Prevention of Acute Renal Failure in the Critically Ill

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Acute renal failure (ARF) is a common problem in the intensive care unit (ICU). Even modest degrees of acute renal failure not resulting in dialysis treatment increase the risk of death approximately fivefold (1). Prerenal azotemia and acute tubular necrosis (ATN) are the most frequent causes of ARF in the critically ill. ATN can be thought of as intrinsic renal disease that is not caused by either acute glomerulonephritis or acute interstitial nephritis and can be distinguished from prerenal azotemia by its failure to resolve with augmentation of renal perfusion. Although ATN and renal hypoperfusion lie along a continuum, and ATN may result from a severe or protracted course of a prerenal state, there often appears to be important synergy in exposure to both hypoxic and toxic insults in the development of ATN. Despite intensive investigation into the pathophysiology of ATN, there has been remarkably little translation into effective preventive strategies. This article reviews the currently available treatments used in the prevention of ARF in the setting of cardiovascular surgery, sepsis, rhabdomyolysis, radiocontrast exposure, and cirrhosis. The role of renal replacement therapy was the subject of a prior update in the *American Journal of Respiratory and Critical Care Medicine* (2) and is not covered in this review.

CARDIAC AND VASCULAR SURGERY

The incidence of ARF after cardiac surgery may approach 30%. A recent cohort study found a 1.1% incidence of ARF requiring dialysis; this was associated with a mortality of 63.7%, versus 4.3% in those patients not requiring dialysis (3). Abdominal aortic and thoracoabdominal aortic surgery are associated with an incidence of oliguric renal failure of 2 to 7% and 15 to 50%, respectively, and mortality rates of 50 to 90% (4). The pathogenesis of ARF in these settings is believed to be predominantly a consequence of renal hypoperfusion and ischemia, particularly of the renal medulla. Therefore, preventive strategies have focused on methods that may augment renal perfusion or reduce renal oxygen consumption.

Low-dose dopamine is known to result in renal artery dilatation, natriuresis, and diuresis. This is mediated, at least in part, by activation of the DA-1 receptor. Low-dose dopamine continues to be widely used to protect against ARF and ameliorate established ARF. In a small randomized, controlled trial of patients undergoing major vascular surgery, dopamine at 3 μg/kg/min had no effect on the eventual development of ARF or survival (5). Similarly, in a randomized, controlled trial in patients undergoing cardiac surgery, there was no effect of low-dose dopamine on either renal function or mortality (6).

Diuretics, including mannitol and furosemide, have been advocated as preventive agents in the setting of cardiovascular surgery. This is based on their potential ability to decrease renal oxygen consumption and to prevent the accumulation of intraluminal debris that may cause obstructing casts. Mannitol may have the additional property of scavenging free oxygen radicals. Conger reviewed the available clinical data regarding the prophylactic use of mannitol in nontransplant surgery and found no evidence to support its use (7). In a small study of cardiac surgery patients, prophylactic use of furosemide infused at 0.5 μg/kg/min was associated with significant worsening of renal outcome compared with placebo (6).

Atrial natriuretic peptide (ANP) is a potent diuretic and natriuretic substance that can increase glomerular filtration rate (GFR), reverse renal vasoconstriction, and block sodium reabsorption. In 11 patients who developed ARF after cardiac surgery, a 48-h infusion of ANP was found to improve renal blood flow and GFR (8). None of the patients required dialysis, and hemodynamic measurements were similar both during and after ANP infusion, suggesting that the hypotensive effect of the medication can be safely managed.

Unfortunately, there is currently no established pharmacologic intervention to prevent renal failure in cardiovascular surgery patients. As intravascular volume depletion is believed to exacerbate renal hypoperfusion and accentuate the risk for postoperative ARF, close attention to volume status is important. The use of dopamine as a prophylactic agent should be abandoned, and its use should be limited to those settings in which it will exert a desirable hemodynamic effect. Likewise, the use of furosemide should be limited to those circumstances in which the induction of diuresis is desirable. The role of mannitol should be more limited and probably confined to the circumstance of rhabdomyolysis. It is important to note that although dopamine, furosemide, and mannitol can induce diuresis and convert an oliguric state to a nonoliguric state, and this may facilitate fluid and electrolyte management, there remains an absence of evidence that this conversion is associated with a mortality benefit. Further investigation of the effect of ANP is warranted, but there is insufficient evidence at present to support its routine use.

SEPSIS

Sepsis is a frequent cause of ARF and is associated with a worse prognosis than other causes. Although a variety of pathophysiologic changes occur in sepsis, the relative importance of hypotension, reduced cardiac output, abnormalities in intrarenal blood flow distribution, and impaired cellular oxygen utilization remains unclear.

It is generally accepted that optimization of systemic and renal perfusion is important in the management of patients with sepsis, but unfortunately, what constitutes optimal hemodynamics remains largely undefined. A variety of vasoactive

(*Received in original form June 20, 2001; accepted in final form October 17, 2001*)

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Am J Respir Crit Care Med Vol 165. pp 320–324, 2002
DOI: 10.1164/rccm2106086
Internet address: www.atsjournals.org

drugs, including dopamine, have been administered to patients with sepsis. Low-dose dopamine has been widely used in patients with sepsis for many of the same reasons it has been used in surgical patients. Patients with sepsis have demonstrated transient improvements in renal blood flow and GFR with low-dose dopamine, but the effects tend to dissipate by 48 h. A review of the nonrandomized use of low-dose dopamine in 395 oliguric, septic patients found no difference in the mortality or need for dialysis (9). A recent randomized controlled trial examined the effect of low-dose dopamine (2 μg/kg/min) in over 300 medical and surgical patients with systemic inflammatory response syndrome (SIRS) and early renal dysfunction (oliguria or increase in creatinine concentration). In this large, multicenter study, there was no effect of low-dose dopamine on renal function, need for dialysis, ICU or hospital length of stay, or mortality (10). Although vasoactive agents other than dopamine are commonly used in the management of sepsis, very few clinical studies have examined their effect on renal function in sepsis. In a nonrandomized study of 56 patients with sepsis and hypotension, the addition of norepinephrine to low-dose dopamine was associated with an increase in the mean creatinine clearance from 75 to 102 ml/min (11). Finally, in a large, multicenter study, therapy (volume expansion and vasoactive drugs) aimed at achieving supranormal values for the cardiac index or normal values for the mixed venous oxygen saturation had no effect on the frequency or severity of renal dysfunction (12).

In a study of 504 critically ill patients with ATN, there was no effect of a 24-h infusion of anaritide, a synthetic ANP, on dialysis-free survival (13). However, subgroup analysis demonstrated that in patients with oliguria, treatment with anaritide was associated with 27% dialysis-free survival compared with only 8% in the placebo group. Nonoliguric patients fared slightly worse in the anaritide group with a dialysis-free survival of 48% versus 59% in the control group. Another study of 222 oliguric patients with ATN treated with anaritide for 24 h found a nonsignificant trend toward improvement in 14-d and 21-d dialysis-free survival in the anaritide group, but 60-d mortality rates were similar (14). Hypotension occurred significantly more frequently in the anaritide group. This study was criticized for using a time-limited infusion of anaritide at an excessive rate, thereby leading to hypotension and possibly compromising its efficacy.

Free oxygen radical injury is believed to be an important component of SIRS, and selenium-dependent glutathione peroxidase is one of the main free radical scavenging systems. The role of selenium deficiency and replacement was explored in a randomized trial of 42 ICU patients diagnosed with SIRS whose mean selenium levels were approximately 40 to 50% of the normal values (15). In the group assigned to receive repletion with intravenous sodium selenite, the mean creatinine concentration was significantly lower and only 3 of the 21 patients required continuous venovenous hemodialysis, compared with 9 of the 21 control patients. Mortality was also reduced in the selenium repleted group, particularly in those with the highest Acute Physiology and Chronic Health Evaluation III (APACHE III) scores (36% versus 89%). No side effects of the selenium repletion regimen were recognized. Because the investigators found an increase in the activity level of selenium-dependent glutathione peroxidase, one possibility is that selenium may exert its effects by improving the ability of patients with SIRS to cope with toxic free radical species.

Treatment of Infection

Aminoglycosides are well-recognized nephrotoxins that are often used in the treatment of serious gram-negative infections. The incidence of ARF with aminoglycoside therapy varies with the definition used, but ranges from 5 to 25%. The accumulation of drug in renal tubular epithelial cells appears to be an important pathophysiologic mechanism, but alterations in renal plasma flow may also occur. Renal hypoperfusion or acute renal ischemia clearly predisposes to aminoglycoside nephrotoxicity. Careful monitoring of drug levels has been a disappointing strategy in the prevention of nephrotoxicity, as trough levels do not begin to rise until substantial renal injury has already occurred. Prins and colleagues found that compared with conventional thrice-daily dosing, once-daily aminoglycoside dosing resulted in a marked reduction in the incidence of ARF (defined as an increase in serum creatinine of 0.5 mg/dl) from 24% to only 5% (16). Two recent meta-analyses subsequently demonstrated nonsignificant trends toward less nephrotoxicity, with relative risks of ARF of 0.74 to 0.87. Equal clinical and microbiologic efficacy have been consistently demonstrated (17, 18).

Although newer antifungal agents such as fluconazole and itraconazole have narrowed the indications for amphotericin B, and additional new agents appear on the horizon, amphotericin B remains the antifungal agent of choice for some patients with suspected or proven invasive fungal infections. Salt loading ameliorates amphotericin B nephrotoxicity (19), but significant renal dysfunction still occurs and sometimes limits its use. The toxicity and efficacy of liposomal or lipid complexed amphotericin B have been studied in patients with persistent neutropenic fever or hematologic malignancies, including critically ill bone marrow transplant patients. In a randomized trial of liposomal amphotericin B versus conventional amphotericin B in patients with sustained neutropenic fever, ARF, defined as either a doubling of serum creatinine or a level greater than 3 mg/dl, occurred in only 12% of patients treated with liposomal amphotericin B versus 26% in the conventional group (20). Clinical efficacy was the same in both groups.

To summarize, in the setting of sepsis, optimization of renal perfusion is perhaps the most current renal preservation strategy. Although there is as yet unsettled controversy about the role of colloids versus crystalloids in fluid resuscitation, a recent study found that in patients with severe sepsis, the use of hydroxyethylstarch was associated with a significantly higher risk of ARF than gelatin (a colloid available in Europe) (21); whether crystalloids are also associated with a lower risk of ARF than hydroxyethylstarch is unknown. If aminoglycoside use is necessary, once-daily dosing may reduce the incidence of renal toxicity without compromising efficacy. Likewise, liposomal amphotericin B, though much more expensive (e.g., pharmacy cost at our institution for an "average daily dose" is roughly $3 for amphotericin B and $300 for liposomal amphotericin), should be considered for patients with preexisting or acquired renal failure or those facing a prolonged treatment course. Finally, although much larger studies are warranted, the repletion of selenium levels should be considered for selenium-deficient patients with SIRS.

RHABDOMYOLYSIS AND MYOGLOBINURIC RENAL FAILURE

Rhabdomyolysis and myoglobinuria occur in several clinical settings, including trauma, arterial thrombosis, prolonged seizures, and drug toxicity. In animal models of myoglobinuria, volume depletion and an acidic urine pH predispose to the development of ARF, whereas volume repletion, high urine flow rates, and an alkaline pH are protective. These experimental observations form the basis for the management of myoglobinuria in humans. In a retrospective study of 20 patients with

myoglobinuria, all of whom had oliguria and azotemia despite the correction of volume deficits, the administration of mannitol and sodium bicarbonate was associated with increases in urinary output and prompt resolution of renal failure (22). Ward examined 157 patients with both traumatic and nontraumatic rhabdomyolysis, and analyzed factors predictive for the development of ARF (23). Multivariate analysis revealed that the presence of dehydration on presentation was an independent risk factor for ARF. More recently, Homsi and coworkers performed a retrospective analysis of 24 patients with rhabdomyolysis admitted to an ICU, 15 of whom were treated with saline, mannitol, and sodium bicarbonate, and the remainder with saline alone (24). There were no significant differences between the two treatment groups in the evolution of the serum creatinine, leading the investigators to suggest that mannitol and bicarbonate are unimportant components of therapy.

Unfortunately, there are no randomized, controlled clinical trials on which to base management decisions, and many of the uncontrolled trials of prophylaxis against myoglobinuric renal failure have involved small numbers of patients. Patients with rhabdomyolysis should undergo prompt and aggressive volume resuscitation, particularly in patients with traumatic rhabdomyolysis in whom the requirement for crystalloid may be quite large. We favor urinary alkalinization with bicarbonate containing intravenous fluids and the administration of mannitol (after adequate volume resuscitation) in patients with severe rhabdomyolysis. Although the efficacy of bicarbonate and mannitol administration remains unproven, animal studies support their use, and in the absence of complicating factors such as severe hypokalemia and hypocalcemia, the risk of treatment with these agents in this setting is low.

CONTRAST-INDUCED ARF

Radiographic contrast agents are one of the leading causes of hospital-acquired ARF. The pathogenesis of contrast-induced renal failure is uncertain, but is thought to involve renal vasoconstriction; adenosine may play a particularly important role in mediating the response. Although the incidence of contrast-induced renal failure in the ICU is unknown, critically ill patients frequently undergo a variety of diagnostic studies that involve the administration of radiographic contrast agents.

Solomon and colleagues studied the effects of saline, mannitol, and furosemide on renal function in 78 patients with a mean baseline creatinine concentration of 2.1 mg/dl who underwent cardiac angiography (25). All patients, including those in the mannitol and furosemide groups, underwent hydration with 0.45% saline for 12 h before and 12 h after angiography. In the saline group, 11% of the patients had a rise in creatinine of at least 0.5 mg/dl, whereas 28% of the mannitol group and 40% of the furosemide group had such an increase in the serum creatinine. Thus, in this study, hydration with saline alone provided better protection against contrast-induced ARF than did hydration with saline plus mannitol or furosemide.

In a recent study of 83 patients with a mean creatinine concentration of 2.4 mg/dl, the addition of the oral antioxidant acetylcysteine to intravenous saline reduced the frequency of contrast-induced renal failure (26). In this study, the acetylcysteine was given orally at a dose of 600 mg twice daily on the day before and on the day of administration of the contrast. One of the 41 patients in the acetylcysteine group and nine of the 42 patients in the control group had an increase of at least 0.5 mg/dl in the serum creatinine concentration. None of the patients required dialysis.

Numerous other agents have been examined for their ability to prevent contrast-induced decreases in renal function. Most have been the subject of only a small number of studies. Table 1 provides an overview of selected treatment regimens.

There are several difficulties in applying the results of these studies to the care of the critically ill. First, almost all of the studies performed to date have involved stable patients undergoing elective radiographic procedures. Many of the studies included patients with mild to moderate chronic renal insufficiency, but none of the studies included patients with acute decreases in renal function, multiple organ failure, or other acute, life-threatening illnesses. It is unknown whether factors related to critical illness modify the effect of any of the aforementioned prophylactic regimens on the incidence of contrast-induced renal failure. Second, although a variety of prophylactic regimens have been studied, there have been few studies comparing the relative efficacy of different regimens, and virtually no studies employing multiple prophylactic strategies in combination. Third, the clinical significance of the protective effect afforded by most regimens is unknown. In most cases, the magnitude of the effect was modest—the difference in the change in creatinine concentration between the treatment and control groups was often on the order of 0.5 mg/dl or less, and the changes in renal function were most often an asymptomatic laboratory finding. Fourth, in critically ill patients, many radiographic studies involving the administration of contrast are done on an urgent or emergent basis, which may not provide sufficient time for the prophylactic regimens described previously.

Despite the lack of studies in the critically ill, we think the following is a reasonable approach to the prevention of contrast-induced renal failure in critically ill patients. The correction of any volume deficits is of paramount importance and should be accomplished as rapidly as possible before the administration of contrast. Mannitol and furosemide increase urinary output but do not reduce the risk of worsening renal function; their use should be avoided in this setting. Acetylcysteine is an inexpensive treatment (pharmacy cost at our institution is only $4 per 600 mg dose) with generally mild adverse effects. Although its efficacy has not been demonstrated in the critically ill, its use should be considered, particularly in patients with some degree of renal insufficiency. The remaining treatment options outlined in Table 1 involve greater expense or potential for adverse effects, or both, and cannot be recommended at this time.

LIVER DISEASE

Patients with cirrhosis are particularly prone to the development of impaired renal function, which confers a poor prognosis. In some patients, a discrete precipitating event, such as spontaneous bacterial peritonitis (SBP), can be identified. Sort and colleagues examined the effect of albumin administration on renal function in 126 patients with SBP (27). In this randomized study, patients were treated with either cefotaxime and intravenous albumin or cefotaxime alone. The patients in the cefotaxime plus albumin group received albumin at a dose of 1.5 g/kg at the time of diagnosis, and 1 g/kg on treatment Day 3. Renal impairment, defined by the study investigators as a greater than 50% rise in blood urea nitrogen or creatinine, occurred in 33% of the patients treated with cefotaxime alone, but in only 10% of the patients receiving both cefotaxime and albumin. The administration of albumin was also associated with a significant reduction in mortality.

In some patients with advanced cirrhosis, renal failure occurs in the absence of identifiable precipitants such as hypovolemia, infection, or treatment with nephrotoxic drugs. These patients are said to have hepatorenal syndrome (HRS),

TABLE 1. MISCELLANEOUS AGENTS USED IN THE PREVENTION OF CONTRAST-INDUCED ACUTE RENAL FAILURE

Treatment	Rationale	Reference	Study Population	Effect of Treatment
Dopamine	Increases renal blood flow	Hans *et al.* (34)	55 patients with baseline mean creatinine 1.9 mg/dl undergoing arteriography	Dopamine prevented slight rise in creatinine and slight decrease in GFR
Theophylline	Adenosine antagonist	Kolonko *et al.* (35)	58 patients with normal renal function	Small, transient drop in GFR and rise in creatinine that occurred in placebo group was prevented by theophylline
Atrial natriuretic peptide	Protects against contrast-induced renal failure in animal studies	Kurnik *et al.* (36)	247 patients with mean creatinine 2.1 mg/dl undergoing elective radiographic study	No effect on incidence of contrast-induced renal failure
Captopril	Blunts contrast-induced vasoconstrictor response	Gupta *et al.* (37)	71 diabetic patients undergoing coronary angiography	Mean rise in creatinine of 0.2 mg/dl in control group; no change in captopril group
Prostaglandin E_1	Exerts vasodilatory effect	Koch *et al.* (38)	117 patients with mean baseline creatinine 2.2 mg/dl	Slightly lower rise in creatinine in patients receiving prostaglandin E_1

which is thought to arise as a result of the severe circulatory derangement that accompanies cirrhosis. Specifically, cirrhosis is associated with splanchnic vasodilation, which may cause reflex activation of the sympathetic nervous system and the renin–angiotensin system, thereby leading to renal vasoconstriction and decreased renal perfusion. In theory, reversal of the splanchnic vasodilation could lead to interruption of the cycle of events implicated in renal hypoperfusion.

Several recent studies have examined the effect of splanchnic vasoconstrictors in patients with HRS. Guevara and associates administered ornipressin, a synthetic derivative of arginine-vasopressin, to 16 patients with HRS that was unresponsive to volume expansion (28). Four patients received a 15-d infusion of ornipressin along with albumin at a dose of 20 to 40 g/d. This regimen led to a marked decrease in creatinine and increase in GFR (mean baseline GFR was 16 ml/min/m^2; mean GFR at Day 15 was 71 ml/min/m^2) as well as evidence of decreased systemic vasoconstrictor activity. However, a similar regimen administered for 3 d had no significant effect on renal function. Uriz and coworkers reported reversal of HRS in 7 of 9 patients receiving an average of 9 d of terlipressin, a vasopressin analog, and albumin (29). A 20-d infusion of midodrine, an oral α-adrenergic agonist, and octreotide led to significant improvement in renal function (mean creatinine decreased from 5.0 mg/dl at baseline to 1.8 mg/dl at Day 20) (30). In contrast, 3 d of low-dose vasopressin led to significant increases in urinary flow, but GFR actually decreased (31).

Transjugular intrahepatic shunts (TIPS) have an established role in the management of cirrhotic patients with variceal bleeding, but there have been few investigations into their effects on renal function. Guevara and associates reported seven patients with HRS who underwent TIPS (32). On average, the patients had slow but progressive improvements in renal function such that by 30 d post-TIPS, the mean creatinine had decreased from 5.0 to 1.8 mg/dl. However, TIPS was associated with the development of hepatic encephalopathy, and the median survival was only 45 d.

The aforementioned studies of treatment with splanchnic vasoconstrictors and TIPS have all been nonrandomized series of small numbers of patients with HRS. The usual concerns about nonrandomized studies are offset somewhat by the rarity with which renal function improves spontaneously in patients with HRS. However, even if one accepts the tentative finding that splanchnic vasoconstrictors and TIPS improve renal function and lead to reversal of HRS in some patients, their impact on survival is less clear. Despite significant improvement in renal function, many of the reported "success stories" in these series represent patients who died within weeks to months of the improvement in their renal function. Thus, in the absence of controlled studies demonstrating a survival benefit, we think it is reasonable to consider treatment with TIPS or splanchnic vasoconstrictors in patients with HRS as a possible bridge to liver transplantation, but we think there is insufficient evidence to support their routine use in the treatment of HRS.

SUMMARY

Although ARF is an independent predictor of mortality in the critically ill, there is a striking paucity of studies that have examined the prevention of ARF in the critically ill, and to date, no intervention has been shown in a large, randomized clinical trial to prevent renal failure in critically ill patients. One caveat is that some of the negative studies were small and may have lacked sufficient power to detect clinically significant benefit. We have made a number of treatment recommendations, many of which are necessarily based only on small studies or extrapolation from studies done in non–critically ill patients. The development of more exacting guidelines for the prevention of ARF must await the completion of additional controlled studies in critically ill patients. Unfortunately, some initially promising agents, such as human insulin-like growth factor, failed to benefit patients with ARF (33), and it remains uncertain whether other new therapies, such as fenoldopam (a specific DA-1 receptor agonist), endothelin antagonists, or adhesion molecule antagonists will prove effective in the prevention of ARF. It is also possible that a combination of treatment strategies will enhance our ability to prevent the development of ARF.

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