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REVIEW

Novel Therapies for Acute Kidney Injury

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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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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,

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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