dietary ingestion of cooked meat, however, and creatinine can be secreted into the proximal tubule through an organic cation pathway (especially in advanced progressive chronic kidney disease), leading to overestimation of GFR. When a timed collection for CrCl is not available, decisions about drug dosing must be based on P_{Cr} alone. Two formulas are used widely to estimate kidney function from P_{Cr}: (1) Cockcroft-Gault and (2) four-variable MDRD (Modification of Diet in Renal Disease).

$$\text{Cockcroft-Gault: CrCl (mL/min)} = (140 - \text{age (years)}) \times \text{weight (kg)} \times [0.85 \text{ if female}]/(72 \times P_{Cr} \text{ (mg/dL)}).$$

$$\text{MDRD: eGFR (mL/min per 1.73 m}^2) = 186.3 \times P_{Cr}^{(-1.154)} \times \text{age}^{(-0.203)} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}).$$

Numerous websites are available to assist with these calculations (*www.kidney.org/professionals/kdoqi/gfr_calculator.cfm*). A newer CKD-EPI eGFR, which was developed by pooling several cohorts with and without kidney disease who had data on directly measured GFR, appears to be more accurate:

$$\text{CKD-EPI: eGFR} = 141 \times \min(P_{Cr}/k, 1)^{a} \times \max(P_{Cr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]},$$

where P_{Cr} is plasma creatinine, *k* is 0.7 for females and 0.9 for males, *a* is −0.329 for females and −0.411 for males, *min* indicates the minimum of P_{Cr}/k or 1, and *max* indicates the maximum of P_{Cr}/k or 1 (*http://www.qxmd.com/renal/Calculate-CKD-EPI-GFR.php*).

There are limitations to all creatinine-based estimates of GFR. Each equation, along with 24-h urine collection for measurement of creatinine clearance, is based on the assumption that the patient is in *steady state*, without daily increases or decreases in P_{Cr} as a result of rapidly changing GFR. The MDRD equation is better correlated with true GFR when the GFR is <60 mL/min per 1.73 m^2. The gradual loss of muscle from chronic illness, chronic use of glucocorticoids, or malnutrition can mask significant changes in GFR with small or imperceptible changes in P_{Cr}. Cystatin C, a member of the cystatin superfamily of cysteine protease inhibitors, is produced at a relatively constant rate from all nucleated cells. Serum cystatin C has been proposed to be a more sensitive marker of early GFR decline than is P_{Cr}; however, like serum creatinine, cystatin C is influenced by the patient's age, race, and sex and also is associated with diabetes, smoking, and markers of inflammation.

APPROACH TO THE PATIENT: **Azotemia**

Once GFR reduction has been established, the physician must decide if it represents acute or chronic renal injury. The clinical situation, history, and laboratory data often make this an easy distinction. However, the laboratory abnormalities characteristic of chronic renal failure, including anemia, hypocalcemia, and hyperphosphatemia, often are present as well in patients presenting with acute renal failure. Radiographic evidence of renal osteodystrophy (Chap. 335) can be seen only in chronic renal failure but is a very late finding, and these patients are usually undergoing dialysis. The urinalysis and renal ultrasound can facilitate distinguishing acute from chronic renal failure. An approach to the evaluation of azotemic patients is shown in Fig. 61-1. Patients with advanced chronic renal insufficiency often have some proteinuria, nonconcentrated urine (isosthenuria; isosmotic with plasma), and small kidneys on ultrasound, characterized by increased echogenicity and cortical thinning. Treatment should be directed toward slowing the progression of renal disease and providing symptomatic relief for edema, acidosis, anemia, and hyperphosphatemia, as discussed in Chap. 335. Acute renal failure (Chap. 334) can result from processes that affect renal blood flow (prerenal azotemia), intrinsic renal diseases (affecting small vessels, glomeruli, or tubules), or postrenal processes (obstruction of urine flow in ureters, bladder, or urethra) (Chap. 343).

PRERENAL FAILURE

Decreased renal perfusion accounts for 40–80% of cases of acute renal failure and, if appropriately treated, is readily reversible. The etiologies of prerenal azotemia include any cause of decreased circulating blood volume (gastrointestinal hemorrhage, burns, diarrhea, diuretics), volume sequestration (pancreatitis, peritonitis, rhabdomyolysis), or decreased effective arterial volume (cardiogenic shock, sepsis). Renal perfusion also can be affected by reductions in cardiac output from peripheral vasodilation (sepsis, drugs) or profound renal vasoconstriction (severe heart failure, hepatorenal syndrome, agents such as nonsteroidal anti-inflammatory drugs [NSAIDs]). True or "effective" arterial hypovolemia leads to a fall in mean arterial pressure, which in turn triggers a series of neural and humoral responses, including activation of the sympathetic nervous and renin-angiotensin-aldosterone systems and antidiuretic hormone (ADH) release. GFR is maintained by prostaglandin-mediated relaxation of afferent arterioles and angiotensin II–mediated constriction of efferent arterioles. Once the mean arterial pressure falls below 80 mmHg, GFR declines steeply.

Blockade of prostaglandin production by NSAIDs can result in severe vasoconstriction and acute renal failure. Blocking angiotensin action with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) decreases efferent arteriolar tone and in turn decreases glomerular capillary perfusion pressure. Patients taking NSAIDs and/or ACE inhibitors/ARBs are most susceptible to hemodynamically mediated acute renal failure when blood volume is reduced for any reason. Patients with bilateral renal artery stenosis (or stenosis in a solitary kidney) are dependent on efferent arteriolar vasoconstriction for maintenance of glomerular filtration pressure and are particularly susceptible to a precipitous decline in GFR when given ACE inhibitors or ARBs.

Prolonged renal hypoperfusion may lead to acute tubular necrosis (ATN), an intrinsic renal disease that is discussed below. The urinalysis and urinary electrolyte measurements can be useful in distinguishing prerenal azotemia from ATN (Table 61-2). The urine Na and osmolality of patients with prerenal azotemia can be predicted from the stimulatory actions of norepinephrine, angiotensin II, ADH, and low tubule fluid flow rate. In prerenal conditions, the tubules are intact, leading to a concentrated urine (>500 mosmol), avid Na retention (urine Na concentration, <20 mmol/L; fractional excretion of Na, <1%), and U_{Cr}/P_{Cr} >40 (Table 61-2). The prerenal urine sediment is usually normal or has hyaline and granular casts, whereas the sediment of ATN usually is filled with cellular debris, tubular epithelial casts, and dark (muddy brown) granular casts.

POSTRENAL AZOTEMIA

Urinary tract obstruction accounts for <5% of cases of acute renal failure but is usually reversible and must be ruled out early in the evaluation (Fig. 61-1). Since a single kidney is capable of adequate

TABLE 61-2 LABORATORY FINDINGS IN ACUTE RENAL FAILURE

Index	Prerenal Azotemia	Oliguric Acute Renal Failure
BUN/P_{Cr} ratio	>20:1	10–15:1
Urine sodium U_{Na}, meq/L	<20	>40
Urine osmolality, mosmol/L H_2O	>500	<350
Fractional excretion of sodium[a]	<1%	>2%
Urine/plasma creatinine U_{Cr}/P_{Cr}	>40	<20
Urinalysis (casts)	None or hyaline/granular	Muddy brown

[a] $FE_{Na} = \dfrac{U_{Na} \times P_{Cr} \times 100}{P_{Na} \times U_{Cr}}$.

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