexist, the gestation is more likely to be complicated, either by severe increments in BP or by additional reductions in renal function. Women with well-controlled BP and only mild renal dysfunction may have relatively uncomplicated pregnancies; however, they must be seen frequently and should understand that their gestation may be terminated early if renal function deteriorates or if their BP becomes difficult to control.

E. Proteinuria. Urinary protein excretion, which increases in normal pregnancy, may increase markedly in pregnant women with underlying parenchymal renal disease. In one large series, one-third of the patients with preexisting renal disease developed nephrotic-range proteinuria during gestation. These increments do not necessarily reflect worsening of the underlying kidney disease.

1. **Renal Hemodynamics.** Gravidas with kidney disorders who have only minimal renal dysfunction usually experience increments in GFR during gestation, although levels do not reach those seen in healthy pregnant women. Therefore, a decrement in serum creatinine level early in pregnancy is a good prognostic sign. If serum creatinine levels before

Table 14-2. Summary of Pregnancy in Women with Preexisting Renal Disease

Disease	Comments
Chronic glomerulonephritis and focal and segmental glomerular sclerosis (FSGS)	Increased incidence of high blood pressure, usually later in gestation, but usually no adverse effect results if renal function is preserved and hypertension is absent before gestation; some cases of exacerbation in pregnancy have been reported in women with immunoglobulin A nephropathy, membranoproliferative glomerulonephritis, and FSGS
Systemic lupus erythematosus	Controversial: prognosis is most favorable if disease is in remission 6 mo or more before conception
Vasculitis	Case reports of Wegener's GN suggest acceptable outcomes if disease is in remission and renal function is normal; scleroderma and polyarteritis may be associated with severe and accelerated hypertension during pregnancy
Diabetic nephropathy	No adverse effect on the renal lesion. Increased frequency of infections; high incidence of heavy proteinuria and hypertension near term; optimal time for pregnancy is when renal function is normal, hypertension absent, and albuminuria is <300 mg/d
Vesicoureteral reflux	Bacteriuria in pregnancy may lead to exacerbation; urinary infection is common
Polycystic kidney disease	Few problems when function is preserved and hypertension is absent; however, the incidence of preeclampsia is increased
Urolithiasis	Ureteral dilation and stasis do not seem to affect natural history, but infections can be more frequent; stents have been successfully placed during gestation
Previous urologic surgery	Urinary tract infection is common with urinary diversion, and renal function may undergo reversible decrease; cesarean section might be necessary to avoid disruption of the continence mechanism if artificial sphincters or neourethras have been constructed
After nephrectomy, solitary pelvic kidneys	Pregnancy is well tolerated; might be associated with other malformations of the urogenital tract; dystocia occurs rarely with a pelvic kidney

GN, glomerulonephritis.

Generalizations are for women with only mild renal dysfunction (serum creatinine level less than 1.5 mg/dL) and without hypertension at conception.

Table 14-3. Pregnancy and Renal Disease: Functional Renal Status

	Category		
	Mild	**Moderate**	**Severe**
Prospects	Cr <1.5 mg/dL	Cr 1.5–3.0 mg/dL	Cr >3.0 mg/dL
Pregnancy complications	25%	47%	86%
Successful obstetric outcome	96% (85%)	90% (59%)	47% (8%)
Long-term sequelae	<3% (9%)	25% (71%)	53% (92%)

Cr, creatinine.

Estimates are based on 1,862 women with 2,799 pregnancies (1973 to 1992) and do not include collagen diseases. Numbers in parentheses refer to prospects when complication(s) develop before 28 weeks' gestation.

From Davison JM, Lindheimer MD. Renal disorders. In: Creasy RK, Resnick RK, eds. *Maternal–fetal medicine*, 3rd ed. Philadelphia, PA: WB Saunders, 1994. Reprinted with permission.

conception exceed 1.5 mg/dL, decrements during gestation are less common, and, as noted, the prognosis of such pregnancies is more guarded.

F. Glomerulonephritis. Glomerulonephritides in women of childbearing age include immunoglobulin (Ig) A nephropathy, focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, minimal change nephritis, and membranous nephropathy. Data that support the notion that histologic subtype confers a specific prognosis for pregnancy are absent. Rather, when kidney function is normal and hypertension absent, prognosis is good. Absence of gravidas in large epidemiologic surveys of poststreptococcal glomerulonephritis is remarkable and has led to speculations that pregnancy protects women from this disease. However, this form of immune complex nephritis does occur rarely in gestation, in which it may mimic preeclampsia. Its prognosis is favorable, because in those instances in which the occurrence of acute poststreptococcal glomerulonephritis during gestation was properly documented, renal function recovered rapidly and the pregnancy usually had a successful outcome.

G. Collagen Vascular Disease

1. **Lupus Nephritis.** The effect of gestation in women with lupus erythematosus who have renal involvement is difficult to evaluate, in part because of the unpredictable course of the disease regardless of pregnancy. Activity of the disease in the 6 months before conception is often a useful prognostic guide (the longer the remission the better the outlook). Although most pregnancies, in the presence of preserved

function, proceed uneventfully or are accompanied by only transient functional declines, in approximately 10%, gestation appears to cause permanent renal damage and to accelerate the renal disease. Also, placental transmission of maternal autoantibodies is associated with an increased frequency of spontaneous abortion in these women, and certain anticytoplasmic antibodies [especially anti–Sjögren's syndrome antigen (ASS-A/Ro)] cause a neonatal lupus syndrome characterized by congenital heart block, transient cutaneous lesions, or both. Women with systemic lupus erythematosus (SLE) have a high incidence of detectable levels of antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulant). High titers of these antibodies are associated with several complications of pregnancy, including spontaneous fetal loss, hypertensive syndromes indistinguishable from preeclampsia, and thrombotic events including deep vein thrombosis, pulmonary embolus, myocardial infarction, and strokes. Also, pregnant women with circulating antiphospholipid antibodies can manifest a rare form of rapid renal failure postpartum, associated with glomerular thrombi. Therefore, women with SLE should be screened for antiphospholipid antibodies early in gestation. The therapeutic approach when gravidas manifest antiphospholipid antibodies is disputed, and many would not treat asymptomatic patients who manifest low titers. However, when titers are elevated (more than 40 GPL IgG antiphospholipid level), most authorities prescribe aspirin (80 to 325 mg/day). Heparin in combination with aspirin is recommended for patients with a history of thrombotic events and may also be advisable when titers are higher than 80 GPL.

A flare of lupus nephritis may be difficult to distinguish from preeclampsia when a woman with a history of lupus develops worsening renal function, proteinuria, and hypertension. Elevation in liver enzymes and new-onset severe hypertension is more consistent with preeclampsia. Hypocomplementemia, and severe nephritic syndrome without hypertension, is more consistent with lupus nephritis. Often, a flare of nephritis in the third trimester appears to trigger "superimposed preeclampsia," and improvement in BP and proteinuria occurs only after delivery. However, in the presence of abnormal serologic testing, it is often reasonable to treat worsening proteinuria and azotemia with increased prednisone in the hope that it will improve, particularly if the fetus is immature. However, close maternal and fetal surveillance is of utmost importance, and delivery should be considered in the setting of obvious signs of HELLP syndrome, accelerating hypertension and/or azotemia, and other signs of worsening maternal condition.

Previously, patients with lupus nephropathy were believed to be prone to relapse in the immediate puerperium, and some physicians still start or increase steroid treatment during and after delivery. Such views of "stormy puerperium" are now disputed, and most authorities institute or change therapy only if signs of increased or de novo disease activity appear.

2. Pregnancy in patients with other **vasculitides** has only rarely been reported. Several successful pregnancies in women with Wegener's granulomatosis have been reported. Women may be treated with corticosteroids, azathioprine, cyclosporine, and intravenous immunoglobulin

(IVIg) with safety. Cyclophosphamide is contraindicated in pregnancy. Such pregnancies are high risk and should be managed by a multidisciplinary team, and when possible women should be advised to wait until their disease is in remission before contemplating pregnancy. Polyarteritis nodosa **and scleroderma with renal involvement** are rare and potentially dangerous conditions in pregnancy because of the associated hypertension, which may become malignant.

H. Diabetic Nephropathy. Diabetes is one of the most common medical disorders encountered during pregnancy, and most cases are due to gestational diabetes. Preexisting diabetes poses significant risks to pregnancy. Many younger women with pregestational diabetes have type 1 diabetes, and if their disease has been present for 10 to 15 years, they may show early signs of diabetic nephropathy. Women with microalbuminuria rather than macroalbuminuria, well-preserved kidney function, and normal BP have a good prognosis for pregnancy, although they are at increased risk for transient, pregnancy-associated increases in proteinuria, preeclampsia, and urinary infection. Women with type 1 diabetes with microalbuminuria and normal kidney function and normotension should be encouraged *not* to postpone pregnancy because of the worse prognosis once overt nephropathy develops. Few studies of pregnancy and nephropathy associated with type 2 diabetes are available. However, the limited evidence suggests similar outcomes to individuals with type 1 diabetes.

The effects of gestation in diabetic patients with overt nephropathy are similar to those in women with other forms of renal parenchymal disease. Prognosis is determined by the degree of hypertension and renal functional impairment.

I. Nephrotic-Range Proteinuria during Pregnancy. The most common cause of nephrotic-range proteinuria (more than 3.5 g/day) in late pregnancy is preeclampsia, a diagnosis that may be missed when diastolic pressures are between 85 and 95 mmHg. The fetal prognosis in preeclampsia with heavy proteinuria is poorer than in other preeclamptic states, but maternal prognosis is similar. Most of the usual causes of nephrotic syndrome, including membranous nephropathy, proliferative or membranoproliferative glomerulonephritis, minimal change disease, diabetic nephropathy, amyloidosis, and focal segmental glomerulosclerosis, have been described in gravidas. The pros and cons of renal biopsy during pregnancy have already been mentioned.

One should not confuse physiologic changes during gestation with the exacerbation of a disease causing the nephrotic syndrome; many women with a variety of nonnephrotic renal disorders develop heavy proteinuria when pregnant. Such increments in urinary protein may relate to the increased renal hemodynamics, alterations in the glomerular barrier, and possibly a rise in renal vein pressure. Other alterations in pregnancy that simulate symptoms accompanying nephrotic syndrome include decrements in serum albumin (approximately 0.5 to 1.0 g/dL), increments in the levels of cholesterol and other circulating lipids, and edema, which can occur at one time or another in up to 80% of normal gestations.

Diuretic therapy for treatment of edema should be used with caution during pregnancy, particularly when BP is not elevated. The concern is that intravascular volume depletion might impair uteroplacental perfusion.

Exceptions to this, however, are women with hypertension, in whom diuretics may be necessary to control BP.

Prognosis in most nephrotic gravidas with preserved function is good; however, there is some evidence to suggest that fetal outcome may be worse in the setting of significant and sustained maternal proteinuria. Focal segmental glomerulosclerosis, a frequent cause of nephrotic syndrome in women of childbearing age, is a disease in which the natural history during gestation remains disputed. Some claim pregnancy leads to irreversible functional loss and hypertension-sustained postpartum; others find the natural history of this entity in pregnancy similar to that of most other disorders.

J. Tubulointerstitial Disease

1. **Vesicoureteral Reflux.** Reflux nephropathy due to vesicoureteral reflux (VUR) may cause CKD in young women. A prospective study of 54 pregnancies in 46 women with reflux nephropathy found that preeclampsia occurred in 24% and was more common in women with hypertension. Nine (18%) experienced deterioration in kidney function during pregnancy, and those with preexisting reduced kidney function were at greater risk. One-third of the infants were delivered preterm, and 43% had VUR. These high-risk women should be screened with urine cultures, and should be treated promptly when infections are present with consideration to suppressive antibiotic therapy for the duration of pregnancy in some cases.
2. **Adult dominant polycystic kidney disease** may remain undetected in gestation. Careful questioning of gravidas for a family history of renal problems and ultrasonography may lead to its earlier detection. Patients with minimal functional impairment have few complications, but are at increased risk for preeclampsia. They are also prone to UTIs, and it may therefore be prudent to culture their urines more frequently. Hypertension usually accompanies or antedates the onset of functional deterioration, and pregnancy in such gravidas is more hazardous.

   Some women with autosomal dominant polycystic kidney disease have cysts in their livers that may enlarge with repeated pregnancy as well as with oral contraceptive use. A high incidence of cerebral aneurysms also occurs in certain affected families. When aware of such family clustering, usually identified by a history of subarachnoid hemorrhages among relatives, the patient should undergo screening using magnetic resonance angiography. If an aneurysm is detected, neurosurgical consultation should be obtained, and the obstetrician may wish to avoid natural labor. All these patients should undergo genetic counseling before pregnancy to ensure they are aware that 50% of their offspring are at risk. Finally, predicting the fetal outcome using molecular probes on cells cultured from the amniotic fluid is possible.
3. **Solitary Kidneys.** Women with solitary kidneys appear to tolerate gestation well. However, if the nephrectomy was performed for nephrolithiasis or chronic pyelonephritis, the remaining kidney may be infected. Patients with these conditions must be carefully scrutinized by frequent examination and culture of the urine throughout pregnancy and in the puerperium.

K. Pelvic kidneys may be associated with other malformations of the urogenital tract of the mother. In addition, dystocia may occur when the kidney is in the true pelvis.

L. Urolithiasis and Hematuria. The prevalence of urolithiasis in gestation varies between 0.03% and 0.35% in the Western hemisphere. Many of the stones contain calcium, and some are infective in origin. A survey of 148 gestations in 78 nonselected stone formers suggests that pregnancy has little influence on the course of stone disease (although women with renal calculi may have an increased incidence of spontaneous abortions). It should be noted that most of the reported series focus on women whose calculi are mainly of the noninfective variety, and little is known of the natural history of the more serious infected struvite stones during gestation. In any event, UTI in the presence of nephrolithiasis requires prompt and prolonged treatment (3 to 5 weeks), followed by suppressive therapy through the immediate puerperium, because the calculus may represent a nidus of infection resistant to sterilization.

Experience with cystinuria in pregnancy is limited, but most women with this disease also do well in gestation. D-Penicillamine as used in these patients appears to have no apparent adverse effects on the mother or fetus.

Renal calculi are among the most common causes of abdominal pain (of nonobstetric origin) requiring hospitalization during gestation, and, when complications suggest the need for surgical intervention, pregnancy should not be a deterrent to x-ray examination. If the stone obstructs the ureter, intervention with ureteral stenting, percutaneous nephrostomy, or, rarely, surgery is indicated. Spontaneous gross or microscopic hematuria occasionally complicates an otherwise uneventful gestation. The differential diagnosis includes all causes of hematuria in nongravid patients (see Chapter 8), but frequently no etiology is demonstrable, and the bleeding subsides postpartum. It has been suggested that these events are due to the rupture of small veins around the dilated renal pelvis. Hematuria may or may not occur in subsequent gestations. In any event, investigation of the hematuria can often be deferred until after delivery, and noninvasive techniques such as ultrasonography and magnetic resonance imaging are helpful in arriving at such decisions.

IV. RENAL TRANSPLANTATION

A. Menstruation and fertility resume in most women from 1 to 12 months after kidney transplant. Pregnancy is not uncommon following kidney transplantation and the risk to mother and baby is much lower in this population than in pregnant patients on dialysis. Although pregnancy has become common after transplantation, there is little other than case reports, series, and voluntary databases to guide practice; a Consensus Conference generated a report in 2005 summarizing the literature and generated practice guidelines as well as identified gaps in knowledge. Most pregnancies (greater than 90%) that proceed beyond the first trimester succeed. However, there are maternal and fetal complications due to immunosuppressant effects, preexisting hypertension, and kidney dysfunction. These include maternal complications of glucocorticosteroid therapy such as impaired glucose tolerance, hypertension (47% to 73%), preeclampsia (30%), and increased infection.

Fetal complications are generally seen in transplant recipients with impaired kidney function (creatinine ≥1.5 mg/dL and preexisting hypertension). In this group, adverse outcomes include a higher incidence of preterm delivery (50% to 54%), small-for-gestational-age infants (33% to 45%), and increased neonatal mortality (1% to 3%) compared with the general population (12.3%, 5%, and 0.68%, respectively). Despite the higher incidence of preterm delivery and lower birth weight, long-term studies show that children born to transplant recipients develop normally.

Best practice guidelines have outlined criteria for considering pregnancy in kidney transplant recipients and it is suggested that those contemplating pregnancy should meet the following:

- Good health and stable kidney function for 1 to 2 years after transplantation with no recent acute or ongoing rejection or infections
- Absent or minimal proteinuria (less than 0.5 g/day)
- Normal BP or easily managed hypertension
- No evidence of pelvicalyceal distension on ultrasonography before conception
- Serum creatinine less than 1.5 mg/dL
- Drug therapy: prednisone 15 mg daily or less, azathioprine 2 mg/kg or less, cyclosporine less than 5 mg/kg/day.

Although cyclosporine levels tend to decrease during pregnancy, there is no information regarding whether or not drug dosage should be increased. Tacrolimus has not been used as widely in pregnancy as cyclosporine, although growing experience suggests that it is safe, with a similar side effect profile to cyclosporine. Considerations regarding hypertension and growth restriction are important; there is no established BP target, although 140/90 mmHg is suggested and antihypertensives should be switched to those safe in pregnancy. Mycophenolate mofetil has been reported to be embryotoxic in animals and is associated with ear and other deformities including hypoplastic nails, short fingers, cleft palate, and Tetralogy of Fallot in humans. This drug should be discontinued before conception, and women should be switched to azathioprine if indicated. Sirolimus causes delayed ossification in animal studies, and although successful live-born human outcomes have been reported, its use is contraindicated in humans until more data are available. Finally, data from the National Transplantation Pregnancy Registry and the European Dialysis and Transplant Association suggest that in women with stable, near-normal kidney function, pregnancy rarely negatively affects the graft, although there may be minor increases in serum creatinine postpartum compared with prepregnancy creatinine. On the other hand, women with significantly reduced transplant function antepartum are at risk for irreversible deterioration after delivery, as observed with CKD in native kidneys. Rejection is difficult to diagnose in pregnancy and kidney biopsy may be required; the consensus opinion is that corticosteroids and IVIg are safe treatments for acute rejection, but the safety of antilymphocyte globulins and rituximab in pregnancy is unknown.

V. DIALYSIS. Fertility is reduced in patients undergoing dialysis, due to abnormalities of pituitary luteinizing hormone release leading to anovulation. Pregnancy that does occur in patients undergoing maintenance dialysis is extremely high risk, and conception should be strongly discouraged due to very

high fetal mortality; in large surveys only 42% to 60% of such pregnancies result in a live-born infant. Prematurity, very low birthweight, and intrauterine growth restriction are common, and approximately 85% of infants born to women who conceive after starting dialysis are born before 36 weeks' gestation. The single most important factor influencing fetal outcome in patients on dialysis is the maternal plasma urea level. In patients undergoing hemodialysis, both the number of dialysis sessions per week and the time per session must be increased to a minimum of 20 hours/week, aiming for a predialysis urea of 30 to 50 mg/dL (5 to 8 mmol/L). Heparinization should be minimized to prevent obstetric bleeding. Dialysate bicarbonate should be decreased to 25 mEq/L, in keeping with the expected lower bicarbonate levels of pregnancy. If peritoneal dialysis is being used, decreasing exchange volumes by increasing exchange frequency or cycler use are recommended. Adequate calorie and protein intake is required; 1 g/kg/day protein intake plus an additional 20 g/day has been suggested. After the first trimester, maternal "dry" weight should be increased by approximately 1 lb (400 g) per week to adjust for the expected progressive weight increase in pregnancy. Antihypertensive therapy should be adjusted for pregnancy by discontinuing angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and aiming for maintenance of maternal diastolic pressure of 80 to 90 mmHg, using methyldopa, labetalol, and sustained release nifedipine in standard doses to achieve target. Anemia should be treated with supplemental iron, folic acid, and erythropoietin. Erythropoietin is safe in pregnancy, and pregnancy-related erythropoietin resistance requires a dose increase of approximately 50% to maintain hemoglobin target levels of 10 to 11 g/dL. Owing to placental 25-hydroxyvitamin D_3 conversion, decreased supplemental vitamin D may be required and should be guided by levels of vitamin D, parathyroid hormone, calcium, and phosphorus. Magnesium supplementation may be needed to maintain serum magnesium level at 5 to 7 mg/dL (2 to 3 mmol/L). Low-dose aspirin has been suggested to prevent preeclampsia. Babies born to mothers on dialysis may require monitoring for osmotic diuresis in the immediate postpartum period if maternal urea was high at the time of delivery.

VI. HYPERTENSIVE DISORDERS OF PREGNANCY.

Hypertension during gestation remains a major cause of morbidity and death in both mother and child.

A. Of the many **classifications** proposed for hypertension complicating pregnancy, that of the Committee on Terminology of the American College of Obstetricians and Gynecologists (1972) has been the most useful. The National High Blood Pressure Education Program in the United States endorsed this system in 1990 and again in 2000. The four categories of hypertensive disorders in pregnancy are as follows:

1. Preeclampsia. Preeclampsia, which affects between 2% and 7% of pregnant women, is characterized by hypertension, proteinuria, edema, and, at times, coagulation and liver function abnormalities, occurs in late pregnancy (after 20 weeks), primarily in nulliparas. Third-trimester hypertension is defined as a BP of 140/90 mmHg or greater (Korotkoff V) sustained for 4 to 6 hours.

Attempts have been made to categorize this disease as severe (e.g., diastolic and systolic pressures of 110 and 160 mmHg or greater, heavy proteinuria, oliguria, and neurologic symptoms) or mild. Because a

patient with seemingly mild preeclampsia (e.g., a teenage gravida with a systolic BP of 140/85 mmHg and trace proteinuria) may suddenly convulse (in which case the disease is called *eclampsia*, a complication associated with maternal mortality), terms such as *mild* and *severe* may be misleading. Hypertension during late pregnancy in a nullipara, whether or not other signs are present, is sufficient reason to consider hospitalization and treatment as if the patient were potentially preeclamptic.

2. **Chronic Hypertension.** Most women in this category have essential hypertension, but in some the elevated BP is secondary to such conditions as renal artery stenosis, coarctation of the aorta, renal disease, primary aldosteronism, and pheochromocytoma. Evidence of arteriolar disease and knowledge that hypertension was present before conception or early in gestation are helpful in establishing a diagnosis. Cocaine abuse may masquerade as chronic hypertension in pregnancy. Pheochromocytoma has a catastrophic outcome during pregnancy; therefore, measurement of plasma metanephrines should be considered in selected hypertensive gravidas not previously evaluated.
3. **Chronic Hypertension with Superimposed Preeclampsia.** Hypertensive women are at increased risk for the development of superimposed preeclampsia, and, when this occurs, maternal and fetal morbidity and mortality are greater than when preeclampsia develops in a previously normotensive woman. Many of the maternal deaths attributable to hypertensive disease occur in previously hypertensive women with superimposed preeclampsia.
4. **Gestational hypertension**, which is high BP appearing first after midpregnancy, is distinguished from preeclampsia by the absence of proteinuria. This category is broad and includes women who later develop diagnostic criteria for preeclampsia, as well as women with chronic hypertension in whom BP decreased in early pregnancy, masking the true diagnosis. Gestational hypertension that resolves postpartum, and which was not in retrospect preeclampsia, is more likely to occur in women who develop essential hypertension later in life.
5. The physician should be aware that on rare occasions convulsions and hypertension may develop after delivery. So-called late postpartum eclampsia (hypertension and convulsions 48 hours to weeks after delivery) is poorly understood and is treated by hospitalization, magnesium sulfate, and supportive care.

   Recent studies suggest that hypertension during pregnancy is associated with increased risk of cardiovascular disease, kidney disease, and diabetes. This is true for all types of hypertension during pregnancy.

B. Pathophysiology of Preeclampsia. Preeclampsia is a syndrome, the manifestations of which affect many organ systems, including the brain, liver, kidney, blood vessels, and placenta. Therefore, while the focus may be on hypertension and proteinuria, we must always be aware that such signs and symptoms may be minimal, whereas other, life-threatening syndromes develop, including convulsions and liver failure, both often associated with thrombocytopenia, as well as signs of DIC.

The placenta may be critically involved in the genesis of preeclampsia, and failure of cytotrophoblastic invasion of the uterine spiral arteries is

one of the earliest changes in this disorder. Therefore, these vessels do not undergo the expected transformation into the dilated blood vessels characteristic of normal placentation. This aberration may underlie the poor placental perfusion and growth restriction characteristic of preeclampsia. The reason for the failure of the trophoblast to invade the uterine spiral arteries is obscure. Research has focused on the abnormal modulation of cytotrophoblast adhesion molecules, integrins, and abnormal vascular endothelial growth factor (VEGF) receptor–ligand interactions. The abnormal placentation leading to the maternal syndrome of preeclampsia is believed to occur early in pregnancy (10 to 20 weeks' gestation). Finally, a growing body of evidence has implicated the production of antiangiogenic factors such as sFlt-1 and endoglin in the genesis of preeclampsia. Women with preeclampsia have been found to have increased circulating levels of a soluble, splice variant of a receptor for VEGF called *sFlt-1*. SFlt-1 is believed to be released from the placenta into the maternal blood, and by binding to VEGF causes decreased bioavailability of VEGF, maternal vascular endothelial cell dysfunction, and the characteristic clinical features such as hypertension and proteinuria. Experimental administration of sFlt-1 and endoglin to pregnant rats recapitulates the classic renal histologic findings of glomerular endotheliosis. Current studies are in progress to determine whether measurement of sFlt-1 is a useful test for either screening or early diagnosis of preeclampsia.

The mediators of hypertension in preeclampsia are not clearly understood. Evidence suggests that vasoconstriction results from a complex interplay of hormonal and vascular alterations. The renin–angiotensin system is stimulated in normal pregnancy and relatively suppressed in women with preeclampsia. However, patients with preeclampsia are more sensitive to the pressor effects of angiotensin II, and therefore this pressor peptide may play a role in their elevated BP. Aldosterone levels are also lower in preeclamptic women than in women with normal pregnancies, although still higher than nonpregnant levels.

Alterations in vascular endothelial cell function are important features of the pathophysiology of preeclampsia. Endothelial cells produce a variety of substances important in modulating vascular tone and coagulation (e.g., NO, prostacyclin, and endothelin). Animal studies of gestational hypertension as well as clinical studies in women suggest that decreased NO and prostacyclin, and increased endothelin, in addition to antiangiogenic factors mentioned earlier, are both sequelae and contributory factors leading to vasoconstriction, platelet aggregation, and increased intravascular coagulation and, finally, the maternal clinical manifestations of preeclampsia.

The ability to excrete sodium may be impaired in preeclampsia, but the degree to which this occurs varies, as severe disease can occur in the absence of edema (the "dry preeclamptic" patient). Even when edema is marked, plasma volume is below that for normal pregnancy, and hemoconcentration is often present. This latter phenomenon may relate to the development of a "leaky" vasculature (therefore, hypoalbuminemia in this disease may have three components: renal protein loss, liver dysfunction, and extravasation from the intravascular to the interstitial space). A decrement or suboptimal increase in intravascular volume also appears to precede the onset of overt hypertension.

Cardiac output is often decreased, and central venous and pulmonary capillary wedge pressures are normal or low. Therefore, high BP is

maintained by a marked increase in peripheral resistance. The alterations in cardiac output, combined with the decrements in intravascular volume, and the fact that placental perfusion is decreased in preeclampsia are major reasons why diuretic use is discouraged in this disease.

In one variant of preeclampsia, HELLP, coagulation abnormalities, and liver dysfunction predominate, whereas hypertension and proteinuria may be minimal. This syndrome is life threatening because platelet counts may plunge far below 100 mm^3, whereas transaminase and lactic acid dehydrogenase levels rise above 1,000 units/L and evidence of a marked microangiopathic hemolytic anemia appears on the peripheral blood smear, all in less than 24 hours. Early recognition of this HELLP variant and prompt termination of gestation are important; such action avoids substantial maternal morbidity.

The pathogenesis of the eclamptic convulsion is also poorly understood. Vasospasm, ischemia, and local hemorrhage may all play a role. The importance of hypertension per se in the genesis of the seizures is debated, because convulsions may be observed in women whose BP is only mildly elevated. Descriptions of the syndrome of reversible posterior leukoencephalopathy syndrome, which is characterized by altered cerebrovascular autoregulation, endothelial dysfunction, and dramatic clinical sequelae in the setting of elevated BP, may be relevant to eclampsia.

C. Kidney Function and Morphology in Preeclampsia

1. **GFR and RPF.** Both GFR and RPF decrease in preeclampsia. The decrements approximate 25% in most instances, so that the GFR of preeclamptic women often remains above pregravid values. However, in rare instances, large decreases in function may occur and, on occasion, lead to acute tubular or cortical necrosis.
2. **Uric Acid.** Changes occur in the renal handling of urate in preeclampsia. A decrease in the clearance of uric acid, accompanied by increments in blood levels of this solute, may occur weeks before any clinical signs of the disease appear. In pregnancy, serum urate levels above 4.5 mg/dL are suspect [to convert to SI units (μmol/L), multiply mg/dL by 59.48]. The level of hyperuricemia also correlates with the severity of the preeclamptic renal lesion, as well as with fetal outcome.
3. Increased **proteinuria**, which may be moderate or heavy, is a feature of preeclampsia, and the diagnosis is suspect in its absence. The magnitude of proteinuria does not appear to affect maternal prognosis, but protein excretion in the nephrotic range is associated with greater fetal loss.
4. **Calcium.** Studies have demonstrated that renal calcium handling is altered in preeclampsia, and that in contrast to normotensive gravidas, or those with chronic or transient hypertension, patients with preeclampsia demonstrate marked hypocalciuria. The basis for this abnormality is unknown. Levels of 1,25 vitamin D are lower, and parathormone higher when compared with normal pregnancy.
5. Preeclampsia is accompanied by a characteristic histologic lesion: **glomerular capillary endotheliosis** (Fig. 14-2). In women diagnosed clinically as preeclamptic, this lesion is present in only approximately 85% of biopsies obtained from primiparas and in considerably fewer biopsies

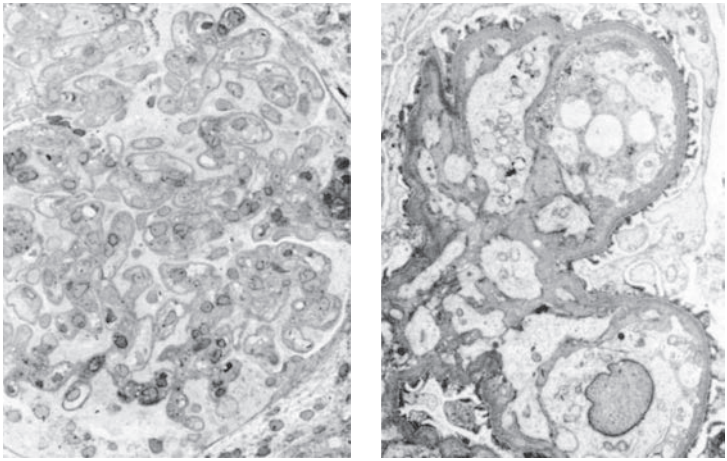

Figure 14-2. **A:** Electron micrograph demonstrating complete capillary obliteration by a swollen endothelial cell. Note, however, that the basement membrane is normal and the epithelial foot processes are intact. **B:** Micrograph showing glomerulus from a preeclamptic kidney. Swollen endothelial and mesangial cells that display prominent vacuolization encroach on the capillary lumina. (Courtesy of B. H. Spargo, M.D.)

from multiparas. The remaining patients have evidence of nephrosclerosis or another parenchymal disease. Glomerular endotheliosis is characterized by swollen glomerular capillary endothelial cells with the appearance of a "bloodless glomerulus." Some claim that preeclampsia is a cause of focal glomerular sclerosis, but others believe preeclampsia lesions to be completely reversible, with the presence of focal glomerular sclerosis reflecting preexisting nephrosclerosis or primary renal disease. Women with glomerular endotheliosis alone tend to have uneventful subsequent gestations, but when focal glomerular sclerosis or alterations in the renal vessels are present, hypertension is more likely to recur in later pregnancies.

D. Management of Preeclampsia

1. **Hospitalization.** Ambulatory treatment is risky in the management of preeclampsia. Therefore, suspicion of the disease is sufficient to consider hospitalization. Such an approach diminishes the frequency of convulsions and other consequences of diagnostic error. In general, fetal maturity is evaluated; if the gestation is near term, induction is the therapy of choice, whereas attempts to temporize are made if the pregnancy is at an earlier stage. Rest is an extremely important part of the therapeutic regimen, which must be prescribed rather than suggested. Termination of pregnancy should be considered when signs of impending eclampsia (e.g., hyperreflexia, headaches, and epigastric pain) develop or persist; BP cannot be controlled; serum creatinine, urea nitrogen, and uric acid rise; laboratory evidence suggests DIC or abnormal liver function (increased transaminases); or specific obstetric test results suggest fetal

jeopardy. When signs of impending convulsions (eclampsia) are present, parenteral magnesium sulfate is the drug of choice.

2. **Treatment of Hypertension.** The approach to treatment of high BP in gravidas is disputed. As noted, morphologic examination of preeclamptic placentae demonstrates decreased trophoblastic invasion of the uterine spiral arteries, causing these vessels to be more constricted than normal. Thus, perfusion of the placenta is compromised. Therefore, aggressive reduction in maternal BP may decrease uteroplacental perfusion even further (i.e., poor autoregulation of uterine blood flow). Thus, large decrements in the mother's mean pressure should be avoided, especially in acute emergencies. Data on human pregnancy are limited, but they suggest that decrements in maternal pressure may indeed reduce placental perfusion. Others have argued that, based on evidence obtained from animal studies, uterine blood flow is autoregulated, and therefore hypertension should be aggressively treated. Assuming that autoregulation of uterine blood flow exists, a critical but unanswered question is how quickly it takes place, because fetuses may be damaged by short periods of ischemia. Therefore, the author prescribes the careful use of parenteral hydralazine or labetalol, in addition to close maternal scrutiny and fetal monitoring, when acute hypertension exceeds diastolic levels of 100 mmHg or systolic levels of 150 mmHg (Table 14-5). This approach is successful in most gravidas. Long-acting oral calcium channel blockers have also been used to treat acute hypertension associated with preeclampsia.

   Diazoxide can be used in rare resistant cases and should be administered only in small doses (30 mg at a time). Sodium nitroprusside should be avoided, because cyanide poisoning and fetal death have been observed in laboratory animals. ACE inhibitors and ARBs should not be used in pregnancy.

3. **Treatment of the Eclamptic Convulsion.** Several large clinical trials have demonstrated that magnesium sulfate is superior to other anticonvulsants for prevention of recurrent eclamptic convulsions, and also for primary prevention of eclampsia in women with preeclampsia. The usual protocol is to administer a loading dose of 4 g magnesium sulfate, infused over 15 minutes, followed by a sustaining infusion of 1 to 2 g/hour, aiming to achieve plasma levels of 2 to 4 μmol/L. Because the incidence of convulsion is highest in the immediate puerperium, it is common practice to begin magnesium sulfate immediately after delivery and continue it for 24 hours.

E. Prevention of Preeclampsia. Many strategies have been investigated in well-conducted clinical trials (including thousands of women) of antiplatelet therapy, nutritional supplementation, and antioxidant vitamins for the prevention of preeclampsia. These trials, and subsequent meta-analyses, demonstrate a small (10% to 15% reduction in relative risk) benefit for low-dose aspirin for the prevention of preeclampsia and meaningful adverse maternal and fetal outcomes. With respect to nutritional strategies, calcium supplementation appears to have a small benefit in women ingesting a baseline low-calcium diet, and not much benefit in women ingesting a normal calcium diet. To date, antioxidant supplementation with vitamins C and E has not shown benefit in three large randomized controlled trials.

Although prevention of preeclampsia is usually not possible, avoidance of severe complications may be accomplished by early recognition of the disease before such complications develop. If early signs are detected, hospitalization should be strongly considered to permit close monitoring of the patient. If preeclampsia is detected early, bedrest and close monitoring of maternal and fetal condition may enable prolongation of pregnancy in some cases.

F. The Hypertensive Patient without Preeclampsia. Pregnancies in women with chronic hypertension are associated with increased maternal as well as fetal risks. Complications include superimposed preeclampsia, placental abruption, acute tubular and cortical necrosis, retardation of intrauterine growth, and midtrimester fetal death. Such events seem to correlate with the age of the gravida and the duration of her high BP. Therefore, most of these complications occur in women older than 30 years or with evidence of end-organ damage. Conversely, most women (approximately 85%) with essential hypertension have uncomplicated and successful gestations.

Women with chronic hypertension often have reductions in BP by midpregnancy, so that their BP may not exceed that observed in normotensive pregnant women. The failure of this decrement to occur, or increases in BP in early or midtrimester pregnancy, indicates a guarded prognosis for the gestation. Fetal outcome is poorer in hypertensive women with superimposed preeclampsia than in previously normotensive women with this complication, and the combination of chronic hypertension and preeclampsia increases the risk of cerebral hemorrhage. Patients with chronic hypertension and superimposed preeclampsia should be hospitalized and their hypertension controlled. Delivery should be considered if either maternal or fetal condition is unstable.

1. **Antihypertensive Therapy.** Guidelines for antihypertensive therapy during gestation are less clear than those for nonpregnant hypertensive women. For the latter, compelling data exist from large population studies to document the benefits of lowering BP with medication, even in women with only mild hypertension. During pregnancy, however, although maternal safety remains the primary concern, there is also a desire to minimize exposure of the fetus to drugs, given their unknown long-term effects on growth and development. A systematic review of clinical trials of hypertension found only 13 randomized clinical trials comparing antihypertensive therapy to either no treatment or placebo in women with chronic hypertension. The most commonly used drug, methyldopa, was given to just more than 200 subjects. Six trials showed no reduction in perinatal mortality with antihypertensive treatment, whereas three reported a trend toward lower perinatal mortality with treatment. A debatable issue is whether lowering BP will prevent superimposed preeclampsia, but little or no convincing evidence supports this contention. Therefore, it is permissible to tolerate higher BP levels during gestation that do no harm in the short term, while limiting use of antihypertensive drugs. In this respect, most pregnant women with chronic hypertension have only mild or very moderate elevations in BP and require little or no medication at all. However, "appropriate" or "tolerable" levels of BP for these patients during gestation seem to have been set empirically, and multicenter clinical trials are needed to support or reject such practices.

Whether mild degrees of hypertension during gestation should be treated is not generally agreed on. Although one group claimed that such therapy decreases the incidence of superimposed preeclampsia, most would withhold treatment until diastolic levels are at least 15 mmHg above borderline hypertension (defined in the author's clinics as 75 mmHg in the second trimester and 85 mmHg in late gestation). Very young gravidas, however, may require treatment at lower levels. Tables 14-4 and 14-5 summarize current knowledge on the use of antihypertensive drugs in pregnancy. The available information regarding the safety and efficacy of these medications in pregnant women is limited.

Table 14-4. Guidelines for Treating Severe Hypertension Near Term or during Labor

Regulation of blood pressure
The degree to which blood pressure should be decreased is disputed; maintaining diastolic levels between 90 and 100 mmHg is recommended
Drug therapy
Labetalol, administered intravenously, is an effective and safe agent for preeclamptic hypertension; start with 20 mg and repeat the dose every 20 min, up to 200 mg, until desired blood pressure is achieved. Side effects include headache
Hydralazine administered intravenously may also be used; start with low doses (5 mg as an intravenous bolus), then administer 5 to 10 mg every 20–30 min to avoid precipitous decreases in pressure; side effects include tachycardia and headache
Calcium channel blockers (*long acting*) have been used, p.o.
Diazoxide should be used only in the rare instance that hydralazine, labetalol, or calcium channel blockers have been unsuccessful; small doses (30 mg at a time) have been reported to be effective; side effects include arrest of labor and neonatal hypoglycemia
Refrain from using *sodium nitroprusside*, because fetal cyanide poisoning has been reported in animals; however, maternal well-being should dictate the choice of therapy
Prevention of convulsions
Parenteral *magnesium sulfate* is the drug of choice for preventing eclamptic convulsions; therapy should be continued for 12–24 h postpartum, because one-third of women with eclampsia have convulsions during this period

Table 14-5.	Antihypertensive Drugs Used to Treat Chronic Hypertension in Pregnancy
α_2-Adrenergic receptor agonists	
Methyldopa is the most extensively used drug in this group. Its safety and efficacy are supported by evidence from randomized trials and a 7.5-year follow-up study of children born to mothers treated with methyldopa	
β-Adrenergic receptor antagonists	
These drugs, especially *atenolol* and *metoprolol*, appear to be safe and efficacious in late pregnancy, but fetal growth retardation has been reported when treatment was started in early or midgestation. Fetal bradycardia can occur, and animal studies suggest that the fetus' ability to tolerate hypoxic stress may be compromised	
α-Adrenergic receptor and β-adrenergic receptor antagonists	
Labetalol appears to be as effective as methyldopa, but no follow-up studies of children born to mothers given labetalol have been carried out, and concern about maternal hepatotoxicity still exists	
Calcium channel blockers	
Several small studies and reviews suggest that both dihydropyridines (long acting) and verapamil and diltiazem are safe and effective in pregnancy	
Direct-acting vasodilators	
Hydralazine is frequently used as adjunctive therapy with methyldopa and β-adrenergic receptor antagonists. Rarely, neonatal thrombocytopenia has been reported. The experience with *minoxidil* is limited, and this drug is not recommended	
Angiotensin-converting enzyme (ACE) inhibitors	
Captopril causes fetal death in diverse animal species, and several ACE inhibitors have been associated with oligohydramnios and neonatal renal failure when administered to humans; do not use at any time in pregnancy	
Angiotensin II receptor blockers	
These drugs have not been used in pregnancy; in view of the deleterious effects of blocking angiotensin II generation with ACE inhibitors, angiotensin II receptor antagonists are also considered to be contraindicated in pregnancy	
Diuretics	
Diuretics may be used in women with salt-sensitive hypertension and/or renal disease; attempts should be made to use the lowest possible dose and avoid volume depletion	

A reasonable strategy, based on available data, is to treat maternal hypertension when BP exceeds 145 to 150 mmHg systolic, 95 to 100 mmHg diastolic. Exceptions, however, include parenchymal renal disease and evidence of target organ damage (e.g., retinopathy and cardiac hypertrophy), in which therapy is recommended once levels are 90 mmHg or more.

The argument of whether to treat is debatable when only fetal well-being is considered. Some evidence suggests fetal benefits when mild to moderate hypertension is treated with antihypertensive drugs during pregnancy.

In summary, the unknown but potential hazards of antihypertensive treatment during pregnancy are sufficient reasons for withholding drug treatment when mild hypertension (systolic 140 to 150 mmHg, diastolic 90 to 95 mmHg) is present, particularly during the initial trimester. As noted, many of these patients experience a physiologic decrease in BP that on occasion reaches normotensive levels. Patients with evidence of renal disease or end-organ damage require the initiation of treatment at lower levels (less than 90 mmHg).

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15 The Patient with Hypertension

Seth Furgeson, Charles R. Nolan, and Robert W. Schrier

I. DEFINITION AND CLASSIFICATION OF HYPERTENSION. The definition of hypertension is somewhat arbitrary, because blood pressure (BP) is not distributed bimodally in the population. Instead, the distribution of BP readings in the population is unimodal, and an arbitrary level of BP must be defined as the threshold above which hypertension can be diagnosed. The correlation between the levels of systolic BP (SBP) and diastolic BP (DBP) and cardiovascular risk has long been recognized. It has become clear that in patients older than 50 years, SBP of more than 140 mmHg is a much more important cardiovascular disease risk factor than is DBP. Increasing BP clearly has an adverse effect on mortality over the entire range of recorded pressures, even those generally considered to be in the normal range. The goal of identifying and treating high BP is to reduce the risk of cardiovascular disease and associated morbidity and mortality. The seventh report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has established criteria for the diagnosis and classification of BP in adult patients (Table 15-1). The optimal BP in an individual who is not acutely ill is lower than 120/80 mmHg. Individuals with an SBP of 120 to 139 mmHg or a DBP of 80 to 89 mmHg should be considered as prehypertensive; these patients require health-promoting lifestyle modifications to prevent cardiovascular disease. Patients with prehypertension are at twice the risk of developing hypertension as those with lower values. Although normotensive by definition, these prehypertensive patients should be rechecked annually to exclude the development of hypertension. Hypertension is arbitrarily defined as an SBP of 140 mmHg or greater or a DBP of 90 mmHg or greater, or by virtue of the patient taking antihypertensive medications. The stage of hypertension (stage 1 or 2) is determined by the levels of both SBP and DBP (Table 15-1). This classification should be based on the average of two or more BP readings at each of two or more visits after the initial BP screening. When SBP and DBP fall into different categories, the higher category should be selected to classify the individual's BP.

II. EPIDEMIOLOGY OF HYPERTENSION. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that approximately 28% of the adult population in the United States has hypertension, a number that has remained relatively stable over the last decade. According to the same study, prevalence of hypertension increases sharply with age. The increasing burden of hypertension is not only the result of the increased size of the population but also reflects the increased prevalence of obesity and the overall aging of the population. Data from the Framingham Heart Study indicate that

Table 15-1. Classification of Blood Pressure (BP) for Adults[a]

BP Classification[b]	Systolic BP (mmHg)[c]		Diastolic BP (mmHg)[c]
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

[a]Adults aged 18 years and older.
[b]Classification should be based on the mean of two or more properly measured seated blood pressure readings obtained on each of two or more office visits.
[c]When systolic and diastolic BP fall into different categories, classify based on the higher category.
Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003;289:2560–2572.

even individuals who are normotensive at 55 years have a 90% lifetime risk of developing hypertension. Many hypertensive patients have a positive family history of parental hypertension. The mode of inheritance is complex and probably polygenic in most instances. Black men and women have a twofold higher prevalence of hypertension (30%) than white men and women (15%) in a sampling of almost 18,000 American adults aged 48 to 75 years in the NHANES data. Prevalence appears to be equal in men and women in most surveys. Obese individuals have significantly more hypertension than nonobese individuals. In childhood, obesity is a major cause of hypertension. More than one-half of the adult population is overweight [body mass index (BMI) of 25 to 29.9] or obese (BMI ≥ 30). Data from NHANES III show that among men and women, whites, blacks, and Mexican Americans, the prevalence of hypertension and the mean levels of SBP and DBP increase as BMI increases at ages younger than 60 years. Overall, the prevalence of hypertension in obese adults is 41.4% for men and 37.8% for women; compared with 14.9% for men and 15.2% for women with BMI ≤ 25. Further proof of the significant relationship between body weight and BP is found in the observation that BP falls with even modest weight reduction. The intake of dietary salt (sodium chloride) has significant effects on BP, especially in patients with other factors predisposing to the development of hypertension, such as advancing age, obesity, adult-onset diabetes, positive family history of hypertension, black race, or underlying renal disease. Numerous epidemiologic studies have shown that the dietary intake of salt correlates with the average BP in a population. Northern Japanese fishermen who ingest 450 mEq of sodium daily have a 40% prevalence of hypertension. In contrast, indigenous Alaskan populations and the Yanomamo Indians in Brazil and Venezuela, who have dietary intake of 1 mEq of sodium daily, do not develop hypertension at any age. Intersalt, an international epidemiologic

study, examined the relation between dietary sodium intake (based on 24-hour urinary sodium excretion) and BP in more than 10,000 individuals aged 20 to 59 years from 52 countries around the world. The results demonstrate a significant correlation between median SBP and DBP and dietary sodium intake. These observations can be explained based on the role of abnormal renal sodium handling in the pathogenesis of hypertension, which is discussed in Section IV. The therapeutic implications of these observations include dietary sodium restriction as part of nonpharmacologic therapy and the recommendation of thiazide diuretics as first-line drug therapy for the treatment of hypertension in most patients. Despite the known cardiovascular risks of untreated hypertension and the widespread availability of effective pharmacologic treatment, the identification and effective control of hypertension remain a significant public health problem in the United States. According to the most recent NHANES data, there have been gradual improvements in hypertension control in the United States from 1988 to 2008. In 2008, 81% of patients were aware that they had hypertension and 73% of patients were on treatment. However, only 50% of all patients with hypertension had controlled BP. The continued high prevalence of hypertension and hypertension-related complications such as stroke, cardiovascular complications, heart failure, and end-stage renal disease (ESRD) represents a major public health challenge.

III. CARDIOVASCULAR DISEASE RISK. The relationship of BP to cardiovascular risk is continuous and independent of other cardiovascular risk factors. Beginning at 115/75 mmHg and across the entire BP range, each increment of 20/10 mmHg doubles the risk of cardiovascular disease. The overall risk of cardiovascular morbidity and mortality in patients with hypertension is determined not only by the stage of hypertension but also by the presence of other risk factors, such as smoking, hyperlipidemia, and diabetes, and by the existence of target organ damage (Table 15-2). The major target organs affected by hypertension are the heart, peripheral vasculature, central nervous system, kidney, and the eye. Most of the consequences of hypertension are the result of progressive vascular injury. Hypertension accelerates atherosclerotic vascular disease and aggravates the deleterious effects of diabetes, smoking, and hyperlipidemia on the aorta and its major branches. Atherosclerotic disease results in significant morbidity from myocardial infarction (MI), atherothrombotic cerebral infarction, peripheral vascular disease with claudication, and renal disease due to ischemia or cholesterol embolization. Hypertensive renal disease may result from hypertension-induced vasculitis in the setting of malignant hypertension or more insidious renal injury from long-standing essential hypertension with benign hypertensive nephrosclerosis. Hypertension is also an important cofactor in the progression of other renal diseases, especially diabetic nephropathy. Hypertension may also cause cerebrovascular disease in the form of lacunar infarction or intracerebral hemorrhage. Left ventricular hypertrophy (LVH) and congestive heart failure (CHF), often due to isolated diastolic dysfunction, are the result of the heightened peripheral vascular resistance (afterload) imposed by systemic hypertension. In clinical trials, antihypertensive therapy has been associated with significant reductions in the incidence of stroke (35% to 40%), MI (20% to 25%), and heart failure (50%). It has been estimated that in patients with stage 1 hypertension (SBP 140 to 159 mmHg and/or DBP 90 to 99 mmHg) and additional cardiovascular risk factors, achieving a

Table 15-2.	Cardiovascular Risk Factors and Target Organ Damage
Major Risk Factors	
Hypertension[a]	
Cigarette smoking	
Obesity (BMI)[b] >30[a]	
Physical inactivity	
Dyslipidemia[a]	
Diabetes mellitus[a]	
Microalbuminuria or estimated GFR < 60 mL/min	
Age (older than 55 yr for men, older than 65 yr for women)	
Family history of premature cardiovascular disease (men younger than 55 yr or women younger than 65 yr)	
Target Organ Damage	
Heart	
Left ventricular hypertrophy	
Angina or prior myocardial infarction	
Prior coronary revascularization	
Heart failure	
Brain	
Prior stroke or transient ischemic attack	
Chronic kidney disease	
Peripheral arterial disease	
Retinopathy (Table 15-8)	

BMI, body mass index; GFR, glomerular filtration rate.
[a]Components of the metabolic syndrome associated with insulin resistance and hyperinsulinemia.
[b]BMI is calculated as weight in kilograms divided by the square of height in meters.
Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003;289:2560–2572.

sustained 12 mmHg reduction in SBP for 10 years will prevent one death for every 11 patients treated. In the setting of preexisting cardiovascular disease or target organ damage, treatment of nine patients would prevent one death.

IV. PATHOGENESIS OF HYPERTENSION. A large body of experimental data has demonstrated the importance of the kidney in the pathogenesis of hypertension. To date, each of the genetic causes of hypertension that have been elucidated has been shown to relate to an abnormality of renal sodium handling. For example, Liddle's syndrome results from enhanced distal tubular sodium reabsorption due to an abnormality in sodium channels in the distal nephron. Cross-transplant experiments in hypertensive and normotensive rat strains validate the importance of the kidney in the pathogenesis of hypertension, because the presence or absence of hypertension depends on the donor source of the kidney.

Guyton's hypothesis states that the most important and fundamental mechanism in determining the long-term control of BP is the renal fluid–volume feedback mechanism. In simple terms, through this basic mechanism, the kidneys regulate arterial pressure by altering renal excretion of sodium and water, thereby controlling circulatory volume and cardiac output. Changes in BP, in turn, directly influence the renal excretion of sodium and water, thereby providing a negative feedback mechanism for the control of extracellular fluid (ECF) volume, cardiac output, and BP. For instance, an increase in systemic BP will lead to an increase in sodium excretion, a process known as pressure natriuresis. The hypothesis is that derangements in this renal fluid–volume pressure control mechanism are the fundamental cause of virtually all hypertensive states (Fig. 15-1). In every hypertensive state, an underlying abnormality exists in the intrinsic natriuretic capacity of the kidney, so that the daily salt intake cannot be excreted at a normal BP, and the development of hypertension is necessary to induce a pressure natriuresis that allows the kidney to excrete the daily salt intake. Normal sodium balance and ECF volume are maintained, but at the expense of systemic hypertension. The underlying cause for the abnormality in the natriuretic capacity depends on the etiology of hypertension. In essential hypertension, some underlying abnormality increases renal avidity for sodium. In patients with obesity and insulin resistance (metabolic syndrome), hyperinsulinemia increases proximal tubular sodium reabsorption. Increased angiotensin II levels and sympathetic nervous system activity also enhance sodium reabsorption. Mineralocorticoids enhance distal tubular sodium reabsorption. Renal parenchymal disease causes nephron loss, resulting in a natriuretic defect. Abnormalities in renal endothelin or nitric oxide levels may also impair natriuresis. Guyton's hypothesis states that this decreased natriuretic capacity of the kidney initially leads to renal salt and water retention, ECF volume expansion, and increased cardiac output with hypertension. This phase of volume expansion and high cardiac output is short lived. In the setting of high cardiac output, autoregulatory vasoconstriction of each vascular bed matches the blood flow to the metabolic requirements of the tissues. This phenomenon of circulatory autoregulation leads to an increase in systemic vascular resistance (SVR). Therefore, hypertension that was initially caused by high cardiac output becomes high-SVR hypertension.

The development of hypertension represents a protective mechanism, because it induces the kidney to undergo a pressure natriuresis and diuresis,

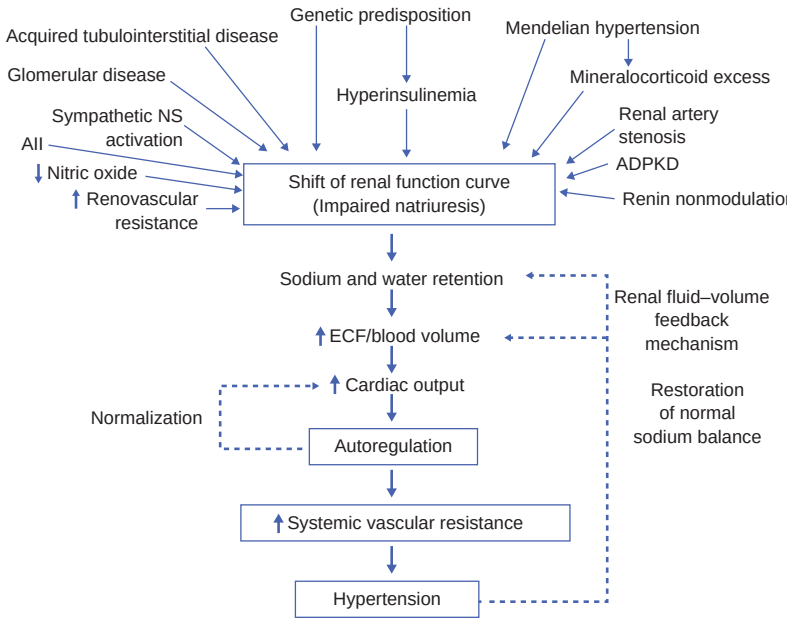

Figure 15-1. Abnormal renal sodium handling in the pathogenesis of hypertension (Guyton's hypothesis). In the setting of essential hypertension, primary renal disease, mineralocorticoid excess, or insulin resistance with hyperinsulinemia, a defect in the intrinsic natriuretic capacity of the kidney is present that prevents sodium balance from being maintained at a normal level of BP. Initially, this impairment in natriuresis leads to increases in extracellular fluid (ECF) volume and cardiac output. However, this hemodynamic state is short lived. Circulatory autoregulation occurs to maintain normal perfusion of the tissues, resulting in an increase in the systemic vascular resistance (SVR). The increase in SVR leads to systemic hypertension. With pressure-induced natriuresis, the renal fluid–volume feedback mechanism returns sodium balance, ECF volume, and cardiac output to normal. Systemic hypertension can be conceptualized as an essentially protective mechanism that prevents life-threatening fluid overload in the setting of reduced renal natriuretic capacity. Normal salt balance and fluid volume are maintained, but at the expense of systemic hypertension. (ADPKD, autosomal dominant polycystic kidney disease; NS, nervous system; AII, angiotensin II.) (Adapted with permission from Nolan CR, Schrier RW. The kidney in hypertension. In: Schrier RW, ed. *Renal and electrolyte disorders*, 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2003.)

thereby restoring normal salt balance and returning ECF volume to normal. This mechanism explains why an underlying problem with sodium excretion, as in salt-sensitive hypertension, is manifest as high-SVR hypertension without evidence of overt fluid overload. In the absence of pressure natriuresis, patients with a primary disorder in sodium retention would progressively develop overt fluid overload and consequences such as pulmonary edema. Support for this hypothesis is found in animal models of mineralocorticoid-induced hypertension. To substantiate the role of direct pressure-induced natriuresis in the

regulation of sodium balance in mineralocorticoid hypertension, Hall et al. compared the systemic BP and natriuretic effect of aldosterone infusion in a dog model in which the renal perfusion pressure was either allowed to increase or mechanically servocontrolled to maintain renal artery pressure at normal levels. In the intact animal, continuous aldosterone infusion caused a transient period of sodium and water retention with a mild increase in BP. This sodium retention lasted only a few days, however, and was followed by an escape from the sodium-retaining effects of aldosterone and a restoration of normal sodium balance. In contrast, when the renal perfusion pressure was servocontrolled to maintain normal renal perfusion pressure during aldosterone infusion, no aldosterone escape occurred, and a relentless increase in sodium and water retention occurred, accompanied by severe hypertension, edema, ascites, and pulmonary edema. When the servocontrol device was removed and the renal perfusion pressure was allowed to rise to the systemic level, a prompt natriuresis and diuresis ensued, with the restoration of sodium balance and a fall in BP. These observations highlight the pivotal role of BP in the regulation of renal sodium and water excretion. Moreover, the observation that abnormal renal sodium handling is central in the pathogenesis of all forms of hypertension provides a sound pathophysiologic rationale for the JNC 7 recommendation regarding thiazide-type diuretics as first-line antihypertensive therapy in most patients.

V. DIAGNOSTIC EVALUATION OF HYPERTENSION. Detection of hypertension begins with proper measurement of BP at each health care encounter. Repeated BP measurements are used to determine whether initial elevations persist and require prompt attention or have returned to normal values and require only periodic surveillance. BP measurement should be standardized as follows: After at least 5 minutes of rest, the patient should be seated in a chair with the back supported and one arm bared and supported at heart level. The patient should refrain from smoking or ingesting caffeine for 30 minutes before the examination. For an appropriately sized cuff, the bladder should encircle at least 80% of the arm. Many patients require a large adult cuff. Measurements should ideally be taken with a mercury sphygmomanometer. Alternatively, a recently calibrated aneroid manometer or a validated electronic device can be used. The first appearance of sound (phase 1) is used to define SBP. The disappearance of sound (phase 5) is used to define DBP. The BP should be confirmed in the contralateral arm. Measurement of BP outside of the physician's office may provide some valuable information with regard to the diagnosis and treatment of hypertension. Self-measurement is useful in distinguishing sustained hypertension from "white coat hypertension," a condition in which the patient's pressure is consistently elevated in the clinician's office but normal at other times. Self-measurement may also be used to assess the response to antihypertensive medications and as a tool to improve patient adherence to treatment. Ambulatory monitoring is useful for the evaluation of suspected white coat hypertension, patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, and episodic hypertension. However, ambulatory BP measurement is not appropriate for the routine evaluation of patients with suspected hypertension. In elderly patients, the possibility of **pseudohypertension** should always be considered in the diagnostic evaluation of possible hypertension. Pseudohypertension is a condition in which the indirect measurement of arterial pressure using a cuff sphygmomanometer is artificially high in comparison

to direct intra-arterial pressure measurement. Failure to recognize pseudohypertension can result in unwarranted and sometimes frankly dangerous treatment. Pseudohypertension can result from Monckeberg's medial calcification (a clinically benign form of arterial calcification) or advanced atherosclerosis with widespread calcification of intimal plaques. In these entities, stiffening of the arterial wall may prevent its collapse by externally applied pressure, resulting in artificially high indirect BP readings affecting both systolic and diastolic measurements. The presence of a positive Osler's maneuver, in which the radial or brachial artery remains palpable despite being made pulseless by proximal inflation of a cuff above systolic pressure, is an important physical examination finding that should suggest the diagnosis. Roentgenograms of the extremities frequently reveal calcified vessels. The diagnosis can only be made definitely by a direct measurement of intra-arterial pressure. Patients with pseudohypertension are often elderly and therefore may have a critical limitation of blood flow to the brain or heart, such that inappropriate BP treatment may precipitate life-threatening ischemic events.

The initial history and physical examination of patients with documented hypertension should be designed to assess lifestyle, identify other cardiovascular risk factors, and identify the presence of target organ damage that may affect prognosis and impact treatment decisions (Table 15-2). Although the vast majority of hypertensive patients have essential (primary) hypertension without a clearly definable etiology, the initial evaluation is also designed to screen for identifiable causes of secondary hypertension (Table 15-3). A medical history should include information about prior BP measurements, to assess the duration of hypertension, and details about adverse effects from any prior antihypertensive therapy. History or symptoms of coronary heart disease, CHF, cerebrovascular disease, peripheral vascular disease, or renal disease should be carefully evaluated. Symptoms suggesting unusual secondary causes of hypertension should be queried, such as weakness (hyperaldosteronism) or episodic anxiety, headache, diaphoresis, and palpitations (pheochromocytoma). Information regarding other risk factors, such as diabetes, tobacco use, hyperlipidemia, physical activity, and any recent weight gain, should be obtained. Dietary assessment regarding the intake of salt, alcohol, and saturated fat is also important. Detailed information should be sought regarding all prescription and over-the-counter medication use, including herbal remedies and illicit drugs, some of which may raise BP or interfere with the effectiveness of antihypertensive therapy. For example, nonsteroidal anti-inflammatory drugs impair the response to virtually all antihypertensive agents and increase the risk of hyperkalemia or renal insufficiency with angiotensin-converting enzyme (ACE) inhibitor therapy. Stimulants such as cocaine, ephedra, amphetamines, and anabolic steroids can raise BP. A family history of hypertension, diabetes, premature cardiovascular disease, or renal disease should be sought. A psychosocial history is important to identify family situation, working conditions, employment status, educational level, and sexual dysfunction that may influence adherence to antihypertensive treatment.

Physical examination should include the measurement of height and weight and calculation of BMI (weight in kilogram divided by the square of height in meters). Funduscopic examination is important to identify striate hemorrhages, cotton wool spots, and papilledema, the characteristic findings of hypertensive neuroretinopathy (HNR), which are indicative of the presence

Table 15-3.	Identifiable Causes of Hypertension
Metabolic syndrome (obesity, insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension)	
Obstructive sleep apnea	
Drug-induced hypertension (Table 15-7)	
Chronic kidney disease	
Primary hyperaldosteronism	
Renovascular disease	
Chronic steroid use or Cushing's syndrome	
Pheochromocytoma	
Coarctation of the aorta	
Thyroid or parathyroid disease	

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of malignant hypertension. Documentation of the presence of arteriosclerotic retinopathy (e.g., arteriolar narrowing, arteriovenous crossing changes, changes in light reflexes) is less important, given its lack of prognostic significance with regard to the potential long-term cardiovascular complications of hypertension. Examination of the neck for carotid bruits, distended neck veins, and thyromegaly is important. Cardiac examination should include investigation for abnormalities of rate or rhythm, murmurs, and third or fourth heart sounds. The lungs should be examined for rales and evidence of bronchospasm. Abdominal examination should include auscultation for bruits (an epigastric bruit present in both systole and diastole suggests renal artery stenosis), abdominal or flank masses (polycystic kidney disease), or increased aortic pulsation (abdominal aortic aneurysm). Peripheral pulses should be examined for quality and bruits. The lower extremities should be examined for edema. A neurologic screening examination is used to identify prior cerebrovascular events. Routine laboratory tests are recommended before the initiation of antihypertensive therapy to identify other risk factors and screen for the presence of target organ damage. These routine tests include blood chemistry (sodium, potassium, creatinine, fasting glucose), lipid profile [total cholesterol, low-density lipoprotein) and high-density lipoprotein (HDL) cholesterol], and a complete blood cell count. Creatinine clearance should be estimated using either the Cockcroft-Gault or the Modification of Diet in Renal Disease (MDRD) formulae. A urinalysis is used to identify proteinuria or hematuria that would suggest the presence of

underlying primary renal disease. A 12-lead electrocardiogram is used to identify left atrial enlargement, LVH, or prior MI. Optional tests, depending on the clinical situation, include 24-hour creatinine clearance, 24-hour urine protein or a spot urine protein to creatinine ratio, serum uric acid, glycosylated hemoglobin, and thyroid function tests. An echocardiogram to identify the presence of LVH may be useful in selected patients to determine the clinical significance of labile hypertension. Most patients with hypertension have primary (essential) hypertension in which no clearly definable underlying etiology is apparent.

In contrast, a wide variety of uncommon conditions can lead to so-called **secondary hypertension**, some of which are potentially amenable to surgical correction (Table 15-3). Secondary causes of hypertension include underlying chronic kidney disease (CKD), primary hyperaldosteronism (PHA), pheochromocytoma, renovascular hypertension due to fibromuscular dysplasia or atherosclerotic renal artery stenosis, coarctation of the aorta, and Cushing's syndrome. Secondary causes of hypertension amenable to surgical intervention are so uncommon that extensive diagnostic testing is not warranted. Secondary hypertension should be considered when the patient has onset of hypertension at an early age (younger than 30 years) or late age (older than 55 years); inadequate BP control in a compliant patient on a three-drug regimen which includes a diuretic (resistant hypertension); previously well-controlled hypertension becomes uncontrolled in a compliant patient; hematuria or proteinuria (underlying renal disease) or elevated serum creatinine (renal disease or ischemic nephropathy due to bilateral renal artery stenosis). The initial history, physical examination, and routine laboratory tests are usually all that is required to evaluate for the possibility of secondary hypertension. A normal estimated creatinine clearance and urinalysis are usually sufficient to exclude underlying renal disease as a secondary cause of hypertension. Detection of abdominal or flank masses may indicate polycystic kidney disease, a diagnosis that can be confirmed with ultrasound. Because most patients with PHA have unprovoked hypokalemia while not on diuretic therapy, a measurement of serum potassium is a suitable screening test, and routine measurement of aldosterone levels or plasma aldosterone/renin ratio is not necessary. However, some patients with PHA are normokalemic (when not receiving diuretic therapy). Although routine screening of all patients with hypertension for PHA is not warranted, in a patient with drug-resistant hypertension or significant hypokalemia induced by low-dose diuretic therapy, the possibility of PHA should be considered. In this regard, patients with resistant hypertension due to PHA often have a dramatic BP response following the initiation of a mineralocorticoid antagonist (spironolactone or eplerenone). Assessment for any delay or diminution of pulses in the lower extremities, or a discrepancy between arm and leg BP can be used to screen for coarctation of the aorta. A careful assessment of a history of episodic hypertension, associated with headache, palpitations, diaphoresis, and pallor, is all that is usually required to screen for pheochromocytoma. The routine measurement of serum or urine catecholamines is not warranted. Likewise, evaluation for truncal obesity and abdominal purple striae is all that is usually required to screen for Cushing's syndrome; therefore, routine measurement of serum cortisol or cortisol suppression testing is unnecessary. Several tests are notably absent from the recommended list of routine screening tests for secondary hypertension. Hypertensive intravenous pyelography, renal scanning, captopril renography, and arterial digital subtraction angiography all lack sufficient specificity to be

of any value as routine screening tests for renovascular hypertension. In this regard, the prevalence of renovascular hypertension in the general hypertensive population is so low that the predictive value of a positive test from any of these procedures is abysmal when used as a general screening test.

Obstructive sleep apnea (OSA) is now recognized as an important treatable cause of hypertension. Clues to the presence of OSA include morbid obesity, daytime hypersomnolence, headache, snoring, or fitful sleep. The diagnosis can be confirmed with a sleep study to document apneic episodes. Appropriate treatment with a continuous positive airway pressure device may result in a significant reduction in BP.

VI. TREATMENT OF HYPERTENSION

A. Goals of Treatment. The goal of treating hypertension is the reduction of cardiovascular and renal morbidity and mortality. Because SBP correlates best with target organ damage and mortality, the primary focus should be on achieving the SBP goal. The goal of treatment is a SBP less than 140 mmHg and a DBP less than 90 mmHg. In hypertensive patients with diabetes or underlying CKD, a BP goal of less than 130/80 mmHg is recommended.

B. Nonpharmacologic Treatment. Lifestyle modification is recommended in the management of all individuals with hypertension, even in those who require antihypertensive drug treatment. All patients should be encouraged to adopt the lifestyle modifications outlined in Table 15-4, especially if they have additional cardiovascular risk factors such as hyperlipidemia or diabetes. Modest weight reduction of as little as 4 kg (10 lb) significantly reduces BP. In addition to the positive effects on overall health, regular aerobic exercise is associated with a significant reduction in BP.

Changes in diet can have significant effects on BP. Dietary sodium intake in the form of sodium chloride (NaCl; table salt) has a strong epidemiologic link to hypertension. Meta-analysis of clinical trials indicates that the limitation of dietary sodium intake to 75 to 100 mEq/day lowers BP over a period of several weeks to a few years. The restriction of sodium intake has been shown to reduce the need for antihypertensive medication, reduce diuretic-induced renal potassium wasting, lead to regression of LVH, and prevent renal stones through a reduction in renal calcium excretion. The average American dietary sodium intake is in excess of 150 mEq/day, most of which (75%) is derived from processed foods. Moderation of sodium intake to a level of less than 100 mEq/day (2.4 g of sodium or 6 g of sodium chloride) is recommended for the nonpharmacologic treatment of hypertension.

The Dietary Approaches to Stop Hypertension (DASH) study group compared a diet rich in fruits and vegetables to a control diet in patients with mild diastolic hypertension (DBP $>$ 95 mmHg). The DASH diet lowered both SBP and DBP significantly in this population. A follow-up study, the DASH-sodium study, randomized patients with stage 1 hypertension to the DASH diet or a control diet. Within each group, patients were randomized to three levels of sodium intake. Sodium reduction decreased BP and the DASH diet decreased BP at all levels of sodium

Table 15-4. Lifestyle Modifications to Manage Hypertension

Modification	Recommendation	Approximate SBP Reduction
Weight loss	Maintain normal weight (BMI[a] 18.5–24.9)	5–20 mmHg/10 kg
Dietary sodium restriction	Limit dietary sodium intake to <100 mEq/d (2.4 g sodium or 6 g sodium chloride)	2–8 mmHg
Adopt DASH diet	Consume diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mmHg
Increase physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/d, most days of the week)	4–9 mmHg
Moderate alcohol consumption	Limit consumption to no more than two drinks per day (1 oz or 30 mL ethanol per d; e.g., 24 oz beer, 10 oz wine, 3 oz 80-proof whiskey) in most men, and no more than one drink per day in women and lighter-weight men	2–4 mmHg

BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; SBP, systolic blood pressure.
[a]BMI is calculated as weight in kilograms divided by the square of height in meters.
Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003;289:2560–2572.

intake. Patients in the low-sodium DASH group had an SBP that was 8 mmHg lower than patients in the high-sodium control group, a change similar to that seen with antihypertensic agents.

Excessive intake of ethanol is an important risk factor for high BP, and it can lead to resistant hypertension. Ethanol intake should be limited to not more than 30 mL (1 oz) per day in men and 15 mL (0.5 oz) per day in women and lighter-weight men. This type of moderate ethanol intake may be associated with a reduction in the risk of coronary heart disease.

Smoking cessation and reductions in dietary fat and cholesterol are also recommended to reduce the overall cardiovascular risk. Although caffeine

may acutely raise BP, tolerance to this effect develops quickly. Most epidemiologic studies have found no direct relationship between caffeine intake and BP.

C. Pharmacologic Treatment of Hypertension. The decision to treat hypertension with medications after the failure of lifestyle modifications to adequately control BP, or initially as an adjunct to lifestyle modifications, is based on the severity (stage) of hypertension and an assessment of the risk of cardiovascular morbidity, given the presence of other cardiovascular risk factors and preexisting target organ damage or cardiovascular disease (Table 15-2). Reducing BP with drugs clearly decreases cardiovascular morbidity and mortality regardless of age, gender, race, stage of hypertension, or socioeconomic status. Benefit has been demonstrated for stroke, coronary events, heart failure, progression of primary renal disease, prevention of progression to malignant hypertension, and all-cause mortality. Numerous clinical trials have demonstrated that lowering BP with several classes of drugs, including thiazide-type diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), β-blockers, and calcium channel blockers (CCBs), reduces all the complications of hypertension.

If therapy with one agent is begun, the recommendation of JNC 7 is that most patients with essential hypertension should be treated with a thiazide-type diuretic (Fig. 15-2). These recommendations are based on several long-term studies, the largest of which is the pivotal Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT studied 41,000 patients over 55 years old with stage 1 or 2 hypertension and with at least one other cardiovascular risk factor. The patients received first-line treatment with chlorthalidone (thiazide-type diuretic), doxazosin (selective α-blocker), amlodipine (CCB), or lisinopril (ACE inhibitor). In this study, 47% of patients were women, 35% were black, 19% were Hispanic, 36% were diabetic, and the mean BMI was approximately 30. The doxazosin arm was terminated prematurely because of an excess risk of CHF. After a mean follow-up of 4.9 years, neither the primary clinical outcome (fatal coronary heart disease or nonfatal MI) nor the secondary outcomes of all-cause mortality, combined coronary heart disease, peripheral arterial disease, cancer, or ESRD had occurred more often in the chlorthalidone group than in the amlodipine or lisinopril groups. Furthermore, event rates were significantly lower in the chlorthalidone group than in one or both of the other groups for some of the secondary outcomes (Table 15-5). As expected, patients in the chlorthalidone group developed higher cholesterol levels, lower serum potassium levels, and higher fasting blood glucose levels than patients in the other groups. Nonetheless, the presence of these metabolic abnormalities did not translate into more cardiovascular events or deaths in the chlorthalidone group. Diuretic therapy potentiates the antihypertensive effect of most other antihypertensive drugs. For this reason, the drug treatment algorithm outlined in JNC 7 recommends the addition of diuretic as a second-step agent if BP is inadequately controlled with any other drug chosen as a first-line agent. The mechanism of action of thiazide diuretics is to block sodium reabsorption by inhibiting the thiazide-sensitive NaCl cotransporter in the distal tubule. The sustained antihypertensive effect of thiazides, however, is mediated through a reduction in SVR rather than through chronic volume depletion and a reduction of cardiac output,

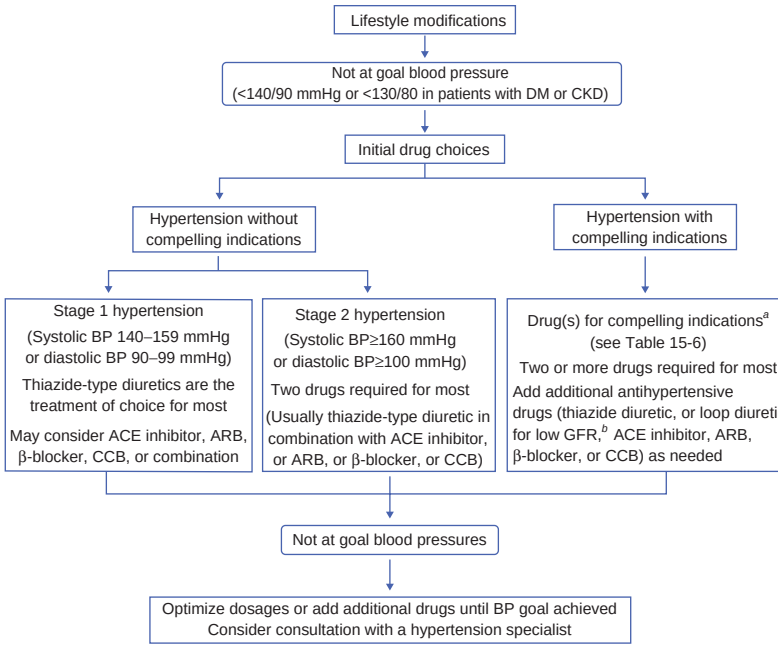

Figure 15-2. Algorithm for treatment of hypertension. [a]Compelling indications are special high-risk conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs: treatment of hypertension in the setting of diabetes, chronic kidney disease, heart failure, high coronary disease risk, post-MI, and for recurrent stroke prevention. [b]In the setting of advanced CKD with GFR less than 30 mL/minute or in patients with fluid overload unresponsive to thiazide diuretics, more potent loop diuretic therapy may be required. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; DM, diabetes mellitus; GFR, glomerular filtration rate.) (Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003;289:2560–2572.)

as one might predict. In fact, thiazides do not cause a large, sustained decrease in intravascular volume or negative sodium balance when used for the treatment of hypertension. Within a few days to weeks of the initiation of therapy with thiazide diuretics, salt balance returns toward normal, and total body sodium and intravascular volume returns toward pretreatment levels. This seeming paradox can be understood in the context of Guyton's hypothesis regarding the pathogenesis of hypertension, whereby the development of systemic hypertension is conceptualized as an essential protective mechanism to maintain normal fluid volume in various disease states in which an underlying renal impairment exists with regard to excreting the daily sodium load at a normal BP (Fig. 15-2). In this context, diuretics lower BP by addressing the primary renal defect in salt excretion, so that

Table 15-5. Results of the Antihypertensive Lipid-Lowering to Prevent Heart Attack Trial

Outcome	6-Yr incidence (%)		
	Chlorthalidone	Amlodipine	Lisinopril
Primary Outcome			
Coronary heart disease[a]	11.5	11.3	11.4
Secondary Outcomes			
All-cause mortality	17.3	16.8	17.2
Stroke	5.6	5.4	6.3[b]
Combined coronary heart disease[c]	19.9	19.9	20.8
Combined cardiovascular disease[d]	30.9	32.0	33.3[b]
Angina	12.1	12.6	13.6[b]
Coronary revascularization	9.2	10.0	10.2[b]
Heart failure	7.7	10.2[b]	8.7[b]
End-stage renal disease	1.8	2.1	2.0
Cancer	9.7	10.0	9.9

[a]Fatal coronary heart disease or nonfatal myocardial infarction.
[b]$p \leq 0.05$.
[c]Combined coronary heart disease death, nonfatal myocardial infarction, coronary revascularization, and hospitalized angina.
[d]Combined coronary heart disease death, nonfatal myocardial infarction, coronary revascularization, angina, heart failure, and peripheral arterial disease.
Adapted with permission from The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981–2997.

systemic hypertension (high SVR) is no longer a prerequisite for maintaining sodium balance. It should be noted that in ALLHAT and most clinical trials, achievement of the desired BP goal often requires treatment with two or more antihypertensive agents. Addition of a second drug from a different class should be implemented when use of a single drug in optimal doses fails to adequately control BP.

An alternative approach to initial therapy has been proposed by the European Society of Hypertension. The recent 2013 guidelines state that reducing BP is more important than the specific agent. In most trials comparing different agents, there are no significant differences in outcomes if achieved BP is the same. For example, in ALLHAT, although there were benefits in some secondary outcomes with chlorthalidone, there was also a significantly lower BP in the chlorthalidone group.

Since the publication of the ALLHAT study and the JNC 7 recommendations, data from the ACCOMPLISH trial have challenged the role of diuretics as first-line agents in patients with essential hypertension. The ACCOMPLISH trial enrolled over 11,000 patients with hypertension and high cardiac risk and randomized them to either benazepril-amlodipine or benazepril-hydrochlorothiazide. After 3 years, the patients in the benazepril-amlodipine were less likely to reach the primary endpoint.

Given the above data, in a patient with stage 1 hypertension, monotherapy with a thiazide is a reasonable option given the number of long-term randomized controlled trials supporting their use. Alternatively, as suggested by the ACCOMPLISH trial, one could consider a CCB or ACE inhibitor with the plan to add the other drug if BP is still not controlled. In stage 2 hypertension, at least one large trial supports ACE inhibitor and CCB over a diuretic but given the large amount of data supporting thiazides, a combination therapy with a diuretic would also be appropriate. Since control of hypertension is still suboptimal nationwide, focusing on achieved BP rather than specific agents is probably most important.

D. Treatment of Hypertension in Patients with Diabetes. Several large clinical trials have demonstrated that control of hypertension in patients with diabetes reduces diabetic complications and improves outcomes (Table 15-6). The United Kingdom Prospective Diabetes Study Group (UKPDS) compared tight BP control (SBP $<$ 150 mmHg) to control (SBP $>$ 180 mmHg) in 1,148 patients with diabetes and hypertension. Those in the lower BP group had fewer diabetic complications (retinopathy) and fewer diabetes-related deaths. The ADVANCE trial was a placebo-controlled study comparing perindopril-indapamide to placebo in over 11,000 diabetic patients. Patients mainly had stage 1 hypertension with an average entry SBP of 145 mmHg. The drug therapy was associated with a decrease in microvascular and macrovascular events as well as all-cause mortality.

The ideal initial antihypertensive in diabetic patients without nephropathy is not clear. The UKPDS and ADVANCE trials used ACE inhibitors (captopril or perindopril), atenolol, and indapamide. Post hoc analyses of diabetic subgroups in other large trials support diuretics and ACE inhibitors. In ALLHAT, diabetic patients had no significant difference for the primary outcome (fatal coronary heart disease or nonfatal MI) whether they were treated with amlodipine, lisinopril, or chlorthalidone.

The appropriate goal BP in diabetics has been the subject of many large trials. The Appropriate Blood Pressure Control in Diabetes (ABCD) study was a randomized prospective intervention clinical trial with 5 years of follow-up that examined the role of intensive (goal DBP 75 mmHg) versus standard (goal DBP 80 to 90 mmHg) BP control in 950 patients with type 2 diabetes. Within each BP treatment goal group, patients were

Table 15-6. Clinical Trial and Guideline Basis for Compelling Indications for Treatment with Individual Drug Classes

High-Risk Condition with Compelling Indication	Diuretic	β-Blocker	ACE Inhibitor	ARB	CCB	Aldosterone antagonist	Clinical trial basis[a]
Diabetes mellitus	■	■	■	■	■	—	ALLHAT, UKPDS, NKF Guideline, ADA Guideline
Chronic kidney disease	—	—	■	■	—	—	Captopril Trial, RENAAL, IDNT, REIN, AASK, NKF Guideline
Heart failure	■	■	■	■	—	■	ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES
High coronary disease risk	■	■	■	—	■	—	ALLHAT, HOPE, ANBP2, LIFE, CONVINCE
Postmyocardial infarction	—	■	■	—	—	■	ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS
Recurrent stroke prevention	■	—	■	—	—	—	PROGRESS

AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; AIRE, Acute Infarction Ramipril Efficacy; ALLHAT, Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, angiotensin receptor blocker; BHAT, β-Blocker Heart Attack Trial; CCB, calcium channel blocker; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Irbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension Study; MERIT-HF, Metoprolol CR/SL Randomized Intervention Trial in Congestive Heart Failure; MI, myocardial infection; NKF, National Kidney Foundation; PROGRESS, Perindopril Protection against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Noninsulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT, Valsartan Heart Failure Trial.

[a]Compelling indications for certain classes of antihypertensive drugs are based on proven benefit from outcome studies or existing clinical practice guidelines. The compelling indication must be managed in parallel with blood pressure. Patients with these high-risk conditions usually require combination treatment with two to three additional antihypertensive drugs from different classes in order to achieve the recommended blood pressure treatment goal.

Adapted from Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003;289:2560–2572.

randomly assigned to treatment with a long-acting dihydropyridine CCB (nisoldipine) or an ACE inhibitor (enalapril). In hypertensive diabetic subjects enrolled in the ABCD study, a significant decrease in mortality was found in the intensive BP control group compared with the standard BP control group. In normotensive diabetic patients, intensive BP control also resulted in significant slowing of the progression of nephropathy (as assessed by urinary albumin excretion) and retinopathy, and was associated with fewer strokes. This occurred independently whether the initial BP treatment was with enalapril or nisoldipine. Importantly, significantly fewer MIs occurred in patients with diabetes allocated to initial therapy with the ACE inhibitor enalapril. The ABCD results indicate that intensive BP control reduces all-cause mortality in diabetic patients and that ACE inhibitor therapy should be preferred over CCB therapy as part of the multidrug regimen often required for intensive treatment of hypertension in diabetic patients. Data from the Hypertension Optimal Treatment (HOT) trial support the target BP of the ABCD trial. HOT randomized patients to three goal DBPs: less than 90, 85, or 80 mmHg. Amongst the 1,501 patients with diabetes in the trial, a DBP $<$80 mmHg was associated with the fewest cardiovascular events.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial randomized 4,733 diabetic patients at high cardiovascular risk to two different BP goals—SBP of 120 versus 140 mmHg. After 4 years, there was no difference in the primary endpoint of death. However, the lower BP group did have a lower rate of strokes but a higher rate of adverse events, such as hypotension and elevation in serum creatinine. Thus, less than 130/80 mmHg, as in the ABCD study, may be optimal in diabetic patients.

E. Treatment of Hypertension in Patients with Cardiac Disease. LVH is an independent risk factor for subsequent cardiovascular disease. Regression of LVH occurs with aggressive BP management using all classes of drugs except the direct-acting vasodilators such as hydralazine and minoxidil. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial compared losartan to atenolol in over 9,000 patients with electrocardiogram evidence of LVH. Both therapies caused regression in LVH but the losartan group had significantly greater reduction in LVH as compared to the atenolol group. Ischemic heart disease is a common form of target organ damage in hypertension. In patients with hypertension and stable angina pectoris, the treatment regimen should include a β-blocker or, alternatively, a long-acting CCB. In patients with acute coronary syndromes (unstable angina or acute MI), hypertension should be treated initially with β-blockers and ACE inhibitors, with the addition of other agents such as thiazide diuretics as needed for BP control. In the chronic BP management of post-MI patients, β-blockers, ACE inhibitors, and aldosterone receptor antagonists have proven to be of highest benefit. In patients with ischemic heart disease, low-dose aspirin therapy and intensive lipid-lowering therapy are also indicated. Heart failure represents another special hypertensive patient population; it can occur in the setting of either systolic or diastolic dysfunction. In asymptomatic patients with LV dysfunction, ACE inhibitors and β-blockers are recommended. In patients with symptomatic heart failure or end-stage heart disease, ACE inhibitors, β-blockers, ARBs, and

aldosterone receptor blockers (spironolactone or eplerenone) are recommended, along with potent loop diuretics as needed for fluid overload.

F. Treatment of Hypertension in the Elderly. The treatment of elderly patients with predominant systolic hypertension should follow the same treatment algorithm. In the Systolic Hypertension in the Elderly Program (SHEP) trial, a double-blind placebo-controlled trial of low-dose chlorthalidone in patients older than 60 years with isolated systolic hypertension (SBP greater than 160 mmHg with DBP less than 90 mmHg), the relative risks (RRs) of stroke, left ventricular failure, nonfatal MI or fatal coronary heart disease, and the requirement for coronary artery bypass grafting were all significantly reduced in the active treatment group. The Hypertension in the Very Elderly Trial (HYVET) studied patients over 80 years of age. Over 3,000 patients were assigned to either indapamide-perindopril or placebo with a target SBP in the treatment group of less than 150 mmHg. The primary endpoint was stroke and fatal stroke; the treatment group had a 30% reduction in stroke, 39% reduction in fatal stroke, and 20% reduction in rate of death from any cause. Due to the risks of orthostatic hypotension and falls, selective α-blockers should be avoided in the treatment of older individuals with hypertension.

G. Treatment of Hypertension in Patients with Metabolic Syndrome. Long-term studies comparing different antihypertensive classes solely in hypertensive patients with metabolic syndrome have not been done. In the past, concerns have often been raised that diuretics should not be used as first-line therapy for hypertension because they have unfavorable effects on insulin sensitivity and increase the risk of new-onset diabetes, thereby having the potential to adversely affect cardiovascular and renal outcomes. A retrospective analysis of ALLHAT compared different antihypertensive classes in patients with metabolic syndrome. The metabolic syndrome is a clustering of clinical and biochemical characteristics related to insulin resistance and hyperinsulinemia. It is characterized by hypertension, central obesity, dyslipidemia (high triglycerides and low HDL cholesterol levels), and elevated glucose levels. In study participants with metabolic syndrome, at 4 years of follow-up, the incidence of newly diagnosed diabetes (fasting glucose greater than 126 mg/dL) was 17.1% for chlorthalidone, 16.0% for amlodipine ($p = 0.49$ versus chlorthalidone), and 12.6% for lisinopril ($p < 0.05$ versus chlorthalidone). For those without metabolic syndrome, the rate of newly diagnosed diabetes was 7.7% for chlorthalidone, 4.2% for amlodipine, and 4.7% for lisinopril ($p < 0.05$ for both drugs versus chlorthalidone). Among participants with metabolic syndrome, the RRs for the primary outcome (fatal coronary heart disease or nonfatal MI) and the secondary cardiovascular outcomes were not different for amlodipine versus chlorthalidone. However, the risk of heart failure was higher in participants without metabolic syndrome treated with amlodipine [RR for amlodipine versus chlorthalidone, 1.55; 95% confidence interval (CI), 1.25 to 1.35]. In participants with metabolic syndrome, outcomes were superior with chlorthalidone versus lisinopril for heart failure (RR 1.31; 95% CI, 1.04 to 1.64) and for the combined cardiovascular disease endpoint (coronary heart disease, stroke, treated angina, and heart failure; RR, 1.19; 95% CI, 1.07 to 1.32). The authors concluded that despite a less favorable metabolic profile, and a higher risk of new-onset diabetes, thiazide-like diuretics are

the preferred initial treatment for hypertension in older individuals with the metabolic syndrome, compared with ACE inhibitors and CCBs.

H. Treatment of Hypertension in Patients with CKD. The Kidney Disease Improving Global Outcomes (K-DIGO) recommendations regarding BP control in kidney disease were recently released. In nondiabetic patients with nonproteinuric kidney disease (<300 mg/day), they recommend treating patients to a goal BP <140/90 mm Hg and did not specify an antihypertensive trial. Evidence for this BP goal comes from long-term follow-up of patients in the African American Study of Kidney Disease and Hypertension (AASK) trial. For one component of the study, AASK study randomized patients with hypertension and CKD to two goal BPs—mean arterial pressure (MAP) 92 or 102 mmHg. During the trial, the low BP group had a mean BP of 130/78 mm Hg and the other group had a BP of 141/86 mm Hg. After 9 years of follow-up, there was no difference in outcomes in patients with little proteinuria. The MDRD study did show a benefit with lower BP goals. The MDRD study also randomized nondiabetics with CKD to two different BP goals. In the low BP goal group, the achieved BP was 126/77 mm Hg, and in the other group, the BP was 134/81 mm Hg. The patients in the low BP group were less likely to reach the primary endpoint of renal failure or mortality; however, the patients in the low BP group were more likely to receive ACE inhibitors.

According to the K-DIGO guidelines, patients with nondiabetic kidney disease and proteinuria should be treated to a goal BP of 130/80 mm Hg, preferably with an ACE inhibitor or an ARB. Support for the BP goal comes from follow-up of the AASK study. Patients with significant proteinuria were much more likely to reach the endpoint in the AASK study, which was a composite of doubling of serum creatinine, ESRD, or death. Amongst these high-risk patients, the lower BP goal significantly reduced the risk of meeting the endpoint.

Treating proteinuric patients with ACE inhibitors or ARBs has significant experimental and clinical support. Since ACE inhibitors and ARBs decrease efferent arteriolar tone, they should decrease intraglomerular hypertension. In the Benazepril trial, patients already in reasonable BP control were randomized to treatment with benazepril or placebo. Patients on benazepril had a greater reduction in BP and a 25% reduction in protein excretion. The risk of progression to a primary endpoint (doubling of serum creatinine or progression to dialysis) was reduced by 53% in the benazepril-treated patients. The benefits of ACE inhibitor therapy were seen mainly in patients with chronic glomerular diseases or diabetic nephropathy, whereas there was no benefit in patients with polycystic kidney disease or other CKD excreting less than 1 g of protein per day. These are settings in which hemodynamically mediated factors may not be as important in disease progression. In the Ramipril Efficacy in Nephropathy (REIN) trial, patients with nondiabetic renal disease were randomized to ramipril or placebo plus other antihypertensive therapy as needed to achieve DBP below 90 mmHg. The trial was terminated prematurely among patients excreting more than 3 g protein per day because of a significant benefit with ACE inhibitor treatment with regard to ameliorating the rate of decline of renal function. Although the final results of the AASK trial showed no difference among the drug treatment groups in the rate of decline of GFR, the ramipril group had

a 22% reduction in risk of the composite endpoint (reduction in GFR by more than 50% from baseline, ESRD, or death). In the REIN-2 trial, dihydropyridine CCB failed to provide renoprotection in patients with nondiabetic renal disease, despite further reduction of BP from that obtained with fixed doses of ACE inhibitors. The nondihydropyridine CCBs (diltiazem and verapamil) have antiproteinuric effects, whereas the dihydropyridines (amlodipine and nifedipine) have been shown to increase proteinuria in some studies. This paradox may be explained by the varied effect of the different classes of CCBs on renal autoregulation. In this regard, dihydropyridines cause preferential afferent arteriolar dilation, which allows more of the systemic pressure to be transmitted to the glomerulus, thereby increasing glomerular pressure and limiting their antiproteinuric effect.

In diabetic patients with CKD and without proteinuria, K-DIGO recommends treatment to goal BP of less than 140/90 mm Hg. The two trials upon which this recommendation is based are the previously mentioned ABCD and ACCORD trials. Tighter BP control than 140/90 mm Hg is associated with some cardiovascular benefits but, as seen in the ACCORD study, is also associated with possible harm. In proteinuric diabetic nephropathy, K-DIGO recommends a goal BP of 130/80 mm Hg and treatment with an ACE inhibitor or ARB. If this BP goal is not achieved after initial therapy with an ACE inhibitor or an ARB, a diuretic should be added to the regimen. Addition of a diuretic is logical therapy given the central role of impaired natriuresis in the pathogenesis of hypertension in the setting of CKD. Thiazide diuretics may be effective in the early stages of CKD, whereas loop diuretics may be necessary in patients with more advanced kidney disease or diuretic resistance in the setting of nephrotic syndrome.

I. Treatment of the Patient with Resistant Hypertension. Resistant hypertension is defined as a failure to reach BP less than 140/90 mmHg in an adherent patient treated with a three-drug regimen including a diuretic. Providers must first ensure that the patient has resistant hypertension by following all of the steps above regarding the diagnosis of hypertension (Section V). Truly resistant hypertension should prompt an investigation for underlying potentially treatable forms of secondary hypertension (Table 15-3). Table 15-7 outlines other causes of resistant hypertension. Currently, an experimental therapy known as renal denervation is showing promise as a treatment for resistant hypertension. Renal denervation is performed via percutaneous catheterization of the renal arteries. Radiofrequency ablation is applied 4 to 6 times per renal artery. A recent study, Symplicity-HTN 2, was a phase II trial done in patients with resistant hypertension. On average, patients had a fall in BP of 32/12 mmHg at a 6-month follow-up. The therapy is still experimental in the United States and larger studies are ongoing. Consultation with a hypertension specialist should be considered if the BP goal cannot be achieved.

VII. HYPERTENSIVE CRISES

A. Definition of Hypertensive Crises. The vast majority of hypertensive patients are asymptomatic for many years until complications due to atherosclerosis, cerebrovascular disease, or CHF supervene. In a minority of patients, this "benign" course is punctuated by a hypertensive crisis. A hypertensive crisis is defined as the turning point in the course of an illness

Table 15-7.	Causes of Resistant Hypertension
Improper blood pressure (BP) measurement (use of inadequately sized BP cuff in obese patients)	
Pseudohypertension in elderly individuals	
White coat (office) hypertension	
Volume overload or pseudotolerance	
Excess dietary sodium intake	
Fluid retention from underlying renal disease	
Inadequate diuretic therapy (failure to use loop diuretic with advanced CKD)	
Noncompliance	
Patient nonadherence with therapy due to ignorance, cost, or side effects	
Physician noncompliance (inadequate drug dosage or failure to include diuretic in regimen)	
Drug induced	
Nonsteroidal anti-inflammatory agents or cyclooxygenase 2 inhibitors	
Cocaine, amphetamines, or other illicit drugs	
Sympathomimetics (decongestants or anoretic agents)	
Oral contraceptives	
Adrenal steroids	
Erythropoietin	
Licorice	
Over-the-counter dietary supplements (ephedra, ma huang, bitter orange)	
Excessive alcohol consumption	
Identifiable secondary causes of hypertension (Table 15-3)	

CKD, chronic kidney disease.

at which acute management of the elevated BP plays a decisive role in the eventual outcome. The haste with which the BP must be controlled varies with the type of hypertensive crisis. However, the crucial role of hypertension in the disease process must be identified and a plan for managing the

BP successfully implemented if the patient's outcome is to be optimal. The absolute level of the BP is clearly not the most important factor in determining the existence of a hypertensive crisis. For example, in children, pregnant women, and other previously normotensive individuals in whom mild to moderate hypertension develops suddenly, a hypertensive crisis can occur at a BP level that is normally well tolerated by adults with chronic hypertension. Furthermore, in adults with mild to moderate hypertension, a crisis can occur with the onset of acute end-organ dysfunction involving the heart or brain. Table 15-9 outlines the spectrum of hypertensive crises.

B. Malignant hypertension is a clinical syndrome characterized by a marked elevation of BP with widespread acute arteriolar injury (hypertensive vasculopathy). Funduscopy reveals HNR with flame-shaped hemorrhages, cotton wool spots (soft exudates), and sometimes papilledema (Fig. 15-3, Table 15-8). Regardless of the severity of BP elevation, in the absence of HNR, malignant hypertension cannot be diagnosed. HNR is therefore an extremely important clinical finding, indicating the presence of a hypertension-induced arteriolitis that may involve the kidneys, heart, and central nervous system. With malignant hypertension, a rapid and relentless progression to ESRD occurs if effective BP control is not implemented. Mortality can result from acute hypertensive heart failure, intracerebral hemorrhage, hypertensive encephalopathy, or complications of uremia. Malignant hypertension represents a hypertensive crisis; adequate control of BP clearly prevents these morbid complications.

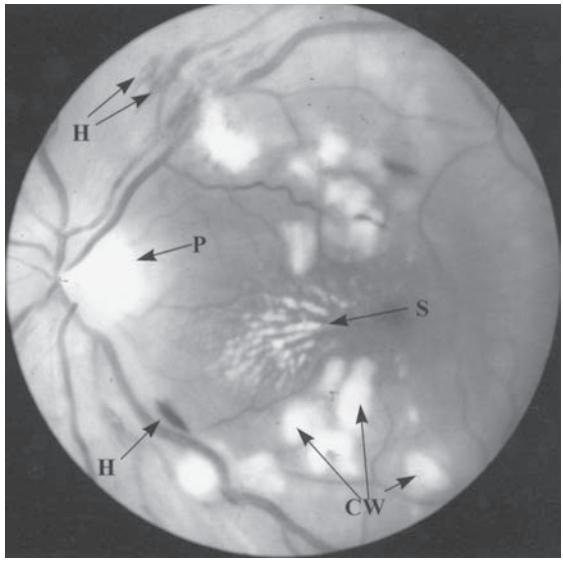

Figure 15-3. Hypertensive neuroretinopathy in malignant hypertension. Fundus photograph in a 30-year-old man with malignant hypertension demonstrates all the characteristic features of hypertensive neuroretinopathy, including striate hemorrhages (*H*), cotton wool spots (*CW*), papilledema (*P*), and a star figure at the macula (*S*).

Table 15-8. Classification of Hypertensive Retinopathy
Retinal Arteriosclerosis and Arteriosclerotic Retinopathy (Characteristic of Benign Hypertension)
Arteriolar narrowing (focal or diffuse)
Arteriovenous crossing changes
Broadening of the arteriolar light reflex
Copper or silver wiring changes
Perivasculitis
Solitary round retinal hemorrhages
Hard exudates
Central or branch venous occlusion
Hypertensive Neuroretinopathy (Sine Qua Non of Malignant Hypertension)
Generalized arteriolar narrowing
Striate (flame-shaped hemorrhages)[a]
Cotton wool spots (soft exudates)[a]
Bilateral papilledema[a]
Star figure at the macula
[a]These features distinguish retinal arteriosclerosis (benign hypertension) from hypertensive neuroretinopathy (malignant hypertension). Adapted with permission from Nolan CR. Malignant hypertension and other hypertensive crises. In: Schrier RW, ed. *Diseases of the kidney and urinary tract*, 8th ed. Boston, MA: Lippincott Williams & Wilkins, 2007:1370–1436.

C. Hypertensive Crises Due to Nonmalignant Hypertension with Acute Complications. Even in patients with benign hypertension, in whom HNR is absent, a hypertensive crisis may be diagnosed based on the presence of concomitant acute end-organ dysfunction (Table 15-9). Hypertensive crises due to nonmalignant hypertension with acute complications include hypertension accompanied by hypertensive encephalopathy, acute hypertensive heart failure, acute aortic dissection, intracerebral hemorrhage, subarachnoid hemorrhage, severe head trauma, acute MI or unstable angina, and active bleeding. Poorly controlled hypertension in a patient requiring surgery increases the risk of intraoperative cerebral or myocardial ischemia and postoperative acute renal failure. Severe postoperative hypertension, including post-coronary artery bypass hypertension

Table 15-9.	Spectrum of Hypertensive Crises
Malignant hypertension (*hypertensive neuroretinopathy present*)	
Hypertensive encephalopathy (*occurs with either malignant or severe benign hypertension*)	
Nonmalignant ("benign") hypertension with acute complications (*acute end-organ dysfunction in the absence of hypertensive neuroretinopathy*)	
Acute hypertensive heart failure (pulmonary edema due to acute diastolic dysfunction)	
Acute coronary syndromes	
Acute myocardial infarction	
Unstable angina	
Acute aortic dissection	
Central nervous system catastrophe	
Hypertensive encephalopathy	
Intracerebral hemorrhage	
Subarachnoid hemorrhage	
Severe head trauma	
Catecholamine excess states	
Pheochromocytoma crisis	
Monoamine oxidase inhibitor–tyramine interactions	
Antihypertensive drug withdrawal syndromes	
Phenylpropanolamine overdose	
Preeclampsia and eclampsia	
Active bleeding (including postoperative bleeding)	
Poorly controlled hypertension in patients requiring emergency surgery	
Severe postoperative hypertension	
Post–coronary artery bypass hypertension	
Post–carotid endarterectomy hypertension	
Scleroderma renal crisis	
Autonomic hyperreflexia in quadriplegic patients	

Adapted from Nolan CR. Malignant hypertension and other hypertensive crises. In: Schrier RW, ed. *Diseases of the kidney and urinary tract,* 8th ed. Boston, MA: Lippincott Williams & Wilkins, 2007:1370–1436.

and post–carotid endarterectomy hypertension, increases the risk of postoperative bleeding, hypertensive encephalopathy, pulmonary edema, and myocardial ischemia. The various catecholamine excess states can cause a hypertensive crisis with hypertensive encephalopathy or acute hypertensive heart failure. Preeclampsia and eclampsia represent hypertensive crises that are unique to pregnancy. Scleroderma renal crisis is a hypertensive crisis in which failure to adequately control BP with a regimen that includes an ACE inhibitor results in rapid irreversible loss of renal function. Hypertensive crises can also occur in quadriplegic patients due to autonomic hyperreflexia induced by bowel or bladder distension. The sudden onset of hypertension in this setting can lead to hypertensive encephalopathy or acute pulmonary edema.

D. Treatment of Malignant Hypertension. Malignant hypertension must be treated expeditiously to prevent complications such as hypertensive encephalopathy, acute hypertensive heart failure, and renal failure. The traditional approach to patients with malignant hypertension has been the initiation of potent parenteral agents. In general, parenteral therapy should be used in patients with evidence of acute end-organ dysfunction (hypertensive encephalopathy or pulmonary edema) or those unable to tolerate oral medications. Nitroprusside or intravenous (IV) labetalol are the treatments of choice for patients requiring parenteral therapy. In general, reducing the mean arterial pressure by 20% or to a level of 160 to 170/100 to 110 mmHg is safe. The use of a short-acting agent such as nitroprusside has obvious advantages, because BP can quickly be stabilized at a higher level if complications develop during rapid BP reduction. If no evidence of vital organ hypoperfusion is apparent during the initial reduction, the BP can gradually be lowered to less than 140/90 mmHg over a period of 12 to 36 hours. Oral antihypertensive agents should be initiated as soon as possible to minimize the duration of parenteral therapy. The infusion can be weaned as the oral agents become effective. The cornerstone of initial oral therapy should be arteriolar vasodilators such as hydralazine or minoxidil. β-Blockers are required to control reflex tachycardia, and a diuretic must be initiated within a few days to prevent salt and water retention in response to vasodilator therapy when the patient's dietary salt intake increases. Diuretics may not be necessary as a part of initial parenteral therapy, because patients with malignant hypertension often present with volume depletion due to pressure-induced natriuresis. Although many patients with malignant hypertension definitely require initial parenteral therapy, some patients may not yet have evidence of cerebral or cardiac dysfunction or rapidly deteriorating renal function and therefore do not require instantaneous control of BP. These patients can often be managed with an intensive oral regimen, often with a β-blocker and minoxidil, designed to bring the BP under control within 12 to 24 hours. After the immediate crisis has resolved and the hypertension has been controlled with initial parenteral therapy, oral therapy, or both, lifelong surveillance of BP is mandatory. If control lapses, malignant hypertension can recur even after years of successful antihypertensive therapy. Triple therapy with a diuretic, a β-blocker, and a vasodilator is often required to maintain satisfactory long-term BP control.

E. Treatment of Other Hypertensive Crises. Sodium nitroprusside is the drug of choice for the management of virtually all hypertensive crises outlined in Table 15-9, including malignant hypertension, hypertensive encephalopathy, acute hypertensive heart failure, intracerebral hemorrhage, perioperative hypertension, catecholamine-related hypertensive crises, and acute aortic dissection (in combination with β-blockers). IV labetalol is also an appropriate treatment for most hypertensive crises. Intravenous nitroglycerin may also be useful in patients with concomitant myocardial ischemia, because it dilates intracoronary collaterals.

Sodium nitroprusside is a potent intravenous hypotensive agent with an immediate onset and brief duration of action. The site of action is the vascular smooth muscle. It has no direct action on the myocardium, although it may indirectly affect cardiac performance through alterations in systemic hemodynamics. Nitroprusside is an iron-coordination complex with five cyanide moieties and a nitroso group. The nitroso group combines with cysteine to form nitrosocysteine, a potent activator of guanylate cyclase that causes cyclic guanosine monophosphate (cGMP) accumulation and the relaxation of vascular smooth muscle. Nitroprusside causes vasodilation of both arteriolar resistance vessels and venous capacitance vessels. Its hypotensive action is a result of decrease in SVR. The combined decrease in preload and afterload reduces myocardial wall tension and myocardial oxygen demand. The net effect of nitroprusside on cardiac output and heart rate depends on the intrinsic state of the myocardium. In patients with left ventricular systolic dysfunction and elevated left ventricular end-diastolic pressure, it causes an increase in stroke volume and cardiac output as a result of afterload reduction. Heart rate may actually decrease in response to improved cardiac performance. In contrast, in the absence of left ventricular dysfunction, venodilation and preload reduction can result in a reflex increase in sympathetic tone and heart rate. For this reason, nitroprusside must be used in conjunction with a β-blocker in acute aortic dissection.

The hypotensive action of nitroprusside appears within seconds and is immediately reversible when the infusion is stopped. The cGMP in vascular smooth muscle is rapidly degraded by cGMP-specific phosphodiesterases. Nitroprusside is rapidly metabolized, with a half-life of 3 to 4 minutes. Cyanide is formed, as a short-lived intermediate product, by direct combination with sulfhydryl groups in red blood cells and tissues. The cyanide groups are rapidly converted to thiocyanate by the liver, in a reaction in which thiosulfate acts as a sulfur donor. Thiocyanate is excreted by the kidney, with a half-life of 1 week in patients with normal renal function. Thiocyanate accumulation and toxicity can occur when a high dose or prolonged infusion is required, especially in patients with renal insufficiency. When these risk factors are present, thiocyanate levels should be monitored and the infusion stopped if the level is more than 10 mg/dL. Thiocyanate toxicity is rare in patients with normal renal function requiring less than 3 μg/kg/minute for less than 72 hours. Cyanide poisoning is a very rare complication, unless hepatic clearance of cyanide is impaired by severe liver disease, or massive doses of nitroprusside (more than 10 μg/kg/minute) are used to induce deliberate hypotension during surgery. Once the hypertensive crisis has resolved and the BP is

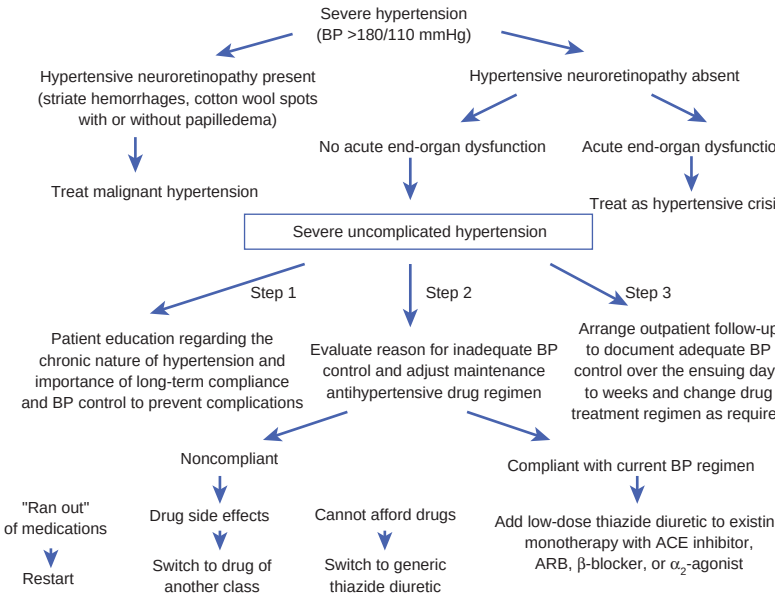

Figure 15-4. Algorithm for treatment of severe uncomplicated hypertension. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker.) (Adapted with permission from Nolan CR. Hypertensive crises. In: Schrier RW, ed. *Atlas of diseases of the kidney*, Vol. 3. Philadelphia, PA: Current Medicine, 1999.)

adequately controlled, oral antihypertensive therapy should be initiated. The nitroprusside infusion is weaned as the oral antihypertensive agents become effective.

F. Treatment of Severe Uncomplicated Hypertension in the Acute Care Setting. The benefits of acute reduction in BP in the setting of true hypertensive crisis are obvious (Fig. 15-4). Fortunately, true hypertensive crises are relatively rare events that never affect the vast majority of hypertensive patients. Much more common than true hypertensive crisis is the patient who presents with markedly elevated BP (greater than 180/100 mmHg) in the absence of HNR (malignant hypertension) or acute end-organ damage that would signify a true crisis. This entity, known as *severe uncomplicated hypertension*, is very common in the emergency department or other acute care settings. Of patients with severe uncomplicated hypertension, 60% are entirely asymptomatic and present for prescription refills or routine BP checks, or are found to have elevated pressure during routine physical examinations. The other 40% present with nonspecific findings such as headache, dizziness, or weakness in the absence of evidence of acute end-organ dysfunction.

In the past, this entity was referred to as *urgent hypertension*, reflecting the erroneous notion that an acute reduction of BP over a few hours before discharge from the acute care facility was essential to minimize the

risk of short-term complications from severe hypertension. Commonly used treatment regimens included oral clonidine loading or sublingual nifedipine. However, the practice of acute BP reduction in severe uncomplicated hypertension is no longer considered the standard of care. The Veterans Administration Cooperative Study of patients with severe hypertension included 70 placebo-treated patients who had an average DBP of 121 mmHg at entry. Among these untreated patients, 27 experienced morbid events at a mean of 11 (±2) months of follow-up. However, the earliest morbid event occurred after 2 months. These data suggest that in patients with severe uncomplicated hypertension in which severe hypertension is not accompanied by evidence of malignant hypertension or acute end-organ dysfunction, eventual complications due to stroke, MI, or heart failure tend to occur over a time frame of months to years rather than hours to days. Although the long-term control of BP can clearly prevent these eventual complications, a hypertensive crisis cannot be diagnosed, because no evidence indicates that the acute reduction of BP results in an improvement in short- or long-term prognosis. Although the acute reduction of BP in patients with severe uncomplicated hypertension using sublingual nifedipine or oral clonidine loading was once the de facto standard of care, this practice was often an emotional response on the part of the treating physician to the dramatic elevation of BP, or it was motivated by the fear of medicolegal repercussions in the unlikely event of a hypertensive complication occurring within hours to days. Observing and documenting the dramatic fall in BP is a satisfying therapeutic maneuver, but no scientific basis for this approach exists. No literature supports the notion that some goal level of BP reduction must be achieved before the patient with severe uncomplicated hypertension leaves the acute care setting. In fact, the acute reduction of BP is often counterproductive, because it can produce untoward side effects that render the patient less likely to comply with long-term drug therapy. Instead, the acute therapeutic intervention should focus on tailoring an effective, well-tolerated maintenance antihypertensive regimen, with patient education regarding the chronic nature of the disease process and the importance of long-term compliance and medical follow-up. If the patient has simply run out of medicines, reinstitution of the previously effective drug regimen should suffice. If the patient is thought to be compliant with an existing drug regimen, a sensible change in the regimen, such as an increase in a suboptimal dosage of an existing drug or the addition of a drug of another class, is appropriate. In this regard, the addition of a low dose of a thiazide diuretic as a second-step agent to existing monotherapy with ACE inhibitor, ARB, CCB, β-blocker, or central α-agonist is often remarkably effective. Another essential goal of the acute intervention should be to arrange suitable outpatient follow-up within a few days. A gradual reduction of BP to normotensive levels over a few days to a week should be accomplished in conjunction with frequent outpatient visits to modify the drug regimen and reinforce the importance of lifelong compliance with therapy. Although less dramatic than the acute reduction of BP in the acute care setting, this type of approach to the treatment of chronic hypertension is more likely to prevent long-term hypertensive complications and recurrent episodes of severe uncomplicated hypertension.

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16 Practical Guidelines for Drug Dosing in Patients with Impaired Kidney Function

Ali Olyaei and William M. Bennett

Decreased renal function, regardless of etiology, presents significant challenges to prescribing providers. Additional considerations when selecting and dosing medications for patients with renal dysfunction include comorbidities (hypertension, diabetes, heart disease, advanced age) and the multiple drugs used to manage those conditions. These factors highlight the critical importance of establishing baseline kidney function prior to initiating new medication regimens, as well as appropriately frequent monitoring of renal function throughout the course of medication management. Monitoring therapeutic plasma concentration, if possible, is an important consideration. However, for many pharmacotherapeutic agents, plasma concentration cannot be monitored in the clinical setting. Thus, it is important for health care providers to understand the relationship between reduced or impaired renal function, pharmacokinetics and appropriate drug selection and dosing protocol for specific disease state.

Properly functioning kidneys facilitate homeostasis required for optimal cellular and metabolic functioning through regulating solute and water transport, excreting metabolic waste products, conserving nutrients, and balancing acids and bases. These functional components play integral roles in the absorption, distribution, metabolism, and especially the excretion of medications and metabolites. Chronic kidney disease (CKD) and in particular uremic state influences every organ system and every aspect of drug disposition. The physiological changes associated with CKD are not limited only to drugs with high renal excretion; in fact, renal disease has pronounced effects on the pharmacology of many drugs. Any significant decrease in kidney function, as indicated by a glomerular filtration rate (GFR), presents therapeutic drug selection and dosing challenges. Decreased GFR is commonly seen in elderly patients and obviously in patients with acute kidney injury (AKI) and CKD.

While many prescribers realize that CKD-related decreases in renal function and end-stage renal disease (ESRD) significantly alter the pharmacokinetics and pharmacodynamics of many medications, there is an increased awareness that many more patients are affected by poor renal function than previously thought. Therefore, establishing baseline renal function, as well as systematic and ongoing assessment of renal function on all appropriate patients throughout the therapeutic regimen is necessary in order to avoid further damage to the kidneys, as well as to achieve the desired clinical outcome for the patient.

Decreases in age-related renal function are caused primarily by a decrease in patient size, blood flow, and subsequently GFR. With changes in renal vasculature

and profusion, the number of nephrons also decreases. The speed of this loss accelerates as the patient progresses to ESRD. The kidneys also undergo degenerative changes that decrease the ability of the kidneys to concentrate urine. In addition, the injured kidney loses its ability to adapt to various stresses; glucose, sodium, and bicarbonate are not reabsorbed as efficiently, and because of decreased rates of secretion, hyperkalemia can occur more commonly. Acid–base balance is more difficult to maintain, changes in pH and fluid load can lead to critical imbalances that can lead to and exacerbate toxicity in medications that are metabolized and eliminated via renal processes.

CHRONIC KIDNEY DISEASE AND DRUG PHARMACOKINETIC

Absorption

Drug absorption in CKD is affected by possible increases in gastric pH, gastroparesis, bowel wall edema, vomiting and diarrhea, and decreasing intestinal CYP450 activity. In general, it is difficult to assess the effect of CKD on drug absorption as many of these patients take multiple medications, many of which cannot be discontinued or withheld to study the alterations in absorption of other drugs. Medications taken by CKD patients to manage these conditions, such as antacids, proton pump inhibitors, and H2 receptor antagonists, also impact other drug's absorption. Increased gastric pH decreases the absorption, and therefore the bioavailability of drugs that are more readily absorbed in an acidic environment. Taking antacids can also decrease drug absorption, especially of tetracyclines and fluoroquinolones, through chelation of those components into insoluble compounds. Gastroparesis, or delayed gastric emptying, is common in CKD patients, and can increase the amount of time needed to achieve maximum drug concentrations, although this appears to only impact very short-acting medications. Also, bowel wall edema, vomiting, and diarrhea can decrease overall drug absorption in CKD patients. Lastly, renal insufficiency is linked with decreased gastrointestinal (GI) CYP450 activity. This can drastically increase the amount of drug absorbed by significantly reducing the amount of drug metabolized via CYP450 in the GI tract.

Distribution

Drug distribution in CKD patients is affected by alterations in fluid states and changes in the extent of protein binding in plasma, which impacts therapeutic drug concentrations, and tissue binding, which affects volume of distribution. Patients with advanced renal insufficiency are commonly uremic and have low plasma albumin levels. Acidic drugs are most significantly affected by hypoalbuminemia because of increased competition for available binding sites. This can lead to both accumulation of other medications and metabolites while also increasing levels of free drug in the plasma, which can also lead to toxicity or conversely to more drug undergoing biotransformation, resulting in decreased drug action. Fluid status and overall body composition are also significantly impacted by CKD and are important considerations when choosing and dosing drugs. Prescribers must be aware that volume of distribution will change in patients with ascites, edema, and overall hydration status, especially with hydrophilic drugs. Increased adipose tissue and decreased lean muscle mass, or patients with muscle wasting, is also common for elderly patients and CKD patients. These changes in body composition can reduce the volume of distribution, thereby increasing serum levels of hydrophilic drugs.

Metabolism

Metabolism of both renal and nonrenal metabolized drugs and metabolites is significantly slowed in patients with renal impairment. This can lead to accumulation of drugs, pharmacologically active agents, as well as toxic metabolites and can lead to significant adverse events. When a drug undergoes biotransformation, an active drug metabolite is a frequent by-product. These metabolites have an effect and action, and while the initial drug may be effectively excreted via urine, the still-active metabolite can easily accumulate to potentially dangerous levels, causing adverse clinical outcomes. CKD also impacts drug metabolism through impaired CYP450 activities in both Phase I and Phase II reactions, which are necessary for drugs to undergo predictable biotransformation and subsequent therapeutic outcomes.

Elimination

Drug elimination of drug and active metabolites is dependent on several aspects of renal functioning; GFR, tubular secretion, and reabsorption. Drug elimination via glomerular filtration in CKD patients occurs in relation to the patient's level of GFR, the amount of free drug compared with the amount of drug bound to protein. CKD patients also experience decreased tubular secretion, as well as reduced medication reabsorption, which is indicated by higher levels of urine concentrations of renally eliminated drugs. Finally, it is important to review that renal insufficiency slows the elimination of active drug metabolites, which are still biologically active, and when they reach a certain level of accumulation can cause adverse clinical outcomes. For many drugs, the kidneys are the primary route for drug elimination within the body. CKD reduces glomerular filtration and can be assessed by creatinine clearance. To calculate renal function or adjust for drug elimination, the following calculations are recommended when determining creatinine clearance for those adults with stable renal function.

Cockcroft-Gault (CG) equation

CrCl (mL/min) = [(140 − age) × Weight in kg]/(serum creatinine × 72) × (0.85 if female)
Ideal body weight (IBW) was used unless actual body weight (ABW) < IBW. If ABW was >30% of IBW, adjusted body weight was used where:

adjusted body weight = [(ABW − IBW) × 0.4] + IBW.
IBWmale = 50 + 2.3 × (Height in inches – 60);
IBWfemale = 45.5 + 2.3 × (Height in inches – 60)

For obese men and women the equation should be modified:

$$\text{(obese men)} = \frac{(137 - \text{age}) \times [(0.285 \times \text{wgt}) + (12.1 \times \text{hgt}^2)]}{51 \times \text{SCr}}$$

$$\text{(obese women)} = \frac{(146 - \text{age}) \times [(0.287 \times \text{wgt}) + (9.74 \times \text{hgt}^2)]}{60 \times \text{SCr}}$$

wgt = patient's weight in kg
hgt = patient's height in cm

Modification of Diet in Renal Disease re-expressed equation (MDRD)

eGFR MDRD = 175 × SCr − 1.154 × Age − 0.203 × (0.742 if female) × (1.21 if AA)
AA refers to African American

Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)

eGFR CKD-EPI= 141 × min(SCr/κ, 1)α × max(SCr/κ, 1) − 1.209 × 0.993 Age × 1.018 [if female] × 1.159 [if African American], where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

It is very important to mention that these equations can only be applied in patients with stable renal function. Thus, during AKI, the serum creatinine or creatinine clearance will no longer reflect the true renal or drug clearance rate. In these cases, other methods should be applied (a timed urine collection) to estimate renal function. Finally, in oliguric patients, the creatinine clearance should be considered as less than 5 mL/minute.

One of the main limitations of the newer available GFR estimation equations (CKD-EPI and MDRD) is the lack of information about drug dosing in CKD. For obese and older patients, growing evidence suggests that the Cockcroft-Gault equation is superior to the other GFR estimates obtained by use of the MDRD and CKD-EPI. For all these equations, the recognition of the limitations of these estimation equations is essential when considering for drug dosing in kidney impairment.

DRUG DOSING IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Selecting and dosing drugs for patients with CKD is a significant clinical challenge and requires close coordination between the patient, the prescriber, and the pharmacist. A comprehensive initial assessment of the patient, including liver function tests, serum albumin levels, allergies, degree of renal functioning, fluid status, in addition to all medications, over the counter and prescribed, allergies and comorbidities, is paramount. The review of the patient's medication list at this time is to ensure a clinical valid reason for maintaining that therapy and to ensure that medications are not a causal agent in the patient's decreased renal functioning. If additional drugs are needed, it is critical to choose the least nephrotoxic drug available and to work closely with the pharmacist to select the appropriate loading and maintenance doses. Finally, frequent monitoring of drug levels when available and of renal function is critical to ensure protection of remaining kidney function (Table 16-1). There are two methods for dosage adjustment in patients with reduced renal function: prolonged interval or reduced dose. Prolonging the dose interval is often a convenient and cost-effective method for altering the drug dose in patients with renal impairment. This method is particularly useful for drugs with wide therapeutic ranges and long plasma half-lives. Extended parenteral therapy can be completed without prolonged hospitalization when the dose interval can safely be lengthened to allow for home therapy. If the range between the therapeutic and toxic levels is too narrow, either potentially toxic or subtherapeutic plasma concentrations may result.

To maintain the same dose interval as for patients with normal renal function, one may decrease the amount of each individual dose given to renal impaired patients. This method is effective for drugs with narrow therapeutic ranges and short plasma half-lives in patients with renal insufficiency. In practice, a combination of the methods is often effective and convenient. The combination method uses modification of both the dose and dose interval. For drugs with particularly long half-lives in patients with impaired renal function, give the total daily dose as a single dose each day. Similarly, divide the total daily dose in half and give twice daily. The decision to extend the dosing interval beyond a 24-hour period should be based on the necessity

Table 16-1. Therapeutic Drug Monitoring in Patients with Chronic Kidney Disease

Drug Name	Therapeutic Range	When to Draw Sample	How Often to Draw Levels
Aminoglycosides (conventional dosing) Gentamicin, Tobramycin, Amikacin	Gentamicin and Tobramycin: Trough: 0.5–2 mg/L Peak: 5–8 mg/L Amikacin: Peak: 20–30 mg/L Trough: <10 mg/L	Trough: Immediately prior to dose Peak: 30 min after a 30–45 min infusion	Check peak and trough with third dose For therapy less than 72 h, levels not necessary. Repeat drug levels weekly or if renal function changes
Aminoglycosides (24-h dosing) Gentamicin, Tobramycin, Amikacin	0.5–3 mg/L	Obtain random drug level 12 h after dose	After initial dose, repeat drug level in 1 week or if renal function changes
Carbamazepine	4–12 μg/mL	Trough: Immediately prior to dosing	Check 2–4 days after first dose or change in dose
Cyclosporin	150–400 ng/mL	Trough: Immediately prior to dosing	Daily for first week, then weekly
Digoxin	0.8–2.0 ng/mL	12 h after maintenance dose	5–7 days after first dose for patients with normal renal and hepatic function; 15–20 days in anephric patients
Lidocaine	1–5 μg/mL	8 h after i.v. infusion started or changed	
Lithium	Acute: 0.8–1.2 mmol/L Chronic: 0.6–0.8 mmol/L	Trough: Before a.m. dose at least 12 h since last dose	
Phenobarbital	15–40 μg/mL	Trough: Immediately prior to dosing	Check 2 weeks after first dose or change in dose. Follow-up level in 1–2 months

(*continued*)

Table 16-1. (Continued)

Drug Name	Therapeutic Range	When to Draw Sample	How Often to Draw Levels
Phenytoin Free Phenytoin	10–20 μg/mL 1–2 μg/mL	Trough: Immediately prior to dosing	5–7 day after first dose or after change in dose
Procainamide NAPA (n-acetyl procainamide), a procainamide metabolite	4–10 μg/mL Trough: 4 μg/mL Peak: 8 μg/mL 10–30 μg/mL	Trough: Immediately prior to next dose or 12–18 h after starting or changing an infusion Draw with procainamide sample	
Quinidine	1–5 μg/mL	Trough: Immediately prior to next dose	
Sirolimus	10–20 ng/dL	Trough: Immediately prior to next dose	
Tacrolimus (FK-506)	10–15 ng/mL	Trough: Immediately prior to next dose	Daily for first week, then weekly
Theophylline p.o. or Aminophylline i.v.	15–20 μg/mL	Trough: Immediately prior to next dose	
Valproic acid (divalproex sodium)	40–100 μg/mL	Trough: Immediately prior to next dose	Check 2–4 d after first dose or change in dose
Vancomycin	Trough: 5–15 mg/L Peak: 25–40 mg/L	Trough: Immediately prior to dose Peak: 60 min after a 60 min infusion	With third dose (when initially starting therapy, or after each dosage adjustment). For therapy less than 72 h, levels not necessary. Repeat drug levels if renal function changes

to maintain therapeutic peak or trough drug levels. When the peak level is most important, prolong the dose interval. However, when the minimum trough level must be maintained, modification of the individual dose or a combination of the dose and interval methods may be preferred. The following tables provide information about drug dosing in several categories in patients with CKD.

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Antimicrobial Dosing in Renal Failure

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Aminoglycoside antibiotics						Nephrotoxic. Ototoxic. Toxicity worse when hyperbilirubinemic. Measure serum levels for efficacy and toxicity. Peritoneal absorption increases with presence of inflammation. Volume of distribution (Vd) increases with edema, obesity, and ascites
Streptomycin	7.5 mg/kg q12h (1.0 g q24h for tuberculosis)	60%	q24h	q24–72h	q72–96h	For the treatment of tuberculosis. May be less nephrotoxic than other members of class
Kanamycin	7.5 mg/kg q8h	50–90%	60–90% q12h or 100% q12–24h	30–70% q12–18h or 100% q24–48h	20–30% q24–48h or 100% q48–72h	Nephrotoxic. Ototoxic. Toxicity worse when hyperbilirubinemic. Vd increases with edema, obesity, and ascites. Do not use once-daily dosing in patients with creatinine clearance less than 30–40 mL/min or in patients with acute renal failure or uncertain level of kidney function
Gentamicin	1.7 mg/kg q8h	95%	60–90% q8–12h or 100% q12–24h	30–70% q12h or 100% q24–48h	20–30% q24–48h or 100% q48–72h	Concurrent penicillins may result in subtherapeutic aminoglycoside levels. Peak 6–8, trough <2

Tobramicin	1.7 mg/kg q8h	95%	60–90% q8–12h or 100% q12–24h	30–70% q12h or 100% q24–48h	20–30% q24–48h or 100% q48–72h	Concurrent penicillins may result in subtherapeutic aminoglycoside levels. Peak 6–8, trough <2
Netilmicin	2 mg/kg q8h	95%	50–90% q8–12h or100% q12–24h	20–60% q12h or 100% q24–48h	10–20% q24–48h or 100% q48–72h	May be less ototoxic than other members of class. Peak 6–8, trough <2
Amikacin	7.5 mg/kg q12h	95%	60–90% q12h or 100% q12–24h	30–70% q12–18h or 100% q24–48h	20–30% q24–48h or 100% q48–72h	Monitor levels. Peak 20–30, trough <5
Cephalosporin						Coagulation abnormalities, transitory elevation of blood urea nitrogen, rash and serum sickness-like syndrome
Oral Cephalosporin						
Cefaclor	250–500 mg tid	70%	100%	100%	50%	
Cefadroxil	500 mg–1 g bid	80%	100%	100%	50%	
Cefixime	200–400 mg q12h	85%	100%	100%	50%	
Cefpodoxime	200 mg q12h	30%	100%	100%	100%	

(*continued*)

Antimicrobial Dosing in Renal Failure (Continued)						
Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Ceftibuten	400 mg q24h	70%	100%	100%	50%	
Cefuroxime axetil	250–500 mg tid	90%	100%	100%	100%	Malabsorbed in presence of H2 blockers. Absorbed better with food
Cephalexin	250–500 mg tid	95%	100%	100%	100%	Rare allergic interstitial nephritis. Absorbed well when given intraperitoneally. May cause bleeding from impaired prothrombin biosynthesis
Cephradine	250–500 mg tid	100%	100%	100%	50%	Rare allergic interstitial nephritis. Absorbed well when given intraperitoneally. May cause bleeding from impaired prothrombin biosynthesis.
IV Cephalo-Sporin						
Cefamandole	1–2 g IV q6–8h	100%	q6h	q8h	q12h	
Cefazolin	1–2 g IV q8h	80%	q8h	q12h	q12–24h	
Cefepime	1–2 g IV q8h	85%	q8–12h	q12h	q24h	
Cefmetazole	1–2 g IV q8h	85%	q8h	q12h	q24h	

Cefoperazone	1–2 g IV q12h	20%	No renal adjustment is required			Displaced from protein by bilirubin. Reduce dose by 50% for jaundice. May prolong prothrombin time
Cefotaxime	1–2 g IV q6–8h	60%	q8h	q12h	q12–24h	Active metabolite in ESRD. Reduce does further for combined hepatic and renal failure
Cefotetan	1–2 g IV q12h	75%	q12h	q12–24h	q24h	
Cefoxitin	1–2 g IV q6h	80%	q6h	q8–12h	q12h	May produce false increase in serum creatinine by interference with assay
Ceftazidime	1–2 g IV q8h	70%	q8h	q12h	q24h	
Ceftriaxone	1–2 g IV q24h	50%	No renal adjustment is required			
Cefuroxime sodium	0.75–1.5 g IV q8h	90%	q8h	q8–12h	q12–24h	Rare allergic interstitial nephritis. Absorbed well when given intraperitoneally. May cause bleeding from impaired prothrombin biosynthesis
Penicillin						Bleeding abnormalities, hypersensitivity, seizures
Oral Penicillin						
Amoxicillin	500 mg p.o. tid	60%	100%	100%	50–75%	
Ampicillin	500 mg p.o. q6h	60%	100%	100%	50–75%	

(*continued*)

Antimicrobial Dosing in Renal Failure (Continued)						
Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Dicloxacillin	250–500 mg p.o. q6h	50%	100%	100%	50–75%	
Penicillin V	250–500 mg p.o. q6h	70%	100%	100%	50–75%	
IV Penicillin						
Ampicillin	1–2 g IV q6h	60%	q6h	q8h	q12h	
Nafcillin	1–2 g IV q4h	35%	No renal adjustment is required			
Penicillin G	2–3 million units IV q4h	70%	q4–6h	q6h	q8h	Seizures. False-positive urine protein reactions. Six million units/d upper limit dose in ESRD
Piperacillin	3–4 g IV q4–6h		No renal adjustment is required			Specific toxicity: Sodium, 1.9 mEq/g
Ticarcillin/ clavulanate	3.1 g IV q4–6h	85%	1–2 g q4h	1–2 g q8h	1–2 g q12h	Specific toxicity: Sodium, 5.2 mEq/g
Piperacillin/ tazobactam	3.375 g IV q6–8h	75–90%	q4–6h	q6–8h	q8h	Specific toxicity: Sodium, 1.9 mEq/g

Quinolones						Photosensitivity, food, dairy products, tube feeding, and Al(OH)3 may decrease the absorption of quinolones
Cinoxacin	500 mg q12h	55%	100%	50%	Avoid	
Fleroxacin	400 mg q12h	70%	100%	50–75%	50%	
Ciprofloxacin	200–400 mg IV q24h	60%	q12h	q12–24h	q24h	Poorly absorbed with antacids, sucralfate, and phosphate binders. Intravenous dose 1/3 of oral dose. Decreases phenytoin levels
Lomefloxacin	400 mg q24h	76%	100%	200–400 mg q48h	50%	Agents in this group are malabsorbed in the presence of magnesium, calcium, aluminum, and iron. Theophylline metabolism is impaired. Higher oral doses may be needed to treat CAPD peritonitis
Levofloxacin	500 mg p.o. qd	70%	q12h	250 q12h	250 q12h	L-isomer of ofloxacin: appears to have similar pharmacokinetics and toxicities
Moxifloxacin	400 mg qd	20%	No renal adjustment is required			
Nalidixic acid	1.0 g q6h	High	100%	Avoid	Avoid	Agents in this group are malabsorbed in the presence of magnesium, calcium, aluminum, and iron. Theophylline metabolism is impaired. Higher oral doses may be needed to treat CAPD peritonitis

(*continued*)

Antimicrobial Dosing in Renal Failure (Continued)						
Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Norfloxacin	400 mg p.o. q12h	30%	q12h	q12–24h	q24h	See above
Ofloxacin	200–400 mg p.o. q12h	70%	q12h	q12–24h	q24h	See above
Pefloxacin	400 mg q24h	11%	100%	100%	100%	Excellent bidirectional transperitoneal movement
Sparfloxacin	400 mg q24h	10%	100%	50–75%	50% q48h	
Trovafloxacin	200–300 mg p.o. q12h	10%	No renal adjustment is required			
Miscellaneous Agents						
Azithromycin	250–500 mg p.o. qd	6%	No renal adjustment is required			No drug–drug interaction with Cyclosporine/Tacrolimus (CSA/FK)
Clarithromycin	500 mg p.o. bid					20%
Clindamycin	150–450 mg p.o. tid	10%	No renal adjustment is required			Increase CSA/FK level

Dirithromycin	500 mg p.o. qd		No renal adjustment is required			Nonenzymatically hydrolyzed to active compound erythromycylamine
Erythromycin	250–500 mg p.o. qid	15%	No renal adjustment is required			Increase CSA/FK level, avoid in transplant patients
Imipenem/ Cilastatin	250–500 mg IV q6h	50%	500 mg q8h	250–500 q8–12h	250 mg q12h	Seizures in ESRD. Nonrenal clearance in acute renal failure is less than in chronic renal failure. Administered with cilastatin to prevent nephrotoxicity of renal metabolite
Meropenem	1 g IV q8h	65%	1 g q8h	0.5–1 g q12h	0.5–1 g q24h	
Metronidazole	500 mg IV q6h	20%	No renal adjustment is required			Peripheral neuropathy, increase LFTs, disulfiram reaction with alcoholic beverages
Pentamidine	4 mg/kg/day	5%	q24h	q24h	q48h	Inhalation may cause bronchospasm, IV administration may cause hypotension, hypoglycemia, and nephrotoxicity
Trimethoprim/ sulfamethoxazole	800/160 mg p.o. bid	70%	q12h	q18h	q24h	Increase serum creatinine. Can cause hyperkalemia

(*continued*)

Antimicrobial Dosing in Renal Failure (Continued)

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Vancomycin	1 g IV q12h	90%	q12h	q24–36h	q48–72h	Nephrotoxic, ototoxic, may prolong the neuromuscular blockade effect of muscle relaxants. Peak 30, trough 5–10
Vancomycin	125–250 mg p.o. qid	0%	100%	100%	100%	Oral vancomycin is indicated only for the treatment of *C. difficile*
Antituberculosis Antibiotics						
Rifampin	300–600 mg p.o. qd	20%	No renal adjustment is required			Decrease CSA/FK level. Many drug interactions
Antifungal Agents						
Amphotericin B	0.5–1.5 mg/kg/day	<1%	No renal adjustment is required			Nephrotoxic, infusion-related reactions, give 250 cc NS before each dose
Amphotec	4–6 mg/kg/day	<1%	No renal adjustment is required			
Abelcet	5 mg/kg/day	<1%	No renal adjustment is required			
AmBisome	3–5 mg/kg/day	<1%	No renal adjustment is required			

Azoles and Other Antifungals						Increase CSA/FK level
Fluconazole	200–800 mg IV qd/bid	70%	100%	100%	50%	
Flucytosine	37.5 mg/kg	90%	q12h	q16h	q24h	Hepatic dysfunction. Marrow suppression more common in azotemic patients
Griseofulvin	125–250 mg q6h	1%	100%	100%	100%	
Itraconazole	200 mg q12h	35%	100%	100%	50%	Poor oral absorption
Ketoconazole	200–400 mg p.o. qd	15%	100%	100%	100%	Hepatotoxic
Miconazole	1,200–3,600 mg/day	1%	100%	100%	100%	
Terbinafine	250 mg p.o. qd	>1%	100%	100%	100%	
Voriconazole	4 mg/kg q12h	>1%	100%	100%	100%	IV use should be limited for only few doses in patients with CrCl <30 mL/min

(*continued*)

Antimicrobial Dosing in Renal Failure (Continued)						
Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Antiviral Agents						
Acyclovir	200–800 mg p.o. 5×/day	50%	100%	100%	50%	Poor absorption. Neurotoxicity in ESRD. Intravenous preparation can cause renal failure if injected rapidly
Adefovir	10 mg	45%	100%	10 mg q48h	10 mg q72h	Nephrotoxic
Amantadine	100–200 mg q12h	90%	100%	50%	25%	
Cidofovir	5 mg/kg weekly ×2 (induction). 5 mg/kg every 2 weeks	90%	No data: avoid	No data: avoid	No data: avoid	Dose-limiting nephrotoxicity with preteinuria, glycosuria, renal insufficiency—nephrotoxicity and renal clearance reduced with coadministration of probenecid
Delavirdine	400 mg q8h	5%	No data: 100%	No data: 100%	No data: 100%	
Didanosine	200 mg q12h (125 mg if <60 kg)	40–69%	q12h	q24h	50% q24h	Pancreatitis

Famciclovir	250–500 mg p.o. bid to tid	60%	q8h	q12h	q24h	VZV: 500 mg p.o. tid; HSV: 250 p.o. bid. Metabolized to active compound penciclovir
Foscarnet	40–80 mg IV q8h	85%	40–20 mg q8–24 h according to ClCr			Nephrotoxic, neurotoxic, hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia
Ganciclovir IV	5 mg/kg q12h	95%	q12h	q24h	2.5 mg/kg qd	Granulocytopenia and thrombocytopenia
Ganciclovir p.o.	1,000 mg p.o. tid	95%	1,000 mg tid	1,000 mg bid	1,000 mg qd	Oral ganciclovir should be used only for prevention of cytomegalovirus (CMV) infection. Always use IV ganciclovir for the treatment of CMV infection
Indinavir	800 mg q8h	10%	No data: 100%	No data: 100%	No data: 100%	Nephrolithiasis—acute renal failure due to crystalluria, tubulointerstitial nephritis
Lamivudine	150 mg p.o. bid	80%	q12h	q24h	50 mg q24h	For hepatitis B
Nelfinavir	750 mg q8h	No data	No data	No data	No data	
Nevirapine	200 mg q24h × 14d	<3%	No data: 100%	No data: 100%	No data: 100%	May be partially cleared by hemodialysis and peritoneal dialysis
Ribavirin	500–600 mg q12h	30%	100%	100%	50%	Hemolytic uremic syndrome

(*continued*)

Antimicrobial Dosing in Renal Failure (Continued)						
Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Rifabutin	300 mg q24h	5–10%	100%	100%	100%	
Rimantadine	100 mg p.o. bid	25%	100%	100%	50%	
Ritonavir	600 mg q12h	3.50%	No data: 100%	No data: 100%	No data: 100%	Many drug interactions
Saquinavir	600 mg q8h	<4%	No data: 100%	No data: 100%	No data: 100%	
Stavudine	30–40 mg q12h	35–40%	100%	50% q12–24h	50% q24h	
Valacyclovir	500–1,000 mg q8h	50%	100%	50%	25%	Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
Vidarabine	15 mg/kg infusion q24h	50%	100%	100%	75%	
Zanamivir	2 puffs bid × 5 days	1%	100%	100%	100%	Bioavailability from inhalation and systemic exposure to drug is low
Zalcitabine	0.75 mg q8h	75%	100%	q12h	q24h	
Zidovudine	200 mg q8h, 300 mg q12h	8–25%	100%	100%	100 mg q8h	Enormous interpatient variation. Metabolite renally excreted

Analgesic Drug Dosing in Renal Failure						
Analgesics	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Narcotics and Narcotic Antagonists						
Alfentanil	Anesthetic induction 8–40 μg/kg	Hepatic	100%	100%	100%	Titrate the dose regimen
Butorphanol	2 mg q3–4h	Hepatic	100%	75%	50%	
Codeine	30–60 mg q4–6h	Hepatic	100%	75%	50%	
Fentanyl	Anesthetic induction (individualized)	Hepatic	100%	75%	50%	Continuous Renal Replacement Therapy (CRRT)—titrate
Meperidine	50–100 mg q3–4h	Hepatic	100%	Avoid	Avoid	Normeperidine, an active metabolite, accumulates in ESRD and may cause seizures. Protein binding is reduced in ESRD. 20–25% excreted unchanged in acidic urine
Methadone	2.5–5 mg q6–8h	Hepatic	100%	100%	50–75%	Should not be used for acute pain

(*continued*)

Analgesic Drug Dosing in Renal Failure (Continued)						
			Dosage Adjustment in Renal Failure			
Analgesics	Normal Dosage	% of Renal Excretion	GFR >50	GFR 10–50	GFR <10	Comments
Morphine	20–25 mg q4h	Hepatic	100%	75%	50%	Increased sensitivity to drug effect in ESRD Active metabolites
Naloxone	2 mg IV	Hepatic	100%	100%	100%	
Pentazocine	50 mg q4h	Hepatic	100%	75%	75%	
Propoxyphene	65 mg p.o. q6–8h	Hepatic	100%	100%	Avoid	Active metabolite norpropoxyphene accumulates in ESRD Cardiotoxic
Sufentanil	Anesthetic induction	Hepatic	100%	100%	100%	CRRT—titrate
Nonnarcotics						
Acetaminophen	650 mg q4h	Hepatic	q4h	q6h	q8h	Overdose may be nephrotoxic. Drug is major metabolite of phenacetin
Acetylsalicylic acid	650 mg q4h	Hepatic (renal)	q4h	q4–6h	Avoid	Nephrotoxic in high doses. May decrease GFR when renal blood flow is prostaglandin dependent. May add to uremic GI and hematologic symptoms. Protein binding reduced in ESRD

Antihypertensive and Cardiovascular Agent Dosing in Renal Failure							
Antihypertensive and Cardiovascular Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
ACE inhibitors							Hyperkalemia, acute renal failure, angio-edema, rash, cough, anemia, and liver toxicity
Benazepril	10 mg qd	80 mg qd	20%	100%	75%	25–50%	
Captopril	6.25–25 mg p.o. tid	100 mg tid	35%	100%	75%	50%	Rare proteinuria, nephrotic syndrome, dysgeusia, granulocyto-penia. Increases serum digoxin levels
Enalapril	5 mg qd	20 mg bid	45%	100%	75%	50%	Enalaprilat, the active moiety formed in liver
Fosinopril	10 mg p.o. qd	40 mg bid	20%	100%	100%	75%	Fosinoprilat, the active moiety formed in liver. Drug less likely than other angiotensin-converting enzyme inhibitors to accumulate in renal failure

(*continued*)

Antihypertensive and Cardiovascular Agent Dosing in Renal Failure (Continued)

Antihypertensive and Cardiovascular Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Lisinopril	2.5 mg qd	20 mg bid	80%	100%	50–75%	25–50%	Lysine analog of a pharmacologically active enalapril metabolite
Pentopril	125 mg q24h	80–90%	100%	50–75%	50%		
Perindopril	2 mg q24h	<10%	100%	75%	50%		Active metabolite is perindoprilat. The clearance of perindoprilat and its metabolites is almost exclusively renal. Approximately 60% of circulating perindopril is bound to plasma proteins, and only 10–20% of perindoprilat is bound
Quinapril	10 mg qd	20 mg qd	30%	100%	75–100%	75%	Active metabolite is quinaprilat. 96% of quinaprilat is excreted renally

Ramipril	2.5 mg qd	10 bid	15%	100%	50–75%	25–50%	Active metabolite is ramiprilat. Data are for ramiprilat
Trandolapril	1–2 mg qd	4 mg qd	33%	100%	50–100%	50%	
Angiotensin-II-Receptor Antagonists							Hyperkalemia, angio-edema (less common than ACE inhibitors
Candesartan	16 mg qd	32 mg qd	33%	100%	100%	50%	Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan
Eprosartan	600 mg qd	400–800 mg qd	25%	100%	100%	100%	Eprosartan pharmacokinetics more variable ESRD. Decreased protein binding in uremia
Irbesartan	150 mg qd	300 mg qd	20%	100%	100%	100%	
Losartan	50 mg qd	100 mg qd	13%	100%	100%	100%	

(*continued*)

Antihypertensive and Cardiovascular Agent Dosing in Renal Failure (Continued)							
Antihypertensive and Cardiovascular Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Valsartan	80 mg qd	160 mg bid	7%	100%	100%	100%	
Telmisartan	20–80 mg qd		<5%	100%	100%	100%	
Beta blockers							Decrease HDL, mask symptoms of hypoglycemia, bronchospasm, fatigue, insomnia, depression, and sexual dysfunction
Acebutolol	400 mg q24h or bid	600 mg q24h or bid	55%	100%	50%	30–50%	Active metabolites with long half-life
Atenolol	25 mg qd	100 mg qd	90%	100%	75%	50%	Accumulates in ESRD
Betaxolol	20 mg q24h	80–90%	100%	100%	50%	50%	

Bopindolol	1 mg q24h	4 mg q24h	<10%	100%	100%	100%	
Carteolol	0.5 mg q24h	10 mg q24h	<50%	100%	50%	25%	
Carvedilol	3.125 mg p.o. tid	25 mg tid	2%	100%	100%	100%	Kinetics is dose dependent. Plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment
Celiprolol	200 mg q24h		10%	100%	100%	75%	
Dilevalol	200 mg bid	400 mg bid	<5%	100%	100%	100%	
Esmolol (IV only)	50 µg/kg/min	300 µg/kg/min	10%	100%	100%	100%	Active metabolite retained in renal failure
Labetalol	50 mg p.o. bid	400 mg bid	5%	100%	100%	100%	For IV use: 20 mg slow intravenous injection over a 2-min period. Additional injections of 40 or 80 mg can be given at 10-min intervals until a total of 300 mg or continuous infusion of 2 mg/min

(*continued*)

Antihypertensive and Cardiovascular Agent Dosing in Renal Failure (Continued)							
Antihypertensive and Cardiovascular Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Metoprolol	50 mg bid		100 mg bid	<5%	100%	100%	
Nadolol	80 mg qd	160 mg bid	90%	100%	50%	25%	Start with prolonged interval and titrate
Penbutolol	10 mg q24h	40 mg q24h	<10%	100%	100%	100%	
Pindolol	10 mg bid	40 mg bid	40%	100%	100%	100%	
Propranolol	40–160 mg tid	320 mg/day	<5%	100%	100%	100%	Bioavailability may increase in ESRD. Metabolites may cause increased bilirubin by assay interference in ESRD. Hypoglycemia reported in ESRD.

Sotalol	80 bid	160 mg bid	70%	100%	50%	25–50%	Extreme caution should be exercised in the use of sotalol in patients with renal failure undergoing hemodialysis. To minimize the risk of induced arrhythmia, patients initiated or re-initiated on BETAPACE® should be placed for a minimum of three days (on their maintenance dose) in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring.
Timolol	10 mg bid	20 mg bid	15%	100%	100%	100%	
Calcium Channel Blockers							Dihydropyridine: headache, ankle edema, gingival hyperplasia and flushing Nondihydropyridine: bradycardia, constipation, gingival hyperplasia and AV block

(*continued*)

Antihypertensive and Cardiovascular Agent Dosing in Renal Failure (Continued)							
Antihypertensive and Cardiovascular Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Amlodipine	2.5 p.o. qd	10 mg qd	10%	100%	100%	100%	May increase digoxin and cyclosporine levels.
Bepridil	No data	<1%	No data	No data	No data	Weak vasodilator and antihypertensive.	
Diltiazem	30 mg tid	90 mg tid	10%	100%	100%	100%	Acute renal dysfunction. May exacerbate hyperkalemia. May increase digoxin and cyclosporine levels.
Felodipine	5 mg p.o. bid	20 mg qd	1%	100%	100%	100%	May increase digoxin levels.
Isradipine	5 mg p.o. bid	10 mg bid	<5%	100%	100%	100%	May increase digoxin levels.

Nicardipine	20 mg p.o. tid		30 mg p.o. tid	<1%	100%	100%	Uremia inhibits hepatic metabolism. May increase digoxin levels.
Nifedipine XL	30 qd	90 mg bid	10%	100%	100%	100%	Avoid short-acting nifedipine formulation
Nimodipine	30 mg q8h		10%	100%	100%	100%	May lower blood pressure
Nisoldipine	20 mg qd	30 mg bid	10%	100%	100%	100%	May increase digoxin levels
Verapamil	40 mg tid	240 mg/d	10%	100%	100%	100%	Acute renal dysfunction. Active metabolites accumulate particularly with sustained-release forms.
Diuretics							Hypokalemia/hyperkalemia (potassium sparing agents), hyperuricemia, hyperglycemia, hypomagnesemia, increase serum cholesterol.

(*continued*)

Antihypertensive and Cardiovascular Agent Dosing in Renal Failure (Continued)							
Antihypertensive and Cardiovascular Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Acetazolamide	125 mg p.o. tid	500 mg p.o. tid	90%	100%	50%	Avoid	May potentiate acidosis. Ineffective as diuretic in ESRD. May cause neurologic side effects in dialysis patients.
Amiloride	5 mg p.o. qd	10 mg p.o. qd	50%	100%	100%	Avoid	Hyperkalemia with GFR <30 mL/min, especially in diabetics. Hyperchloremic metabolic acidosis.
Bumetanide	1–2 mg p.o. qd	2–4 mg p.o. qd	35%	100%	100%	100%	Ototoxicity increased in ESRD in combination with aminoglycosides. High doses effective in ESRD. Muscle pain, gynecomastia.
Chlorthalidone	25 mg q24h	50%	q24h	q24h	Avoid	Ineffective with low GFR	

Ethacrynic acid	50 mg p.o. qd	100 mg p.o. bid	20%	100%	100%	100%	Ototoxicity increased in ESRD in combination with aminoglycosides.
Furosemide	40–80 mg p.o. qd	120 mg p.o. tid	70%	100%	100%	100%	Ototoxicity increased in ESRD, especially in combination with amino-glycosides. High doses effective in ESRD.
Indapamide	2.5 mg q24h	<5%	100%	100%	Avoid	Ineffective in ESRD	
Metolazone	2.5 mg p.o. qd		10 mg p.o. bid	70%	100%	100%	High doses effective in ESRD. Gynecomastia, impotence.
Piretanide	6 mg q24h	12 mg q24h	40–60%	100%	100%	100%	High doses effective in ESRD. Ototoxicity.
Spironolactone	100 mg p.o. qd	300 mg p.o. qd	25%	100%	100%	Avoid	Active metabolites with long half-life. Hyperkalemia com-mon when GFR <30, especially in diabetics. Gynecomastia, hyper-chloremic acidosis. Increases serum by immunoassay interference.

(*continued*)

Antihypertensive and Cardiovascular Agent Dosing in Renal Failure (Continued)							
Antihypertensive and Cardiovascular Agents	**Normal Dosage**		**% of Renal Excretion**	**Dosage Adjustment in Renal Failure**			**Comments**
				GFR >50	**GFR 10–50**	**GFR <10**	
Thiazides	25 mg bid		50 mg bid	>95%	100%	100%	Avoid
Torasemide	5 mg p.o. bid	20 mg qd	25%	100%	100%	100%	High doses effective in ESRD. Ototoxicity.
Triamterene	25 mg bid	50 mg bid	5–10%	q12h	q12h	Avoid	Hyperkalemia common when GFR <30, especially in diabetics. Active metabolite with long half-life in ESRD. Folic acid antagonist. Urolithiasis. Crystalluria in acid urine. May cause acute renal failure.
Miscellaneous Agents							
Amrinone	5 mg/kg/min daily dose <10 mg/kg	10 mg/kg/min daily does <10 mg/kg	10–40%	100%	100%	100%	Thrombocytopenia. Nausea, vomiting in ESRD.

Clonidine	0.1 p.o. bid/tid	1.2 mg/ day	45%	100%	100%	100%	Sexual dysfunction, dizziness, postal hypo-tension
Digoxin	0.125 mg qid/qd	0.25 mg p.o. qd	25%	100%	100%	100%	Decrease loading dose by 50% in ESRD. Radioimmunoassay may overestimate serum lev-els in uremia. Clearance decreased by amio-darone, spironolactone, quinidine, verapamil. Hypokalemia, hypo-magnesemia enhance toxicity. Vd and total body clearance decreased in ESRD. Serum level 12 hours after dose is best guide in ESRD. Digoxin immune anti-bodies can treat severe toxicity in ESRD.
Hydralazine	10 mg p.o. qid	100 mg p.o. qid	25%	100%	100%	100%	Lupus-like reaction
Midodrine	No data	No data	75–80%	5–10 mg q8h	5–10 mg q8h	No data	Increased blood pressure

(*continued*)

Antihypertensive and Cardiovascular Agent Dosing in Renal Failure (Continued)							
Antihypertensive and Cardiovascular Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Minoxidil	2.5 mg p.o. bid	10 mg p.o. bid	20%	100%	100%	100%	Pericardial effusion, fluid retention, hypertrichosis and tachycardia
Nitroprusside	1 μg/kg/min	10 μg/kg/min	<10%	100%	100%	100%	Cyanide toxicity
Amrinone	5 μg/kg/min	10 μg/kg/min	25%	100%	100%	100%	Thrombocytopenia. Nausea, vomiting in ESRD.
Dobutamine	2.5 μg/kg/min	15 μg/kg/min	10%	100%	100%	100%	
Milrinone	0.375 μg/kg/min	0.75 μg/kg/min		100%	100%	100%	

Endocrine and Metabolic Agent Dosing in Renal Failure							
Hypoglycemic Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
							Avoid all oral hypoglycemic agents on CRRT.
Acarbose	25 mg tid	100 mg tid	35%	100%	50%	Avoid	Abdominal pain, N/V and Flatulence
Acetohexamide	250 mg q24h	1,500 mg q24h	None	Avoid	Avoid	Avoid	Diuretic effect. May falsely elevate serum creatinine. Active metabolite has $T_{1/2}$ of 5–8 hours in healthy subjects and is eliminated by the kidney. Prolonged hypoglycemia in azotemic patients.
Chlorpropamide	100 mg q24h	500 mg q24h	47%	50%	Avoid	Avoid	Impairs water excretion. Prolonged hypoglycemia in azotemic patients.
Glibornuride	12.5 mg q24h	100 mg q14h	No data	No data	No data	No data	
Gliclazide	80 mg q24h	320 mg q24h	<20%	50–100%	Avoid	Avoid	

(*continued*)

Endocrine and Metabolic Agent Dosing in Renal Failure (Continued)							
Hypoglycemic Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Glipizide	5 mg qd	20 mg bid	5%	100%	50%	50%	
Glyburide	2.5 mg qd	10 mg bid	50%	100%	50%	Avoid	
Metformin	500 mg bid	2,550 mg/d (bid or tid)	95%	100%	Avoid	Avoid	Lactic acidosis
Repaglinide	0.5–1 mg	4 mg tid					
Tolazamide	100 mg q24h	250 mg q24h	7%	100%	100%	100%	Diuretic effects***
Tolbutamide	1 g q24h	2 g q24h	None	100%	100%	100%	May impair water excretion
Troglitazone	200 mg qd	600 mg qd	3%	100%	Avoid	Avoid	Decrease CSA level, Hepatotoxic
Parenteral Agents							Dosage guided by blood glucose levels
Insulin	Variable		None	100%	75%	50%	Renal metabolism of insulin decreases with azotemia
Lispro insulin	Variable		No data	100%	75%	50%	Avoid all oral hypoglycemic agents on CRRT

Atorvastatin	10 mg/d	80 mg/d	<2%	100%	100%	100%	Liver dysfunction, myalgia, and rhabdomyolysis with CSA/FK
Bezafibrate	200 mg bid–qid 400 mg SR q24h		50%	50–100%	25–50%	Avoid	
Cholestyramine	4 gm bid	24 gm/day	None	100%	100%	100%	
Clofibrate	500 mg bid	1,000 mg bid	40–70%	q6–12h	q12–18h	Avoid	
Colestipol	5 gm bid	30 gm/day	None	100%	100%	100%	
Fluvastatin	20 mg daily	80 mg/day	<1%	100%	100%	100%	
Gemfibrozil	600 bid	600 bid	None	100%	100%	100%	
Lovastatin	5 mg daily	20 mg/day	None	100%	100%	100%	
Nicotinic acid	1 g tid	2 g tid	None	100%	50%	25%	
Pravastatin	10–40 mg daily	80 mg/day	<10%	100%	100%	100%	
Probucol	500 mg bid		<2%	100%	100%	100%	
Crestor	5–20 mg/day	40 mg/day		100%	100%	100%	
Simvastatin	5–20 mg daily	20 mg/day	13%	100%	100%	100%	

Antithyroid Dosing in Renal Failure						
Antithyroid Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Methimazole	5–20 mg tid	7	100%	100%	100%	
Propylthiouracil	100 mg tid	<10	100%	100%	100%	

Gastrointestinal Agents							
Gastrointestinal Agents	Normal Doses		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
	Starting Dose	Maximum Dose		GFR >50	GFR 10–50	GFR <10	
Cimetidine	300 mg p.o. tid	800 mg p.o. bid	60%	100%	75%	25%	Multiple drug–drug interactions—beta blockers, sulfonylurea, theophylline, warfarin, etc.
Famotidine	20 mg p.o. bid	40 mg p.o. bid	70%	100%	75%	25%	Headache, fatigue, thrombocytopenia, alopecia
Lansoprazole	15 mg p.o. qd	30 mg bid	None	100%	100%	100%	Headache, diarrhea
Nizatidine	150 mg p.o. bid	300 mg p.o. bid	20%	100%	75%	25%	Headache, fatigue, thrombocytopenia, alopecia
Omeprazole	20 mg p.o. qd	40 mg p.o. bid	None	100%	100%	100%	Headache, diarrhea
Rabeprazole	20 mg p.o. qd	40 mg p.o. bid	None	100%	100%	100%	Headache, diarrhea
Pantoprazole	40 mg p.o. qd	80 mg p.o. bid	None	100%	100%	100%	Headache, diarrhea

(*continued*)

Gastrointestinal Agents (Continued)							
Gastrointestinal Agents	Normal Doses		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
	Starting Dose	Maximum Dose		GFR >50	GFR 10–50	GFR <10	
Ranitidine	150 mg p.o. bid	300 mg p.o. bid	80%	100%	75%	25%	Headache, fatigue, thrombocytopenia, alopecia
Cisapride	10 mg p.o. tid	20 mg qid	5%	100%	100%	50–75%	Avoid with azole antifungal, macrolide antibiotics, and other P450 IIIA-4 inhibitors
Metoclopramide	10 mg p.o. tid	30 mg p.o. qid	15%	100%	100%	50–75%	Increase cyclosporine/tacrolimus level. Neurotoxic
Misoprostol	100 µg p.o. bid	200 µg p.o. qid		100%	100%	100%	Diarrhea, N/V Abortifacient agent
Sucralfate	1 g p.o. qid	1 g p.o. qid	None	100%	100%	100%	Constipation, decrease absorption of MMF

Neurologic/Anticonvulsant Dosing in Renal Failure							
Anticonvulsants	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Carbamazepine	2–8 mg/kg/day— adjust for side effect and TDM		2%	100%	100%	100%	Plasma concentration: 4–12, double vision, fluid retention, mylosuppression
Clonazepam	0.5 mg tid	2 mg tid	1%	100%	100%	100%	Although no dose reduction is recommended, the drug has not been studied in patients with renal impairment. Recommendations are based on known drug characteristics not clinical trials data
Ethosuximide	5 mg/kg/day—adjust for side effect and TDM		20%	100%	100%	100%	Plasma concentration: 40–100, headache
Felbamate	400 mg/ tid	1,200 mg/ tid	90%	100%	50%	25%	Anorexia, vomiting, insomnia, nausea
Gabapentin	150 mg tid	900 mg tid	77%	100%	50%	25%	Less CNS side effects compared with other agents
Lamotrigine	25–50 mg/day	150 mg/ day	1%	100%	100%	100%	Auto-induction, major drug–drug interaction with valproate

(*continued*)

Neurologic/Anticonvulsant Dosing in Renal Failure (Continued)							
Anticonvulsants	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Levetiracetam	500 mg bid	1,500 mg bid	66%	100%	50%	50%	
Oxcarbazepine	300 mg bid	600 mg bid	1%	100%	100%	100%	Less effect on P450 compared with carbamazepine
Phenobarbital	20 mg/kg/day—adjust for side effect and TDM		1%	100%	100%	100%	Plasma concentration: 15–40, insomnia
Phenytoin	20 mg/kg/day—adjust for side effect and TDM		1%	Adjust for renal failure and low Albumin			Plasma concentration: 10–20, nystagmus, check free phenytoin level
Primidone	50 mg	100 mg	1%	100%	100%	100%	Plasma concentration: 5–20
Sodium valproate	7.5–15 mg/kg/day—adjust for side effect and TDM		1%	100%	100%	100%	Plasma concentration: 50–150, weight gain, hepatitis, check free valproate level
Tiagabine	4 mg qd, increase 4 mg/day, titrate weekly		2%	100%	100%	100%	Total daily dose may be increased by 4–8 mg at weekly intervals until clinical response is achieved or up to 32 mg/day. The total daily dose should be given in divided doses two to four times daily

Topiramate	50 mg/day	200 mg bid	70%	100%	50%	Avoid	Kidney stone
Trimethadione	300 mg tid–qid	600 mg tid–qid	None	q8h	q8–12h	q12–24h	Active metabolites with long half-life in ESRD. Nephrotic syndrome
Vigabatrin	1 g bid	2 g bid	70%	100%	50%	25%	Encephalopathy with drug accumulation
Zonisamide	100 mg qd	100–300 mg qd–bid	30%	100%	75%	50%	Manufacturer recommends that Zonisamide should not be used in patients with renal failure (estimated GFR <50 mL/min) as there has been insufficient experience concerning drug dosing and toxicity. Zonisamide doses of 100–600 mg/day are effective for normal renal function. Dose recommendations for renal impairment based on clearance ratios

Rheumatologic Dosing in Renal Failure						
Arthritis and Gout Agents	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Allopurinol	300 mg q24h	30%	75%	50%	25%	Interstitial nephritis. Rare xanthine stones. Renal excretion of active metabolite with $T_{1/2}$ of 25 hours in normal renal function—$T_{1/2}$ 1 week in patients with ESRD. Exfoliative dermatitis
Auranofin	6 mg q24h	50%	50%	Avoid	Avoid	Proteinuria and nephritic syndrome
Colchicine	Acute: 2 mg then 0.5 mg q6h. Chronic: 0.5–1.0 mg q24h	5–17%	100%	50–100%	25%	Avoid prolonged use if GFR <50 mL/min
Gold sodium	25–50 mg	60–90%	50%	Avoid	Avoid	Thiomalate proteinuria—Nephritic syndrome—membranous nephritis
Penicillamine	250–1,000 mg q24h	40%	100%	Avoid	Avoid	Nephrotic syndrome
Probenecid	500 mg bid	<2%	100%	Avoid	Avoid	Ineffective at decreased GFR

Nonsteroidal anti-inflammatory drugs						May decrease renal function. Decrease platelet aggregation. Nephrotic syndrome. Interstitial nephritis. Hyperkalemia. Sodium retention.
Diclofenac	25–75 mg bid	<1%	50–100%	25–50%	25%	
Diflunisal	250–500 mg bid	<3%	100%	50%	50%	
Etodolac	200 mg bid	Negligible	100%	100%	100%	
Fenoprofen	300–600 mg qid	30%	100%	100%	100%	
Flurbiprofen	100 mg bid–tid	20%	100%	100%	100%	
Ibuprofen	800 mg tid	1%	100%	100%	100%	
Indomethacin	25–50 mg tid	30%	100%	100%	100%	
Ketoprofen	25–75 mg tid	<1%	100%	100%	100%	
Ketorolac	30–60 mg load then 15–30 mg q6h	30–60%	100%	50%	25–50%	Acute hearing loss in ESRD
Meclofenamic acid	50–100 tid–qid	2–4%	100%	100%	100%	

(*continued*)

Rheumatologic Dosing in Renal Failure (Continued)						
Arthritis and Gout Agents	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Mefanamic acid	250 mg qid	<6%	100%	100%	100%	
Nabumetone	1.0–2.0 g q24h	<1%	100%	50–100%	50–100%	
Naproxen	500 mg bid	<1%	100%	100%	100%	
Oxaproxin	1,200 mg q24h	<1%	100%	100%	100%	
Phenylbutazone	100 mg tid–qid	1%	100%	100%	100%	
Piroxicam	20 mg q24h	10%	100%	100%	100%	
Sulindac	200 mg bid	7%	100%	100%	100%	Active sulfide metabolite in ESRD
Tolmetin	400 mg tid	15%	100%	100%	100%	

Sedative Dosing in Renal Failure						
Sedatives	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Barbiturates						May cause excessive sedation, increase osteomalacia in ESRD. Charcoal hemoperfusion and hemodialysis more effective than peritoneal dialysis for poisoning
Pentobarbital	30 mg q6–8h	Hepatic	100%	100%	100%	
Phenobarbital	50–100 mg q8–12h	Hepatic (renal)	q8–12h	q8–12h	q12–16h	Up to 50% unchanged drug excreted with urine with alkaline diuresis
Secobarbital	30–50 mg q6–8h	Hepatic	100%	100%	100%	
Thiopental	Anesthesia induction (individualized)	Hepatic	100%	100%	100%	
Benzodiazepines						May cause excessive sedation and encephalopathy in ESRD

(*continued*)

Sedative Dosing in Renal Failure (Continued)						
Sedatives	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Alprazolam	0.25–5.0 mg q8h	Hepatic	100%	100%	100%	
Clorazepate	15–60 mg q24h	Hepatic (renal)	100%	100%	100%	
Chlordiazepoxide	15–100 mg q24h	Hepatic	100%	100%	50%	
Clonazepam	1.5 mg q24h	Hepatic	100%	100%	100%	Although no dose reduction is recommended, the drug has not been studied in patients with renal impairment. Recommendations are based on known drug characteristics not clinical trials data
Diazepam	5–40 mg q24h	Hepatic	100%	100%	100%	Active metabolites, desmethyldiazepam and oxazepam may accumulate in renal failure. Dose should be reduced if given longer than a few days. Protein binding decreases in uremia

Estazolam	1 mg qhs	Hepatic	100%	100%	100%	
Flurazepam	15–30 mg qhs	Hepatic	100%	100%	100%	
Lorazepam	1–2 mg q8–12h	Hepatic	100%	100%	100%	
Midazolam	Individualized	Hepatic	100%	100%	50%	
Oxazepam	30–120 mg q24h	Hepatic	100%	100%	100%	
Quazepam	15 mg qhs	Hepatic	No data	No data	No data	
Temazepam	30 mg qhs	Hepatic	100%	100%	100%	
Triazolam	0.25–0.50 mg qhs	Hepatic	100%	100%	100%	Protein binding correlates with alpha-1 acid glycoprotein concentration
Benzodiazepines: Benzodiazepine antagonist						May cause excessive sedation and encephalopathy in ESRD
Flumazenil	0.2 mg IV over 15 sec	Hepatic	100%	100%	100%	

(*continued*)

Sedative Dosing in Renal Failure (Continued)						
Sedatives	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Miscellaneous sedative agents						
Buspirone	5 mg q8h	Hepatic	100%	100%	100%	
Ethchlorvynol	500 mg qhs	Hepatic	100%	Avoid	Avoid	Removed by hemoperfusion. Excessive sedation
Haloperidol	1–2 mg q8–12h	Hepatic	100%	100%	100%	Hypertension, excessive sedation
Lithium carbonate	0.9–1.2 g q24h	Renal	100%	50–75%	25–50%	Nephrotoxic. Nephrogenic diabetes insipidus. Nephrotic syndrome. Renal tubular acidosis. Interstitial fibrosis. Acute toxicity when serum levels >1.2 mEq/L. Serum levels should be measured periodically 12 h after dose. $T_{1/2}$ does not reflect extensive tissue accumulation. Plasma levels rebound after dialysis. Toxicity enhanced by volume depletion, NSAIDs, and diuretics
Meprobamate	1.2–1.6 g q24h	Hepatic (renal)	q6h	q9–12h	q12–18h	Excessive sedation. Excretion enhanced by forced diuresis.

Anti-Parkinson Dosing in Renal Failure						
Anti-Parkinson Agents	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Carbidopa	1 tab tid to 6 tabs daily	30	100%	100%	100%	Requires careful titration of dose according to clinical response
Levodopa	25–500 mg bid to 8 g q24h	None	100%	50–100%	50–100%	Active and inactive metabolites excreted in urine. Active metabolites with long $T_{1/2}$ in ESRD

Antipsychotic Dosing in Renal Failure						
Antipsychotics	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
			GFR >50	GFR 10–50	GFR <10	
Phenothiazines						Orthostatic hypotension, extrapyramidal symptoms, and confusion can occur
Chlorpromazine	300–800 mg q24h	Hepatic	100%	100%	100%	No comments
Promethazine	20–100 mg q24h	Hepatic	100%	100%	100%	Excessive sedation may occur in ESRD
Thioridazine	50–100 mg p.o. tid. Increase gradually. Maximum of 800 mg/day	Hepatic	100%	100%	100%	
Trifluoperazine	1–2 mg bid. Increase to no more than 6 mg	Hepatic	100%	100%	100%	
Perphenazine	8–16 mg p.o. bid, tid, or qid. Increase to 64 mg daily	Hepatic	100%	100%	100%	

Thiothixene	2 mg p.o. tid. Increase gradually to 15 mg daily	Hepatic	100%	100%	100%	
Haloperidol	1–2 mg q8–12h	Hepatic	100%	100%	100%	Hypotension, excessive sedation
Loxapine	12.5–50 mg IM q4–6h					Do not administer drug IV
Clozapine	12.5 mg p.o. 25–50 daily to 300–450 by end of 2 weeks. Maximum: 900 mg daily	Metabolism nearly complete	100%	100%	100%	
Risperidone	1 mg p.o. bid. Increase to 3 mg bid.		100%	100%	100%	
Olanzapine	5–10 mg	Hepatic	100%	100%	100%	Potential hypotensive effects
Quetiapine	25 mg p.o. bid. Increase in increments of 25–50 bid or tid. 300–400 mg daily by day 4	Hepatic	100%	100%	100%	
Ziprasidone	20–100 mg q12h	Hepatic	100%	100%	100%	May aggravate azotemia, Na^+ retention, glucose intolerance, and hypertension

Miscellaneous Dosing in Renal Failure						
			Dosage Adjustment in Renal Failure			
Corticosteroids	Normal Dosage	% of Renal Excretion	GFR >50	GFR 10–50	GFR <10	Comments
Betamethasone	0.5–9.0 mg q24h	5%	100%	100%	100%	
Budesonide	No data	None	100%	100%	100%	
Cortisone	25–500 mg q24h	None	100%	100%	100%	
Dexamethasone	0.75–9.0 mg q24h	8%	100%	100%	100%	
Hydrocortisone	20–500 mg q24h	None	100%	100%	100%	
Methylprednisolone	4–48 mg q24h	<10%	100%	100%	100%	
Prednisolone	5–60 mg q24h	34%	100%	100%	100%	
Prednisone	5–60 mg q24h	34%	100%	100%	100%	
Triamcinolone	4–48 mg q24h	No data	100%	100%	100%	

Anticoagulants	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Alteplase	60 mg over 1 h then 20 mg/h for 2h		No data	100%	100%	100%	tissue-type plasminogen activator [tPa]
Aspirin	81 mg/day	325 mg/day	10%	100%	100%	100%	GI irritation and bleeding tendency
Clopidogrel	75 mg/day	75 mg/day	50%	100%	100%	100%	GI irritation and bleeding tendency
Dalteparin	2,500 units Sq/day	5,000 units Sq/day	Unknown	100%	100%	50%	
Dipyridamole	50 mg tid		No data	100%	100%	100%	
Enoxaparin	20 mg/day	30 mg bid	8%	100%	75–50%	50%	1 mg/kg q12h for treatment of DVT. Check antifactor Xa activity 4 hours after second dose in patients with renal dysfunction. Some evidence of drug accumulation in renal failure
Heparin	75 U/kg load then 15 U/kg/hr		None	100%	100%	100%	Half-life increases with dose

(*continued*)

Miscellaneous Dosing in Renal Failure (Continued)							
Anticoagulants	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
				GFR >50	GFR 10–50	GFR <10	
Iloprost	0.5–2.0 ng/kg/min for 5–12h		No data	100%	100%	50%	
Indobufen	100 mg bid	200 mg bid	<15%	100%	50%	25%	
Streptokinase	250,000 U load then 100,000 U/h		None	100%	100%	100%	
Sulfinpyrazone	200 mg bid		25–50%	100%	100%	Avoid	Acute renal failure. Uricosuric effect at low GFR
Ticlopidine	250 mg bid	250 mg bid	2%	100%	100%	100%	Decrease CSA level—may cause severe neutropenia and thrombocytopenia
Tranexamic acid	25 mg/kg tid–qid		90%	50%	25%	10%	
Urokinase	4,400 U/kg load then 4,400 U/kg qh		No data	No data	No data	No data	
Warfarin	2.5–5 mg/day	Adjust per INR	<1%	100%	100%	100%	Monitor INR very closely. Start at 5 mg/day. 1 mg Vitamin K IV over 30 minutes or 2.5–5 mg p.o. can be used to normalize INR

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