Drugs 2000 Jan; 59 (1): 79-91
0012-6667/00/0001-0079/$25.00/0

An Evaluation of Pharmacological Strategies for the Prevention and Treatment of Acute Renal Failure

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Contents

Abstract

Acute renal failure (ARF) occurs frequently in hospitalised patients, and is associated with significant morbidity and mortality. The most common and generalised forms of acute renal failure are pre-renal conditions and intra-renal acute tubular necrosis (ATN). Pre-renal ARF in its pure state should be entirely reversible by restoring renal perfusion, but in some cases ATN has already occurred.

ATN remains a more vexing problem, and is seen most often with hypotension, perioperative or systemic inflammatory stresses, radiocontrast administration, and exposure to nephrotoxins. Among the available pharmacological options for prevention or treatment of ATN, there is a remarkable lack of definitive evidence supporting specific therapy in any setting. Although loop diuretics, mannitol, and dopamine are frequently used for prevention and/or treatment of ATN, clinical studies have failed to prove value. Other drugs with theoretical value, specifically atrial natriuretic peptide analogues, adenosine blockers, and calcium antagonists, have been insufficiently studied to recommend use. Other pharmacological options may arise in the future. Ensuring adequate intravascular fluid volume remains the only approach to managing ATN which can be considered relatively effective and safe. Given the abundant theoretical basis for the prevention and treatment of ATN with drugs, well conducted clinical studies with relevant outcome measures are clearly warranted.

1. Definition and Incidence of Acute Renal Failure

Acute renal failure (ARF) is defined as an abrupt and sustained decline in renal glomerular filtration rate (GFR),[1] which leads to accumulation of nitrogenous waste products and other toxins. One commonly cited critical illness severity scoring system (APACHE III) defines ARF as serum creatinine elevation ≥1.5 mg/dl/day with urine output <410 ml/ day and no pre-existing chronic dialysis.[2] Severe ARF, a state in which homeostasis of fluids, electrolytes, and waste products is sufficiently impaired to threaten survival, is generally indicated by a serum creatinine level above 5.0 mg/dl or by a requirement for renal replacement therapy.

ARF affects nearly 5% of all hospitalised patients and as many as 15% of critically ill patients.[3,4] The mortality rate of an isolated episode of ARF is approximately 10 to 15%.[5] However, when ARF occurs in association with multiple organ dysfunction, mortality rates are much higher and vary in published series between 50 and 90%. In one review, the in-hospital mortality rate of patients who developed ARF requiring dialysis after interventional cardiology procedures was 35.7%.[6]

Standard classification of ARF is summarised in table I. Pre-renal dysfunction is the most common renal impairment in hospitalised patients. Intrarenal ARF is most frequently consequent to acute tubular necrosis (ATN) resulting from an ischaemic or nephrotoxic injury.[3] Pre-renal ARF can lead to ATN, so a distinction between the 2 patterns is not always present. The patient with a pre-renal condition will often manifest signs of hypovolaemia, including orthostatic hypotension and/or tachycardia, low central venous pressure, dry mucous membranes, and oliguria. Laboratory analysis might reveal concentrated urine, a fractional excretion of sodium <1%, and blood urea nitrogen elevated out of proportion to serum creatinine levels. The patient with ATN may have any volume status, so physical signs will often be unhelpful. There may or may not be oliguria. Laboratory analysis might reveal urinary granular casts, a fractional excretion of sodium >1%, and a more parallel rise in blood urea nitrogen and creatinine levels.

Several risk factors for ARF have been identified, including hypovolaemia, hypotension, sepsis,

Table I. Types of acute renal failure

Type	% of patients	Aetiology
Pre-renal (functional)	40-80	Renal hypoperfusion (decreased cardiac output, systemic hypotension, local renal arterial disease, sepsis)
Intra-renal	10-50	Parenchymal injury (acute tubular necrosis, interstitial nephritis, athero-embolic disease, glomerulonephritis, vasculitis, small vessel obstruction)
Post-renal	<10	Urinary tract obstruction

diabetes mellitus, pre-existing renal, hepatic or cardiac dysfunction, and exposure to nephrotoxins.[7-11] In the critically ill, ARF rarely occurs in isolation and is usually associated with multiple organ dysfunction.[12] In the perioperative setting, the risk of ARF is influenced by factors such as the duration of aortic clamping, and elective versus emergency surgery. In the setting of interventional cardiology, one large study identified baseline creatinine clearance below 47 ml/min, diabetes mellitus, and dose of contrast media >100ml as independent risk factors for ARF.[6]

Several other causes of ARF exist, which have specific treatment standards quite different from those for ATN. These include interstitial nephritis and the varieties of glomerulonephritis, but these conditions are outside the scope of this paper. However, it is important to note that specific drug therapies do exist for some of these conditions (e.g. steroids for rapidly progressive glomerulonephritis).

2. Pre-Renal and ATN Pathophysiology

Renal blood flow (RBF) is maintained at about 20% of cardiac output by glomerular filtration needs. This results in a 'luxurious' level of oxygen delivery compared with total renal oxygen consumption, with total renal oxygen extraction averaging about 10%. However, RBF is very heterogeneous, and under normal conditions the outer medulla exists in a condition bordering on hypoxia, with oxygen extraction in the range of 80 to 90% and tissue oxygen partial pressure (pO_2) less than 20mm Hg (fig. 1). The outer medulla is also the location of very active segments of the nephron, in particular the medullary thick ascending limb of Henle's loop and the pars recta of the proximal tubule. Because of its low pO_2 and its high metabolic activity, the outer medulla is at great risk of ischaemia, even in the setting of normal RBF.[14]

Intrarenal oxygen homeostasis is largely maintained through blood flow autoregulation and a mechanism known as tubuloglomerular feedback (TGF). Blood flow autoregulation, a process common to many organs, occurs within the normal blood pressure range via changes in arteriolar tone. Unlike

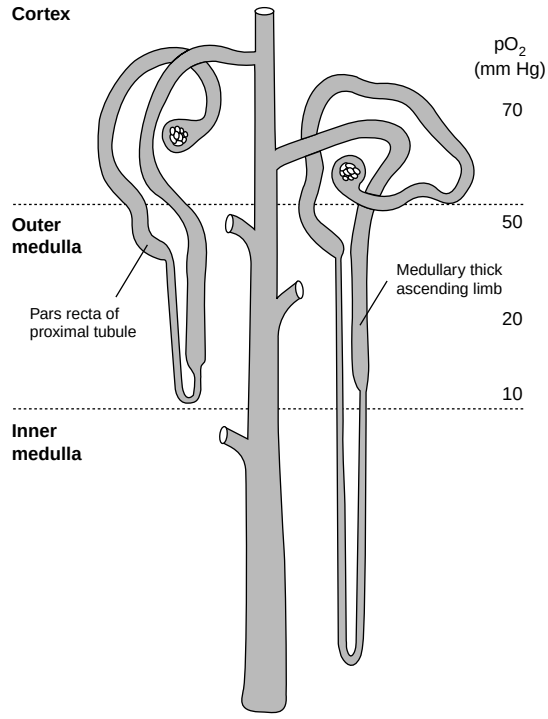

Fig. 1. Schematic drawing of a nephron. Note location in outer medulla, the site of lowest intrarenal oxygen partial pressure (pO_2), of straight portion of proximal tubule and thick ascending limb of Henle's loop. Decreases in medullary blood flow and/or increases in active solute reabsorption can precipitate medullary ischaemia, leading to ATN.[13]

autoregulation, the TGF mechanism is unique to the kidney, and is mediated at least partly by adenosine,[15] which appears to have vasoconstrictive effects in the renal cortex and either constrictive or dilating effects in the medulla, depending on the balance of adenosine A_1 and A_2 receptor stimulation.[16] The TGF mechanism induces preglomerular arteriolar constriction in response to increased solute delivery to the distal nephron, thereby reducing GFR and oxygen-requiring work of the kidney when solute filtration outpaces reabsorptive capacity.

Ischaemic ATN occurs when renal oxygen balance is adversely disturbed. Clinically, this occurs most often when an insult is superimposed on a pre-existing condition of compromised oxygen reserve, such as hypotension or drug effects in the

setting of a pre-renal state. Even in the absence of a pre-renal state, pre-existing conditions such as sepsis, diabetes mellitus and atherosclerosis induce vascular dysfunction which may allow ischaemic ATN in the setting of otherwise tolerable hypotension or drug therapy. Drugs with vasoactive actions impair renal autoregulation,[17] and therefore, may do harm rather than good. Many such agents are used clinically in efforts to prevent or attenuate ATN even in the absence of clinical outcome studies proving their benefit. The effects of drugs on the TGF mechanism are almost universally unknown, but to the extent that TGF is adaptive, its preservation would seem to be a desirable goal.

It is essential to recognise that therapy aimed at enhancing GFR, which increases solute load in the distal tubule and thus increases the medullary workload, might induce or worsen medullary ischaemia. Indeed, the idea that oliguria might be an adaptive response to ischaemic stress has led some to suggest the term 'acute renal success' for this condition.[18] The fact that preglomerular vasoconstriction occurs following ATN[19] suggests that reduction in GFR is adaptive, and that enhancing GFR may be inappropriate. It is reasonable to conclude that purely pre-renal ARF should be reversible with fluid repletion alone, but that the prevention and treatment of ATN is a more difficult matter requiring clinical outcome data to properly assess strategies.

Several clinical syndromes of ATN have been studied using specific models. Accordingly, it is difficult to consider the issue of whether drugs are useful in ATN without first considering the specific pathophysiology of these syndromes. A brief discussion of some of the more common clinical settings of ATN is thus necessary.

2.1 Specific Pathophysiological Conditions

2.1.1 Radiocontrast-Induced ATN

One of the most commonly anticipated aetiologies of ATN is the use of intravascular radiocontrast agents for imaging studies.[20] Although the pathogenesis of renal injury is not entirely understood, it appears to be due to medullary ischaemia.[21,22] It has been postulated that this ischaemic injury occurs on the basis of decreased RBF secondary to renal vasoconstriction. However, some studies have shown that RBF actually increases with radiocontrast,[23] while others suggest that there is a biphasic response of initial vasodilation followed by more prolonged constriction.[24] This has lead some investigators to hypothesise that an ionic load contributes to medullary ischaemia.[13]

2.1.2 Endotoxaemia/Sepsis/ Systemic Inflammation

This pathophysiological state probably combines with pre-renal and nephrotoxic stresses to cause the majority of ARF in critical care settings. Renal disturbances depend not only on the initiating event (infection, trauma, etc.) but also on specific immunomodulatory responses to events.[25] These responses include release of vasodilating and vasoconstricting mediators (eicosanoids, endothelin, nitric oxide), as well as direct damage to the vascular endothelium leading to glomerular thrombosis. Nitric oxide donors protect against endotoxin-induced glomerular thrombosis in rats,[26] suggesting that nitroglycerin or similar agents might be of use, although clinical studies are lacking.

2.1.3 Rhabdomyolysis

Myoglobin from injured muscle cells induces ATN through at least 2 mechanisms. Intravenous infusion of myoglobin in rats induces a decrease in outer medullary blood flow and pO_2, to a degree consistent with ischaemic ATN.[27] Myoglobin is also directly nephrotoxic, particularly with concomitant hypovolaemia and aciduria, conditions which favour myoglobin breakdown and free radical formation.[28] Severe ATN can occur, and the standard approach to management of rhabdomyolysis includes aggressive fluid replacement, with forced diuresis and/or alkalinisation of urine being controversial.[29] These issues are addressed in section 3.3.

2.1.4 Renal Transplantation

The procurement, preservation, and subsequent reperfusion of donor kidneys induces ischaemic ATN. Furthermore, in every case the effect of acute cyclosporin or tacrolimus nephrotoxicity is diffi-

cult to separate from that of primary ischaemic injury. In particular, calcium antagonists have become advocated in this setting.[30] The extrapolation of data from this setting to any other is difficult, so conclusions must be limited in scope.

2.1.5 Hepatorenal Syndrome

Patients with end stage liver disease often develop a state of renal vasoconstriction and resultant decreased GFR, which is resistant to volume expansion and withdrawal of diuretics. The pathophysiology is complex and controversial, and no drug therapy is currently available. A number of studies have been published suggesting that the administration of vasoactive agents,[31,32] possibly in combination with volume expansion,[33] may hold promise. However, no specific recommendations can be made at this time.

2.2. Nephrotoxins

2.2.1 Aminoglycosides

Unlike many nephrotoxic agents that produce ATN through ischaemia, aminoglycosides are transported into tubular cells where they are directly toxic. ATN associated with aminoglycoside use complicates up to 20% of serious Gram-negative infections.[10] Dosage regimens with longer intervals between doses, although not proven, are now thought to be safer than more frequent administration.[34] This is due in part to saturation of the tubular uptake mechanism, so that longer intervals allow less total uptake of toxin into cells.

2.2.2 Amphotericin

Amphotericin produces dose-dependent nephrotoxicity ostensibly through alteration of cell membrane permeability with resultant tubular dysfunction, and possibly vasoconstriction.[35] Limitation of total dose is widely recommended, while minimisation of infusion rate and volume loading might be helpful. Recently available liposomal preparations of amphotericin may reduce renal toxicity, but are expensive. In addition, it is important to realise that these preparations, although safer, do not eliminate the risk of renal injury, so that dose limitation and volume loading remain advisable.

2.2.3 Cyclosporin

Cyclosporin and related compounds, such as tacrolimus, produce reversible intra-renal vasoconstriction resulting in reduced RBF and GFR. This may be mediated by reduced production of endogenous vasodilators, increased production of vasoconstrictors, or both. It is not clear whether cyclosporin toxicity in the absence of other risk factors can lead to ischaemic ATN, but hypovolaemia or concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) appears to increase this risk.[36]

2.2.4 Nonsteroidal Anti-Inflammatory Drugs

NSAIDs induce ischaemic ATN by interfering with prostaglandin synthesis, resulting in impaired intra-renal blood flow homeostasis and medullary ischaemia.[22] This effect is unusual in those without risk factors but is particularly common in the setting of a pre-renal state. Avoiding NSAIDs in high risk settings is commonly advised.

3. Prevention, Support, and Therapy

3.1 General Principles

The approach to management of ARF consists of preventive, supportive, and therapeutic strategies. Currently available strategies are either preventive or supportive, while therapy aimed at stimulating the recovery of ischaemically injured cells remains investigational. Supportive treatment includes renal replacement via intermittent or continuous methods, management of electrolyte, acid/base, and fluid problems. Preventive strategies aim to prevent renal injury in high risk situations, and to prevent further renal injury in the setting of clinical ARF. These strategies, specifically volume loading, diuresis, and modulation of renal vascular tone, will be the primary focus of this section.

3.2 Intravascular Volume

It is clear that hypovolaemia, or a pre-renal state, is a major risk factor for ATN. Fluid loading may reduce this risk by assuring adequate RBF, reducing renal vasoconstrictive stimuli, and by limiting exposure to nephrotoxins through more rapid urine

flow. Fluid repletion is widely recognised as a prerequisite for reducing the risk of nephrotoxic and ischaemic ATN. Despite this, fluids alone have not been rigorously studied, but are often included as part of overall management of patients in clinical studies. In certain settings, such as traumatic rhabdomyolysis, early and aggressive fluid resuscitation has had clear benefits when compared with historical controls.[29] In the setting of radiocontrast administration, one randomised trial in 78 'high risk' patients found that 2 different combined diuretic and saline loading regimens were less effective in preventing ATN than saline loading alone.[21] Although all patients in this trial received saline loading, this manoeuvre appeared to be beneficial when compared with historical data. Although the evidence for fluid loading is not complete, the volumes of fluids recommended (1 to 1.5 litres) and the rates of infusion (generally <0.5 L/hr) have little potential for harm in the vast majority of patients.

3.3 Pharmacological Strategies to Prevent Onset or Progression of ATN

3.3.1 Loop Diuretics

Loop diuretics decrease the metabolic demand of the renal tubular cell, reducing its oxygen requirement and thereby, in theory, increasing its resistance to ischaemia[37] and perhaps to other toxic insults. A greater urine flow may also reduce tubular obstruction and thus the back leak of filtrate.[38] Although no data exist in humans, evidence from animal experiments suggests that diuretics may be useful if given within minutes to perhaps a few hours after a renal insult.[39] If diuretics are given after ATN is established, they may be of no benefit, in part because their effect is dependent on intact GFR to deliver drug to the active site in the tubular lumen. Furthermore, diuretics may be harmful by inducing a pre-renal state. This is particularly important in patients with oedema and/or hypoalbuminaemia, who may have intravascular volume depletion coexisting with total body volume overload.[40]

The use of loop diuretics has become routine prior to aortic clamping in many institutions, although there appears to be no evidence to support this approach. The stress responses induced by cardiopulmonary bypass circulation or major surgery may produce renal injury which progresses over time, with ongoing risk of further insult. In these conditions it is often compelling to attempt to prevent or reduce renal injury as it evolves. One clinical study[41] randomised 121 patients to receive either low dose furosemide (1 mg/hr intravenous infusion) or placebo starting immediately after major thoracoabdominal or vascular surgery and continuing throughout the intensive care unit (ICU) stay. The authors found no difference in creatinine clearance between furosemide and placebo recipients. The data are clearly insufficient to recommend perioperative loop diuretic use for renal protection.

In the setting of radiocontrast administration, Solomon and co-workers[21] compared furosemide/saline to mannitol/saline with saline loading alone in 'high risk' patients and found that both diuretic regimens were less effective in preventing ATN than saline alone. Another study[42] found that renal function significantly deteriorated after radiocontrast administration in patients pretreated with furosemide, which may have been due to the creation of a pre-renal state as suggested by negative fluid balance achieved with furosemide treatment. The available evidence supports volume loading with saline, but not diuretic use, in the prevention of radiocontrast induced renal injury.

Diuretics can convert oliguria to nonoliguria,[43] which may make patient management easier, with less volume overload and electrolyte imbalances. However, there is no evidence that this is effective in reducing mortality or the need for dialysis. In 1 study[44] of 66 patients with oliguric ATN randomised to receive furosemide or placebo, the furosemide group did increase urine output, but there were no significant differences among the 2 groups in terms of renal recovery, days on dialysis or mortality. In a second study,[45] 58 patients were given a single large dose of furosemide (1 gram) and then randomised to receive continued diuretic therapy

or not. Again, there were no differences between the 2 groups in terms of need for dialysis or survival. Lastly, in a study of 92 patients with ARF randomised to receive either loop diuretics or placebo in addition to dopamine and mannitol, there was increased urine flow for 24 hours with loop diuretics but no difference in renal outcome or death.[46] While these 3 studies together lack sufficient power to entirely rule out a beneficial effect on survival, the available literature to date does not support a survival benefit for loop diuretics.

A randomised, crossover trial[47] found continuous infusion of bumetanide produced more net sodium excretion and less toxicity than bolus bumetanide administration. This study suggests that if the choice is made to use diuretic therapy, continuous infusion may be more effective in achieving diuresis with fewer adverse effects. It is also important to note that large bolus doses of loop diuretics may cause transient renal vasoconstriction.

3.3.2 Mannitol

Unlike the loop diuretics, mannitol is an intravascular volume expander and may also function as a free radical scavenger, as well as an osmotic diuretic. The study by Solomon,[21] which included mannitol/saline as 1 of 3 treatment arms in radiocontrast administration, again suggests that it is hydration, not mannitol, that can reduce nephrotoxicity in this setting. A concern about mannitol, of unknown clinical significance, is that it reduces renal medullary pO_2, as documented in rat kidney by Breziz et al.[48] The osmotic diuresis induced by mannitol might increase tubular oxygen demand to a detrimental degree, regardless of the potential protective effects of the drug.

A controlled study in 1963 compared outcomes in 30 patients undergoing elective abdominal aortic aneurysm repair, who were randomised to receive either no preoperative fluid, intravenous hydration only, or hydration plus mannitol as required to keep urine output >60 ml/hr.[49] In this underpowered study, no difference was detected in renal function or postoperative urine output between the latter 2 groups. The following year, an uncontrolled study of 104 patients treated with mannitol reported that all patients had an increase in urine output and none developed ATN.[50] In other types of surgery, such as coronary artery bypass[51] or biliary surgery,[52] small studies have not demonstrated a benefit with mannitol. In the absence of stronger clinical evidence, mannitol cannot be recommended to prevent perioperative ATN.

Evidence exists from case-controlled studies to support the use of aggressive hydration along with forced alkaline/osmotic diuresis with mannitol for the treatment of ATN secondary to traumatic rhabdomyolysis. In a series of 7 patients,[53] prompt treatment was 100% successful in avoiding this complication, although the authors have suggested that hydration alone may have been sufficient to produce the good outcome. This point of view is supported by a recent study[54] which compared saline, mannitol and bicarbonate with saline alone in 24 patients with rhabdomyolysis. Although small, this study found that the addition of mannitol and bicarbonate added nothing to saline alone in terms of renal protection. In addition, mannitol can reduce the severity of muscular compartment syndromes, as demonstrated in a study in dogs,[55] suggesting that early use of mannitol in muscular crush or compression might reduce the extent of damage and subsequent release of myoglobin. Although some would argue vigorously for mannitol in traumatic rhabdomyolysis, the evidence is not conclusive for anything other than early aggressive hydration.

3.3.3 Dopamine

Dopamine is frequently used to increase urine output in ARF, in the hope that such a manoeuvre might attenuate renal injury or improve survival. Dopamine may increase GFR by direct vasodilation (via dopamine receptors), by increasing cardiac output (via β-receptors) or by increasing perfusion pressure (via α-receptors). At lower doses, particularly less than 2 μg/kg/min, the dopaminergic effects tend to predominate, although wide variability can exist across patients and clinical conditions.[56] In the appropriate clinical settings, any of these mechanisms might increase effective renal plasma flow and thus increase urine output.

Dopamine may increase urine output by another mechanism, that is, inhibition of sodium-potassium ATPase at the tubular epithelial cell level,[57] resulting in diuresis. The natriuretic/diuretic effects of dopamine are of importance not only because the increase in urine output can confound the assessment of renal function, but also because the increase in urine output may come with unexpected effects. A recent study demonstrated that although dopamine increased outer medullary blood flow in hypovolemic rats, it failed to improve outer medullary oxygenation.[58] Furthermore, the increased solute delivery to the distal tubular cells produced by the natriuretic effects of dopamine might actually increase distal oxygen consumption and therefore increase the risk of ischaemia.[59]

Dopamine has a number of potential disadvantages. In 1 study,[60] low dose dopamine caused earlier onset of gut ischaemia in a model of haemorrhagic shock. Even at low doses, dopamine may increase cardiac contractility and systemic resistance, and low dose dopamine has been reported to cause tissue necrosis.[61] Furthermore, even if dopamine were without risk, its effects can be unpredictable. For example, the maximal effect of low dose dopamine infusion in oliguric, euvolaemic patients in ICUs is temporally quite variable.[62] Also, it has been suggested that desensitisation of renal dopaminergic receptors occurs with prolonged administration.[63] These considerations argue against the routine use of 'renal-dose' dopamine for patients with (or at risk of) renal insufficiency.

Two clinical trials have been published using dopamine to prevent radiocontrast-induced ATN. One study[64] assessed the effects of dopamine infusion on serum creatinine at day 3 after radiocontrast administration in patients with baseline serum creatinine levels of >2.0 mg/dl. This study showed an improvement in serum creatinine levels with dopamine compared with a control group who received mannitol. However, given the evidence that mannitol may actually be harmful in this setting,[21] this was probably not the appropriate control group. In the only other controlled trial,[23] there was no difference in the incidence of ATN (30 to 40%) with or without dopamine in a small series. For this indication dopamine has not been proven to be helpful, while volume expansion with saline is unproven but potentially helpful.

At least thirty clinical trials have been published to date, both for prevention of ATN and treatment of early ATN (including radiocontrast-induced ATN) with dopamine.[56] Many of these, however, used surrogate markers (urine output, RBF, serum creatinine levels or creatinine clearance) rather than clinical outcomes (mortality, haemodialysis). Only 3 were positive, one being the study by Hall et al. cited above.[64] In one of the other studies,[65] a significant difference in creatinine clearance and a decrease in ARF were found in liver transplant patients treated with 2 μg/kg/min of dopamine. However, the findings of this study were not supported by a study,[66] also in liver transplant patients, which used dopamine 3 μg/kg/min and found no difference compared with placebo in terms of creatinine clearance or the incidence of ARF (4% in both groups). The results of a small study[67] appear to suggest that dopamine may be useful in shortening the recovery time from interleukin-2-induced ARF. Apart from these studies, the remainder are all negative. Among these is a recent study[63] in which dopamine infusion failed to improve renal function in patients with sepsis except for a transient increase in creatinine clearance in patients not in shock. Of note, in a small study (n = 18) of critically ill patients at high risk for ATN,[68] low dose dobutamine improved creatinine clearance without diuresis, while low dose dopamine produced diuresis without a change in creatinine clearance.

Clinical trials have failed to demonstrate a beneficial effect from dopamine infusion for treatment or prevention of ATN.[69] Accordingly, based on existing evidence, the use of dopamine specifically to improve renal function cannot be supported. At the same time, some patients may benefit from the combined inotropic, vasopressor, renal vasodilator and diuretic effects of this drug. However, as always, when apparently safer alternatives are available, they should be used first. For example, loop diuretics are much more effective diuretics than dopa-

mine and are probably safer. Similarly, dobutamine or norepinephrine (noradrenaline) may be better choices for patients requiring more specific haemodynamic support.

Although there is clinical evidence in healthy, normotensive humans that concomitant low dose dopamine infusion can prevent the decrease in RBF caused by moderate dose norepinephrine infusion,[70] the clinical significance of this finding in patients with hypotension is uncertain. In addition, a recent study in dogs demonstrated that norepinephrine infusion during endotoxic shock increased, rather than decreased, RBF.[71]

3.3.4 Atrial Natriuretic Peptide Analogues

Atrial natriuretic peptide (ANP), a 28-amino acid circulating peptide secreted by cardiac atria, promotes preglomerular arteriolar dilation and postglomerular arteriolar constriction, resulting in an increased GFR which can be independent of RBF. Studies of synthetic analogues of ANP in animal models of ATN have demonstrated the expected haemodynamic changes.[72] In an open-label study of 53 patients with intrinsic ARF, human ANP infusion improved GFR and reduced the need for dialysis, while mortality was not changed.[73] A multicentre trial of 504 patients with ATN evaluated treatment with the synthetic ANP analogue anaritide compared with placebo.[74] Unfortunately, overall mortality and dialysis-free survival were not affected, although subgroup analysis suggested that oliguric patients (<400ml urine/day) had improved dialysis-free survival, while nonoliguric patients had worsened dialysis-free survival with anaritide. This worsening in outcome in nonoliguric patients was thought to be due to the hypotensive adverse effects of anaritide. Some data also exist regarding the use of ANP analogues to prevent radiocontrast-induced ATN, primarily a small clinical study in which ANP attenuated the RBF decrease in patients with diabetes mellitus exposed to radiocontrast, but the study was too small to interpret outcomes.[75]

A renal natriuretic peptide, from the same gene as ANP, is transcribed and released from renal tubular cells into the distal tubule. This peptide, called ularitide (urodilatin), has renal haemodynamic and natriuretic effects similar to those of ANP but apparently with less systemic hypotension.[76] Several small clinical studies have been conducted in the settings of liver transplantation and cardiac surgery,[77,78] the results of which suggest that ularitide is safe when administered intravenously; however, larger positive studies are required to warrant clinical use of the drug.

Although the results of the anaritide trial[74] might lead some to advocate the use of ANP analogues in oliguric ATN, the uncertainty regarding why this subgroup improved while nonoliguric patients worsened calls for at least one confirmatory trial before bringing ANP analogues into practice. The effects of ANP analogues on medullary oxygenation are not yet clear, and thus in some patients there may be risk of doing harm rather than good.

3.3.5 Adenosine Antagonists

It has been hypothesised that adenosine receptor blockade using theophylline and pentoxifylline may be a way to prevent ATN in certain settings, specifically radiocontrast administration. Animal studies of radiocontrast administration using theophylline pretreatment, have demonstrated attenuation of intrarenal vasoconstriction.[79] Subsequently, in a study of humans receiving low osmolar radiocontrast, GFR decreased modestly without treatment but was unchanged with theophylline 5 mg/kg pretreatment.[80] In another study of 58 patients receiving high osmolar radiocontrast, pretreatment with theophylline 165mg abolished the decline in GFR seen with placebo.[81] The implications of these data, in terms of clinical outcomes, are not clear, and routine use of theophylline is not yet warranted. Specifically, recent data differentiating the renal location and effects of different adenosine receptor subtypes suggests that selective adenosine receptor antagonists warrant investigation.[16]

3.3.6 Calcium Antagonists

Calcium antagonists induce preglomerular arteriolar dilation and an independent natriuresis.[82] With acute administration, they generally produce a parallel rise in RBF and GFR, whereas with chronic administration these effects diminish.[83] Additional effects include reduction of intracellular calcium flux

associated with cell injury, blockade of angiotensin-induced cytokine formation, and oxygen free-radical scavenging.[84] Whether these additional effects play any role in the utility of calcium antagonists in preventing or slowing the progression of either acute or chronic renal failure, is not clear. Although 3 main classes of calcium antagonists exist, available data suggest that renovascular effects are similar across classes, and that there is little reason at present to select one class over another with regard to renal protection.[83] In acute renal failure, calcium channel blockade has been advocated and studied in several settings, and there are sufficient data available for review for radiocontrast administration, and for renal transplantation accompanied by cyclosporin administration.

In animal models of acute toxicity from radiocontrast media, data indicate that calcium channel blockade does indeed attenuate renal vasoconstriction.[85] A clinical study of 35 patients given nitrendipine 20 mg/day for 3 days, starting the day before radiocontrast, demonstrated a preservation of GFR and attenuation of renal tubular enzymuria compared with placebo.[86] In another clinical study,[30] 20 patients considered at high risk for nephrotoxicity were given a single dose of nifedipine 20mg prior to contrast, with the untreated group showing a decrease in urine output and sodium excretion, but no difference in creatinine levels when compared with treated patients. A third patient study[87] demonstrated that prophylactic nifedipine appeared to abolish changes in renal haemodynamics observed with high osmolarity contrast. However, another patient study[88] failed to show any renal effect of nifedipine in radiocontrast administration. In summary, although calcium channel blockade has been studied for some time in this setting, there is presently no evidence that relevant outcomes are affected, and the risks of routine or selective prophylaxis are not known.

Renal transplantation is a unique scenario in which the risk of ischaemic ATN is usually followed quickly by the risk of cyclosporin- (or tacrolimus-) related toxicity. Calcium antagonists are often routinely included in donor preservation solutions. In one controlled but nonblinded clinical study[89] in which diltiazem was not only included in the preservation solution, but also given to recipients before and after renal transplantation, treated patients had less ATN, less total haemodialysis, and higher GFR despite higher cyclosporin plasma levels. Other clinical studies have demonstrated shorter hospital stays and lower serum creatinine levels at 1 month with nifedipine,[90] and reduced incidence of post-transplant ATN.[91]

In summary, available data support the use of calcium antagonists in renal transplant patients. Whether their effects are mainly to reduce primary ATN or to reduce cyclosporin toxicity is not clear, nor is it clear whether it is important to administer them to the recipient pretransplantation. Furthermore, when administering calcium antagonists in this setting, the effect of these agents as inhibitors of cyclosporin metabolism must be considered,[92] and dosage of cyclosporin adjusted as needed. Indeed, the problems associated with this drug interaction may be greater than any benefit from the drug.

3.3.7 Other Drugs

A variety of other pharmacological approaches have been proposed to have potential benefit in preventing or attenuating ATN. These include nitric oxide modulation, endothelin inhibition, attenuation of oxidative stress, and modulation of the activity of integrins and intercellular adhesion molecules.[93] These are all clinically untested.

4. Pharmacological Therapy to Enhance Recovery

Therapies that enhance recovery from established ARF do not yet exist. Currently there is interest in several growth factors, specifically epidermal growth factor, an insulin-like growth factor, and hepatocyte growth factor, each of which is under investigation in laboratory settings.[94] Interestingly, although some specific animal models of ATN have benefitted from growth factor therapy, so far none of this success has been translated to ATN as it occurs in humans. Whether the problem lies with the species or the details of the models,

drug therapy to enhance renal recovery is still on the distant horizon.

5. Conclusion

In making rational drug treatment decisions, clinicians must synthesise general concepts of renal pathophysiology, evidence from laboratory and clinical studies, and the specific aspects of each patient. No clear evidence exists mandating specific drug therapy in specific instances of ischaemic or nephrotoxic ATN. At the same time, any drug therapy has potential adverse effects which must be considered. The following approach is supported by the available evidence detailed above:

1. Identify and (when possible) eliminate suspected causes of renal injury.

2. Correct hypovolaemia. Volume loading, while not proven, probably provides the greatest balance of benefit to risk of all active therapies.

3. Provide support as needed, including renal replacement.

4. Avoid loop diuretics for renal protection recognising that their benefit is unproven, and that the risk of worsening hypovolaemia exists and may outweigh any benefit.

5. Avoid mannitol. Recognise that any benefit is unproven, and that the risks of worsening hypovolaemia and of increasing renal medullary oxygen demand may outweigh any benefit.

6. Use dopamine only in patients whose systemic haemodynamic profiles suggest the need for either modest inotropic or vasopressor support. Do not use dopamine as a renal protective agent or as a substitute for appropriate volume loading. Recognise that dopamine may have significant risks, and any benefit is unproven.

7. There is no proven indication for atrial natriuretic peptide analogues or adenosine antagonists (e.g. theophylline) in the prevention or management of ARF.

8. Calcium antagonists appear to be useful in protecting renal function after renal transplantation. The extent to which this is due to attenuation of cyclosporin-induced vasoconstriction is not clear. There are no other proven indications for calcium antagonists in the prevention or management of ARF.

9. For prophylaxis against radiocontrast-induced ATN, saline infusion should be administered for optimal hydration. Neither diuretics nor dopamine appear effective and may be harmful.

10. In the management of rhabdomyolysis, aggressive fluid loading is advised, while diuretics are unproven and probably unnecessary.

11. When loop diuretics are used in the management of ATN, continuous infusion may be more efficacious than bolus administration in achieving diuresis. However, there is no evidence that this manoeuvre improves survival or renal recovery.

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