

Novel Therapies for Acute Kidney Injury



Huaizhen Chen¹ and Laurence William Busse¹

¹Department of Medicine, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Emory University School of Medicine, Atlanta, Georgia, USA

Acute kidney injury (AKI) is a common disease with a complex pathophysiology. The old paradigm of identifying renal injury based on location—prerenal, intrarenal, and postrenal—is now being supplanted with a new paradigm based on observable kidney injury patterns. The pathophysiology of AKI on a molecular and microanatomical level includes inflammation, immune dysregulation, oxidative injury, and impaired microcirculation. Treatment has traditionally been supportive, including the avoidance of nephrotoxins, judicious volume and blood pressure management, hemodynamic monitoring, and renal replacement therapy. Fluid overload and chloride-rich fluids are now implicated in the development of AKI, and resuscitation with a balanced, buffered solution at a conservative rate will mitigate risk. Novel therapies, which address specific observable kidney injury patterns include direct oxygen-free radical scavengers such as α -lipoic acid, curcumin, sodium-2-mercaptoethane sulphonate, propofol, and selenium. In addition, angiotensin II and adenosine receptor antagonists hope to ameliorate kidney injury via manipulation of renal hemodynamics and tubulo-glomerular feedback. Alkaline phosphatase, sphingosine 1 phosphate analogues, and dipeptidylpeptidase-4 inhibitors counteract kidney injury via manipulation of inflammatory pathways. Finally, genetic modifiers such as 5INP may mitigate AKI via transcriptive processes.

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KEYWORDS: acute kidney injury; angiotensin II; inflammation; intravenous fluids; oxidative stress

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Renal injury has traditionally been understood in the context of anatomical location (prerenal, intrarenal, and postrenal). The supportive nature of current therapeutic options stems from a relatively nascent understanding of the complex pathophysiology of acute kidney injury (AKI). Traditionally, therapy for AKI has revolved around maintaining adequate macrovascular renal perfusion through volume and hemodynamic management, as well as the avoidance of nephrotoxins. Renal replacement therapy can be implemented while awaiting signs of recovery. Recently, the amount and type of resuscitative fluids in AKI have come into question as more and more evidence suggests the harmful effects of over-resuscitation.^{1,2} Moreover, as we improve our understanding of AKI, we can now point to a complex cascade of microvascular dysregulation and cellular injury that occurs via inflammation, immune dysregulation, and oxidative injury. An array of novel therapies that target specific enzymes or molecules involved in these pathways are in various

stages of development.³ This review provides a summary of the emerging understanding of renal injury based on molecular and microvascular injury patterns, before delving into the most recent thinking regarding optimal fluid management for AKI. It will then discuss novel treatment options that target the molecular pathways now implicated in AKI. **Tables 1** and **2** summarize the findings.

Renal Injury

The traditional anatomically-based classification of kidney injury is being supplanted by a more functional paradigm, in which tissue pathology, regardless of anatomic location, dictates the type of injury. Prerenal disease has traditionally been invoked when the clinical scenario involves the compromise of renal blood flow. Intrarenal disease is traditionally associated with evidence of parenchymal disease in the urine, such as renal tubular casts. Postrenal disease is associated with known or suspected obstruction to urine flow. Although the adequacy of renal blood flow is still important, we have a better understanding, from both microvascular and macrovascular levels, of renal hemodynamics. Insufficient renal perfusion happens both prerenally on a macrovascular scale, such as in states of shock, as well as intra-renally on a microvascular scale, such as with ischemia–reperfusion injury,

Correspondence: Laurence Busse, Medical Director MS ICU, Emory Saint Joseph’s Hospital, 5665 Peachtree Dunwoody Road, Atlanta, GA 30342, USA. E-mail: Laurence.w.busse@emory.edu

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Table 1. Novel therapeutic agents for acute kidney injury

Agent	Mechanism of action	Potential indication(s)
Renal blood flow modifiers		
Angiotensin	Constricts efferent arterioles to a greater degree than afferent arterioles Regulates release of aldosterone and vasopressin	Sepsis
Adenosine antagonists	Reduces GFR in response to hypoxia Constricts afferent arterioles → increase NaCl levels in proximal tubules	CIN IRI Cardiorenal syndrome
Antioxidants		
Alpha-lipoic acid	Reduced form eliminates free radicals Improves glomerular function Reduces renal inflammation	IRI CIN
Selenium	Cofactor that reduces free radicals	Cisplatin injury ECSL
MESNA	Scavenges for free radical oxygen species	CIN
Propofol	Converts free oxygen radicals into a phenoxyl form	IRI
Curcumin	Scavenges for free oxygen radicals Stimulates activity of antioxidant molecules such as superoxide dismutase, catalase, and glutathione peroxidase	IRI Diabetic nephropathy Lupus nephritis
Anti-inflammatory mediators		
Alkaline phosphatase	Dephosphorylates lipopolysaccharide Dephosphorylates ATP	Gram-negative sepsis
Dipeptidylpeptidase-4 Inhibitors	Extends half-life of glucagon-like peptide-1	Diabetic nephropathy Cisplatin injury
Sphingosine 1 phosphate (S1P) analogues	Mitigates endothelial damage Decreases recruitment of inflammatory mediators to the renal tubules	None to date
Genetic modifiers		
i5NP	Inhibits p53 gene	IRI

ATP, adenosine triphosphate; CIN, contrast induced nephropathy; ECSL, extracorporeal shockwave lithotripsy; GFR, glomerular filtration rate; IRI, ischemia reperfusion injury; MESNA, sodium 2-mercaptoethane sulfonate; NaCl, sodium chloride.

angiotensin-converting enzyme inhibitor or nonsteroidal anti-inflammatory drug (NSAID) use. Macrovascular renal blood flow may or may not correlate with glomerular perfusion, because changes in glomerular perfusion can occur even in periods of preserved blood pressure via differential effects on afferent and efferent arterioles.²² A significant amount of evidence exists that identifies the appropriate amount of macrovascular renal perfusion pressure required to prevent injury in various states of disease.^{23–25} Accordingly, standard of care today includes maintenance of mean arterial pressure at or above approximately 65 mm Hg to preserve renal blood flow. Perfusion at the glomerular level is mediated through the differential dilation and constriction of the afferent and efferent arterioles. In normal human physiology, afferent arteriolar tone is controlled via tubuloglomerular feedback from the juxtaglomerular apparatus, mediated by any of a number of innate molecules, including angiotensin II, thromboxane, catecholamines, nitric oxide, and adenosine.²⁶ Efferent tone is mediated largely by angiotensin II in response to neurohormonal activation of the renin-angiotensin-aldosterone system (RAAS).²² Within physiological blood pressure ranges and absent any external forces affecting afferent or efferent tone, glomerular perfusion pressure is maintained by harmonious autoregulatory mechanisms at a transglomerular pressure gradient of

approximately 10 mm Hg.²⁷ Figure 1 illustrates the physiology and pathophysiology of glomerular filtration. Within the past couple of decades, we have begun to understand how afferent and efferent microvascular tone can change in states of disease but also how they are intentionally or unintentionally manipulated. Moreover, we can predict with increasing levels of sophistication the consequences of these effects on glomerular perfusion pressure and ultimately, kidney injury.^{22,28,29}

Although renal perfusion is an important factor in understanding the mechanisms of kidney injury, it is by no means the only one, nor does it act in isolation. Injury can occur in the absence of hypotension,²² and glomerular hypoperfusion can lead to tubular damage.³⁰ Tubular damage has also been linked to oxidative stress^{31,32} and inflammation.^{33,34} Figure 2 illustrates the complex pathway from toxic or ischemic insult to tubular injury in AKI, which can be mediated by microvascular dysfunction, oxidative stress, inflammation, and immune dysregulation. An abundance of inflammatory and immune molecules, including intracellular adhesion molecule-1; tumor necrosis factor- α (TNF- α); interleukin-1 (IL-1), -6, and -8; transforming growth factor- β ; and toll-like receptors, have all been identified in AKI.³⁵ AKI may also result from cell death or senescence facilitated by genetic factors, such as cell cycle arrest, which are believed to prevent cell

Table 2. Therapeutics by disease state with evidence

Treatment	Study authors/registration name and number on clinicaltrials.gov	Results of study
<i>Sepsis</i>		
Alkaline phosphatase	Heemskerk <i>et al.</i> ⁴	Improvement in serum creatinine compared with placebo in gram-negative sepsis
Alkaline phosphatase	Pickkers <i>et al.</i> ⁵	Lower serum creatinine and inflammatory markers in patients with sepsis
Alkaline phosphatase	Safety, Tolerability, Efficacy and QoL Study of Human recAP in the Treatment of Patients With SA-AKI (STOP-AKI) (NCT02182440) in progress	Evaluating safety, efficacy, and optimum dosage of ALP in patients with AKI from sepsis
<i>Hypoperfusion/shock</i>		
Angiotensin	Angiotensin in Septic Kidney Injury Trial (ASK-IT) (NCT007111789) in progress	Evaluating effect of angiotensin on hemodynamics and urine output in septic shock
Angiotensin	Khanna <i>et al.</i> ⁶⁴	Evaluated angiotensin as a vasopressor for catecholamine-resistant hypotension; AKI as exploratory endpoint
<i>Contrast-induced nephropathy</i>		
Adenosine antagonists	Bagshaw and Ghali ⁶	Theophylline reduced risk of CIN
Adenosine antagonists	Dai <i>et al.</i> ⁷	Theophylline reduced risk of CIN
Adenosine antagonists	NCT01469624 in progress	Evaluating effect of pentoxifylline on CIN
Alpha-lipoic acid	Jo <i>et al.</i> ⁸	Older patients (age >70 yr), higher contrast load, "high-risk group" had decreased incidence of AKI
MESNA	Ludwig <i>et al.</i> ⁹	Pretreatment with MESNA decreased risk of CIN
<i>Renal transplantation</i>		
Alpha-lipoic acid	Ambrosi <i>et al.</i> ¹⁰	Fewer inflammatory markers for kidney-pancreas transplant recipients if given to both donors and recipients
Propofol	NCT01132157 in progress	Evaluating incidence of ischemic–reperfusion kidney injury using desflurane versus propofol in renal transplant patients
Propofol	NCT01870011 in progress	Evaluating incidence of ischemic–reperfusion kidney injury using desflurane versus propofol in renal transplant patients
I5NP	NCT00802347 in progress	Evaluating safety, maximum-tolerated dose, and amelioration of delayed graft function of I5NP in renal transplant patients
<i>Drug-induced AIN</i>		
Selenium	Ghorbani <i>et al.</i> ¹¹	Decreased incidence of AKI for cancer patients treated with cisplatin
Dipeptidylpeptidase-4 Inhibitors	NCT02250872 in progress	Evaluating effect of DPP-4 inhibitors on AKI due to cisplatin
<i>Postoperative (nonrenal transplant)</i>		
Selenium	SodiUm SeleniTe Administration IN Cardiac Surgery (SUSTAIN CSX-Trial; SUSTAINCSX) (NCT02002247) in progress	Evaluating effects of selenium on organ dysfunction and mortality in patients undergoing high-risk cardiac surgery
Propofol	Yoo <i>et al.</i> ¹²	Lower serum renal biomarkers and lower hospital length of stay compared with sevoflurane for patients receiving valvular surgery
Propofol	Bang <i>et al.</i> ¹³	Decreased incidence of AKI and shorter ICU stay compared with sevoflurane in colorectal surgery patients
Propofol	Ammar <i>et al.</i> ¹⁴	Decreased incidence of AKI and serum renal biomarkers compared to sevoflurane in AAA repair patients
Propofol	NCT02009280 in progress	Evaluating the incidence of AKI when using propofol in lung transplant patients on ECMO
Propofol	NCT01384643 in progress	Evaluating ability of propofol to reduce ischemic–reperfusion kidney injury in valvular surgery patients
Circumin	NCT01225094 in progress	Evaluating prevention of AKI in AAA repair patients
I5NP	NCT00554359 in progress	Evaluating safety and pharmacokinetics of I5NP in patients undergoing cardiovascular surgery who are at high risk of AKI
<i>Diabetic nephropathy</i>		
Circumin	Yang <i>et al.</i> ¹¹⁰	Decreased microalbuminuria and serum inflammatory markers in patients with type 2 diabetes
DPP-4 inhibitors	Shih <i>et al.</i> ¹⁵	Patients with type 2 diabetes who were hospitalized for AKI were more likely to be on DPP-4 inhibitors
DPP-4 inhibitors	Kawasaki <i>et al.</i> ¹⁶	Sitagliptin decreased eGFR in type 2 diabetes patients
DPP-4 inhibitors	Scirica <i>et al.</i> ¹⁷	Saxagliptin decreased eGFR compared with placebo in patients with type 2 diabetes
DPP-4 inhibitors	Pendergrass <i>et al.</i> ¹⁸	No association between sitagliptin and renal failure
DPP-4 inhibitors	Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)	No association between sitagliptin and renal failure
<i>Miscellaneous</i>		
Adenosine antagonists	Pharmacology of Aminophylline for Acute Kidney Injury in Neonates (PAANS) trial (NCT02276170) in progress	Evaluating aminophylline as treatment for AKI in neonates (excluding congenital defects)
Propofol	Leite <i>et al.</i> ¹⁹	Decreased need for renal replacement therapy and mortality compared with midazolam in critical care patients
Circumin	Khajehdehi <i>et al.</i> ²⁰	Decreased microalbuminuria and serum inflammatory markers in patients with SLE
Propofol	Feng <i>et al.</i> ²¹	Decreased rates of apoptosis and increased proliferation in renal tubule epithelial cells exposed to anoxia

AAA, abdominal aortic aneurysm; AIN, acute interstitial nephritis; ALP, alkaline phosphatase; AKI, acute kidney injury; CIN, contrast-induced nephropathy; DPP, dipeptidylpeptidase; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; MESNA, sodium 2-mercaptoethane sulfonate.

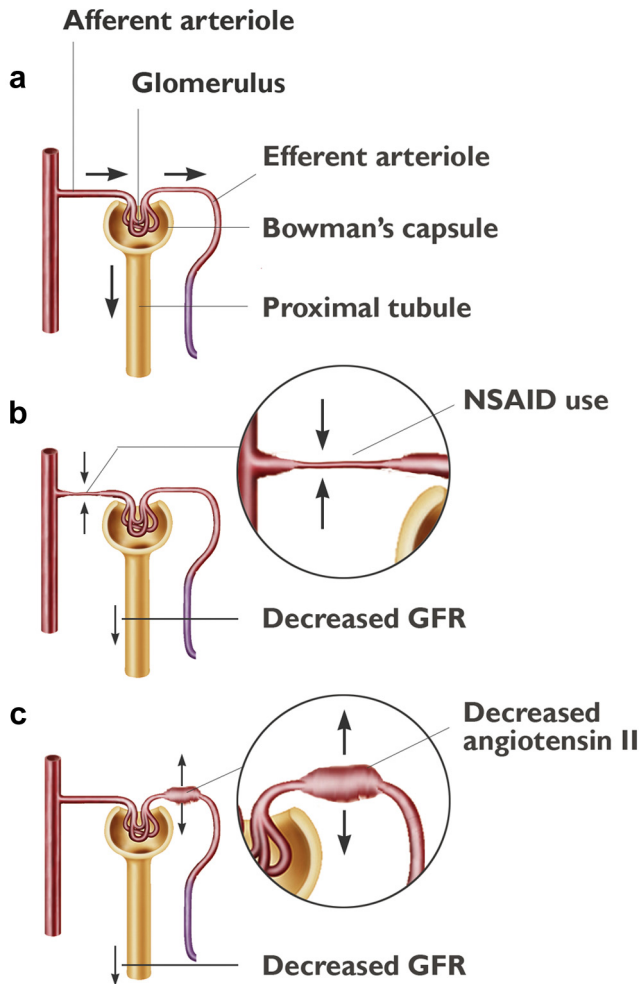


Figure 1. In normal human physiology, glomerular hydrostatic pressure is created via a complex but harmonious manipulation of afferent and efferent arterioles, which maintains a transglomerular pressure gradient that allows for flow of urine across Bowman's capsule (a). In various states of disease and with nonsteroidal anti-inflammatory drug (NSAID) use, afferent arteriolar vasoconstriction can decrease flow into the glomerulus and across Bowman's capsule (b). Dilation (or ineffective constriction) of the efferent arteriole, as seen with angiotensin II deficiency in angiotensin-converting enzyme inhibition, can result in the same phenomenon (c). GFR, glomerular filtration rate. Source: Stocktrek Images, Inc./Alamy Stock Photo.

division when DNA may be damaged.³⁶ Anachronistically, oxidative stress, immune dysregulation, and genetically-mediated cell death may all have been considered intrarenal disease, and treated with supportive care, alleviation of precipitating factors, and the tincture of time. However, as our understanding of these mechanisms has grown, so too have potential therapeutic options aimed at addressing the specific pathophysiological mechanisms implicated in renal injury. Current and potential therapeutic options address macrovascular hypoperfusion, microvascular blood flow alteration (glomerular hypoperfusion), tubular and cellular damage from oxidative stress, immune dysregulation and inflammation, and genetic failure, such as cell-cycle arrest.

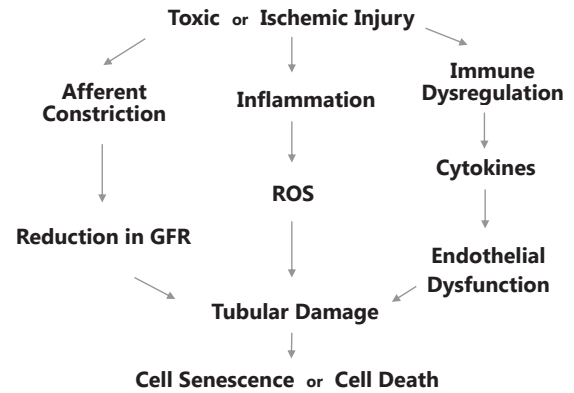


Figure 2. A complex relationship exists between toxic or ischemic insult and acute kidney injury. Injury can be mediated via inflammatory and immune mechanisms and microvascular dysfunction, which need not be mutually exclusive. Reactive oxygen species (ROS) and immune mediators (such as interleukins and tumor necrosis factors) can cause mitochondrial failure and trigger apoptosis from cell cycle arrest. Numerous therapies are being developed to counteract the pathophysiological processes involved in acute kidney injury. GFR, glomerular filtration rate.

Fluid Management

The mainstay of management of AKI from a macrovascular perspective revolves around judicious use of i.v. fluids. To maintain adequate renal macrovascular perfusion, liberal administration of i.v. fluid has historically been standard of care. Numerous studies have focused on the determination of the optimal amount of resuscitation in the mitigation of AKI, which has not necessarily correlated with resuscitation goals for cardiac output or blood volume.^{37,38} Recent data from the Sepsis Occurrence in Acutely Ill Patients (SOAP) and Program to Improve Care in Acute Renal Disease (PICARD) studies have suggested that a liberal fluid strategy may actually increase the incidence of AKI.^{39,40} Increases in intra-abdominal pressure, interstitial edema, and renal vasculature congestion, which result in disruptions in microanatomy, oxygen transport defects, and small vessel congestion on a cellular level, are believed to be causative.⁴¹ The Fluid And Catheter Treatment Trial (FACTT), a multicenter, prospective, randomized, controlled trial that evaluated the effect of a liberal fluid strategy versus conservative fluid strategy on mortality in patients with acute lung injury, found a positive correlation between a liberal fluid strategy and the incidence of AKI.⁴² Volume overload was also found to independently increase the risk of AKI and death in another prospective, observational, multicenter study—the Beijing Acute Kidney Injury Trial.⁴³ Figure 3 highlights the mortality implications of volume overload.

In addition, evidence has emerged regarding the type of fluid resuscitation used in AKI. Synthetic colloids (starches) are no longer recommended for resuscitation

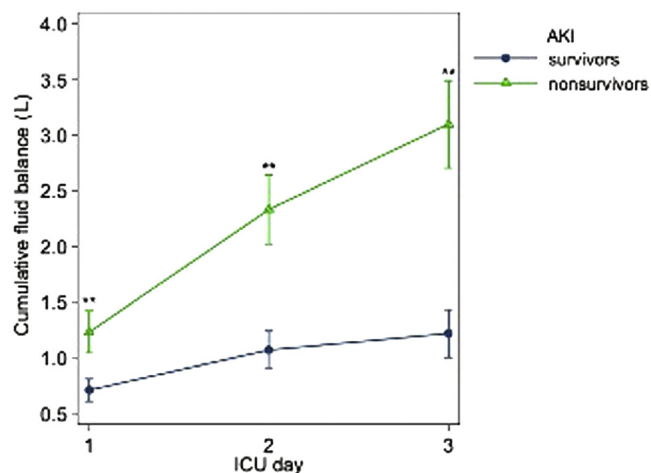


Figure 3. Results from the Beijing trial shows the mortality associated with cumulative fluid balance in acute kidney injury (AKI) survivors and nonsurvivors during their first 3 days in the intensive care unit (ICU). (From Wang N, Jiang L, Zhu B, et al. Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study. *Crit Care*. 2015;19:371.⁴³ This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

based on accumulating evidence. The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) Trial compared hydroxyethyl starch (HES) with lactated Ringer's solution in a parallel group, randomized, blinded trial that ultimately found an increased risk of AKI in the HES group.⁴⁴ HES and normal saline were also compared in the Crystalloid vs Hydroxyethyl Starch Trial (CHEST), which showed no difference in 90-day mortality, but did show a higher incidence of AKI and requirement for renal replacement therapy in the starch group.⁴⁵ HES was also determined to have an increased risk of AKI and death compared with other crystalloids, albumin, and gelatin in a recent meta-analysis.⁴⁶

Albumin solutions are believed to increase oncotic pressure and thereby better preserve intravascular volume and renal perfusion pressure than crystalloids.⁴⁷ Data has been conflicting regarding the use of albumin solutions in resuscitation and prevention of AKI. A 2010 meta-analysis that compared 20% albumin with various isotonic fluids (normal saline, 4%–5% albumin, and lactated Ringer's) showed that albumin decreased the odds of AKI markedly.⁴⁸ However, in the Albumin Italian Outcome Sepsis (ALBIOS) trial, 20% albumin and crystalloids were found to be equivalent with regard to mortality at 28 days (primary outcome) and all secondary outcomes, including AKI.⁴⁹ Studies also do not support the use of isotonic colloids (i.e., 4%–5% albumin) over crystalloid solutions. The Saline versus Albumin Fluid Evaluation (SAFE) trial found that 4% albumin and normal saline were equivalent with regard to all-cause mortality, organ

dysfunction, hospital length of stay, ICU length of stay, days requiring mechanical ventilation, and days requiring renal replacement therapy.⁵⁰

Recent evidence has suggested that chloride-rich solutions may be deleterious to kidney function by inducing renal vasoconstriction and decreasing glomerular filtration rate (GFR).⁵¹ Yunos *et al.* found chloride-rich fluids to be an independent risk factor for AKI that necessitated renal replacement therapy compared with a balanced solution, such as Hartmann solution, Plasma-Lyte 148, and 20% albumin.^{52,53} The authors hypothesized that kidney injury was the result of renal vasoconstriction and changes in tubule-glomerular feedback precipitated by the chloride. In contrast, the 2015 0.9% Saline versus Plasma-Lyte 148 (PL-148) for ICU fluid Therapy (SPLIT) randomized clinical trial compared resuscitation with normal saline versus a balanced solution in critically ill patients, and did not find an increased incidence of AKI.⁵⁴

In summary, renal perfusion should be monitored at the macrovascular level and maintained via volume and blood pressure adjustment. Kidney injury may be mitigated through the judicious use of fluids to avoid over-resuscitation, avoidance of excessive chloride, and maintenance of mean arterial pressure ≥ 65 mm Hg. Evidence supporting colloid solutions versus crystalloid solutions is lacking.

Renal Flow Modifiers

Alteration in microvascular renal blood flow at the level of the single nephron has been implicated in AKI. Disease states such as ischemia–reperfusion injury, hypercalcemia, and hepatorenal syndrome, as well as iatrogenic factors, including the use of certain medications (NSAIDs, cyclooxygenase-2 inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) can result in an inadequate transglomerular pressure gradient and a reduction in glomerular filtration.²² The loss of an adequate transglomerular pressure gradient can evolve into tubular damage, because the highly metabolically active tubular epithelial cells are starved of adenosine triphosphate (ATP).³⁰ As such, research has focused on the modification of renal microvascular blood flow to mitigate AKI in the aforementioned clinical conditions. These renal flow modifiers can augment GFR by directly affecting microvascular tone. Within a single nephron, GFR is preserved via sufficient afferent arteriolar vasodilation to allow for adequate blood flow into the glomerulus, but also sufficient efferent arteriolar tone, which results in adequate transglomerular pressure gradient.⁵⁵ Novel therapeutics such as angiotensin II and adenosine analogues seek to address these microvascular issues.

Angiotensin

The RAAS affects the ability of the kidney to reabsorb water and maintain euvolemia. Increased adrenergic tone and activation of the RAAS occurs as a result of volume depletion to increase renal reabsorption of water. Angiotensin II is an octapeptide with multiple functions.⁵⁶ In the kidney, angiotensin II participates in the regulation of the release of aldosterone, the maintenance of sodium and water homeostasis, and the release of vasopressin.⁵⁷ It has been found to cause constriction of efferent arterioles to a greater degree than afferent arterioles, thereby increasing intraglomerular flow and augmenting the transglomerular pressure gradient.⁵⁸ Figure 1 shows the effect of angiotensin II on the renal microvasculature. In inflammatory or immunoactive states such as sepsis, dysfunction of the RAAS⁵⁹ and activation of the RAAS leads to a downregulation of angiotensin I type of angiotensin receptors.⁶⁰ The relative scarcity of angiotensin II may result in inadequately low intraglomerular pressures, which could potentially be mitigated via exogenous angiotensin II.⁶¹

In sheep studies, angiotensin II administration was found to increase urine output and creatinine clearance.⁶² Renal blood flow was noted to be decreased, without inhibition of renal cellular metabolism.⁶³ In contrast, the effect of angiotensin II, norepinephrine, and enalapril on renal plasma flow, prevalence of AKI, and mitochondrial activity was evaluated in a septic pig model, and no difference was noted.⁶¹

There are limited data regarding the efficacy of angiotensin II in humans. Older studies evaluated its effect on renal function, but none were randomized, placebo-controlled trials. A pilot study of 20 patients was conducted that assessed the use of angiotensin II as a pressor in high-output shock, but there was inadequate power to determine the effect of the drug on renal function.⁵⁶ Currently, the Angiotensin in Septic Kidney Injury Trial (ASK-IT) is attempting to evaluate the effect of angiotensin on hemodynamics and urine output in patients with septic shock and acute renal failure (NCT00711789). The recently published Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) phase 3 clinical trial evaluated angiotensin as a vasopressor to treat catecholamine-resistant hypotension, and found a trend toward improved survival at 28 days with no increase in AKI-related adverse events.⁶⁴ Baseline incidence of AKI in both groups was high, but there was no statistical difference in urine output. Additional research regarding angiotensin II is ongoing.

Adenosine Antagonists

Adenosine has both intra and extrarenal effects that differ depending on the type of receptor. Systemically,

it manipulates vascular tone to regulate adequate oxygen delivery to local tissues. In the kidney, adenosine can cause a reduction in GFR in response to hypoxia or an increased level of sodium chloride in the tubule via the constriction afferent arterioles.⁶⁵ Both A1R and A2R receptors are potential therapeutic targets, and both adenosine agonists of the A2R receptors and adenosine antagonists have been proposed for potentially protective effects.

In animal studies, activation of selective adenosine 2A receptors was found to be protective of kidney injury following ischemia in rodents.^{66,67} In humans, theophylline, a nonselective adenosine A1R and A2R antagonist, has been compared with N-acetylcysteine in the prevention of contrast-induced nephropathy (CIN). A meta-analysis published in 2005 found a temporary benefit in the prevention of CIN with the use of theophylline, but there was significant heterogeneity within the study.⁶ Another meta-analysis by Dai *et al.* noted a reduction in the risk of CIN-related AKI with the use of theophylline (odds ratio 0.48).⁷ In contrast, the nonselective adenosine antagonist aminophylline showed no beneficial effect on the incidence of kidney injury compared with placebo in children with congenital heart disease.⁶⁸ A similar result was noted with rolofylline in the PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofoylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study.⁶⁹ Despite the mixed results, there is still considerable interest in the evaluation of adenosine antagonism in AKI. The Pharmacology of Aminophylline for Acute Kidney Injury in Neonates (PAANS) trial (NCT02276170) is attempting to evaluate aminophylline as a treatment for AKI by measuring changes in urine output, creatinine, and other urine biomarkers. Another study is examining the effect of pentoxifylline on CIN (NCT01469624).

Antioxidants

There is an increasing amount of data describing the role of free radical oxygen species in the development of AKI. Once formed, oxygen radicals enact deleterious effects on the kidney via oxidation of proteins, peroxidation of lipids, damage to DNA, and induction of apoptosis.⁷⁰ Free radical oxygen species are formed under such disease states as ischemia–reperfusion injury, CIN, sepsis, and malignancy (especially with the use of chemotherapeutic agents). There are some potential therapies that directly target free radicals in the prevention of AKI caused by these clinical scenarios.

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) eliminates free radicals when it is converted to its reduced form in tissues.⁷¹ In animal models, ALA both improves glomerular function and reduces renal inflammation.^{72,73} In humans, ALA has been used to treat diabetic neuropathy and retinopathy, and it has been proposed in the treatment of both CIN and ischemia–reperfusion kidney injury. Blood urea nitrogen (BUN), creatinine, cystatin C, and urinary neutrophil gelatinase-associated lipocalin have been found to be elevated in CIN.^{74–76} A 2013 study assessed the effect of ALA on the incidence of CIN in diabetic patients using the biomarkers neutrophil gelatinase-associated lipocalin and cystatin C in addition to the conventional biomarkers (BUN and creatinine) and found no beneficial effect.⁷⁷ Another 2013 study measured the effect of ALA on the incidence of CIN in 200 patients with chronic renal disease (creatinine clearance <60 ml/min) and found no appreciable difference between the control and experimental groups.⁸ However, patients aged older than 70 years and those in a predefined high-risk group who received a higher contrast load did experience a protective effect with ALA. ALA may also have some anti-inflammatory properties independent of its antioxidant properties. In patients who receive kidney-pancreas transplantations, when ALA was given to both the donor and recipient, markers of inflammation were diminished compared with the untreated group or the recipient-only treated group.¹⁰ Currently, no human studies are being conducted using ALA, but in animal studies, ALA continues to show improvement in surrogate and clinical outcomes when used in such disease processes as ischemia–reperfusion injury,⁷⁸ sepsis,⁷⁹ toxic injury,^{72,80} and obstructive uropathy.⁸¹

Selenium

Selenium is a trace element that is involved in the reduction of free radicals during cellular aerobic respiration.⁸² Deficiency in selenium has been linked to AKI in rat models.⁸³ Selenium supplementation correlated with improved serum creatinine, urea, and histopathological evidence in cisplatin-induced kidney injury in rats.⁸² Rats with gentamycin-induced AKI exhibited similar histological and functional improvements with selenium.⁸⁴ When given in combination with erythropoietin in a murine model, selenium seemed to bestow some benefit in ischemia–reperfusion injury.⁸⁵ In a porcine model, selenium improved the antioxidant profile (byproducts of ischemia–reperfusion injury) on immunohistopathology of transplanted kidneys in pigs.⁸⁶

The data regarding the renal protective effect of selenium in humans are more ambiguous. Although

patients who were pretreated with selenium showed better kidney biomarker profiles (urine N-acetylglucosaminidase, γ -glutamyl transpeptidase, alanine aminopeptidase, leucine aminopeptidase, and alkaline phosphatase) after receiving cisplatin, this did not translate into any clinical benefit.⁸⁷ A European study of cisplatin-based chemotherapy patients pretreated with a multivitamin cocktail that included selenium showed that creatinine clearance was equivalent in the control group versus the pretreatment group.⁸⁸ Micronutrient supplementation (including selenium) failed to provide a benefit in patients who underwent extracorporeal shockwave lithotripsy, cardiac surgery, major trauma, or subarachnoid hemorrhages.^{89,90} In contrast, a randomized, controlled trial by Ghorbani *et al.* in 2013 found that cancer patients who received cisplatin therapy had a decreased incidence of AKI when pretreated with selenium.¹¹ At this time, the Sodium Selenite Administration in Cardiac Surgery (SUSTAIN CSX) trial is attempting to compare the effects of selenium versus placebo on organ dysfunction (including renal function) and mortality in 1400 critically ill patients.⁹¹

Sodium-2-Mercaptoethane Sulphonate

The sulfhydryl moiety in sodium-2-mercaptoethane sulphonate (MESNA) is a scavenger of free radical oxygen species. It is found in high concentrations in the renal tubular cells and is easily filtered across the glomerulus.⁹² In a mouse model, MESNA was noted to ameliorate renal injury, both histologically and functionally, after ischemia–reperfusion injury.⁹² Throughout the early 1990s, MESNA was widely used as a means to protect renal function when paired with chemotherapy.^{93–95} In 2011, a study that consisted of 100 patients suggested that MESNA might decrease the risk of CIN if used as pretreatment to contrast administration.⁹ This is the only randomized controlled trial of MESNA in kidney injury to date.

Propofol

Because of its molecular structure which is similar to that of vitamin E, propofol exhibits antioxidant properties by converting free oxygen radicals into a less toxic phenoxyl form.⁹⁶ Propofol has been studied in a variety of animal models and has been associated with lower incidences of AKI. As an anesthetic, propofol correlated with lower levels of serum creatinine and other inflammatory markers such as TNF- α , IL-1, and interferon- γ compared with that of sevoflurane in pigs.⁹⁷ Propofol tempered the degree of renal injury due to ischemia–reperfusion injury in both piglets and rats.^{98,99}

Propofol has been studied in humans both *in vitro* and *in vivo*. Human renal tubular cells exhibited

decreased rates of apoptosis and abundant proliferation when treated with propofol.²¹ In numerous surgical studies, propofol proved superior to sevoflurane for protecting the kidneys. Yoo *et al.* found that in comparison to the general anesthetic sevoflurane in 112 valvular surgery patients, certain biomarkers such as serum creatinine and cystatin C were lower with propofol, and hospital length of stay was also shorter.¹² A retrospective study of 4320 colorectal surgery patients found that anesthesia with propofol resulted in a decreased incidence of AKI and shorter intensive care unit and hospital lengths of stay compared with sevoflurane.¹³ In addition, patients who were anesthetized with propofol before undergoing cardiopulmonary bypass surgery for elective open abdominal aortic aneurysm repair experienced less kidney injury, as measured in serum biomarkers compared with sevoflurane.¹⁴ When propofol was compared with midazolam in a retrospective trial with propensity-matched critically ill patients, a similar trend was noted, as well as a decreased need for renal replacement therapy and mortality.¹⁹ Additional research is ongoing in other settings, including extracorporeal mechanical oxygen-assisted lung transplantation (NCT02009280), valvular heart surgery (NCT01384643), and renal transplantation (NCT01132157, NCT01870011).

Curcumin

Curcumin is an herbal supplement related to turmeric, which is typically used as food coloring. However, it is also a scavenger of free oxygen radicals and stimulates the activity of additional antioxidant molecules such as superoxide dismutase, catalase, and glutathione peroxidase.¹⁰⁰

Numerous rat models have demonstrated the protective effect of curcumin on the kidneys. Curcumin has been found to mitigate cisplatin, gentamicin, and carbon-tetrachloride-induced kidney injury in pretreated rats, resulting in histological improvement of inflammation, curtailment of inflammatory markers (TNF- α , myeloperoxidase, IL-1 β), reduction in serum creatinine and BUN, and inhibited expression of proapoptotic genes such as p53.^{100,101} In a septic rat model, pretreatment with curcumin resulted in a mortality benefit, reduction in TNF- α , and decline of fibrin deposition in the glomerulus.¹⁰² Multiple animals subjected to ischemia-reperfusion injury and treated with curcumin exhibited attenuated renal damage.^{103–107} In contrast, there appeared to be no benefit from curcumin if renal disease was induced by hypertonic glycerol in rats.¹⁰⁸

In humans, curcumin has been shown to diminish the apoptotic and necrotic effects of shiga toxin on renal proximal tubule cells *in vitro*, but the authors hypothesized this to be the result of activation of heat

shock proteins rather than any antioxidant properties.¹⁰⁹ Among human trials, most of the benefit has been demonstrated in diabetic nephropathy, where curcumin was noted to reduce proteinuria and inflammatory markers.^{110–112} A similar effect was found in an randomized control trial of patients with lupus nephritis.²⁰ Notably, these human studies were conducted on patients with chronic renal disease rather than AKI. Currently, curcumin is being evaluated in the prevention of kidney injury after abdominal aortic aneurysm repair using endpoints, including serum creatinine, urine IL-18, time to dialysis, and mortality (NCT01225094).

Inflammatory Mediators

Kidney injury is associated with the release of inflammatory cytokines and chemokines that in turn attract immune cells such as neutrophils, macrophages, and natural killer cells.³ The dysregulation of these molecular and cellular elements results in the functional impairment of the kidney. Inflammation and immune dysregulation occur in such disease states as gram-negative sepsis, ischemia-reperfusion, diabetes (highlighted by chronic inflammation), and cancer (especially with the use of chemotherapeutic agents). As such, the various proteins involved in these complex pathways could serve as targets for innovative therapies.

Alkaline Phosphatase

Alkaline phosphatase (AP) confers renal protection during sepsis via the dephosphorylation of lipopolysaccharide, which activates inflammatory pathways when the lipid-A molecule is phosphorylated.^{113,114} The presence of lipopolysaccharide results in oxidative stress and release of inflammatory cytokines such as TNF- α and IL-6, which leads to endothelial damage and regional hypoxia within the kidney.^{115–117} In addition, in sepsis, mitochondria release large quantities of adenosine triphosphate in response to inflammatory cytokines and hypoxia.¹¹⁸ AP dephosphorylates adenosine triphosphate, converting it to adenosine. *In vitro*, adenosine has exhibited some protective effects on proximal renal tubule cells, depending on the receptor activated.¹¹⁹ However, the effect of adenosine, as previously noted, is quite variable, and its manipulation is the subject of alternative therapies.

Recent studies have evaluated the effect of AP on AKI in humans. A 2009 study found AP significantly improved serum creatinine compared with placebo in a small group of patients with gram-negative sepsis. However, the study was underpowered with regard to clinical outcome data.⁴ In a 2012 study, AP was found to lower creatinine clearance and levels of inflammatory markers in septic patients, although there was no significant difference between AP and placebo with

regard to the need for renal replacement therapy.⁵ The ongoing STOP-AKI trial is designed to evaluate the efficacy of a human recombinant form of AP in reducing serum creatinine and progression to renal replacement therapy.¹²⁰

Dipeptidylpeptidase-4 Inhibitors

Dipeptidylpeptidase-4 (DPP-4) inhibitors were originally designed to extend the biological half-life of glucagon-like peptide-1 (GLP-1). GLP-1 is an incretin hormone, and is known to play a role in blood glucose regulation via stimulation of insulin secretion while inhibiting glucagon secretion.¹²¹ However, evidence suggests that GLP-1 also has anti-inflammatory properties by suppressing the activity of various proinflammatory cytokines such as TNF- α and - γ , IL-1 β , plasminogen activator inhibitor type-1, and intercellular adhesion molecule-1.^{122–124} GLP-1 receptors have been found in the glomeruli of animal models, and it has been hypothesized that a deficiency in the receptors is involved in the pathogenesis of diabetic nephropathy.^{125–127} DPP-4 inhibitors may have a benefit in renal disease, particularly when associated with diabetes.¹²¹

In rats with type 1 diabetes, DPP-4 inhibitors were found to decrease the level of inflammatory markers and oxidative stress, resulting in less albuminuria and glomerular hyperfiltration.¹²⁸ This result has been replicated in other animal models as well.^{129–131} In nondiabetic rat kidneys, DPP-4 inhibitors were found to decrease the levels of inflammatory macrophages,¹³² and mice exposed to cisplatin had lower serum BUN and creatinine when pretreated with DPP-4 inhibitors.¹³³ When sitagliptin was administered to rats who experience renal ischemia–reperfusion injury, serum creatinine and BUN were lower, whereas urine output was increased at 24 and 72 hours.¹³⁴

Human studies of DPP-4 inhibitors have been more inconclusive. Shih *et al.* found retrospectively that DPP-4 inhibition was associated with an increased risk of AKI in a case–control study of 13,000 diabetic patients (one-half of whom were taking DPP-4 inhibitors).¹⁵ An observational study found a decrease in the estimated glomerular filtration rate in 247 diabetic patients who received sitagliptin.¹⁶ In addition, the large Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial, which evaluated the effect of saxagliptin versus placebo on cardiovascular events in patients with type 2 diabetes mellitus, found that DPP-4 inhibitor use was associated with decreased GFR compared with placebo.¹⁷ Conversely, a retrospective analysis by Pendergrass *et al.* showed no association between

sitagliptin and renal failure.¹⁸ The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study randomized 14,000 diabetic patients to sitagliptin versus placebo and echoed these findings.¹³⁵ However, subsequent analysis using the TECOS trial data with primary renal endpoints failed to find any improvement in renal function with sitagliptin.¹³⁶ The effect of DPP-4 inhibitors on renal dysfunction continues to be evaluated in at least 1 clinical trial (NCT02250872).

Sphingosine 1 Phosphate Analogues

Sphingosine 1 phosphate (S1P) analogues mitigate endothelial damage and decrease recruitment of inflammatory mediators in the renal tubules. In mice subjected to cisplatin, the S1P analogue FTY720 was found to decrease the levels of TNF- α and IL-6.¹³⁷ This same effect was also seen with ischemia–reperfusion kidney injury in mice with both FTY720 and the S1P analogue SEW2871,¹³⁸ whereas SEW2871 was found to reduce tubular necrosis, lower serum creatinine, and lessen leukocyte infiltration of glomerular tissue.¹³⁹ However, when used as an immunosuppressant for renal allografts in mice, FTY720 showed no improvement in graft survival and was associated with worsening kidney function.¹⁴⁰ Data on S1P analogues in humans is lacking, and currently, there are no clinical trials evaluating S1P analogues in human AKI.

Genetic Modifiers

In AKI, there is damage to the highly metabolically active cells in the tubular epithelium, which signals quiescent and terminally differentiated cells to enter the cell cycle as part of the repair process.¹⁴¹ The cell cycle arrest and apoptosis during repair may ultimately lead to acute tubular necrosis.³⁶ Cell cycle arrest, apoptosis, or cellular senescence is often mediated by the p53 tumor suppressor protein (resulting from the transcription of the TP53 gene) in response to stress signals, including DNA damage.¹⁴² Genetic modification or manipulation of this process may be of benefit in ameliorating AKI.

I5NP

I5NP, a small interfering RNA (siRNA) that can be filtered through the glomerulus and inhibit p53 in the renal tubules, has been found to decrease serum creatinine.^{143,144} I5NP interferes with the transcriptive process of p53, which in the tubular epithelium, may result in delay of apoptosis, permitting repair of damaged DNA, and ultimately, cellular function.¹⁴⁴ Inhibition of the well-studied pro-apoptotic p53 gene in animal models has shown some benefit after ischemic and toxic injury to the kidney. In models of ischemia–reperfusion kidney injury (cross-clamp) and toxin-mediated kidney injury (cisplatin) in rats, I5NP

was found to be associated with lower serum creatinine.¹⁴⁵ Administration of an siRNA molecule after ischemia–reperfusion injury resulted in improved tubular injury, less frequent apoptosis, and reduced swelling of mitochondria in cells of the thick ascending limb of Henle at the outer medullary regions in mice.¹⁴⁶

A few studies have tried to evaluate the safety and dose escalation of I5NP with regard to AKI in patients undergoing cardiovascular surgery (NCT00683553, NCT00554359) and renal transplantation (NCT00802347), but results were never reported. Genetic manipulation of transcriptive processes through the delivery of I5NP and other siRNA molecules through various mechanisms is an evolving area of research, especially in the arena of renal transplantation medicine.¹⁴⁷

Conclusion

AKI is a common disease, but heretofore has been poorly understood. Rudimentary understanding of the pathophysiology of AKI has meant that effective therapeutics to treat this disease are scarce. Although current therapy is supportive, a great deal of data has emerged that calls the conventional practices into question. More conservative resuscitation practices have supplanted traditional liberal volume resuscitation with normal saline. Accumulating evidence suggests chloride-rich fluids worsen renal function, and increasingly, balanced, buffered solutions are being considered for resuscitation. Crystalloids are still the mainstay of therapy, with equivocal data supporting the use of albumin over crystalloid therapy. Based on the most recent evidence, synthetic starches are no longer recommended. Research is also beginning to elucidate the microvascular and molecular pathways that lead to patterns of injury in AKI, which has resulted in a number of new and prospective therapies to prevent this disease. Renal flow modulators such as angiotensin II and adenosine antagonists convey benefit to the kidney through the manipulation of renal microvasculature. Antioxidants such as ALA, selenium, propofol, MESNA, and curcumin mitigate the effects of free radical oxygen species commonly found in AKI. Inflammatory modifiers such as AP, DPP-4 inhibitors, and SIP analogues attenuate inflammatory kidney injury processes via direct effect on immune-active molecules, such as TNFs and IIs. Finally, genetic modifiers seek to derail the genetic processes that lead to cell cycle arrest and apoptosis in kidney failure. Although many of these novel therapies have yet to be studied extensively in humans, their promise in animal models or smaller human studies lays the groundwork for more thorough future investigation.

DISCLOSURE

LWB reports having received consulting fees from La Jolla Pharmaceutical Company. The other author declared no competing interests.

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