Management of Acute Kidney Injury and Acid-Base Balance in the Septic Patient

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KEYWORDS

• Acute kidney injury • Acute renal failure • Sepsis • Acid-base • Biomarkers
• Renal replacement therapy

KEY POINTS

- Acute kidney injury (AKI) is an abrupt decrease in kidney function that takes place over hours to days that is associated with increased morbidity and mortality in sepsis.
- Many trials have studied pharmacotherapies to prevent or treat AKI, with disappointing results.
- Management strategies for septic AKI should focus around treatment of underlying sepsis, maintaining adequate intravascular volume and avoiding fluid overload, maintaining adequate mean arterial pressure for renal perfusion, and avoidance of nephrotoxic agents.
- The mainstay of current treatment for septic AKI is renal replacement therapy, which can be delivered either intermittently or continuously.

INTRODUCTION

Definitions

Broadly speaking, acute kidney injury (AKI, also known as acute renal failure) is an abrupt decrease in kidney function that occurs over hours to days. This is in contradistinction to chronic kidney disease (CKD), where renal function declines over the course of months to years. In 2004, the Acute Dialysis Quality Initiative (ADQI) published the first AKI consensus definition, with the goal of standardizing disease recognition and endpoints for clinicians as well as for research studies, including clinical trials.[1] The RIFLE criteria (an acronym that stands for risk, injury, failure, loss, and end-stage renal disease [ESRD]) use acute changes in serum creatinine and urine output, 2 readily available measurements, to define 3 progressive levels of renal dysfunction (R, I, and F) and 2 clinical outcomes (L, E). These criteria were subsequently refined by the Acute Kidney Injury Network (AKIN) and then by the Kidney Disease Improving Global Outcomes (KDIGO) group (**Table 1**).[2,3] The association of AKI defined by these criteria with adverse outcomes has now been validated in a large number of clinical studies.[4–8]

Epidemiology

These consensus definitions for AKI have greatly facilitated large epidemiologic studies examining the incidence and outcomes of AKI. Using RIFLE

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Table 1
Comparison of creatinine-based consensus definitions for acute kidney injury

	RIFLE Criteria		AKIN Criteria	KDIGO Criteria
R(isk)	SCr ≥150% baseline within 7 d, OR >25% decrease in eGFR	Stage 1	SCr ≥150% baseline, OR SCr ≥0.3 mg/L increase within 48 h	SCr ≥150% baseline within 7 d, OR SCr ≥0.3 mg/L increase within 48 h
I(njury)	SCr ≥200% baseline, OR >50% decrease in eGFR	Stage 2	SCr ≥200% baseline	SCr ≥200% baseline
F(ailure)	SCr ≥300% baseline OR SCr >4 mg/dL with acute rise >0.5 mg/dL, OR >75% decrease in eGFR	Stage 3	SCr ≥300% baseline, OR SCr ≥4 mg/dL with acute rise of ≥0.5 mg/dL, OR initiation of RRT	SCr ≥300% baseline, OR SCr ≥4 mg/dL,[a] OR Initiation of RRT, OR If <18 y, eGFR <35 mL/min/1.73m2
L(oss)	Persistent loss for >4 wk	—	—	—
E(nd-stage kidney disease)	ESRD >3 mo	—	—	—

Urine output criteria are the same for all 3 staging systems and are as follows: stage 1: <0.5 ml/kg per hour for 6 to 12 hours; stage 2: <0.5 ml/kg per hour for ≥12 hours; stage 3 <0.3 ml/kg per hour for ≥24 hours OR anuria ≥12 hours.

Abbreviations: AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; KDIGO, Kidney Disease Improving Global Outcomes; RRT, renal replacement therapy.

[a] Must meet criteria for stage 1 as well.

criteria to define AKI, numerous large studies have found that the incidence of AKI during an admission to the intensive care unit (ICU) is often greater than 60%, although this rate will vary depending on the ICU population (medical ICU vs neurosurgery ICU, for example).[4,9–11] Other studies have found that sepsis contributes in 33% to 50% of all cases of AKI, making sepsis the leading cause of AKI.[5,12,13] Along the same lines, sepsis studies have found that AKI develops in 40% to 60% of these patients.[14–19] Not surprisingly, sepsis that is complicated by AKI has a higher mortality rate than sepsis alone, and the severity of sepsis correlates with the severity of AKI.[16,20] Mortality rates of patients with AKI needing renal replacement therapy (RRT) are approximately 35% to 50%, although again will vary based on the population.[21,22]

Pathophysiology

Septic AKI was classically thought to be caused by an ischemic "pre-renal" etiology, attributed to hypoperfusion due to decreased renal blood flow in the setting of leaky vasculature and systemic vasodilation leading to decreased preload. However, several studies have disputed this notion, and research studies are ongoing. For example, arguing against a central role for hypoperfusion per se, a large cohort study found that 25% of hospitalized patients with community-acquired pneumonia who never developed shock or required ICU admission developed AKI.[23]

A major insight in the pathophysiology of sepsis-induced AKI came from an autopsy series of 44 patients who died of sepsis, which found that the degree of renal tubular cell injury in most patients was regional within the kidney, not severe enough to explain the AKI, and most tubular cells appeared relatively normal by electron microscopy.[24] Furthermore, it is unclear if renal blood flow uniformly decreases during sepsis in humans. A systematic review on this topic concluded that cardiac output is the major determinant of renal blood flow, and because cardiac output is typically increased in sepsis, consequently global renal blood flow may therefore be unchanged or even increased.[25] However, the glomerular filtration rate (GFR) may still be reduced in the face of normal or supranormal blood flow due to changes in afferent and efferent arteriole vasoconstriction.

Thus, it is thought that a large component of septic AKI is due to functional rather than structural or ischemic injury per se.[26] This is supported by histopathology from large animal models.[27] These effects may be mediated by proinflammatory cytokines and other plasma mediators. For example, plasma from patients with septic AKI can induce changes in polarity in podocytes and renal tubular epithelial cells in *in vitro* cell culture.[28] Recently, Gomez and colleagues[29] proposed a "unifying theory" of septic AKI. In this analysis,