Prevention of acute renal failure in the intensive care unit

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INTRODUCTION

Acute renal failure (ARF) as a result of acute tubular necrosis (ATN) may develop in 10% of all patients admitted to the intensive care unit (ICU), and is associated with high morbidity and mortality rates.1-3 Despite increased understanding of the pathophysiologic mechanisms operative in ATN, and the success of various treatments in reversing or ameliorating ATN in animal models, there are currently no proven therapies in human ARF, in which mortality rates remain in excess of 50%.4

Arguments offered to explain the discrepancy between laboratory and clinical studies include the lack of an appropriate model of human disease in the ICU, and the untimeliness of intervention in clinical trials.5,6 The mechanisms of ARF in the ICU are complex, involving issues of renal hypoperfusion, nephrotoxic insults, and accompanying acute and chronic illness, often in the face of the systemic inflammatory response syndrome (SIRS) or sepsis. Additionally, the use of positive pressure ventilation and administration of vasoactive medications can have adverse effects on renal function.7,8,9

The various animal models used to study ATN lack these complexities. Furthermore, ATN is an evolving process. Early on, renal ischemia and redistribution of renal blood flow play a prominent role.10 Later, apoptosis and inflammation are key players.11 Therefore, there is probably a limited time window for different therapeutic agents to provide benefit12 (Fig. 5.1). In animal studies, the timing of a particular insult is known and therapy is applied without reliance on first detecting a fall in glomerular filtration rate (GFR). On the other hand, in clinical trials, because of the dependence on using changes in serum creatinine levels to detect a fall in GFR, there is an inherent delay in initiating potentially beneficial treatment. For vasoactive agents such as dopamine and atrial natriuretic peptide (ANP) to be effective it is possible they need to be given early in ARF, when renal ischemia is prominent. These agents may provide no benefit when given at a later stage of ATN. In the majority of studies on ARF in ICU patients, treatment is given late in its course.13,14 The lack of efficacy of the various interventions could be the result of this delay, either because the mechanism of decreased GFR is no longer responsive to therapy or simply because too much functional renal mass has already been lost. Therefore, prevention of ATN remains a cornerstone in the treatment of the critically ill patient.

Prevention of ATN in patients in the ICU requires an understanding of certain key issues:

1. the pathophysiologic mechanism of a particular insult
2. risk factors for the development of ARF in the ICU
3. the contribution of acute and chronic organ dysfunction to renal failure
4. the effect of therapies such as vasopressors and positive pressure ventilation on renal function
5. the appropriate hemodynamic profile for a particular patient that optimizes renal blood flow (RBF).

Unfortunately, many of these factors are poorly understood or unknown.

GENERAL PRINCIPLES

In the ICU, patients are exposed to multiple potential renal insults. Frank ischemia or relative renal
hypoperfusion from capillary leak syndrome, hypoalbuminemia, and diuretics are frequently present in ICU patients. Potential exogenous insults to the kidneys, including myoglobin, radiocontrast media, aminoglycoside antibiotics, and amphotericin B preparations, often produce both ischemic and nephrotoxic damage. Distant organ dysfunction can contribute to the complexity by adversely affecting renal function, as occurs in hepatorenal syndrome and veno-occlusive disease of the liver (VOD). Therefore, it is difficult to devise a simple prevention strategy for all patients in the ICU (Fig. 5.2; Box 5.1).

Avoidance of potential nephrotoxins such as intravenous radiocontrast, aminoglycoside antibiotics, and antifungal agents is prudent, when possible. Although nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, generally have a low nephrotoxic risk, the potential renal vasoconstrictive effect of these agents may be significant in selected patients, such as those with sepsis, heart failure, cirrhosis, nephrotic syndrome, volume depletion, and hypoalbuminemia. Single daily dosing of aminoglycoside antibiotics is associated with a lower risk of nephrotoxicity and equivalent antimicrobial efficacy compared to multiple dosing strategies. Drug modifications such as nonionic radiocontrast and lipid-emulsified amphotericin B may also reduce the incidence of ATN. Aggressive diuresis must be avoided when possible, particularly in conjunction with the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, and must be accompanied by careful monitoring of fluid balance and renal function. Monitoring the serum levels of potentially nephrotoxic drugs such as aminoglycosides, cyclosporin A (CSA), tacrolimus, and vancomycin is recommended, although studies proving that therapeutic drug monitoring decreases the incidence of ATN are lacking. General measures that may decrease the incidence of ARF are listed in Box 5.1. The role of hemodynamic monitoring and support with fluids and vasoactive drugs in the prevention of ARF in the ICU is clearly important. The relationship between renal perfusion and function is discussed in depth in Chapter 4, but will be discussed in

**Figure 5.1.** Relationship between the clinical phases and the cellular phases of ischemic acute renal failure (ARF), and the temporal impact on organ function as represented by the glomerular filtration rate (GFR). Prerenal azotemia exists when a reduction in renal blood flow causes a reduction in GFR. A variety of cellular and vascular adaptations maintain renal epithelial cell integrity during this phase. The initiation phase occurs when a further reduction in renal blood flow results in cellular injury, particularly the renal tubular epithelial cells, and a continued decline in GFR. Vascular and inflammatory processes that contribute to further cell injury and a further decline in GFR usher in the proposed extension phase. During the maintenance phase, GFR reaches a stable nadir as cellular repair processes are initiated in order to maintain and re-establish organ integrity. The recovery phase is marked by a return of normal cell and organ function that results in an improvement in GFR. (CMJ = corticomedullary junction, BBM = brush border membrane.) (Reproduced with permission from Sutton et al.)
Intravascular volume depletion and hypotension
Gastrointestinal, renal, and dermal losses; hemorrhage; shock

Decreased effective intravascular volume
Congestive heart failure, cirrhosis, nephrosis, peritonitis

Medications
Cyclosporine, tacrolimus, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, radiographic agents, amphotericin B

Large-vessel renal vascular disease
Renal artery thrombosis or embolism, operative arterial cross-clamping, renal artery stenosis

Small-vessel renal vascular disease
Vasculitis, atheroembolism, hemolytic-uremic syndrome, malignant hypertension, scleroderma, pre-eclampsia, sickle cell anemia, hypercalcemia, transplant rejection

Hepatorenal syndrome
Sepsis

Ischemic acute renal failure

Figure 5.2 Conditions that lead to ischemic acute renal failure. A wide spectrum of clinical conditions can result in a generalized or localized reduction in renal blood flow, thus increasing the likelihood of ischemic acute renal failure. The most common condition leading to ischemic acute renal failure is severe and sustained prerenal azotemia. Kidney ischemia and acute renal failure are often the result of a combination of factors. (Reproduced with permission from Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med 1996;334:1448–60.)

terms of ARF prophylaxis in this chapter, along with other approaches to avoid or ameliorate ARF in critically ill patients.

PREDICTION OF ACUTE RENAL FAILURE

For prevention of ARF to be an achievable goal, it is imperative that there is a means of accurately predicting the development of ARF. Although much research continues to center on predicting outcome in patients who experience ARF in the ICU, surprisingly little work has been done in the area of predicting who will develop ARF. To date, a reliable prediction model is not available. Studies using multiple linear or logistic regression analysis suggest that a combination of factors such as age, hypotension, hypoxia, the presence of two of four markers of SIRS, use of vasopressors, positive pressure ventilation, chronic renal failure, and sepsis have some prediction value, but none have the precision to allow application of true preventive measures. An analogous situation is found in attempting to predict mortality rates in ICU patients with ARF. Although scoring methods such as APACHE II and APACHE III are reasonably good at predicting overall mortality in ICU patients, they routinely underestimate the rate in the presence of ARF. Predictive scores designed specifically for ICU patients with renal failure, such as the Cleveland Clinic Score and the Liano Score, have better accuracy, but may not be applicable to other medical centers.

RENAL BLOOD FLOW

Providing adequate renal perfusion in the face of critical illness appears to be an appropriate goal. Often, patients in the ICU already have some component of prerenal failure that can progress to frank ischemic ATN if not corrected. However, what amount of perfusion is needed, where it should be distributed, and how to measure
Box 5.1 Strategies to decrease ARF in the ICU

**Proven**
- Avoidance of nephrotoxins
- Single daily dosing of aminoglycosides

**Drug modifications:**
- Liposomal amphotericin B
- Nonionic radiocontrast

**Hydration:**
- Radiocontrast
- Cisplatin
- Rhabdomyolysis
- Tumor lysis syndrome

**Tight glycemic control in the critically ill**

**Possibly effective**
- Monitoring drug levels
- Adequate renal perfusion
- Low-dose fenoldopam
- N-acetylcysteine (radiocontrast)
- Alkalization of the urine:
  - Rhabdomyolysis
  - Methotrexate
  - Tumor lysis syndrome

**Ineffective**
- Low-dose dopamine
- Mannitol
- Diuretics
- Aminophylline
- Atrial natriuretic peptide

Adequacy are all unknown factors. A fall in renal perfusion is both a result and a response to injury. A decrease or a redistribution of blood flow away from a damaged tubule to prevent solute loss is an adaptive response to guard against hypovolemic shock. When enough nephron loss occurs, nitrogenous waste accumulates and ARF ensues. As discussed in Chapter 4, indiscriminate increases in blood flow could have deleterious effects on the course of ATN by increasing solute loss, maintaining toxin exposure to injured tubules, or promoting reperfusion oxidant injury. In fact, although renal vasoconstriction in ATN could be viewed as a maladaptive response perpetuating ARF, this phenomenon should not be considered a purely inappropriate response like sodium retention in congestive heart failure (CHF). In CHF, although retention of sodium to improve cardiac preload is an adaptive response to perceived poor perfusion, it is detrimental to the patient and must be treated with diuretics. In contrast, increasing RBF with vasodilators in the presence of ATN may reverse a protective hemodynamic response of injured kidneys; this may be an inappropriate therapy for what has been termed “acute renal success.”

There are no reliable indicators of adequate RBF except (presumably) normal renal function. Urine output correlates best with degree of renal injury (i.e., oliguric ATN has a worse prognosis, thought to reflect more severe renal injury). Except in the case of prerenal failure, where a volume infusion reverses the low flow state, urine output is an unreliable marker of renal perfusion. Most often, a predetermined mean arterial pressure (MAP) reading is considered proof of adequate renal perfusion. Vasopressor algorithms used in the ICU usually specify an arbitrary MAP goal for titration of the medications. However, the appropriate MAP for a critically ill patient with ARF is not defined. The three major determinants of renal blood flow are cardiac output, intravascular volume, and renal perfusion pressure.

**Cardiac output**

Increasing cardiac output by administration of intravenous fluid or cardiac inotropes should increase renal blood flow in low flow states such as cardiogenic shock and prerenal azotemia. In patients with ARF, decreased renal perfusion is the result of an imbalance between local renal vasoconstrictor and vasodilator influences. This imbalance causes both global renal hypoperfusion and shunting of blood flow away from the renal medulla. There is no evidence that increasing cardiac output to “supranormal” levels counteracts this imbalance. Most studies in critically ill patients comparing normal to enhanced cardiac output measured by oxygen delivery or cardiac index have failed to show benefit on survival rates. One recent study of aggressive hemodynamic management of 263 septic patients on arrival to the emergency center did demonstrate a survival benefit, but effects on renal function were not described, and its relevance to preventing ARF in established ICU patients is unknown. Currently, there are no randomized controlled trials comparing different cardiac outputs and the
subsequent development of ARF in high-risk individuals.

**Intravascular fluid expansion**

Both animal and human studies suggest that intravascular fluid expansion decreases the risk of ARF from radiocontrast agents and various nephrotoxic insults. However, what role it plays in preventing ATN in patients in the ICU with multiple risk factors is purely speculative. Because ICU patients usually have capillary leak syndrome and impaired pulmonary function, indiscriminate fluid administration can have deleterious effects. Therefore, measuring volume status in ICU patients often requires invasive monitoring of right atrial pressure or pulmonary artery occlusion pressure. At this time, no data are available to indicate that a certain degree of intravascular filling is more protective of renal function than another.

The putative superiority of colloid over crystalloid fluids in the resuscitation of the critically ill patient has been a source of considerable controversy. Aggressive hydration with crystalloid solutions such as 0.9% sodium chloride can worsen interstitial edema and pulmonary function. Colloidal solutions such as various starches and human albumin might appear to be attractive alternatives, but there is little solid evidence of their superiority in clinical trials. Systematic reviews of randomized controlled trials comparing crystalloids with colloids have yielded conflicting results. Some trials have found an increased mortality rate associated with the administration of human albumin and hydroxyethylstarch, whereas others have not. Most recently, a large randomized, controlled prospective trial of albumin vs saline in almost 7000 critically ill patients found no benefit of one over the other. Specifically, there was no demonstrable effect on mortality, renal function, or the frequency of renal replacement therapy. Of note, patients with cirrhosis were excluded from this trial, and limited data suggest that albumin is useful to prevent ARF in cirrhotic patients with spontaneous bacterial peritonitis (see below), or undergoing large volume paracentesis. As discussed below, for prevention of radiocontrast nephropathy normal saline is superior to half-normal saline, and an equimolar solution of sodium bicarbonate is superior to normal saline.

Otherwise, despite the importance of fluid therapy in the prevention of ARF, the nature of the optimum fluid resuscitation regimen remains a disputed topic. For the time being it appears that treatment of the underlying diagnosis, usually sepsis, and general supportive efforts are the mainstays of therapy.

**Renal perfusion pressure**

In the critically ill patient attention is usually focused on improving cardiac output and intravascular volume to maintain adequate perfusion to the heart and brain, the ‘vital organs.’ What is often unappreciated is that in the normal kidney loss of autoregulation of renal blood flow occurs at a MAP of 75–80 mmHg, and that the loss of autoregulation of GFR occurs at approximately 80–85 mmHg. In the face of long-standing hypertension present in many ICU patients, autoregulation fails at even higher MAP levels. Therefore, ICU protocols that titrate vasopressors to an MAP of 65 or 70 mmHg can result in persistent renal ischemia (Fig. 5.3). There are no randomized controlled trials comparing MAP values and the development of ARF in ICU patients. However, the current treatment strategies may be inappropriate in some individuals.

**PHARMACOLOGIC AGENTS**

**N-acetylcysteine (NAC, Mucomyst)**

NAC is an antioxidant and causes renal vasodilation by generating increased levels of nitric oxide (NO). Based on these effects, NAC was used in several small human trials for the prevention of ARF from radiocontrast agents in high-risk individuals. The trials have shown that its administration results in a significantly smaller change from baseline of serum creatinine values compared to changes in the placebo group. A recent meta-analysis of 8 randomized controlled trials supported the use of NAC to prevent radiocontrast nephropathy (RCN). However, whether or not it prevents severe ARF and the need for dialysis has not been determined. Furthermore, emerging literature suggests that NAC causes a GFR-independent decrease in serum creatinine, perhaps by inhibiting creatine phosphokinase-mediated generation of creatinine. This may explain the puzzling but consistent decrease in serum creatinine below baseline levels observed in NAC-treated patients with chronic kidney disease undergoing RCN.
prophylaxis, which was previously assumed to be an effect of volume expansion. It is thus conceivable that the putative renoprotective effect of NAC in contrast nephropathy is an artifact. NAC has also been administered intravenously to 100 critically ill patients in a randomized placebo-controlled trial to prevent progression of multiple organ dysfunction syndrome (MODS). There was no significant difference between the groups in mortality rate, days of inotropic support, mechanical ventilation, ICU length of stay, or development of ARF.

At this point, it is probably harmless to provide NAC prior to radiocontrast administration in patients at risk for the development of ARF pending further research, provided that it is combined with appropriate volume expansion, and that the effect of NAC on serum creatinine is remembered while assessing post-dye renal function. However, there are no convincing data to support the routine administration of NAC in RCN or other clinical circumstances to prevent the development of ATN, and it may soon be proven ineffective for such purposes.

**Low-dose dopamine**

Low-dose dopamine administration (1-3 μg/kg/min) to normal individuals causes renal vasodilation and increased GFR, and acts as a proximal tubular diuretic. Due to these effects, numerous studies have used low-dose dopamine to either prevent or treat ATN in a variety of clinical settings. It has been given as prophylaxis for ARF associated with radiocontrast administration, repair of aortic aneurysms, orthotopic liver transplantation, unilateral nephrectomy, renal transplantation, and chemotherapy with interferon. Yet despite more than 20 years of clinical experience, prevention trials with low-dose dopamine have all been small, inadequately randomized, or limited statistical power, and with endpoints of questionable clinical significance. Furthermore, there is concern for the potential harmful effects of dopamine, even at low doses. It can trigger tachyarrhythmias and myocardial ischemia, decrease intestinal blood flow, cause hypothyroidism, and suppress T-cell function. It has also been shown to increase the risk of RCN when given prophylactically to patients with diabetic nephropathy.

Numerous trials using low-dose dopamine to treat established ATN have also been reported in the last several years and suggest its use is beneficial. However, most studies were either uncontrolled case series or small randomized trials with limited statistical power. Kellum and Decker found no benefit of dopamine for prevention or therapy of ARF in an adequately powered meta-analysis. More recently, a large randomized placebo-controlled trial in 328 critically ill patients, with early ARF sufficiently powered to detect a small benefit, reported no effect of low-dose dopamine on renal function, need for dialysis, ICU or hospital length of stay, or mortality. These findings combined with the aforementioned potential deleterious effects of low-dose dopamine are strong arguments for abandoning its use entirely for the prevention and therapy of ARF.
Low-dose fenoldopam mesylate

Fenoldopam mesylate is a pure dopamine type-1 receptor agonist that has similar hemodynamic effects to dopamine in the kidney without α- and β-adrenergic stimulation. Limited trials suggested that administration of fenoldopam mesylate reduced the occurrence of ARF from radiocontrast agents and following aortic aneurysm repair. However, a recently reported large randomized controlled trial of fenoldopam mesylate to prevent contrast nephropathy in 315 patients demonstrated that its administration had no beneficial effect on urine output, change in serum creatinine levels, incidence of ARF, or need for dialysis. Promising data from a recent randomized, placebo-controlled pilot trial of low-dose fenoldopam mesylate in 155 ICU patients with early ATN showed that fenoldopam patients tended to have lower 21-day mortality rates and decreased need for dialysis, but the study was underpowered. A larger study is required to determine if fenoldopam ameliorates the course of ATN.

Diuretics

Furosemide is a loop diuretic and vasodilator that may decrease oxygen consumption in the loop of Henle by inhibiting sodium transport, thus potentially lessening ischemic injury. By increasing urinary flow, it may also reduce intratubular obstruction and backleak of filtrate. Based on these properties, furosemide might be expected to prevent ARF (Fig. 5.4). However, there are little data to support its use. Furosemide was found to be ineffective or harmful when used to prevent ARF after cardiac surgery, and to increase the risk of ARF when given to prevent contrast nephropathy.

Similarly, there is little evidence of benefit from diuretic therapy in established ARF. A single recent study in 100 patients with oliguric ARF after cardiac surgery suggested that a cocktail infusion of furosemide, mannitol, and dopamine improved renal function postcardiac surgery compared to intermittent loop diuretics alone. In patients with established ATN, several studies have found no

![Figure 5.4 Pathophysiologic mechanisms of acute renal failure (ARF). Tubular damage by ischemia, nephrotoxins, or both, leads to decreased glomerular filtration rate (GFR) by a combination of mechanisms. (1) Renal vasoconstriction via activation of tubuloglomerular feedback, and decreased vasodilator substances (PGI₂, prostacyclin; NO, nitric oxide), is a prominent functional mechanism of decreased GFR in acute tubular necrosis (ATN). (2) Backpressure from tubular obstruction by casts directly decreases GFR. (3) Backleak of glomerular filtrate into peritubular capillaries decreases the efficiency of glomerular filtration, effectively decreasing GFR. (4) There is increasing evidence for a role of interstitial inflammation in the extension phase of ATN. (5) Direct glomerular effects (mesangial contraction, decreased filtration surface area) may also play a role in decreasing GFR in the presence of ATN.](image-url)
benefit of loop diuretics: their use did not accelerate renal recovery, decrease the need for dialysis, or reduce mortality. It was shown that the mortality rate of oliguric patients who responded to furosemide with a diuresis was lower than those who did not. However, the clinical characteristics, severity of renal failure, and mortality rates were similar in patients with either spontaneous nonoliguric ARF or patients who became nonoliguric after furosemide. This implies that those patients able to respond to furosemide have less severe renal damage than nonresponders, rather than deriving any true therapeutic benefit from furosemide administration. Although administration of furosemide might facilitate improved fluid management if it induces a diuresis, a retrospective review of a recent trial in critically ill patients with ATN raised concerns of possible harm from loop diuretics in ARF. The authors found that diuretic use was associated with an increased risk of death and nonrecovery of renal function. Most of the increased risk, however, was seen in those patients unresponsive to high doses of diuretics, implying they had more severe disease. Therefore, diuretics should be used with caution in critically ill patients, and iatrogenic hypovolemia and superimposed prerenal azotemia must be avoided. Diuretics should be withdrawn if there is no response, to avoid ototoxicity. In patients who experience an increase in urine output, hypotension must be avoided, since kidneys with ATN are susceptible to further damage from decreases in perfusion pressure. To maintain the diuresis, a continuous infusion of drug is probably preferable to intermittent bolus administration. Although there are no large randomized controlled trials, the overall evidence suggests that continuous infusion of diuretics as opposed to bolus administration is more effective and associated with less toxicity and delayed development of diuretic resistance.

Mannitol is an osmotic diuretic that can decrease cell swelling, scavenge free radicals, and cause renal vasodilatation by inducing intrarenal prostaglandin production. It may be beneficial when added to organ preservation solutions during renal transplantation and may protect against ARF caused by rhabdomyolysis if given extremely early. Otherwise, mannitol has not been shown to be useful in the prevention of ARF. In fact, mannitol may aggravate ARF from radiocontrast agents. Furthermore, mannitol may precipitate pulmonary edema if given to volume-overloaded patients who remain oliguric, can exacerbate the hyperosmolar state of azotemia, and may even cause acute renal failure (‘osmotic nephrosis’).

### Atrial natriuretic peptide

Atrial natriuretic peptide causes vasodilation of the afferent arteriole and constriction of the efferent arteriole, resulting in an increased GFR. It also inhibits renal tubular sodium reabsorption. Most studies with ANP involved the treatment of established ATN. However, in two studies that administered ANP in renal transplant recipients to prevent primary renal dysfunction, no benefit was found. As with mannitol and low-dose dopamine, one study suggested that ANP prophylaxis might worsen renal function in diabetic patients receiving radiocontrast agents.

Based on the positive results of small clinical studies using ANP to treat ATN, a randomized placebo-controlled trial of 504 critically ill patients with ARF was conducted. Despite the large size of the trial, ANP administration had no effect on 21-day dialysis-free survival, mortality, or change in plasma creatinine concentration. Of note, the mean serum creatinine values at enrollment (about 4.4–5 mg/dl) in this study confirm that intervention in this trial was extremely late in the course of ATN. Although a subgroup analysis of the study suggested that ANP might be beneficial in those patients with oliguric renal failure, a subsequent trial in patients with oliguric renal failure failed to demonstrate any benefit of ANP. Hypotension was significantly more common in ANP-treated patients in this study, and may have negated any potential benefit of renal vasodilation in these patients. Hence, there is no convincing evidence to support the use of ANP in the prevention or treatment of ARF. A new, promising, but underpowered (61 patients) positive study of ANP to treat ARF immediately following cardiac surgery showed a decreased rate of postoperative renal replacement therapy compared to placebo-treated patients; a larger prospective trial in this setting appears warranted.

### Insulin-like growth factor-1

Insulin-like growth factor-1 (IGF-1) increases renal blood flow and induces cell proliferation and differentiation. In addition, it reverses apoptosis. In animal models, it ameliorates renal injury associated with ischemia and may prevent injury following
renal transplantation. However, a recent small clinical trial found no benefit of IGF-1 therapy for delayed graft function in postcadaveric renal transplant in humans. IGF-1 has been given to a small group of patients in a single trial for prophylaxis of ARF following aortic aneurysm repair. IGF-1 was started post-operatively in a randomized placebo-controlled fashion; it was well tolerated, and produced a modest increase in the creatinine clearance in the treated group compared to the placebo group, possibly by vasodilation rather than a ‘trophic’ effect. However, no patients developed ARF that necessitated dialysis. Hence, the role, if any, for IGF-1 in the prevention of ARF remains unknown.

Based on the positive effects of IGF-1 in animal models of ATN, a randomized placebo-controlled trial was conducted in 72 critically ill patients with established ARF. The results showed there was no difference in the two groups in post-treatment GFR, need for dialysis, or mortality, although it should be noted that GFR at randomization was only 6.4–8.7 ml/min, and ATN was possibly too established for a successful intervention in this study population. In anuric patients, IGF-1 administration was associated with a slower rate of improvement in urine output and GFR. So, despite the ample evidence that IGF-1 accelerates renal recovery in animal models of ARF, there is no support for its use in humans.

Thyroxine

The administration of thyroid hormone following the initiation of ATN in a variety of ischemic and nephrotoxic animal models was found to be effective in promoting recovery of renal function. Based on these results, thyroxine was administered to 59 patients with ARF in a randomized placebo-controlled trial. Patients were well matched in baseline characteristics. Administration of thyroxine had no effect on any renal parameter. However, the trial was terminated early because of a significantly higher mortality rate in the patients who received thyroxine.

Intensive insulin therapy

Hyperglycemia associated with insulin resistance is common in critically ill patients, independent of a history of diabetes mellitus. Studies involving nondiabetic patients have found that the plasma glucose level on admission is an independent predictor of prognosis after myocardial infarction or of the need for coronary artery bypass grafting. Furthermore, the in-vitro responsiveness of leukocytes stimulated by inflammatory mediators is inversely correlated with glycemic control. Based on these findings, a randomized controlled trial was conducted involving 1500 ICU patients who received either intensive or conventional glycemic control. All patients were receiving mechanical ventilation, the majority postoperatively. The study was terminated early because the mortality rate in the intensive treatment group was significantly lower than in the conventional treatment arm. Moreover, the incidence of severe renal insufficiency (peak serum creatinine >2.5 mg/dl; 11.2% conventional, 7.7% intensive, \( p = 0.04 \)) and need for renal replacement therapy (8.2% conventional, 4.8% intensive, \( p = 0.007 \)) were significantly lower in the intensive glycemic control group. Whether these results can be readily extrapolated to patients in a nonsurgical ICU or to those with other types of critical illness is currently unknown. Similar trials in other groups of patients will be necessary to confirm the observed benefits.

Anti-TNF-α therapy

Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine that plays a pivotal role in the host response to infection. In addition to systemic effects, TNF-α may have specific renal effects. In-vivo TNF-α infusion in animals or perfusion of the isolated rat kidney with TNF-α decreased GFR. TNF-α caused leukocyte and fibrin accumulation in glomerular capillary lumens and induced apoptosis in glomerular endothelial cells. A large number of studies in diverse animal models have shown that anti-TNF antibodies confer protection against the morbidity and mortality from both Gram-positive and Gram-negative sepsis, including the development of ARF. Emerging animal data suggest that anti-TNF therapies may have the potential to prevent septic ARF, despite the failure of such therapies to improve mortality in sepsis syndrome. For example, Cunningham and colleagues found that renal susceptibility to renal injury in endotoxemic mice with or without TNF receptor knockouts was associated with TNF receptor expression in the kidneys rather than the hosts, as determined by performing renal transplants between knockouts and wild-type mice. On the other hand, they recently found that...
systemic expression of Toll-like receptor-4 is also required for development of endotoxemic ARF. Limited clinical data similarly suggest that TNF receptor expression may play a role in the susceptibility to ARF in patients with sepsis.

Several large trials with neutralizing monoclonal anti-TNF-α antibodies or soluble TNF receptor fusion proteins have failed to consistently show significant survival benefits or a reduced incidence of ARF in patients with sepsis. This apparent lack of efficacy may be related to the heterogeneity of the patient population. Age, immune status, and genetic predisposition may all alter the inflammatory reaction in critical illness and lead to different responses to anticytokine therapies. Therefore, despite the apparent success of anti-TNF therapies in animal models in decreasing both mortality and renal failure, the beneficial effects of these strategies in humans are marginal at best.

Inhibitors of coagulation

Disseminated intravascular coagulation is common in ICU patients and is associated with an adverse prognosis. It is characterized by a generalized activation of the coagulation cascade, resulting in the intravascular formation of fibrin clots and endothelial damage. Impaired tissue blood supply contributes to organ dysfunction, including ARF. Several agents that block coagulation at different levels have been evaluated as adjunctive therapy in sepsis.

Protein C is activated by the thrombin-thrombomodulin complex on endothelial cells and inhibits thrombin generation. Besides its effects on coagulation, activated protein C has direct anti-inflammatory properties, including impairment of leukocyte adhesion to the endothelium and inhibition of the production of inflammatory cytokines. In a randomized, multicenter trial conducted in 1690 patients with severe sepsis, recombinant human activated protein C significantly reduced mortality. It was particularly effective in the most seriously ill patients, as assessed by the APACHE II score, the number of failing organs, and the presence of shock; effects on the incidence or course of ARF were not described in study publications.

Tissue factor forms a complex with factor VIIa and initiates thrombin generation. Tissue factor is inhibited by a natural anticoagulant, tissue factor pathway inhibitor (TFPI). A phase II trial comparing placebo and recombinant TFPI in 210 patients with severe sepsis showed a trend toward mortality reduction in the recombinant TFPI-treated group. However, a recently completed pivotal phase III trial of TFPI in 1700 patients with sepsis or severe sepsis failed to show a survival benefit; ARF incidence in the groups was not reported.

Antithrombin III blocks several proteases involved in coagulation and plasma levels are usually markedly reduced in patients with sepsis. In a double-blind, placebo-controlled multicenter trial of 2300 patients with severe sepsis and septic shock, high-dose antithrombin III had no effect on 28-day mortality and was associated with an increased risk of hemorrhage when co-administered with heparin.

A complex interaction between the pro-inflammatory, coagulation, and fibrinolytic networks plays a pivotal role in organ damage in sepsis. Although several strategies to inhibit coagulation have been evaluated in sepsis, only the administration of activated protein C has proved successful, and its efficacy may depend on its combined effects on coagulation, fibrinolysis, and inflammation. Activated protein C is currently approved for the treatment of severe sepsis, although current trials are assessing its effectiveness in less-ill patients. Specific renoprotective effects have not been demonstrated in humans, but emerging data suggest that activated protein C may be broadly protective against ischemia–reperfusion injury in a variety of settings.

Nitric oxide synthase inhibition

Nitric oxide (NO) is the metabolic product of L-arginine and is produced by three major NO synthase (NOS) isoforms: endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS). Within the kidney, eNOS is constitutively expressed in endothelial cells and produces vascular relaxation and inhibition of leukocyte adhesion and platelet aggregation. Excessive generation of NO by iNOS has been implicated as an important mediator of the hemodynamic alterations in sepsis, particularly the vascular hyporesponsiveness and vasodilation.

Animal studies using nonspecific inhibitors of NOS have yielded conflicting results, although use of specific iNOS inhibitors has been more encouraging. The ubiquitous nature and the pleiotropic effects of the NO system, as well as its complex alterations in sepsis and ARF, probably explain why NOS inhibition fails to show reproducible
beneficial effects. NO release by the endothelial cells of the renal microcirculation is essential to counterbalance the vasoconstrictor influences and maintain RBF, to inhibit infiltration of leukocytes, and to prevent thrombosis. Several animal studies have shown that whereas nonselective NOS inhibition worsens septic ARF while raising blood pressure, iNOS-selective agents improve both systemic hemodynamics and renal function. In the phase II trial involving over 800 patients, the trial was stopped prematurely when interim analysis demonstrated increased mortality in the L-NMMA-treated group. This discordant result may be due to differences in patient enrollment and hemodynamic management protocols, and the nonspecific nature of NOS inhibition. Future strategies that inhibit iNOS but amplify eNOS may prove beneficial.

Endothelin antagonism

Endothelin-1 (ET-1) is a peptide with potent vasoconstrictor effects on the renal microcirculation, thereby reducing RBF and GFR. Experimental studies with ET-receptor antagonists in animal models of ARF demonstrated improved renal function. However, no studies with ET receptor antagonists have been performed in patients with sepsis. A nonselective ET antagonist increased the risk of contrast nephropathy in patients with chronic renal failure undergoing coronary angiography, perhaps because ET receptors cause vasodilation and ET receptors cause vasoconstriction. This paradoxical finding may make it difficult to perform studies of ET antagonism in patients with ARF and sepsis, although results may be better with an ET receptor-selective agent.

Inhibitors of arachidonic acid metabolism

Metabolism of arachidonic acid by cyclooxygenase results in the generation of prostaglandins and thromboxanes, whereas lipoxygenase yields leukotrienes. Both prostaglandin E and prosta-cyclin cause renal vasodilatation and natriuresis, whereas thromboxane A, leukotrienes, and prostaglandins F and H are potent renal vaso-constrictors. Endotoxin and various inflammatory cytokines stimulate the synthesis of thromboxane A and leukotrienes in the kidney and in inflammatory cells.

In animal models of sepsis, cyclooxygenase inhibition with indomethacin, selective thromboxane inhibition, and leukotriene antagonism all had beneficial effects on renal function. However, in 455 patients with sepsis, cyclooxygenase inhibition with intravenous ibuprofen reduced the synthesis of thromboxane and prostacyclin, but it had no effect on the development of shock or renal failure and did not improve survival. In the absence of clinical studies with selective thromboxane or leukotriene inhibitors, no meaningful conclusions on their potential benefit can be drawn.

Inhibition of leukocyte adhesion

The recruitment of circulating leukocytes into a tissue is directed by specific adhesive interactions between the leukocyte and the vascular endothelium. Selectins mediate the initial contact between the leukocyte and the endothelium, and adherence and migration are mediated by interactions between integrins on the leukocyte and surface receptors on the endothelium such as intercellular adhesion molecule-1 (ICAM-1). Studies suggest that during sepsis and ischemia leukocytes infiltrate the kidneys, resulting in renal dysfunction, and provide a rationale for the inhibition of leukocyte recruitment in these settings. Several mechanisms may be operative in leukocyte-mediated renal injury. Leukocytes release reactive oxygen species and enzymes that may directly injure cells. The production of cytokines attracts additional inflammatory cells and up-regulates adhesion molecules, creating a cycle of injury. Release of vasoconstrictor arachidonic acid metabolites, as well as physical congestion of medullary capillaries, contributes to persistent hypoxia. However, no results from human trials with antibodies to leukocyte adhesion molecules are available. Inhibition of leukocyte recruitment is a potential promising approach in the treatment of septic ARF, but data in humans are required before relevant conclusions can be drawn.
SPECIFIC CLINICAL SCENARIOS

Radiocontrast agents

An acute rise in serum creatinine levels following administration of radiocontrast material is defined as contrast nephropathy. Clinical trials assessing the effectiveness of various prevention strategies have utilized different absolute changes in creatinine to define ARF, making comparisons between studies difficult and obscuring the actual benefit achieved. Preventing increases in serum creatinine values as small as 25% have been used to define successful intervention instead of relying on endpoints such as hospital length of stay, need for dialysis, or mortality rates. However, a retrospective review of 16,000 patients who received intravenous radiocontrast showed that patients with a 50% or more increase in serum creatinine had a 6-fold higher mortality rate compared to those who did not.\textsuperscript{119} Hence, using modest changes in serum creatinine as a surrogate for more serious complications may be a reasonable approach. As shown in Box 5.2, numerous risk factors are known for the development of RCN, including chronic kidney disease (especially diabetic nephropathy), volume depletion, uncompensated CHF, and high contrast volume.

The pathogenesis of ARF from radiocontrast is complex and incompletely understood.\textsuperscript{118-121} After intravenous injection, a brief period of renal vasodilation is followed by intensive vasoconstriction, in part mediated by endothelin and adenosine. Medullary blood flow is more profoundly affected than is cortical blood flow. Hence, concomitant administration of drugs that affect RBF particularly NSAIDs, may act synergistically with radiocontrast to produce ARF. This vasoactive mechanism probably explains the increased risk of contrast nephropathy observed in patients with CHF, volume depletion, and nephrotic syndrome, as well as the therapeutic benefit of saline loading. Direct tubular toxicity also contributes to ARF from radiocontrast. Proximal tubular cells exposed to contrast material demonstrate altered cellular metabolism and intracellular enzyme release, probably mediated by oxygen free radicals and reactive oxygen species.

Prevention strategies

\textit{Hydration}. Intravenous administration of 0.45% saline has long been the standard of care therapy to reduce the incidence of contrast nephropathy in high-risk patients undergoing coronary arteriography, although it has never been studied in a placebo-controlled trial. In a study of 78 patients with underlying renal dysfunction (mean baseline creatinine of 2.1 mg/dl), randomization to 0.45% saline was superior to 0.45% saline plus either mannitol or furosemide in preventing a 0.5 mg/dl increase in serum creatinine levels.\textsuperscript{28} A variety of renal vasodilators (dopamine, fenoldopam, ANP) have proven ineffective in addition to saline. A more recent trial of comparable patients demonstrated that 0.9% saline was more beneficial than 0.45% saline in preventing contrast nephropathy.\textsuperscript{35} Most recently, administration of an equimolar sodium bicarbonate solution was superior to normal saline for RCN prophylaxis, infused as 3 mEq/L/h for 1 hour precontrast, then 1 ml/kg/h for 6 hours.\textsuperscript{36} It is interesting to note that experimental data from animals support the concept that urinary alkalization ameliorates renal ischemia-reperfusion injury, but the mechanism is unexplained.

\textit{NAC}. NAC is a free radical scavenger and, by generating nitric oxide, a renal vasodilator. By comparing changes in mean creatinine values for treatment groups or absolute changes in creatinine levels, several studies have demonstrated the effectiveness of Mucomyst (NAC) in preventing contrast nephropathy.\textsuperscript{38,40} All studies to date have relied on these changes as surrogates for more meaningful endpoints such as need for dialysis and mortality rates. A recent meta-analysis of 8 randomized controlled trials involving 855 patients reported that the use of Mucomyst reduced the risk of radiocontrast by 59%.\textsuperscript{41} However, emerging data suggest that NAC causes a decrement in serum creatinine (but not cystatin C)

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\hline
\textbf{Box 5.2 Risk factors for the development of radiocontrast nephropathy} \\
\hline
Chronic renal insufficiency (particularly in diabetics) \\
Volume depletion \\
High contrast dose \\
Myeloma kidney \\
Nephrotic syndrome \\
Older age \\
Congestive heart failure \\
Nephrotic syndrome \\
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by a GFR-independent mechanism, perhaps by inhibiting creatinine phosphokinase function. Nevertheless, given the available data, oral administration of Mucomyst to patients at high risk of developing contrast nephropathy appears warranted.

**Fenoldopam mesylate.** Limited trials suggested that administration of fenoldopam mesylate reduced the occurrence of ARF from radiocontrast agents. However, a large randomized placebo-controlled trial (the CONTRAST Trial) was published that refutes the evidence accumulated in the previous reports. In 315 patients at risk for contrast nephropathy undergoing coronary arteriography who were given a standardized hydration regimen, randomization to low-dose fenoldopam had no effect on urine output, change in serum creatinine levels up to 96 hours, or the need for dialysis. This study is strong evidence against the indiscriminate administration of fenoldopam mesylate for prevention of contrast nephropathy.

**Dialysis.** Radiocontrast is a small molecule easily removed from the circulation by dialysis; therefore, there remains an interest in performing dialysis in high-risk individuals who receive radiocontrast to prevent the development of ARF. In two studies of postcontrast hemodialysis, the subsequent need for dialysis for ARF was unchanged or increased by prophylactic hemodialysis.

A more recent randomized trial of hemofiltration started in high-risk patients before administration of radiocontrast demonstrated a benefit of therapy. In this study, 114 consecutive patients with serum creatinine levels >2 mg/dl undergoing coronary interventions were randomly assigned to either hemofiltration in an ICU or isotonic saline hydration at a rate of 1 ml/kg/h in a step-down unit. Hemofiltration or hydration was initiated 4–8 hours before coronary intervention and continued for 18–24 hours after the procedure was completed. A 25% or more increase in baseline serum creatinine level, need for temporary dialysis, in-hospital mortality rate, and 1-year mortality rate were all significantly lower in the hemofiltration group compared to the hydration group. However, numerous concerns surround this study. Although arguments continue about the superiority of hemofiltration compared to hemodialysis in treating critically ill patients with ARF because of better middle molecule removal with hemofiltration, there is no plausible explanation for its positive effects in removing a low-molecular-weight substance such as radiocontrast. Many of the control patients subsequently required dialysis for pulmonary edema, probably as a result of the hydration regimen used in these cardiac patients. Although such patients represent a therapeutic challenge, provocation of pulmonary edema with hydration does not prove the superiority of hemofiltration. It is also difficult to interpret the incidence of contrast nephropathy when one group has a fall in serum creatinine as a direct result of the intervention. It is interesting to speculate that bicarbonate administration in the hemofiltration group may have been another benefit of this therapy in RCN prophylaxis, in view of the subsequent data showing a protective effect of sodium bicarbonate. It is also challenging to explain how limited hemofiltration would decrease the rate of acute myocardial infarction, ischemic stroke, and multiple organ failure, the most common causes of death in the hydration group. More to the point, treatment details of the placebo group were inadequately described. From the available data, it is unclear if the placebo group did worse because of the lack of hemofiltration or because ideal medical management was not provided. Given the cost and invasiveness of hemofiltration, further data will be required before it can be recommended as a preventive measure in contrast nephropathy.

In summary, volume expansion with saline or perhaps sodium bicarbonate remains the only proven method for RCN prophylaxis. Avoidance of iohinated radiocontrast agents in high-risk patients is preferred where possible, perhaps by using alternate imaging methods such as magnetic resonance angiography with gadolinium. When radiocontrast is required, the least nephrotoxic agent available is preferred. Currently, the isosmolar, dimeric, nonionic contrast medium, iohixanol is thought to be the least nephrotoxic agent available. In a study of 129 diabetics with chronic renal insufficiency, iohixanol caused significantly less RCN than the low-osmolar, nonionic, monomeric contrast medium, iohexol. Although many positive studies suggest benefit, the value of NAC for RCN prevention is now uncertain. Finally, although a single positive study suggesting the use of prophylactic hemofiltration has added to the growing list of potentially effective preventive strategies, we do not regard this as a proven approach.
Aminoglycosides

Aminoglycosides cause ATN in approximately 10% of patients who are treated with them for more than 2–3 days. The serum creatinine typically rises 7–10 days after the drug is initiated. Aminoglycosides concentrate in the proximal tubular cells, causing cellular damage. Risk factors for aminoglycoside-induced ARF are advanced age, chronic kidney disease, volume depletion, liver disease, and prolonged use of the drug.

Aminoglycosides have concentration-dependent bactericidal activity as well as a ‘post-antibiotic’ effect on bacterial growth. Therefore, single-daily dosing is as effective as multiple daily dosing in treating infections by Gram-negative bacteria. The rate of renal cortical uptake of aminoglycosides is saturable, so accumulation of drug is less when given in one large dose rather than in divided doses. Therefore, single daily dosing of aminoglycosides should lower the incidence of nephrotoxicity. In a randomized controlled trial of 123 patients, single daily dosing of gentamicin was as effective in treating infection as multiple dosing, and significantly decreased the incidence of ARF. Two meta-analyses also support this conclusion.

Amphotericin B

Amphotericin B and its liposomal derivatives are a common cause of ATN in the ICU, particularly in patients who have undergone bone marrow transplant. Eighty percent of patients who receive amphotericin B will develop some degree of renal impairment. The initial nephrotoxic injury from amphotericin B results from renal vasoconstriction of the preglomerular arterioles and predisposes the patient to an ischemic insult. Direct tubular toxicity follows. The newer liposomal forms of amphotericin B lack the solubilizing agent deoxycholate that contributes to tubular toxicity. Although such agents have been shown to cause less nephrotoxicity, renal failure still develops in a significant proportion of patients.

Effective strategies to prevent the nephrotoxicity of amphotericin B are not clearly defined due to the lack of rigorous clinical trials and the inherent complexities of patients who require amphotericin B. Several retrospective or uncontrolled prospective trials suggest that salt-loading reduces the risk of nephrotoxicity. A small, randomized placebo-controlled trial of 20 patients confirmed this finding. Animal studies also suggest that administration of calcium channel blockers or aminophylline are protective, although no human trials have been reported.

Cisplatin

Nephrotoxicity is the most common dose-limiting side effect of cisplatin administration. The primary site for clearance of cisplatin is the kidney. Cisplatin asserts its toxicity on the tubules, resulting in a tubular wasting syndrome that is often severe. The proximal tubule is most often affected but the distal nephron is also vulnerable. The direct tubular toxicity associated with cisplatin is exacerbated in a low-chloride environment. In the intracellular compartment, chloride molecules are replaced with water molecules in the cis position of cisplatin, forming hydroxyl radicals that injure the neutrophilic binding sites on DNA. The decline in GFR associated with cisplatin toxicity usually occurs 7–14 days after the exposure. Doses of cisplatin >50 mg/m² are sufficient to cause renal insufficiency. The renal injury is typically reversible but repeated doses of cisplatin in excess of 100 mg/m² may cause irreversible renal damage.

Hydration and avoidance of concomitant nephrotoxins is the most effective way to prevent cisplatin-induced nephrotoxicity. Numerous trials proposing various hydration regimens have been reported, but it appears that 3 L of normal saline over 8–10 hours before and after cisplatin is sufficient to avoid most toxicity associated with conventional doses. When cisplatin is given in very high doses (>100 mg/m²), administration in 3% saline is also protective. Amifostine has also been shown to reduce cisplatin nephrotoxicity.

Calcineurin inhibitors

The calcineurin-inhibitors CSA and tacrolimus are widely used as immunosuppressants in solid organ and bone marrow transplantation. CSA and tacrolimus cause both ARF and chronic renal failure. The nephrotoxicity seen in the critically ill patient is the result of direct afferent arteriolar vasoconstriction, leading to a decrease in the glomerular filtration pressure and GFR. The vascular effect associated with CSA and tacrolimus is reversible with discontinuation of the drug. A dose reduction is sometimes enough to reverse the
prerenal effect. Calcium channel blockers (CCBs) decrease ischemic damage and reverse CSA-induced renal vasoconstriction in animal models. However, small clinical trials in humans have had conflicting results. It has been suggested that the positive response to CCBs may be due to their ability to increase plasma levels of CSA, thereby decreasing acute rejection, as well as directly modifying T-cell function.

Hemolytic uremic syndrome (HUS) is a rare complication of CSA and tacrolimus therapy. The mechanism of CSA- or tacrolimus-induced HUS is direct damage to the vascular endothelium in a dose-dependent fashion. With discontinuation of the drug, patients may have partial recovery. The utility of therapeutic plasma exchange in the treatment of HUS induced by calcineurin inhibitors has not been well studied.

Myoglobin

The principal causes of pigment nephropathy are (1) rhabdomyolysis and (2) hemoglobinuria due to hemolysis. The majority of rhabdomyolysis cases are subclinical, with mild elevations in the creatine kinase, lactic dehydrogenase, or aspartate aminotransferase enzyme levels. In severe cases, ARF may ensue from myoglobinuria. Commonly encountered causes of rhabdomyolysis are listed in Box 5.3. Rhabdomyolysis has been thought to cause ATN through three mechanisms: renal vasoconstriction, intratubular cast formation, and heme-mediated proximal tubular injury. It is also known that oxidant stress is increased with the release of heme proteins. Free heme proteins are suspected of reducing the formation of nitric oxide and increasing endothelin levels, which results in vasoconstriction and the decline in GFR. Intratubular obstruction occurs with the interaction of myoglobin and Tamm–Horsfall protein in an aciduric environment.

To prevent and treat the ARF of rhabdomyolysis, aggressive hydration is effective. Alkalization of the urine has also been advocated to increase the solubility of the heme proteins in the urine, with the goal of achieving a urine pH >6.5. Alkalization may also reduce the production of reactive oxygen species, thus reducing the oxidant stress. Caution must be exercised when administering bicarbonate, since the resulting alkalemia can worsen the hypocalcemia often present in patients with severe rhabdomyolysis and precipitate generalized seizures. Some of bicarbonate’s salutary effect stem from its serving as a nonreabsorbed solute which promotes an osmotic diuresis. It is not known whether or not alkalinization of the urine is beneficial once a brisk diuresis is established with saline or diuretics.

Mannitol has also been advocated for the treatment of pigment nephropathy based on experimental models of myohemoglobinuric ARF. The protective effect has been attributed to its diuretic, renal vasodilatory, and hydroxyl scavenging properties. However, in a glycerol model of myoglobinuric ARF, mannitol’s protective effect could
be completely ascribed to a solute diuresis and increased heme excretion.\textsuperscript{152} Also, although mannitol is a potent renal vasodilator, it may actually worsen cellular energetics during the induction of ARF. If administered immediately after renal ischemia, renal cortical ATP levels may abruptly decline by increasing the metabolic cost of sodium reabsorption by the loop of Henle.\textsuperscript{151-153} Therefore, intravenous fluids or perhaps furosemide may be the preferable diuretic. If mannitol is used, it is essential to monitor serum osmolality to avoid a hyperosmolar state.

Because of its size, myoglobin removal by peritoneal dialysis or hemodialysis is poor, although a study by Amyot and colleagues suggests its clearance may be enhanced by continuous hemofiltration.\textsuperscript{154} In addition, myoglobin levels fall exponentially with cessation of muscular release due to hepatic and splenic uptake.\textsuperscript{155} It is also unclear whether or not myoglobin is a major contributor to the pathogenesis of rhabdomyolysis-induced ARF. Currently, there is no compelling evidence for the use of extracorporeal therapies in the treatment of myoglobinuric ARF.

\section*{Methotrexate}

Methotrexate (MTX)-induced ARF is caused by the precipitation of the drug and its metabolites in the tubular lumen and is also a tubular cytotoxin.\textsuperscript{137} High doses of MTX (>1 g/m\textsuperscript{2}) increase the risk of ARF. Once ARF develops, the excretion of MTX is reduced and the systemic toxicity of MTX is increased. Hydration and high urine output are essential to preventing MTX renal toxicity. Isotonic saline infusion and furosemide may be necessary to keep the urine output $>100$ ml/h. Alkalization of the urine to a pH $>6.5$ is also recommended, to decrease tubular precipitation and increase renal MTX clearance. Once ARF has developed, it may be necessary to remove the drug with dialysis. Hemodialysis using high blood flow rates with a high-flux dialyzer is an effective method of removing methotrexate.\textsuperscript{156} High-dose leucovorin therapy can reduce the systemic toxicity associated with MTX and ARF, and is routinely used when plasma levels are excessive 48 hours post-dose.\textsuperscript{157,158}

\section*{Tumor lysis syndrome}

Tumor lysis syndrome is often a dramatic presentation of ARF in patients with malignancy. It is characterized by the development of hyperphosphatemia, hypocalcemia, hyperuricemia, and hyperkalemia. Tumor lysis syndrome can occur spontaneously during the rapid growth phase of malignancies such as bulky lymphoblastomas and Burkitt's and non-Burkitt's lymphomas that have extremely rapid cell turnover rates.\textsuperscript{159} More commonly, it is seen when cytotoxic chemotherapy induces lysis of malignant cells in patients with large tumor burdens. Tumor lysis syndrome has developed in patients with non-Hodgkin's lymphoma, acute lymphoblastic leukemia, chronic myelogenous leukemia in blast crises, small cell lung cancer, and metastatic breast cancer.\textsuperscript{160} In most patients the ARF is reversible after aggressive supportive therapy including dialysis.

The pathophysiology of ARF associated with tumor lysis syndrome is related to two main factors: (1) pre-existing volume depletion prior to the onset of renal failure and (2) the precipitation of uric acid and calcium phosphate complexes in the renal tubules and tissue.\textsuperscript{161} Patients may be volume-depleted from anorexia or nausea and vomiting associated with the malignancy, or from increased insensible losses from fever or tachypnea. Therefore, it is important to establish brisk flow of hypotonic urine to prevent or ameliorate ARF associated with tumor lysis syndrome.

Hyperuricemia is either present before treatment with chemotheraphy or develops after therapy despite prophylaxis with allopurinol.\textsuperscript{162} Uric acid is nearly completely ionized at physiologic pH, but becomes progressively insoluble in the acidic environment of the renal tubules. Precipitation of uric acid causes intratubular obstruction, leading to increased renal vascular resistance and decreased GFR.\textsuperscript{163} Moreover, a granulomatous reaction to intraluminal uric acid crystals and necrosis of tubular epithelium can be found on biopsy specimens.

Hyperphosphatemia and hypocalcemia also occur in tumor lysis syndrome. In patients who do not develop hyperuricemia in tumor lysis syndrome, ARF has been attributed to metastatic intrarenal calcification or acute nephrocalcinosis.\textsuperscript{164} Tumor lysis with release of inorganic phosphate causes acute hypocalcemia and metastatic calcification, resulting in ARF.

Therefore, ARF associated with tumor lysis syndrome is the result of the combination of volume depletion in the face of urinary precipitation of uric acid in the renal tubules and parenchyma, and acute nephrocalcinosis from severe hyperphosphatemia. Since patients at risk for tumor
ysis often have intra-abdominal lymphoma, urinary tract obstruction can be a contributing factor in the development of ARF. Given the aforementioned pathogenetic factors for ARF, patients who are undergoing treatment with malignancies who are likely to experience rapid cell lysis should receive vigorous intravenous hydration to maintain good urinary flow and urinary dilution. In addition, because uric acid is very soluble at physiologic acid urine pH, sodium bicarbonate should be added to the intravenous fluid to achieve a urinary pH >6.5. Since metabolic acidosis can aggravate hypocalcemia, caution should be exercised when using alkali in patients with low serum calcium levels. It is advisable to stop the infusion if the serum bicarbonate level is >30 mEq/L. Furthermore, it is conceivable that the use of urinary alkalinization to prevent uric acid nephropathy might actually precipitate or worsen calcium phosphate-induced ARF. Allopurinol is administered to inhibit uric acid formation. Through its metabolite oxypurinol, allopurinol inhibits xanthine oxidase and thereby blocks the conversion of hypoxanthine and xanthine to uric acid. During massive tumor lysis, uric acid excretion can still increase despite the administration of allopurinol, so that intravenous hydration is still necessary to prevent ARF. Since allopurinol and its metabolites are excreted in the urine, the dose should be reduced in the face of impaired renal function. Uricase has been recently approved for use in the United States. It converts uric acid to water-soluble allantoin, thereby decreasing serum uric acid levels and urinary uric acid excretion. The use of uricase may obviate the need for urinary alkalinization, but good urine flow with hydration should be maintained given the probability of pre-existing volume depletion.

Dialysis for ARF associated with tumor lysis syndrome may be required for the traditional indications of fluid overload, hyperkalemia, hyperphosphatemia, or hyperuricemia unresponsive to medical management. There is some interest in using dialysis in patients at high risk of tumor lysis syndrome to prevent the development of renal failure. In a small trial involving five children, continuous hemofiltration was started prior to administration of chemotherapy and appeared to prevent renal failure in 80% of the patients. However, given that continuous dialysis is complicated, expensive, and not without risk, its routine use as prophylaxis cannot be recommended.

Liver failure, bacterial peritonitis, and hepatorenal syndrome

Spontaneous bacterial peritonitis (SBP) is a common and severe disorder in patients with liver cirrhosis and ascites. In one-third of patients, renal impairment develops despite treatment of the infection with non-nephrotoxic antibiotics. Development of renal failure is the best predictor of hospital mortality in these patients and is thought to result from a decrease in the effective arterial blood volume caused by sepsis. In a randomized trial of 126 patients with SBP, administration of albumin plus antibiotics compared to antibiotics alone significantly decreased the incidence of renal impairment, in-hospital mortality, and 3-month mortality. This study was not blinded, potentially introducing bias, and the quantity of albumin used was substantial, leading to significant cost. Also, there was no 'hydration' arm in the antibiotic-only group that would provide proof of the superiority of albumin over crystalloid solutions. However, these encouraging results will probably lead to further clinical investigations.

Hepatorenal syndrome (HRS) is a unique cause of renal vasoconstriction, with a decline in GFR in the face of normal renal histology that occurs in the setting of liver failure. The clinical picture associated with HRS is that of prerenal azotemia with oliguria and low FENa (urinary fractional excretion of sodium). In true HRS without confounding renal injuries, the renal failure will resolve with liver transplantation. The pathogenesis of HRS is incompletely understood. Systemic and splanchnic vascular resistance is decreased, leading to a decrease in the effective arterial blood volume and renal hypoperfusion. The compensatory hemodynamic response to systemic vasodilation includes an increase in the mediators of renal vasoconstriction, including increased renin-angiotensin–aldosterone activity, antidiuretic hormone (ADH) levels, sympathetic tone, and endothelin levels. The renal response is an increase in salt and water avidity, leading to worsening ascites and edema. Liver transplant is the definitive therapy for HRS. However, patients who develop HRS prior to transplant have worse graft and patient survival.

Newer pharmacologic therapy with vasopressin analogs (e.g. oripressin and terlipressin), which are splanchnic vasoconstrictors, has shown some benefit. Oripressin and albumin was administered to a total of 16 patients with HRS for either 3 or 15 days (8 patients in each group). The 3-day
regimen was associated with a normalization of the overactivity of renin–angiotensin and sympathetic nervous systems, ANP levels, and only a slight improvement in renal function. However, treatment for 15 days resulted in improved serum creatinine levels, renal plasma flow, and glomerular filtration rate. Similar results were seen in 9 patients who received intravenous terlipressin. However, a major complication associated with these medications is mesenteric ischemia. Oral midodrine (a selective α₁-adrenergic agonist) in combination with octreotide also showed benefit in renal function in a small series of patients. Mucomyst given intravenously to 12 patients increased RBF without changing the hemodynamic derangements associated with HRS. Several small studies have shown that transjugular intrahepatic portosystemic shunting (TIPS) has prolonged survival and improved renal function in patients with HRS. Firm conclusions about efficacy of these therapies await the results of randomized controlled trials.

**Renal transplantation**

Acute renal failure remains a common complication of renal transplantation. It may occur at any time point in the life of the transplant, although it usually develops in the immediate postoperative period and is referred to as delayed graft function. The causes of delayed graft function are listed in Box 5.4, and include obstruction, volume depletion, and acute rejection, although the most common etiology remains ischemic ATN. Risk factors for ATN are advanced donor age, intraoperative or postoperative hypotension, prolonged warm or cold ischemia times, and initial high CSA dosage. Reperfusion injury as a result of direct endothelial trauma, oxygen free-radical generation, and neutrophil activation also contributes to the development of ATN.

Patients with delayed graft function have longer hospitalization rates and more complications, including a lower 5-year graft survival rate. Therefore, prevention of ischemic ATN in the post-transplant setting may prolong renal survival. As in all patients at risk for the development of ischemic ATN, optimization of hemodynamic parameters in both recipient and donor is a key element and may require monitoring of central venous pressures; Carlier and colleagues showed that higher wedge pressures at the time of renal allograft revascularization were associated with improved early graft function. Some studies have suggested that intraoperative administration of mannitol decreases the incidence of ATN. Decreasing warm and cold ischemia times should also decrease the occurrence of post-transplant delayed graft function. The use of the University of Wisconsin preservation solution during cold ischemia reduces the incidence of delayed graft function. Renal vasodilators such as low-dose dopamine and fenoldopam, IGF-1, and ANP have not shown significant benefit in small clinical trials. As previously discussed, although CCBs reverse CSA vasoconstriction and prevent ischemic injury in animal models, the benefit in clinical trials has been inconsistent. Current clinical trials aimed at lessening reperfusion injury by blocking adhesion molecule interactions are ongoing.

**Postoperative states**

Many critically ill patients who undergo surgery will go on to develop ARF, and a large proportion of these will require renal replacement therapy. In addition to the traditional risk factors for ARF present in any critically ill patient, the surgical patient may be exposed to the potentially harmful effects of cardiopulmonary bypass, hypothermic circulatory arrest, or aortic crossclamp. The most common cause of ARF in the surgical setting is

<table>
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<tr>
<th>Box 5.4 Causes of delayed graft function in renal transplant</th>
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<tr>
<td><strong>Prerenal</strong></td>
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<tr>
<td>Hypovolemia</td>
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<td>Renal artery thrombosis</td>
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<td><strong>Renal</strong></td>
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<td>Ischemic ATN</td>
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<td>Hyperacute rejection</td>
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<td>Acute rejection</td>
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<td>Acute calcineurin nephrotoxicity</td>
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<td><strong>Postrenal</strong></td>
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<td>Urinary leak</td>
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<td>Ureteral necrosis</td>
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ischemic ATN that occurs in the face of critical illness and MODS. Often, there has been a preceding period of relative renal hypoperfusion from either true or effective volume depletion.

Risk assessment

In terms of risk assessment and characterization, there are no specific scoring systems that can predict accurately who will develop postoperative organ dysfunction. The American Society of Anesthesiologists (ASA) scoring system is among the simplest and most reproducible general risk assessment tools. It stratifies patients into high-, moderate-, or low-risk categories but does not specify the actual type of harm. Several studies have demonstrated that the presence of pre-existing renal disease, CHF, obstructive jaundice, diabetes mellitus, peripheral vascular disease, hypertension, and coronary artery disease are all risk factors for developing postoperative ARF. This observation suggests that patient-related factors have a significant impact on the development of postoperative complications. In addition, overall risk can be thought of as having both genetic and environmental components. The environmental risk consists of the nature of the planned operation, its urgency, and the surgical skill of the personnel involved. The environmental risk further entails those unpredictable events such as catastrophic intraoperative hemorrhage and technical errors. Genetic risk is subtle and has only recently become recognized as important. The field of the genetics of complex-trait diseases is evolving, and the best tools for its analysis are still under debate. Currently, how genetic variability affects an individual's response to underlying illness, injury, treatment, and drug therapy is poorly defined. However, genetic variability probably has some effect on both the risk of developing a postoperative complication and on the response of the individual to its treatment.

Certain operations carry a higher risk for ARF because of the nature of the surgical procedure and the underlying medical condition of patients requiring the surgery. Patients undergoing surgery for either traumatic or thermal injuries are at high risk for ARF. The ARF is usually multifactorial in nature, with ischemia, rhabdomyolysis, nephrotoxins, and sepsis all having a contributory role.

Cardiac surgery requiring cardiopulmonary bypass (CPB) may cause some degree of renal dysfunction in up to 50% of patients. Cardiopulmonary bypass is a state of hypotension that triggers release of several renal vasoconstrictor agents, resulting in renal hypoperfusion. Although overt ARF may develop in less than 5% of patients with normal preoperative renal function, tubular enzynuric suggests that subclinical injury is much more common. Preoperative left ventricular dysfunction and time on CPB increase the risk of ARF. The type of CPB (pulsatile or nonpulsatile) and bypass pressure do not appear to be significant factors in determining renal outcome.

Vascular surgery, particularly when cross-clamping the aorta is required, is associated with a higher incidence of postoperative ARF. The best predictors of ARF are pre-existing renal insufficiency and hemodynamic instability during surgery.

Preoperative period

In general terms, the predisposition to a prerenal state can often be avoided by an overnight intravenous fluid infusion. Surgical patients are typically starved overnight, and administration of a bowel preparation routine can compound the volume depletion. Intravenous fluid administration is a simple means of preventing the development of a prerenal state from hypovolemia.

More specific therapies begun preoperatively to prevent postoperative ARF have not been proven effective. In part, because the incidence of postoperative ARF is low, large numbers of patients would need to be randomized in order to either demonstrate a positive effect, or to conclusively show such an effect does not exist. This problem has plagued ARF clinical research in general, and the surgical setting has been no exception. As previously detailed, various trials using low-dose dopamine, the diuretics furosemide and mannitol, growth factors, and ANP have failed to decrease the incidence of ARF. Small trials suggest that preoperative administration of fenoldopam mesylate and N-acetylcysteine may decrease the development of postoperative ARF, but these require larger confirmatory effectiveness trials. However, to date, there are no large, randomized controlled clinical trials examining these agents in the operative setting.

Recently, studies have been published suggesting that for those patients with chronic renal impairment a period of elective renal replacement therapy may subsequently improve both renal and overall outcome. In a single study of 44 patients with chronic renal failure (mean serum creatinine level of 3.3 mg/dl) undergoing coronary artery
bypass grafting (CABG) and CPB, randomization to prophylactic hemodialysis appeared to decrease mortality, hospital and ICU length of stay, and the incidence of postoperative ARF compared to standard care. However, the study was small and details of medical therapy in the nondialysis arm (such as the use of ACE inhibitors, diuretics, and fluid balance) were not described. Furthermore, it is difficult to explain the benefits based on any sound physiologic principle. If frank fluid overload, which should have prompted therapeutic dialysis, was not present in these patients, then it is hard to explain how limited small solute clearance would decrease mortality or the incidence of postoperative ARF. In fact, there is good evidence that hemodialysis can prolong or perpetuate ARF by triggering ischemia or inflammation. In an uncontrolled cohort study of patients on chronic hemodialysis, intensive dialysis prior to cardiothoracic surgery in 13 consecutive patients resulted in similar postoperative outcomes compared to patients with normal renal function. Both of these studies probably demonstrate that in renal failure patients, aggressive management of fluid overload and electrolyte imbalances results in better postoperative outcomes. However, proof that dialysis is superior to medical management will depend on the results of large, randomized controlled clinical trials.

**Intraoperative period**

Most anesthetic agents cause dose-dependent venous and arterial vasodilatation, with an accompanying reduction in cardiac pre- and afterload. Hypotension may be exacerbated by neural impairment from spinal or epidural blockade. A mild reduction in blood pressure leads to less bleeding and is usually well tolerated, since anesthetic agents generally also reduce oxygen demand. Typically, crystalloid or colloid solutions are administered to expand the intravascular space in response to the mild drop in blood pressure that almost universally accompanies induction of anesthesia. A urine output of 1–2 ml/kg/h during surgery is considered evidence of adequate organ perfusion, although adequate urine output certainly does not preclude the presence of renal hypoperfusion and ischemia. Hemodynamic monitoring, including central venous pressure (CVP), cardiac index, systemic vascular resistance, and pulmonary artery occlusion pressure, is often used in critically ill patients. However, the ideal blood pressure, cardiac output, vascular tone, and intravascular volume for patients undergoing major surgery are not known because of a lack of appropriate studies. No studies have proven that intensive hemodynamic monitoring improves outcome. In fact, some studies actually suggest that the use of pulmonary artery catheters is associated with worse outcome. For now, interventions that maximize the chance of good renal outcome include avoidance or treatment of hypoxemia, hypercarbia, hypotension, hyperglycemia, and anemia.

**Postoperative period**

Immediately after surgery, the emphasis on prevention of ARF shifts away from monitoring the minute-to-minute changes in hemodynamics to observation for bleeding, organ hypoperfusion, infection, and coagulation complications. Hypoxemia may arise from shunting through atelectatic areas of lung, or hypoventilation from narcotic analgesics or residual neuromuscular blockade. Impaired oxygen delivery can exacerbate any reduction in cardiac output, leading to decreased renal perfusion. Large fluid shifts may accompany major surgery and can manifest as severe anemia, electrolyte disturbances, acid-base abnormalities, or changes in cognition.

Later in the postoperative course, the greatest risk is posed by the development of severe sepsis syndrome, which can cause postoperative ARF from ischemic ATN. Sepsis induces vascular endothelial changes, organ and tissue ischemia, cellular apoptosis and necrosis, as well as coagulation abnormalities that exacerbate and accelerate the pathologic process. To date, activated protein C has been the only agent administered to critically ill surgical patients that has significantly improved survival rates in the ICU.

**Abdominal compartment syndrome**

Abdominal compartment syndrome (ACS) was first reported in 1876, in a paper describing the reduction in urine flow associated with elevated intra-abdominal pressure (IAP). Acute increases in IAP are deleterious for both intra-abdominal and distant organ function, including the kidneys. Acutely, the abdomen functions as a closed space; thus, any increase in the volume of its contents leads to a rise in compartmental pressure. Intra-abdominal hemodynamics are compromised when the IAP approaches and then exceeds 10 cmH₂O. ACS is present when the IAP reaches 20–25 cmH₂O, and unless decompressed,
irreversible organ failure may result. ACS is characterized by an acute rise in IAP, coupled with evidence of organ dysfunction, usually reduced urine output. The pathogenesis of this reduction in urine formation is complex and attributed to three major factors:

1. Compression of the great veins reduces venous return to the right heart, which manifests as relative hypovolemia and can become frank volume depletion if third spacing of fluid is extensive. Increased renal venous back pressure associated with high CVP may cause renal vein compression.

2. Direct pressure on the renal cortex can shunt blood away from the vulnerable cortico-medullary junction by altering renal vascular resistance and induce an ischemic injury in this area.

3. Direct pressure on the ureters can lead to obstructive nephropathy, particularly if there is a predisposing condition such as extensive lymphadenopathy.

Regardless of the underlying cause, a reduction in urine output ± azotemia in the presence of a measured IAP over 15 cmH₂O is certainly cause for concern and should prompt intervention. IAP can be measured in a number of ways, although the transvesical method is the most commonly used. In this technique, 50–100 ml of sterile saline solution is instilled through the bladder catheter into the bladder and the drainage port then clamped distal to the sampling port. A conventional pressure monitoring line is then attached by hypodermic needle through the sampling port and the pressure measured directly, with the symphysis pubis taken as the zero reference point. This technique is straightforward, reliable, simple, and reproducible. An estimate of IAP can also be obtained by elevating the bladder catheter above the bed, since the pressure of urine in the bladder will then equilibrate with that in the tubing. This method represents a simple screening tool, and thus should be used in any patient who may be at risk of ACS.

The causes of an increased IAP are listed in Box 5.5. ACS should be managed with attention to preservation of underlying organ function, and is usually treated with urgent surgical decompression. Clearly, this is a highly complex situation and skilled surgical supervision is mandatory if the patient is ultimately to do well.

**Multisystem trauma**

Although the incidence of ARF following major trauma is generally low, it is associated with a high mortality rate. Opinion has varied as to whether pre-existing medical conditions such as diabetes and hypertension are more important risk factors than the timeliness and type of resuscitation. Mechanical ventilation with high PEEP (positive end-expiratory pressure), hemoperitoneum, and rhabdomyolysis have been identified as the three conditions most strongly associated with ARF after major trauma. Rhabdomyolysis may be caused by extensive skeletal muscle damage and worsened by subsequent infection, fever, drugs, and electrolyte abnormalities. The degree of elevation of serum creatine kinase is usually proportional to the extent of the muscle injury. Acute renal failure develops in rhabdomyolysis because of tubular obstruction, oxidant injury, and renal vasoconstriction, and thus preventive measures have been largely aimed at promoting tubular flow and restoring renal perfusion. The single most important feature of ARF prevention is volume expansion. Alkalinization of the urine is usually recommended also, since this improves myoglobin washout, prevents lipid peroxidation, and minimizes renal vasoconstriction. The use of mannitol is controversial. Although it has theoretic benefits such as reduced compartment pressure and cellular swelling, and mild antioxidant properties, it has not been shown to produce results superior to those of volume expansion alone.

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**Box 5.5 Causes of Increased Intra-abdominal pressure**

- Peritoneal tissue edema (trauma, peritonitis)
- Fluid overload in shock
- Retroperitoneal hematoma
- Surgical trauma
- Reperfusion injury after bowel ischemia
- Pancreatitis
- Ileus or obstruction
- Abdominal packing to control hemorrhage
- Abdominal closure under tension
- Severe ascites
SUMMARY

Acute renal failure as a result of ATN is a common development in critically ill medical and surgical patients that is associated with significant morbidity and mortality. Despite improvements in the understanding of the pathophysiologic mechanisms of ARF and the numerous agents effective in treating ARF in animal models, there are currently no effective treatments for ATN in human subjects. Therefore, prevention of ARF remains the best way to improve renal dysfunction-related outcome in the ICU. To date, most specific pharmacologic agents used to prevent ARF have been proven ineffective in clinical trials. Until further data is available, it seems that simple measures such as maintaining adequate renal perfusion, avoiding excessively aggressive diuresis and nephrotoxins, and monitoring levels of potentially nephrotoxic drugs are important goals in the care of the critically ill patient.

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