CHAPTER 52

Novel Drugs for Acute Kidney Injury

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OBJECTIVES

This chapter will:

1. Review the current literature guiding fluid type and amount of resuscitation in treating acute kidney injury.
2. Examine current and future therapies designed to treat intrinsic renal disease.

Acute kidney injury (AKI) is a complex disease with a myriad of causes. The understanding of molecular basis of AKI is nascent, and its definition until very recently has been pathophysiologically simplistic.[1] Treatment has been largely supportive. Mainstays of therapy include volume management, avoidance of nephrotoxic agents, hemodynamic management, and renal replacement therapy. In addition, there has been in the past decade recent efforts aimed at looking at fluids and their impact on kidney function. Recent data have emerged that implicate chloride in the development of acute kidney injury.[2] However, there are other clinical trial data that suggest this effect may be small or nonexistent, leaving more questions than answers with regard to how to treat AKI.[3]

There have been efforts recently aimed at looking deeper into the causes of acute kidney injury. These efforts have yielded new information as to pathophysiology at the cellular and subcellular level. Much of the recent focus has been on inflammation, immune dysregulation, and oxidative injury.[4] Considerable strides have been made in identifying

molecules, enzymes, genes, and metabolic pathways that contribute to AKI. These new targets have been correlated to certain types of kidney injury, such as metalloproteinase, which are reflective of cellular dysfunction. Others include intermedin, adenosine, inducible nitric oxide synthase, vitamin D, and sphingosine 1 phosphate and are implicated variously in inflammation, apoptosis, and oxidative damage. Despite recent progress in understanding the basic science of AKI, there has been a tremendous challenge in identifying novel therapies. There are, however, some candidate therapies that have been studied recently that show promise in certain types of kidney injury.

NOVEL THERAPIES FOR PRERENAL DISEASE

Prerenal azotemia is characterized as a physiologic response to reduced effective extracellular volume.[5] As volume depletion occurs, neurohormonal mechanisms, including increased adrenergic tone and the renin-angiotensin-aldosterone axis, influence the tubular reabsorption of water. The reduction in glomerular filtration rate (GFR) in prerenal azotemia is seen when reabsorption is inadequate. Treatment of low circulating volume hinges on the administration of fluid. Recently, research has focused on the types and amounts of fluids in the treatment of prerenal azotemia.

Fluid Restriction

Conventionally, one of the hallmarks in the treatment of AKI has been liberal administration of intravenous fluid. The rationale for this strategy has been the restoration of cardiac output, improvement in systemic blood pressure, and the maintenance of renal perfusion via the augmentation of transglomerular pressure gradient.[6] This conventional approach, however, has been challenged recently. Interstitial edema, increased intraabdominal pressure, and renal vascular congestion have been implicated in the development of AKI from fluid overload. On a cellular level, fluid overload can lead to changes in microanatomy, defects in oxygen and metabolite transfer, and capillary and lymphatic congestion.[7] A number of studies have identified a positive fluid balance as a risk factor for the development of AKI, including the important Sepsis Occurrence in Acutely Ill Patients (SOAP) and Program to Improve Care in Acute Renal Disease (PICARD) studies.[8,9] In a secondary analysis of the prospective randomized, controlled Fluid and Catheter Treatment Trial (FACTT), investigators compared a fluid-restrictive strategy versus a fluid liberal strategy in critically ill patients and found that fluid balance was correlated positively with AKI.[10] In a more recent data analysis from the prospective, observational, multicenter Beijing Acute Kidney Injury Trial, fluid overload was found to be an independent risk factor for the incidence of AKI and also was correlated positively to the risk of death.[11] Although a conservative fluid management strategy is not a novel therapeutic agent in the strict sense, the concept still applies and represents an emerging tactic in the fight against AKI. Many authorities now endorse a guided approach to fluid management, although how this is achieved is still debated.

Type of Fluid

In addition to the recent work on the quantity of fluids administered to patients and the development of AKI, recent research has focused on the types of fluids administered and kidney injury. Much of the recent effort has focused on the use of balanced versus chloride-rich solutions, colloids versus crystalloids, and synthetic colloids (starches).

Hydroxyethyl starch (HES) was compared with Ringer's acetate in the 6S trial, a parallel-group, randomized blinded trial, and found to be associated with an increased risk of AKI.[12] Similar results were seen in the Crystalloid vs Hydroxyethyl Starch Trial (CHEST), a randomized control trial (RCT) comparison of HES and normal saline published of the same year.[13] A more recent meta-analysis found that in comparison with other fluids (including crystalloids, albumin, and gelatin) resuscitation with HES was associated with an increased risk of AKI and death.[14] Accordingly, HES has fallen out of favor as a resuscitative fluid.

Albumin has been compared with normal saline as early as 2004 in the Saline versus Albumin Fluid Evaluation (SAFE) trial, which concluded that the two fluids were more or less equivalent with regard to their effects on multiple organ systems.[15] A 2010 meta-analysis comparing hyperoncotic (20%) albumin to various fluids (including, among others, normal saline, isotonic [4% to 5%] albumin, and lactated Ringer's) found that hyperoncotic albumin decreased the odds of AKI substantially.[16] Hypertonic albumin recently was evaluated against crystalloid solution in more than 1800 septic and septic shock patients in the Albumin Italian Outcome Sepsis (ALBIOS) study.[17] The investigators of this study concluded that there was no difference in either the primary outcome metric (death) or the secondary metrics, which included renal function.

Chloride-rich solutions may be deleterious to kidney function. In animal models, renal vasoconstriction and a decrease in GFR have been described.[18] The 2012 JAMA study by Yunos et al. compared normal saline with a balanced solution (Hartmann, Plasma-Lyte 148, or chloride-poor 20% albumin) on kidney injury and found that saline was an independent risk factor for AKI and the use of renal replacement therapy (RRT).[2] The authors opined that this effect was directly a result of chloride-mediated renal vasoconstriction and changes in tubule-glomerular feedback, which regulates GFR. A follow-up analysis by the same authors yielded the same results.[19] In contrast, the 2015 SPLIT Randomized Clinical Trial found that the incidence of AKI did not increase in a population of critically ill patients who received saline versus a balanced solution.[3] These diverging results, the authors opine, may be related to the lack of inclusion of colloidal solutions (albumin and gelatin) as a comparator. The optimal solution for the prevention or mitigation of AKI is still hotly debated.

NOVEL THERAPIES FOR INTRINSIC DISEASE

Intrinsic disease can result from dysfunction in the renal parenchyma, which is made up of diverse tissue types, including glomerular units, tubules, interstitium, and microvasculature. Because of the complexity of renal histology and function, it is difficult to pinpoint the root cause of injury in AKI. However, there does seem to be a commonality among many of the different pathologic processes in AKI. Inflammation, immune hyperreactivity, and oxidative stress have been elucidated in renal ischemia/reperfusion injury, toxic insult, and sepsis. The inflammatory milieu seen in AKI is associated with tubular phenotypic changes, intrarenal microvascular hemodynamic factors, cellular metabolic imbalance, and alterations in transtubular dynamics.[20] Candidate therapies have been proposed to address

TABLE 52.1

Novel Therapeutics for Intrinsic Renal Disease

DRUG	MECHANISM(S) OF ACTION	PROPOSED INDICATION(S)
• Alpha lipoic acid	• Antioxidant • Free radical scavenger	• IRI • CIN
• I5NP	• Inhibitor of p53 gene • Prevents cell cycle arrest	• IRI
• Alkaline phosphatase	• Dephosphorylation of LPS • Reduction of ATP	• Gram-negative sepsis
• Selenium	• Co-factor in enzymatic antioxidation	• Cisplatin injury • ECSL
• MESNA	• Antioxidant • Free radical scavenger	• CIN
• Propofol	• Antioxidant • Free radical scavenger	• IRI
• ATII	• Enhance glomerular perfusion • Correct RAS deficiencies	• Sepsis
• Curcumin	• Antioxidant • Free radical scavenger	• IRI • Diabetic nephropathy • Lupus nephritis
• DPP-4 inhibitors	• Enhance GLP-1 activity • Antiinflammatory	• Diabetic nephropathy • Cisplatin injury
• S1P analogue	• Antiinflammatory • Immunosuppressant	• None to date
• Adenosine analogues	• Alteration of arteriolar blood flow	• CIN • IRI • Cardiorenal syndrome

ATII, Angiotensin II; *ATP,* adenosine triphosphate; *CIN,* contrast-induced nephropathy; *DPP-4,* dipeptidylpeptidase-4; *ECSL,* extracorporeal shockwave lithotripsy; *GLP-1,* glucagon-like peptide-1; *IRI,* ischemia/reperfusion injury; *LPS,* lipopolysaccharide; *MESNA,* sodium 2-mercaptoethane sulfonate; *RAS,* renin-angiotensin system; *S1P,* sphingosine 1 phosphate.

generalized renal inflammation as well as specific components of pathophysiology, as outlined above (Table 52.1).

Alpha Lipoic Acid

Endothelial dysfunction caused by oxidative stress has been implicated in kidney injury. Alpha lipoic acid (ALA) is a potent antioxidant that reduces oxidative stress as it converts to its reduced form in tissues, and it acts as a scavenger of free radicals.[21] It has been shown in animal models to improve glomerular function, as well as reduce inflammation in kidney cells.[22,23] ALA is used in the treatment of diabetic neuropathy and retinopathy and has been evaluated in humans for ischemia reperfusion injury and contrast-induced nephropathy. A 2013 study evaluated ALA prospectively in patients with diabetes receiving contrast as part of coronary angiography.[24] This study evaluated the number of end points, including plasma cystatin C and urinary neutrophil gelatinase-associated lipocalin (NGAL), which have been shown to be highly correlated to CIN.[25–27] Traditional biomarkers including serum creatinine, creatinine clearance, and blood urea nitrogen (BUN) also were evaluated. The study concluded that there was no appreciable amelioration of acute kidney injury after contrast in the group receiving ALA versus the control. A similar study from the same year evaluated more than 200 patients with baseline kidney dysfunction (defined as a creatinine clearance of less than 60 mL/minute) who were to undergo percutaneous coronary intervention and receive contrast intravenously.[28] End points included peak increase in serum creatinine as well as CIN incidence. The study found no difference between the group receiving ALA and the control group. However, ALA showed benefit in the predefined high-risk subgroups of patients who received a larger dose of contrast (lower serum creatinine increase) and patients over the age of 70 (lower incidence of CIN). A 2016 study of patients receiving a simultaneous kidney-pancreas (SLK) transplant showed decreased markers of inflammation when the donor and the recipient were treated with ALA compared with the control group (untreated) and recipient-only treated group.[29] Although it could be argued that these patients do not have acute kidney injury but rather chronic disease, this study showed a reduced detrimental effect of the newly transplanted kidney in patients receiving ALA, suggesting that, in the acute setting, the mediation of inflammatory molecules may be of benefit. There are currently no actively enrolling human trials listed on ClinicalTrials.gov that seek to evaluate ALA in acute kidney injury (a 2013 study as a status listed as "unknown" and appears not to be enrolling [NCT01978405]). However, there is a considerable amount of ongoing and completed animal research that points to an improved surrogate and clinical outcomes, including in disease processes such as ischemia-reperfusion injury,[30] sepsis,[31] toxic injury,[23,32] and obstructive aeropathy.[33]

I5NP

Cell cycle arrest in the setting of hypoxia and oxidative stress has been implicated as one of the pathophysiologic mechanisms of acute tubular necrosis (ATN).[34] The pro-apoptotic gene p53 is activated as part of this process.[35] Preclinical evaluations of p53 inhibition elucidated a benefit in ischemic and toxic animal models of AKI.[36] I5NP is a synthetically derived, small interfering RNA (siRNA) that temporarily inhibits p53 and is active in the tubules after being filtered through the glomerulus. I5NP has been evaluated in animal models for safety and pharmacokinetics and in a rat model of ischemia-reperfusion, where it has been shown to lessen the rise of serum creatinine (SCr).[37,38] A couple of dose escalation and safety studies of I5NP for

AKI in patients undergoing major cardiovascular surgery were considered, with results never reported by the study sponsor (NCT00683553, NCT00554359). A third study by the same sponsor sought to evaluate I5NP in the setting of kidney transplant, but also has not reported any results (NCT00802347).

Alkaline Phosphatase

The enzyme alkaline phosphatase (AP) may have a beneficial role in amelioration of kidney injury during gram-negative sepsis. Lipopolysaccharide (LPS), a component of endotoxin, has been characterized thoroughly as one of the major pathogenic contributors to the inflammatory cascade, immune alteration, and cellular dysregulation in gram-negative sepsis.[39] In the kidney, LPS has been shown to accumulate during sepsis, where it causes oxidative stress and the release of immune-modulating cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[40,41] These factors result in intrarenal microvascular endothelial damage and regional hypoxia, with ensuing kidney injury.[42] The structure of LPS contributes to its pathogenicity, specifically with regard to its Lipid A component, which is phosphorylated. AP acts to dephosphorylate LPS, rendering it far less toxic, as has been shown in numerous animal models.[43] In addition to its role in the detoxification of LPS, AP also plays a role in reducing the harmful effects of adenosine triphosphate, which is released from mitochondria during periods of endotoxemic-induced inflammation and hypoxia.[44] Adenosine, the dephosphorylated form of ATP, which is converted with the enzyme AP, has been shown in vitro to protect human renal proximal tubular epithelial cells from oxidative injury.[45]

The effect of AP on the kidney has been evaluated in humans. A 2009 randomized controlled trial evaluated AP's effects on certain markers of kidney injury in 36 patients with gram-negative sepsis and found a significant improvement in serum creatinine compared with placebo.[46] In subgroup analysis, AP attenuated the metabolism of nitric oxide, and subsequent inflammatory cytokines, in the kidneys of patients compared with that of placebo. This study was underpowered, however, to elucidate clinical outcome data. An additional 36 patients were evaluated in a 2012 study for creatinine clearance and progression to renal replacement therapy.[47] Although creatinine clearance was significantly lower in the AP group compared with placebo, progression to RRT between the two groups did not meet statistical significance. Secondary end points, consisting of levels of markers of inflammation, were also lower. A phase I trial in healthy volunteers showed safety in healthy volunteers and set the stage for the larger STOP-AKI trial (Safety, Tolerability, efficacy and quality of life Of a human recombinant alkaline Phosphatase in patients with sepsis-associated Acute Kidney Injury).[48] STOP-AKI seeks to evaluate a human recombinant form of AP in sepsis-associated AKI in at least 290 patients for changes in serum creatinine and need for renal replacement therapy.[49]

Selenium

Selenium plays an active role in enzymatic antioxidation, and a deficiency in this trace element has been linked to acute kidney injury.[50] Glutathione peroxidase, an important cytosolic enzyme in the peroxidation of free radicals during cellular aerobic respiration, is linked to the level of selenium in the plasma.[51] Preclinical models have established the role of selenium in preserving kidney function or mitigating kidney injury in a variety of settings. Selenium administration was associated with improved metrics of serum creatinine, urea, and histopathologic evidence of injury in a rat model of cisplatin-induced kidney injury.[51] Similar effects were seen histologically and functionally in rats subjected to gentamicin-related acute kidney injury.[52] Selenium also appeared to be of some benefit in ischemia-reperfusion injury in a murine model, when given in combination with erythropoietin.[53] In a porcine model, selenium improved the antioxidant profile of the transplanted kidney on immunohistopathology.[54]

Human studies have shown that selenium may or may not confer a potential clinical benefit in preventing or attenuating kidney injury. An early analysis by Hu et al. showed an improved kidney biomarker profile in patients pretreated with selenium before receiving cisplatin chemotherapy.[55] However, this did not translate into a clinical benefit in a 2004 double-blinded study, which found no difference in creatinine clearance between micronutrient-pretreated (including selenium) cancer patients and control patients who were to receive cisplatin.[56] In a 2013 randomized, controlled trial, Ghorbani et al. noted a decreased incidence of AKI in cancer patients who were to receive cisplatin chemotherapy when pretreated with selenium.[57] A micronutrient bundle (including selenium) conferred no benefit in the prevention of kidney failure to patients undergoing extracorporeal shockwave lithotripsy.[58] Similarly, a combination of selenium, zinc, vitamin C, and vitamin B1 failed to improve the incidence of kidney failure in critically ill cardiac surgery, major trauma, and subarachnoid hemorrhage patients in a 2008 study.[59] Numerous studies have evaluated selenium and its effect on overall mortality, composite end points, and organ dysfunction scores, but few of these articles mention of renal-specific effects, which are underwhelming.[60,61] The currently enrolling SodiUm SeleniTe Administration IN Cardiac Surgery (SUSTAIN CSX) trial is planning to compare the effect on persisting organ dysfunction and death in 1400 critically ill patients who will be randomized to selenium administration versus placebo and will include markers of renal function.[62]

Sodium-2-Mercaptoethane Sulphonate

Sodium-2-mercaptoethane sulphonate (MESNA) is a small molecule containing a sulfhydryl moiety, which allows it to scavenge for reactive oxygen species. Administered intravenously, it is filtered readily across the glomerulus and taken up by renal tubular cells within 30 minutes, where it is found in high concentrations.[63] MESNA was considered as a renoprotective adjunctive therapy to chemotherapy, where it was described thoroughly by the early 1990s.[64–66] MESNA was evaluated in an ischemia-reperfusion kidney injury in rats in 2001, where it was found to ameliorate histologic kidney damage but also functional kidney damage, preserving GFR and fractional excretion of sodium (FENa).[63]

MESNA was evaluated as a prophylactic agent for contrast-induced nephropathy in 2011. This study, which evaluated 100 patients with preserved eGFR, found that the incidence of contrast-induced nephropathy was significantly lower when patients were pretreated with MESNA compared with the untreated group.[67] As of a 2014 review article published by the same authors, the 2011 study thus far has been the only randomized controlled trial of MESNA in kidney injury.[68]

Propofol

The anesthetic propofol is similar in chemical structure to alpha-tocopherol (vitamin E), which is a known antioxidant. Propofol acts as a free radical scavenger by converting free oxygen radical species into a less toxic phenoxyl form.[69] In animal models, propofol has been found to ameliorate both markers of systemic inflammation as well as specific markers of renal health. In a 2006 piglet study comparing propofol to the volatile anesthetic sevoflurane during aortic surgery (cardiopulmonary bypass), propofol was associated with lower levels of serum creatinine, TNF-α, interleukin-1 (IL-1), interferon-gamma, and other markers.[70] A similar result was achieved in a piglet model of ischemia-reperfusion in 2008.[71] A 2007 study by Wang et al. showed attenuation of kidney injury with propofol in an ischemia/reperfusion rat model.[72] Kidney injury resulting from ureteral obstruction also was attenuated in a 2016 mouse model.[73] Human renal tubular cells were pretreated with propofol in an in vitro experiment in 2008 and showed decreased rates of apoptosis and increased rates of proliferation compared with untreated cells.[74]

As early as 2001, two of the volatile anesthetics and propofol were evaluated in vivo in humans with regard to renal impairment.[75] In this fairly large open-label study of 354 cardiopulmonary bypass patients, there was no appreciable difference in serum creatinine between the three groups. In contrast, Yoo et al. found a decreased incidence of AKI (defined by Acute Kidney Injury Network [AKIN] criteria) in cardiopulmonary bypass patients receiving propofol general anesthesia compared with sevoflurane general anesthesia.[76] The biomarkers serum creatinine and cystatin C were significantly lower, as was hospital length of stay. A more recent retrospective analysis of propensity-matched critical care patients receiving either propofol or midazolam elucidated a lower incidence of AKI (by serum creatinine and urine output levels), the need for renal replacement therapy, and mortality.[77] Propofol's apparent renoprotective effect was elucidated further in yet another retrospective analysis of 4320 patients receiving either propofol or sevoflurane as general anesthesia during colorectal surgery.[78] In this propensity-matched analysis, AKI (by AKIN and Risk, Injury, Failure, Loss, and End-stage Kidney [RIFLE]) was more likely in the sevoflurane group compared with the propofol group, as was hospital length of stay and ICU readmission. Results of a randomized clinical trial in humans undergoing cardiopulmonary bypass as part of elective open abdominal aortic repair comparing propofol to sevoflurane for general anesthesia were published recently.[79] In this study, renal and systemic biomarkers were measured in 50 patients who were randomized to receive one of the two anesthetics, and all of the measured biomarkers were significantly lower in the propofol group. A recent comparison of renal impairment using propofol and sevoflurane during extracorporeal mechanically assisted (ECMO) lung transplant showed improvement in NGAL but not serum creatinine or other clinical markers.[79a] Other studies examining propofol in renal transplant patients (NCT01132157, NCT01870011) were never published.

Overall, the preponderance of evidence suggests that propofol exerts a beneficial effect on the kidney during episodes of ischemia/reperfusion, and possibly other scenarios.

Angiotensin

Angiotensin II (ATII) is a well-described octapeptide that contributes in a complex way to homeostasis in human physiology. In addition to contributing to vasomotor tone, it serves various important autocrine and paracrine functions.[80] A component of the renin-angiotensin system (RAS), AT2 is extremely active in the kidney, where it regulates adrenal aldosterone release, sodium and water homeostasis in the proximal tubular cells, and vasopressin secretion.[81]

There is evidence linking the RAS dysfunction to immune-active and inflammatory states, as seen in endotoxemic sepsis and sepsis-induced kidney failure.[82] RAS dysregulation leads to a relative deficiency in aldosterone, despite high renin levels, which results in hypotension, organ hypoperfusion, and subsequent failure.[83] RAS upregulation in sepsis is well described[84] and is accompanied by the downregulation of AT-1 type of angiotensin receptors.[85] It has been contemplated this relative substrate deficiency may contribute to the development of shock in sepsis and that exogenous ATII would mitigate the hormonal deficiencies seen in this disease state.[86]

There is emerging consensus that an alteration in intraglomerular pressure may contribute to the onset of AKI in septic shock. It is well established that angiotensin blockade results in decreased glomerular filtration fraction and intraglomerular pressure,[87] which may result in decreased creatinine clearance and an elevation on serum creatinine. ATII acts to constrict efferent renal arterioles more so than afferent arterioles and therefore can improve intraglomerular flow. Exogenous ATII administration has been shown in sheep to increase urine output and creatinine clearance, despite a decrease in renal blood flow.[88] Renal bioenergetics also were examined in a sheep model and found to be unaffected by intravenous ATII, suggesting that the reduction in renal blood flow did not compromise renal cellular metabolism.[89] In a subsequent septic pig model by Correa et al., the effects of intravenous ATII, norepinephrine, and enalapril on a number of physiologic parameters (including renal plasma flow and prevalence of AKI) and biochemical parameters (mitochondrial activity) were compared.[86] The investigators found no decrement in kidney function with the use of ATII compared to norepinephrine, as well as no significant effect on renal mitochondrial activity.

Data on the use in humans of ATII to treat AKI are sparse. A number of older studies have evaluated ATII and its effects on kidney function, which included decreased GFR,[90–96] alteration in glomerular pore size,[97] decreased fractional excretion of sodium,[91,92,96,98–107] and decreased renal plasma flow.[91–96,98–100,103–105,108–113] None of these older studies, however, was designed as a randomized, placebo-controlled trial with renal function as a primary end point. The ongoing Angiotensin in Septic Kidney Injury Trial (ASK-IT) seeks to evaluate the effect of a systemic infusion of ATII as a selective efferent arteriolar vasoconstrictor on hemodynamics and urine output in critically ill patients with severe sepsis/septic shock and acute renal failure (NCT00711789). ATII has been evaluated recently as a novel pressor in high output shock, but this pilot study of 20 patients was not powered to evaluate for the drug's effects on kidney function.[80]

Curcumin

Curcumin, a member of the ginger family, is related to turmeric and is sold as an herbal supplement. It is used as a food-coloring agent and as an antioxidant, where it is thought to be a direct scavenger of superoxide, hydroxyl, hydrogen peroxide, and peroxyl radicals, as well as a catalyst for the upregulation of the antioxidant molecules superoxide dismutase, catalase, and glutathione peroxidase.[114] Curcumin

has been evaluated in a number of different animal models of AKI, in which its renoprotective effect is well established.

In a 2016 rat model of cisplatin-induced kidney injury, curcumin was found to attenuate AKI by histopathology and function (serum creatinine), a number of inflammatory markers (including TNF-α, myeloperoxidase, and IL-1β), and the expression of a number of proapoptotic genes on immunohistology (including p53).[114] Similar findings were made in a rat model of carbon-tetrachloride (CCl4)-induced kidney injury, including histologic improvement of inflammation as well as functional markers of renal function (serum creatinine and blood urea nitrogen).[115] Gentamycin-mediated AKI (by serum biomarkers creatinine, BUN, NGAL, and kidney injury molecule-1 (KIM-1) as well as histologic examination) in rats was mitigated significantly when the rats were pretreated with curcumin.[116] Other investigators similarly have elucidated curcumin's beneficial impact on toxin-mediated AKI.[117–121] One negative study found no benefit in kidney function with curcumin after a hypertonic glycerol-induced kidney injury.[122] Amelioration of kidney function (serum creatinine, BUN) and inflammatory markers (indices of oxidative stress) were noted in rat models of renal ischemia/reperfusion[123,124] as well as another rat model of secondary renal failure (remote alteration phenomenon) from limb ischemia/reperfusion.[125] Similar results were obtained by a number investigators examining curcumin's impact on ischemia/reperfusion injury in animals.[126–130] A single 2007 rat study evaluated the effect of curcumin on endotoxemic sepsis and disseminated intravascular coagulation and found that curcumin was associated with a reduction in glomerular deposition of fibrin, as well as a mortality benefit.[131] In this study, the rats pretreated with curcumin showed a reduction in the inflammatory cytokine TNF-α.

Despite an inordinate amount of preclinical research, human studies of curcumin's effects on acute kidney injury are lacking. In vitro, curcumin was shown to attenuate the apoptotic and necrotic effects of Shiga toxin on human renal proximal tubular cells.[132] Interestingly, the investigators attributed this benefit not to curcumin's antioxidant properties, but rather to the induction of heat shock proteins. A handful of trials have examined the beneficial effects of curcumin on chronic kidney disease, specifically with regard to diabetic nephropathy.[133–135] Khajehdehi et al. randomized diabetic nephropathy patients to receive either placebo or curcumin and found an attenuation in proteinuria as well as inflammatory markers in the curcumin group.[136] The same authors found a similar benefit in lupus nephritis patients in a 2012 randomized controlled trial.[137] Neither of these studies, obviously, dealt directly with the question of AKI. An ongoing trial seeks to evaluate curcumin in the prevention of renal complications related to abdominal aortic aneurysm (AAA) repair and will include biomarker endpoints such as serum creatinine and urine IL-18 as well as functional parameters like time-to-dialysis and death (NCT01225094). As of the time of publication, this trial has ended but results have not been published.

Dipeptidylpeptidase-4 Inhibitors

Glucagon-like peptide-1 (GLP-1) is a well-characterized incretin hormone, with wide-ranging activity in the body, including blood glucose control and stimulation of insulin secretion and inhibition of glucagon secretion.[138] Emerging research has elucidated the antiinflammatory properties of GLP-1 throughout the body (such as the pancreas, vascular endothelium, and brain), including the suppression of IL-1β, TNF-α, TNF-γ, plasminogen activator inhibitor type-1 (PAI-1), and intercellular adhesion molecule-1.[139–141] Dipeptidylpeptidase-4 (DPP-4) inhibitors inhibit the conversion of GLP-1 to its inactive breakdown products by the enzyme DPP-4. Inhibition of DPP-4 results in the enhancement of the biologic half-life of GLP-1. DPP-4 inhibitors originally were approved by the United States Food and Drug Administration (US FDA) and launched in the mid-2000s as a novel oral antidiabetic therapy. Used in this way, DPP-4 inhibitors act to attenuate the inflammation, insulin resistance, and insensitivity, and islet cell destruction seen in diabetes.[138]

Based on their antiinflammatory properties, DPP-4 inhibitors have been evaluated in the prevention and mitigation of diabetic nephropathy and nondiabetic kidney disease. GLP-1 receptors have been described in the glomeruli of mice, rats, and pigs.[142–144] A deficiency in GLP-1 receptors has been proposed as a pathogenesis for diabetic nephropathy and that the presence of an adequate amount of GLP-1, both receptors and substrate, would mitigate the onset of kidney failure.

A number of animal studies have evaluated the effect of various DPP-4 inhibitors on kidney function. Kodera et al. evaluated a DPP-4 inhibitor on renal function and inflammation in diabetic rats and found decreased albuminuria and glomerular hyperfiltration, as well as decreased levels of inflammatory markers and evidence of oxidative stress.[145] Comparable results were reported in other diabetic animal models.[146–148] In the nondiabetic kidney, there is also evidence of amelioration of kidney injury. Higashijima et al. found decreased numbers of inflammatory macrophages in a glomerulonephritis rat model.[149] In mice exposed to cisplatin, pretreatment with a DPP-4 inhibitor ameliorated functional renal injury (BUN and serum creatinine) as well as histologic evidence of tubular injury.[150] Finally, in an ischemia/reperfusion rat model, the DPP-4 inhibitor sitagliptin improved kidney injury and inflammatory marker profiles compared with control.[151]

The results seen in animal models have not been as straightforward in humans. In a large retrospective analysis by Shih et al., DPP-4 use actually was associated with an increase in the risk of AKI.[152] However, another retrospective review concluded that no association was found between the DPP-4 inhibitor sitagliptin and renal failure.[153] The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) randomized more than 14,000 patients with diabetes to the DPP-4 inhibitor sitagliptin or placebo and found that, as a secondary endpoint, there was no difference in renal function.[154] These results echoed the results of the even larger saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus (SAVOR-TIMI 53) trial.[155] Data from the TECOS trial were examined for primary renal end points in a subsequent analysis and were consistent with the conclusions of the original trial, that there was no significant degradation of renal function in the DPP-4 group.[156] In contrast, a recently conducted nonrandomized and noncontrolled observational study found a decrease in eGFR in a population of 247 patients with diabetes.[157] Finally, in a case-control study of more than 13,000 diabetic patients (half of whom were taking DPP-4 inhibitors), the investigators found an increase in AKI in the DPP-4 group compared with the control group.[152] Based on the available evidence, the question of DPP-4 inhibition on renal function is far from answered, and more research is being conducted, including The Effects of DPP4 Inhibitor on Cisplatin Induced Acute Kidney Injury trial (NCT02250872). This trial currently

is enrolling patients and seeks to evaluate the renoprotective effect of DPP-4 inhibitor on cisplatin-induced AKI in 182 patients.

Sphingosine 1 Phosphate Analogues

Sphingosine 1 phosphate (S1P) analogues recently have been evaluated in AKI. These molecules are thought to enhance cellular survival by inhibiting endothelial damage and decreasing the recruitment of inflammatory mediators in renal tubules. The S1P analogue FTY720 (fingolimod, an approved therapy in multiple sclerosis) has been evaluated in a mouse model of cisplatin-mediated AKI and was found to attenuate kidney injury, as well as levels of inflammatory markers including TNF-α and IL-6.[158] Likewise, in a model of ischemia/reperfusion, FTY720 was found to be renoprotective.[159] A newly identified S1P1-selective agonist, SEW2871, also has been evaluated in a mouse model of ischemia/reperfusion and was associated with a significant reduction in serum creatinine levels, tubular necrosis, infiltration of leukocytes, and markers of infiltration.[160] Awad el al. evaluated FTY720 and SWE2871 in mice and observed an attenuated effect of ischemia/reperfusion injury with both drugs.[161] FTY720 was evaluated as a renal allograft immunosuppressant and was associated with worsening kidney function and no improvement in graft survival.[162] However, human trials designed specifically to evaluate S1P analogues and kidney function have not occurred yet.

Adenosine Analogues

The well-known molecule adenosine and its various receptors are found throughout the body, including the kidney. Adenosine controls cellular metabolism through local vasodilatation or vasoconstriction, depending on the receptor type and location within the body, which allows for adjustment of oxygen delivery to match local tissue needs.[163] In the kidney, adenosine is generated at enhanced rates in response to increased tubular sodium chloride or during hypoxia in renal cells, and depending on the location within the kidney can have various effects, including reduction of GFR. The adenosine antagonist theophylline has been evaluated in preventing contrast-induced nephropathy. A 2005 meta-analysis concluded that there was a transitory benefit in preventing CIN with the use of theophylline, comparable to that on N-acetyl cysteine.[164] However, there was considerable heterogeneity within the meta-analysis. A more recent meta-analysis by Dai et al. found that the adenosine antagonist theophylline was protective and reduced the risk of AKI by half (odds ratio 0.48).[165] Recent animal studies of selective adenosine 2A receptor agonists in rodents was found in to be renal protective after ischemia/reperfusion.[166,167] No human trials of selective adenosine 2A receptor agonists have been conducted, but a recently published randomized controlled trial of children receiving congenital heart surgery compared aminophylline, a nonselective adenosine receptor antagonist, to placebo and found there was no effect on the development of kidney function.[168] Likewise, the large PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) randomized controlled study of heart failure patients found that the adenosine receptor antagonist rolofylline did not prevent persistent worsening renal function.[169] These negative studies add to the debate, which heretofore has been promulgated by a myriad of positive and negative studies on the use of adenosine receptor antagonism in AKI.[170–174] Interest continues, though, in adenosine antagonism in the prevention of AKI. The Pharmacology of Aminophylline for Acute Kidney Injury in Neonates (PAANS) trial currently is enrolling (NCT02276170) and at least one other study is exploring of the use of pentoxyfylline in AKI (NCT01469624).

CONCLUSION

AKI remains an important health concern and is marked by a paucity of available treatment options. Prerenal azotemia traditionally has been treated with fluid administration. However, new data exist that elucidate the importance of the amount and type of fluid given. The trend in current practice habits is to adopt a conservative fluid administration strategy, aided by goal-directed therapy. Moreover, chloride-rich solutions are falling out of favor in lieu of more balanced buffered solutions.

The complexities of intrinsic renal disease have made it difficult to identify therapies aimed at preventing acute kidney injury. Focus has turned, instead, to the common pathway found in many types of renal injury: inflammation, immune hyperreactivity, and oxidative stress. Many of the novel therapies discussed in this chapter are being developed to address this pathophysiology. Some, including curcumin, I5NP, MESNA, propofol, and selenium, act as direct oxygen free radical scavengers. Others, such as angiotensin II and adenosine receptor antagonists, hope to ameliorate kidney injury via manipulation of renal hemodynamics and tubule-glomerular feedback. Still others, such as S1P analogues, alkaline phosphatase and DPP-4 inhibitors, act via manipulation of inflammatory pathways. Research continues on all of these potential therapeutics, and as the complexities of renal pathophysiology continue to unfold, interest will only grow.

Key Points

1. The treatment of prerenal acute kidney injury includes a goal-directed, goal-conservative fluid administration strategy, with balanced buffered solutions preferred over chloride-rich solutions.
2. The common pathway found in many types of renal injury includes inflammation, immune hyperreactivity, and oxidative stress.
3. Curcumin, I5NP, MESNA, propofol, ALA, and selenium act as direct oxygen free radical scavengers, whereas S1P analogues, alkaline phosphatase and DPP-4 inhibitors act via manipulation of inflammatory pathways.
4. Angiotensin II and adenosine receptor antagonists ameliorate kidney injury via manipulation of renal hemodynamics and tubule-glomerular feedback.

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