Protecting the kidney during critical illness

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Purpose of review

Acute renal failure causes considerable morbidity and mortality in critically ill patients. To date, there are few therapies available to clinicians that alter outcome. This review will focus on clinical and basic science research efforts related to the diagnosis, pathophysiology, prevention, and treatment of acute renal failure.

Recent findings

The incidence of acute renal failure may be increasing and the mortality rate continues to be significant. The development of sensitive, predictive biomarkers of acute renal failure may help to diagnose the syndrome earlier and allow for meaningful therapeutic intervention. A number of new therapies are in development for acute renal failure. Many show promise in animal models of acute renal failure but prospective studies in humans are lacking.

Summary

Despite the present lack of therapies for the treatment and prevention of acute renal failure, there are reasons to be optimistic. Recent research has led to the development of several different strategies that may provide a breakthrough in the treatment of acute renal failure.

Keywords

acute kidney injury, acute renal failure, acute tubular necrosis, biomarkers, renal protection

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Abbreviations

ARF	acute renal failure
ATN	acute tubular necrosis
GFR	glomerular filtration rate
ICU	intensive care unit
IL	interleukin
MSC	mesenchymal stem cell
NGAL	neutrophil gelatinase-associated lipocalin
RRT	renal replacement therapy

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Introduction

Acute renal failure (ARF) is a syndrome characterized by a rapid decline in glomerular filtration rate (GFR) [1•]. A more precise definition of ARF remains elusive as sudden changes in renal function are not rapidly detectable by present standard laboratory tests. As Bellomo *et al.* [2] describe in their review of renal physiology, renal function encompasses tasks ranging from hormone production, to acid–base status, to modulation of blood pressure. At present, clinicians rely on measures of urine production and serum creatinine to monitor renal function and to guide therapy in the face of renal failure.

Despite significant medical and scientific effort, ARF continues to cause considerable patient morbidity and mortality. A recent systematic review compiled mortality rates for ARF in medical and surgical patients from 1956 to 2003 [3•]. A comparison of 5-year cohorts demonstrated a mortality rate of approximately 50% with no improvement in survival in the intervening 47 years. In contrast to this, other recent studies suggest that while the incidence of ARF continues to increase, the mortality rate of ARF may be closer to 20–30% for in-hospital patients [4•,5]. With respect to critically ill patients, the Beginning and Ending Supportive Therapy (BEST) for the Kidney study of ARF in intensive care unit (ICU) patients reported a mortality of 60.3% [6•]. A population-based surveillance cohort study of adult ICU patients with ARF requiring renal replacement therapy reported a 1-year mortality of 64% [7].

In 2004, the Acute Dialysis Quality Initiative (ADQI) Group proposed a definition for ARF in critically ill patients [8]. Known as the RIFLE criteria (risk, injury, failure, loss, and end stage) this classification is based on changes in serum creatinine and urine output. A retrospective review of over 20 000 patients found that the RIFLE criteria independently predicted hospital mortality in patients with ARF [9•]. Another retrospective study also found the RIFLE criteria to predict mortality from ARF in cardiac surgery patients [10•].

While the RIFLE criteria are a major step forward in the diagnosis of ARF, whether they can identify patients early enough in the development of renal injury to allow for meaningful intervention remains to be elucidated. As Hewitt *et al.* [11] discuss in their review of protein biomarkers, a troponin-like marker of renal injury may enable even earlier recognition of the disease and more timely intervention. The present lack of progress in the

prevention of ARF is summarized in a recent Cochrane review that concluded there was insufficient evidence to recommend any specific therapy to prevent ARF during surgery [12].

Recent advances in the diagnosis and treatment of ARF, however, give reason for optimism. This review will describe some of the pertinent pathophysiology of ARF and biomarkers of renal injury under investigation. Also, novel therapeutic targets and drugs will be discussed as they relate to the prevention and treatment of ARF.

Causes of acute renal failure

ARF is classically divided into prerenal, intrinsic renal, and postrenal causes [13••]. Prerenal azotemia is due to absolute or relative renal hypoperfusion which if not corrected can progress to ischemic acute tubular necrosis (ATN). Renal causes can be subdivided into vascular, glomerular, interstitial, and tubular categories. Postrenal causes include obstruction of the bladder or ureters [13••].

In the critical care population most cases of ARF are due to intrinsic renal causes [14]. ATN is the underlying cause in the majority of these cases, with an incidence greater than 70% reported in the literature [14]. Often multifactorial in origin, ATN can be caused by ischemia or toxic processes [1•,13••,14–16]. Implicated in approximately 50% of ARF cases, sepsis is the number one cause of ARF in an ICU setting [14]. For the purposes of this review ARF and ATN will be considered as synonymous.

Pathophysiology of acute tubular necrosis

ATN was first used to describe the histologic findings of ARF found on autopsy [17]. Tubular necrosis occurs in the S3 segment of the proximal tubule and to a lesser extent the thick ascending limb. This area corresponds to the relatively hypoxic outer medullary region of the kidney [1•,17].

A detailed review of the pathophysiology of ATN is beyond the scope of this review. The reader is referred to recent reviews on this topic [1•,13••,15,17]. Hypoxia, ischemia–reperfusion injury, necrosis, apoptosis, and inflammation all seem to contribute to the pathogenesis of ARF. It is postulated that hemodynamic alterations lead to renal vasoconstriction and medullary congestion [1•]. This in turn leads to a cascade of altered calcium handling, endothelial injury, and increased inflammatory markers [17]. Renal tubule dysfunction leads to ATP depletion, induction of apoptosis, cytoskeleton alterations, free radical formation, and oxidant injury [1•].

Sepsis-induced ARF is generally thought to stem in part from renal vasoconstriction secondary to norepinephrine, angiotensin II, and endothelin [15]. A recent study of ARF induced by live *Escherichia coli* infusion in conscious sheep found the opposite and challenges this widely held view [18••]. Flow probes were placed around the pulmonary artery and left renal artery while invasive measures of arterial blood pressure and central venous pressure were monitored. *E. coli* infusion resulted in a hyperdynamic state with systemic vasodilatation, renal vascular vasodilatation, and significant increases in renal blood flow [18••]. After 48 h serum creatinine significantly increased and creatinine clearance decreased 80%. This study raises questions about other animal models' ability to replicate the pathogenesis of sepsis-induced ARF in humans.

Biomarkers of acute renal failure

Serum creatinine lacks sensitivity and specificity as a marker of GFR [2,19]. As Fig. 1 shows, changes in creatinine do not occur until many hours after a marked reduction in GFR [20]. Moreover, acute kidney injury (AKI), defined as a small change (0.1–0.5 mg/dl) in plasma creatinine that does not lead to dialysis-dependent ARF, has significant clinical implications. Recent studies demonstrated small changes in plasma creatinine lead to increased ICU and hospital length of stay, increased morbidity and mortality after cardiac surgery, and may increase the risk of subsequent renal failure [2,8]. Thus, early recognition and therapy of ARF could potentially have a positive impact on outcome. In order to diagnose and treat ARF earlier in its time course, efforts are underway to find a biomarker of ARF. A biomarker can be defined as any measurable patient parameter that can be used as an indicator of normal function, progression of disease, or response to therapy [11].

Neutrophil gelatinase-associated lipocalin (NGAL) is an iron chelator/transporter expressed in the early phase of acute tubular injury [21•]. The exact role is unclear but it is thought to be involved in the repair processes after ischemia–reperfusion injury; perhaps with tubule re-epithelialization [22]. Recent data suggest that NGAL is a sensitive marker of renal injury. In a study of renal transplant recipients, both urinary NGAL and interleukin 18 (IL-18) increases predicted delayed graft function approximately 24 h faster than the rise in serum creatinine [23•]. A prospective study of cardiac surgery patients found that urinary NGAL levels were significantly elevated within 1 h of surgery (Fig. 2) [24•].

Caspases are a family of intracellular cysteine proteases that are thought to play a role in a wide variety of cellular functions including apoptosis and inflammation [25•]. IL-18 is a proinflammatory cytokine produced by caspase-1 that has been implicated in the pathogenesis of ARF [26]. Recent studies suggest that urine IL-18 is an early biomarker of acute kidney injury both in patients undergoing cardiopulmonary bypass and for ICU patients [27•,28•].

Figure 1 Relationship between glomerular filtration rate (GFR), creatinine clearance, and plasma creatinine levels

As depicted in the upper panel, a sudden decrease in GFR corresponds to a dramatic reduction in creatinine clearance. This in turn causes a slow increase in plasma creatinine levels as depicted in the lower panel. Modified with permission from Moran and Myers. [20].

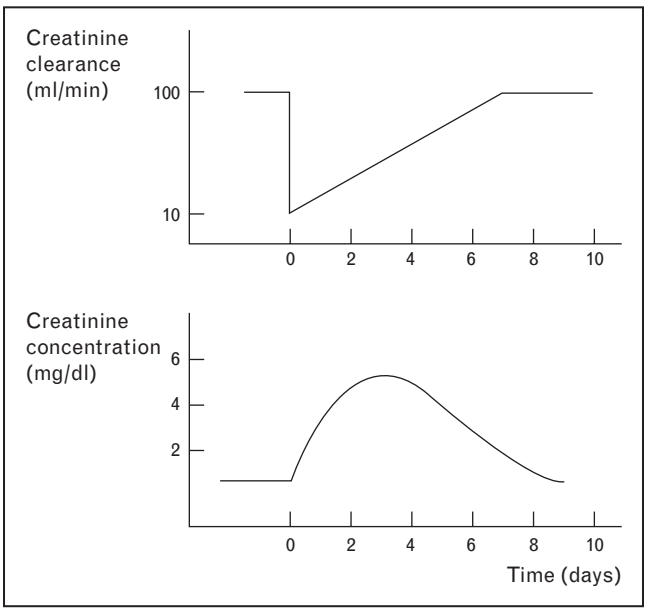
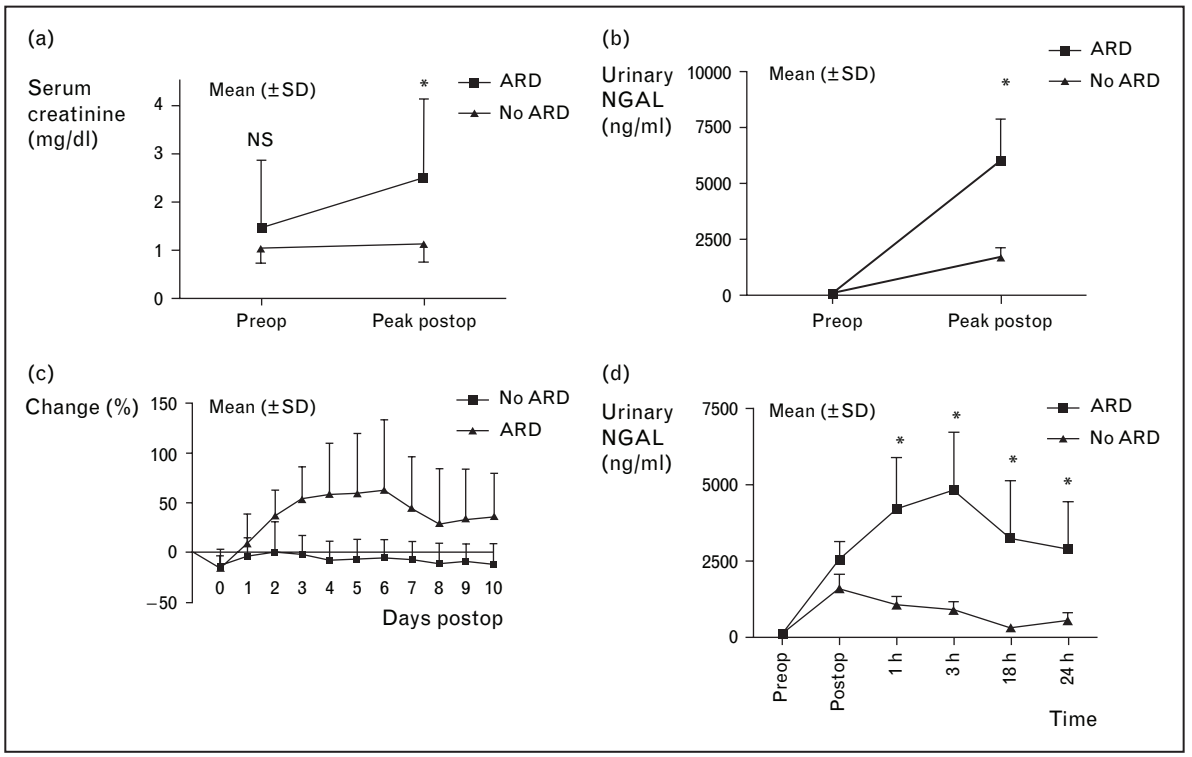


Figure 2 Change in urinary neutrophil gelatinase-associated lipocalin (NGAL) concentration in patients with postoperative acute renal dysfunction (ARD) versus no ARD after cardiopulmonary bypass (CPB)



(a) Change in preoperative (preop) and peak postoperative (postop) serum creatinine concentrations. (b) Change in preoperative and peak postoperative (within 24 h of surgery) urinary NGAL. (c) Change in serum creatinine. (d) Urinary NGAL concentration after CPB. Within 1 h of surgery, urinary NGAL levels were significantly elevated in the ARD group compared with those without ARD. NS, nonsignificant; $^{*}P < 0.05$ for ARD versus no ARD. Modified with permission from Wagener *et al.* [24•].

Cystatin C is a basic protein produced by nucleated cells that is freely filtered at the glomerulus then reabsorbed and catabolized by tubular epithelial cells [29]. Studies evaluating whether serum cystatin C levels are an improvement over serum creatinine based measurements of GFR have provided conflicting results [30,31]. With respect to cystatin C levels during ARF, an ICU-based study found it took 3 days for serum cystatin C to become significantly elevated, no different than for plasma creatinine [32].

Kidney injury molecule-1 (KIM-1) is a transmembrane protein expressed in dedifferentiated proximal tubule epithelial cells after tubular injury and also in renal cell carcinoma patients [33•,34]. In ARF, KIM-1 can be detected within 12 h of ischemic injury but larger prospective studies are needed to validate these initial findings [35].

Prevention and treatment of acute renal failure

Given the present lack of evidence for therapies to prevent or treat ARF, clinicians typically rely on maintenance of renal perfusion, maintenance of euvolemia, and avoidance of known nephrotoxic agents as cornerstones of care. Other suggested therapies include diuretics, vasoactive agents, antioxidants, and renal replacement therapy (RRT) [12,36].

The difficulty in evaluating the literature on this topic stems from the previous lack of a standardized definition for ARF, the multifactorial nature of ARF, and the lack of the availability and use of early, predictive biomarkers for ARF.

Diuretics

A cohort study of 552 patients with ARF, after adjusting for covariates and propensity scores, found that diuretic use was associated with increased risk of death and nonrecovery of renal function [37]. In contrast, a more recent prospective, multicenter study by the BEST Kidney Investigators found that diuretic use was not associated with increased mortality in ARF patients [38]. In a rat ischemia–reperfusion model of ARF, furosemide was found to increase renal blood flow and to attenuate ischemia-induced gene expression [39]. In patients with established ARF requiring dialysis, furosemide did not alter survival or renal recovery [40]. Overall, there remains no compelling evidence to recommend the routine use of diuretics in patients with ARF. Despite promising animal studies with diuretics this research has not led to similar results in human studies of ARF.

Vasoactive agents

The use of dopamine in the treatment of ARF has been extensively reviewed [41•]. Dopamine has been shown to worsen renal perfusion in the critically ill and its use cannot be recommended [42].

The selective dopamine-1 agonist, fenoldopam mesylate, increases renal blood flow and may have a benefit in the treatment of ARF. In a critically ill population at risk of ARF, 0.1 μg/kg/min fenoldopam did not cause hemodynamic changes and produced a more significant decrease in creatinine than 2 μg/kg/min of dopamine [43]. A prospective, double-blind, placebo-controlled trial of fenoldopam in septic patients found that 0.09 μg/kg/min fenoldopam prevented the development of ARF [44•]. In contrast to this, another double-blind, placebo-controlled trial found that fenoldopam did not alter the incidence of death or dialysis in critically ill patients with early ARF [45]. Overall, the role of fenoldopam in prevention and treatment of ARF is promising but ultimately remains to be determined in larger, multicentered trials.

Antioxidants

N-Acetylcysteine is an antioxidant that has been evaluated for the prevention of contrast-induced nephropathy (CIN). Recent studies suggest that N-acetylcysteine may have a beneficial dose-dependent effect in populations at high risk of CIN [46•,47]. In animal studies, N-acetylcysteine has a positive effect on renal blood flow and GFR in an ischemic model of ARF [48]. An ischemia–reperfusion model of ARF found that N-acetylcysteine failed to improve renal hemodynamics after reperfusion but decreased interstitial inflammation and oxidative stress [49•,50]. When extended to surgical patients undergoing open repair of abdominal aortic aneurysm or coronary artery bypass graft, N-acetylcysteine treatment failed to show benefit [51•,52•].

Renal replacement therapy

Patients with ARF who require RRT have a mortality rate of approximately 50% [53]. Despite conflicting reports, there is clinical evidence that an increased dialysis dose may confer a survival advantage for patients with ARF [54,55]. Recent research has shown that continuous veno-venous hemodiafiltration compared with continuous veno-venous hemofiltration alone significantly increases survival in critically ill patients with ARF [56••]. Further study is required to optimize the specific type and dose of RRT.

Experimental pharmacotherapy for acute renal failure

Beyond the aforementioned 'standard' therapies for ARF, a number of experimental pharmacotherapies are on the horizon, including volatile anesthetics, erythropoietin, adenosine receptor agonists and antagonists, and stem cells. Their efficacy in animal models of ARF must be tempered with the realization that many successful

treatment strategies in animals have not translated to successful clinical studies in humans.

Volatile anesthetics

Volatile anesthetics protect against renal ischemia–reperfusion injury in rats [57]. Sevoflurane has direct antiinflammatory and antinecrotic effects *in vitro* in human kidney proximal tubule cells [58•]. In clinically relevant doses, 4 h of sevoflurane anesthesia activated prosurvival kinases ERK and Akt and upregulation of heat shock protein-70 [58•].

Erythropoietin

Erythropoietin receptors are expressed in multiple tissues including the human kidney. In animal models of ischemia–reperfusion injury erythropoietin can reduce damage at the endothelial and tubular level [59]. An in-vivo model of ischemia–reperfusion injury found that the delayed administration of either darbepoetin or erythropoietin significantly inhibited apoptotic cell death and augmented functional recovery [60••]. Darbepoietin or erythropoietin was effective with a 6 h delay after the ischemic insult which reinforces the need for early biomarkers of ARF to allow for meaningful intervention. A retrospective cohort study did not find that erythropoietin administration was associated with renal recovery in critically ill patients with ARF requiring RRT [61•]. A prospective randomized controlled trial is needed to address the potential benefits of erythropoietin in ARF.

Adenosine

The role of adenosine in kidney function has been extensively reviewed [62•]. Adenosine can mediate a variety of effects in the kidney depending on the receptor subtype involved, including vasoconstriction, vasodilatation, tubuloglomerular feedback, and inhibition of renin secretion [62•]. Adenosine's role in ischemia–reperfusion injury is complex as beneficial effects have been reported with both A_1 receptor agonists, A_{2a} receptor agonists, and the unselective adenosine receptor antagonist theophylline [63–65]. Recent research found that theophylline improved allograft function in a rat kidney transplant model [66•]. At present the role of adenosine receptors in treatment of ischemia–reperfusion injury in ARF holds potential but ultimately remains to be determined.

Stem cells

Another strategy in the treatment of ARF is to supply stem cells to aid in regeneration of damaged tubular cells. Studies have provided evidence in animal models of ischemia–reperfusion injury and cisplatin nephrotoxicity that mesenchymal stem cells (MSCs) improve renal function and recovery [67,68•]. Recent studies also suggest that MSCs may act via a paracrine mechanism in the kidney rather than by transdifferentiating into renal tubule cells [68•]. A magnetic resonance imaging study showing iron-dextran labeled MSCs in the glomeruli rather than the tubules or vascular endothelium lends support to this hypothesis [69•].

Conclusion

Despite tremendous scientific effort, ARF continues to cause significant patient morbidity and mortality. The diagnosis of ARF with the RIFLE criteria is a major step forward as a means to standardize and compare future research. A further advance in the diagnosis of ARF would be the development of a biomarker of the disease. Several potential biomarkers are being investigated and ultimately serum creatinine may lose its designation as the standard clinical measure to follow renal injury. Before this becomes a reality many more questions about the efficacy of biomarkers remain to be answered. Foremost, biomarkers must prove themselves to be versatile across a variety of populations with different coexisting diseases and without confounding influences. Present therapies for the prevention and treatment of ARF are limited but research also shows that several different strategies are being developed that may provide a breakthrough in the treatment of ARF.

Acknowledgement

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 158).

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