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A M E R I C A N C O L L E G E O F



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Prevention of Acute Renal Failure*

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Acute renal failure (ARF) comprises a family of syndromes that is characterized by an abrupt and sustained decrease in the glomerular filtration rate. In the ICU, ARF is most often due to sepsis and other systemic inflammatory states. ARF is common among the critically ill and injured and significantly adds to morbidity and mortality of these patients. Despite many advances in medical technology, the mortality and morbidity of ARF in the ICU continue to remain high and have not improved significantly over the past 2 decades. Primary strategies to prevent ARF still include adequate hydration, maintenance of mean arterial pressure, and minimizing nephrotoxin exposure. Diuretics and dopamine have been shown to be ineffective in the prevention of ARF or improving outcomes once ARF occurs. Increasing insight into mechanisms leading to ARF and the importance of facilitating renal recovery has prompted investigators to evaluate the role of newer therapeutic agents in the prevention of ARF. (CHEST 2007; 131:300–308)

Key words: acute renal failure; diuretics; dopamine; prevention

Abbreviations: ANP = atrial natriuretic peptide; ARF = acute renal failure; ATN = acute tubular necrosis; CI = confidence interval; GFR = glomerular filtration rate; NAC = N-acetylcysteine; OR = odds ratio; RCT = randomized controlled trial

Acute renal failure (ARF) is defined as an abrupt and sustained decline in the glomerular filtration rate (GFR),¹ which leads to accumulation of nitrogenous waste products and uremic toxins. In critically ill patients, > 90% of episodes of ARF are believed to be due to acute tubular necrosis (ATN) and are the result of ischemic or toxic etiology or a combination of both. The reported incidence and mortality of ARF in the ICU vary widely depending on the population studied and the definition used.^{2–5} ARF in the ICU usually occurs in association with multiple organ dysfunction and carries a much higher mortality than that seen outside the ICU.² In a

recent large multicenter observational study of 29,269 critically ill patients, Uchino et al⁶ found that 5.7% had severe ARF (requiring renal replacement therapy or urine output < 200 mL in 12 h and/or marked azotemia defined as a BUN level > 84 mg/dL) during their ICU stay. Of the patients who had this degree of ARF in the ICU, 72.5% were treated with renal replacement therapy. In this study,⁶ the most common contributing factor for ARF in the ICU was septic shock (47.5%) and the overall hospital mortality was 60.3%. There is now clear evidence that ARF is associated with excess mortality,^{7,8} irrespective of whether the patient requires renal replacement therapy.^{8–11}

Given the apparent impact of even “milder forms” of ARF on mortality, it is important to prevent or hasten the resolution of even the mildest forms of ARF. The goals of a preventive strategy for the syndrome of ARF are to preserve renal function, to prevent death, to prevent complications of ARF (volume overload, acid-base disturbances, and electrolyte abnormalities), and to prevent the need for chronic dialysis, with minimum adverse effects. In this review, we have categorized preventive strategies for ARF into nonpharmacologic, pharmacologic, and dialytic strategies.

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NONPHARMACOLOGIC STRATEGIES FOR ARF PREVENTION

Main nonpharmacologic strategies to prevent ARF include ensuring adequate hydration (reversing dehydration), maintenance of adequate mean arterial pressure, and minimizing exposure to nephrotoxins. Four particular strategies are notable: fluids, aminoglycoside dosing, lipid preparations of amphotericin, and nonionic radiocontrast agents.

Hydration

Volume depletion is an important risk factor for the development of ARF. However, there are no randomized controlled trials (RCTs) that have directly evaluated the role of fluid hydration vs placebo in the prevention of ARF. However RCTs have compared different fluids and have combined fluid hydration with other interventions.¹² Furthermore, comparisons between outcomes seen in these trials¹² and historical untreated control subjects¹³ suggest a large benefit from fluids. One small RCT¹⁴ of 53 patients who underwent nonemergent cardiac catheterization compared IV 0.9% saline solution hydration (1 mL/kg/h for 24 h) begun 12 h before catheterization to unrestricted oral fluid hydration. In the saline solution group, 3.7% of patients had contrast nephropathy, compared to 34.6% of patients in the unrestricted oral fluid group (relative risk, 0.11; 95% confidence interval [CI], 0.015 to 0.79). Thus, IV hydration appears to be effective in prevention of at least some forms of ARF.

Furthermore, the type of IV fluids used may also be important. Mueller et al¹⁵ compared hydration using 0.9% saline solution infusion with 0.45% saline solution in dextrose for prevention of contrast nephropathy in 1,620 patients undergoing coronary angiography. In this study,¹⁵ hydration with 0.9% saline solution infusion significantly reduced contrast nephropathy, compared to 0.45% saline solution in dextrose hydration (0.7% with 0.9% saline solution vs 2% with 0.45% saline solution; $p = 0.04$). However, a recent, small single-center RCT¹⁶ enrolling 119 patients with stable serum creatinine of at least 1.1 mg/dL, randomized to either infusion of isotonic sodium chloride ($n = 59$) or isotonic sodium bicarbonate ($n = 60$) before and after radiocontrast (iopamidol) administration. Radiocontrast nephropathy (defined as an increase of $\geq 25\%$ in serum creatinine from baseline within 48 h) developed in 1 of 60 patients (1.7%) in the bicarbonate group, compared to 8 of 59 patients (13.6%) in the saline solution group ($p = 0.02$). Although this study is underpowered and single centered, and although the clinical significance of preventing a small increase in serum

creatinine is unclear, the intervention should be nearly risk free in most patients.

The traditional approach to prevention and treatment of pigment-induced ARF is to use saline solution resuscitation followed by a forced mannitol-alkaline diuresis to maintain the urine pH > 6.5 .¹⁷ Theoretically, urine alkalinization helps prevent tubular pigment cast formation and may also reduce the conversion of hemoglobin to methemoglobin, and release of iron from myoglobin. However, this approach is controversial because there is no clinical evidence that mannitol or bicarbonate are more effective than saline solution alone. Furthermore, there are potential risks to bicarbonate therapy, including precipitation of calcium phosphate and inducing or exacerbating hypocalcemia.¹⁸ Mannitol should be used with great caution, if at all, since it may result in a hyperosmolar state particular when renal failure has already occurred.

Based on clinical trials, we recommend that isotonic fluids be used for prevention of contrast nephropathy. The ideal composition of such a fluid (saline solution, Ringer solution, bicarbonate based or even colloid) and the optimal rate of infusion remain unclear and should be individualized. Importantly, just as IV fluids may be beneficial in preventing radiocontrast nephropathy, volume depletion is an important risk. Diuretics should be viewed as potentiating the nephrotoxicity of radiocontrast agents¹² and possible other toxins.

Maintaining Renal Perfusion Pressure

In the acute setting, the two most significant threats to renal perfusion pressure are systemic arterial hypotension and increased intra-abdominal pressure (including so-called *abdominal compartment syndrome*). Specific recommendations to maintain perfusion are difficult to make given available evidence. However, the following general guidelines apply. First, based on their pharmacology as vasoconstrictors, vasopressor medications (eg, norepinephrine) should be used only to treat arterial hypotension once intravascular volume has been restored, although in practice vasopressors are often started as volume loading is underway and discontinued if no longer required once hypovolemia has been reversed.¹⁹ Second, there is no evidence from clinical studies or appropriately designed animal experiments^{20,21} to suggest that norepinephrine is associated with increased risk of ARF when used to treat arterial hypotension. Indeed, a large observational study²² and small RCTs^{23,24} suggest that dopamine may be less efficacious compared to norepinephrine and possibly associated with lower survival. Third, specific arterial pressure targets for titration

of therapy to avoid renal hypoperfusion are not known. Many clinicians and clinical protocols target a mean arterial pressure of 60 to 65 mm Hg. However, patients with long-standing hypertension and/or renal vascular disease may require substantially higher pressures to maintain renal perfusion. Fourth, intra-abdominal hypertension is associated with decreased renal perfusion and may result in ARF.²⁵ Prompt recognition, often guided by urinary bladder pressure measurement, and surgical treatment offer the best potential for recovery.²⁵

Nephrotoxin Exposure

Minimizing nephrotoxin exposure is an important strategy to prevent ARF in the ICU setting. Aminoglycosides, amphotericin, and radiocontrast are the most commonly encountered nephrotoxins in the ICU. In addition to IV fluid administration as discussed above, specific strategies for minimizing nephrotoxicity have been developed.

Aminoglycoside Dosing: Aminoglycoside nephrotoxicity develops in approximately 10 to 15% of patients treated with aminoglycosides. Since aminoglycosides are excreted entirely by glomerular filtration, dosing of these drugs appears to be a critical factor in the development of ARF. With multiple daily dosing schedules, elevated peak levels appear to correlate with toxicity. Since aminoglycoside uptake by proximal tubular cells is saturable, once-daily dosing is postulated to decrease tubular cell toxicity by reducing the fraction of the cumulative dose of drug taken up by proximal tubular cells.²⁶ Two metaanalyses and one systematic review,^{27–29} have been performed comparing the efficacy and toxicity of multiple-daily and once-daily aminoglycoside dosing schedules. All three studies^{27–29} have demonstrated that although there were no differences in the efficacy of aminoglycosides when dosed once daily, there was a trend toward lower nephrotoxicity in the once-daily dosing groups.

Amphotericin B-Associated Nephrotoxicity: ARF associated with amphotericin B occurs in as many as one third of patients, with progressive increase in the risk of ARF with increases in cumulative dose.³⁰ The use of lipid formulations of amphotericin B seems to cause less nephrotoxicity compared with standard formulations. In one small study³¹ of 55 patients with neutropenic fever, amphotericin B colloid dispersion was associated with equal therapeutic efficacy as conventional amphotericin B but reduced nephrotoxicity from 55 to 36% ($p < 0.001$). Data from a phase II trial³² of a lipid formulation of amphotericin B ($n = 556$) found an incidence of renal toxicity of

24%. This compares with 60 to 80% incidence reported with standard formulation of amphotericin B. In addition, patients with a baseline serum creatinine level > 2.5 mg/dL on standard amphotericin B showed a significant decrease in serum creatinine when transferred to the lipid formulation ($p < 0.001$).³² Walsh et al³³ compared liposomal amphotericin B with conventional amphotericin B as empirical antifungal therapy in 687 patients with persistent fever and neutropenia. Although, liposomal amphotericin B was as effective as conventional amphotericin B for empirical antifungal therapy, it was associated with less nephrotoxicity (19% with amphotericin lipid complex vs 34% in the conventional amphotericin B group; $p < 0.001$). On the basis of these data, we recommend that lipid forms of amphotericin B be used preferentially in patients with renal insufficiency or evidence of renal tubular dysfunction.

Radiocontrast Nephrotoxicity: Apart from hydration, the type and volume of contrast media administered also influence the risk of contrast nephropathy in critically ill patients. One systematic review³⁴ comparing “low osmolality” contrast media with standard contrast media showed that low-osmolality contrast media did not influence the development of ARF or need for dialysis (these are rare events), but there was less nephrotoxicity with low-osmolality contrast media. The overall benefit was small for people without prior renal failure (odds ratio [OR], 0.75; 95% CI, 0.52 to 1.10) and was greatest in people with underlying renal impairment (OR, 0.50; 95% CI, 0.36 to 0.68). However, so-called *low-osmolality radiocontrast agents* are still very hypertonic (700 to 800 mosm) relative to plasma and, thus, newer iso-osmotic (200 to 300 mosm) agents have been developed. One RCT³⁵ ($n = 129$ diabetic patients with baseline renal insufficiency) compared iso-osmolar nonionic contrast media (iodixanol) to low-osmolar contrast media (iohexol) in patients undergoing cardiac or vascular angiography, and found that iso-osmolar nonionic contrast exposure significantly reduced contrast nephropathy compared to low-osmolar contrast exposure (OR, 0.09; 95% CI, 0.02 to 0.4). This study was limited in that hydration regimes of the two groups were not standardized and the low-osmolar contrast group had an exceptionally high incidence (26%) of contrast nephropathy. There is some indirect evidence to suggest that viscosity of contrast media might influence the incidence of nephrotoxicity.^{36,37} For example, no significant differences exist in the reported rates of contrast nephropathy associated with iopamidol (low-osmolar contrast media with low viscosity) and iodixanol (iso-osmolar contrast media with higher

viscosity). This can perhaps be explained by the increased viscosity of iodixanol relative to many of the low-osmolar agents. However, based on the existing evidence we recommend that the lowest volume necessary of nonionic, iso-osmolar, contrast medium be used in conjunction with IV isotonic fluids in all high-risk patients.

PHARMACOLOGIC STRATEGIES FOR ARF PREVENTION

Despite the fact that ARF in the ICU is extremely common (some studies^{9,38} suggest that as many as two thirds of all critically patients have evidence of renal dysfunction), experts do not agree on the underlying pathophysiology. While some cases of ARF in the ICU appear to be precipitated by hypotension and presumed renal hypoperfusion, the majority do not.⁶ Moreover, isolated systemic hypotension, even when profound, is a relatively rare cause of ARF. More commonly, ARF in the ICU occurs in the setting of multiorgan failure and numerous lines of evidence support inflammatory, oxidative stress and epithelial dysfunction as primary mechanisms of sepsis-induced ARF,^{39–41} rather than more traditional notions of ischemia.⁴² Data from biopsies or autopsies in humans with clinical “ATN” show little or no changes consistent with ischemia,⁴³ further casting doubt on the notion of impaired renal blood flow in sepsis. Finally, animal models do not support a renal hypoperfusion mechanism when cardiac output is maintained.^{20,21}

Not surprisingly, pharmacologic strategies predicated on the notion of increasing renal blood flow or decreasing renal oxygen have been unsuccessful. Most agents generally have been shown to improve renal blood flow, renal plasma flow, GFR, and or urine output with little or no clinical benefit and sometimes with evidence of harm.¹²

Loop Diuretics

Traditionally, nonoliguric renal failure has been shown to have a better prognosis than oliguric renal failure. In addition, it is commonly held that the oliguria accompanying ATN is due to tubular obstruction caused by debris including denuded epithelium, and that this obstruction leads to the back leak of glomerular filtrate into the renal interstitium, further perpetuating the injury. This line of reasoning has led to the idea that maintaining a greater urine flow in the setting of a renal insult is desirable. Subsequently, multiple small clinical trials with methodologic limitations have studied the efficacy of loop diuretics in preventing ARF and have provided conflicting results. One systematic review⁴⁴ com-

pared fluids alone with diuretics in people at risk for ARF from various causes and found no benefit from diuretics with regards to incidence of ARF, need for dialysis, or mortality. In a cohort study, Mehta et al⁴⁵ studied 552 patients with ARF in the ICU, and characterized them by the use of diuretics on or before the day of renal consultation. In this study,⁴⁵ with adjustments for relevant covariates and propensity scores, diuretic use was associated with significantly increased risk of death or nonrecovery of renal function (OR, 1.77; 95% CI, 1.14 to 2.76). Furthermore, a multinational, multicenter, observational study⁴⁶ (n = 1,743), evaluated the effect of loop diuretics on clinical outcomes. The study investigators⁴⁶ created three multivariate models to assess the relationship between diuretics and mortality and found that although diuretic use was not significantly associated with increased mortality, there was no evidence of benefit either (OR for death was 1.2 in all three models). Based on these data, it is possible to conclude that there is no evidence to support the use of loop diuretics in the prevention of ARF. However, critically ill patients in the ICU having ATN often receive large volume of fluids as nutrition, vasopressors, and antibiotics. Volume overload is common and diuretics may provide symptomatic benefit. However, there is no evidence that these agents improve outcome and may cause harm.^{45,46}

Mannitol

Mannitol, when administered IV, is readily filtered by the glomeruli into the tubular fluid, where it acts as an osmotic diuretic. There are various mechanisms by which mannitol might theoretically attenuate renal injury. Like loop diuretics, mannitol “flushes” out intratubular casts and increases tubular flow, thereby decreasing the back-leak of the filtrate into the interstitium. Mannitol has also been shown to increase renal blood flow, and act as a free-radical scavenger during reperfusion of the kidney.^{47,48} However, several small clinical trials^{12,49–51} have evaluated mannitol for the prevention of ARF and have found conflicting results. In one study, Solomon et al¹² compared furosemide/saline solution to mannitol/saline solution to saline solution loading alone in high-risk patients receiving radiocontrast administration, and found that both the diuretic regimes were less effective in preventing ATN than saline solution alone. In summary, despite the presence of animal and anecdotal human evidence of the beneficial effects of mannitol, there are no adequately powered prospective, randomized clinical trials comparing these effects with that of saline solution hydration alone. In the absence of strong evidence for their use, along with data suggesting potential

harm, we recommend that mannitol should not be used to prevent or treat ARF from any cause.

Dopamine and Fenoldopam

Dopamine increases GFR by direct vasodilation through dopaminergic receptors, by increasing the cardiac output by β -adrenergic stimulation or by increasing perfusion pressure by α -stimulation. Three systematic reviews⁵²⁻⁵⁴ and one large RCT⁵⁵ evaluated the role of dopamine in preventing deterioration of renal function in the ICU. All three systematic reviews⁵²⁻⁵⁴ reached the same conclusion that dopamine did not prevent onset of ARF, need for dialysis, or mortality. The large multicenter RCT⁵⁵ ($n = 328$) randomized patients with early renal dysfunction to "low-dose dopamine" ($2 \mu\text{g}/\text{kg}/\text{min}$) or placebo.⁵⁵ This study⁵⁵ also found no difference between the groups in the peak serum creatinine concentrations, ICU/hospital length of stay, or need for renal replacement therapy. Thus, overwhelming evidence exists to suggest that there is no role for "low-dose" dopamine in the prevention of ARF from any etiology.

The selective dopamine-1 receptor agonist fenoldopam has been shown to improve renal perfusion and decrease serum creatinine.^{56,57} However, it has failed to decrease the occurrence of ARF in critically ill patients,⁵⁸ or to prevent contrast nephropathy in patients with chronic renal insufficiency.⁵⁹ In a large RCT, Stone et al⁵⁹ randomized 315 patients with creatinine clearance $< 60 \text{ mL}/\text{min}$ to fenoldopam mesylate or placebo. Patients were hydrated and randomized to receive the study drug, starting 1 h prior to angiography and continuing for 12 h. The primary end point of contrast-induced nephropathy (25% increase in serum creatinine within 96 h after the procedure) occurred in 33.6% of patients assigned to receive fenoldopam vs 30.1% assigned to receive placebo (relative risk, 1.11; 95% CI, 0.79 to 1.57; $p = 0.61$). However, a recent single-center study⁶⁰ using a longer duration of fenoldopam (mean, 10 days) in critically ill patients showed a reduction in ARF defined by an increase in serum creatinine to $> 150 \mu\text{mol}/\text{L}$ ($1.7 \text{ mg}/\text{dL}$) and trend toward improved survival (OR, 0.68; $p = 0.1$). Thus, although additional study is likely and may even be warranted, fenoldopam would appear to be an unlikely candidate for the prevention of ARF at least as a vasodilator.⁶¹ Moreover, fenoldopam might even worsen renal injury by causing hypotension.⁶²

Natriuretic Peptides

The family of atrial peptides possess natriuretic, diuretic, and smooth-muscle relaxant activity through both hemodynamic and tubular mecha-

nisms. One of the main sites of action is the glomerulus, where these peptides induce preglomerular vasodilation and postglomerular vasoconstriction and thereby increase the GFR.⁶³ While atrial natriuretic peptide (ANP)-induced natriuresis and diuresis are probably secondary to increased GFR, a tubular effect of the peptide is also thought to exist, and ANP has been shown to reduce tubular sodium reabsorption in the medullary collecting duct.⁶⁴ In light of these potential physiologically beneficial effects of natriuretic peptides, investigators have evaluated its use in the prevention of ARF.

Four RCTs,⁶⁵⁻⁶⁸ have evaluated ANP in the prevention of ARF and failed to show any benefit. In the largest RCT,⁶⁵ prospectively defined subgroup analysis suggested that oliguric patients ($< 400 \text{ mL}/\text{d}$ of urine) had improved dialysis-free survival ($p = 0.008$), in comparison to the placebo group, while nonoliguric patients had worsened dialysis-free survival with anaritide than control groups ($p = 0.03$). However, in a subsequent RCT⁶⁷ in oliguric patients, anaritide did not improve dialysis-free survival. Interestingly, a small, single-center RCT⁶⁹ studied 61 patients after cardiac surgery using a continuous infusion of low-dose human recombinant natriuretic peptide ($50 \text{ ng}/\text{kg}/\text{min}$). This trial,⁶⁹ unlike the larger studies in the past, showed a decreased use of dialysis (hazard ratio, 0.28; 95% CI, 0.1 to 0.73; $p = 0.009$) and improved dialysis-free survival in treated patients compared to placebo. Although the results of this small study are interesting, anaritide should not be used to prevent ARF in the general ICU setting. Further, larger RCTs are necessary in the cardiac surgical population with low-dose human recombinant natriuretic peptide prior to its routine clinical use in this population.

Adenosine Antagonists (Theophylline)

Adenosine, in contrast to its general systemic effect as a vasodilator, is a renal arterial vasoconstrictor. This unique effect has been implicated as part of the tubuloglomerular feedback mechanism,⁷⁰ which increases afferent arteriolar tone in response to increased distal tubular solute delivery. Adenosine also acts synergistically with angiotensin II to constrict afferent arterioles.⁷¹ Adenosine via A-1 receptors has now been shown to be a possible mediator of the intrarenal hemodynamic changes that lead to ATN following radiocontrast administration.⁷² Animal studies of radiocontrast administration using theophylline pretreatment have demonstrated attenuation of this intrarenal vasoconstriction.

Subsequently, several small clinical studies⁷³⁻⁷⁶ have been done to evaluate the role of theophylline, an adenosine antagonist, in the prevention of con-

trast nephropathy, and have shown conflicting results. However, a metaanalysis⁷⁷ (including 7 of the 10 published clinical trials) showed that patients who received theophylline had a smaller increase in serum creatinine compared to those who received placebo ($p = 0.004$). This study excluded three trials either because they did not report relevant clinical end points, had a case-control study design, or the subjects were included in another RCT. However, this metaanalysis⁷⁷ included studies that did not control for hydration status and used, as an end point, changes in creatinine as opposed to pre-defined criteria for ARF. Accordingly, it remains unclear if theophylline might be useful preventing contrast nephropathy in some patients. However, larger multicenter RCTs examining valid clinical outcomes (dialysis requirement, mortality) will be necessary to adequately address this issue, before routine use of theophylline to prevent contrast nephropathy.

N-Acetylcysteine

Radiocontrast agents reduce renal function by altering renal hemodynamics and by exerting direct toxic effects on tubular epithelium. There is also increasing evidence that renal free-radical production increases after contrast agent administration and may in part be responsible for the renal injury.⁷⁸ Superoxide dismutase, a free-radical scavenger, has been shown to preserve renal function in animal models of radiocontrast-induced nephropathy.⁷⁹ N-Acetylcysteine (NAC), a thiol-containing antioxidant, has been shown to ameliorate ischemic renal failure in animals⁸⁰ and has been used in humans to prevent a reduction in renal function in patients with acetaminophen-induced liver failure.⁸¹ Based on these observations, several clinical studies^{82–85} have evaluated the efficacy of NAC in the prevention of radiocontrast nephropathy.

The use of NAC in several small studies^{82–85} has been shown to decrease the incidence of contrast nephropathy, defined as a 25% increase in serum creatinine after radiocontrast administration. Subsequently, several metaanalyses^{86–90} have pooled the existing data and have consistently found that NAC along with hydration decreases incidence of contrast nephropathy compared to hydration alone. In the largest metaanalysis,⁹⁰ the pooled random-effect relative risk was 0.65 (CI, 0.43 to 1.00; $p = 0.049$), indicating that NAC significantly reduced the incidence of contrast nephropathy. However, there was evidence of significant heterogeneity in NAC effect across studies ($Q = 26.3$, $p = 0.02$). In a recent, large, single-center RCT,⁹¹ 354 patients undergoing primary angioplasty after acute myocardial infarction

were randomized to three groups: 116 patients were assigned to a standard dose of NAC (600-mg IV bolus before primary angioplasty and 600 mg po bid for the 48 h after angioplasty), 119 patients were assigned to a double dose of NAC (1,200-mg IV bolus and 1,200 mg po bid for the 48 h after intervention), and 119 patients were assigned to placebo. The incidence of contrast nephropathy (increase in serum creatinine $\geq 25\%$ from baseline) was 33% in control group vs 15% in the standard NAC group vs 8% in the high-dose NAC group ($p < 0.001$). The rate for the composite end point of death, ARF requiring temporary renal replacement therapy, or the need for mechanical ventilation was 21 patients (18%), 8 patients (7%), and 6 patients (5%) in the three groups, respectively ($p = 0.002$).

However, NAC has been shown to decrease serum creatinine without affecting GFR⁹² by activating creatinine kinase,⁹³ and possibly by increasing tubular secretion. Hence the implications of dose-dependent reduction in serum creatinine after contrast administration with the use of NAC remain unclear and need to be further explored. Until such time, we recommend use of NAC in high-risk patients to prevent contrast nephropathy given its potential benefit, low cost, and excellent side effect profile. Importantly however, NAC should never take the place of IV fluids, which likely have a more substantiated benefit in terms of preventing contrast nephropathy.

DIALYTIC STRATEGIES FOR ARF PREVENTION

Although contrast media can be removed by dialysis,⁹⁴ insufficient evidence exists for the routine use of prophylactic dialysis to prevent contrast nephropathy. One small, single-center RCT⁹⁵ evaluated the role of low-dose hemofiltration with hydration alone in the prevention of contrast nephropathy and found that hemofiltration decreased the incidence of contrast nephropathy, in-hospital mortality, and 1-year cumulative mortality. However, this study⁹⁵ had several important limitations, including the lack of standardized hydration regime, and lack of iso-osmolar contrast media or NAC. Finally, the study compared ICU care plus hemofiltration to care on the medical ward. Thus, there is currently insufficient evidence to support the use of prophylactic hemofiltration to prevent contrast nephropathy.

CONCLUSION

Current available evidence suggests that nonpharmacologic strategies may be more effective than

Table 1—Prevention of ARF

Strategies that are likely to be effective
Isotonic hydration (IV route)
Once-daily dosing of aminoglycosides
Use of lipid formulations of amphotericin B
Use of iso-osmolar nonionic contrast media
Strategies of unknown efficacy
NAC
Theophylline
Low-dose recombinant ANP (in cardiac surgical patients)
Strategies that are not effective
Loop diuretics
Dopamine and dopamine receptor agonists
ANPs
Prophylactic hemofiltration

drugs in the prevention of ARF. Adequate hydration, maintenance of mean arterial pressure, and minimizing nephrotoxin exposure still remain the most effective strategies to prevent ARF (Table 1). Once-daily dosing of aminoglycosides, lipid formulations of amphotericin B, and iso-osmotic contrast media should be used in preference to older agents or dosing in all high-risk patients. Although good evidence points toward the use of isotonic fluids for hydration, the ideal composition of these fluids or rate and volume of administration still remain unclear. Small studies notwithstanding, there is now convincing evidence that diuretics, dopamine agonists, and natriuretic peptides do not prevent ARF or improve outcomes once ARF occurs. Considering its low cost, toxicity, and potential benefit, NAC should be considered along with IV hydration to decrease the incidence of contrast nephropathy in high-risk patients. Theophylline and human recombinant natriuretic peptide may have possible benefits in specific patient populations, but further larger clinical trials are needed to confirm their efficacy. The role of prophylactic use of dialysis to prevent contrast nephropathy is unproven.

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