

## 259 ADAPTATION TO RENAL INJURY

Robert M. Brenner, Barry M. Brenner

Near constancy of the internal environment, including the volume, composition, and compartmental distribution of the body fluids, is essential to survival. With normal day-to-day variations in the intake of food and water, preservation of the internal environment requires the excretion in amounts that balance the quantities ingested. While losses from intestines, lungs, and skin contribute, the greatest responsibility for solute and water excretion is borne by the kidneys. This chapter reviews the excretory functions of the kidney and examines how these functions are affected by chronic renal disease.

### EFFECTS OF NEPHRON LOSS ON RENAL EXCRETORY MECHANISMS

**GLOMERULAR ULTRAFILTRATION** Urine production begins at the glomerulus where an ultrafiltrate of plasma is formed. The rate of glomerular ultrafiltration (glomerular filtration rate, GFR) is governed chiefly by forces favoring filtration on the one hand (hydraulic pressure in the glomerular capillaries) and forces opposing filtration on the other (the sum of hydraulic pressure in Bowman's space and colloid osmotic pressure of blood in the glomerular capillaries). The rate of glomerular plasma flow and the total surface area of the glomerular capillaries are also determinants of GFR. Decreased GFR can therefore be expected when (1) glomerular hydraulic pressure is reduced (as in circulatory shock); (2) tubule (hence Bowman's space) hydraulic pressure is elevated, as in urinary tract obstruction; (3) plasma colloid osmotic pressure rises to high levels (hemoconcentration due to severe volume depletion, or myeloma, other dysproteinemias); (4) renal, and hence glomerular, blood flow is reduced (severe hypovolemia, cardiac failure); (5) permeability is reduced (diffuse glomerular disease); or (6) filtration surface area is diminished, through nephron loss in progressive renal failure.

The glomerular capillary wall is specially adapted to allow passage of extremely large volumes of water while retaining all but the smallest solute molecules. Molecules the size of inulin (approximately 5200 mol wt) pass freely across the glomerular filtration barrier, appearing at approximately the same concentration in Bowman's space as in plasma. The passage of solutes across the glomerular barrier decreases progressively with increasing molecular size such that, as the molecular weight of albumin is approached, most of the solute is retained in the plasma. Albumin, a polyanionic molecule in plasma, is further retarded at the glomerular filtration barrier by *electrostatic forces* imparted by negatively charged cell-surface molecules on the epithelial foot processes that form the *filtration slits* and the *slit diaphragms*. With disruption of these structural and electrostatic barriers, as in many forms of glomerular injury (Chap. 264), large quantities of plasma proteins gain access to the glomerular filtrate.

**GLOMERULAR ADAPTATIONS TO NEPHRON LOSS** With loss of nephron mass, the remaining functional (or least injured) nephrons tend to hypertrophy and take on an increased workload so that the overall loss of function is minimized. For example, a patient with a unilateral nephrectomy loses one-half of the nephron mass, resulting in a 50% reduction in GFR at the time of surgery. However, within several months total GFR may rise to 80% of the preoperative value. This indicates that the GFR of the individual remaining nephrons has increased above normal, a state known as *hyperfiltration*. Increases in single-nephron GFR may be achieved by renal hemodynamic adjustments (increased glomerular plasma flow and increased glomerular capillary hydraulic pressure), which augment the forces driving ultra-

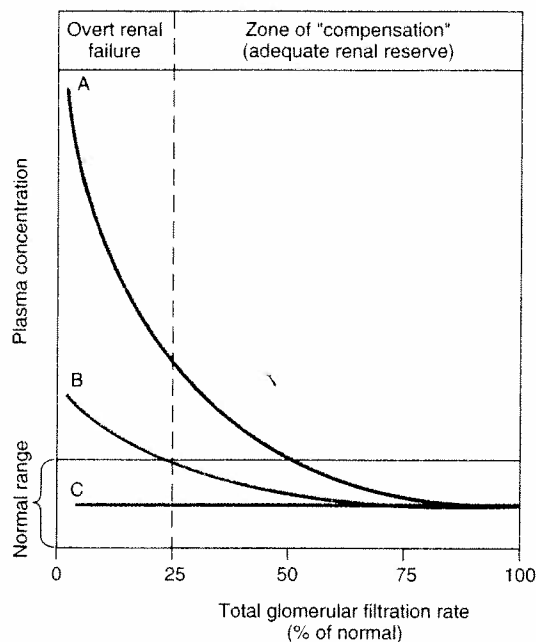
filtration, and by glomerular hypertrophy, which increases the maximum surface area available for filtration. These structural adaptations are evident from the enlargement of glomeruli (and tubules) seen on histologic sections from persons with single kidneys. Similar structural changes are observed in kidneys damaged by chronic disease processes; foci of hypertrophied glomeruli and tubules are interspersed with areas of atrophic or scarred parenchyma. Although direct measurements of single-nephron GFR cannot be made in humans, it is reasonable to conclude that focal nephron enlargement as occurs in chronically diseased kidneys generally signifies focally increased single-nephron GFR, and that these dynamic adaptations represent compensatory adjustments for the effects of nephron loss through disease.

**GLOMERULOTUBULAR BALANCE** The close integration of glomerular and tubular functions (*glomerulotubular balance*) seen in chronic renal failure (CRF) supports the notion that progressive nephron obliteration is the usual mode of GFR reduction in CRF. Preservation of glomerulotubular balance until the terminal stages of CRF is fundamental to the *intact-nephron hypothesis*, which states that as CRF advances, kidney function is supported by a diminishing pool of functioning (or hyperfunctioning) nephrons, rather than relatively constant numbers of nephrons, each with diminishing function. This hypothesis has important implications for the mechanisms of disease progression in CRF. A considerable amount of evidence suggests that nephrons subjected to increased excretory burdens for prolonged periods actually sustain injury as a result of these adaptations: thus the cost of these compensatory adaptations to nephron loss may ultimately be relentless destruction of the remaining nephron pool.

The magnitude of the single-nephron hyperfiltration induced by loss of 50% of the total nephron mass usually has no serious adverse clinical consequences, even when sustained over two to three decades. When more than 50% of the total nephron mass is lost, however, as in renal-sparing surgery for bilateral trauma or neoplasm or from a renal disease whose activity has abated, the remaining nephrons are forced to the limits of their compensatory capacity. While these adaptations achieve remarkable short-term success at offsetting the tendency for GFR to fall, over time, proteinuria and focal and segmental glomerulosclerosis develop, the more so where greater amounts of nephrons are lost or removed. As a result, a progressive decline in GFR ensues. Experimental study of the processes that advance glomerular injury show that the adverse long-term consequences of severe nephron deficits are invariably preceded by increases in glomerular capillary hydraulic pressure (glomerular capillary hypertension), glomerular hyperperfusion, and hypertrophy. Interventions directed against these compensatory and maladaptive responses can greatly ameliorate the subsequent development of renal failure. In particular, drugs (e.g., angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and other interventions (such as dietary protein restriction) that lower glomerular pressure can slow the rate of progression of experimental and human renal disease. In the absence of such interventions, more and more glomeruli cease to function through advancing glomerulosclerosis and disruption of tubule structure and function, leading eventually to marked or even total loss of GFR (i.e., end-stage renal disease). This *final common pathway* for chronic renal injury helps to explain the observed progressive nature of chronic renal failure resulting from many different kidney diseases.

### BIOLOGIC CONSEQUENCES OF SUSTAINED REDUCTIONS IN GFR

Figure 259-1 depicts the major types of response to impaired GFR. The degree of reduction in total GFR is plotted on the abscissa, expressed as a percentage of normal (100%). The renal handling of most solutes normally present in glomerular filtrate conforms to one of three



**FIGURE 259-1** Representative patterns of adaptation for different types of solutes in body fluids in chronic renal failure. [After NS Bricker et al, in BM Brenner (ed): *Brenner and Rector's The Kidney*, 6th ed. Philadelphia, Saunders, 2000.]

patterns. Curve A describes the pattern with substances such as creatinine and urea that normally depend largely on glomerular filtration for urinary excretion, i.e., secretion contributes little to overall excretion. Therefore, as illustrated, gradual reductions in GFR are accompanied by progressive increases in plasma levels of creatinine, urea, and other substances normally excreted primarily by filtration.

The clinical course of CRF usually also approximates the pattern described by curve A. Patients with CRF usually pass from a long asymptomatic period of "compensation" to a more accelerated and clinically overt terminal phase. In other words, despite chronic injury leading to destruction of more than 50% of nephrons, plasma elevations of creatinine and urea may still lie within the normal limits for these substances. With further nephron loss and reduction in GFR, however, the limits of renal reserve are exceeded and continued accumulations of curve A-type solutes lead to abnormally elevated plasma concentrations (Fig. 259-1). Because some of these retained solutes are thought to exert "toxic" effects on all organ systems, clinical manifestations of CRF may now become apparent.

The accumulation of curve A-type solutes with chronic loss of renal function proceeds until external balance is restored, i.e., intake and/or production rates exactly match excretion rates. In the case of creatinine, for example, assuming a constant rate of creatinine production, a 50% reduction in GFR results in an approximate doubling of the plasma creatinine concentration. The latter restores the filtered load of creatinine (i.e., the product of GFR and plasma creatinine concentration) to normal, and the urinary excretion rate once again is equivalent to creatinine production. *In practice, so long as the net rates of acquisition and production (i.e., liver function and muscle mass) remain reasonably constant, the inverse relationship between plasma concentrations of solutes such as creatinine and urea and GFR is sufficiently reliable to serve as clinical indices of GFR.* However, where muscle mass is low, as with severe weight loss, even normal plasma levels of creatinine may belie substantial reductions in GFR.

In contrast to solutes of the curve A type, plasma levels of phosphate ( $\text{PO}_4^{3-}$ ), urate, and potassium ( $\text{K}^+$ ) and hydrogen ( $\text{H}^+$ ) ions usually do not rise until the GFR falls to a small percentage of normal. With progressive renal failure this pattern of response (curve B in Fig. 259-1) reflects the participation of tubule transport mechanisms in the excretion of these substances. In other words, *as GFR declines, the*

*tubules facilitate greater elimination of these substances, by enhancing secretion and/or by diminishing reabsorption, so that a greater fraction of the filtered load is excreted.* Plasma levels of curve B-type solutes, therefore, rise less than those of curve A because, with progressive reductions in GFR, *excretion rate per nephron* and therefore *fractional excretion* both increase. Eventually, however, with further loss of GFR, enhanced fractional excretion can no longer mitigate the reduction in net filtered load of these solutes and plasma levels rise (Fig. 259-1). For urate,  $\text{PO}_4^{3-}$ , and  $\text{K}^+$ , at least, increased fractional excretion serves to maintain normal plasma levels until GFR falls to less than one-fourth of normal.

Finally, for certain solutes, such as sodium chloride ( $\text{NaCl}$ ), plasma concentrations remain normal throughout the course of CRF, despite unrestricted intake of these substances (curve C in Fig. 259-1). The compensatory mechanism required to achieve this represents a fundamental adaptation to chronic renal injury. To illustrate the magnitude of this adaptation, it is useful to compare the excretion of sodium ( $\text{Na}^+$ ) in a normal individual (GFR of 125 mL/min) with that of a patient with advanced renal failure (GFR of 2 mL/min). Both individuals consume a conventional diet containing 7 g/d of salt (120 mmol  $\text{Na}^+$ ). With a serum  $\text{Na}^+$  concentration of 140 mmol/L, external  $\text{Na}^+$  balance is achieved in the normal subject by excreting approximately 0.5% of the filtered load. By contrast, for external balance to be maintained in the patient with CRF, fractional excretion of  $\text{Na}^+$  must rise to 30%. In other words, *to maintain external  $\text{Na}^+$  balance*, the same amount of  $\text{Na}^+$  must be excreted into the urine each day in the patient with CRF as in the normal individual. Given the drastic reduction in GFR in CRF, external balance can only be maintained by marked adaptations in the reabsorptive processes in surviving tubules. In this manner, a progressively larger fraction of the filtered load escapes reabsorption and appears in the final urine.

#### ADAPTATIONS IN TUBULE TRANSPORT MECHANISMS IN RESPONSE TO NEPHRON LOSS

Despite progressive nephron loss, many mechanisms that regulate renal solute and water balance differ only quantitatively, and not qualitatively, from those that operate normally. Thus, glomerulotubular balance is maintained. The most important of these mechanisms are considered below.

**TUBULAR TRANSPORT OF SODIUM CHLORIDE AND WATER** Most of the filtered water and sodium salts are reabsorbed by the tubules, leaving small and variable amounts, equivalent on average to the quantities ingested, to reach the final urine. About two-thirds of the glomerular ultrafiltrate is reabsorbed in the *proximal tubule* with little change in the osmolality or  $\text{Na}^+$  concentration of the unreabsorbed fraction (Fig. 259-2). In other words, fluid reabsorption in the proximal tubule is nearly *isosmotic* and is coupled to the active transport of  $\text{Na}^+$ . Since chloride ( $\text{Cl}^-$ ) and bicarbonate ( $\text{HCO}_3^-$ ) are the primary anions in the extracellular fluid, they constitute the main solutes that accompany  $\text{Na}^+$  reabsorption in the renal tubules. In the earliest portion of the proximal tubule, bicarbonate is the principal anion that accompanies the reabsorption of  $\text{Na}^+$ . This process occurs via a  $\text{Na}^+/\text{H}^+$  exchanger at the luminal brush border and is dependent on the activity of carbonic anhydrase. Glucose, amino acids, and other organic solutes (e.g., lactate) are also extensively reabsorbed in the proximal tubule by cotransport mechanisms that link the cellular entry of these organic molecules with  $\text{Na}^+$ .

The coupling of water absorption (i.e., volume) with solute absorption appears to be dependent upon three processes. First, given the remarkably high water permeability of this segment, very small transepithelial osmolality differences, i.e., *luminal hypotonicity* of the order of 2 to 3 mosmol/L produced by solute absorption, could drive water absorption. Second, due to preferential absorption of  $\text{HCO}_3^-$  and organic solutes in the early portions of the proximal tubule, the concentrations of these substances decrease along the proximal tubule while that of chloride increases. Volume reabsorption would then occur if the diffusion of  $\text{Na}^+$  and  $\text{Cl}^-$  down their respective electrochemical gradients across the proximal tubule epithelium occurred more

cing  
rac-  
type  
pro-  
fore  
ther  
the  
rise  
onal  
s to

ma  
pite  
The  
unde  
a)  
ent  
on-  
).  
nce  
of  
in  
%.  
nt  
ith  
R  
a-  
er,  
on

e-  
l-  
ar  
e

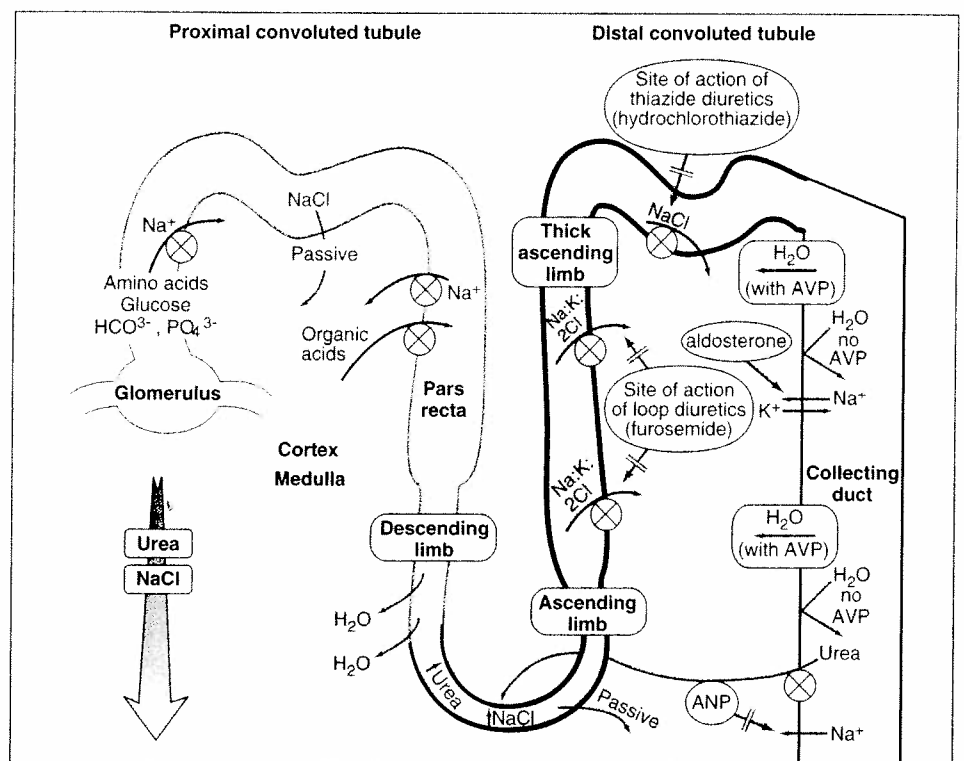
d  
ll  
l.  
e  
y  
1  
-  
-  
l

easily than the back-diffusion of sodium bicarbonate into the lumen, creating an effective osmotic pressure gradient. Finally, lateral interstitial space hypertonicity produced by differences in the rates at which solutes are transported into the spaces or exit them by diffusion may also contribute to the coupling of water and solute reabsorption.

**Reabsorption of Fluid from Proximal Convolted Tubules** This is sensitive to Starling forces, i.e., the hydraulic and colloid osmotic (or oncotic) pressures acting across the walls of the peritubular capillaries. Because the plasma proteins in glomerular capillaries are concentrated by ultrafiltration, oncotic pressure rises along the glomerular capillary network. This step-up in oncotic pressure is transmitted largely unchanged to the first branches of the peritubular capillaries where hydraulic pressure exceeds oncotic pressure, favoring filtration. The extent to which oncotic pressure exceeds hydraulic pressure in the peritubular capillary network modulates the overall rate of fluid absorption by the peritubular capillaries. Therefore, when peritubular capillary oncotic pressure falls, or hydraulic pressure rises, uptake of fluid by these capillaries is reduced. As a result, fluid is retained in the interstitial space, tending to increase hydraulic pressure, ultimately retarding the egress of fluid from the lateral intercellular channels.

Without an adequate route of drainage, fluid in the intercellular channels leaks back into the tubule lumen, thereby diminishing net fluid reabsorption from this tubule segment. The opposite occurs in states where peritubular oncotic pressure is increased (increased filtration fraction) or hydraulic pressure is decreased (enhanced efferent arteriolar tone). Under these circumstances, peritubular capillary uptake of reabsorbate is augmented, leading ultimately to enhanced net fluid reabsorption by the proximal tubule. Although physical factors appear to be the major determinants of fluid reabsorption in the proximal tubule, hormones (e.g., angiotensin II) may also modulate fluid reabsorption directly, by enhancing luminal Na<sup>+</sup> entry into proximal tubule cells via an apical Na<sup>+</sup>/H<sup>+</sup> exchanger.

**The Limbs of Henle's Loop** In contrast to the proximal tubule, active outward transport of Na<sup>+</sup> has not been established for the thin descending or ascending limbs of Henle's loop. However, passive outward salt transport does occur, as indicated in Fig. 259-2. In the next nephron segment, the medullary thick ascending limb of Henle, the concentration of NaCl is reduced as fluid traverses this segment. Here Cl<sup>-</sup> absorption occurs by an active process involving a Na<sup>+</sup>:K<sup>+</sup>:2Cl<sup>-</sup> cotransport mechanism in the luminal membrane, with one-half of Na<sup>+</sup> absorption pro-



**FIGURE 259-2** Transport functions of the various anatomical segments of the mammalian nephron. Fluid reabsorption across the proximal tubule is isosmotic and accounts for reabsorption of approximately two-thirds of the filtered Na<sup>+</sup> and H<sub>2</sub>O. The major portions of the filtered HCO<sub>3</sub><sup>-</sup>, amino acids, glucose, and phosphate are reabsorbed in the early proximal convoluted tubule. Reabsorption of glucose and amino acids is coupled to Na<sup>+</sup> transport and thereby generates a negative potential difference within the tubule lumen. At the same time, HCO<sub>3</sub><sup>-</sup> is reabsorbed by a nonelectrogenic mechanism, via H<sup>+</sup> secretion. The active transport of these solutes results in transepithelial concentration and effective osmotic pressure gradients promoting H<sub>2</sub>O flow across the proximal tubule, into the peritubular capillaries. The rise in tubule fluid Cl<sup>-</sup> concentration is a necessary reciprocal consequence of the decreased luminal HCO<sub>3</sub><sup>-</sup> concentration. The resultant high concentration of Cl<sup>-</sup> becomes an important force for the outward passive transport of Cl<sup>-</sup> down its concentration gradient, resulting in a lumen-positive potential difference in the late proximal convoluted tubule.

The pars recta of the proximal tubule is capable of active electrogenic transport of Na<sup>+</sup> independent of organic solute transport. Under normal conditions, approximately one-third of the glomerular filtrate enters the descending limb of Henle's loop. This segment is incapable of active outward NaCl transport and is characterized by low permeability to Na<sup>+</sup> but high H<sub>2</sub>O permeability, H<sub>2</sub>O is abstracted passively as the fluid approaches the bend of Henle's loop. Hypertonic fluid with a greater NaCl concentration but lower urea concentration than the surrounding medullary interstitium thus enters the thin ascending limb of Henle, which is largely impermeable to H<sub>2</sub>O and urea but highly permeable to NaCl. This permits passive outward diffusion of NaCl. Active Na:K:2Cl transport across the water-impermeable thick ascending limb of Henle enables tubule fluid to become dilute and the medullary interstitium hypertonic.

Irrespective of the final osmolality of the urine, the fluid that enters the distal convoluted tubule (DCT) is always hyposmotic. This segment exhibits active Na<sup>+</sup> reabsorption. All but the terminal portion of the DCT is water-impermeable, even in the presence of arginine vasopressin (AVP). Aldosterone exerts its effect in this segment by enhancing Na<sup>+</sup> reabsorption, which is variably coupled to K<sup>+</sup> and H<sup>+</sup> secretion. The cortical and papillary portions of the collecting duct are sites where AVP exerts its principal effect. The permeability of these segments to H<sub>2</sub>O in the absence of AVP is very low but can be greatly enhanced in the presence of AVP. These segments are also characterized by active Na<sup>+</sup> reabsorption, which appears to depend on the presence of mineralocorticoid. In the absence of AVP, the collecting tubule is water-impermeable so that hypotonic tubule fluid courses through it. However, in the presence of AVP, water is avidly reabsorbed here, resulting in hypertonic final urine. Sites of action of furosemide and thiazide diuretics and of aldosterone and atrial natriuretic peptide (ANP) are shown.

ceeding passively, driven by the lumen positive transepithelial voltage difference. This cotransporter is the site of action of the powerful loop diuretics, and mutations give rise to Bartter's syndrome. Since the ascending limb of Henle is impermeable to water, net NaCl reabsorption generates a hypotonic tubule fluid and gives rise to the high NaCl concentration of the outer medullary interstitium (Fig. 259-2).

**Distal Tubule** The fluid leaving the thick ascending limb of Henle is normally of low NaCl concentration, a characteristic independent of the organism's hydration status. In the distal tubule, water reabsorption is variable, depending on the state of hydration or, specifically, on the presence or absence of arginine vasopressin (AVP) in plasma. In the absence of AVP, this and more distal nephron segments are impermeable to water, so that hypotonic fluid entering this segment is excreted as dilute urine. Indeed, continued salt reabsorption along the distal convoluted tubule (DCT) and connecting tubule segments, a

process that can be inhibited by thiazide diuretics, results in further dilution of the urine. In the presence of AVP, the permeability of these nephron segments to water increases. This is made possible by the insertion of proteins known as *aquaporins* into the luminal cell membrane of DCT cells. These proteins facilitate water movement from the low-osmolality environment of the DCT lumen into the higher osmolality of the medullary interstitium, thereby contributing to the creation of a concentrated final urine. NaCl continues to be reabsorbed from the tubule lumen against moderately steep chemical and electrical gradients. The reabsorption of NaCl at the collecting tubule is enhanced by *aldosterone*.

**Collecting Tubules and Ducts** The *cortical collecting tubule* possesses a low permeability to water in the absence of AVP, whereas permeability increases in the presence of this hormone. The sensitivity of this segment to AVP appears to be more pronounced than that of the DCT. As with the DCT, the cortical collecting tubule is capable of active reabsorption of NaCl and its stimulation by aldosterone.

The terminal segment of the distal nephron is the highly branched *papillary collecting duct*. Continued electrolyte transport in this segment results in the large ion concentration differences that normally exist between urine and plasma. As in the cortical collecting tubule, Na<sup>+</sup> transport appears to be active, since reabsorption proceeds against sizeable electrochemical gradients. The rate of Na<sup>+</sup> transport in this segment depends on the load of Na<sup>+</sup> delivered from more proximal segments and is also affected by aldosterone. The permeability to water is also increased markedly in the presence of AVP.

**EFFECTS OF NEPHRON LOSS ON SODIUM CHLORIDE TRANSPORT IN SURVIVING NEPHRONS** With progressive nephron loss, *maintenance of external balance for NaCl requires that fractional salt excretion increases in concert with the decline in GFR*. Several mechanisms contribute to this adaptive increase in fractional Na<sup>+</sup> excretion. With loss of functioning nephrons, peritubular capillary Starling forces are altered in directions that serve to reduce proximal tubule reabsorption of NaCl and water. For example, a rise in peritubular capillary hydraulic pressure, which tends to inhibit net proximal fluid reabsorption, might be anticipated with systemic hypertension, a common feature of CRF. Similarly, reductions in peritubular capillary oncotic pressures may be anticipated due to reductions in both filtration fraction and hypoalbuminemia.

Several factors that regulate NaCl transport across tubules under normal conditions are also likely to contribute to the enhanced fractional excretion of NaCl in renal insufficiency. Atrial natriuretic peptides are released from the heart in response to elevated cardiac (atrial) filling pressures as seen with increased plasma volume or atrial tachyarrhythmias. These peptides affect natriuresis by reducing net Na<sup>+</sup> reabsorption through complementary actions on Na<sup>+</sup> transport in the collecting duct and by altering Starling forces in the adjacent vasa recta. Other modulators of tubule transport processes may also contribute to increased single-nephron natriuresis in the setting of nephron loss. Vasodilator prostaglandins are present at increased plasma levels in CRF, as are other inhibitors of transport, including inhibitor(s) of the Na<sup>+</sup>.K<sup>+</sup>-ATPase. Serum and urine from patients with uremia contain retained toxins capable of inhibiting this enzyme.

The obligatory high rate of solute excretion per surviving nephron (so-called osmotic diuresis due to urea and other retained solutes) also contributes to enhancing fractional NaCl excretion, much as occurs in normal individuals after the administration of mannitol or other non-reabsorbable solutes. Finally, certain forms of CRF are associated with unusually large losses of salt in the urine. These *salt-wasting nephropathies* include chronic pyelonephritis and other tubulointerstitial diseases (Chap. 266) as well as polycystic and medullary cystic diseases. These disorders have in common greater destruction of medullary and tubulointerstitial, rather than cortical and glomerular, portions of the renal parenchyma. →*For discussion of clinical derangements that*

*alter renal handling of NaCl in CRF (including hypo- and hypervolemia, hypertension, etc.), see Chap. 261.*

#### EFFECTS OF NEPHRON LOSS ON WATER REABSORPTION IN SURVIVING NEPHRONS

As with NaCl, there is a progressive increase in the fractional excretion of water with advancing renal insufficiency, so that external water balance can be maintained even with a total GFR of 5 mL/min or less. The adaptations of water handling by the diseased kidney are of importance in the defects in urinary concentration and dilution and hence the polyuria, nocturia, and tendency to develop water retention encountered in CRF (Chap. 40). To appreciate the mechanisms involved, the responses of a normal individual and a patient with CRF maintaining external water balance need to be considered. Assuming both individuals have the same dietary and fluid intakes, total solute and volume excretion in both should be identical as well. If the *obligatory solute load* to be excreted by each is 600 mmol/d (600 mosmol/d) and the urine osmolality is 300 mmol/kg water (300 mosmol/kg), a urine volume of 2 L/d will be required to excrete the total solute. If the GFR in normal individuals and the patient with CRF totals 180 and 4 L/d, respectively, urinary volume excretion of 2 L/d represents excretion of slightly more than 1% of the total glomerular filtrate in the normal subject compared with 50% in the patient with CRF. Since the range of urine osmolalities that the diseased kidney can achieve [250 to 350 mmol/kg (250 to 350 mosmol/kg)] is narrower than in the normal kidney [40 to 1200 mmol/kg (40 to 1200 mosmol/kg)], the individual with normal function is able to excrete the obligatory daily solute load of 600 mmol (600 mosmol) in as little as 500 mL urine per day or as much as 15 L/d, compared with the narrower range in CRF, from about 1.7 to 2.4 L/d.

In CRF, the limited capacity to concentrate the urine often correlates with other measures of impaired renal function. Isosthenuria (urine of similar osmolality to plasma) is therefore an almost universal finding when the GFR falls below 25 mL/min. At this level of GFR and below, urine osmolality does not rise even when supraphysiologic doses of AVP are administered, suggesting that the concentrating defect relates to impaired concentrating capacity in surviving nephrons. The associated increased fractional excretion per nephron of a variety of solutes produces an obligatory water loss (solute diuresis) at roughly isotonic proportions. Consequently, formation of a concentrated urine is prevented. Disease-induced abnormalities of the architecture of the renal medulla (loops of Henle, vasa recta), aberrations in medullary blood flow, and defective transport of NaCl in the ascending limb of Henle also contribute to this defect in urine concentration.

Since patients with CRF are unable to excrete concentrated or dilute urine, they must have access to adequate, and to some extent, relatively constant amounts of water per day to ensure that they have adequate water to eliminate total daily solute loads. For this reason, restriction of fluid intake may be hazardous in patients with CRF. Likewise, impairment of diluting capacity may prevent many patients from excreting excess ingested fluid. →*For discussion of the consequences of the abnormal patterns of water excretion, and the attendant susceptibilities to develop hypo- and hypernatremia, see Chaps. 41 and 261.*

#### TUBULE TRANSPORT OF PHOSPHATE WITH NORMAL AND REDUCED NEPHRON MASS

Under normal physiologic conditions, about 80 to 90% of phosphate is reabsorbed, mainly in the proximal tubule. *Parathyroid hormone* (PTH), by augmenting phosphate excretion via inhibition of this proximal reabsorptive process (Chap. 331), plays a central role in phosphate homeostasis. When dietary phosphate intake increases, a *transient* rise in plasma phosphate concentration is usually observed. This results in a similarly transient reduction in the plasma ionized calcium level (due largely to deposition of calcium phosphate in bone), which is sensed by a specific receptor on parathyroid cells, stimulating PTH secretion. By enhancing fractional phosphate excretion, PTH restores external phosphate balance and normophosphatemia. This enables plasma ionized calcium and hence phosphate levels to return to normal, thereby removing the stimulus to PTH release.

With advancing renal failure and constant dietary intake of phosphate, external phosphate balance is achieved by progressive reduction

in fractional phosphate reabsorption. Enhanced PTH secretion is an important determinant of this phosphaturic response. With succeeding decrements in total GFR, the amount of phosphate filtered by surviving glomeruli is reduced, leading to transient phosphate retention and, therefore, a rise (albeit small) in plasma phosphate concentration. This leads to a small, reciprocal decline in plasma levels of ionized calcium and a corresponding increase in PTH secretion. Although the phosphaturic response of surviving tubules to this elevation in circulating PTH restores plasma phosphate and calcium to normal levels (at least in the "compensated" stage of CRF described by curve *B* in Fig. 259-1), the new steady-state conditions are only achieved at the cost of *persistently elevated plasma PTH levels*. With progressive reductions in GFR, the process is repeated, resulting in substantially elevated PTH levels.

**Alterations in Vitamin D Metabolism** The kidney is normally the major site of conversion of vitamin D to its active metabolites. As discussed in Chap. 331, vitamin D, synthesized in skin or acquired in the diet, undergoes initial hydroxylation in the liver to form 25-hydroxyvitamin D [25(OH)D]. The kidney is the site of a second important conversion to 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D]. This active form of vitamin D acts directly on the parathyroid gland to suppress PTH secretion as well as to enhance intestinal absorption of calcium and promote its resorption from bone. With advancing renal disease, nephron loss reduces the renal capacity for vitamin D hydroxylation; phosphate retention also impairs this reaction. Not only are the circulating levels of 1,25(OH)<sub>2</sub>D diminished in CRF, but the receptors that mediate its action at the parathyroid gland are also diminished. These two effects remove inhibitory influences on PTH secretion, leading again to increased plasma PTH levels. Reduction in circulating 1,25(OH)<sub>2</sub>D levels, by suppressing intestinal calcium absorption, contributes to the development of the hypocalcemia and hyperparathyroidism of CRF (Chap. 261). →*For a discussion of hyperparathyroidism in chronic renal failure, see Chap. 261.*

**HYDROGEN AND BICARBONATE TRANSPORT WITH NORMAL AND REDUCED RENAL MASS** As discussed in Chap. 42, the pH of extracellular fluid is normally maintained within a narrow range (7.36 to 7.44) despite day-to-day fluctuations in the quantity of acids added to the extracellular fluid from dietary and metabolic sources (approximately 1 mmol H<sup>+</sup> per kilogram of body weight per day). These acids consume buffers from both extracellular and intracellular fluid, of which HCO<sub>3</sub><sup>-</sup> is the most important in the intracellular compartment. Such buffering minimizes changes in pH. Long-term effectiveness of the HCO<sub>3</sub><sup>-</sup> buffer system, however, requires mechanisms for replenishment, otherwise unrelenting acquisition of nonvolatile acids from dietary and metabolic sources would ultimately exhaust buffering capacity, culminating in fatal acidosis. The kidneys normally function to prevent this eventuality by *regenerating* bicarbonate, thereby maintaining plasma concentrations of HCO<sub>3</sub><sup>-</sup>. In addition, the kidneys also *reclaim* HCO<sub>3</sub><sup>-</sup> in the glomerular ultrafiltrate.

The *reabsorption* of filtered HCO<sub>3</sub><sup>-</sup> occurs by the following mechanism. Filtered bicarbonate combines with H<sup>+</sup> secreted from proximal tubule cells via the Na<sup>+</sup>/H<sup>+</sup> exchange, to form carbonic acid (H<sub>2</sub>CO<sub>3</sub>). Dehydration of carbonic acid under the influence of *luminal* carbonic anhydrase yields H<sub>2</sub>O and CO<sub>2</sub>, which is free to diffuse from lumen to peritubular blood. In the proximal tubule cell, the OH<sup>-</sup> left behind by the H<sup>+</sup> secretion reacts with CO<sub>2</sub>, under the influence of *intracellular* carbonic anhydrase, forming HCO<sub>3</sub><sup>-</sup>. This ion is transported across the contraluminal proximal tubule cell membrane, via an electrogenic Na/HCO<sub>3</sub><sup>-</sup> cotransporter, to reenter the extracellular HCO<sub>3</sub><sup>-</sup> pool. The net result is *reclamation of a filtered bicarbonate ion*. Hydrogen ions in the urine are bound to filtered buffers (e.g., phosphate) in amounts equivalent to the amounts of alkali required to titrate the pH of the urine up to the pH of the blood (the so-called titratable acid). It is not usually possible to excrete all the daily acid load in the form of titratable acid due to limits of urinary pH. Metabolism of glutamine by proximal tubule cells to yield ammonium (ammoniogenesis) serves as an additional mechanism for H<sup>+</sup> elimination and bicarbonate re-

generation. Glutamine metabolism forms not only NH<sub>4</sub><sup>+</sup> (i.e., NH<sub>3</sub> plus H<sup>+</sup>) but also HCO<sub>3</sub><sup>-</sup>, which is transported across the proximal tubule (HCO<sub>3</sub><sup>-</sup> regeneration). The NH<sub>4</sub><sup>+</sup> must be excreted in the urine for this process to be effective in bicarbonate regeneration. *Ammoniogenesis* is responsive to the acid-base needs of the individual. When faced with an acute acid burden and an increased need for HCO<sub>3</sub><sup>-</sup> regeneration, the rate of renal ammonia synthesis increases sharply.

The quantity of hydrogen ions excreted as titratable acid and NH<sub>4</sub><sup>+</sup> is equal to the quantity of HCO<sub>3</sub><sup>-</sup> regenerated in tubule cells and added to plasma. Under steady-state conditions, the net quantity of acid excreted into the urine (the sum of titratable acid and NH<sub>4</sub><sup>+</sup> less HCO<sub>3</sub><sup>-</sup>) must equal the quantity of acid gained by the extracellular fluid from all sources. Metabolic acidosis and alkalosis result when this delicate balance is perturbed, the former the result of insufficient net acid excretion, and the latter due to excessive acid excretion (Chap. 42).

Progressive loss of renal function usually causes little or no change in arterial pH, plasma bicarbonate concentration, or arterial carbon dioxide tension (P<sub>CO<sub>2</sub></sub>) until GFR falls below 25% of normal. Thereafter, all three tend to decline as *metabolic acidosis* ensues. In general, the metabolic acidosis of CRF is not due to overproduction of acids but is rather a reflection of nephron loss, which limits the amount of NH<sub>3</sub> (and therefore also HCO<sub>3</sub><sup>-</sup>) that can be generated. Although surviving nephrons appear to be capable of generating supranormal amounts of NH<sub>3</sub> *per nephron*, the diminished nephron population causes overall production to be reduced to an extent that is insufficient to permit adequate buffering of H<sup>+</sup> in urine. As a result, although patients with CRF may be able to acidify their urine normally (i.e., urine pH as low as 4.5), the defect in NH<sub>3</sub> production limits daily net acid excretion to 30 to 40 mmol, or one-half to two-thirds the quantity of nonvolatile acid added to the extracellular fluid in the same time period. Metabolic acidosis resulting from this daily positive balance of H<sup>+</sup> is seldom florid in CRF of mild to moderate severity. Relative stability of plasma bicarbonate (albeit at reduced levels of 14 to 18 mmol/L) is maintained at the expense of buffering by bone. Because it contains large reserves of alkaline salts (calcium phosphate and calcium bicarbonate), bone constitutes a major reserve of buffering capacity. Dissolution of these buffers contributes to the osteodystrophy of CRF (see Fig. 261-1).

Although the acidosis of CRF is due to loss of tubule mass, it nevertheless depends to a large part on the level of GFR. When GFR is reduced to only a moderate extent (i.e., to about 50% of normal), retention of anions, principally sulfates and phosphates, is not pronounced. Therefore, as the plasma HCO<sub>3</sub><sup>-</sup> falls owing to dysfunction or loss of tubules, retention of Cl<sup>-</sup> by the kidneys leads to a *hyperchloremic acidosis*. At this stage *the anion gap is normal*. With further reductions in GFR and progressive azotemia, however, the retention of phosphates, sulfates, and other *unmeasured* anions ensues and plasma Cl<sup>-</sup> falls to normal levels despite the reduction in plasma HCO<sub>3</sub><sup>-</sup> concentration. *An elevated anion gap therefore develops.*

#### TUBULE POTASSIUM TRANSPORT WITH NORMAL AND REDUCED NEPHRON MASS

As with H<sup>+</sup>, the concentration of K<sup>+</sup> in extracellular fluid is normally maintained within a relatively narrow range, 4 to 5 mmol/L. At least 95% of total-body K<sup>+</sup> is in the intracellular compartment, where the intracellular concentration is approximately 160 mmol/L. Normal individuals maintain external K<sup>+</sup> balance by excreting amounts into the urine that equal the intake, less the relatively small losses in stool and sweat. K<sup>+</sup> is freely filtered at the glomerulus, although the amount excreted usually represents no more than about 20% of the quantity filtered. The great bulk of the K<sup>+</sup> filtered is reabsorbed in the early portions of the nephron, about two-thirds in the proximal tubule, and an additional 20 to 25% in the loop of Henle. A K<sup>+</sup> secretory process operates in the distal tubule and terminal nephron segments. This process is largely dependent on Na<sup>+</sup> reabsorption and the accompanying lumen-negative voltage creating an electrical gradient across the tubule wall, favoring K<sup>+</sup> secretion into the lumen of the distal tubule and collecting duct.

The ability to maintain external  $K^+$  balance and normal plasma  $K^+$  concentration until relatively late in the course of CRF is a consequence primarily of a progressive increase in fractional excretion of  $K^+$ . Greatly enhanced rates of  $K^+$  secretion occur in distal portions of surviving tubules. The augmented secretion rate of aldosterone contributes to enhanced tubule secretion of  $K^+$ . In addition, both the increased distal tubule flow rates in surviving nephrons, due to the osmotic diuresis, and enhanced luminal electronegativity, created by the increased presence of highly impermeable anions such as phosphate and sulfate, enhance  $K^+$  secretion. Aldosterone also stimulates net entry of  $K^+$  into the lumen of the colon, a mechanism known to be

enhanced in CRF. —For more detailed discussions of abnormal  $K^+$  homeostasis in acute and chronic forms of renal failure, see Chaps. 260 and 261.

#### FURTHER READING

- BRENNER BM et al: Diverse biological actions of atrial natriuretic peptides. *Physiol Rev* 70:665, 1990
- O'CALLAGHAN CA, BRENNER BM: *The Kidney at a Glance*. Oxford, Blackwell Science Ltd., 2000
- TAAL MW et al: Adaptation to nephron loss, in *Brenner and Rector's The Kidney*, 7th ed, BM Brenner, (ed). Philadelphia, Saunders, 2004
- TAAL MW, BRENNER BM: Renoprotective benefits of RAS inhibition: From ACEI to angiotensin II antagonists. *Kidney Int* 57:1803, 2000

## 260

### ACUTE RENAL FAILURE

Hugh R. Brady, Barry M. Brenner

Acute renal failure (ARF) is a syndrome characterized by rapid decline in glomerular filtration rate (hours to days), retention of nitrogenous waste products, and perturbation of extracellular fluid volume and electrolyte and acid-base homeostasis. ARF complicates approximately 5% of hospital admissions and up to 30% of admissions to intensive care units. Oliguria (urine output < 400 mL/d) is a frequent but not invariable clinical feature (~50%). ARF is usually asymptomatic and diagnosed when biochemical monitoring of hospitalized patients reveals a recent increase in blood urea and creatinine concentrations. It may complicate a wide range of diseases, which for purposes of diagnosis and management are conveniently divided into three categories: (1) diseases that cause renal hypoperfusion without compromising the integrity of renal parenchyma (*prerenal ARF*, *prerenal azotemia*) (~55%); (2) diseases that directly involve renal parenchyma (*intrinsic renal ARF*, *renal azotemia*) (~40%); and (3) diseases associated with urinary tract obstruction (*postrenal ARF*, *postrenal azotemia*) (~5%). Most ARF is reversible, the kidney being relatively unique among major organs in its ability to recover from almost complete loss of function. Nevertheless, ARF is associated with major in-hospital morbidity and mortality, in large part due to the serious nature of the illnesses that precipitate the ARF.

#### ETIOLOGY AND PATHOPHYSIOLOGY

**PRERENAL ARF (PRERENAL AZOTEMIA)** Prerenal ARF is the most common form of ARF and represents a physiologic response to mild to moderate renal hypoperfusion. Prerenal ARF is by definition rapidly reversible upon restoration of renal blood flow and glomerular ultrafiltration pressure. Renal parenchymal tissue is not damaged; indeed, kidneys from individuals with prerenal ARF function well when transplanted into recipients with normal cardiovascular function. More severe hypoperfusion may lead to ischemic injury of renal parenchyma and intrinsic renal ARF (see below). Thus, prerenal ARF and intrinsic renal ARF due to ischemia are part of a spectrum of manifestations of renal hypoperfusion. As shown in Table 260-1, prerenal ARF can complicate any disease that induces hypovolemia, low cardiac output, systemic vasodilatation, or selective intrarenal vasoconstriction.

Hypovolemia leads to a fall in mean systemic arterial pressure, which is detected as reduced stretch by arterial (e.g., carotid sinus) and cardiac baroreceptors. Activated baroreceptors trigger a coordinated series of neural and humoral responses designed to restore blood volume and arterial pressure. These include activation of the sympathetic nervous system and renin-angiotensin-aldosterone system and release of arginine vasopressin (AVP; formerly called antidiuretic hormone). Norepinephrine, angiotensin II, and AVP act in concert in an attempt to preserve cardiac and cerebral perfusion by stimulating vasoconstriction in relatively "nonessential" vascular beds, such as the

musculoskeletal and splanchnic circulations, by inhibiting salt loss through sweat glands, by stimulating thirst and salt appetite, and by promoting renal salt and water retention. Glomerular perfusion, ultrafiltration pressure, and filtration rate are preserved during mild hypoperfusion through several compensatory mechanisms. Stretch receptors in afferent arterioles, in response to a reduction in perfusion pressure, trigger afferent arteriolar vasodilatation through a local myogenic reflex (autoregulation). Biosynthesis of vasodilator prostaglandins (e.g., prostaglandin  $E_2$  and prostacyclin) is also enhanced, and these compounds preferentially dilate afferent arterioles. In addition, angiotensin II induces preferential constriction of efferent arterioles. As a result, intraglomerular pressure is maintained, the fraction of plasma flowing through glomerular capillaries that is filtered is increased (filtration fraction), and glomerular filtration rate (GFR) is preserved. During states of more severe hypoperfusion, these compensatory responses are overwhelmed and GFR falls, leading to prerenal ARF.

Autoregulatory dilatation of afferent arterioles is maximal at mean systemic arterial blood pressures of ~80 mmHg, and hypotension below this level is associated with a precipitous decline in GFR. Lesser degrees of hypotension may provoke prerenal ARF in the elderly and in patients with diseases affecting the integrity of afferent arterioles (e.g., hypertensive nephrosclerosis, diabetic vasculopathy). In addition, drugs that interfere with adaptive responses in the renal microcirculation may convert compensated renal hypoperfusion into overt prerenal ARF or trigger progression of prerenal ARF to ischemic intrinsic renal ARF (see below). Pharmacologic inhibitors of either renal prostaglandin biosynthesis [*cyclooxygenase inhibitors*; nonsteroidal anti-inflammatory drugs (NSAIDs)] or angiotensin-converting enzyme (ACE) activity (ACE inhibitors) and angiotensin II receptor blockers are the major culprits and should be used judiciously in the setting of suspected renal hypoperfusion. NSAIDs do not compromise GFR in healthy individuals but may precipitate prerenal ARF in patients with volume depletion or in those with chronic renal insufficiency in whom GFR is maintained, in part, through prostaglandin-mediated hyperfiltration by the remaining functional nephrons. ACE inhibitors should be used with special care in patients with bilateral renal artery stenosis or unilateral stenosis in a solitary functioning kidney. In these settings glomerular perfusion and filtration may be exquisitely dependent on the actions of angiotensin II. Angiotensin II preserves glomerular filtration pressure distal to stenoses by elevating systemic arterial pressure and by triggering selective constriction of efferent arterioles. ACE inhibitors blunt these responses and precipitate ARF, usually reversible, in ~30% of these patients.

**Hepatorenal Syndrome** This is a particularly aggressive form of ARF, with many of the features of prerenal ARF, that frequently complicates hepatic failure due to advanced cirrhosis or other liver diseases, including malignancy, hepatic resection, and biliary obstruction. In full-blown hepatorenal syndrome, ARF progresses even after optimization

**PRERENAL ARF**

- I. Hypovolemia
  - A. Hemorrhage, burns, dehydration
  - B. Gastrointestinal fluid loss: vomiting, surgical drainage, diarrhea
  - C. Renal fluid loss: diuretics, osmotic diuresis (e.g., diabetes mellitus), hypoadrenalism
  - D. Sequestration in extravascular space: pancreatitis, peritonitis, trauma, burns, severe hypoalbuminemia
- II. Low cardiac output
  - A. Diseases of myocardium, valves, and pericardium; arrhythmias; tamponade
  - B. Other: pulmonary hypertension, massive pulmonary embolus, positive pressure mechanical ventilation
- III. Altered renal systemic vascular resistance ratio
  - A. Systemic vasodilatation: sepsis, antihypertensives, afterload reducers, anesthesia, anaphylaxis
  - B. Renal vasoconstriction: hypercalcemia, norepinephrine, epinephrine, cyclosporine, tacrolimus, amphotericin B
  - C. Cirrhosis with ascites (hepatorenal syndrome)
- IV. Renal hypoperfusion with impairment of renal autoregulatory responses
  - Cyclooxygenase inhibitors, angiotensin-converting enzyme inhibitors
- V. Hyperviscosity syndrome (rare)
  - Multiple myeloma, macroglobulinemia, polycythemia

**INTRINSIC RENAL ARF**

- I. Renovascular obstruction (bilateral or unilateral in the setting of one functioning kidney)
    - A. Renal artery obstruction: atherosclerotic plaque, thrombosis, embolism, dissecting aneurysm, vasculitis
    - B. Renal vein obstruction: thrombosis, compression
  - II. Disease of glomeruli or renal microvasculature
    - A. Glomerulonephritis and vasculitis
    - B. Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, toxemia of pregnancy, accelerated hypertension, radiation nephritis, systemic lupus erythematosus, scleroderma
  - III. Acute tubular necrosis
    - A. Ischemia: as for prerenal ARF (hypovolemia, low cardiac output, renal vasoconstriction, systemic vasodilatation), obstetric complications (abruptio placentae, postpartum hemorrhage)
    - B. Toxins
      1. Exogenous: radiocontrast, cyclosporine, antibiotics (e.g., aminoglycosides), chemotherapy (e.g., cisplatin), organic solvents (e.g., ethylene glycol), acetaminophen, illegal abortifacients
      2. Endogenous: rhabdomyolysis, hemolysis, uric acid, oxalate, plasma cell dyscrasia (e.g., myeloma)
  - IV. Interstitial nephritis
    - A. Allergic: antibiotics (e.g.,  $\beta$ -lactams, sulfonamides, trimethoprim, rifampicin), nonsteroidal anti-inflammatory agents, diuretics, captopril
    - B. Infection: bacterial (e.g., acute pyelonephritis, leptospirosis), viral (e.g., cytomegalovirus), fungal (e.g., candidiasis)
    - C. Infiltration: lymphoma, leukemia, sarcoidosis
    - D. Idiopathic
  - V. Intratubular deposition and obstruction
    - Myeloma proteins, uric acid, oxalate, acyclovir, methotrexate, sulfonamides
  - VI. Renal allograft rejection
- POSTRENAL ARF (OBSTRUCTION)**
- I. Ureteric
    - Calculi, blood clot, sloughed papillae, cancer, external compression (e.g., retroperitoneal fibrosis)
  - II. Bladder neck
    - Neurogenic bladder, prostatic hypertrophy, calculi, cancer, blood clot
  - III. Urethra
    - Stricture, congenital valve, phimosis

renal ARF into (1) diseases of larger renal vessels, (2) diseases of the renal microcirculation and glomeruli, (3) ischemic and nephrotoxic ARF, and (4) tubulointerstitial inflammation (Table 260-1). Most intrinsic renal ARF is triggered by ischemia (ischemic ARF) or nephrotoxins (nephrotoxic ARF), insults that classically induce acute tubular necrosis (ATN). Accordingly, the terms ARF and ATN are usually used interchangeably in these settings. However, as many as 20 to 30% of patients with ischemic or nephrotoxic ARF do not have clinical (granular or tubular cell urinary casts) or morphologic evidence of tubular necrosis, underscoring the role of sublethal injury to tubular epithelium and injury to other renal cells (e.g., endothelial cells) in the pathophysiology of this syndrome.

**Etiology and Pathophysiology of Ischemic ARF** Prerenal ARF and ischemic ARF are part of a spectrum of manifestations of renal hypoperfusion. Ischemic ARF differs from prerenal ARF in that the hypoperfusion induces ischemic injury to renal parenchymal cells, particularly tubular epithelium, and recovery typically takes 1 to 2 weeks after normalization of renal perfusion as it requires repair and regeneration of renal cells. In its most extreme form, ischemia leads to bilateral renal cortical necrosis and irreversible renal failure. Ischemic ARF occurs most frequently in patients undergoing major cardiovascular surgery or suffering severe trauma, hemorrhage, sepsis, and/or volume depletion (Table 260-1). Ischemic ARF can also complicate milder forms of true hypovolemia or reduced "effective" arterial blood volume if they occur in the presence of other insults (e.g., nephrotoxins or sepsis) or in patients with compromised autoregulatory defense mechanisms or pre-existing renal disease.

The course of ischemic ARF is typically characterized by three phases: the initiation, maintenance, and recovery phases. The *initiation phase* (hours to days) is the initial period of renal hypoperfusion during which ischemic injury is evolving. GFR declines because (1) glomerular ultrafiltration pressure is reduced as a consequence of the fall in renal blood flow, (2) the flow of glomerular filtrate within tubules is obstructed by casts comprised of epithelial cells and necrotic debris derived from ischemic tubule epithelium, and (3) there is backleak of glomerular filtrate through injured tubular epithelium (Fig. 260-1). Ischemic injury is most prominent in the terminal medullary portion of the proximal tubule ( $S_3$  segment, pars recta) and the medullary portion of the thick ascending limb of the loop of Henle. Both segments have high rates of active (ATP-dependent) solute transport and oxygen consumption and are located in a zone of the kidney (the outer medulla) that is relatively ischemic, even under basal conditions, by virtue of the unique countercurrent arrangement of the medullary vasculature. Cellular ischemia results in a series of alterations in energetics, ion transport, and membrane integrity that ultimately lead to cell injury and, if severe, cell apoptosis or necrosis. These alterations include depletion of ATP, inhibition of active sodium transport and transport of other solutes, impairment of cell volume regulation and cell swelling, cytoskeletal disruption and loss of cell polarity, cell-cell and cell-matrix attachment, accumulation of intracellular calcium, altered phospholipid metabolism, oxygen free radical formation, and peroxidation of membrane lipids. Importantly, renal injury can be limited by restoration of renal blood flow during this period.

The initiation phase is followed by a *maintenance phase* (typically 1 to 2 weeks) during which renal cell injury is established, GFR stabilizes at its nadir (typically 5 to 10 mL/min), urine output is lowest, and uremic complications arise (see below). The reasons why the GFR remains low during this phase, despite correction of systemic hemodynamics, are still being defined. Putative mechanisms include persistent intrarenal vasoconstriction and medullary ischemia triggered by dysregulated release of vasoactive mediators from injured endothelial cells (e.g., decreased nitric oxide, increased endothelin-1, adenosine, and platelet-activating factor), congestion of medullary blood vessels, and reperfusion injury induced by reactive oxygen species and other mediators derived from leukocytes or renal parenchymal cells

of systemic hemodynamics and carries a mortality rate of >90%.  
 →The diagnosis and management of this condition are discussed in Chaps. 289 and 291.

**INTRINSIC RENAL ARF (INTRINSIC RENAL AZOTEMIA)** Intrinsic renal ARF can complicate many diverse diseases of the renal parenchyma. From a clinicopathologic viewpoint, it is useful to divide the causes of intrinsic

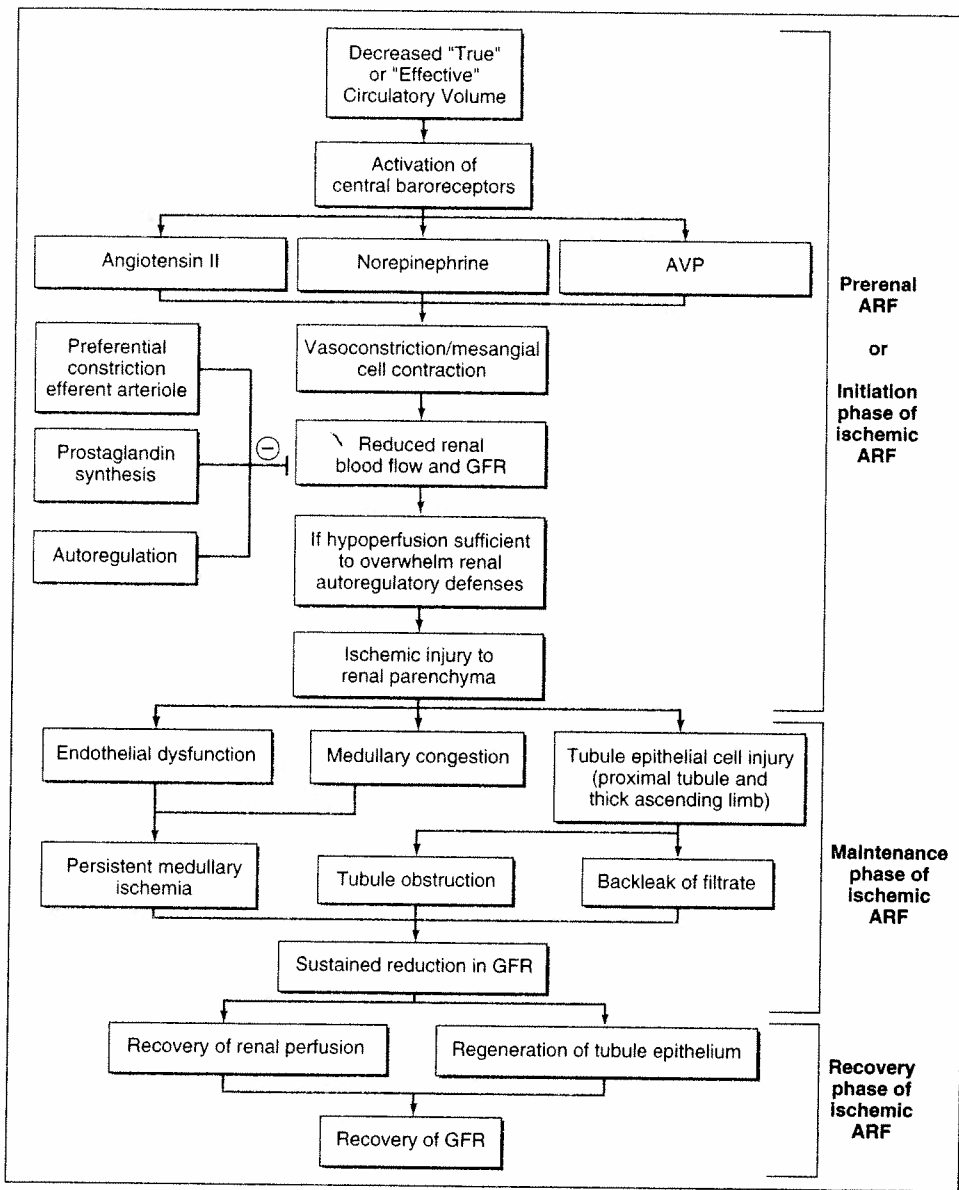


FIGURE 260-1 Overview of the pathophysiology of prerenal ARF and ischemic intrinsic renal ARF: A spectrum of manifestations of renal hypoperfusion. ARF, acute renal failure; AVP, arginine vasopressin; GFR, glomerular filtration rate.

(Fig. 260-1). In addition, epithelial cell injury per se may contribute to persistent intrarenal vasoconstriction by a process termed *tubuloglomerular feedback*. Specialized epithelial cells in the macula densa region of distal tubules detect increases in distal salt (probably chloride) delivery that occur as a consequence of impaired reabsorption by more proximal nephron segments. Macula densa cells in turn stimulate constriction of adjacent afferent arterioles by a poorly defined mechanism and further compromise glomerular perfusion and filtration, thereby contributing to a vicious cycle. A *recovery phase* is characterized by renal parenchymal cell, particularly tubule epithelial cell, repair and regeneration and a gradual return of GFR to or towards premorbid levels. The recovery phase may be complicated by a marked diuretic phase due to excretion of retained salt and water and other solutes, continued use of diuretics, and/or delayed recovery of epithelial cell function (solute and water reabsorption) relative to glomerular filtration (see below).

**Etiology and Pathophysiology of Nephrotoxic ARF** Acute intrinsic renal ARF can complicate exposure to many structurally diverse pharmacologic agents (Table 260-1). With most nephrotoxins, the incidence of ARF is increased in the elderly and in patients with preexisting chronic renal insufficiency, true or "effective" hypovolemia, or concomitant exposure to other toxins.

Intrarenal vasoconstriction is a pivotal event in ARF that is triggered by *radiocontrast agents* (contrast nephropathy), *cyclosporine*, and *tacrolimus (FK506)*. In keeping with this pathophysiology, both agents induce ARF that shares features with prerenal ARF: namely, an acute fall in renal blood flow and GFR, a relatively benign urine sediment, and a low fractional excretion of sodium (see below). Severe cases may show clinical or pathologic evidence of ATN. Contrast nephropathy classically presents as an acute (onset within 24 to 48 h) but reversible (peak 3 to 5 days, resolution within 1 week) rise in blood urea nitrogen and creatinine and is most common in individuals with preexisting chronic renal insufficiency, diabetes mellitus, congestive heart failure, hypovolemia, or multiple myeloma. The syndrome appears to be dose-related, and its incidence is only slightly reduced in high-risk individuals by use of more expensive low osmolality, nonionic contrast agents.

Direct toxicity to tubule epithelial cells and/or intratubular obstruction are major pathophysiologic events in ARF induced by many antibiotics and anticancer drugs. Frequent offenders are the antimicrobial agents, such as acyclovir, foscarnet, aminoglycosides, amphotericin B, and pentamidine, and chemotherapeutic agents, such as cisplatin, carboplatin, and ifosfamide. ARF complicates 10 to 30% of courses of *aminoglycoside antibiotics*, even in the presence of therapeutic levels. *Amphotericin B* causes dose-related ARF through intrarenal vasoconstriction and direct toxicity to proximal tubule epithelium. Cisplatin and carboplatin, like the aminoglycosides, are accumulated by proximal tubule cells and typically provoke ARF after 7 to 10 days of exposure by inducing mitochondrial injury, inhibition of ATPase activity and solute transport, free radical-mediated injury to cell membranes, apoptosis, and/or necrosis.

The most common endogenous nephrotoxins are calcium, myoglobin, hemoglobin, urate, oxalate, and myeloma light chains. Hypercalcemia can compromise GFR, predominantly by inducing intrarenal vasoconstriction. Calcium phosphate deposition within the kidney may also contribute. Both *rhabdomyolysis* and *hemolysis* can induce ARF, particularly in hypovolemic or acidotic individuals. Myoglobinuric ARF complicates approximately 30% of cases of rhabdomyolysis. Common causes of the latter include traumatic crush injury, acute muscle ischemia, seizures, excessive exercise, heat stroke or malignant hyperthermia, intoxications (e.g., alcohol, cocaine), and infectious or metabolic disorders. ARF due to hemolysis is relatively rare and is observed following massive blood transfusion reactions. It has been postulated that myoglobin and hemoglobin or other compounds released from muscle or red blood cells cause ARF via toxic effects on tubule epithelial cells, by promoting intrarenal oxidative stress and by inducing intratubular cast formation. Hypovolemia or acidosis may contribute to the pathogenesis of ARF in this setting by promoting intratubular cast formation. In addition, both hemoglobin and myoglobin are potent inhibitors of nitric oxide bioactivity and may trigger

intrarenal vasoconstriction and ischemia in patients with borderline renal hypoperfusion. The formation of intratubular casts containing filtered immunoglobulin light chains and other proteins, including Tamm-Horsfall protein produced by thick ascending limb cells, is the major trigger for ARF in patients with *multiple myeloma* (myeloma cast nephropathy). In addition, light chains are directly toxic to tubule epithelial cells. Intratubular obstruction is also an important cause of ARF in patients with severe *hyperuricosuria* or *hyperoxaluria*. Acute uric acid nephropathy typically complicates treatment of lymphoproliferative or myeloproliferative disorders but occasionally occurs in other forms of primary or secondary hyperuricemia if the urine is concentrated.

**Pathology of Ischemic and Nephrotoxic ARF** The classic pathologic features of ischemic ARF are patchy and focal necrosis of tubule epithelium with detachment from its basement membrane and occlusion of tubule lumens with casts composed of intact or degenerating epithelial cells, cellular debris, Tamm-Horsfall mucoprotein, and pigments. Leukocyte accumulation is frequently observed in vasa recta; however, the morphology of the glomeruli and renal vasculature is characteristically normal. Necrosis is most severe in the straight portion (*pars recta*) of proximal tubules but may also affect the medullary thick ascending limb of the loop of Henle.

In nephrotoxic ARF, morphologic changes tend to be most prominent in both the convoluted and straight portions of proximal tubules. Tubule cell necrosis is less pronounced than in ischemic ARF.

**Other Causes of Intrinsic Renal ARF** Patients with advanced atherosclerosis can develop ARF after manipulation of the aorta or renal arteries at surgery or angiography, following trauma, or, rarely, spontaneously due to embolization of cholesterol crystals to the renal vasculature (atheroembolic ARF). Cholesterol crystals lodge in small- and medium-sized arteries and incite a giant cell and fibrotic reaction in the vessel wall with narrowing or obstruction of the vessel lumen. Atheroembolic ARF is frequently irreversible. A myriad of structurally diverse pharmacologic agents induce ARF by triggering allergic interstitial nephritis, a disease characterized by infiltration of the tubulointerstitium by granulocytes (typically but not invariably eosinophils), macrophages, and/or lymphocytes and by interstitial edema. The most common offenders are antibiotics (e.g., penicillins, cephalosporins, trimethoprim, sulfonamides, rifampicin) and NSAIDs (Table 260-1).

**POSTRENAL ARF** (See also Chap. 270) Urinary tract obstruction accounts for fewer than 5% of cases of ARF. Because one kidney has sufficient clearance capacity to excrete the nitrogenous waste products generated daily, ARF from obstruction requires obstruction to urine flow between the external urethral meatus and bladder neck, bilateral ureteric obstruction, or unilateral ureteric obstruction in a patient with one functioning kidney or with preexisting chronic renal insufficiency. Bladder neck obstruction represents the most common cause of postrenal ARF and is usually due to prostatic disease (e.g., hypertrophy, neoplasia, or infection), neurogenic bladder, or therapy with anticholinergic drugs. Less common causes of acute lower urinary tract obstruction include blood clots, calculi, and urethritis with spasm. Ureteric obstruction may result from intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae), infiltration of the ureteric wall (e.g., neoplasia), or external compression (e.g., retroperitoneal fibrosis, neoplasia or abscess, inadvertent surgical ligature). During the early stages of obstruction (hours to days), continued glomerular filtration leads to increased intraluminal pressure upstream to the site of obstruction. As a result there is gradual distention of the proximal ureter, renal pelvis, and calyces and a fall in GFR. Acute obstruction is initially associated with modest increase in renal blood flow, but arteriolar vasoconstriction soon supervenes, leading to a further decline in glomerular filtration.

#### CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

Patients presenting with renal failure should be assessed initially to determine if the decline in GFR is acute or chronic. An acute process

is easily established if a review of laboratory records reveals a recent rise in blood urea and creatinine levels, but previous measurements are not always available. Findings that suggest chronic renal failure (Chap. 261) include anemia, neuropathy, and radiologic evidence of renal osteodystrophy or small scarred kidneys. However, it should be noted that anemia may also complicate ARF (see below), and renal size may be normal or increased in several chronic renal diseases (e.g., diabetic nephropathy, amyloidosis, polycystic kidney disease). Once a diagnosis of ARF has been established, several issues should be addressed promptly: (1) the identification of the cause of ARF, (2) the elimination of the triggering insult (e.g., nephrotoxin) and/or institution of disease-specific therapies, and (3) the prevention and management of uremic complications.

**CLINICAL ASSESSMENT** Clinical clues to *prerenal* ARF are symptoms of thirst and orthostatic dizziness and physical evidence of orthostatic hypotension and tachycardia, reduced jugular venous pressure, decreased skin turgor, dry mucous membranes, and reduced axillary sweating. Case records should be reviewed for documentation of a progressive fall in urine output and body weight and recent initiation of treatment with NSAIDs, ACE inhibitors, or angiotensin II receptor blockers. Careful clinical examination may reveal stigmata of chronic liver disease and portal hypertension, advanced cardiac failure, sepsis, or other causes of reduced "effective" arterial blood volume (Table 260-1).

*Intrinsic renal* ARF due to ischemia is likely following severe renal hypoperfusion complicating hypovolemic or septic shock or following major surgery. The likelihood of ischemic ARF is increased further if ARF persists despite normalization of systemic hemodynamics. Diagnosis of nephrotoxic ARF requires careful review of the clinical data and pharmacy, nursing, and radiology records for evidence of recent exposure to nephrotoxic medications or radiocontrast agents or to endogenous toxins (e.g., myoglobin, hemoglobin, uric acid, myeloma protein, or elevated levels of serum calcium).

Although ischemic and nephrotoxic ARF account for more than 90% of cases of intrinsic renal ARF, other renal parenchymal diseases must be considered (Table 260-2). Flank pain may be a prominent symptom following occlusion of a renal artery or vein and with other parenchymal diseases distending the renal capsule (e.g., severe glomerulonephritis or pyelonephritis). Subcutaneous nodules, livedo reticularis, bright orange retinal arteriolar plaques, and digital ischemia, despite palpable pedal pulses, are clues to atheroembolization. ARF in association with oliguria, edema, hypertension, and an "active" urine sediment (nephritic syndrome) suggests acute glomerulonephritis or vasculitis. Malignant hypertension is a likely cause of ARF in patients with severe hypertension and evidence of hypertensive injury to other organs (e.g., left ventricular hypertrophy and failure, hypertensive retinopathy and papilledema, neurologic dysfunction). Fever, arthralgias, and a pruritic erythematous rash following exposure to a new drug suggest allergic interstitial nephritis, although systemic features of hypersensitivity are frequently absent.

*Postrenal* ARF presents with suprapubic and flank pain due to distention of the bladder and of the renal collecting system and capsule, respectively. Colicky flank pain radiating to the groin suggests acute ureteric obstruction. Prostatic disease is likely if there is a history of nocturia, frequency, and hesitancy and enlargement or induration of the prostate on rectal examination. Neurogenic bladder should be suspected in patients receiving anticholinergic medications or with physical evidence of autonomic dysfunction. Definitive diagnosis of postrenal ARF hinges on judicious use of radiologic investigations and rapid improvement in renal function following relief of obstruction.

**URINALYSIS** Anuria suggests complete urinary tract obstruction but may complicate severe cases of prerenal or intrinsic renal ARF. Wide fluctuations in urine output raise the possibility of intermittent obstruction, whereas patients with partial urinary tract obstruction can present with polyuria due to impairment of urine concentrating mechanisms.

TABLE 250-2 Useful Clinical Features, Urinary Findings, and Confirmatory Tests in the Differential Diagnosis of Major Causes of ARF

Cause of Acute Renal Failure	Suggestive Clinical Features	Typical Urinalysis	Some Confirmatory Tests
I. Prerenal ARF	Evidence of true volume depletion (thirst, postural or absolute hypotension and tachycardia, low jugular venous pressure, dry mucous membranes/axillae, weight loss, fluid output > input) or decreased "effective" circulatory volume (e.g., heart failure, liver failure), treatment with NSAIDs or ACE inhibitors	Hyaline casts FE <sub>Na</sub> <1% U <sub>Na</sub> <10 mmol/L SG >1.018	Occasionally requires invasive hemodynamic monitoring; rapid resolution of ARF upon restoration of renal perfusion
II. Intrinsic renal ARF			
A. Diseases involving large renal vessels			
1. Renal artery thrombosis	History of atrial fibrillation or recent myocardial infarct; flank or abdominal pain	Mild proteinuria Occasionally red cells	Elevated LDH with normal transaminases, renal arteriogram
2. Atheroembolism	Age usually > 50 years, recent manipulation of aorta, retinal plaques, subcutaneous nodules, palpable purpura, livedo reticularis, vasculopathy, hypertension, anticoagulation	Often normal, eosinophiluria, rarely casts	Eosinophilia, hypocomplementemia, skin biopsy, renal biopsy
3. Renal vein thrombosis	Evidence of nephrotic syndrome or pulmonary embolism, flank pain	Proteinuria, hematuria	Inferior vena cavagram and selective renal venogram
B. Diseases of small vessels and glomeruli			
1. Glomerulonephritis/vasculitis	Compatible clinical history (e.g., recent infection), sinusitis, lung hemorrhage, skin rash or ulcers, arthralgias, new cardiac murmur, history of hepatitis B or C infection	Red cell or granular casts, red cells, white cells, mild proteinuria	Low C3, ANCA, anti-GBM Ab, ANA, ASO, anti-DNase, cryoglobulins, blood cultures, renal biopsy
2. Hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura	Compatible clinical history (e.g., recent gastrointestinal infection, cyclosporine, anovulants), fever, pallor, ecchymoses, neurologic abnormalities	May be normal, red cells, mild proteinuria, rarely red cell/granular casts	Anemia, thrombocytopenia, schistocytes on blood smear, increased LDH, renal biopsy
3. Malignant hypertension	Severe hypertension with headaches, cardiac failure, retinopathy, neurologic dysfunction, papilledema	Red cells, red cell casts, proteinuria	LVH by echocardiography/ECG, resolution of ARF with control of blood pressure
C. ARF mediated by ischemia or toxins (ATN)			
1. Ischemia	Recent hemorrhage, hypotension (e.g., cardiac arrest), surgery	Muddy brown granular or tubular epithelial cell casts FE <sub>Na</sub> >1% U <sub>Na</sub> >20 mmol/L SG <1.015	Clinical assessment and urinalysis usually sufficient for diagnosis
2. Exogenous toxins	Recent radiocontrast study, nephrotoxic antibiotics or anticancer agents often coexistent with volume depletion, sepsis, or chronic renal insufficiency	Muddy brown granular or tubular epithelial cell casts FE <sub>Na</sub> >1% U <sub>Na</sub> >20 mmol/L SG <1.015	Clinical assessment and urinalysis usually sufficient for diagnosis
3. Endogenous toxins	History suggestive of rhabdomyolysis (seizures, coma, ethanol abuse, trauma)  History suggestive of hemolysis (blood transfusion)  History suggestive of tumor lysis (recent chemotherapy), myeloma (bone pain), or ethylene glycol ingestion	Urine supernatant positive for heme  Urine supernatant pink and positive for heme  Urate crystals, dipstick-negative proteinuria, oxalate crystals, respectively	Hyperkalemia, hyperphosphatemia, hypocalcemia, increased circulating myoglobin, CPK (MM), and uric acid  Hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, pink plasma positive for hemoglobin  Hyperuricemia, hyperkalemia, hyperphosphatemia (for tumor lysis); circulating or urinary monoclonal spike (for myeloma); toxicology screen, acidosis, osmolar gap (for ethylene glycol)
D. Acute diseases of the tubulointerstitium			
1. Allergic interstitial nephritis	Recent ingestion of drug, and fever, rash, or arthralgias	White cell casts, white cells (frequently eosinophiluria), red cells, rarely red cell casts, proteinuria (occasionally nephrotic)	Systemic eosinophilia, skin biopsy of rash (leukocytoclastic vasculitis), renal biopsy
2. Acute bilateral pyelonephritis	Flank pain and tenderness, toxic, febrile	Leukocytes, proteinuria, red cells, bacteria	Urine and blood cultures
III. Postrenal ARF	Abdominal or flank pain, palpable bladder	Frequently normal, hematuria if stones, hemorrhage, malignancy, or prostatic hypertrophy	Plain film, renal ultrasound, IVP, retrograde or antegrade pyelography, CT scan

Note: U<sub>Na</sub>, urine sodium concentration; SG, specific gravity; LDH, lactate dehydrogenase; C3, complement component; ANCA, antineutrophil cytoplasmic autoantibody; anti-GBM Ab, anti-glomerular basement membrane antibody; ANA, antinuclear antibody; ASO, anti-

streptolysin O; LVH, left ventricular hypertrophy; ECG, electrocardiogram; CK, creatine kinase; IVP, intravenous pyelogram; CT, computed tomography.

Source: Adapted with permission from Brady et al.

In prerenal ARF, the sediment is characteristically acellular and contains transparent hyaline casts ("bland," "benign," "inactive" urine sediment). Hyaline casts are formed in concentrated urine from normal constituents of urine—principally Tamm-Horsfall protein, which is secreted by epithelial cells of the loop of Henle. Postrenal ARF may also present with an inactive sediment, although hematuria and pyuria are common in patients with intraluminal obstruction or prostatic disease. Pigmented "muddy brown" granular casts and casts containing tubule epithelial cells are characteristic of ATN and suggest ischemic or nephrotoxic ARF. They are usually found in association with microscopic hematuria and mild "tubular" proteinuria (<1 g/d); the latter reflects impaired reabsorption and processing of filtered proteins by injured proximal tubules. Casts are absent, however, in 20 to 30% of patients with ischemic or nephrotoxic ARF and are not a requisite for diagnosis. In general, red blood cell casts indicate glomerular injury or, less often, acute tubulointerstitial nephritis. White cell casts and nonpigmented granular casts suggest interstitial nephritis, whereas broad granular casts are characteristic of chronic renal disease and probably reflect interstitial fibrosis and dilatation of tubules. Eosinophiluria (>5% of urine leukocytes) is a common finding (~90%) in antibiotic-induced allergic interstitial nephritis when studied using Hansel's stain; however, lymphocytes may predominate in allergic interstitial nephritis induced by NSAIDs. Eosinophiluria is also a feature of atheroembolic ARF. Occasional uric acid crystals (pleomorphic in shape) are common in the concentrated urine of prerenal ARF but suggest acute urate nephropathy if seen in abundance. Oxalate (envelope-shaped) and hippurate (needle-shaped) crystals raise the possibility of ethylene glycol ingestion and toxicity.

Proteinuria of >1 g/d suggests injury to the glomerular ultrafiltration barrier ("glomerular proteinuria") or excretion of myeloma light chains. The latter are not detected by conventional dipsticks (which detect albumin) and must be sought by other means (e.g., sulfosalicylic acid test, immunoelectrophoresis). Heavy proteinuria is also a frequent finding (~80%) in patients who develop combined allergic interstitial nephritis and minimal change glomerulopathy when treated with NSAIDs. A similar syndrome can be triggered by ampicillin, rifampicin, or interferon  $\alpha$ . Hemoglobinuria or myoglobinuria should be suspected if urine is strongly positive for heme by dipstick, but contains few red cells, and if the supernatant of centrifuged urine is positive for free heme. Bilirubinuria may provide a clue to the presence of hepatorenal syndrome.

**RENAL FAILURE INDICES** Analysis of urine and blood biochemistry is particularly useful for distinguishing prerenal ARF from ischemic or nephrotoxic intrinsic renal ARF (Table 260-3). The fractional excretion of sodium ( $FE_{Na}$ ) is most useful in this regard. The  $FE_{Na}$  relates sodium clearance to creatinine clearance. Sodium is reabsorbed avidly from glomerular filtrate in patients with prerenal ARF, in an attempt to restore intravascular volume, but not in patients with ischemic or nephrotoxic intrinsic ARF, as a result of tubular epithelial cell injury. In contrast, creatinine is not reabsorbed in either setting. Consequently, patients with prerenal ARF typically have a  $FE_{Na}$  of <1.0% (frequently <0.1%), whereas the  $FE_{Na}$  in patients with ischemic or nephrotoxic ARF is usually >1.0%. The *renal failure index* (Table 260-3) provides comparable information, since clinical variations in serum sodium concentration are relatively small. *Urine sodium concentration* is a less sensitive index for distinguishing prerenal ARF from ischemic and nephrotoxic ARF as values overlap between groups. Similarly, indices of urinary concentrating ability such as urine specific gravity, urine osmolality, urine-to-plasma urea ratio, and blood urea-to-creatinine ratio are of limited value in differential diagnosis.

Many caveats apply when interpreting biochemical renal failure indices.  $FE_{Na}$  may be >1.0% in prerenal ARF if patients are receiving diuretics or have bicarbonaturia (accompanied by sodium to maintain electroneutrality), preexisting chronic renal failure complicated by salt wasting, or adrenal insufficiency. In contrast, the  $FE_{Na}$  is <1.0% in approximately 15% of patients with nonoliguric ischemic or nephrotoxic ARF, probably reflecting patchy injury to tubular epithelium with

TABLE 260-3 Urine Diagnostic Indices in Differentiation of Prerenal versus Intrinsic Renal ARF

Diagnostic Index	Typical Findings in ARF	
	Prerenal	Intrinsic Renal
Fractional excretion of sodium (%) <sup>a</sup>	<1	>1
$\frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}} \times 100$		
Urine sodium concentration (mmol/L)	<10	>20
Urine creatinine to plasma creatinine ratio	>40	<20
Urine urea nitrogen to plasma urea nitrogen ratio	>8	<3
Urine specific gravity	>1.020	~1.010
Urine osmolality (mosmol/kg H <sub>2</sub> O)	>500	~300
Plasma BUN/creatinine ratio	>20	<10–15
Renal failure index <sup>a</sup>	<1	>1
$\frac{U_{Na}}{U_{Cr}/P_{Cr}}$		
Urinary sediment	Hyaline casts	Muddy brown granular casts

<sup>a</sup> Most sensitive indices.

Note:  $U_{Na}$ , urine sodium concentration;  $P_{Cr}$ , plasma creatinine concentration;  $P_{Na}$ , plasma sodium concentration;  $U_{Cr}$ , urine creatinine concentration; BUN, blood urea nitrogen.

preservation of reabsorptive function in some areas. The  $FE_{Na}$  is also often <1.0% in ARF due to urinary tract obstruction, glomerulonephritis, and vascular diseases.

**LABORATORY FINDINGS** Serial measurements of serum creatinine can provide useful pointers to the cause of ARF. Prerenal ARF is typified by fluctuating levels that parallel changes in hemodynamic function. Creatinine rises rapidly (within 24 to 48 h) in patients with ARF following renal ischemia, atheroembolization, and radiocontrast exposure. Peak creatinine levels are observed after 3 to 5 days with contrast nephropathy and return to baseline after 5 to 7 days. In contrast, creatinine levels typically peak later (7 to 10 days) in ischemic ARF and atheroembolic disease. The initial rise in serum creatinine is characteristically delayed until the second week of therapy with many tubule epithelial cell toxins (e.g., aminoglycosides, cisplatin) and probably reflects the need for accumulation of these agents within cells before GFR falls.

Hyperkalemia, hyperphosphatemia, hypocalcemia, and elevations in serum uric acid and creatine kinase (MM isoenzyme) levels at presentation suggest a diagnosis of rhabdomyolysis. Hyperuricemia [ $>890 \mu\text{mol/L}$  ( $>15 \text{ mg/dL}$ )] in association with hyperkalemia, hyperphosphatemia, and increased circulating levels of intracellular enzymes such as lactate dehydrogenase may indicate acute urate nephropathy and tumor lysis syndrome following cancer chemotherapy. A wide serum anion and osmolal gap (measured serum osmolality minus the serum osmolality calculated from serum sodium, glucose, and urea concentrations) indicate the presence of an unusual anion or osmole in the circulation and are clues to diagnosis of ethylene glycol or methanol ingestion. Severe anemia in the absence of hemorrhage raises the possibility of hemolysis, multiple myeloma, or thrombotic microangiopathy. Systemic eosinophilia suggests allergic interstitial nephritis but is also a feature of atheroembolic disease and polyangiitis nodosa.

**RADIOLOGIC FINDINGS** Imaging of the urinary tract by ultrasonography is useful to exclude postrenal ARF. Computed tomography and magnetic resonance imaging are alternative imaging modalities. Whereas pelvicalyceal dilatation is usual with urinary tract obstruction (98% sensitivity), dilatation may be absent immediately following obstruc-

tion or in patients with ureteric encasement (e.g., retroperitoneal fibrosis, neoplasia). Retrograde or anterograde pyelography are more definitive investigations in complex cases and provide precise localization of the site of obstruction. A plain film of the abdomen, with tomography if necessary, is a valuable initial screening technique in patients with suspected nephrolithiasis. Doppler ultrasonography and magnetic resonance angiography are useful for assessment of patency of renal arteries and veins in patients with suspected vascular obstruction; however, contrast angiography is usually required for definitive diagnosis.

**RENAL BIOPSY** Biopsy is reserved for patients in whom prerenal and postrenal ARF have been excluded and the cause of intrinsic renal ARF is unclear. Renal biopsy is particularly useful when clinical assessment and laboratory investigations suggest diagnoses other than ischemic or nephrotoxic injury that may respond to disease-specific therapy. Examples include glomerulonephritis, vasculitis, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, and allergic interstitial nephritis.

### COMPLICATIONS

ARF impairs renal excretion of sodium, potassium, and water and perturbs divalent cation homeostasis and urinary acidification mechanisms. As a result, ARF is frequently complicated by intravascular volume overload, hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypermagnesemia, and metabolic acidosis. In addition, patients are unable to excrete nitrogenous waste products and are prone to develop the uremic syndrome (Chap. 261). The speed of development and the severity of these complications reflect the degree of renal impairment and catabolic state of the patient.

*Expansion of extracellular fluid volume* is an inevitable consequence of diminished salt and water excretion in oliguric or anuric individuals. Whereas milder forms are characterized by weight gain, bibasilar lung rales, raised jugular venous pressure, and dependent edema, continued volume expansion may precipitate life-threatening pulmonary edema. Hypervolemia may be particularly problematic in patients receiving multiple intravenous medications and enteral or parenteral nutrition. Excessive administration of free water either through ingestion and nasogastric administration or as hypotonic saline or isotonic dextrose solutions (dextrose being metabolized) can induce *hyposmolality* and *hyponatremia*, which, if severe, lead to cerebral edema and neurologic abnormalities, including seizures.

*Hyperkalemia* is a frequent complication of ARF. Serum potassium typically rises by 0.5 mmol/L per day in oliguric and anuric patients due to impaired excretion of ingested or infused potassium and potassium released from injured tissue. Coexistent metabolic acidosis may exacerbate hyperkalemia by promoting potassium efflux from cells. Hyperkalemia may be particularly severe, even at the time of diagnosis, in patients with rhabdomyolysis, hemolysis, and tumor lysis syndrome. Mild hyperkalemia (<6.0 mmol/L) is usually asymptomatic. Higher levels may trigger electrocardiographic abnormalities and/or arrhythmias (Chap. 210).

Metabolism of dietary protein yields between 50 and 100 mmol/d of fixed nonvolatile acids that are normally excreted by the kidneys. Consequently, ARF is typically complicated by *metabolic acidosis*, often with an increased serum anion gap (Chap. 42). Acidosis can be particularly severe when endogenous production of hydrogen ions is increased by other mechanisms (e.g., diabetic or fasting ketoacidosis; lactic acidosis complicating generalized tissue hypoperfusion, liver disease, or sepsis; metabolism of ethylene glycol or methanol).

Mild *hyperphosphatemia* is an almost invariable complication of ARF. Severe hyperphosphatemia may develop in highly catabolic patients or following rhabdomyolysis, hemolysis, or tumor lysis. Metastatic deposition of calcium phosphate can lead to *hypocalcemia*, particularly when the product of serum calcium (mg/dL) and phosphate (mg/dL) concentrations exceeds 70. Other factors that contribute

to hypocalcemia include tissue resistance to the actions of parathyroid hormone and reduced levels of 1,25-dihydroxyvitamin D. Hypocalcemia is often asymptomatic but can cause perioral paresthesia, muscle cramps, seizures, hallucinations and confusion, and prolongation of the QT interval and nonspecific T-wave changes on electrocardiography (Chap. 332).

*Anemia* develops rapidly in ARF and is usually mild and multifactorial in origin. Contributing factors include impaired erythropoiesis, hemolysis, bleeding, hemodilution, and reduced red cell survival time. Prolongation of the *bleeding time* and *leukocytosis* are also common. Common contributors to the bleeding diathesis include mild thrombocytopenia, platelet dysfunction, and/or clotting factor abnormalities (e.g., factor VIII dysfunction), whereas leukocytosis usually reflects sepsis, a stress response, or other concurrent illness. *Infection* is a common and serious complication of ARF, occurring in 50 to 90% of cases and accounting for up to 75% of deaths. It is unclear whether patients with ARF have a clinically significant defect in host immune responses or whether the high incidence of infection reflects repeated breaches of mucocutaneous barriers (e.g., intravenous cannulae, mechanical ventilation, bladder catheterization). *Cardiopulmonary complications* of ARF include arrhythmias, myocardial infarction, pericarditis and pericardial effusion, pulmonary edema, and pulmonary embolism. Mild *gastrointestinal bleeding* is common (10 to 30%) and is usually due to stress ulceration of gastric or small intestinal mucosa.

Protracted periods of severe ARF are invariably associated with the development of the *uremic syndrome* (Chap. 261).

A *vigorous diuresis* can occur during the recovery phase of ARF (see above), which may on occasions be inappropriate and lead to intravascular volume depletion and delayed recovery of GFR by causing secondary prerenal ARF. *Hypernatremia* can also complicate recovery if water losses via hypotonic urine are not replaced or if losses are inappropriately replaced by relatively hypertonic saline solutions. *Hypokalemia*, *hypomagnesemia*, *hypophosphatemia*, and *hypocalcemia* are less common metabolic complications during this period.

### R<sub>x</sub> TREATMENT

**Prevention** Because there are no specific therapies for ischemic or nephrotoxic ARF, prevention is of paramount importance. Many cases of ischemic ARF can be avoided by close attention to cardiovascular function and intravascular volume in high-risk patients, such as the elderly and those with preexisting renal insufficiency. Indeed, aggressive restoration of intravascular volume has been shown to reduce dramatically the incidence of ischemic ARF after major surgery or trauma, burns, or cholera. The incidence of nephrotoxic ARF can be reduced by tailoring the dosage of nephrotoxic drugs to body size and GFR; for example, reducing the dose or frequency of administration of drugs in patients with preexisting renal impairment. In this regard, it should be noted that serum creatinine is a relatively insensitive index of GFR and may overestimate GFR considerably in small or elderly patients. For purposes of drug dosing, it is advisable to estimate the GFR using the Cockcroft-Gault formula, which factors in the variables of age and weight (Chap. 40). Adjusting drug dosage according to circulating drug levels also appears to limit renal injury in patients receiving aminoglycoside antibiotics, cyclosporine, or tacrolimus. Diuretics, cyclooxygenase inhibitors, ACE inhibitors, angiotensin II receptor blockers, and other vasodilators should be used with caution in patients with suspected true or "effective" hypovolemia or renovascular disease as they may precipitate prerenal ARF or convert the latter to ischemic ARF. Allopurinol and forced alkaline diuresis are useful prophylactic measures in patients at high risk for acute urate nephropathy (e.g., cancer chemotherapy in hematologic malignancies) to limit uric acid generation and prevent precipitation of urate crystals in renal tubules. Forced alkaline diuresis may also prevent or attenuate ARF in patients receiving high-dose methotrexate or suffering from rhabdomyolysis. *N*-acetylcysteine limits acetaminophen-induced renal injury if given within 24 h of ingestion. Dimercaprol, a chelating agent.

may prevent heavy metal nephrotoxicity. Ethanol inhibits ethylene glycol metabolism to oxalic acid and other toxic metabolites and is an important adjunct to hemodialysis in the emergency management of ethylene glycol intoxication.

**Specific Therapies** By definition, prerenal ARF is rapidly reversible upon correction of the primary hemodynamic abnormality, and postrenal ARF resolves upon relief of obstruction. To date, there are no specific therapies for established intrinsic renal ARF due to ischemia or nephrotoxicity. Management of these disorders should focus on elimination of the causative hemodynamic abnormality or toxin, avoidance of additional insults, and prevention and treatment of complications. Specific treatment of other causes of intrinsic renal ARF depends on the underlying pathology.

**PRERENAL ARF** The composition of replacement fluids for treatment of prerenal ARF due to hypovolemia must be tailored according to the composition of the lost fluid. Severe hypovolemia due to hemorrhage should be corrected with packed red cells, whereas isotonic saline is usually appropriate replacement for mild to moderate hemorrhage or plasma loss (e.g., burns, pancreatitis). Urinary and gastrointestinal fluids can vary greatly in composition but are usually hypotonic. Hypotonic solutions (e.g., 0.45% saline) are usually recommended as initial replacement in patients with prerenal ARF due to increased urinary or gastrointestinal fluid losses, although isotonic saline may be more appropriate in severe cases. Subsequent therapy should be based on measurements of the volume and ionic content of excreted or drained fluids. Serum potassium and acid-base status should be monitored carefully, and potassium and bicarbonate supplemented as appropriate. Cardiac failure may require aggressive management with positive inotropes, preload and afterload reducing agents, antiarrhythmic drugs, and mechanical aids such as intraaortic balloon pumps. Invasive hemodynamic monitoring may be required to guide therapy for complications in patients in whom clinical assessment of cardiovascular function and intravascular volume is difficult.

Fluid management may be particularly challenging in patients with cirrhosis complicated by ascites. In this setting, it is important to distinguish between full-blown hepatorenal syndrome (Chap. 289), which carries a grave prognosis, and reversible ARF due to true or "effective" hypovolemia induced by overzealous use of diuretics or sepsis (e.g., spontaneous bacterial peritonitis). The contribution of hypovolemia to ARF can be definitively assessed only by administration of a fluid challenge. Fluids should be administered slowly and titrated against jugular venous pressure and, if necessary, central venous and pulmonary capillary wedge pressure, abdominal girth, and urine output. Patients with a reversible prerenal component typically have an increase in urine output and fall in serum creatinine, whereas patients with hepatorenal syndrome do not and may suffer increased ascites formation and pulmonary compromise if not monitored closely. Large volumes of ascitic fluid can usually be drained by paracentesis without deterioration in renal function if intravenous albumin is administered simultaneously. Indeed, "large-volume paracentesis" may afford an increase in GFR, possibly by lowering intraabdominal pressure and improving flow in renal veins. Shunting of ascitic fluid from the peritoneum to a central vein (peritoneojugular shunt, LeVeen or Denver shunts) is an alternative approach in refractory cases but has not been shown to improve survival in controlled trials. The efficacy of the newer technique of transjugular intrahepatic portosystemic shunting (TIPS procedure) is currently undergoing rigorous clinical assessment. Shunting can also improve GFR and sodium excretion transiently, probably because the increase in central blood volume stimulates release of atrial natriuretic peptides (ANPs) and inhibits secretion of aldosterone and norepinephrine.

**INTRINSIC RENAL ARF** Many different approaches have been tested for their ability to attenuate injury or hasten recovery in ischemic and nephrotoxic ARF. These include ANP, low-dose dopamine, endothelin antagonists, loop-blocking diuretics, calcium channel blockers,  $\alpha$ -adrenoreceptor blockers, prostaglandin analogues, antioxidants, antibodies against leukocyte adhesion molecules, and insulin-like growth

factor type I. Whereas many of these are beneficial in experimental models of ischemic or nephrotoxic ARF, they have either failed to confer consistent benefit or proved ineffective in humans.

ARF due to other intrinsic renal diseases such as acute glomerulonephritis or vasculitis may respond to glucocorticoids, alkylating agents, and/or plasmapheresis, depending on the primary pathology. Glucocorticoids also hasten remission in some cases of allergic interstitial nephritis. Aggressive control of systemic arterial pressure is of paramount importance in limiting renal injury in malignant hypertensive nephrosclerosis, toxemia of pregnancy, and other vascular diseases. Hypertension and ARF due to scleroderma may be exquisitely sensitive to treatment with ACE inhibitors.

**POSTRENAL ARF** Management of postrenal ARF requires close collaboration between nephrologist, urologist, and radiologist. Obstruction of the urethra or bladder neck is usually managed initially by transurethral or suprapubic placement of a bladder catheter, which provides temporary relief while the obstructing lesion is identified and treated definitively. Similarly, ureteric obstruction may be treated initially by percutaneous catheterization of the dilated renal pelvis or ureter. Indeed, obstructing lesions can often be removed percutaneously (e.g., calculus, sloughed papilla) or bypassed by insertion of a ureteric stent (e.g., carcinoma). Most patients experience an appropriate diuresis for several days following relief of obstruction. Approximately 5% of patients develop a transient salt-wasting syndrome that may require administration of intravenous saline to maintain blood pressure.

**Supportive Measures** (Table 260-4) Following correction of hypovolemia, salt and water intake are tailored to match losses. Hypervolemia can usually be managed by restriction of salt and water intake and diuretics. Indeed, there is, as yet, no proven rationale for administration of diuretics in ARF except to treat this complication. High doses of loop-blocking diuretics such as furosemide (up to 200 to 400 mg intravenously) or bumetanide (up to 10 mg intravenously administered as a bolus or by continuous infusion) may promote diuresis in patients who fail to respond to conventional doses. Despite the fact that subpressor doses of dopamine may transiently promote salt and water excretion by increasing renal blood flow and GFR and by inhibiting tubule sodium reabsorption, subpressor ("low-dose," "renal-dose,") dopamine has proved ineffective in clinical trials, may trigger arrhythmias and sudden cardiac death in critically ill patients, and should not be used as a renoprotective agent in this setting. Ultrafiltration or dialysis is used to treat severe hypervolemia when conservative measures fail. Hyponatremia and hypoosmolality can usually be controlled by restriction of free water intake. Conversely, hypernatremia is treated by administration of water or intravenous hypotonic saline or isotonic dextrose-containing solutions. *—The management of hyperkalemia is described in Chap. 41.*

Metabolic acidosis is not usually treated unless serum bicarbonate concentration falls below 15 mmol/L or arterial pH falls below 7.2. More severe acidosis is corrected by oral or intravenous sodium bicarbonate. Initial rates of replacement are guided by estimates of bicarbonate deficit and adjusted thereafter according to serum levels (Chap. 42). Patients are monitored for complications of sodium bicarbonate administration such as hypervolemia, metabolic alkalosis, hypocalcemia, and hypokalemia. From a practical point of view, most patients requiring sodium bicarbonate need emergency dialysis within days. Hyperphosphatemia is usually controlled by restriction of dietary phosphate and by oral aluminum hydroxide or calcium carbonate, which reduce gastrointestinal absorption of phosphate. Hypocalcemia does not usually require treatment unless severe, as may occur with rhabdomyolysis or pancreatitis or following administration of bicarbonate. Hyperuricemia is typically mild [ $<890 \mu\text{mol/L}$  ( $<15 \text{ mg/dL}$ )] and does not require intervention.

The objective of *nutritional management* during the maintenance phase of ARF is to provide sufficient calories to avoid catabolism and starvation ketoacidosis, while minimizing production of nitrogenous

TABLE 260-4 Management of Ischemic and Nephrotoxic Acute Renal Failure\*

Management Issue	Therapy
<b>REVERSE CAUSATIVE RENAL INSULT</b>	
Ischemic ARF	Restore systemic hemodynamics and renal perfusion
Nephrotoxic ARF	Eliminate nephrotoxins Consider specific measures (e.g., forced alkaline diuresis, chelators: see text)
<b>PREVENTION AND TREATMENT OF COMPLICATIONS</b>	
Intravascular volume overload	Salt (1–2 g/d) and water (usually <1 L/d) restriction Diuretics (usually loop blockers ± thiazide) Ultrafiltration or dialysis
Hyponatremia	Restriction of enteral free water intake (<1 L/d) Avoid hypotonic intravenous solutions (including dextrose solutions)
Hyperkalemia	Restriction of dietary K <sup>+</sup> intake (usually <40 mmol/d) Eliminate K <sup>+</sup> supplements and K <sup>+</sup> -sparing diuretics Potassium-binding ion-exchange resins (e.g., sodium polystyrene sulphonate) Glucose (50 mL of 50% dextrose) and insulin (10 units regular) Sodium bicarbonate (usually 50–100 mmol) Calcium gluconate (10 mL of 10% solution over 5 min) Dialysis (with low K <sup>+</sup> dialysate)
Metabolic acidosis	Restriction of dietary protein (usually 0.6 g/kg per day of high biologic value) Sodium bicarbonate (maintain serum bicarbonate >15 mmol/L or arterial pH >7.2) Dialysis
Hyperphosphatemia	Restriction of dietary phosphate intake (usually <800 mg/d) Phosphate binding agents (calcium carbonate, aluminum hydroxide)
Hypocalcemia	Calcium carbonate (if symptomatic or if sodium bicarbonate to be administered) Calcium gluconate (10–20 mL of 10% solution)
Hypermagnesemia	Discontinue Mg <sup>2+</sup> -containing antacids
Hyperuricemia	Treatment usually not necessary [if <890 μmol/L (<15 mg/dL)]
Nutrition	Restriction of dietary protein (~0.6 g/kg per day) Carbohydrate (~100 g/d) Enteral or parenteral nutrition (if recovery prolonged or patient very catabolic)
Indications for dialysis	Clinical evidence (symptoms or signs) of uremia Intractable intravascular volume overload Hyperkalemia or severe acidosis resistant to conservative measures ?Prophylactic dialysis when urea >100–150 mg/dL or creatinine >8–10 mg/dL
<b>PRESCRIBING OF MEDICATIONS</b>	
Choice of agents	Avoid other nephrotoxins, ACE inhibitors, cyclooxygenase inhibitors, and radiocontrast unless absolute indication and no alternative agent
Drug dosing	Adjust doses and frequency of administration for degree of renal impairment

\* These are general recommendations and must be tailored to needs of individual patients.

waste. This is best achieved by restricting dietary protein to approximately 0.6 g/kg per day of protein of high biologic value (i.e., rich in essential amino acids) and to provide most calories as carbohydrate (approximately 100 g daily). Nutritional management is easier in non-oliguric patients and following institution of dialysis. Vigorous parenteral hyperalimentation is claimed to improve prognosis; however, convincing benefit has yet to be demonstrated in controlled trials.

Anemia may necessitate blood transfusion if severe or if recovery is delayed. In contrast to chronic renal failure, recombinant human erythropoietin is rarely used in ARF because bone marrow resistance to erythropoietin is common, more immediate treatment of anemia (if any) is required, and renal failure is usually self-limiting. Uremic bleeding usually responds to correction of anemia, administration of desmopressin or estrogens, or dialysis. Regular doses of antacids appear to reduce the incidence of gastrointestinal hemorrhage significantly and may be more effective in this regard than H<sub>2</sub> antagonists or proton pump inhibitors. Meticulous care of intravenous cannulae, bladder catheters, and other invasive devices is mandatory to avoid infections. Unfortunately, prophylactic antibiotics have not been shown to reduce the incidence of infection in these high-risk patients.

**INDICATIONS AND MODALITIES OF DIALYSIS** (See also Chap. 262) Dialysis replaces renal function until regeneration and repair restore renal function. Hemodialysis and peritoneal dialysis appear equally effective for management of ARF. Thus, the dialysis modality is chosen according to the needs of individual patients (e.g., peritoneal dialysis may be preferable if the patient is hemodynamically unstable, and hemodialysis after abdominal surgery involving the peritoneum), the expertise of the nephrologist, and the facilities of the institution. Vascular access for conventional intermittent hemodialysis is best achieved by insertion of a temporary double-lumen hemodialysis catheter into the internal jugular vein. The subclavian and femoral veins are alternative access sites. Peritoneal dialysis is achieved by insertion of a cuffed catheter into the peritoneal cavity. Absolute indications for dialysis include symptoms or signs of the uremic syndrome and management of refractory hypervolemia, hyperkalemia, or acidosis. Most nephrologists also initiate dialysis empirically for blood urea levels of >100 mg/dL, even in the absence of clinical uremia; however, this approach has yet to be validated in controlled clinical trials. Recent evidence suggests that more intensive hemodialysis (e.g., daily rather than alternate-day intermittent dialysis) is clinically superior and confers improved survival in ARF once dialysis is required. This conclusion may not be as intuitive as it first appears as dialysis itself has been postulated to prolong the period of oliguria in some cases by inducing hypotension and further renal ischemia and through activation of leukocytes on the dialysis membrane, which may then proceed to aggravate renal injury.

Continuous renal replacement therapies (CRRTs) are alternatives to conventional intermittent hemodialysis techniques for treatment of ARF. They are particularly valuable techniques in patients in whom intermittent hemodialysis fails to control hypervolemia or uremia and for those who do not tolerate intermittent hemodialysis and in whom peritoneal dialysis is not possible. Continuous arteriovenous hemodiafiltration (CAVHD) requires both arterial and venous access. The patient's own blood pressure generates an ultrafiltrate of plasma across a porous biocompatible dialysis membrane. A physiologic crystalloid solution is passed along the other side of the membrane to achieve diffusive clearance. Continuous venovenous hemodiafiltration (CVVHD), in contrast, requires only a double-lumen venous catheter as a blood pump generates ultrafiltration pressure across the dialysis membrane. In the more simple techniques of continuous arteriovenous hemofiltration (CAVH) and continuous venovenous hemofiltration (CVVH) the dialysis step is eliminated and an ultrafiltrate of plasma is removed across the dialysis membrane and replaced by a physiologic crystalloid solution. The bulk of evidence to date suggests that intermittent and continuous dialytic therapies are equally effective in the context of ARF. The choice of technique is currently tailored to the specific needs of the patient, the resources of the institution, and the expertise of the physician. Potential disadvantages of continuous hemodialysis techniques are the need for prolonged immobilization in bed, systemic anticoagulation, arterial cannulation (in CAVH), and prolonged exposure of blood to synthetic, albeit relatively biocompatible, dialysis membranes.

## OUTCOME AND LONG-TERM PROGNOSIS

The mortality rate among patients with ARF approximates 50% and has changed little over the past 30 years. It should be stressed, however, that patients usually die from sequelae of the primary illness that induced ARF and not from ARF itself. Indeed, the kidney is one of the few organs whose function can be replaced artificially (i.e., by dialysis) for protracted periods of time. In agreement with this interpretation, mortality rates vary greatly depending on the cause of ARF: ~15% in obstetric patients, ~30% in toxin-related ARF, and ~60% following trauma or major surgery. Oliguria (<400 mL/d) at time of presentation and a rise in serum creatinine of >265  $\mu\text{mol/L}$  (>3 mg/dL) are associated with a poor prognosis and probably reflect the severity of renal injury and of the primary illness. Mortality rates are higher in older debilitated patients and in those with multiple organ failure. Most patients who survive an episode of ARF recover sufficient renal function to live normal lives. However, 50% have subclinical impairment of renal function or residual scarring on renal biopsy. Approximately 5% of patients never recover function and require long-

term renal replacement with dialysis or transplantation. An additional 5% suffer progressive decline in GFR, following an initial recovery phase, probably due to hemodynamic stress and sclerosis of remnant glomeruli (Chap. 264).

## FURTHER READING

- BRADY HR et al: Acute renal failure, in *Brenner and Rector's The Kidney*, 7th ed., BM Brenner (ed). Philadelphia, Saunders, 2004
- DAUGIRDAS JT et al (eds): *Handbook of Dialysis*. New York, Little, Brown, 2001
- DENTON MD et al: "Renal-dose" dopamine for the treatment of acute renal failure: Scientific rationale, experimental studies and clinical trials. *Kidney Int* 49:4, 1996
- RONCO C et al: Effect of different doses of continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* 355:26, 2000
- SCHIFFL H et al: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 346:305; 2002

# 261 CHRONIC RENAL FAILURE

Karl Skorecki, Jacob Green,<sup>†</sup> Barry M. Brenner

## MECHANISMS OF CHRONIC RENAL FAILURE

**DEFINITIONS** *Chronic renal disease* (CRD) is a pathophysiologic process with multiple etiologies, resulting in the inexorable attrition of nephron number and function and frequently leading to *end-stage renal disease* (ESRD). In turn, ESRD represents a clinical state or condition in which there has been an irreversible loss of endogenous renal function, of a degree sufficient to render the patient permanently dependent upon renal replacement therapy (dialysis or transplantation) in order to avoid life-threatening *uremia*. Uremia is the clinical and laboratory syndrome, reflecting dysfunction of all organ systems as a result of untreated or undertreated acute or chronic renal failure. Given the capacity of the kidneys to regain function following acute injury (Chap. 260), the vast majority (>90%) of patients with ESRD have reached this state as a result of CRD.

**PATHOPHYSIOLOGY OF CRD** (See also Chap. 259) The pathophysiology of CRD involves initiating mechanisms specific to the underlying etiology as well as a set of progressive mechanisms that are a common consequence following long-term reduction of renal mass, irrespective of etiology. Such reduction of renal mass causes structural and functional hypertrophy of surviving nephrons. This compensatory hypertrophy is mediated by vasoactive molecules, cytokines, and growth factors and is due initially to adaptive hyperfiltration, in turn mediated by increases in glomerular capillary pressure and flow. Eventually, these short-term adaptations prove maladaptive, in that they predispose to sclerosis of the remaining viable nephron population. Increased intrarenal activity of the renin-angiotensin axis appears to contribute both to the initial adaptive hyperfiltration and to the subsequent maladaptive hypertrophy and sclerosis.

The definition of CRD requires that the pathophysiologic process described above last more than 3 months. A recently widely accepted international classification divides CRD into a number of stages (Table 261-1) defined by clinical estimation of the glomerular filtration rate (GFR). These stages help guide clinical diagnostic and management approaches. First, it is important to identify factors that increase the risk for CRD, even in individuals with normal GFR. Such factors include family history of heritable renal disease, hypertension, diabetes, autoimmune disease, older age, past episode of acute renal failure, and current evidence of kidney damage with normal or even

increased GFR. Such evidence of kidney damage in the face of normal or increased GFR places affected individuals into stage 1 CRD and includes proteinuria, abnormal urinary sediment, or urinary tract structural abnormalities (e.g., vesicoureteric reflux) evident on imaging studies. Even at this stage, when baseline GFR is normal, there is often a characteristic loss of renal reserve. This early stage is particularly well documented in diabetic nephropathy. Further stages in the pathogenesis of CRD are characterized by a progressive decline in estimated GFR with mild, moderate, and severe stages defined at GFR levels (mL/min per 1.73 m<sup>2</sup>) of 60 to 89, 30 to 59, and 15 to 29, respectively. At a GFR < 15 mL/min per 1.73 m<sup>2</sup>, renal replacement therapy may be indicated if uremia is present. For purposes of staging CRD, current guidelines recommend estimating GFR using one of the two equations shown in Table 261-2, based on measured plasma creatinine concentration, age, gender, and ethnic origin. The normal annual mean decline in GFR with age beginning at age 20 to 30 years is 1 mL/min per 1.73 m<sup>2</sup>, reaching a mean value in males of 70 at age 70. GFR is slightly lower in women than men. By the time plasma creatinine concentration is even mildly elevated, substantial chronic nephron injury has already occurred.

Albuminuria serves as a key adjunctive tool for monitoring nephron injury and response to therapy in many forms of CRD. Current guidelines recommend use of albumin-specific dipstick measurement or quantitation by measurement of albumin-to-creatinine ratio in a spot first morning urine sample. Persistence of >17 mg albumin per gram of creatinine in adult males and 25 mg albumin per gram of creatinine in adult females usually signifies chronic renal damage, irrespective of GFR, and can be followed in monitoring natural history and response to therapy, especially in CRD consequent to diabetes, hypertension, or glomerulonephritis. →*Further considerations in the overall clinical approach to proteinuria are provided in Chap. 40.*

During stages 1 and 2 CRD, patients often remain free of symp-

TABLE 261-1 Stages of Chronic Renal Disease: CRD

Stage	Description	GFR, mL/min per 1.73 m <sup>2</sup>
1	At increased risk Kidney damage with normal or increased GFR	90 (with CRD risk factors) 90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Renal failure	<15 (or dialysis)

Note: GFR, glomerular filtration rate.

Source: Adapted from Levey, with permission.

<sup>†</sup>Deceased

TABLE 261-2 Recommended Equations for Estimation of Glomerular Filtration Rate (GFR) from Laboratory-Validated Plasma Creatinine Concentration (P<sub>C</sub>)

- Equation from the Modification of Diet in Renal Disease study<sup>a</sup>  
Estimated GFR (mL/min per 1.73 m<sup>2</sup>) =  $1.86 \times (P_C)^{-1.154} \times (\text{age})^{-0.203}$   
Multiply by 0.742 for women  
Multiply by 1.21 for African Americans
- Cockcroft-Gault equation  
Estimated creatinine clearance (mL/min) =  
 $\frac{(140 - \text{age}) \times \text{body weight (kg)}}{72 \times P_C \text{ (mg/dL)}}$   
Multiply by 0.85 for women

<sup>a</sup> Equation is available in hand-held calculators and in tabular form.  
Source: Adapted from Levey, with permission.

toms, other than those that might accompany the underlying etiologic process causing renal disease. As the decline in GFR progresses to stages 3 and 4 (GFR < 60 mL/min per 1.73 m<sup>2</sup>), clinical and laboratory complications of CRD become progressively more prominent. Virtually all organ systems are affected, but the most evident complications include anemia and loss of energy; decreasing appetite and disturbances in nutritional status; abnormalities in calcium and phosphorus metabolism accompanied by metabolic bone disease; and abnormalities in sodium, water, potassium, and acid-base homeostasis. When GFR falls to < 15 mL/min per 1.73 m<sup>2</sup>, patients usually experience a severe disturbance in their activities of daily living, sense of well-being, nutritional status, and water and electrolyte homeostasis, eventuating in an overtly uremic state wherein continued survival without renal replacement therapy becomes impossible.

**ETIOLOGY AND EPIDEMIOLOGY** It has been estimated that at least 6% of the adult U.S. population have chronic renal damage with a GFR > 60 mL/min per 1.73 m<sup>2</sup> (stages 1 and 2 CRD) and hence are at imminent risk of a progressive further decline in GFR. An additional ~4.5% of the U.S. population are in stages 3 and 4 CRD. Diabetic and hypertensive nephropathy are the leading underlying etiologies of both CRD and ESRD. Hypertension is a particularly common cause and consequence of CRD in the elderly, in whom chronic renal ischemia due to renovascular disease may be an underrecognized additional contribution to the pathophysiologic process. It should be noted that cardiovascular mortality precludes most patients with CRD from reaching the stage of ESRD. Identification of CRD as a major risk factor for cardiovascular morbidity and mortality, and the expectation of effective interventions to diminish premature cardiovascular mortality, and increasing longevity overall, will increase the cohort of patients reaching ESRD.

Although the clinical manifestations of the declining GFR per se dominate the clinical presentation in all forms of CRD, in many cases the underlying etiology can be presumed from associated additional clinical information (Table 261-3).

**GENETIC CONSIDERATIONS** Disorders with clear-cut monogenic inheritance comprise a small but important component among the etiologies of CRD. Among these, autosomal dominant polycystic kidney disease is the most common on a world-wide basis (Chap. 265). Alport's hereditary nephritis (Chap. 264) is a less common cause of both benign hematuria without progression to CRD and more severe nephron injury with progression to ESRD, and it most often displays an X-linked pattern of inheritance. Several genetic loci have been identified that encode important components of the glomerular podocyte-associated filtration barrier, and mutations in these genes cause inherited forms of focal segmental glomerular sclerosis with glucocorticoid nonresponsive nephrotic syndrome and progression to ESRD. Nephronophthisis, medullary cystic kidney disease, and Fabry's disease are among other rare causes of progressive CRD with monogenic inheritance based on well-characterized genetic loci. In contrast, the two most common etiologies of CRD, diabetes mellitus (both types

TABLE 261-3 Summary of Clinical Presentations That may Suggest Given Major Categories of Causes of Chronic Renal Disease

Cause	Clinical Presentation
Diabetic kidney disease	History of diabetes, proteinuria, retinopathy
Hypertension	Elevated blood pressure, normal urinalysis, family history
Nondiabetic glomerular disease	Nephritic or nephrotic presentations (Chap. 264)
Cystic kidney disease	Urinary tract symptoms, abnormal urinary sediment, radiologic imaging abnormalities
Tubulointerstitial disease	History of urinary tract infections and reflux, chronic medication and drug exposure, abnormalities in urinary tract imaging, tubular syndromes including urine-concentrating defect, abnormal urinalysis

Source: Adapted from Levey, with permission.

1 and 2) and essential hypertension, display complex polygenic patterns of inheritance.

The striking interindividual variability in the rate of progression to ESRD has an important heritable component, and a number of genetic loci that contribute to the progression of CRD have been identified. Most extensively studied has been an insertion/deletion polymorphism of the angiotensin-converting enzyme (ACE) gene. The homozygous deletion (D/D) variant is associated with the highest expression of endogenous ACE activity and a greater risk of CRD progression. This finding leads to the prediction that ACE inhibitor therapy might be most effective in patients who are homozygous for the "at-risk" allele. Similar conclusions have been reached with respect to genes encoding other components of the renin-angiotensin axis. More recent studies of genetic association with renal failure progression have focused on a region of human chromosome 10, homologous to a well-characterized rodent renal failure susceptibility gene (Rf1).

**PATHOPHYSIOLOGY AND BIOCHEMISTRY OF UREMIA** Azotemia refers to the retention of nitrogenous waste products as renal insufficiency develops. Uremia refers to the more advanced stages of progressive renal insufficiency when the complex, multiorgan system derangements become clinically manifest.

Although not the major cause of overt uremic toxicity, urea may contribute to some of the clinical abnormalities, including anorexia, malaise, vomiting, and headache. Additional categories of nitrogenous excretory products include guanido compounds, urates and hippurates, end products of nucleic acid metabolism, polyamines, myoinositol, phenols, benzoates, and indoles, among others. Nitrogenous compounds with a molecular mass of 500 to 12,000 Da (so-called middle molecules) are also retained in CRD and similarly are believed to contribute to morbidity and mortality in uremic subjects. However, uremia involves more than renal excretory failure alone. A host of metabolic and endocrine functions normally subserved by the kidney are also impaired, resulting in anemia; malnutrition; impaired metabolism of carbohydrates, fats, and proteins; defective utilization of energy; and metabolic bone disease. Furthermore, plasma levels of many polypeptide hormones, including parathyroid hormone (PTH), insulin, glucagon, luteinizing hormone, and prolactin, rise with renal failure, not only because of impaired renal catabolism but also because of enhanced endocrine secretion, occurring as a secondary consequence of primary excretory or synthetic renal dysfunction. On the other hand, the renal production of erythropoietin (EPO) and 1,25-dihydroxycholecalciferol is impaired. Thus, the pathophysiology of the uremic syndrome can be divided into two sets of abnormalities: (1) those consequent to the accumulation of products of protein metabolism; and (2) those consequent to the loss of other renal functions, such as fluid and electrolyte homeostasis and hormonal abnormalities.

Uremia leads to disturbances in the function of every organ system. Chronic dialysis (Chap. 262) reduces the incidence and severity of these disturbances, so that, where modern medicine is practiced, the overt and florid manifestations of uremia have largely disappeared. Unfortunately, as indicated in Table 261-4, even optimal dialysis therapy is not a panacea, because some disturbances resulting from impaired renal function fail to respond fully, while others continue to progress.

**FLUID, ELECTROLYTE, AND ACID-BASE DISORDERS** (See also Chaps. 41, 42, and 259) ■ **Sodium and Water Homeostasis** In most patients with stable CRD, the total body contents of Na<sup>+</sup> and H<sub>2</sub>O are increased modestly, although this may not be clinically apparent. The underlying etiologic disease process may itself disrupt glomerulotubular balance and promote Na<sup>+</sup> retention (e.g., glomerulonephritis), or excessive Na<sup>+</sup> ingestion may lead to cumulative positive Na<sup>+</sup> balance and attendant extracellular fluid volume (ECFV) expansion. Such ECFV expansion contributes to hypertension, which in turn accelerates further the progression of nephron injury. As long as water intake does not exceed the capacity for free water clearance, the ECFV expansion will be isotonic and the patient will remain normonatremic. Hyponatremia is an uncommon complication in predialysis patients, and water restriction is only necessary when hyponatremia is documented. Weight gain usually associated with volume expansion may be offset in patients with CRD by concomitant loss of lean body mass. In the CRD patient who is not yet on dialysis but has clear evidence of ECFV expansion, administration of loop diuretics coupled with restriction of salt intake are the mainstays of therapy. It should be noted that resistance to loop diuretics in renal failure often mandates use of higher doses than those usually used when GFR is well preserved. The combination of loop diuretics with metolazone, which inhibits the Na<sup>+</sup>Cl<sup>-</sup> cotransporter of the distal convoluted tubule, can sometimes overcome diuretic resistance. When the GFR falls to <5 to 10 mL/min per 1.73 m<sup>2</sup>, even high doses of combination diuretics are ineffective. ECFV expansion under these circumstances usually means that dialysis is indicated.

Patients with CRD also have impaired renal mechanisms for con-

serving Na<sup>+</sup> and H<sub>2</sub>O (Chap. 259). When an *extrarenal* cause for fluid loss is present (e.g., vomiting, diarrhea, sweating, fever), these patients are prone to volume depletion. Depletion of ECFV may compromise residual renal function with resulting signs and symptoms of overt uremia. Because of impaired renal Na<sup>+</sup> and H<sub>2</sub>O conservation, the usual indices of prerenal azotemia (oliguria, high urine osmolality, low urinary Na<sup>+</sup> concentration, and low fractional excretion of Na<sup>+</sup>) are not useful. Cautious volume repletion, usually with normal saline, returns ECFV to normal and usually restores renal function to prior levels.

**Potassium Homeostasis** (See also Chap. 41) In CRD, the decline in GFR is not necessarily accompanied by a concomitant and proportionate decline in urinary K<sup>+</sup> excretion. In addition, K<sup>+</sup> excretion in the gastrointestinal tract is augmented in patients with CRD. However, hyperkalemia may be precipitated in a number of clinical situations, including constipation, augmented dietary intake, protein catabolism, hemolysis, hemorrhage, transfusion of stored red blood cells, metabolic acidosis, and following the exposure to a variety of medications that inhibit K<sup>+</sup> entry into cells or K<sup>+</sup> secretion in the distal nephron. Most commonly encountered medications in this regard are beta blockers, ACE inhibitors and angiotensin receptor blockers, K<sup>+</sup>-sparing diuretics (amiloride, triamterene, spironolactone), and nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, certain etiologies of CRD may be associated with earlier and more severe disruption of K<sup>+</sup> secretory mechanisms in the distal nephron, relative to the reduction in GFR. Most important are conditions associated with hyporeninemic hypoaldosteronism (e.g., diabetic nephropathy and certain forms of distal renal tubular acidosis; Chaps. 264 and 265).

*Hypokalemia* is uncommon in CRD and usually reflects markedly reduced dietary K<sup>+</sup> intake, in association with excessive diuretic therapy or gastrointestinal losses. Hypokalemia occurs as a result of primary renal K<sup>+</sup> wasting in association with other solute transport abnormalities, as in Fanconi's syndrome, renal tubular acidosis, or other forms of hereditary or acquired tubulointerstitial diseases. However, even under these circumstances, as GFR declines, the tendency

TABLE 261-4 Clinical Abnormalities in Uremia

<p><b>Fluid and electrolyte disturbances</b>                      Volume expansion and contraction (I)                      Hypermnatremia and hyponatremia (I)                      Hyperkalemia and hypokalemia (I)                      Metabolic acidosis (I)                      Hyperphosphatemia (I)                      Hypocalcemia (I)</p> <p><b>Endocrine-metabolic disturbances</b>                      Secondary hyperparathyroidism (I or P)                      Adynamic osteomalacia (D)                      Vitamin D-deficient osteomalacia (I)                      Carbohydrate intolerance (I)                      Hyperuricemia (I or P)                      Hypertriglyceridemia (I or P)                      Increased Lp(a) level (P)                      Decreased high-density lipoprotein level (P)                      Protein-energy malnutrition (I or P)                      Impaired growth and development (P)                      Infertility and sexual dysfunction (P)                      Amenorrhea (P)                      Hypothermia (I)                      β<sub>2</sub>-Microglobulin deposition (P or D)                      Associated amyloidosis (P)</p>	<p><b>Neuromuscular disturbances</b>                      Fatigue (I)<sup>b</sup>                      Sleep disorders (P)                      Headache (I or P)                      Impaired mentation (I)<sup>b</sup>                      Lethargy (I)<sup>b</sup>                      Asterixis (I)                      Muscular irritability (I)                      Peripheral neuropathy (I or P)                      Restless legs syndrome (I or P)                      Paralysis (I or P)                      Myoclonus (I)                      Seizures (I or P)                      Coma (I)                      Muscle cramps (P or D)                      Dialysis disequilibrium syndrome (D)                      Myopathy (P or D)</p> <p><b>Cardiovascular and pulmonary disturbances</b>                      Arterial hypertension (I or P)                      Congestive heart failure or pulmonary edema (I)                      Pericarditis (I)                      Cardiomyopathy (I or P)                      Uremic lung (I)                      Accelerated atherosclerosis (P or D)                      Hypotension and arrhythmias (D)                      Vascular calcification (P or D)</p>	<p><b>Dermatologic disturbances</b>                      Pallor (I)<sup>b</sup>                      Hyperpigmentation (I, P, or D)                      Pruritus (P)                      Ecchymoses (I)                      Uremic frost (I)</p> <p><b>Gastrointestinal disturbances</b>                      Anorexia (I)                      Nausea and vomiting (I)                      Uremic fetor (I)                      Gastroenteritis (I)                      Peptic ulcer (I or P)                      Gastrointestinal bleeding (I, P, or D)                      Hepatitis (D)                      Idiopathic ascites (D)                      Peritonitis (D)</p> <p><b>Hematologic and immunologic disturbances</b>                      Anemia (I)<sup>b</sup>                      Lymphocytopenia (P)                      Bleeding diathesis (I or D)<sup>b</sup>                      Increased susceptibility to infection (I or P)                      Splenomegaly and hypersplenism (P)                      Leukopenia (D)                      Hypocomplementemia (D)</p>
---	--	---

<sup>a</sup> Virtually all abnormalities in this table are completely reversed in time by successful renal transplantation. The response of these abnormalities to hemodialysis or peritoneal dialysis therapy is more variable. (I) denotes an abnormality that usually improves with an optimal program of dialysis and related therapy; (P) denotes an abnormality that tends

to persist or even progress, despite an optimal program; (D) denotes an abnormality that develops only after initiation of dialysis therapy.

<sup>b</sup> Improves with dialysis and erythropoietin therapy.

Note: Lp(a), lipoprotein A.

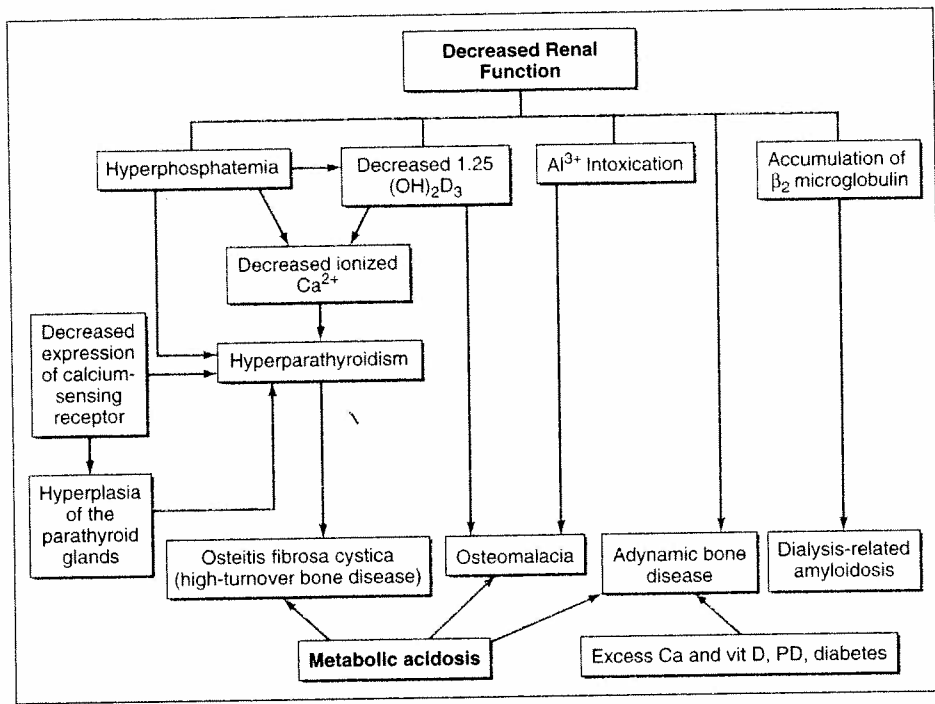


FIGURE 261-1 Flowchart for the development of bone, phosphate, and calcium abnormalities in chronic renal disease. (PD, peritoneal dialysis).

the use of diuretics if they are also indicated for management of sodium balance. Many salt substitutes contain potassium instead of sodium, and patients with CRD seeking to avoid sodium should be cautioned accordingly as part of their dietary counseling. Potassium-binding resins taken with cathartics can promote gastrointestinal potassium losses and thus are useful as temporizing measures in the treatment or avoidance of hyperkalemia in CRD patients. However, the need for such treatment over a prolonged period, in the absence of other reversible causes of hyperkalemia, usually signifies the need to initiate renal replacement therapy.

**BONE DISEASE AND DISORDERS OF CALCIUM AND PHOSPHATE METABOLISM** (Fig. 261-1; see also Chaps. 331 and 332) The major disorders of bone disease in CRD can be classified into those associated with high bone turnover and high PTH levels (including osteitis fibrosa, the hallmark lesion of secondary hyperparathyroidism) and low bone turnover with low or normal PTH levels (osteomalacia and adynamic bone disease).

to hypokalemia diminishes and hyperkalemia may supervene. Accordingly, K<sup>+</sup> supplementation and K<sup>+</sup>-sparing diuretics should generally be avoided as GFR declines.

**Metabolic Acidosis** (See also Chap. 42) Acidosis is a common disturbance during the advanced stages of CRD. Although in a majority of patients with CRD the urine can be acidified normally, these patients have a reduced ability to produce ammonia. Hyperkalemia further depresses urinary ammonium excretion. The combination of hyperkalemia and hyperchloremic metabolic acidosis (known as type IV renal tubular acidosis, or hyporeninemic hypoaldosteronism) is most characteristically seen in patients with diabetes or in those with predominantly tubulointerstitial disease. Treatment of the hyperkalemia frequently improves the acidosis as well.

With advancing renal failure, total urinary net daily acid excretion is usually limited to 30 to 40 mmol, and an anion gap of ~20 mmol/L with a reciprocal fall in plasma [HCO<sub>3</sub><sup>-</sup>] may develop. In most patients, the metabolic acidosis is mild; the pH is rarely <7.35 and can usually be corrected by treating the patient with 20 to 30 mmol of NaHCO<sub>3</sub> or sodium citrate daily. However, the concomitant Na<sup>+</sup> load mandates careful attention to volume status and the potential need for diuretic agents. Also, citrate enhances aluminum absorption in the large bowel, and citrate-containing agents should be avoided if aluminum-containing drugs are also administered. Severe symptomatic manifestations of acid-base imbalance may occur when the patient is challenged with an excessive endogenous or exogenous acid load or loses excessive alkali (e.g., with diarrhea).

**Rx TREATMENT**

Adjustments in dietary intake and use of loop diuretics, occasionally in combination with metolozone, may be needed to maintain salt and hence extracellular fluid volume balance. In contrast, overzealous salt restriction and diuretic use may cause hypovolemia and precipitate a further decline in GFR. Occasional patients with salt-wasting states need to be given sodium-rich diets or sodium supplements. Water restriction is indicated only if there is a demonstrated propensity to hyponatremia. Intractable ECFV expansion, despite dietary restriction and diuretic use, indicates the need to initiate renal replacement therapy. Hyperkalemia often responds to dietary restriction of potassium, avoidance of potassium-containing or -retaining medications, and to

The pathophysiology of bone disease due to secondary hyperparathyroidism is related to abnormal mineral metabolism. (1) Decreased GFR leads to reduced inorganic phosphate (PO<sub>4</sub><sup>3-</sup>) excretion and consequent PO<sub>4</sub><sup>3-</sup> retention, (2) retained PO<sub>4</sub><sup>3-</sup> has a direct stimulatory effect on PTH synthesis and on cellular mass of the parathyroid glands, (3) retained PO<sub>4</sub><sup>3-</sup> also indirectly causes excessive production and secretion of PTH through lowering of ionized Ca<sup>2+</sup> and by suppression of calcitriol (1,25-dihydroxycholecalciferol) production, and (4) reduced calcitriol production in CRD results both from decreased synthesis due to reduced kidney mass and from hyperphosphatemia. Low calcitriol levels, in turn, lead to hyperparathyroidism via both direct and indirect mechanisms. Calcitriol is known to have a direct suppressive effect on PTH transcription (i.e., a genomic effect), and therefore reduced calcitriol in CRD causes elevated levels of PTH. In addition, reduced calcitriol leads to impaired Ca<sup>2+</sup> absorption from the gastrointestinal tract, thereby leading to hypocalcemia, which then increases PTH secretion and production. Taken together, hyperphosphatemia, hypocalcemia, and reduced calcitriol synthesis all promote the production of PTH and the proliferation of parathyroid cells, resulting in secondary hyperparathyroidism.

In addition to excessive release of PTH from individual parathyroid cells, the mass of parathyroid cells increases progressively with CRD. Excessive parathyroid gland cellular mass may assume one of the following patterns: (1) diffuse hyperplasia (polyclonal), (2) nodular growth (monoclonal) within diffuse hyperplastic tissue, or (3) diffuse monoclonal hyperplasia ("adenoma" or tertiary autonomous hyperparathyroidism). Patients with monoclonal ("autonomous") hyperplasia are especially prone to develop hypercalcemia following successful kidney transplantation, often necessitating parathyroidectomy. High PTH levels stimulate osteoblasts and result in high bone turnover, which leads to *osteitis fibrosa cystica*. The latter is characterized by irregularly woven abnormal osteoid, fibrosis, and cyst formation, which result in decreased cortical bone and bone strength and an increased risk of fracture.

Low-turnover bone disease can be classified into two categories—osteomalacia and adynamic bone disease. Both lesions are characterized by a reduced number of osteoclasts and osteoblasts and decreased activity of the latter. In *osteomalacia* there is an accumulation of unmineralized bone matrix, or increased osteoid volume, which may be caused by vitamin D deficiency, excess aluminum deposition, or meta-

bolic acidosis. Adynamic bone disease is now recognized to be as prevalent as the hyperparathyroid bone lesion in patients with CRD and ESRD, and is especially common among diabetic patients. *Adynamic bone disease* is characterized by reduced bone volume and mineralization and may result in part from excessive suppression of PTH production with calcitriol treatment or, currently less common, from aluminum exposure.

Irrespective of the cause for skeletal abnormalities in CRD, bone disease can lead to pain, increased incidence of fractures, and severe incapacity. Bone fractures complicate both the high- and low-turnover types of bone disease, and it is now appreciated that patients with adynamic bone may be more predisposed to fractures than those with osteitis fibrosa cystica. In the latter disorder, however, a PTH-associated proximal myopathy often coexists, giving rise to gait abnormalities and impaired ambulation.

**Other Complications of Abnormal Calcium-Phosphate Product Metabolism** In addition to abnormalities in bone metabolism, abnormal calcium-phosphate product metabolism may lead to *calciphylaxis*, i.e., extraosseous ("metastatic") calcification of soft tissue and blood vessels. Electron beam computed tomography in patients with CRD has revealed highly elevated coronary calcification scores, which likely represent a major factor in the predisposition to occlusive coronary vascular disease in the CRD and ESRD populations. The pathogenesis remains unclear, but hyperphosphatemia, hypercalcemia, elevated calcium-phosphate product, and increased PTH levels are all thought to contribute to this process. Calciphylaxis represents a severe and systemic form of vascular and soft tissue calcium-phosphate product deposition associated with skin and soft tissue necrosis, which can lead to extremity loss.

## **Rx** TREATMENT

Secondary hyperparathyroidism and osteitis fibrosa are best prevented and treated by reducing the plasma  $\text{PO}_4^{3-}$  concentration through the use of a phosphate-restricted diet as well as oral phosphate-binding agents. Calcium carbonate and calcium acetate are useful phosphate-binding agents. Sevelamer, a nonabsorbable, non-calcium-containing polymer has been recently added to the phosphate-lowering armamentarium. It has an advantage over the calcium-based phosphate chelating agents in that it does not predispose CRD patients to hypercalcemia and attenuates calcium deposition in the coronary arteries and aorta.

Daily oral calcitriol, or intermittent oral or intravenous pulses, appears to exert a direct suppressive effect on PTH secretion, in addition to the indirect effect mediated through raising plasma  $\text{Ca}^{2+}$  concentration. The use of calcitriol and calcium preparations in the predialysis population must take into account potential effects of increased  $\text{PO}_4^{3-}$  and  $\text{Ca}^{2+}$  on the rate of progression of CRD. The recommended target plasma  $\text{PO}_4^{3-}$  concentration is approximately 1.4 mmol/L (4.5 mg/dL), with a corresponding plasma  $\text{Ca}^{2+}$  concentration of approximately 2.5 mmol/L (10 mg/dL) in an attempt to suppress parathyroid hyperplasia, thus avoiding or reversing osteitis fibrosa cystica, osteomalacia, and myopathy. It is particularly important to maintain the calcium-phosphate product in the normal range to avoid metastatic calcification. Recognition of the role of the extracellular calcium-sensing receptor has led to the development of calcimimetic agents that enhance the sensitivity to  $\text{Ca}^{2+}$ -suppressive effects on PTH secretion. The first-generation calcimimetic agent tested produced a dose-dependent reduction in PTH and plasma  $\text{Ca}^{2+}$  concentration, and subsequent formulations with improved pharmacokinetic profiles show great promise as effective and safe treatments for secondary hyperparathyroidism. However, since adynamic bone disease is often a consequence of overzealous treatment of secondary hyperparathyroidism, suppression of PTH levels to  $<120$  pg/mL in CRD patients may not be desirable.

The incidence of aluminum-induced osteomalacia has been greatly reduced with the recognition of aluminum as the principal culprit. Therapy for this disorder is based on the complete cessation of the use of aluminum combined with the use of a chelating agent such as deferoxamine.

Management of metabolic acidosis should aim to maintain a nearly normal level of plasma bicarbonate with the administration of calcium acetate or calcium carbonate, with the addition of sodium bicarbonate (limited by considerations of sodium load) if necessary. Excessive administration of alkali should be avoided to minimize risk of urinary precipitation of  $\text{Ca}^{2+}$  phosphate.

**CARDIOVASCULAR ABNORMALITIES** Cardiovascular disease is the leading cause of morbidity and mortality in patients with CRD at all stages. Estimates of the increase in cardiovascular disease risk attributable to CRD range from 10- to 200-fold, depending on the stage of CRD, other risk factors, and comorbid conditions. Between 30 and 45% of patients reaching ESRD already have advanced cardiovascular complications. Thus the management of patients with CRD should emphasize prevention of cardiovascular complications as well as measures aimed at alleviating the progression and complications of CRD itself.

**Ischemic Cardiovascular Disease** CRD at all stages constitutes a major risk factor for ischemic cardiovascular disease, including occlusive coronary heart, cerebrovascular, and peripheral vascular diseases. Increased prevalence of coronary heart disease in CRD derives from both traditional ("classic") and CRD-related ("nontraditional") risk factors. The former include hypertension (see below), hypervolemia, dyslipidemia, sympathetic overactivity, and hyperhomocysteinemia. The CRD-related risks include anemia, hyperphosphatemia, hyperparathyroidism, and a state of "microinflammation" that can be found at all stages of CRD but is undoubtedly aggravated by dialysis. The inflammatory state elicits a rise in acute-phase reactants such as interleukin 6 and C-reactive protein, which contribute to the coronary occlusive process and are predictors of cardiovascular disease risk. Other abnormalities augment myocardial ischemia. These include reduced myocardial tolerance to ischemia due to left ventricular hypertrophy (see below) and microvascular disease. Also, coronary reserve, defined as the increase in coronary blood flow in response to greater demand, is attenuated. Nitric oxide is an important mediator for vascular dilatation. Its availability in CRD is decreased because of increased concentrations of asymmetric dimethyl-L-arginine, even at early stages of CRD, and also because nitric oxide is scavenged by reactive oxygen species. In addition, coronary arteriolar hypertrophy/hyperplasia limits vasodilatory capacity.

**Congestive Heart Failure** (See also Chap. 216) Abnormal cardiac function secondary to myocardial ischemic disease and/or left ventricular hypertrophy, together with salt and water retention in uremia, often result in congestive heart failure and/or pulmonary edema. A unique form of pulmonary congestion and edema may occur even in the absence of volume overload and is associated with normal or mildly elevated intracardiac and pulmonary capillary wedge pressures. This entity, characterized radiologically by peripheral vascular congestion giving rise to a "butterfly wing" distribution, is due to increased permeability of alveolar capillary membranes. This "low-pressure" pulmonary edema as well as cardiopulmonary abnormalities associated with circulatory overload usually respond promptly to vigorous dialysis.

**Hypertension and Left Ventricular Hypertrophy** (See also Chap. 230) Hypertension is the most common complication of CRD and ESRD. It may develop early during the course of CRD and is associated with adverse outcomes—in particular, more rapid loss of renal function and development of cardiovascular disease. Numerous epidemiologic studies and clinical trials have shown a relationship between the level of blood pressure and rate of progression of diabetic and non-diabetic kidney disease (see below).

Administration of EPO (p. 1658) may raise blood pressure and increase the requirement for antihypertensive drugs in CRD patients. Left ventricular hypertrophy and dilated cardiomyopathy are among the most ominous risk factors for excess cardiovascular morbidity and

mortality in patients with CRD and ESRD and are thought to be related primarily to prolonged hypertension and ECFV overload. In addition, anemia and the surgical placement of an arteriovenous anastomosis for future or ongoing dialysis access may generate a high cardiac output state and pulmonary hypertension, which also intensify the burden placed on the left ventricle. *Absence* of hypertension may signify the presence of a salt-wasting form of renal disease (e.g., medullary cystic disease, chronic tubulointerstitial disease, or papillary necrosis), ongoing antihypertensive therapy, volume-depletion due to gastrointestinal causes or diuretic therapy, or reduced cardiac index.

Since volume overload is the major cause of hypertension in uremia, the normotensive state can often be restored by appropriate (not overzealous) use of salt restriction and natriuretic drugs or ultrafiltration in the dialysis setting. Nevertheless, because of hyperreninemia and other disturbances in renal vasoconstrictors and vasodilators, some patients remain hypertensive despite rigorous salt and water restriction and ultrafiltration. Rarely, such patients may develop accelerated or malignant hypertension. Intravenous labetalol, or more recently approved agents such as fenoldopam or urapidil, together with control of ECFV generally control such hypertension. Enalaprilat or other ACE inhibitors may also be considered, but in the face of bilateral renovascular disease they have the potential to further reduce GFR abruptly.

## **Rx** TREATMENT

**Management of Hypertension** (See also Chap. 230) There are two overall goals: to slow the progression of CRD itself and to prevent the extrarenal complications of hypertension, such as cardiovascular disease and stroke. In all patients with CRD, blood pressure should be controlled to at least the level established in the guidelines of the Sixth Joint National Commission on Hypertension Detection Education and Follow-up Program (130/80 to 85 mmHg). In CRD patients with diabetes or proteinuria >1 g per 24 h, blood pressure should be further reduced to 125/75 mmHg. Volume control with salt restriction and diuretics is the mainstay of therapy. When volume management is not sufficient, the choice of antihypertensive agent is similar to that in the general population, with the added consideration of cardioprotective benefit provided by ACE inhibition, or angiotensin receptor blockade. The choice of antihypertensive agents may come from all the major classes, with careful consideration of comorbid conditions. However, powerful direct-acting vasodilators, such as hydralazine or minoxidil, may perpetuate the tendency to cardiac hypertrophy, despite the lowering of blood pressure. Therefore, prolonged use of such agents should be reserved for those very rare patients in whom severe refractory hypertension persists, despite adequate volume reduction and compliance with all other classes of antihypertensives.

**Management of Cardiovascular Disease** Hypertension, hyperhomocysteinemia, and lipid abnormalities promote atherosclerosis but are potentially treatable complications of CRD. Ongoing or prior nephrotic syndrome is also associated with hyperlipidemia and hypercoagulability, which increase the risk of occlusive vascular disease. Since diabetes mellitus and hypertension are themselves the two most frequent etiologies of CRD, it is not surprising that cardiovascular disease is the most frequent cause of death in ESRD patients. Therefore, accepted life-style changes and therapeutic measures for cardiac risk reduction (Chap. 225) are especially important in this group of patients. Hyperhomocysteinemia may respond to vitamin therapy, which includes folate supplementation to between 1 and 5 mg/d. Hyperlipidemia in patients with CRD and ESRD should be managed aggressively according to the guidelines of the National Cholesterol Education Program (Chap. 335). If dietary measures are inadequate, the preferred lipid-lowering medications are gemfibrozil and an HMG-CoA reductase inhibitor. However, caution should be exercised in combining these two classes of agents because of an increased risk of myositis and rhabdomyolysis in CRD and ESRD patients.

**Pericarditis** (See also Chap. 222) With the advent of early initiation of renal replacement therapy, pericarditis is now observed more often in underdialyzed patients than in predialysis CRD patients. Pericardial pain with respiratory accentuation, accompanied by a friction rub, are the hallmarks of uremic pericarditis. The finding of a multicomponent friction rub strongly supports the diagnosis. Classic electrocardiographic abnormalities include PR-interval depression and diffuse ST-segment elevation. Pericarditis may be accompanied by the accumulation of pericardial fluid that is readily detected by echocardiography and that sometimes leads to cardiac tamponade. Pericardial fluid in uremic pericarditis is more often hemorrhagic than in viral pericarditis.

## **Rx** TREATMENT

Uremic pericarditis is an absolute indication for initiation of dialysis or for intensification of the dialysis prescription in those already on dialysis. Because of the propensity to hemorrhagic pericardial fluid, heparin-free dialysis is indicated. Pericardiectomy should be considered only if more conservative measures fail. Nonuremic causes of pericarditis and pericardial effusion include viral, malignant, and tuberculous pericarditis and pericarditis associated with myocardial infarction; these are also more frequent in patients with ESRD and should be managed according to the dictates of the underlying disease process.

**HEMATOLOGIC ABNORMALITIES ■ Anemia** A normocytic, normochromic anemia attributable to CRD is observed beginning at stage 3 CRD and is almost universal at stage 4. If untreated, the anemia of CRD is associated with a number of physiologic abnormalities, including decreased tissue oxygen delivery and utilization, increased cardiac output, cardiac enlargement, ventricular hypertrophy, angina, congestive heart failure, decreased cognition and mental acuity, altered menstrual cycles, and impaired host defense against infection. In addition, anemia may play a role in growth retardation in children with CRD. The primary cause of anemia in patients with CRD is insufficient production of EPO by the diseased kidneys. Additional factors include iron and folate deficiency, severe hyperparathyroidism, acute and chronic inflammation, aluminum toxicity, shortened red cell survival, and associated comorbid conditions such as hemoglobinopathies. These potential contributing factors should be considered and addressed, especially in EPO-resistant patients.

## **Rx** TREATMENT

The anemia of CRD is due to several factors including chronic blood loss, hemolysis, marrow suppression by retained uremic factors and reduced renal production of EPO. The availability of recombinant human EPO, epoetin alfa, has made possible one of the most significant advances in the care of renal patients since the introduction of dialysis and transplantation. More recently, a novel erythropoiesis-stimulating protein has been introduced for the treatment of anemia in CRD patients. This protein, darbopoetin alfa, is a hyperglycosylated analogue of recombinant human EPO that possesses greater biologic activity and prolonged half-life. Thus, dose intervals can be extended and still effectively correct renal anemia in both predialysis and dialysis patients. Guidelines for using epoetin and darbopoetin alfa for the management of anemia of CRD are provided in Table 261-5.

The iron status of the patient with CRD must be assessed, and adequate iron stores should be available before treatment with EPO is initiated. Iron supplementation is usually essential to ensure an adequate response to EPO in patients with CRD, because the demands for iron by the erythroid marrow frequently exceed the amount of iron that is immediately available for erythropoiesis (as measured by percent transferrin saturation) as well as iron stores (as measured by serum ferritin). In most cases, intravenous iron is required to achieve and/or maintain adequate iron. However, excessive iron therapy may be associated with a number of complications, including hemosiderosis, accelerated atherosclerosis, increased susceptibility to infection, and

possibly an increased propensity to the emergence of malignancies. In addition to iron, an adequate supply of the other major substrates and cofactors for erythrocyte production must be assured, especially vitamin B<sub>12</sub> and folate. Anemia resistant to recommended doses of EPO in the face of adequate availability of iron and vitamin factors often suggests inadequate dialysis; uncontrolled hyperparathyroidism; aluminum toxicity; chronic blood loss or hemolysis; associated hemoglobinopathy, malnutrition, chronic infection, multiple myeloma, or another malignancy. Blood transfusions may contribute to suppression of erythropoiesis in CRD; because they increase the risk of hepatitis, hemosiderosis, and transplant sensitization, they should be avoided unless the anemia fails to respond to erythropoietin and the patient is symptomatic.

**Abnormal Hemostasis** This is common in CRD and is associated with prolongation of bleeding time, decreased activity of platelet factor III, abnormal platelet aggregation and adhesiveness, and impaired prothrombin consumption. Clinical manifestations include an increased tendency to abnormal bleeding and bruising; bleeding from surgical wounds; and spontaneous bleeding into the gastrointestinal tract, pericardial sac, or intracranial vault (in the form of subdural hematoma or intracerebral hemorrhage). Notwithstanding these abnormalities in hemostasis, CRD patients have a greater susceptibility to thromboembolic complications, particularly if their underlying disease was characterized by a nephrotic presentation.

## **R<sub>x</sub>** TREATMENT

Abnormal bleeding times and coagulopathy in patients with renal failure may be reversed with desmopressin, cryoprecipitate, conjugated estrogens, and blood transfusions, as well as EPO. On the other hand, patients with CRD should also be viewed as being at greater risk for thromboembolic complications and receive appropriate anticoagulant prophylaxis when indicated. Avoidance or dose adjustment of certain anticoagulants, such as fractionated low-molecular-weight heparin, is necessary in CRD patients.

**NEUROMUSCULAR ABNORMALITIES** Central, peripheral, and autonomic neuropathy, as well as abnormalities in muscle composition and function, are all common complications in CRD. Retained nitrogenous metabolites and middle molecules as well as PTH all contribute to the pathophysiology of neuromuscular abnormalities. Subtle clinical manifestations of uremic neuromuscular disease usually become evident beginning at stage 3 CRD. Early manifestations of central nervous system complications include mild disturbances in memory and concentration and sleep disturbance. Neuromuscular irritability, including hiccups, cramps, and fasciculations/twitching of muscles, becomes evident at later stages. Asterixis, myoclonus, and chorea are common in terminal uremia, which may also be associated with seizures and coma.

Peripheral neuropathy usually becomes clinically evident when the patient has been at stage 4 CRD for >6 months, although electrophysiologic and histologic evidence of peripheral neuropathy occurs earlier. Initially, sensory nerves are involved more than motor nerves, lower extremities more than upper, and distal portions of the extremities more than proximal. The "restless legs syndrome" is characterized by ill-defined sensations of discomfort in the legs and feet requiring frequent leg movement. If dialysis is not instituted soon after onset of sensory abnormalities, motor involvement follows, including muscle weakness and loss of deep tendon reflexes. Accordingly, evidence of

TABLE 261-5 Management Guidelines for Correction of Anemia of Chronic Renal Disease

<b>Erythropoietin</b>	
Starting dosage:	50–150 units/kg per week IV or SC (once, twice, or three times per week)
Target hemoglobin (Hb):	11–12 g/dL
Optimal rate of correction <sup>a</sup> :	Increase Hb by 1–2 g/dL over 4-week period
<b>Darbepoetin alfa</b>	
Starting dosage:	0.45 µg/kg administered as a single IV or SC injection once weekly 0.75 µg/kg administered as a single IV or SC injection once every 2 weeks ≤12 g/dL
Target Hb:	11–12 g/dL
Optimal rate of correction	Increase Hb by 1–2 g/dL over 4-week period
<b>Iron</b>	
1. Monitor iron stores by percent transferrin saturation (TSat) and serum ferritin.	
2. If patient is iron-deficient (TSat <20%; serum ferritin <100 µg/L), administer iron, 50–100 mg IV twice per week for 5 weeks; if iron indices are still low, repeat the same course.	
3. If iron indices are normal yet Hb is still inadequate, administer IV iron as outlined above; monitor Hb, TSat, and ferritin.	
4. Withhold iron therapy when TSat > 50% and/or ferritin > 800 ng/mL (>800 g/L).	

<sup>a</sup> If correction of anemia is inadequate, consider causes for refractoriness as outlined in text. Recent reports of pure red blood cell aplasia, may lead to preferences for IV route for some EPO formulations.

peripheral neuropathy is a firm indication for renal replacement therapy. Some of the central nervous system and neuromuscular complications of advanced uremia resolve with dialysis, although nonspecific electroencephalographic abnormalities may persist. Successful transplantation may reverse residual peripheral neuropathy.

**GASTROINTESTINAL AND NUTRITIONAL ABNORMALITIES** *Uremic fetor*, a urinous odor to the breath, derives from the breakdown of urea to ammonia in saliva and is often associated with an unpleasant metallic taste sensation. Gastritis, peptic disease, and mucosal ulcerations at any level of the gastrointestinal tract occur in uremic patients and can lead to abdominal pain, nausea, vomiting, and blood loss. Other gastrointestinal complications of CRD include an increased incidence of diverticulosis, particularly in patients with polycystic kidney disease, and an increased incidence of pancreatitis. In addition, central nervous system effects of uremia contribute to anorexia, hiccups, nausea, and vomiting. Protein restriction is useful in diminishing nausea and vomiting late in the course of renal failure. However, protein restriction should not be implemented in patients with signs of protein-energy malnutrition, which is a consequence of low protein and caloric intake, resistance to anabolic actions of insulin and other hormones and growth factors, disturbed dietary protein utilization, proinflammatory cytokine activation, and metabolic acidosis. Assessment for protein-energy malnutrition should begin at stage 3 CRD (GFR < 60 mL/min per 1.73 m<sup>2</sup>). A number of indices are useful in this assessment and include dietary history, edema-free body weight, measurement of urinary protein nitrogen appearance, and plasma markers, of which albumin is the most useful. Guidelines for caloric and protein intake in patients with CRD are provided below (p. 1661).

**ENDOCRINE-METABOLIC DISTURBANCES** Disturbances in parathyroid function have already been considered (p. 1656).

*Glucose metabolism* is impaired in CRD, as evidenced by a slowing of the rate at which blood glucose levels decline after a glucose load. Fasting blood glucose is usually normal or only slightly elevated, and the mild glucose intolerance related to uremia per se, when present, does not require specific therapy. Because the kidney contributes significantly to insulin removal from the circulation, plasma levels of insulin are slightly to moderately elevated in most uremic subjects, both in the fasting and postprandial states. However, the response to insulin and glucose utilization is impaired in CRD. Many hypoglycemic drugs require dose reduction in renal failure, and some, such as metformin, are contraindicated when the GFR has diminished by more than approximately 25 to 50%.

In women, *estrogen levels* are low, and amenorrhea and inability to carry pregnancies to term are common manifestations of uremia. When the GFR has declined by ~30%, pregnancy may hasten the progression of CRD. In men with CRD, including those receiving chronic dialysis, impotence, oligospermia, and germinal cell dysplasia

are common, as are reduced plasma testosterone levels. Like growth, sexual maturation is often impaired in adolescent children with CRD, even among those treated with chronic dialysis. Many of these abnormalities improve or reverse with successful renal transplantation.

**DERMATOLOGIC ABNORMALITIES** The skin may show evidence of anemia (pallor), defective hemostasis (ecchymoses and hematomas), calcium-phosphate deposition and secondary hyperparathyroidism (pruritus, excoriations), and deposition of pigmented metabolites or *urochromes* (yellow discoloration) or urea itself (uremic frost). Although many of these cutaneous abnormalities improve with dialysis, *uremic pruritus* often remains a problem. The first lines of management are to rule out unrelated skin disorders and to control  $\text{PO}_4^{3-}$  concentration with avoidance of an elevated calcium-phosphate product. Occasionally, pruritus remains refractory to these measures and to other nonspecific systemic and topical therapies. Skin necrosis can occur as part of the calciphylaxis syndrome, which also includes subcutaneous, vascular, joint, and visceral calcification in patients with poorly controlled calcium-phosphate product.

#### EVALUATION AND MANAGEMENT OF PATIENTS WITH CRD

**INITIAL APPROACH ■ History and Physical Examination** Complaints referred to the kidneys themselves are often conspicuously absent in CRD, and this often surprises patients and is a cause of skepticism and denial. Of special importance in establishing the etiology of CRD are a history of hypertension; diabetes; systemic infectious, inflammatory, or metabolic diseases; exposure to drugs and toxins; and a family history of renal and urologic disease. Drugs of particular importance include analgesics (usage frequently underestimated or denied by the patient), NSAIDs, gold, penicillamine, antimicrobials, lithium, and ACE inhibitors. In evaluating the uremic syndrome, questions about appetite, diet, nausea, vomiting, hiccupping, shortness of breath, edema, weight change, muscle cramps, pruritus, mental acuity, and activities of daily living are especially helpful.

On physical examination, particular attention should be paid to blood pressure, fundoscopy, precordial examination, examination of the abdomen for bruits and palpable renal masses, examination for edema, and neurologic examination for the presence of asterixis, muscle weakness, and neuropathy. In addition the evaluation of prostate size in men, and potential pelvic masses in women should be undertaken.

**Laboratory Investigations** These should also focus on a search for clues to an underlying disease process and its continued activity. Therefore, if the history and physical examination warrant, immunologic tests for systemic lupus erythematosus and vasculitis might be considered. Serum and urinary protein electrophoresis should be undertaken in all patients >40 years with unexplained CRD and anemia, to rule out paraproteinemia. Other tests to determine the stage and chronicity of the disease, including complications of the uremic syndrome, include serial measurements of plasma creatinine and estimation of GFR, urea, electrolytes (including  $\text{HCO}_3^-$ ,  $\text{Ca}^{2+}$ , and  $\text{PO}_4^{3-}$ ), and alkaline phosphatase to assess metabolic bone disease as well as hemoglobin. Urinalysis may be helpful in assessing the presence of ongoing activity of the underlying inflammatory or proteinuric disease process and, when indicated, should be supplemented by a 24-h urine collection for protein excretion. The latter is particularly helpful in guiding management strategies aimed at ameliorating the progression of CRD. The presence of broad casts on examination of the urinary sediment is a nonspecific finding seen with all underlying etiologies and reflects chronic tubulointerstitial scarring and tubular atrophy with widened tubule diameter, usually signifying an advanced stage of CRD.

**Imaging Studies** The most useful imaging study is renal ultrasonography. An ultrasound examination of the kidneys can verify the presence of two symmetric kidneys, provide an estimate of kidney size, and rule out renal masses and obstructive uropathy. The documentation

of symmetric small kidneys supports the diagnosis of progressive CRD with an irreversible component of scarring. Normal kidney size suggests the possibility of an acute rather than chronic process. However, polycystic kidney disease, amyloidosis, diabetes, and HIV-associated renal disease (Chap. 173) may lead to CRD with normal kidney size. Documentation of asymmetric kidney size suggests either a unilateral developmental abnormality or chronic renovascular disease. In the latter case, a vascular imaging procedure, such as duplex doppler sonography of the renal arteries, radionuclide scintigraphy, or magnetic resonance angiography should be strongly considered if the possibility of revascularization is feasible. A spiral computed tomographic scan without contrast may be useful in assessing kidney stone activity. Voiding cystourethrography to rule out reflux may be indicated in some patients with a history of enuresis or with a family history of reflux. However, in most cases by the time CRD is established, reflux has resolved, and even if present, its repair does not stabilize renal function. In any case, imaging studies should avoid exposure to intravenous radiocontrast dye where possible because of its nephrotoxicity.

**Renal Biopsy** This procedure should be reserved for patients with near-normal kidney size, in whom a clear-cut diagnosis cannot be made by less invasive means and when the possibility of a reversible underlying disease process remains tenable, such that clarification of the underlying etiology may alter management. The extent of tubulointerstitial scarring on kidney biopsy generally provides the most reliable pathologic correlate indicating prognosis for continued deterioration toward ESRD. Contraindications to renal biopsy include bilateral small kidneys, polycystic kidney disease, uncontrolled hypertension, urinary tract or perinephric infection, bleeding diathesis, respiratory distress, and morbid obesity. Ultrasound-guided percutaneous biopsy is the favored approach, but surgical approaches, including laparoscopic biopsy, may be considered in special circumstances such as biopsy of a solitary kidney.

**ESTABLISHING THE DIAGNOSIS AND ETIOLOGY OF CRD** The most important initial step in the evaluation of a patient presenting de novo with biochemical or clinical evidence of renal failure is to distinguish newly diagnosed CRD from acute renal failure. Availability of past medical records documenting serial measurements of the plasma urea and/or creatinine concentrations can be of great help in this regard. In the absence of such information, some of the laboratory tests and imaging studies outlined above can be useful. In particular, a urinary sediment that is inactive or reveals proteinuria and broad casts; the demonstration of evidence of chronic metabolic bone disease with hyperphosphatemia, hypocalcemia, elevated PTH levels, and radiologic bone disease; normocytic and normochromic anemia; and the finding of bilaterally reduced kidney size (< 8.5 cm) by imaging studies, strongly favor a long-standing process consistent with CRD. However, these findings do not rule out the superimposition of an acute and reversible exacerbating factor that may have accelerated the decline in GFR (see below).

In the early stages of CRD it is often possible to establish the underlying etiology. Integration of a particular constellation of clinical, laboratory, and imaging findings based on the approach noted above strongly supports a particular presumed underlying etiologic disease process. For example, in a patient with insulin-dependent type 1 diabetes mellitus of 15 to 20 years duration, diabetic retinopathy, and nephrotic-range albuminuria without hematuria, the diagnosis of *diabetic nephropathy* is likely. The diagnosis of *chronic hypertensive nephrosclerosis* requires a history of long-standing hypertension, in the absence of evidence for another renal disease process, and hence it is usually a diagnosis of exclusion. Usually proteinuria is mild to moderate (< 3 g/d) and the urine sediment inactive. It should be noted that in many cases of presumed hypertensive nephrosclerosis, renovascular disease not only may be the cause of hypertension but also may cause ischemic renal damage. In this regard, bilateral renovascular ischemic disease may be a greatly underdiagnosed cause of CRD. This is of therapeutic significance from two points of view: (1) documentation of ischemic renal disease secondary to occlusive vascular dis-

ease may prompt revascularization therapy in some subgroups of patients, with occasional stabilization and improvement in renal function: (2) renovascular ischemic disease is a contraindication to ACE inhibitor therapy in most cases. *Analgesic-associated chronic tubulointerstitial nephropathy* is also an underdiagnosed cause of CRD. Imaging studies, including computed tomography, often reveal pathognomonic features such as papillary calcification and necrosis. Under such circumstances, cessation of analgesic exposure may dramatically stabilize renal function.

In the absence of an etiologically suggestive clinical constellation, renal biopsy may be the only recourse to establish etiology in early CRD. However, in advanced stages of CRD, definitively establishing an underlying etiology becomes less feasible and is also of less therapeutic significance.

## Rx TREATMENT

Specific treatments aimed at selected underlying etiologies of CRD are provided in the respective chapters describing these disease states. The optimal time for such therapy is usually well before there has been a measurable decline in baseline GFR and usually well before CRD is established. It is of benefit to follow and plot the rate of decline in GFR in all patients. Any acceleration in the rate of decline should prompt a search for superimposed acute processes that may lead to an acute and reversible decline in GFR in patients with CRD. These include superimposed volume depletion, accelerated and uncontrolled hypertension, urinary tract infection, superimposed obstructive uropathy (e.g., due to stone disease, papillary necrosis), nephrotoxic effect of medications (e.g., NSAIDs) and radiocontrast agents, and reactivation or flare of the original underlying etiologic disease process.

**SLOWING THE PROGRESSION OF CRD** While there is great interindividual variation in the rate of decline of GFR in patients with CRD, a series of therapeutic interventions should be pursued that aim to stabilize the GFR or reduce the annual rate of decline.

**Protein Restriction** (Table 261-6) A major goal of protein restriction in CRD, beyond ameliorating the complications of uremia, is to slow the rate of nephron injury. This concept is based on clinical and experimental evidence demonstrating the role of protein-mediated hyperfiltration in progressive nephron injury. The effectiveness of protein restriction in slowing the progression of CRD has been shown in controlled clinical trials in patients with both diabetic and nondiabetic renal disease.

Protein restriction should be carried out in the context of an overall dietary program that optimizes nutritional status and avoids malnutrition, especially as patients near dialysis or transplantation. Metabolic and nutritional studies indicate that protein requirements for patients with CRD are similar to those for normal adults and are in the range

of 0.6 g/kg per day. However, there is a particular requirement in patients with CRD that the composition of dietary protein be higher in essential amino acids, and that this be combined with an overall energy supply sufficient to mitigate a catabolic state. Energy requirements in the range of 35 kcal/kg per day are recommended. Fortunately, even patients with advanced CRD (GFR ~ 10 to 15 mL/min per 1.73 m<sup>2</sup>) are able to activate the same adaptive responses to dietary protein restriction as healthy individuals, i.e., a postprandial suppression of whole-body protein degradation and a marked inhibition of amino acid oxidation. These compensatory responses to dietary protein restriction and nutritional indices are sustained during long-term therapy.

### Reducing Intraglomerular Hypertension and Proteinuria (See also p. 1657)

In addition to reduction of cardiovascular disease risk, antihypertensive therapy in patients with CRD also aims to slow the progression of nephron injury, by ameliorating intraglomerular hypertension and hypertrophy. Progressive renal injury in CRD appears to be most closely related to the height of intraglomerular pressure and/or the extent of glomerular hypertrophy. Control of hypertension is as at least as important as dietary protein restriction in slowing the progression of CRD. Furthermore, the target for pharmacologic therapy is highly dependent on the level of proteinuria. Indeed, proteinuria is now considered a risk factor for both progressive nephron injury as well cardiovascular disease. Elevated blood pressure increases proteinuria due to the transmission to the glomeruli of the elevated systemic pressure. Conversely, the renoprotective effect of antihypertensive medications is evident through the curtailment of proteinuria. Thus, the more effective a given treatment is in lowering proteinuria, the greater the subsequent impact on protection from GFR decline. This is the basis for the treatment guideline establishing 125/75 mmHg as the target blood pressure value in proteinuric CRD patients.

Owing to their unique effect on the glomerular microcirculation (i.e., dilatation of the efferent arteriole), which is related to inhibition of the renin-angiotensin system, ACE inhibitors and angiotensin receptor blockers are now clearly established as effective, antiproteinuric agents. Several multicenter studies have shown that these drugs are effective in slowing the progression of renal failure in patients with both diabetic and nondiabetic renal failure. The slowing in the progression of renal failure by these drugs is strongly related to their proteinuria-lowering effect. In the absence of a significant antiproteinuric response, combined treatment with both an ACE inhibitor and angiotensin receptor blocker can be tried. Contraindications to or adverse effects of the use of these classes of agents (e.g., intractable cough, anaphylaxis, hyperkalemia not controlled by dietary restriction) may prompt the choice of calcium channel blockers as a second-line therapeutic approach. Among the calcium channel blockers, diltiazem and verapamil may exhibit superior antiproteinuric and renal protective effects. Available clinical studies have indicated that calcium antagonists as a group do not adversely affect renal function in patients with nondiabetic renal insufficiency, and also indicate that they may be more effective in preventing or ameliorating progressive renal injury than some other classes of antihypertensive drugs in this group of patients. Thus, it appears that at least two different categories of responses may exist: one in which progression is strongly associated with systemic and intraglomerular hypertension and with proteinuria (e.g., diabetic nephropathy, glomerular diseases) and in which ACE inhibitors and angiotensin receptor blockers are likely to be the first choice; and the second in which proteinuria is mild or absent (e.g., adult polycystic kidney disease), probably with a less prominent role for intraglomerular hypertension, and which might respond as well to calcium entry blockers.

**SLOWING DIABETIC RENAL DISEASE** (See also Chap. 323) Diabetic nephropathy is now the leading cause of CRD eventuating in ESRD in many parts of the world. Furthermore, the prognosis of diabetic patients on chronic renal replacement therapy is very poor, owing to

TABLE 261-6 Management Guidelines for Dietary Protein Restriction in CRD

CRD Stage	Protein, g/kg per d	Phosphorus, g/kg per d
Stages 1 and 2	Protein restriction not usually recommended	No restriction
Stage 3	0.6 g/kg per d including $\geq 0.35$ g/kg per d of HBV	$\leq 10$
Stages 4 and 5	0.6 g/kg per d including $\geq 0.35$ g/kg per d of HBV	$\leq 10$
	or 0.3 g/kg per d supplemented with EAA or KA	$\leq 9$
GFR <60 mL/min per 1.73 m <sup>2</sup> (nephrotic syndrome)	0.8 g/kg per d (plus 1 g protein/g proteinuria)	$\leq 12$
	or 0.3 g/kg per d supplemented with EAA or KA (plus 1 g protein/g proteinuria)	$\leq 9$

Note: CRD, chronic renal disease; GFR, glomerular filtration rate; HBV, high biologic value protein; EAA, essential amino acid supplement; KA, ketoanalogue supplement.

accelerated cardiovascular disease. Therefore, it is particularly compelling to search for strategies whose aim is to prevent or slow the progression of this complication of diabetes mellitus.

**Glucose Control** Although tight glycemic control reduces the risk of kidney disease in patients with type 1 diabetes, there has been prolonged controversy over whether the same is true in patients with type 2 diabetes. The results of recent controlled prospective studies provide incontrovertible evidence that in type 2 diabetes mellitus the risk of the development and progression of albuminuria and CRD can also be substantially reduced by improving glycemic control. The United Kingdom Prospective Diabetes Study showed that the way in which glycemic control was achieved, whether by insulin or oral antihyperglycemic agents such as sulfonylureas or metformin, was far less important than success in achieving control. Achieving a target hemoglobin A<sub>1c</sub> level of <7.2%, as compared to >9%, is associated with an approximately 50% reduction in the occurrence of indices of progressive nephropathy. As a result of these findings, recommendations for glucose control aim to achieve plasma values for preprandial glucose in the range of 90 to 130 mg/dL, and for average bedtime glucose of 110 to 150 mg/dL and hemoglobin A<sub>1c</sub> < 7%. Reduction in GFR mandates dose adjustment of many antihyperglycemic agents, and in particular the discontinuation of metformin when the plasma creatinine is >133 μmol/L (1.5 mg/dL).

**Control of Blood Pressure and Proteinuria** Hypertension or an abnormal circadian blood pressure profile is found in 80% of type 2 diabetic patients at the time of diagnosis. Both of these findings correlate with the presence of albuminuria and are powerful predictors of cardiovascular and renal events. The onset of microalbuminuria precedes the decline in GFR in diabetic patients and heralds renal as well as cardiovascular complications. Therefore, microalbuminuria testing is recommended in all diabetic patients at least annually, and more frequently to follow therapeutic interventions. Antihypertensive treatment reduces albuminuria and diminishes the risk of progression of albuminuria even in normotensive patients with diabetes. There is now compelling evidence that ACE inhibitors and angiotensin receptor blockers have specific renoprotective properties in diabetic patients with microalbuminuria or overt proteinuria. These salutary effects are almost certainly mediated by reducing intraglomerular pressure and inhibition of transforming growth factor β-mediated sclerosing pathways.

**MANAGING OTHER COMPLICATIONS OF CHRONIC RENAL FAILURE** ■ **Impending Uremic Symptomatology** Temporary relief of symptoms and signs of impending uremia, such as anorexia, nausea, vomiting, asterixis, lassitude, and other central nervous system manifestations, may be achieved with protein restriction. However, this must be associated with careful monitoring of nutritional status, so as to avoid protein-energy malnutrition, evidence of which serves as a clear-cut indication for initiation of renal replacement therapy.

**Medication Dose Adjustment** (See also Chap. 3) Although the loading dose of most drugs is not affected by CRD, maintenance doses of many drugs need to be adjusted. For those drugs in which >70% excretion is by a nonrenal (e.g., hepatic or intestinal) route, dosage adjustment may not be needed. Some drugs that should be entirely avoided include meperidine, metformin, and other oral hypoglycemics with a renal route of elimination. Commonly used medications that require either a reduction in dosage or changes in interval include allopurinol, many antibiotics, several antihypertensives, and antiarrhythmics. For a comprehensive detailed and authoritative listing of the recommended dose adjustment for most of the commonly used medications, the reader is referred to the American College of Physicians' handbook "Drug Prescribing in Renal Failure" (see [www.acponline.org](http://www.acponline.org)). In addition to dose adjustment requirements, many drugs have nephrotoxicity as a prominent side effect, to which patients with CRD are more susceptible. Of particular notoriety in this regard are NSAIDs, because of

their widespread availability and usage. These drugs aggravate the tendency to sodium retention, hypertension, hyperkalemia, and hyponatremia and further reduce GFR in patients with CRD. In this regard, there is no advantage to more selective inhibitors of cyclooxygenase-2.

**Preparation for Renal Replacement Therapy** (See also Chaps. 262 and 263) Over the past 40 years, renal replacement therapy using dialysis and transplantation has prolonged the lives of hundreds of thousands of patients with ESRD. Renal replacement therapy should *not* be initiated when the patient is totally asymptomatic; however, dialysis and/or transplantation should be started sufficiently early to prevent serious complications of the uremic state. Clear indications for initiation of renal replacement therapy include pericarditis, progressive neuropathy attributable to uremia, encephalopathy, muscle irritability, anorexia and nausea that are not ameliorated by reasonable protein restriction, evidence of protein-energy malnutrition, and fluid and electrolyte abnormalities that are refractory to conservative measures. The latter include volume overload unresponsive to diuretic therapy, hyperkalemia unresponsive to dietary potassium restriction, and progressive metabolic acidosis that cannot be managed with alkali therapy. Clinical clues indicating the imminent development of uremic complications are a history of hiccups, intractable pruritus, morning nausea and vomiting, muscle twitching and cramps, and the presence of asterixis on physical examination. In addition, the patient whose follow-up and compliance with conservative management are questionable should be considered for earlier initiation of renal replacement therapy, lest potentially life-threatening uremic complications or electrolyte disturbances supervene.

Since there is considerable interindividual variability in the severity of uremic symptoms and renal function, it is ill-advised to assign a certain "usual" level of blood urea nitrogen, serum creatinine, or GFR to the need to start dialysis. Nevertheless, in the United States, the Health Care Financing Administration has assigned levels of serum creatinine and creatinine clearance to qualify for reimbursement from Medicare for patients receiving dialysis. Serum creatinine must be  $\geq 700$  μmol/L ( $\geq 8.0$  mg/dL) and the creatinine clearance must be  $\leq 10$  mL/min. Recent controlled studies have failed to show a survival advantage for early initiation of renal replacement therapy prior to onset of clinical indications.

**Patient Education and Adjustment** Social, psychological, and physical preparation for the transition to renal replacement therapy and choice of the optimal initial modality is best accomplished with a gradual approach involving a multidisciplinary team. While conservative measures are being carried out in patients with CRD, it is important to prepare them with an intensive educational program, explaining the likelihood and timing of initiation of renal replacement therapy and the various forms of therapy available. The more knowledgeable patients are concerning hemodialysis, peritoneal dialysis, and transplantation, the easier and more appropriate will be their decisions at a later time. Exploration of social service support resources is of great importance. In those who may perform home dialysis or undergo transplantation, early education of family members for selection and preparation as a home dialysis helper or a related donor for transplantation should occur long before the onset of symptomatic renal failure.

Selection of patients to be treated with various modalities of dialysis or transplantation is a matter of some debate, with considerable variation in different parts of the world. In general, in the United States and some other countries, nearly all patients who have reached ESRD are accepted for dialysis if they or their families desire prolongation of life, irrespective of age.

Only kidney transplantation (Chap. 263) offers the potential for nearly complete rehabilitation. This is because dialysis techniques replace only 10 to 15% of normal kidney function at the level of small-solute removal and are even less efficient at the removal of larger solutes. Generally, kidney transplantation follows a prior period of dialysis treatment. All patients in whom an acute reversible component of renal failure has not been completely excluded should be supported

with dialysis first, at least for some period of time, to allow for possible return of renal function before consideration of transplantation. Recovery of endogenous renal function in patients treated with dialysis for >6 months is a rare occurrence. For patients approaching ESRD in whom a reversible component has been excluded, and who have a good antigenic match with a willing donor, consideration should be given to preemptive or primary transplantation without intervening dialysis.

#### FURTHER READING

- ALJAMA P et al: New insights in ESRD. *Kidney Int (Suppl)* No. 80, 2002  
 BRENNER BM et al: For the RENAAL Study Investigators: Effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861, 2001

- COZZOLINO M et al: Role of calcium-phosphate product and bone-associated proteins on vascular calcification in renal failure. *J Am Soc Nephrol* 12: 2511, 2001  
 GOODMAN WG: Recent developments in the management of secondary hyperparathyroidism. *Kidney Int* 59:1187, 2001  
 LEVEY AS et al: National Kidney Foundation K/DOQI *Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification*. *Am J Kidney Dis* 39(Suppl 1):S1, 2002  
 LIM VS et al: Protein metabolism in patients with chronic renal failure: Role of uremia and dialysis. *Kidney Int* 58:1, 2000  
 MAXWELL AP: Novel erythropoiesis-stimulating protein in the management of the anemia of chronic renal failure. *Kidney Int* 62:720, 2002

## 262 DIALYSIS IN THE TREATMENT OF RENAL FAILURE

Ajay K. Singh, Barry M. Brenner

With the widespread availability of dialysis, the lives of hundreds of thousands of patients with end-stage renal disease (ESRD) have been prolonged. In the United States alone, there are now approximately 400,000 patients with ESRD. The overall incidence of ESRD is 260 cases per million population per year. The incident population of patients with ESRD is increasing at approximately 6% each year. The incidence of ESRD is disproportionately higher in African Americans (843 per million population per year) as compared with white Americans (189 per million population per year). In the United States, the leading cause of ESRD is diabetes mellitus, currently accounting for nearly 45% of newly diagnosed cases of ESRD. The second most common cause is hypertension, which is estimated to cause 28% of ESRD cases. Other causes of ESRD include glomerulonephritis, polycystic kidney disease, and obstructive uropathy. The mortality of patients with ESRD is lowest in Europe and Japan but is very high in the developing world because of the limited availability of dialysis. In the United States, the mortality rate of patients on dialysis is approximately 18% per year. Deaths are due mainly to cardiovascular diseases and infections (approximately 50% and 15% of deaths, respectively).

#### TREATMENT OPTIONS FOR ESRD PATIENTS

Commonly accepted criteria for placing patients on dialysis include the presence of the uremic syndrome: the presence of hyperkalemia unresponsive to conservative measures; extracellular volume expansion; acidosis refractory to medical therapy; a bleeding diathesis; and a creatinine clearance of 10 mL/min per 1.73 m<sup>2</sup>. Early referral to a nephrologist for advanced planning and creation of a dialysis access, education about ESRD treatment options, and the aggressive management of the complications of chronic renal failure, including acidosis, anemia, and hyperparathyroidism, are important. In addition to carefully evaluating patients for the onset of uremia (Chap. 261), regular measurement of renal function is important.

Renal function can be assessed indirectly by measurement of serum creatinine and blood urea nitrogen or of creatinine and urea clearance, or directly by measurement of glomerular filtration rate (GFR) using a radioisotope such as iothalamate. Creatinine clearance usually overestimates GFR because a substantial fraction of creatinine excretion in advanced renal failure occurs as a consequence of proximal tubular secretion. On the other hand, urea clearance invariably underestimates GFR because urea is reabsorbed in the distal nephron. Thus, when measurement of GFR by a direct test is not available, the average of the sum of the creatinine and urea clearance, or a cimetidine-blocked creatinine clearance (cimetidine blocks proximal tubular secretion), is recommended. Alternatively, the GFR can be estimated using a prediction equation that computes a calculated value for GFR. Examples of such equations include the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) equation.

The treatment options available for patients with renal failure depend on whether it is acute or chronic (Fig. 262-1). In acute renal failure, treatments include hemodialysis, continuous renal replacement therapies (Chap. 260), and peritoneal dialysis. In chronic renal failure (ESRD) the options include hemodialysis (in center or at home); peritoneal dialysis, as either continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD); or transplantation (Chap. 263). Although there are geographic variations, hemodialysis remains the most common therapeutic modality for ESRD (>80% of patients in the United States). The choice between hemodialysis and peritoneal dialysis involves the interplay of various factors that include the patient's age, the presence of comorbid conditions, the ability to perform the procedure, and the patient's own conceptions about the therapy. Peritoneal dialysis is favored in younger patients because of their better manual dexterity and greater visual acuity, and because younger patients prefer the independence and flexibility of home-based peritoneal dialysis treatment. In contrast, larger patients (>80 kg), patients with no residual renal function, and patients who have truncal obesity with or without prior abdominal surgery may be more suited to hemodialysis. Larger patients with no residual renal function are more appropriate for hemodialysis because these patients have a large volume of distribution of urea and require significantly higher amounts of peritoneal dialysis, which may be difficult to achieve because of the limited willingness of patients to perform more than four exchanges each day. In some patients, the inability to obtain vascular access necessitates a switch from hemodialysis to peritoneal dialysis.

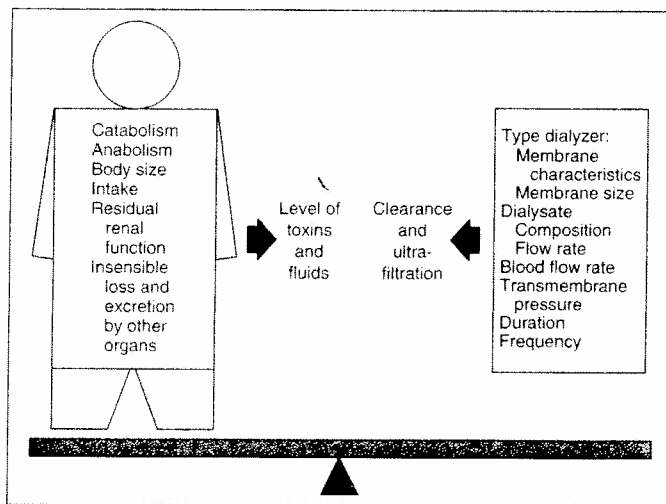


FIGURE 262-1 Factors in the development of the uremic syndrome and considerations in its treatment.

## HEMODIALYSIS

Hemodialysis relies on the principles of solute diffusion across a semipermeable membrane. Movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate. The rate of diffusive transport increases in response to several factors, including the magnitude of the concentration gradient, the membrane surface area, and the mass transfer coefficient of the membrane. The latter is a function of the porosity and thickness of the membrane, the size of the solute molecule, and the conditions of flow on the two sides of the membrane. According to the laws of diffusion, the larger the molecule, the slower its rate of transfer across the membrane. A small molecule such as urea (60 Da) undergoes substantial clearance, whereas a larger molecule such as creatinine (113 Da) is cleared less efficiently. In addition to diffusive clearance, movement of toxic materials such as urea from the circulation into the dialysate may occur as a result of ultrafiltration. Convective clearance occurs because of solvent drag with solutes getting swept along with water across the semipermeable dialysis membrane.

**THE DIALYZER** There are three essential components to dialysis: the dialyzer, the composition and delivery of the dialysate, and the blood delivery system (Fig. 262-2). The dialyzer consists of a plastic device with the facility to perfuse blood and dialysate compartments at very high flow rates. The surface area of dialysis membranes in adult patients is usually in the range of 0.8 to 1.2 m<sup>2</sup>.

There are currently two geometric configurations for dialyzers: hollow fiber and flat plate. The hollow fiber dialyzer is the most common in use in the United States. These dialyzers are composed of bundles of capillary tubes through which blood circulates while dialysate travels on the outside of the fiber bundle. In contrast, the less frequently utilized flat plate dialyzers are composed of sandwiched sheets of membrane in a parallel plate configuration. The advantage of the hollow fiber construction is the lower priming volume (60 to 90 mL vs 100 to 120 mL for the flat plate) and easier reprocessing of the filter for reuse in future dialysis treatments.

Recent advances have led to the development of many different types of membrane material. Broadly, there are four categories of dialysis membranes: cellulose, substituted cellulose, cellulose-synthetic, and synthetic. Over the past two decades, there has been a gradual switch from cellulose-derived to synthetic membranes, because the latter are more biocompatible. Biocompatibility may be defined as the ability of the membrane to activate the complement cascade. Cellulosic membranes are biocompatible because of the presence of free hydroxyl groups on the membrane surface. In contrast, with the substituted cellulose membranes (e.g., cellulose acetate) or the cellulose-synthetic membranes, the hydroxyl groups are chemically bonded to either acetate or tertiary amino groups, resulting in limited complement activation. Synthetic membranes, such as polysulfone, polymethylmethacrylate, and polyacrylonitrile membranes, are more biocompatible because of the absence of these hydroxyl groups. Polysulfone membranes are now used in over 60% of the dialysis treatments in the United States.

Reprocessing and reuse of hemodialyzers are employed for patients on chronic hemodialysis in nearly 80% of dialysis centers in the United States, in large part because of the expense of individual dialyzers. Evidence also suggests that reuse reduces complement activation, the incidence of anaphylactoid reactions to the membrane (first-use syndrome), and, in some studies, mortality rates among dialysis patients. In most centers, only the dialyzer unit is reprocessed and reused, whereas in the developing world blood lines are also frequently reused. The reprocessing procedure can be either manual or automated. It consists of the sequential rinsing of the blood and dialysate compartments with water, a chemical cleansing step with reverse ultrafiltration from the dialysate to the blood compartment, the testing of the patency of the dialyzer, and, finally, disinfection of the dialyzer. Formaldehyde, peracetic acid-hydrogen peroxide, and glutaraldehyde are the most frequently used reprocessing agents, with peracetic acid-hydrogen peroxide being the most common.

**DIALYSATE** The composition of dialysate is listed in Table 262-1. Bicarbonate has replaced acetate as the preferred buffer in the United States. This change has resulted in fewer episodes of hypotension dur-

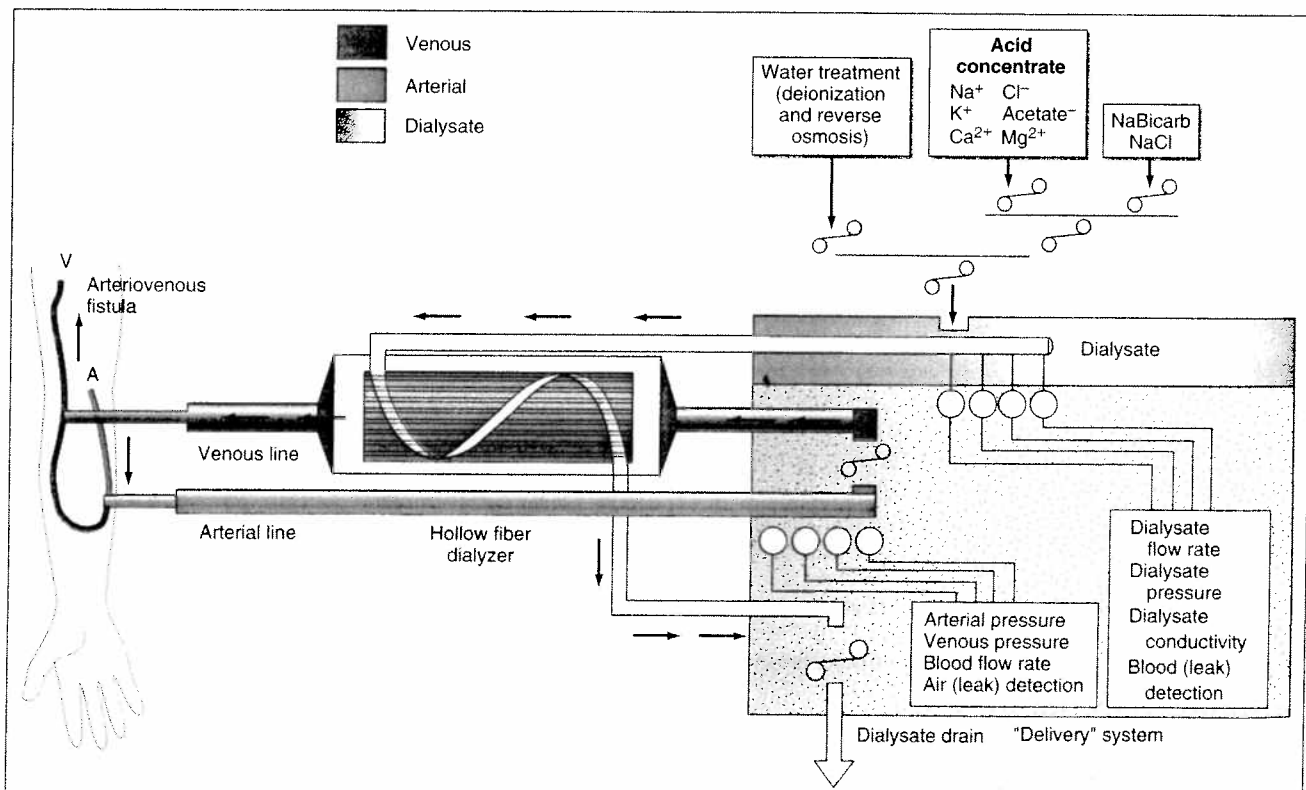


FIGURE 262-2 Schema for hemodialysis.

TABLE 262-1 Composition of Commercial Dialysate for Hemodialysate

Solute	Bicarbonate Dialysate
Sodium (meq/L)	137–143
Potassium (meq/L)	0–4.0
Chloride (meq/L)	100–111
Calcium (meq/L)	0–3.5
Magnesium (meq/L)	0.75–1.5
Acetate (meq/L)	2.0–4.5
Bicarbonate (meq/L)	30–35
Glucose (mg/dL)	0–0.25

ing dialysis. The potassium concentration of dialysate may be varied from 0 to 4 mmol/L depending on the predialysis plasma potassium concentration. The usual dialysate calcium concentration is 1.25 mmol/L (2.5 meq/L). The usual dialysate sodium concentration is 140 mmol/L. Lower dialysate sodium concentrations are associated with a higher frequency of hypotension, cramping, nausea, vomiting, fatigue, and dizziness. In patients who frequently develop hypotension during their dialysis run, sodium modeling to counterbalance urea-related osmolar gradients is now widely used. In this technique, the dialysate sodium concentration is gradually lowered from the range of 148 to 160 meq/L to isotonic levels (140 meq/L) near the end of the dialysis treatment. A dialysate glucose concentration of 200 mg/dL (11 mmol/L) is used to optimize blood glucose concentrations. Because patients are exposed to approximately 120 L of water during each dialysis treatment, untreated water could expose them to a variety of environmental contaminants. Therefore, in 98% of U.S. dialysis centers, water used for the dialysate is subjected to filtration, softening, deionization, and, ultimately, reverse osmosis. During the reverse osmosis process, water is forced through a semipermeable membrane at very high pressure to remove microbiologic contaminants and more than 90% of dissolved ions.

**BLOOD DELIVERY SYSTEM** The blood delivery system is composed of the extracorporeal circuit in the dialysis machine and the dialysis access. The dialysis machine consists of a blood pump, dialysis solution delivery system, and various safety monitors. The blood pump, using a roller mechanism, moves blood from the access site, through the dialyzer, and back to the patient. The blood flow rate may range from 250 to 500 mL/min. Negative hydrostatic pressure on the dialysate side can be manipulated to achieve desirable fluid removal: so-called *ultrafiltration*. Dialysis membranes have different ultrafiltration coefficients (i.e., mL removed/min per mmHg) so that along with hydrostatic changes, fluid removal can be varied. The dialysis solution delivery system dilutes the dialysate concentrate with water and monitors the temperature, conductivity, and flow of dialysate. The dialysate may be delivered to the dialyzer from a storage tank or a proportioning system that manufactures dialysate online.

**Dialysis Access** The fistula, graft, or catheter through which blood is obtained for hemodialysis is often referred to as a *dialysis access*. A native fistula created by the anastomosis of an artery to a vein (e.g., the Cimino-Brescia fistula, in which the cephalic vein is anastomosed to the radial artery) results in arterialization of the vein. This facilitates its subsequent use in the placement of large needles (typically 15 gauge) to access the circulation. Although fistulas have a high patency rate (approximately 60% are patent at 3 years following creation), fistulas are created in only approximately 30% of patients in the United States. In the majority of U.S. dialysis patients, the dialysis access consists of an arteriovenous graft that interposes prosthetic material, such as polytetrafluoroethylene, between an artery and a vein. Reasons for the higher rates of graft placement include the late referral of patients to vascular access surgeons so that by the time surgery is planned, the patient's arm veins have already been obliterated through multiple blood draws; the high prevalence of patients with diabetes mellitus and its associated microvascular disease; and the greater surgical skill required in creating a fistula. However, by 3 years most grafts fail because of thrombosis or infection. Fortunately, grafts may

be inserted in one of several locations: the arm (brachial artery to basilic vein), the chest wall (axillary artery to axillary vein), or the leg (femoral artery to femoral vein). The most common access-related complication is thrombosis due to intimal hyperplasia, which results in stenosis 2 to 3 cm proximal to the venous anastomosis.

A double-lumen cuffed catheter is used in approximately 20% of patients on chronic hemodialysis in the United States. These catheters are used as an alternative to either a native arteriovenous fistula or a graft in selected patients in whom dialysis is required relatively urgently, such as patients who manifest delayed recovery from acute renal failure, or where a further permanent access procedure (e.g., arteriovenous fistula or arteriovenous graft) is not feasible for anatomical reasons. Although double-lumen catheters may permit blood flows comparable to a permanent arteriovenous access, these catheters are prone to infection and to occlusion because of thrombosis. Temporary double-lumen catheters in either the femoral vein or the internal jugular or subclavian vein are usually employed in patients with acute renal failure. The jugular is preferred to the subclavian vein because, for unclear reasons, a catheter placed in a subclavian vein appears to be associated with a higher rate of venous stenosis. Temporary access can be used for 2 to 3 weeks. Thrombosis, low blood flow, and infection limit the life of the catheter.

**GOALS OF DIALYSIS** The hemodialysis procedure is targeted at removing both low- and high-molecular-weight solutes. The procedure consists of pumping heparinized blood through the dialyzer at a flow rate of 300 to 500 mL/min, while dialysate flows in an opposite *counter-current* direction at 500 to 800 mL/min. The clearance of urea ranges from 200 to 350 mL/min, while the clearance of  $\alpha_2$  microglobulin is more modest and ranges from 20 to 25 mL/min. The efficiency of dialysis is determined by blood and dialysate flow through the dialyzer, as well as dialyzer characteristics (i.e., its efficiency in removing solute). The *dose* of dialysis, which is defined as the magnitude of urea clearance during a single dialysis treatment, is further governed by patient size, residual renal function, dietary protein intake, the degree of anabolism or catabolism, and the presence of comorbid conditions.

Since the landmark studies of Sargent and Gatch relating the measurement of the dose of dialysis using urea concentration with patient outcome, the *delivered* dose of dialysis has been correlated with morbidity and mortality. This has led to the development of two major models for assessing the adequacy of the dialysis dose. Fundamentally, these two widely used measures of the adequacy of dialysis are calculated from the decrease in the blood urea nitrogen concentration during the dialysis treatment—that is, the urea reduction ratio (URR), and *KT/V*, an index based on the urea clearance rate, *K*, and the size of the urea pool, represented as the urea distribution volume, *V*. *Kt*, which is the sum of clearance by the dialyzer plus renal clearance, is multiplied by the time spent on dialysis, *T*. Increasingly, *KT/V* has become the preferred marker for dialysis adequacy. Currently, a URR of 65% and a *KT/V* of 1.2 per treatment are minimal standards for adequacy among ESRD patients; lower levels of dialysis treatment are associated with increased morbidity and mortality. The HEMO study examined the effect of dialysis dose and the level of flux of the dialyzer membrane on mortality and morbidity and found that a higher dialysis dose (single pool *KT/V* of  $1.71 \pm 0.11$ ) did not confer a benefit over a standard dialysis dose (single pool *KT/V* of  $1.32 \pm 0.09$ ). Thus, the study supported the continued use of current US Practice Guidelines, which recommend a *KT/V* of at least 1.2. Furthermore, since no benefit of a high flux dialyzer was demonstrated in the study, the use of a high flux dialyzer was also not supported.

For the majority of patients with chronic renal failure, between 9 and 12 h of dialysis is required each week, usually divided into three equal sessions. However, the dialysis dose must be individualized. Recently there has been much interest in the possibility that more frequent dialysis may be associated with improved outcomes in pa-

tients with acute or chronic renal failure. Indeed, it has been suggested that among patients with acute renal failure, daily dialysis may better control uremia, reduce hypotensive episodes, more rapidly resolve acute renal failure, and significantly lower mortality. Therefore, the measurement of dialysis adequacy using  $KT/V$  or the  $URR$  should serve only as a guide; body size, residual renal function, dietary intake, complicating illness, degree of anabolism or catabolism, and the presence of large interdialytic fluid gains should be important factors that are taken into consideration in the dialysis prescription.

**COMPLICATIONS DURING HEMODIALYSIS** Hypotension is the most common acute complication of hemodialysis, particularly among diabetics. Numerous factors appear to increase the risk of hypotension, including excessive ultrafiltration with inadequate compensatory vascular filling, impaired vasoactive or autonomic responses, osmolar shifts, food ingestion, impaired cardiac reserve, diastolic dysfunction, the use of antihypertensive drugs, anemia, and vasodilation due to the use of warm dialysate. Because of the vasodilatory and cardiodepressive effects of acetate, the use of acetate as the buffer in dialysate was once a common cause of hypotension. Since the introduction of bicarbonate-containing dialysate, dialysis-associated hypotension has become less common. The management of hypotension during dialysis consists of discontinuing ultrafiltration, the administration of 100 to 250 mL of isotonic saline or 10 mL of 23% saturated hypertonic saline, and administration of salt-poor albumin. Hypotension during dialysis can frequently be prevented by careful evaluation of the dry weight, withholding of antihypertensive medications on the day prior to and on the day of dialysis, and avoiding heavy meals during dialysis. Additional maneuvers include ultrafiltration modeling, such that more fluid is ultrafiltered at the beginning rather than the end of the dialysis procedure; the performance of sequential ultrafiltration followed by dialysis; the use of midodrine, a selective  $\alpha_1$ -adrenergic pressor agent; and cooling of the dialysate during dialysis treatment.

Muscle cramps during dialysis are also a common complication of the procedure. However, since the introduction of volumetric controls on dialysis machines and sodium modeling, the incidence of cramps has fallen. The etiology of dialysis-associated cramps remains obscure. Changes in muscle perfusion because of excessively aggressive volume removal, particularly below the estimated dry weight, and the use of low-sodium-containing dialysate, have been proposed as precipitants of dialysis-associated cramps. Strategies that may be used to prevent cramps include reducing volume removal during dialysis, the use of higher concentrations of sodium in the dialysate, and the use of quinine sulfate (260 mg 2 h before treatment).

Anaphylactoid reactions to the dialyzer, particularly on its first use, have been reported most frequently with the bioincompatible cellulose-containing membranes. With the gradual phasing out of cuprophane membranes in the United States, the first-use syndrome has become relatively uncommon. The first-use syndrome consists of either an intermediate hypersensitivity reaction due to an IgE-mediated reaction to ethylene oxide used in the sterilization of new dialyzers, or a symptom complex of nonspecific chest and back pain, which appears to result from complement activation and cytokine release.

The major cause of death in patients with ESRD receiving chronic dialysis is cardiovascular disease. The rate of death from cardiac disease is higher in patients on hemodialysis as compared to patients on peritoneal dialysis and renal transplantation. The underlying cause of cardiovascular disease is unclear but may be related to the inadequate treatment of hypertension; the presence of hyperlipidemia, homocystinemia and anemia; the calcification of coronary arteries in patients with an elevated calcium-phosphorus product; and perhaps alterations in cardiovascular dynamics during the dialysis treatment. Intensive investigation of the mechanisms and potential interventions that could impact on reducing the mortality from cardiovascular causes is currently underway.

**CONTINUOUS RENAL REPLACEMENT THERAPY** Continuous renal replacement therapies (CRRT) have become increasingly prevalent in the intensive care unit (ICU) setting for management of acute renal failure. The advantages of CRRT over intermittent hemodialysis are that it is usually better tolerated hemodynamically; it facilitates gradual correction of biochemical abnormalities; it is highly effective in removing fluid; and it is technically simple to perform. Clearance of toxic materials (using urea as the marker) can occur with CRRT from convective clearance alone if the ultrafiltration rate is high and with diffusive clearance if dialysis accompanies ultrafiltration. CRRT techniques include continuous arteriovenous hemodiafiltration (CAVH/D) with or without dialysis, and continuous veno-venous hemodiafiltration (CVVH/D) with or without dialysis.

Veno-venous therapies differ fundamentally from arteriovenous therapies in that veno-venous therapies do not require arterial access. This allows obtaining less risky and easier vascular access. However, because there is no systemic arterial pressure to drive hemofiltration, veno-venous therapies require a blood pump in the extracorporeal circuit. Veno-venous therapies such as CVVH provide substantial flexibility because changing the blood flow rate in the pump can change the ultrafiltration and clearance rates. In contrast, arteriovenous therapies such as CAVH are associated with variable efficiency because the systemic blood pressure is frequently low or unstable in patients with acute renal failure. Furthermore, low blood flow with CAVH may also result in clotting of the extracorporeal circuit. CAVH often results in clearance rates as low as 10 to 15 mL/min, whereas CVVH may generate clearances in the range of 30 to 40 mL/min. Thus, in light of these advantages of CVVH, many centers have completely switched from arteriovenous to veno-venous therapies in patients with acute renal failure in the ICU setting.

Vascular access in patients on CVVH is usually achieved by the insertion of a double-lumen catheter into the femoral vein. The blood pump is typically set to deliver approximately 150 to 180 mL/min. In automated systems, (e.g., the Cobe Prisma system), the treatment is volumetrically governed by continuously weighing the effluent and replacement solutions and using a servomechanism to drive the replacement fluid pump at a rate computed either to balance the inflow and loss of fluid or to maintain a predetermined rate of fluid loss. Anticoagulation of the extracorporeal circuit is via a heparin infusion (200 to 1600 U/h) through the inflow side of the circuit. Alternatively, citrate can be used to chelate calcium in the extracorporeal circuit to provide regional anticoagulation in selected patients who cannot undergo systemic heparinization. The replacement solution in continuous therapies is designed specifically to replace calcium, magnesium, and bicarbonate. In place of bicarbonate, lactate or citrate is the buffer in the replacement solution. However, bicarbonate-based replacement fluid is the preferred option in patients with liver failure because of the impaired ability of the liver to metabolize either lactate or acetate into bicarbonate.

#### PERITONEAL DIALYSIS

Peritoneal dialysis consists of infusing 1 to 3 L of a dextrose-containing solution into the peritoneal cavity and allowing the fluid to dwell for 2 to 4 h. As with hemodialysis, toxic materials are removed through a combination of convective clearance generated through ultrafiltration, and diffusive clearance down a concentration gradient. The clearance of solute and water during a peritoneal dialysis exchange depends on the balance between the movement of solute and water into the peritoneal cavity versus absorption from the peritoneal cavity. The rate of diffusion diminishes with time and eventually stops when equilibrium between plasma and dialysate is reached. Absorption of solutes and water from the peritoneal cavity occurs across the peritoneal membrane into the peritoneal capillary circulation and via peritoneal lymphatics into the lymphatic circulation. The rate of peritoneal solute transport varies from patient to patient and may be altered by the presence of infection (peritonitis), drugs such as beta blockers and calcium channel blockers, and physical factors such as position and exercise.

**FORMS OF PERITONEAL DIALYSIS** Peritoneal dialysis may be carried out as continuous ambulatory peritoneal dialysis (CAPD), continuous cyclic peritoneal dialysis (CCPD), or nocturnal intermittent peritoneal dialysis (NIPD). In CAPD, dialysis solution is manually infused into the peritoneal cavity during the day and exchanged three to four times daily. A nighttime dwell is frequently instilled at bedtime and remains in the peritoneal cavity through the night. The drainage of spent dialysate (effluence) is performed manually with the assistance of gravity to move fluid out of the abdomen. In CCPD, exchanges are performed in an automated fashion, usually at night; the patient is connected to the automated cycler, which then performs four to five exchange cycles while the patient sleeps. Peritoneal dialysis cyclers automatically cycle dialysate in and out of the abdominal cavity. In the morning the patient, with the last exchange remaining in the abdomen, is disconnected from the cycler and goes about his regular daily activities. In NIPD, the patient is given approximately 10 h of cycling each night, with the abdomen left dry during the day.

Peritoneal dialysis solutions are available in various volumes ranging from 0.5 to 3.0 L. The electrolyte composition is shown in Table 262-2. Lactate is the preferred buffer in peritoneal dialysis solutions. Acetate in peritoneal dialysis solutions appears to accelerate peritoneal sclerosis, whereas use of bicarbonate results in precipitation of calcium and caramelization of glucose. The most common additives to peritoneal dialysis solutions are heparin and antibiotics during an episode of acute peritonitis. Insulin may also be added in patients with diabetes mellitus.

**ACCESS TO THE PERITONEAL CAVITY** This is obtained through a peritoneal catheter. These are either *acute* catheters, used to perform acute continuous peritoneal dialysis, usually in an emergency setting, or *chronic* catheters, which have either one or two Dacron cuffs and are tunneled under the skin into the peritoneal cavity. An acute catheter consists of a straight or slightly curved rigid tube with several holes at its distal end. Catheters can be inserted at the bedside by making a small incision in the anterior abdominal wall; the catheter is inserted with the assistance of a guidewire or stylet. Acute catheters are anchored externally with adhesives or sutures and are usually reserved for temporary use because of the risk of infection, which increases after 72 h of use. In contrast, chronic catheters are flexible and made of silicon rubber with numerous side holes at the distal end. These chronic catheters usually have two Dacron cuffs to promote fibroblast proliferation, granulation, and invasion of the cuff. The scarring that occurs around the cuffs anchors the catheter and seals it from bacteria tracking from the skin surface into the peritoneal cavity; it also prevents the external leakage of fluid from the peritoneal cavity. The cuffs are placed in the

preperitoneal plane and approximately 2 cm from the skin surface. The most common chronic peritoneal dialysis catheter in use is the Tenckhoff catheter, which contains two cuffs.

The initial CAPD prescription consists of the infusion of a 2-L volume of a 1.5% dextrose concentration peritoneal dialysis solution into the peritoneal cavity over 10 min and allowing it to dwell for 2.5 h. The effluent solution is then drained over 20 min before the next exchange. Three daytime exchanges are accompanied by a 2-L nighttime dwell as the standard prescription. Because peritoneal membrane characteristics vary from one individual to another, the peritoneal equilibrium test should be employed within 2 months of a patient initiating peritoneal dialysis. This test measures the peritoneal membrane transfer rate for solutes (usually urea and creatinine) based on the ratio of their concentration in dialysate and plasma at specific times during the dialysate dwell. It allows patients to be classified as low-, average-, high-, average-, and high transporters. Approximately 10 to 17% of patients are high transporters, 50% high-average transporters, 25 to 30% low-average transporters, and 1 to 5% low transporters. Identifying the high transporters early is important, since these patients not only demonstrate excellent solute removal, they also absorb glucose rapidly; maximum ultrafiltration occurs early in the dwell, followed by reabsorption of water back into the circulation over the course of the dwell. Such patients benefit from either NIPD or CAPD without a nighttime dwell.

The dose of peritoneal dialysis required to provide adequate or optimal dialysis as measured by patient outcomes is not known. However, there is emerging consensus that the weekly KT/V should be >2.0 and the creatinine clearance >65 L/week per 1.73 m<sup>2</sup>. The most frequently utilized approach to calculating a weekly KT/V and creatinine clearance is to collect the spent dialysate and urine over a 24-h period. The peritoneal dialysis prescription can be tailored to improve suboptimal clearance values by increasing the volume of individual exchanges, increasing the number of exchanges, or combining the CAPD and CCPD techniques. In combining these techniques, the CAPD patient hooks up to a cycler at night and the machine automatically performs one or two nocturnal exchanges, whereas the CCPD patient makes an additional manual daytime exchange.

#### FURTHER READING

- BURKART JM et al: Peritoneal dialysis, in *Brenner and Rector's The Kidney*, 7th ed, BM Brenner (ed). Philadelphia, Saunders, 2004
- DIÁZ-BUXO JA: Early referral and selection of peritoneal dialysis as a treatment modality. *Nephrol Dial Transplant* 15:147, 2000
- EKNOYAN G et al: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 346:2010, 2002
- EKNOYAN G, LEVIN N: NKF-DOQI clinical practice guidelines: Update 2000. *Am J Kidney Dis* 37(Suppl 1):55, 2001
- FORNI LG, HILTON PJ: Current concepts: Continuous hemofiltration in the treatment of acute renal failure. *N Engl J Med* 336:1303, 1997
- IFUDU O: Care of patients undergoing hemodialysis. *N Engl J Med* 339:1054, 1998
- MEYER MM: Renal replacement therapies. *Crit Care Clin* 16:29, 2000
- SCHIFFL H et al: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 346:305, 2002
- U.S. RENAL DATA SYSTEM: USRDS 2001 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 2001

TABLE 262-2 Composition of Peritoneal Dialysate

Solute	Dianeal (PD-2)
Sodium (meq/L)	132
Potassium (meq/L)	0
Chloride (meq/L)	96
Calcium (meq/L)	3.5
Magnesium (meq/L)	0.5
D,L-Lactate (meq/L)	40
Glucose (g%)	
1.5	
2.5	
4.25	
pH	5.2

Transplantation of the human kidney is frequently the most effective treatment of advanced chronic renal failure. Worldwide, tens of thousands of such procedures have been performed. When azathioprine and prednisone were initially used as immunosuppressive drugs in the 1960s, the results with properly matched familial donors were superior to those with organs from cadaveric donors, namely, 75 to 90% compared with 50 to 60% graft survival rates at 1 year. During the 1970s and 1980s, the success rate at the 1-year mark for cadaveric transplants rose progressively. By the time cyclosporine was introduced in the early 1980s, cadaveric donor grafts had a 70% 1-year survival and reached the 82% level in the mid-1990s and 88% by 1998 (Fig. 263-1). After the first year, graft survival curves show an exponential decline in numbers of functioning grafts from which a half-life ( $t_{1/2}$ ) in years is calculated; this has increased by 2 years since the 1980s (Fig. 263-1).

Mortality rates after transplantation are highest in the first year and are age-related: 2% for ages 18 to 34 years, 3% for ages 35 to 49 years, and 6.8% for ages over 50 to 60 years. These rates compare favorably to those in the chronic dialysis population, even after risk adjustments for age, diabetes, and cardiovascular status. Occasionally, acute irreversible rejection may occur after many months of good function, especially if the patient neglects to take the immunosuppressive drugs. Most grafts, however, succumb at varying rates to a chronic vascular and interstitial obliterative process termed *chronic rejection*, although its pathogenesis is incompletely understood. Overall, transplantation returns the majority of patients to an improved lifestyle and an improved life expectancy, as compared to patients on dialysis; however, careful prospective cohort studies have yet to be reported.

**RECIPIENT SELECTION** There are few absolute contraindications to renal transplantation. The transplant procedure is relatively noninvasive, as the organ is placed in the inguinal fossa without entering the peritoneal cavity. Recipients without perioperative complications can often be discharged from the hospital in excellent condition within 5 days of the operation.

Virtually all end-stage renal disease (ESRD) patients who receive a transplant have a higher life expectancy than risk-matched patients who remain on dialysis. Even though diabetics or older candidates

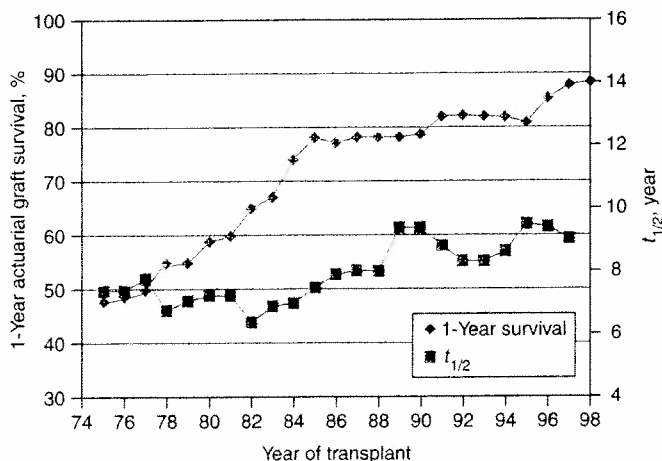


FIGURE 263-1 One-year actuarial graft survival of cohorts of first cadaver kidney transplants performed from 1975 through 1998 is displayed (in purple) along with  $t_{1/2}$  or post-year-one half-life of the same cohorts (green). These registry data are derived from the U.S. Renal Data System 2002 Annual Report. The upper curve represents the 1-year actual graft survival, which approaches 90% by 1998. From 1982 to 1985 there was an impressive rise in the 1-year survival, partially attributable to the introduction of cyclosporine. Since 1985, there has been a consistent, slow increase in 1-year survival. The lower curve represents long-term graft survival, expressed as the half-life ( $t_{1/2}$ ), which has been relatively stable over the past decade.

have a higher mortality rate than other transplant recipients, their survival is improved with transplantation compared to remaining on dialysis. This global benefit of transplantation as a treatment modality poses substantial ethical issues for policy makers, as the number of cadaveric kidneys available is far from sufficient to meet the current needs of the candidates. Waiting lists continue to grow, and the average wait time for a cadaver kidney is now >4 years in many locales. The current standard of care is that the candidate should have a life expectancy of >5 years to be put on a cadaver organ wait list. Even for living donation, the candidate should have >5 years of life expectancy. This is because the benefits of kidney transplantation over dialysis are only realized after a perioperative period in which the mortality is higher in transplanted patients than in dialysis patients with comparable risk profile.

All candidates must have a thorough risk/benefit evaluation prior to being approved for transplantation. In particular, an aggressive approach to diagnosis of correctable coronary artery disease, presence of latent or indolent infection (HIV, hepatitis B or C, tuberculosis), and neoplasm should be a routine part of the candidate workup. Most transplant centers consider overt AIDS and active hepatitis to be an absolute contraindication to transplantation because of the high risk of opportunistic infection. Some centers are now transplanting individuals with hepatitis and even HIV infection under strict protocols to determine whether the risks and benefits favor transplantation over dialysis.

Among the few absolute contraindications to transplantation is the presence of potentially harmful antibody against the donor kidney at the time of the anticipated transplant. Harmful antibodies that can cause very early graft loss include natural antibodies against the ABO blood group antigens and antibodies against HLA-class I (A, B, C) or class II (DR) antigens. These antibodies are routinely excluded by proper pretransplant screening of the candidates, ABO and HLA typing of donor and recipient, and cross-matching of candidate serum with that of the donor.

**DONOR SELECTION** Donors can be cadavers or volunteer living donors. The latter are usually family members selected to have at least partial compatibility for HLA antigens. Living volunteer donors should be normal on physical examination and of the same major ABO blood group, because crossing major blood group barriers prejudices survival of the allograft. It is possible, however, to transplant a kidney of a type O donor into an A, B, or AB recipient. Selective renal arteriography should be performed on donors to rule out the presence of multiple or abnormal renal arteries, because the surgical procedure is difficult and the ischemic time of the transplanted kidney long when vascular abnormalities exist. Transplant surgeons are now using a laparoscopic method to isolate and remove the living donor kidney. This operation has the advantage of less evident surgical scars, and, because there is less tissue trauma, the laparoscopic donors have a substantially shorter hospital stay and less discomfort than those who have the traditional surgery. Cadaveric donors should be free of malignant neoplastic disease, hepatitis, and HIV because of possible transmission to the recipient. Increased risk of graft failure exists when the donor is elderly or has renal failure and when the kidney has a prolonged period of ischemia and storage.

In the United States, there is a coordinated national system of regulations, allocation support, and outcomes analysis for kidney transplantation called the Organ Procurement Transplant Network. It is now possible to remove cadaver kidneys and to maintain them for up to 48 h on cold pulsatile perfusion or simple flushing and cooling. This permits adequate time for typing, cross-matching, transportation, and selection problems to be solved.

**TISSUE TYPING AND CLINICAL IMMUNOGENETICS** Matching for antigens of the HLA major histocompatibility gene complex (Chap. 296) is an

important criterion for selection of donors for renal allografts. Each mammalian species has a single chromosomal region that encodes the strong, or major, transplantation antigens, and this region on the human sixth chromosome is called *HLA*. HLA antigens have been classically defined by serologic techniques, but methods to define specific nucleotide sequences in genomic DNA are increasingly being used. Other antigens, called "minor," may nevertheless play crucial roles. In addition to the ABH(O) blood groups and endothelial antigens that are not shared with lymphocytes. The Rh system is not expressed on graft tissue. Evidence for designation of HLA as the genetic region encoding major transplantation antigens comes from the success rate in living related donor renal and bone marrow transplantation, with superior results in HLA-identical sibling pairs. Nevertheless, 5% of HLA-identical renal allografts are rejected, often within the first weeks after transplantation. These failures represent states of prior sensitization to non-HLA antigens. Non-HLA minor antigens are relatively weak when initially encountered and are therefore suppressible by conventional immunosuppressive therapy. Once priming has occurred, however, secondary responses are much more refractory to treatment. ABO incompatibilities are hazardous because of the presence of natural anti-A and anti-B antibodies in recipients and the normal expression of A and B blood group substances on endothelium, resulting in immediate vascular injury.

**Living Donors** When first-degree relatives are donors, graft survival rates at 1 year are 5 to 7% greater than those for cadaver grafts. The 5-year survival rates still favor the partially matched (3/6 HLA mismatched) family donor over a randomly selected cadaver donor (Table 263-1). In addition, living donors provide the advantage of immediate availability. For both living and cadaveric donors, the 5-year outcomes are poor if there is a complete (6/6) HLA mismatch. Waiting lists for cadaveric kidneys have grown faster than the available organ supply, to the point where most new patients with ESRD wait for >4 years. In response to this increasing disparity between cadaver donor supply and patient demand, living unrelated volunteers, usually spouses or close friends, are being accepted as donors in increasing numbers. The survival rate of living unrelated renal allografts is as good or better than that of perfectly HLA matched cadaver renal transplants and comparable to that of kidneys from living relatives. This is likely to be a consequence both of short cold ischemia time and the extra care taken to document that the condition and renal function of the donor are optimal before proceeding with a living unrelated donation (Table 263-1). It is illegal in the United States to purchase organs for transplantation.

Concern has been expressed regarding the potential risk to a volunteer kidney donor of premature renal failure after several years of increased blood flow and hyperfiltration per nephron in the remaining kidney. There are a few reports of the development of hypertension, proteinuria, and even lesions of focal segmental sclerosis in donors under long-term follow-up. Difficulties in donors followed for  $\geq 20$  years are unusual, however, and it may be that having a single kidney becomes significant only when another condition, such as hyperten-

sion, is superimposed. It is also desirable to consider the risk of development of type 1 diabetes mellitus in a family member who is a potential donor to a diabetic renal failure patient. Anti-insulin and anti-islet antibodies should be measured, and glucose tolerance tests should be performed in such donors to rule out a prediabetic state.

**HLA Matching and Cadaveric Donors** The question of whether matching of HLA antigens in unrelated donor-recipient pairs would approximate the high initial success rates and slow rates of subsequent graft loss with HLA-identical sib pairs could not be answered until the late 1980s when reliable class II histocompatibility (DR) typing became widely available. Now that pooled data on tens of thousands of cadaveric renal transplants from all over the world are available, the HLA-matching effect can be clearly seen, especially in the long-term survival figures. It is shown in Table 263-1 that there is an overall beneficial effect of HLA matching in cadaveric grafts. With increasing numbers of mismatches for cadaveric donors, the 5-year survival drops from 68.2% to 55.3%. The survival rates at the 10-year mark are projected to range from 65 (zero mismatches) to 34% (six mismatches). There is controversy regarding the value of cadaveric organ-sharing rules that are based entirely upon the numbers of HLA mismatches. Giving preference to HLA zero-mismatched candidates (Table 263-1) is a top priority in the United States, however, and 20% of kidneys are transplanted on this basis. Table 263-1 also shows the interaction of HLA matching and graft ischemia on results; namely, kidneys from HLA-incompatible unrelated or spousal donors do better than those from similarly mismatched cadaver donors, suggesting that the additional ischemic injury of organ storage is important. Nevertheless, when such a cadaveric donor is HLA-compatible, the benefit of matching can still be seen.

**Presensitization** A positive cross match of recipient serum with donor T lymphocytes representing anti-HLA class I is usually predictive of an acute vasculitic event termed *hyperacute rejection*. Patients with anti-HLA antibodies can be safely transplanted if careful cross-matching of donor blood lymphocytes with recipient serum is performed. Patients sustained by dialysis often show fluctuating antibody titers and specificity patterns. At the time of assignment of a cadaveric kidney, cross matches are performed with at least a current serum. Previously analyzed antibody specificities and additional cross matches are performed accordingly. Techniques for cross-matching are not universally standardized; however, at least two techniques are employed in most laboratories. The minimal purpose for the cross match is avoidance of hyperacute rejection mediated by recipient antibodies to donor HLA class I antigens. Sensitive tests, such as the use of flow cytometry, can be useful for avoidance of accelerated, and often untreatable, early graft rejection in patients receiving second or third transplants. Donor T lymphocytes, which express only class I antigens, are used as targets for detection of anti-class I (HLA-A and -B) antibodies. Preformed anti-class II (HLA-DR) antibodies against the donor carry a higher risk of graft loss as well, particularly in recipients who have suffered early loss of a prior kidney transplant. B lymphocytes expressing both class I and class II antigens are used in these assays. Non-HLA antigens restricted in expression to endothelium and sometimes monocytes have been described, but clinical relevance is not well established. A series of minor histocompatibility antigens do not elicit antibodies, and sensitization to these is detectable only by cytotoxic T cells, an assay too cumbersome for routine use.

**Blood Transfusions** Exposure to leukocyte HLA antigens during transfusions is a major cause of sensitization that limits transplantation access and increases the risk of early graft rejection. In the 1970s, attempts to avoid all blood exposure in dialysed patients paradoxically increased the risk of graft rejection. The beneficial "transfusion effect" was never fully explained, and it almost disappeared in the 1980s as overall management of patients improved with the use of cyclosporine and more effective means of rejection treatment. Currently, with the use of erythropoietin the need for transfusion is much reduced. It has

TABLE 263-1 Effect of HLA-A, -B, -DR Mismatching on Kidney Graft Survival

Degree of Donor Mismatch	1-Year Survival, %	5-Year Survival, %
Cadaver donor (all)	89.2	61.3
0/6-HLA mismatch	91.3	68.2
3/6-HLA mismatch	90.1	60.8
6/6-HLA mismatch	85.2	55.3
Living related donor (all)	94.7	76.0
0/6-HLA mismatch	96.7	87.0
3/6-HLA mismatch	94.3	73.2
6/6-HLA mismatch	92.7	57.7
Living unrelated donor	95.3	77.4

Note: 0-mismatched related donor transplants are virtually all from HLA-identical siblings, while 3/6-mismatched transplants can be one haplotype mismatched (1-A, 1-B, and 1-DR antigen) from parent, child or sibling; 6/6-HLA-mismatched living related kidneys are derived from siblings or relatives outside of the nuclear family.

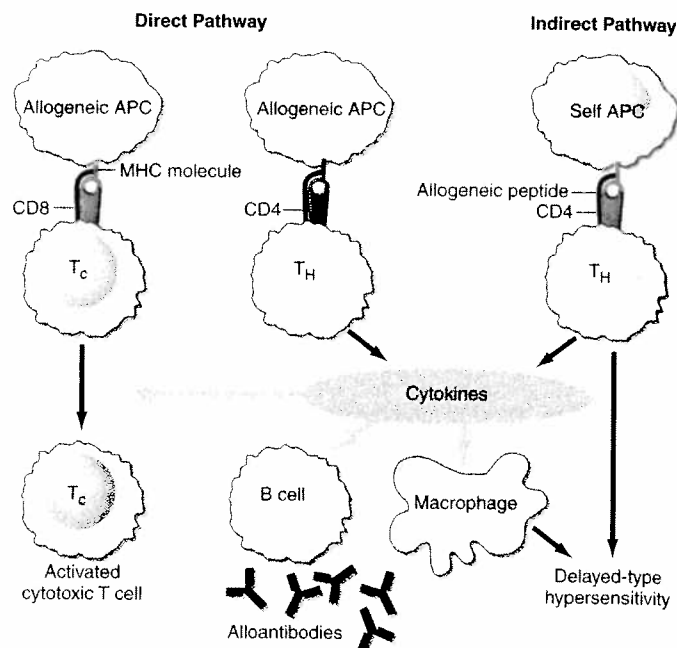
been noted, however, that nontransfused patients do have more rejection activity.

**IMMUNOLOGY OF REJECTION** Both cellular and humoral (antibody-mediated) effector mechanisms can play roles in kidney transplant rejection. Antibodies directed against ABO blood group antigens and HLA class I or class II antigens can cause hyperacute rejection within minutes to hours of engraftment if they are present in the recipient at the time of engraftment. Such antibodies bind to vascular endothelium, cause activation of the complement cascade, and direct endothelial damage, platelet aggregation, microvascular thrombi, and in the most severe cases ischemic necrosis of the organ. Antibodies against ABO are naturally found in humans. Anti-HLA antibodies are produced as a consequence of prior blood transfusions, multiple pregnancies, or rejection of a prior HLA-incompatible transplant. Antibodies that bind to cells within the transplant can also initiate a form of antibody-dependent cell death mediated by recipient cells that bear receptors for the Fc portion of immunoglobulin.

Cellular rejection is mediated by lymphocytes that respond to HLA antigens expressed within the organ. The CD4+ lymphocyte responds to class II (HLA-DR) incompatibility by proliferating and releasing proinflammatory cytokines that augment the proliferative response of both CD4+ and CD8+ cells. CD8+ cytotoxic lymphocyte precursors respond primarily to class I (HLA-A, -B) antigens and mature into cytotoxic effector cells. The cytotoxic effector, or "killer" T, cells cause organ damage through direct contact and lysis of donor target cells. The natural role of HLA antigens is to present processed peptide fragments of antigen to T lymphocytes, the fragments residing in a "groove" of the HLA molecule distal to the cell surface. T cells can be directly stimulated by non-self HLA antigen expressed on donor parenchymal cells and residual donor leukocytes residing in the kidney interstitium. In addition, donor HLA molecules can be processed by a variety of donor or recipient cells capable of antigen presentation and then presented to T cells in the same manner as most other antigens. The former mode of stimulation is sometimes called *direct presentation* and the latter mode called *indirect presentation* (Fig. 263-2). There is evidence that non-HLA antigens can also play a role in renal transplant rejection episodes. Recipients who receive a kidney from an HLA-identical sibling can have rejection episodes and require maintenance immunosuppression, while identical twin transplants require no immunosuppression. There are documented non-HLA antigens, such as an endothelial-specific antigen system with limited polymorphism and a tubular antigen, which can be targets of humoral or cellular rejection responses, respectively.

**IMMUNOSUPPRESSIVE TREATMENT** Immunosuppressive therapy, as presently available, generally suppresses all immune responses, including those to bacteria, fungi, and even malignant tumors. In the 1950s when clinical renal transplantation began, sublethal total-body irradiation was employed. We have now reached the point where sophisticated pharmacologic immunosuppression is available, but it still has the hazard of promoting infection and malignancy. In general, all clinically useful drugs are more selective to primary than to memory immune responses. Agents to suppress the immune response are discussed in the following paragraphs, and those currently in clinical use are listed in Table 263-2.

**Drugs** *Azathioprine*, an analogue of mercaptopurine, was for two decades the keystone to immunosuppressive therapy in humans. This agent can inhibit synthesis of DNA, RNA, or both. Because cell division and proliferation are a necessary part of the immune response to antigenic stimulation, suppression by this agent may be mediated by the inhibition of mitosis of immunologically competent lymphoid cells, interfering with synthesis of DNA. Alternatively, immunosuppression may be brought about by blocking the synthesis of RNA (possibly messenger RNA), inhibiting processing of antigens prior to lymphocyte stimulation. Therapy with azathioprine in doses of 1.5 to



**FIGURE 263-2** Recognition pathways for major histocompatibility complex (MHC) antigens. Graft rejection is initiated by CD4 helper T lymphocytes ( $T_H$ ) having antigen receptors that bind to specific complexes of peptides and MHC class II molecules on antigen-presenting cells (APC). In transplantation, in contrast to other immunologic responses, there are two sets of T cell clones involved in rejection. In the direct pathway the class II MHC of donor allogeneic APCs is recognized by CD4  $T_H$  cells that bind to the intact MHC molecule, and class I MHC allogeneic cells are recognized by CD8 T cells. The latter generally proliferate into cytotoxic cells ( $T_c$ ). In the indirect pathway, the incompatible MHC molecules are processed into peptides that are presented by the self-APCs of the recipient. The indirect, but not the direct, pathway is the normal physiologic process in T cell recognition of foreign antigens. Once  $T_H$  cells are activated, they proliferate, and by secretion of cytokines and direct contact exert strong helper effects on macrophages,  $T_c$ , and B cells. (From Sayegh and Turka, Copyright 1998, Massachusetts Medical Society. All rights reserved.)

2.0 mg/kg per day is generally added to cyclosporine as a means of decreasing the requirements for the latter. Because azathioprine is rapidly metabolized by the liver, its dosage need not be varied directly in relation to renal function, even though renal failure results in retention of the metabolites of azathioprine. Reduction in dosage is required because of leukopenia and occasionally thrombocytopenia. Excessive amounts of azathioprine may also cause jaundice, anemia, and alopecia. If it is essential to administer allopurinol concurrently, the azathioprine dose must be reduced, since inhibition of xanthine oxidase delays degradation. This combination is best avoided.

*Mycophenolate mofetil* is now used in place of azathioprine in many centers. It has a similar mode of action and a mild degree of gastrointestinal toxicity but produces minimal bone marrow suppression. Its advantage is its increased potency in preventing or reversing rejection. Patients with hyperuricemia can be given allopurinol without adjustment of the mycophenylate dose.

*Glucocorticoids* are important adjuncts to immunosuppressive therapy. Of all the agents employed, prednisone has effects that are easiest to assess, and in large doses it is usually effective for the reversal of rejection. In general, 200 to 300 mg prednisone is given immediately prior to or at the time of transplantation, and the dosage is reduced to 30 mg within a week. The side effects of the glucocorticoids, particularly impairment of wound healing and predisposition to infection, make it desirable to taper the dose as rapidly as possible in the immediate postoperative period. Customarily, methylprednisolone, 0.5 to 1.0 g intravenously, is administered immediately upon diagnosis of beginning rejection and continued once daily for 3 days. When the drug is effective, the results are usually apparent within 96 h. Such "pulse" doses are not effective in chronic rejection. Most patients whose renal function is stable after 6 months or a year do not require

large doses of prednisone; maintenance doses of 10 to 15 mg/d are the rule. Many patients tolerate an alternate-day course of steroids without an increased risk of rejection.

A major effect of steroids is on the monocyte-macrophage system, preventing the release of interleukin (IL) 6 and IL-1. Lymphopenia after large doses of glucocorticoids is primarily due to sequestration of recirculating blood lymphocytes to lymphoid tissue.

*Cyclosporine* is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to block transcription of mRNA for IL-2 and other proinflammatory cytokines, thereby inhibiting T cell proliferation. Although it works alone, cyclosporine is more effective in conjunction with glucocorticoids. Since cyclosporine blocks production of IL-2 by T cells, its combination with steroids is expected to produce a double block in the macrophage → IL-6/IL-1 → T cell → IL-2 sequence. Clinical results with tens of thousands of renal transplants have been impressive. Of its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, diabetes), only nephrotoxicity presents a serious management problem and is further discussed below.

*Tacrolimus* (FK-506) is a fungal macrolide that has the same mode of action, and a similar side effect profile, as cyclosporine. It does not produce hirsutism or gingival hyperplasia, however. De novo induction of diabetes mellitus is more common with tacrolimus. The drug was first used in liver transplantation and may substitute for cyclosporine entirely or be tried as an alternative in renal patients whose rejections are poorly controlled by cyclosporine.

*Sirolimus* (previously called rapamycin) is another fungal macrolide but has a different mode of action, i.e., it inhibits T cell growth factor pathways, preventing the response to IL-2 and other cytokines. Sirolimus can be used in conjunction with cyclosporine or tacrolimus as an alternative immunosuppressive regimen. Its use with tacrolimus alone shows promise as a steroid-sparing regimen, especially in patients who would benefit from pancreatic islet transplantation, where steroids have an adverse effect on islet survival.

**Antibodies to Lymphocytes** When serum from animals made immune to host lymphocytes is injected into the recipient, a marked suppression of cellular immunity to the tissue graft results. The action on cell-mediated immunity is greater than on humoral immunity. A globulin fraction of serum [antilymphocyte globulin (ALG)] is the agent generally employed. For use in humans, peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic duct fistulas have been injected into horses, rabbits, or goats to produce antilymphocyte serum, from which the globulin fraction is then separated. Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. OKT3 is directed to the CD3 molecules that form a portion of the T cell antigen-receptor complex; hence CD3 is expressed on all mature T cells. CD4 or CD8 molecules also form part of the fully activated cluster of molecules, and monoclonal antibodies to these offer the potential for more selective targeting of T cell subsets.

Another approach to more selective therapy is to target the 55-kDa alpha chain of the IL-2 receptor, expressed only on T cells that have

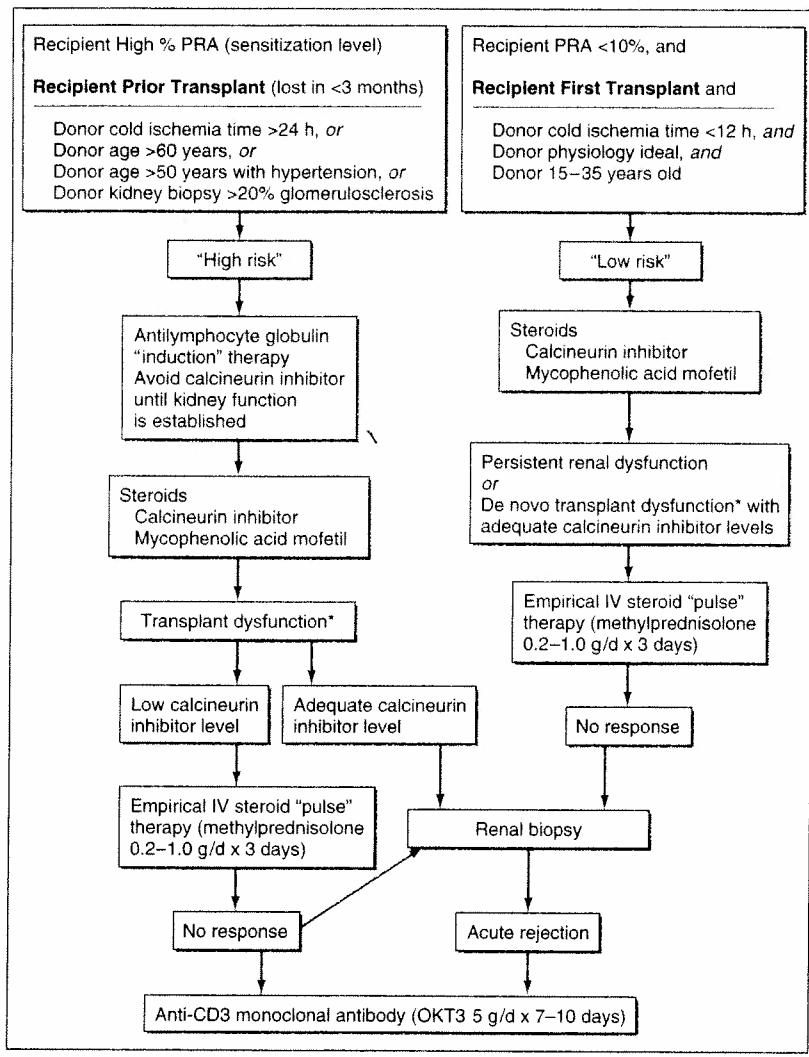
TABLE 263-2 Maintenance Immunosuppressive Drugs

Agent	Pharmacology	Mechanisms	Side Effects
Glucocorticoids	Increased bioavailability with hypoalbuminemia and liver disease; prednisone/prednisolone generally used	Binds cytosolic receptors and heat shock proteins. Blocks transcription of IL-1, -2, -3, -6, TNF- $\alpha$ , and IFN- $\gamma$	Hypertension, glucose intolerance, dyslipidemia, osteoporosis
Cyclosporine (CsA)	Lipid-soluble polypeptide, variable absorption, microemulsion more predictable	Trimolecular complex with cyclophilin and calcineurin → block in cytokine (e.g., IL-2) production; however, stimulates TGF- $\beta$ production	Nephrotoxicity, hypertension, dyslipidemia, glucose intolerance, hirsutism/hyperplasia of gums
Tacrolimus (FK506)	Macrolide, well absorbed	Trimolecular complex with FKBP-12 and calcineurin → block in cytokine (e.g., IL-2) production; may stimulate TGF- $\beta$ production	Similar to CsA, but hirsutism/hyperplasia of gums unusual, and diabetes more likely
Azathioprine	Mercaptopurine analogue	Hepatic metabolites inhibit purine synthesis	Marrow suppression (WBC > RBC > platelets)
Mycophenolate mofetil (MMF)	Metabolized to mycophenolic acid	Inhibits purine synthesis via inosine monophosphate dehydrogenase	Diarrhea/cramps; dose-related liver and marrow suppression is uncommon
Sirolimus	Macrolide, poor oral bioavailability	Complexes with FKBP-12 and then blocks p70 S6 kinase in the IL-2 receptor pathway for proliferation	Hyperlipidemia, thrombocytopenia

Note: IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; TGF, transforming growth factor; FKBP-12, FK506 binding protein 12; WBC, white blood cells; RBC, red blood cells.

been recently activated. The problem with such mouse antibodies is the potential for developing human antimouse antibodies (HAMA), an event that limits the effective period of use. Genetically engineered monoclonal antibodies can solve this problem. Two such antibodies to the IL-2 receptor, in which either a chimeric protein has been made between mouse Fab with human Fc (basiliximab) or "humanized" by splicing the combining sites of the mouse into a molecule that is 90% human IgG (daclizumab), have been approved for prophylaxis of acute rejection in the immediate posttransplant period. They are effective at decreasing the acute rejection rate and have few adverse side effects.

**CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT** Adequate hemodialysis should be performed within 48 h of surgery, and care should be taken that the serum potassium level is not markedly elevated so that intraoperative cardiac arrhythmias can be averted. The diuresis that commonly occurs postoperatively must be carefully monitored; in some instances it may be massive, reflecting the inability of ischemic tubules to regulate sodium and water excretion; with large diureses, massive potassium losses may occur. Most chronically uremic patients have some excess of extracellular fluid, and it is useful to maintain an expanded fluid volume in the immediate postoperative period. Acute tubular necrosis (ATN) may cause immediate oliguria or may follow an initial short period of graft function. ATN is most likely when cadaveric donors have been hypotensive or if the interval between cessation of blood flow and organ harvest (warm ischemic time) is more than a few minutes. Recovery usually occurs within 3 weeks, although periods as long as 6 weeks have been reported. Superimposition of rejection on ATN is common, and the differential diagnosis may be difficult without a graft biopsy. Cyclosporine therapy prolongs ATN, and some patients do not diurese until the dose is drastically reduced. Many centers avoid starting cyclosporine for the first several days, using ALG or a monoclonal antibody along with mycophenolate mofetil and prednisone until renal function is established. Fig. 263-3 illustrates an algorithm followed by many transplant centers for early



**FIGURE 263-3** A typical algorithm for early posttransplant care of the kidney recipient. If any of the recipient or donor "high-risk" factors exist, more aggressive management is called for. Low-risk patients can be treated with a standard immunosuppressive regimen. Patients at higher risk of rejection or early ischemic and nephrotoxic transplant dysfunction are often induced with an antilymphocyte globulin to provide more potent early immunosuppression or to spare calcineurin nephrotoxicity. \*When there is early transplant dysfunction, prerenal, obstructive, and vascular causes must be ruled out by ultrasonographic examination. The panel reactive antibody (PRA) is a quantitation of how much antibody is present in a candidate against a panel of cells representing the distribution of antigens in the donor pool.

posttransplant management of recipients at high or low risk of early renal dysfunction.

**The Rejection Episode** Early diagnosis of rejection allows prompt institution of therapy to preserve renal function and prevent irreversible damage. Clinical evidence of rejection is rarely characterized by fever, swelling, and tenderness over the allograft. Rejection may present only with a rise in serum creatinine, with or without a reduction in urine volume. The focus should be on ruling out other causes of functional deterioration.

Arteriography and radioactive iodohippurate sodium renograms of the transplanted kidney may be useful in ascertaining changes in the renal vasculature and in renal blood flow, even in the absence of urinary flow. Thrombosis of the renal vein occurs rarely; it may be reversible if caused by technical factors and intervention is prompt. Diagnostic ultrasound is the procedure of choice to rule out urinary obstruction or to confirm the presence of perirenal collections of urine, blood, or lymph. When renal function has been good initially, a rise in the serum creatinine level is the most sensitive and reliable indicator of possible rejection and may be the only sign.

Calcineurin inhibitors (cyclosporine or tacrolimus) may cause de-

terioration in renal function in a manner similar to a rejection episode. In fact, rejection processes tend to be more indolent with these inhibitors, and the only way to make a diagnosis may be by renal biopsy. Calcineurin inhibitors have an afferent arteriolar constrictor effect on the kidney and may produce permanent vascular and interstitial injury after sustained high-dose therapy. Addition of angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs are likely to raise serum creatinine levels. The former are generally safe to use after the early months, while the latter are best avoided in all renal transplant patients. There is no universally accepted lesion(s) that makes a diagnosis of calcineurin inhibitor toxicity, although interstitial fibrosis, isometric tubular vacuolization, and thickening of arteriolar walls have been noted by some. Basically, if the biopsy does not reveal moderate and active cellular rejection activity, the serum creatinine will most likely respond to a reduction in dose. Blood levels of drug can be useful if very high or very low but do not correlate precisely with renal function, although serial changes in the biopsy, appropriate therapy is indicated. The first rejection episode is usually treated with intravenous administration of methylprednisolone, 500 to 1000 mg daily for 3 days. Failure to respond is indication for antibody therapy, usually with OKT3.

OKT3 monoclonal antibody, given intravenously for 10 to 14 days, is effective in >90% of first rejections but less so if methylprednisolone pulses have failed and in cases of severe recurrent rejection activity. A major problem with OKT3 is that severe systemic reactions may be produced during the first day or two of therapy. Chills, fever, hypotension, and headache are the direct result of the antibody effects on the targeted T cells, most likely related to the known potential of OKT3 to activate T cells nonspecifically with release of cytokines, especially tumor necrosis factor  $\alpha$ . If the antibody is administered to overhydrated oliguric patients, pulmonary edema may be induced. These reactions are not characteristic of other monoclonal antibodies, such as those to the IL-2 receptor. Recurrent or rebound rejection activity may require additional therapy. In such circumstances, methylprednisolone may be effective even though it failed initially. Second courses of OKT3 may be given in spite of HAMA generated in response to the first course if the titers are low and the human antibodies are not directed to the combining-site region (idiotype) of the OKT3.

**Management Problems** The usual clinical manifestations of infection in the posttransplant period are blunted by immunosuppressive therapy. The major toxic effect of azathioprine is bone marrow suppression, which is less likely with mycophenolate mofetil, while calcineurin inhibitors have no marrow effects. All drugs predispose to unusual opportunistic infections, however. The typical times posttransplant when the most common opportunistic infections occur are tabulated in Table 263-3. The signs and symptoms of infection may be masked or distorted. Fever without obvious cause is common and only after days or weeks may it become apparent that it has a viral or fungal origin. Bacterial infections are most common during the first month after transplantation. The importance of blood cultures in such patients cannot be overemphasized, because systemic infection without obvious foci is frequent, although wound infections with or without urinary fistulas are most common. Particularly ominous are rapidly occurring pulmonary lesions, which may result in death within 5 days of onset. When these become apparent, immunosuppressive agents should be discontinued, except for maintenance doses of prednisone.