

Moving beyond supportive care—current status of specific therapies in pediatric acute kidney injury

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Abstract Acute kidney injury (AKI) remains a significant challenge, leading to increased morbidity, mortality, and medical costs. Therapy for AKI to this point has largely been supportive; specific interventions to treat established AKI have had minimal effect. Review of the pathogenesis of AKI reveals complex, interacting mechanisms, including changes in microcirculation, the immune system, and inflammation, and cell death from both necrosis and apoptosis. Past definitions of AKI have been imprecise; newer methods for AKI identification and classification, including novel biomarkers and improved criteria for defining AKI, may permit earlier intervention with greater potential for success. With improved understanding of pathophysiology and the opportunity for intervention before AKI is fully established, clinicians may be able to move beyond supportive care and improve outcomes.

Keywords Acute kidney injury · Biomarkers · Apoptosis · Inflammation · Stem cells · Therapy

Introduction

Acute kidney injury (AKI) remains a significant challenge, particularly in the critical care setting. Critically ill patients with AKI have higher rates of mortality [1]; this is true for pediatric patients as well as for adults [2]. AKI extends hospital stay and increases cost of care [3]. Patients who suffer an episode of AKI are at risk to develop chronic kidney disease (CKD) and may progress to end-stage renal disease, requiring

long-term support with dialysis or renal transplantation [4]. The epidemiology of pediatric AKI has changed to more closely correlate with that seen in adult populations; primary renal diseases, such as hemolytic uremic syndrome, while still important causes of pediatric AKI, are now eclipsed by sepsis and multi-organ dysfunction syndrome (MODS) as the most common underlying diagnoses in children with AKI [5]. Thus, AKI has a significant impact on hospitalized pediatric patients.

Care for patients with AKI, to this point, has largely been supportive. Traditional conservative methods have included fluid restriction to prevent volume overload, limiting delivery of solutes (e.g., potassium) which could lead to complications in the setting of AKI, providing therapies to counteract metabolic imbalances associated with diminished renal function (e.g., bicarbonate for metabolic acidosis), and watchful waiting with the hopeful assumption that renal function would eventually recover. For those patients in whom metabolic or fluid balance cannot be appropriately maintained during the episode of AKI, renal replacement therapy provides a bridge to recovery.

Given the impact of AKI on mortality, morbidity, and cost, interventions which could interrupt and possibly reverse AKI would be welcome. Unfortunately, specific therapy for AKI remains elusive. This review will discuss past efforts at specific interventions for AKI and possible reasons for their failure, examine the current understanding of the physiology that underlies AKI, report on novel methods for the diagnosis and categorization of AKI, and consider possible new interventions which may lead to more successful specific therapies.

Interventions for AKI—the track record so far

The track record for specific interventions to address AKI is poor. Therapies designed to address issues such as oliguria, suboptimal renal perfusion, inflammation, or renal toxicity from free radicals, while seemingly rational, have proven to be unsuccessful (Table 1).

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Table 1 Unsuccessful therapies for AKI

Diuretics
Mannitol
Dopamine
Glucocorticoids
<i>N</i> -acetylcysteine (? possibly useful for contrast-induced AKI?)

AKI, Acute kidney injury

Diuretics

Diuretics, particularly loop diuretics, are frequently used in the setting of AKI. Reports in adult populations indicate that 59–70 % of patients will receive diuretics as part of AKI therapy [6]. Diuretics can be useful to augment urinary output and assist in fluid balance as part of conservative management of AKI. They may reduce energy needs and oxygen requirements in susceptible areas of the renal tubule and therefore could conceivably limit the risk of AKI progression [7, 8]. Unfortunately, several studies and meta-analyses demonstrate that, for critically ill adult patients with AKI, the use of diuretics does not improve outcome, whether used as prophylaxis for at-risk patients or as therapy in established AKI [9–11]. Some studies have even suggested a deleterious effect [12]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Acute Kidney Injury guideline, diuretics are not recommended to prevent AKI, nor are they recommended in the treatment of established AKI except as an adjunct to the management of volume overload [13].

Mannitol

Mannitol, an osmotic diuretic, could aid in AKI prevention by minimizing cellular edema following ischemic insult. It may also serve as a free radical scavenger [14, 15]. While mannitol can clearly increase urinary output, its use to prevent contrast-induced AKI is associated with worse outcome [16]. Mannitol does not appear to provide a significant reduction in renal injury when added to priming fluid during cardiopulmonary bypass [17]. Published studies of mannitol are hampered by retrospective design and relatively low numbers of subjects. When retained in the setting of poor glomerular filtration rate (GFR), mannitol will lead to hyperosmolality and potentially complicate patient management. Overall, mannitol has not proven to be an effective method to prevent or treat AKI.

Dopamine

Low-dose dopamine increases renal blood flow and can augment sodium excretion [18, 19]. However, it does not appear to improve oxygenation in the renal medulla, an area of the renal anatomy at high risk during ischemic AKI [20].

Nevertheless, low-dose dopamine has a long history as a therapy for AKI and its use continued for many years despite mounting evidence suggesting that it was ineffective. Several placebo-controlled trials and meta-analyses have demonstrated that low-dose dopamine does not prevent or successfully ameliorate AKI [21, 22], leading to the commentary in the KDIGO 2012 Acute Kidney Injury guideline recommending against its use [13].

Glucocorticoids

Glucocorticoids have an important role in the treatment of primary and secondary immune-mediated renal diseases, such as the various glomerulonephritides or severe allergic interstitial nephritis. The administration of glucocorticoids during ischemia and reperfusion appears to ameliorate injury to proximal tubule cells through mechanisms independent of their well-known anti-inflammatory actions [23]. Their use as part of the treatment of sepsis and MODS, in which AKI may be evident, remains controversial. The CORTICUS trial evaluated the use of hydrocortisone as part of therapy for critically ill adults with sepsis; while some improvement in the rate of organ function recovery was observed, there was no survival advantage in the treatment group [24]. Glucocorticoids are unlikely to be an effective method for the treatment of AKI in the critically ill patient; their use is not recommended.

N-acetylcysteine

N-acetylcysteine has been used for the prevention of contrast-induced AKI. While many studies have suggested a benefit [25], controversy regarding its use in this setting remain as the effect of *N*-acetylcysteine to prevent AKI can be variable, and several studies have failed to show a significant benefit. A recent multi-center, randomized, placebo-controlled trial of over 2,000 adults at risk for contrast-induced AKI undergoing angiographic procedures [the Randomized Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT)] demonstrated an identical risk for contrast-induced AKI, defined as a 25 % increase in serum creatinine over baseline, in both the *N*-acetylcysteine group and placebo group (12.7 % risk for each) and no differences in secondary endpoints of mortality or need for dialysis [26]. Although well designed, the ACT had some limitations, including a relatively lower-than-predicted incidence of AKI, use of creatinine as the biomarker, and some variation in co-interventions (other than hydration). Further, it should be recognized that this study evaluated adults at risk for contrast-induced AKI undergoing angiographic procedures, making it challenging to extend the findings to pediatric patients who most often receive radiocontrast in the setting of computed tomography. *N*-acetylcysteine therapy to prevent contrast-induced AKI is currently recommended by the KDIGO Acute Kidney Injury guideline [13]. The results of

the ACT may call into question the current use of *N*-acetylcysteine as a prophylactic measure against contrast-induced AKI and will likely require a careful review of many protocols and recommendations.

Given its apparent effects in contrast-induced AKI, *N*-acetylcysteine therapy has been tried for the prevention of ischemia-related AKI following surgery. A meta-analysis reviewing ten studies of *N*-acetylcysteine use after surgery found no improvement in rates of AKI [27]. KDIGO does not recommend *N*-acetylcysteine for AKI prophylaxis other than for contrast-induced AKI; as noted above, even this recommendation may require review.

Growth factors

With renal tubular injury being a major component in the pathogenesis of AKI, renal tubular repair is a required step for recovery. Growth factors play an important role in the regeneration of epithelial cells. In animal models, several growth factors have been shown to accelerate recovery from renal injury (Table 2) [28]. Erythropoietin appears to reduce necrosis and apoptosis in renal epithelial cells while also promoting cell proliferation [29]. Unfortunately, studies in humans have not demonstrated any AKI-related benefit with the early use of erythropoietin [30]. Similarly, hepatocyte growth factor and insulin-like growth factor-1 (IGF-1) appear to limit apoptosis in animal models of renal injury [31, 32]. Preliminary clinical trials with IGF-1 have not shown benefit to patients, and the KDIGO group recommends against use of IGF-1 in this setting [13].

Emerging understanding of AKI pathophysiology

Why have various targeted interventions designed to address AKI failed? Part of the explanation may rest in the recognition that the physiology underlying AKI is exceedingly complex (Fig. 1). While the traditional medical school triad of “pre-renal, intra-renal, post-renal” causes is a reasonable starting point to evaluate a patient with AKI, this only scratches the surface of the concepts related to AKI pathogenesis. Recent detailed reviews of current understanding related

Table 2 Growth factors shown to accelerate renal recovery in animal models of AKI

Epidermal growth factor
Insulin-like growth factor-1
α-Melanocyte stimulating hormone
Erythropoietin
Hepatocyte growth factor
Bone morphogenetic protein 7

to the origins of AKI clarify why simple mono-therapies have proven unsuccessful and provide insight to potential interventions [28, 33, 34].

Adaptive and autoregulatory effects

The most frequent cause for AKI is pre-renal azotemia, which results from diminished effective circulating volume and renal hypoperfusion. This can be secondary to true volume depletion or to other conditions in which volume may be normal or increased but perfusion is reduced, such as congestive heart failure or sepsis (Table 3). Compensatory mechanisms in this clinical condition lead to activation of the renin–angiotensin–aldosterone system, the sympathetic nervous system, and vasopressin. Activation of angiotensin II maintains glomerular pressure, and thus the GFR, despite the reduced perfusion. With suboptimal renal perfusion, the kidney’s native autoregulatory system also works to preserve GFR.

In the setting of severe circulatory collapse, as might be seen in shock or profound sepsis, the compensatory mechanisms for preserving GFR fail. Higher levels of angiotensin II cause vasoconstriction of both the afferent and efferent arterioles at the glomerulus, leading to lower GFR. Autoregulatory mechanisms do not maintain glomerular pressure. Certain medications, such as non-steroidal anti-inflammatory drugs or angiotensin-converting enzyme inhibitors, interrupt the normal physiological process and may hamper the compensatory systems. Multiple interacting mechanisms lead to more severe AKI in the setting of serious illness.

Cellular injury in AKI

Ischemia and reperfusion, or the effects of nephrotoxins, can cause injury to renal epithelial cells. Renal epithelial cells are particularly susceptible to these effects due to their high oxygen and energy needs, concentration of toxins within epithelial cells, and relatively low oxygen tension within portions of the kidney. Depletion of ATP leads to cellular dysfunction and, if severe enough, cell death. Epithelial cell injury can lead to changes in cell morphology and cytoskeletal structures; polarization is lost, and the normal transport and barrier capabilities of the epithelial cell, required for normal renal function, are compromised. Cell death may occur through necrosis or apoptosis, with several apoptotic pathways appearing to be activated in the setting of renal ischemia. Cell loss further compromises the epithelial barrier of the renal tubule, while cell slough into the lumen of the tubule causes nephron obstruction. All of these events conspire to diminish renal function.

Endothelial cells also suffer injury as a result of ischemia or in the setting of sepsis, leading to microvascular dysregulation in selected regions of the kidney that might not improve when global renal perfusion recovers [33, 35, 36].

Fig. 1 Pathophysiology of acute kidney injury (AKI). Multiple factors may contribute to the development of AKI

Adaptive/Autoregulatory Effects

- Renal under-perfusion
- Loss of autoregulation
- Vasoconstriction

Epithelial/Endothelial Cell Injury

- Ischemia/reperfusion
- ATP depletion
- Depolarization
- Cytoskeletal changes
- Apoptosis or necrosis

Acute Kidney Injury

Inflammation/Immune Mechanism

- Neutrophils
- Macrophages
- T-regulatory cells
- NK cells
- Complement
- Immune system mediators

Intrinsic Repair Mechanisms

- Epithelial cell proliferation
- Stem cell participation (?)

In response to vasoconstricting stimuli, such as endothelin-1, angiotensin II, thromboxane A₂, prostaglandins, adenosine, and sympathetic nerve stimulation, post-ischemic arterioles vasoconstrict more strongly than do arterioles from non-ischemic renal tissue. Counter-regulatory vasodilation under the influence of mediators such as acetylcholine, bradykinin, and nitric oxide is reduced; damaged endothelial cells produce lower amounts of nitric oxide and other vasodilating substances. Damaged endothelial cells also produce increased amounts of adhesion molecules (e.g., ICAM-1)

which activate leukocytes, leading to microvascular obstruction and enhanced local inflammatory effects. Thus, through numerous effects, endothelial injury and subsequent dysfunction may perpetuate and exacerbate epithelial injury.

Inflammation and immune mechanisms

Multiple arms of the immune system participate in the setting of AKI. While this may begin as an adaptive response, related to injury and tissue repair, dysregulated immune activity can serve as a strong catalyst for AKI. Numerous potent mediators of the immune system are secreted by injured epithelial and endothelial cells (Table 4). Cellular participants include neutrophils, macrophages, T-regulatory cells, and natural killer cells. Experimental models of immune cell inhibition that use selective knockouts in mice or antibody-mediated blockade indicate that the various cells will mediate renal tubular injury

Table 3 Causes of renal hypoperfusion

Cause of renal hypoperfusion	Clinical condition
Volume depletion	Hemorrhage
	Vomiting
	Diarrhea
	Polyuria
	Burns
Diminished cardiac output	Capillary leak syndromes
	Congestive heart failure
	Cardiogenic shock
	Sepsis
	Cardiac tamponade
Reduced systemic vascular resistance	Pulmonary hypertension
	Sepsis
	Cirrhosis
	Anaphylaxis
Increased renal arterial resistance	Medications
	Radiocontrast
	Hepatorenal syndrome

Table 4 Locally secreted mediators of inflammation in AKI

Tumor necrosis factor
Interleukin-6
Interleukin-8
Interleukin-1 β
Transforming growth factor β
RANTES
C-C motif chemokine 2
C-C motif chemokine 5
Toll-like receptor 2
Toll-like receptor 4

at differing points in the progression of AKI [28]. Complement activation plays a significant role, especially through the alternative pathway in the setting of ischemia–reperfusion injury [37]. Complement C3 binding in the damaged kidney upregulates the production of endothelial adhesion molecules and leads to further immune activation. Immune cells, along with injured epithelial and endothelial cells, will secrete mediators that further drive the inflammatory response. Multiple reciprocal interactions lead to a complex cascade of inflammatory activity in AKI.

Repair mechanisms

As noted above, cell death (through either necrosis or apoptosis) is one mechanism involved in the pathogenesis of AKI. Following injury, renal epithelial cells have the capacity to greatly increase their basal level of proliferation to reconstitute the renal tubule. Hypothesized sources for regenerating cells in the renal epithelium include bone marrow-derived cell, intrarenal stem cells, or native endothelial cells which survived the initial insult. These repair mechanisms have been a topic of some debate. A current proposed mechanism suggests that the renal epithelium reconstitutes from surviving tubular cells [38] while cells of bone marrow origin, identified in the regenerating renal tubule, are not the source of recovering epithelial cells but rather facilitate repair through local anti-inflammatory effects [39–41].

AKI epidemiology and biomarkers for diagnosis

Successful treatment of AKI is also hampered by challenges in diagnosis. Multiple definitions in the literature for AKI have made analysis and review imprecise, thereby complicating epidemiological study and also care of the individual patient: it is difficult for the treating physician to choose an appropriate intervention if there is a lack of consensus on whether or not the patient actually has AKI. Newer schemas to define AKI, including the Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) criteria [42, 43], the Acute Kidney Injury Network (AKIN) criteria [44], and the KDIGO staging system [13], have taken similar approaches to codify the diagnosis of AKI using clear guidelines. This will be an important step to develop our ability to intervene and hopefully improve outcomes [45].

Even with clear definitions, AKI may be difficult to identify. The most commonly used markers of AKI, serum creatinine and urinary output, are suboptimal diagnostic markers. Serum creatinine is a flawed biomarker of AKI, rising only after injury has occurred and the GFR has already begun to decline. It can show significant variability based on muscle mass and muscle breakdown. Patients with tubular dysfunction, such as those suffering from nephrotoxin injury, may not

have oliguria; this makes the recognition of AKI challenging. Both urinary output and serum creatinine are used as the basis for the newer AKI definitions noted above, and while these new definitions are an advance since they are the result of careful review and consensus, one must recognize the continued limitations related to the benchmarks. Newer biomarkers measured either in the blood or in the urine may provide an opportunity to diagnose AKI before serum creatinine rises or urinary output falls (Table 5). These biomarkers are an active area of study and may permit strategies for early AKI intervention [46]. Careful identification of patients at increased risk will also aid in earlier recognition of AKI. Such patients would constitute an enriched population for whom the newer biomarkers would have greater sensitivity; further, they may help to identify appropriate candidates for enrollment in interventional trials. Just as patients with chest pain and a suggestive medical history represent a population for whom screening for cardiac ischemia is indicated, the concept of “renal angina” has recently been suggested to describe patients with clinical features putting them at the greatest risk for AKI [47, 48]. Such patients would warrant AKI screening with new biomarker assays and careful observation for clinical change.

Potential interventions for AKI based on current knowledge

Given the complex pathophysiology that underlies AKI, and the difficulty in identifying AKI before it is well established, perhaps it is not surprising that many simple interventions, though seemingly rational, prove unsuccessful. One area of success in AKI treatment has been for contrast-induced AKI, where the recognition of risk and implementation of prophylactic measures have been able to mitigate the nephrotoxic effects of radiocontrast agents. This paradigm of early intervention before AKI is established, coupled with the capabilities for earlier diagnosis and better understanding of AKI pathogenesis, may provide inroads for newer therapies of AKI.

Identification of at-risk patients

Factors shown to be associated with risk for AKI in adult patients include age, pre-existing CKD, and proteinuria

Table 5 Novel biomarkers

Neutrophil gelatinase-associated lipocalin (NGAL)
Kidney injury molecule-1 (KIM-1)
Interleukin-18
Liver-type fatty acid binding protein (L-FABP)
Monocyte chemoattractant protein-1 (MCP-1)

[28]. Similar concepts have been applied to children. Specific clinical scenarios, such as cardiopulmonary bypass, patients in the intensive care unit, and those who require extracorporeal life support with membrane oxygenation, can also identify children at increased risk. Other less dramatic circumstances may also increase risk, such as patients after surgery and those exposed to (sometimes multiple) nephrotoxins. Appropriate identification of the various patients at risk for AKI could at the very least permit thoughtful management of volume status to assure the maintenance of gross renal perfusion, as well as a rational approach to the use, or avoidance, of common nephrotoxins. Identifying patients at risk through the use of scoring systems has proven to be challenging. Severity of illness scores [e.g., Pediatric Risk of Mortality (PRISM), Pediatric Index of Mortality (PIM)] and organ dysfunction scores [e.g., Logistic Organ Dysfunction Score (LODS), Sequential Organ Failure Assessment (SOFA), Pediatric Logistic Organ Dysfunction score (PELOD)] were not designed to predict AKI. As noted above, the concept of “renal angina” represents a model to identify and predict those individuals, including children, at increased risk for AKI [48].

Optimization of volume status

Optimizing volume management has already proven effective in mitigating the deleterious renal effects of radiocontrast. KDIGO guidelines recommend intravenous volume expansion for those patients who are at increased risk for developing contrast-induced AKI [13]. Goal-directed fluid resuscitation improves the outcome for patients who present with shock [49] and is an appropriate adjunct to the overall management of the critically ill patient at risk for AKI [13]. Given our greater knowledge about changes in renal microcirculation once AKI is established, pre-morbid or very early volume optimization is more likely to be successful than delayed efforts at improving renal perfusion.

Adenosine receptor antagonism—theophylline

Tubulo-glomerular feedback, a normal regulatory mechanism in response to high content of chloride in the renal tubule, can lead to excessive afferent arteriolar vasoconstriction at the glomerulus, reducing the GFR and promoting ischemic AKI. Vasoconstriction in the glomerulus occurs under the effect of adenosine; consequently, adenosine blockade has been proposed as a rational target to prevent or ameliorate AKI. AKI is a common finding in the asphyxiated neonate and has been reported in up to 60 % of cases [50]. Theophylline, a non-selective adenosine receptor antagonist, has been demonstrated to limit the severity of AKI in asphyxiated neonates; several studies have shown higher GFR, higher urinary output, and less evidence of renal

tubular dysfunction in those neonates who received theophylline as compared to controls [51–53]. It is unclear, however, if this observed difference is important for long-term outcome [52]. KDIGO guidelines do suggest that a single dose of theophylline may be given to neonates with severe asphyxia who are at high risk for AKI [13].

Remote ischemic preconditioning

In ischemic preconditioning, an organ becomes transiently resistant to a future episode of ischemic injury as a result of having undergone a prior ischemic period. This effect seems to be true for the kidney [54]. The duration of protection is unclear. In animal models of renal transplant, ischemic preconditioning is associated with less kidney injury following reperfusion of the allograft [55, 56]. Remote ischemic preconditioning involves inducing a brief period of ischemia in a distant capillary bed, such as by inflating a blood pressure cuff around an extremity for several minutes, in the hope of preventing or ameliorating ischemic injury at a different target organ. A systematic review by the Cochrane group of remote ischemic preconditioning for vascular surgery in humans found no difference in mortality or any other outcome studied, with the exception of a slightly reduced risk for myocardial infarction in the remote ischemic preconditioning group [57]. The authors of the systematic review noted, however, that this positive effect was from the results of only one trial and was not consistently observed. It remains unclear if remote ischemic preconditioning would be helpful to prevent AKI; the use of this technique would require identification of at-risk patients and application of the intervention prior to the insult (e.g., pre-operatively). The Remote Ischemic Preconditioning in Cardiac Surgery Trial (Remote IMPACT) (ClinicalTrials.gov identifier NCT01071265) is a large, randomized, ongoing trial in adults undergoing cardiac surgery. This study, the results of which should be available soon, is evaluating the ability of remote ischemic preconditioning to reduce injury on both the heart and the kidneys.

Inhibition of apoptosis

Since apoptosis has been shown to be a primary pathway for renal epithelial cell death in the setting of AKI, prevention of apoptosis may be a rational target for AKI therapy. Mitochondrial and cell receptor pathways for apoptosis activate the caspase family of proteases. Caspase inhibitors appear to protect against cell injury in experimental models [58]. Minocycline, an inhibitor of matrix metalloproteinases, has anti-apoptotic effects and is associated with improved renal status in models of injury [59]. Minocycline also appears to improve microvascular permeability in rodents with ischemic AKI [60]. Through inhibition of p53 expression, guanosine and the novel agent pifithrin alpha

also appear to reduce apoptosis of renal epithelial cells [61, 62]. Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme that participates in DNA repair. The over-activation of PARP-1 promotes cell death and upregulation of key proinflammatory pathways, while the inhibition of PARP-1 appears to lessen renal cell death in a model of cisplatin-induced kidney injury [63]. PARP inhibitors are being studied as possible antineoplastics and could be used to intervene in AKI.

Immune mediators

Despite the failure of glucocorticoids to improve outcome, inflammation clearly plays a significant role in the pathogenesis of AKI. As previously discussed, the components and cells of the immune system participate in multiple and varied points during the development and progression of AKI. Thus, multi-lateral approaches may be more likely to have a positive effect.

Therapeutic hypothermia

In therapeutic hypothermia, the patient undergoes controlled cooling in an effort to limit organ injury. A recent review discusses the use of therapeutic hypothermia to limit neurological and cardiac injury and presents potential benefits of therapeutic hypothermia in patients with AKI [64]. A trial in Australia and New Zealand evaluating the impact of therapeutic hypothermia on neurological outcome [Prophylactic Hypothermia to Lessen Traumatic Brain Injury (POLAR) trial; ClinicalTrials.gov identifier NCT00987688] is also investigating renal effects in an AKI substudy.

Stem cells

The infusion of stem cells has been shown to attenuate experimental AKI [65–67]. As noted above, the mechanism of repair may not be related to repopulation of denuded renal tubular basement membrane by stem cells themselves, but possibly by proliferation of resident cells stimulated by paracrine effects from the stem cells. Thus, while stem cells may not repopulate the damaged renal tubule, mechanisms to promote stem cell migration to the kidney and augment their supportive functions may be important for the treatment of established AKI.

Conclusions

The poor success of interventions for AKI suggests that changes in approach are warranted. Review of the physiology identifies multiple complex pathways related to AKI pathogenesis, suggesting that unilateral approaches to therapy are

unlikely to be successful. Recognition that certain patients, such as those with pre-existing CKD, multi-morbidities, or combined renal insults, are at greater risk further helps to focus potential measures for intervention. The rare successes in AKI intervention are those where prophylaxis may mitigate or prevent the development of renal dysfunction, such as in the setting of contrast-induced AKI. Newer interventions, specifically targeted at the identified causes and exacerbations of AKI, may have greater chances for success, especially when combined together to address multifactorial causes simultaneously. Better identification through biomarkers, more precise classification of levels of AKI, and deeper understanding of AKI epidemiology will permit earlier interventions that will have a greater likelihood of success.

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