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How can antibiotics worsen AKI but improve survival in experimental sepsis?

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Sepsis and septic shock are the most common causes of morbidity and mortality among critically ill patients, and remains the leading cause of acute kidney injury (AKI) among this population.^{1,2,3} Sepsis-induced AKI is independently associated with increased mortality and longer hospital stay.^{2, 4} AKI severity, as defined by RIFLE and AKIN criteria, parallels with increased hospital mortality in the general intensive care unit population.⁵ Despite much recent attention toward the interaction between sepsis and AKI, their relationship is still murky. Do patients die with AKI or of AKI? A seemingly straightforward study reported in this issue of *Critical Care Medicine* by Peng and colleagues now challenges the way we view sepsis-induced AKI in the ICUs, by showing that a commonly used antibiotic regimen temporarily worsens AKI severity while improving survival in experimental sepsis.⁶ This demonstrates a clear dissociation between AKI status and survival, which requires validation and re-examination in other settings in larger groups. The questions raised in this study could have substantial implications in the way that we view AKI endpoints, and follow-up studies are needed to examine the unintended effects of antibiotics and underlying mechanisms.

Despite important new insights into the pathophysiology of sepsis, one of the cornerstones of sepsis treatment—the use of antibiotics together with volume resuscitation (and source control, if possible)—has not changed over the past four decades.⁷ Effective antibiotic administration within the first hour of documented hypotension is associated with increased survival to hospital discharge in adult patients with septic shock,⁸ and delays to appropriate antimicrobial therapy contribute to significant increases in the incidence of septic AKI.⁹ In a more contemporary cohort of patients with septic shock, AKI development was independently associated with delay to initiation of adequate antibiotics.¹⁰

The use of animal models to study sepsis requires balancing clinical relevance versus simplicity (easier to interpret) and practicality (easier to do). While use of antibiotics and fluid resuscitation are now standard practice in animal models, there is substantial variance between laboratories, probably due to differing adaptations of clinically relevant regimens.

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Editorial to Bactericidal antibiotics temporarily increase inflammation and worsen acute kidney injury in experimental sepsis

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Peng et al. administered antibiotics 18 hours after cecal ligation and puncture (CLP) in rats, which is substantially later than the 6 hour time point that we and others have initiated antibiotics. As expected, Peng and colleagues found that antibiotics improved survival, but paradoxically increased AKI at non-nephrotoxic doses.

How could this happen? One avenue explored by Peng et al. is that within the context of sepsis, antibiotics increase AKI and inflammation along a liver damage and IL-6 axis. Do antibiotics improve survival because of AKI (and/or inflammation) or in spite of it? This dichotomy may depend on the dose, timing, and/or type of antibiotic administered. The authors raise the possibility that bactericidal antibiotics may release endotoxin (LPS) from bacteria, thus inducing inflammation.¹¹ LPS and other bacterial constituents could activate Toll-like receptors (TLRs) and subsequent MyD88-dependent activation of the transcription factor NF- κ B and production of cytokines. If inflammation is beneficial, then a proinflammatory cytokine such as TNF α ¹² could enhance the survival benefit from antibiotics. Conversely, an IL-6 based adjunctive anti-inflammatory therapy¹³ could improve survival if antibiotic-induced inflammation was an unavoidable side-effect of the bactericidal antibiotics. Of note, neither of these studies^{12,13} used antibiotics, and therefore the effects of these treatments could be different within the context of antibiotic treatment.

Peng and colleagues point out an intriguing possibility from their data that antibiotic-treated CLP sepsis survivors recover from AKI and inflammation faster. Does the inflammation accelerate resolution of the infection? It probably depends on the context. Therefore, the clinical relevance of these findings will depend on the universality of the observations by Peng and colleagues. Do antibiotics increase AKI and inflammation while improving survival in other sepsis models such as pneumonia? Similarly, if these phenomena are observed in older animals with sepsis, or those with pre-existing co-morbidities such as chronic kidney disease¹⁴ these observations should have more direct translation to the aging patient population with sepsis.

What if resolution of AKI¹⁵ is indeed more tightly associated with survival--than onset or peak of AKI is associated with mortality? The authors astutely point out that AKI biomarkers may not be adequate intermediate endpoints to develop therapeutic strategies for sepsis-AKI patients. In other words, AKI may not always be on the causal pathway to sepsis-induced mortality; therefore, we need biomarkers that distinguish lethal from 'non-lethal/beneficial' AKI.

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