Infection Post-AKI: Should We Worry?

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Abstract

Acute kidney injury (AKI) continues to be a major problem among hospitalized patients, and there is a growing appreciation that the high mortality in AKI may be due to its deleterious systemic effects. Recent research has begun to disentangle kidney-organ cross talk, wherein the host response to AKI becomes maladaptive, resulting in effects on numerous remote organs such as the lung, heart, liver, spleen, and brain. AKI also adversely affects immune function and is widely considered an immunosuppressed state. A wealth of data has accumulated that patients with AKI have a substantial increased risk of subsequent infection and sepsis. Indeed, sepsis is the leading cause of death in patients with established AKI. Unfortunately, little is known regarding the nature of the abnormal immune response that increases the risk for septic complications which may be persistent and prolonged. Until mechanistic pathways that drive the AKI-immune system-infection process are identified, and physicians should attempt to minimize AKI, its severity, and duration and anticipate infectious complications.

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Acute kidney injury (AKI) is a common and serious problem affecting patients of all ages and illness severity across geographic locations. Across multiple definitions of AKI, stages of severity, and diverse populations of study, AKI is consistently associated with poor patient outcome, including death. Our current understanding of AKI has evolved resulting in a paradigm shift that AKI is no longer an isolated problem and the kidneys are not “innocent bystanders” but a syndrome with far-reaching effects to almost every organ system in the body [1]. It is these deleterious systemic effects triggered by an AKI event that may result in the high mortality of patients with established AKI.

Recent research has begun to disentangle kidney-organ cross talk and, in particular, kidney-immune system cross talk. As with any critical illness, a complex maladaptive host immune response occurs wherein neither the pro- nor anti-inflammatory cytokines are doing their job properly. There is often a counter anti-inflammatory

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response syndrome that occurs simultaneously with a systemic inflammatory response syndrome (SIRS). The cytokine response in AKI has been found to more closely resemble derangements that occur in critically ill patients without AKI than those with CKD [2]. In fact, ex vivo monocyte cytokine production capacity as measured by IL-1 β , TNF- α , and IL-6 was significantly reduced in AKI patients which was similar to that in critically ill patients without AKI and unlike the response that occurred in CKD and ESRD [2]. This state of “immunoparalysis,” an acquired immunodeficiency syndrome that occurs in many critically ill patients, is known to increase both morbidity (sepsis) and mortality if persistent and prolonged [3]. Thus, based on these early data [2] and the fact that sepsis is the leading cause of death in patients with AKI [4], it is possible that the SIRS and counter anti-inflammatory response syndrome responses in AKI result in a state of persistent or prolonged immunoparalysis that increases the risk for subsequent sepsis. Thus, identifying mechanistic derangements in the host immune response in patients with established AKI has the potential to reduce AKI-associated morbidity and mortality.

This association of AKI with subsequent infections and/or sepsis has been demonstrated in 2 studies of patients with and without AKI after cardiac surgery [5, 6]. The first study investigated the association between AKI and infection in children younger than 30 days who underwent the Norwood operation – a complex palliative procedure for univentricular heart disease [6]. AKI occurred in 40% of patients. Infection occurred a median of 6 (IQR: 3–13) days after AKI diagnosis. After adjusting for confounders, there was 3.63 greater odds of developing infection in those with AKI (95% CI: 1.36–9.75). The second study was a propensity-matched analysis among adults with Kidney Disease Improving Global Outcomes (KDIGO) defined stage 1 AKI. While time to infection was not reported, stage 1 AKI conferred 2.24 greater odds of infectious complications in those with AKI.

While some would argue that the cardiac surgery-AKI-infection is a “chicken versus egg” phenomenon, other studies have found similar associations of AKI and subsequent infections complications or sepsis that were independent of the degree of critical illness. A secondary analysis of the Program to Improve Care in Acute Renal Disease (PICARD) database stratified patients by sepsis status and timing of incident sepsis relative to AKI diagnosis [7]. In this study of 618 adults, 40% developed sepsis a median of 5 (IQR: 3–9) days after AKI diagnosis. Specific risk factors for development of infection post-

AKI included at least 3 days of oliguria, higher percent of daily fluid overload, invasive procedures post-AKI, higher severity of illness score, and dialysis requirement.

Although most studies have only assessed the short-term risk of infection/sepsis following AKI in hospitalized patients, there appears to be a long-lasting effect of the AKI-induced effect on the immune response that has now been shown to increase risk for infectious complications well beyond the first 2 weeks following AKI diagnosis. Indeed, a propensity-matched analysis of a large managed care database demonstrated an association of infection in patients with complete recovery of AKI that persisted up to a year following AKI diagnosis [8]. Although CKD is associated with immune dysfunction, the data in this study demonstrate that the increased risk of subsequent infection at 1 year was independent of CKD since recovery of kidney function was a requirement for inclusion in the cohort studied.

Although dialysis is the mainstay of treatment for severe AKI, demonstrating that dialysis reduces mortality in AKI has been a long-standing challenge [9]. Even as far back as the 1950s, it was observed that despite control of uremic symptoms and normalization of electrolyte disturbances, patients still died of other illnesses that specifically included wound infections and sepsis [9, 10]. In fact, dialysis does not appear to have any effect on mitigating the development of subsequent sepsis [11]. Blood stream infections in AKI patients supported with renal replacement therapy (RRT) were greater than reported rates in the general ICU population and in non-AKI patients during the study period of 1995–2000 [12]. A large population-based cohort study using the Taiwan National Health Insurance database found the incidence of severe sepsis was 6.84 per 100 person years among those with dialysis-requiring AKI versus 2.32 per 100 person years among those without AKI during the index hospitalization. In a subgroup analysis, even patients with recovery of dialysis-requiring AKI were at high risk of developing severe sepsis beyond 3 months of discharge [11]. A small single-center pediatric study evaluated infectious complications among children who received continuous RRT (CRRT). In this study, infection occurred a median of 11 days from CRRT initiation (IQR [4–21 days]) [13]. It is possible that removal of important cellular components, cytokines, nutrients, and other factors in patients treated with CRRT may further impair the host immune response. It is important to acknowledge that current evidence does not allow for causal associations to be determined. A refined and detailed molecular approach is necessary to identify the “key stake-

Fig. 1. Pathway of the proposed process of AKI-associated infectious/septic complications. AKI is independently associated with increased morbidity and mortality. AKI may impair cytokine homeostasis and immune cell dysfunction, leading to a state of immunoparalysis. Infectious/septic risks exist up to a year after the AKI episode. AKI, acute kidney injury.

holders" leading to infectious complications after AKI diagnosis. Specifically, molecules and their involvement in mechanistic pathways need to be identified for future novel therapeutic targets to mitigate the risk for infection after AKI.

A systems biology approach was recently used to examine the impact of renal disease and hemodialysis on patient response during critical illness [14]. "Omics" analyses were examined to identify factors associated with early community-acquired sepsis and noninfectious SIRS. Stratification for AKI diagnosis resulted in 58% of the metabolites being different of which the majority of differences were accounted for by AKI diagnosis. Accumulation of toxic substances has been considered to be the driving factor for AKI-associated outcomes, but the study by Tsalik et al. [14] challenges that paradigm in which 7 primary amino acids were reduced in AKI. These specific amino acids have been implicated in both endothelial and immune dysfunctions. Researchers have also identified an interaction between the kidneys and intestinal microbiome [15]. The intestinal microbiota are directly involved in immune homeostasis through regulation and induction of the adaptive and innate immune responses. Interaction between the kidneys and the intes-

tine occurs through direct contact between the host and the microbiota as well as through microbiota-derived metabolites [15]. Further study of the kidney-intestinal microbiome may offer novel therapeutic targets that essentially treat or reduce dysbiosis during AKI and increase removal of harmful metabolites that could contribute to infectious complications [15].

Implementation of care bundles for AKI prevention are now widespread across adult and pediatric hospitals and, in general, have resulted in providers paying better attention to their patients. This has encompassed avoidance of nephrotoxins and fluid overload. Unfortunately, patients still succumb to AKI, whether acquired in the community or in the hospital. Until we have specific treatments for AKI that ultimately reduce the systemic complications such as immune dysfunction, we are left with good doctoring and infection surveillance.

In summary, AKI is independently associated with subsequent infectious complications/sepsis in both adults and children across diverse cohorts of patients (Fig. 1). Improved understanding of the mechanisms that result in AKI-associated infection and the maladaptive immune response is necessary for goal-directed therapy and reducing AKI-associated morbidity and mortality.

Disclosure Statement

Katja M. Gist and Sarah Faubel have no conflicts of interest to declare.

Author Contributions

Katja M. Gist drafted the manuscript and figure. Sarah Faubel reviewed, revised, and edited the manuscript and figure.

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