

# Pharmacologic Treatment of Acute Kidney Injury: Why Drugs Haven't Worked and What Is on the Horizon

Sang Kyung Jo, Mitchell H. Rosner, and Mark D. Okusa

*Department of Medicine, University of Virginia, Charlottesville, Virginia*

**Current strategies to limit the extent of injury in acute renal failure are based on extensive studies that identified cellular and molecular mechanisms of acute kidney injury. Despite successes in various animal models, translation to human studies has failed or studies are inconclusive. This review describes past failures and barriers to successful clinical trials. It also focuses on promising preclinical studies using novel compounds that currently are in or close to human investigation. Implementation of previous or novel compounds in well-designed clinical trials provides hope for the successful treatment of this devastating disorder.**

*Clin J Am Soc Nephrol* 2: 356–365, 2007. doi: 10.2215/CJN.03280906

**A**cute kidney injury (AKI) is due to a variety of conditions and has serious consequences. From large but separate databases of US hospitalizations in the past 10 to 15 yr, there is evidence for a marked increase in the incidence of AKI (1,2). This, in part, reflects the increasing comorbidity and age of patients who have AKI. It is widely recognized that AKI leads to high morbidity and mortality in hospitalized patients. There may be hope, however, that mortality rates are decreasing (1,2); nevertheless, mortality rates remain unacceptably high, and there is an urgent need for effective therapy (3).

Except for a few isolated studies, the vast majority of animal and clinical studies have yet to demonstrate conclusively the benefit of pharmacologic treatment of AKI. This review summarizes barriers to successful outcomes of human studies (Table 1) and describes novel pharmacologic therapies that are on the horizon for the treatment of AKI (Table 2).

## Barriers to Successful Clinical Trials in AKI *Patients and Comorbid Factors*

The rising incidence of AKI over the decades is associated with a changing spectrum of illnesses. In particular, there is evidence for a heavy burden of patients with significant comorbid and extrarenal complications (1,4). Supporting this, using the Deyo-Charlson comorbidity index, patients with higher comorbidity were associated with a higher incidence of AKI, especially when they were on mechanical ventilation (1). In a multicenter study of 618 patients who had AKI and were in the intensive care unit (ICU; Program to Improve Care in Acute Renal Disease Network [PICARD]), the incidence of comorbid conditions was high: 30% with chronic kidney disease, 37% with coronary artery disease, 29% with diabetes, and 21% with

chronic liver disease. AKI was accompanied by extrarenal organ system failure in most patients. These comorbid conditions likely are contributors to failed treatment regimens, especially when mortality is used as an end point for the clinical trial.

## *Pathogenesis of AKI Is Complex*

The pathogenesis of AKI is complex. Ischemia and toxins are major factors that precipitate injury, and although the initiating events may be dissimilar, subsequent injury responses likely involve similar pathways. As an example, AKI that is associated with ischemia is due to a reduction of renal blood flow below the limits of blood flow autoregulation. A variety of molecular responses that are "maladaptive" and stereotypical then occur. These responses lead to endothelial and epithelial cell injury after the onset of reperfusion (5). Pathogenic factors such as vasoconstriction, leukostasis, vascular congestion, apoptosis, and abnormalities in immune modulators and growth factors have formed the basis of rational therapeutic interventions. However, many of these targeted therapies have failed, are inconclusive, or have yet to be performed (6,7). Given the complexity of the pathogenesis of AKI, it may be naïve to expect that one therapeutic intervention would have success unless that intervention focuses on prevention of AKI and targets a specific initiating cause. There are encouraging results from therapeutic interventions in the prevention of contrast nephropathy: Saline (8), sodium bicarbonate (9), low and isosmolar contrast (10,11), and theophylline (12). Given the multiple overlapping pathways that are involved in AKI, therapies may need to target multiple pathways simultaneously to achieve success (13).

## *AKI Is a Multisystem Disease*

Although AKI is an independent risk factor for mortality from cardiopulmonary dysfunction (14), in most studies of AKI, renal failure *per se* usually is not the cause of death (13). In several studies, either congestive heart failure (15,16) or non-cardiogenic acute respiratory distress syndrome (17) was asso-

*Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).*

**Address correspondence to:** Dr. Mark D. Okusa, Division of Nephrology, Box 800133, University of Virginia Health System, Charlottesville, VA 22908. Phone: 434-924-2187; Fax: 434-924-5848; E-mail: [mdu7y@virginia.edu](mailto:mdu7y@virginia.edu)

Table 1. Complexity of human AKI<sup>a</sup>

Barriers to Successful Treatment of AKI
Patient and comorbid factors
Complexity of AKI
AKI is a multisystem disease
Design issues clinical trials
biomarkers
definition of AKI
end points in clinical trials

<sup>a</sup>AKI, acute kidney injury.

ciated with AKI. The potential systemic effects of AKI involve multiple organs and lead to high mortality. Animal studies have confirmed that isolated AKI may lead to distant cardiopulmonary dysfunction (17,18). The complexity that is created by the systemic effects of isolated AKI may have contributed to the ineffectiveness of treatments in the past. These observations also suggest that potential therapeutic strategies should not be limited to treatment of kidney injury alone but should be broad based to treat systemic effects of AKI.

#### Design Issues in Clinical Trials

Common design reasons for the lack of success in clinical trials of AKI include low statistical power, lack of a consensus definition of AKI in previous trials, improper end points, difficulty in timely administration of the drug, adverse effects of the drug, and patient heterogeneity (19). Furthermore, difficulties in patient recruitment and randomization that control for illness severity have proved to be barriers to successful clinical trials. Three clinical trials in AKI serve as examples of these difficulties.

Recombinant human IGF-I (rhIGF-I) reduced kidney injury when administered 30 min after reperfusion in experimental ischemia-reperfusion injury (IRI) (20). In addition, rhIGF-I is known to decrease apoptosis and inflammation in experimental acute renal failure (21,22). Therefore, it was surprising that rhIGF-I failed to reduce AKI in human trials. This may be due, in part, to hypotension associated with rhIGF-I (42 *versus* 27%), but, in addition, administration could have been delayed by as much as 6 d after diagnosis (23). Because the therapeutic window for prevention of AKI is likely to be narrow (as illustrated in Figure 1), delayed treatment is likely to be ineffective.

Similar design issues were seen in the trial of atrial natriuretic peptide (ANP). ANP is known to dilate afferent arterioles, constrict efferent arterioles, induce natriuresis (24), and reduce IRI in animal models. However, when infused into humans, anaritide (human ANP [h-ANP]; 200 ng/kg per min) did not reduce 21-d dialysis-free survival (25). A subgroup with oliguria seemed to fare better with improved 21-d dialysis-free survival, but this outcome was not confirmed in a subsequent prospective study (26). A confounding variable was the low BP that occurred in the h-ANP group. In a subsequent study that used a lower dosage of h-ANP (50 ng/kg per min), significantly less hypotension was observed and 21-d dialysis-free survival,

and estimated GFR was improved (27). This study illustrates the importance of appropriate dosing in designing therapeutic trials. The low BP that was observed in previous studies was due to the four-fold higher dosage used. Therefore, potential adverse effects of the therapeutic agent may offset the benefits of the intervention. In this case, anaritide induced hypotension. Despite these positive results, it is important to emphasize that this study lacked a large enough sample size to ensure that the positive result was not due to chance. The positive results of this small study from two centers will need to be confirmed in a larger, prospective, multicenter, randomized, clinical trial.

Last, dopamine has been shown to be ineffective in the treatment of human AKI despite an increase in natriuresis (28–30). Although these studies do not support the use of “low-dosage” dopamine for the treatment of AKI, it continues to be used today in critically ill patients. In a multicenter, randomized, double-blind, placebo-controlled study of low-dosage dopamine in patients who were admitted to the ICU, 161 patients received low-dosage dopamine (2  $\mu$ g/kg per min) and 163 patients received placebo (28). There was no difference between the dopamine and placebo groups in renal function as assessed by serum creatinine, those who required renal replacement therapy, durations of ICU stay, or deaths. In a recent meta-analysis of 61 clinical trials that randomly assigned 3359 patients, there was no effect of low-dosage dopamine on mortality or need for renal replacement therapy (29). Although the reasons that low-dosage dopamine is ineffective in the treatment of AKI are not known, investigational studies in both animals and humans have shed some light. In animal studies, it has been shown that dopamine increases outer medullary blood flow by 35% but does not increase medullary  $P_{O_2}$ , an important measure of tissue oxygen delivery during IRI. In humans, dopamine reduced renal vascular resistance in patients without AKI but paradoxically increased renal vascular resistance in patients with AKI (31). These results provide mechanisms that may explain in part the lack of success with this agent. In summary, numerous studies and meta-analyses unambiguously support the recommendation that low-dosage dopamine should not be used for the treatment of AKI.

Serum creatinine is a poor biomarker of AKI (3). Many factors regulate the generation, volume of distribution, and excretion of creatinine. Net excretion of creatinine is due to both filtration and, to a variable degree, proximal tubule secretion. Therefore, organic compounds and drugs may block creatinine secretion. Most important, the rise in serum creatinine is slow after AKI. By the time a change is observed in serum creatinine, a critical therapeutic window may have been missed (Figure 1). The earliest evidence of injury precedes frank acute tubular necrosis (depicted as AKI, Figure 1) and rises in serum creatinine and is likely the point at which interventions need to be introduced. This likely is the case in patients with ischemic AKI (*e.g.*, hypotension, severe volume depletion) in which a brief period of prerenal AKI may precede AKI. Conversely, patients may develop AKI with no antecedent period of prerenal AKI (*e.g.*, sepsis, nephrotoxins). In either case, the detection of the earliest evidence of AKI ultimately will necessitate the use of novel serum or urinary biomarkers. For example, patients with

Table 2. Emerging pharmacological agents for treatment of AKI<sup>a</sup>

Action/Mechanism	Drugs
Antiapoptosis/necrosis	Caspase inhibitors Nonselective caspase inhibitors Selective caspases 3 and 7 inhibitors Selective caspase 1 inhibitors Minocycline Guanosine Pifithrin- $\alpha$ PARP inhibitor
Anti-inflammatory	Sphingosine 1 phosphate analog Adenosine 2A agonist $\alpha$ -MSH IL-10 Fibrate PPAR- $\gamma$ agonist Minocycline Activated protein C iNOS inhibitor
Antisepsis	Insulin Activated protein C
Growth factor	Ethyl pyruvate Recombinant erythropoietin Hepatocyte growth factor
Vasodilator	Carbon monoxide release compound and bilirubin Endothelin antagonist Fenoldopam ANP

<sup>a</sup>ANP, atrial natriuretic peptide; iNOS, inducible nitric oxide synthase;  $\alpha$ -MSH, alpha-melanocyte-stimulating hormone; PARP, poly ADP-ribose polymerase; PPAR, peroxisome proliferator-activated receptor.

prerenal AKI could represent a group that demonstrates a graded increase in tubular enzymuria (biomarker) and other biomarkers that suggest the earliest evidence of epithelial cell injury yet insufficient to cause frank necrosis and demonstrable rises in serum creatinine. The use and validation of sensitive biomarkers may permit identification of individuals with early tubular injury and identification of a subgroup of patients who might be the target for early intervention. Currently, several urinary biomarkers are being validated (32–35).

AKI in the ICU leads to significant morbidity and mortality (36). Nephrologists in this setting serve as consultants and typically care for patients only when significant rises in serum creatinine or oliguria develop. As stated, at this point, significant injury has occurred and therapeutic interventions may be unsuccessful. Therefore, to ensure success of any clinical trial, close collaboration between intensivists and nephrologists is required to identify appropriate patients at the earliest stages of injury. Unfortunately, this has not always occurred in the design and implementation of clinical trials.

Defining clinically significant AKI is critical. In the past, clinical trials have used widely varying definitions that ranged from a 20 to 30% rise in serum creatinine to the need for dialysis, which has led to reported incidence of AKI of 1 to 25% (14,37) and mortality rates that varied from 28 to 90% (38,39).

The absence of consensus on a definition for AKI led to the Acute Dialysis Quality Initiative (ADQI) and the development of the Acute Kidney Injury Network (AKIN), which represents the efforts of workgroups that seek to develop consensus and evidence-based statements in the field of AKI. ADQI used a set of criteria called the RIFLE (Risk, Injury, Failure, Loss, and End stage) criteria (40), which were modified recently by AKIN (AKIN Amsterdam Meeting 2006, submitted for publication). Validation of the classification and staging system of AKI will be required in future clinical studies and holds promise that this classification scheme can improve the design of trials.

Finally, appropriate end points for clinical trials in AKI need to be defined (41). The end points can range from the need for dialysis at a specified time point to development of renal recovery or mortality at a specified end point. These specific end point goals have important implications for the appropriate size and power of trials as well as the potential for finding a positive outcome. For instance, an intervention that may have a small effect on renal function would not be discovered in a trial that focused on total mortality and was powered for that outcome.

### What Drugs Are on the Horizon?

Given the failure of multiple pharmaceutical agents in the therapy of AKI, novel agents are needed in well-designed

## Narrow Therapeutic Window

### Need for Sensitive Biomarkers

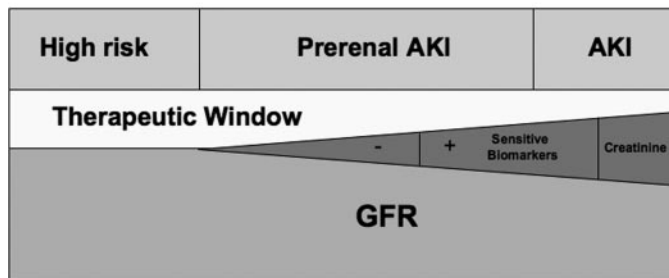


Figure 1. Narrow therapeutic window. Need for sensitive biomarkers. High-risk patients include those with risk factors for acute kidney injury (AKI) but have normal GFR. For example, they may include patients who have diabetes and hypertension or are taking medications such as nonsteroidal anti-inflammatory drugs or angiotensin-converting enzyme inhibitors. These individuals represent a population that needs to be identified to modify risk factors if possible and initiate preventive strategies when indicated (*e.g.*, contrast studies). Patients with prerenal AKI are those with prerenal urinary indices and failure of autoregulatory mechanisms that lead to a decrease in GFR (*e.g.*, dehydration). These individuals have the potential for rapid reversal of their prerenal condition. During this period, injury to brush border of proximal tubule cells may be present but undetectable. However, with novel biomarkers, identification of early injury and treatment is possible. Patients with AKI may represent an extension from severe prerenal AKI. Alternatively, in some conditions, AKI may not be preceded by a prerenal state (*e.g.*, sepsis, exposure to nephrotoxins). Serum creatinine is a late marker and will detect AKI after substantial injury is present. At this point, intervention may be too late.

clinical trials. A number of drugs and investigational compounds seem promising in preclinical studies (Table 2), and promising investigational compounds are used in clinical trials for a variety of indications. When possible, we have indicated whether these agents are in human studies for other indications because this may facilitate human investigation for AKI.

#### Antiapoptosis/Necrosis Agents

**Caspase Inhibitors.** Caspases are a family of proteases that are involved in the initiation and execution phase of apoptosis. Nonselective and selective caspase inhibitors are effective in attenuating renal injury in ischemia- or endotoxemia-induced AKI when administered before or at the time of injury (22,42,43). Pancaspase inhibitors are in early clinical trials (44), and early targets include hepatitis C and orthotopic liver transplantation.

**Minocycline.** Minocyclines are second-generation tetracycline antibiotics with proven human safety data. Minocycline is known to have antiapoptotic and anti-inflammatory effects. When administered 36 h before renal ischemia, minocycline reduced tubular cell apoptosis and mitochondrial release of cytochrome c, p53, and bax (45). Furthermore, minocycline reduced kidney inflammation and also microvascular perme-

ability (46). Minocycline has been used in clinical trials for rheumatoid arthritis (47) and is undergoing testing in phase I/II clinical trials for amyotrophic lateral sclerosis (48).

**Guanosine and Pifithrin- $\alpha$  (p53 Inhibitor).** GTP salvage by exogenous administration of guanosine reduced renal tubular cell apoptosis, an effect that was associated with inhibition of p53 expression (49). Pifithrin- $\alpha$ , a novel p53 inhibitor, also led to decreased tubule cell apoptosis and preserved renal function (50). This agent is nearing clinical trials in cancer therapy.

**Poly ADP-Ribose Polymerase Inhibitor.** Poly ADP-ribose polymerase (PARP) is a ubiquitous nuclear enzyme that participates in DNA repair (51,52). Paradoxically, excessive activation of PARP from cellular injury leads to intracellular NAD<sup>+</sup> and to ATP depletion, ultimately resulting in cell death. PARP overactivation has been known to play a role in the pathogenesis of IRI to kidney, heart, and brain (53–55). Inhibition of PARP immediately at reperfusion reduced injury. PARP inhibitors are in clinical trials for breast cancer (phase I) and cardiac reperfusion injury (phase II).

#### Free Radical Scavengers

**Deferoxamine.** A key early feature of AKI is the generation of reactive oxygen species. The iron chelator deferoxamine is a widely known free radical scavenger. In several models of AKI, deferoxamine was proved effective (56–59). The protective effect of deferoxamine in various models suggests the central role of free radicals in AKI. Studies in AKI are planned to test the efficacy of iron chelation.

#### Antisepsis

**Ethyl Pyruvate.** Pyruvate has been known as a potent endogenous antioxidant and free radical scavenger, and its derivative, ethyl pyruvate, proved to be effective in reducing mortality in animal models of lethal hemorrhagic shock and systemic inflammation caused by endotoxemia or sepsis (60). In addition to an effect on mortality, ethyl pyruvate reduced kidney injury using the technique cecal ligation puncture as a model of sepsis (61). Ethyl pyruvate is a widely used food additive and has been shown to be safe in phase I clinical trials. It now is being tested in a phase II trial in patients who undergo cardiopulmonary bypass surgery.

**Activated Protein C.** Activated protein C (APC) is a physiologic anticoagulant that is generated by thrombin-thrombomodulin complex in endothelial cells. In addition to its effect on coagulation, APC has been shown to have anti-inflammatory, antiapoptotic effects (62,63). APC also attenuated renal IRI by inhibiting leukocyte activation (64). APC is approved by the Food and Drug Administration for treating patients who have severe sepsis and an Acute Physiology, Age, Chronic Health Evaluation (APACHE) score of 25 or higher.

**Insulin.** Insulin resistance and hyperglycemia are common in critically ill patients, and intensive insulin therapy that targeted blood glucose level between 80 and 110 mg/dl reduced the incidence of AKI that required dialysis or hemofiltration (65). The relationship of hyperglycemia and adverse outcome in critically ill patients with AKI also was observed recently in a



subgroup analysis of the PICARD study (66). The mechanism for clinical benefit may relate to the dosage of insulin as opposed to glycemic control (67). Endothelial dysfunction and subsequent hypercoagulation and dyslipidemia, commonly observed in critically ill patients, are corrected partially by insulin independent of its blood glucose-lowering effect (67,68). However, despite these promising results, the effect of intensive insulin treatment in the setting of AKI has not been tested and needs to be confirmed in appropriately powered, randomized, clinical trials.

### Growth Factors

**Recombinant Erythropoietin.** Erythropoietin has been shown to have anti-inflammatory and antiapoptotic effects in ischemic brain damage, spinal cord injury, and retinal damage (69). Exogenously administered erythropoietin before or at the time of reperfusion reduced kidney injury by reducing tubular necrosis and apoptosis (70–72). It enhanced tubular proliferation in cisplatin-induced AKI (73) and also mediated mobilization and proliferation of endothelial progenitor cells from the bone marrow that has been shown to participate in tissue repair (74,75). Clinical use of recombinant erythropoietin should facilitate translation to human PKI.

**Hepatocyte Growth Factor.** Hepatocyte growth factor (HGF) can promote cell growth, motility, and morphogenesis of various types of cells (76,77). Renal expression of HGF and its receptor, c-met, increases after IRI, and exogenous administration of HGF reduces renal injury and accelerates renal regeneration in a murine model of AKI (78–80). The mechanism of protection is thought to involve a decrease in leukocyte–endothelial interaction with reduced inflammation and also a decrease in tubular cell apoptosis (81). Currently, phase I/II study of recombinant human HGF in fulminant hepatic failure patients and another phase II study of HGF *via* plasmid vector in patients with critical limb ischemia and peripheral ischemic ulcer are under way. Experience in these clinical trials may shed light on human AKI.

### Vasodilators

**Carbon Monoxide Release Compounds and Bilirubin.** In a seminal study, Nath *et al.* (82) found that heme oxygenase (HO) induction played a central role in limiting the extent of myoglobin-induced AKI. HO activity leads to the production of carbon monoxide (CO) and a potent antioxidant, bilirubin, and it is thought that the protective effect of HO activation is through these factors (82,83). In renal IRI administration of CO donor compounds tricarbonyldichlororuthenium(II) dimer ( $[\text{Ru}(\text{CO})_3\text{Cl}_2]_2$ ) or tricarbonylchloro(glycinato)ruthenium(II) ( $[\text{Ru}(\text{CO})_3\text{Cl}(\text{glycinate})]$ ) 1 h before the onset of ischemia significantly decreased the levels of plasma creatinine 24 h after reperfusion as compared with vehicle-treated mice (84). This suggests that CO itself may be protective and limit renal damage in ischemia-induced AKI (84). Bilirubin also has been shown to reduce kidney injury from IRI (85), and when biliverdin and CO are used in combination, they are synergistic in improving heart allograft survival (86).

**Endothelin Antagonist.** A potent vasoconstrictor, endothelin-1 (ET-1), has been implicated to play important roles in

animal models of AKI or radiocontrast nephropathy (87,88). ET-1 mediates its biologic effects by binding to ET<sub>A</sub> or ET<sub>B</sub> receptors. In rat kidney, ET<sub>A</sub> receptor stimulation is known to mediate vasoconstriction, whereas ET<sub>B</sub> receptor activation also can mediate vasodilation by generation of nitric oxide and prostacyclin (89,90). In addition, ET-1 can stimulate the expression of adhesion molecules and the production of cytokines from monocytes and neutrophils, suggesting the possible role of ET-1 in inflammation in AKI (91). Several studies demonstrated the beneficial effect of selective ET<sub>A</sub> or nonselective endothelin receptor antagonist in ischemic AKI, but the major limitation of those studies is that endothelin receptor antagonist was administered before injury. Administration of the drug at later time point during the reperfusion was ineffective. However, Wilhelm *et al.* (92) recently showed that tezosertan, a dual ET-1 receptor antagonist, attenuated renal injury even when administered after ischemia.

### Anti-Inflammatory Drugs

Inflammatory cells, including polymorphonuclear cells, monocytes, macrophages, and T cells, have received considerable attention as important contributors to ischemic acute renal failure. Several new compounds seem to be effective in reducing injury for ischemia-reperfusion through direct action on leukocytes.

**Sphingosine 1 Phosphate Analogs.** Sphingosine 1 phosphate (S1P) is a specific ligand for a family of G protein-coupled endothelial differentiation gene receptors (S1PR 1 through 5) that evoke diverse cellular signaling responses. S1PR regulate different biologic processes depending on their pattern of expression and the diverse G proteins present. S1P binds to receptors or acts as a second messenger to stimulate cell survival, inhibit cell apoptosis, and inhibit cell adhesion and movement (93). An S1P analog, FTY720, acts as an agonist at four S1PR, which lead to sequestration of lymphocytes in secondary lymphatic tissue (94). In studies of kidney IRI, FTY720 or similar compounds produced lymphopenia and renal tissue protection (95) (96). With discovery of new S1P analogs, more potent and selective agents will be available for preclinical and clinical studies (97). Recently, in a phase II study, FTY720 reduced the number of lesions that were detected on magnetic resonance imaging and clinical disease activity in patients with multiple sclerosis (98).

**A<sub>2A</sub> Agonists and Other Adenosine Analogs.** Adenosine binds to receptors, which are members of the G protein-coupled receptor family that includes four subtypes: A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>Rs (99). Selective activation of A<sub>2A</sub>Rs reduces parenchymal injury in nonrenal tissue, including heart, liver, spinal cord, lung, and brain (100–102). The selective A<sub>2A</sub>R agonist ATL146e is highly protective against IRI of kidney and reduces injury by 70 to 80% (103–105). After administration either before or immediately at the onset of reperfusion, ATL146e alone or in combination with a phosphodiesterase inhibitor reduced renal injury (106). ATL146e is in human clinical studies for cardiac imaging, and current efforts are directed toward human clinical studies in AKI. Additional studies demonstrate that strategies

that use A<sub>1</sub> agonists or A<sub>3</sub> blockers may be effective in AKI (107,108).

**Inducible Nitric Oxide Synthase Inhibitors.** The role of nitric oxide (NO) and nitric oxide synthases (NOS) has been studied extensively. Both *in vivo* and *in vitro* studies point toward the important role of inducible NOS in mediating injury to proximal tubules (109). A nonselective NOS inhibitor (N<sup>ω</sup>-methyl-L-arginine) has been studied in a phase III clinical trial in septic patients (110). This study was stopped prematurely by the data safety monitoring board because of an excess of mortality in the N<sup>ω</sup>-methyl-L-arginine group. More selective inducible NOS inhibitors are currently used in human investigation for a variety of indications.

**Fibrates.** Peroxisome proliferator-activated receptors (PPAR) are transcription factors that regulate glucose and lipid metabolism. Recent studies indicated that PPAR play an important role in inflammation and immunity (111). Pretreatment of animals with fibrates (PPAR- $\alpha$  ligand) ameliorated cisplatin-induced renal dysfunction, and this was accompanied by suppression of NF- $\kappa$ B activation, cytokine/chemokine expression, and neutrophil infiltration, suggesting that the protective effect of fibrates is mediated through its anti-inflammatory effect (112).

**Other Compounds.** Neutrophil gelatinase-associated lipocalin (113), IL-6 and C5a antagonists (114), IL-10 (115), and  $\alpha$ -melanocyte-stimulating hormone (116) are other potential compounds that have multiple mechanisms of tissue protection and may be beneficial in human AKI.

## Conclusion

Barriers to successful clinical trials have thwarted progress in developing effective therapeutics for AKI. Implementation of strategies to prevent or treat AKI will depend on the coordinated efforts of academic institutions, private industry, and the federal government in developing and testing novel therapeutic agents in well-designed clinical trials. Furthermore, the complexity of AKI is due in part to activation of multiple overlapping and distinct temporal pathways. Inflammation (cellular and humoral) is a key mediator of AKI. It is unlikely that targeting events that occur late in AKI or even a single pathway will be effective. It might be that new strategies to treat or prevent AKI will require compounds that target pathways that are more proximal to onset. Such strategies could include the use of compounds that affect multiple pathways or combination therapy that targets several areas, rather than one. Early diagnosis through the use of novel biomarkers will facilitate timely intervention.

## Acknowledgments

This work was supported by National Institutes of Health grants DK56223, DK62324, and DK58413.

We acknowledge that portions of the discussion in this article were derived from a meeting held by the Acute Kidney Injury Network (AKIN); September 11 to 14, 2006; Vancouver, BC, Canada.

## Disclosures

M.D.D. owns equity in Adenosine Therapeutics, LLC (Charlottesville, VA).

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