Published in final edited form as:

Crit Care Med. 2016 March ; 44(3): 634–635. doi:10.1097/CCM.0000000000001508.

Towards a Nuanced Understanding of the Role of Infection in Readmissions after Sepsis

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Keywords

hospitalization; Critical illness; patient readmission; microbiota

As acute mortality declines, hundreds of thousands of Americans survive sepsis each year¹. Studies consistently show high rates of hospital readmission following sepsis, which are disproportionately due to infection^{2,3}. However, while existing studies have clarified the epidemiology, they have—until now—done little to disentangle the relationship between the initial and recurrent hospitalization.

In this issue of *Critical Care Medicine*, Sun *et al.* report on 444 adult survivors of sepsis hospitalization at the University of Pennsylvania Health System, examining the link between sepsis and subsequent readmissions⁴. The authors performed careful chart abstraction to confirm clinical details of the initial hospitalization, and if present, an unplanned hospital readmission within 30 days. Two authors abstracted each chart, achieving good inter-rater reliability for both the cause of readmission and the relationship between initial and subsequent infections—a clear strength of the study too rarely present in other work.

Consistent with prior reports, nearly one in four sepsis survivors experienced an unplanned readmission within 30 days^{3,5,6}. Over two thirds of the readmissions were for infection, with an even split between new infections (49%) and recurrent/relapsed infections (51%). Of the readmissions deemed infection-related by the authors, only 40% had a principal ICD-9-CM diagnosis of infection. In the other 60%, the infectious etiology was hidden under principal diagnoses reflecting signs or symptoms of infection, such as fever, altered mental status, neutropenia, or hematuria. Together, these findings suggest that claims-based studies—as are often used for public health and benchmarking—may substantially under-estimate the burden of infection-related readmissions.

The high proportion of infection-related readmissions in this study is noteworthy, and suggests that future interventions to reduce re-hospitalizations after sepsis must focus on infection prevention and surveillance. But the finding that only a minority (albeit a large minority) of patients return for recurrence of the *same* infection challenges us to rethink labeling infectious readmission as simply “treatment failures”. Instead, something more complex must be going on.

Sepsis survivors are at increased risk of infection for at least two reasons. First, the pro-inflammatory milieu of sepsis is offset by a concurrent and persistent anti-inflammatory response that impairs patients' ability to fight off subsequent infections⁷. Secondly, critically ill patients experience profound perturbations of their microbiomes, such that their gut microbiota—normally containing hundreds of species—are reduced to as few as two pathogenic species⁸. Perturbation of the microbiome is, in turn, associated with heightened risk of subsequent infection^{9,10}.

Beyond standard infection-prevention measures recommended in adults (e.g. vaccines, hand-washing, avoidance of sick contacts), we do not yet know the ideal approaches to prevent infection in survivors of sepsis. As dozens of immune-modulating therapies have been trialed unsuccessfully in the treatment of acute sepsis, it seems unlikely that immune-boosting medications will prove beneficial during post-sepsis recovery. However, the microbiome is a promising therapeutic target.

Preserving the microbiome with shorter, narrower courses of antibiotics is an appealing option given increasing data on the efficacy of shorter antibiotic courses¹¹. However, this alone is unlikely to solve the problem, particularly given the high proportion of relapsed/recurrent infections seen in this study.

Ideally, antibiotic treatment for sepsis should be long enough to kill the offending organism, but not long enough to destroy a patient's microbiome. In practice, however, this may be difficult—if not impossible—to achieve. Patients almost certainly require variable durations of antibiotic therapy to kill their culprit organism, and there may not be *any* duration that achieves this without substantially disrupting a patient's microbiome.

And so, in addition to limiting broad-spectrum antibiotic exposure when possible, we should consider alternative treatments to preserve and restore patients' microbiomes in order to reduce their risk of subsequent infection. For lower risk patients, this may be as simple as a diet that promotes a healthy microbiome¹². For moderate and higher risk patients, this may mean probiotic supplements¹³, or even fecal microbiota transplantation for those with the utmost disruption¹⁴. While these measures are certainly not standard care currently, the microbiome perturbation seen in critical illness survivors is effectively an organ failure, and one for which we ought to do more.

This study also provides intriguing information to help us develop individualized risk scores in order to tailor such readmission prevention strategies during their development and (hopefully) implementation. Blood product transfusion, total parenteral nutrition, and longer duration of antibiotics were each associated with increased risk of unplanned 30-day readmission. However, as the study is observational, we cannot say how much of this

association is due to “confounding by indication” versus true causation¹⁵. Thus this study does not support changing any of those behaviors in order to prevent readmission. Nonetheless, this study does show that these factors are certainly markers of sepsis survivors at higher risk for readmission who may merit additional services at discharge, such as enrollment in a formal care coordination program or a microbiome-rebalancing trial.

As the population of sepsis survivors continues to grow, we are increasingly challenged to improve the survivor experience. Hospital readmission is a frequent, disruptive event in this population, for which we have few proven prevention strategies. This study, with careful determination of readmission diagnosis, argues that effective infection prevention and surveillance strategies could substantially improve long-term outcomes in sepsis survivors.

Acknowledgments

Copyright form disclosures: Dr. Prescott received support for article research from the National Institutes of Health (NIH) and disclosed off-label product use (The editorial discusses the use of probiotic supplements and fecal microbiota transplantation, which are not FDA approved for microbiome-restoration post sepsis). Her institution received funding from the NIH.

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