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EDITORIAL

Describing Sepsis as a Risk Factor for Cardiovascular Disease

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Sepsis is a dysregulated host response to infection that is estimated to be responsible for 1 in 5 deaths worldwide.[1] Recent data have demonstrated that patients with sepsis are at higher risk for postdischarge complications than common conditions, such as heart failure, pneumonia, and chronic obstructive pulmonary disease.[2] Although there are many reasons for this finding, ranging from persistent immunomodulation to insufficient postdischarge care, there are clear biologic data that some patients with sepsis remain in a state of persistent immune dysfunction and systemic inflammation.[3] This concept may explain why some patients with sepsis are at elevated risk of adverse cardiovascular events. With >50 million cases of sepsis a year worldwide, it is imperative to identify strategies to ameliorate postdischarge morbidity and mortality.[1] A bidirectional relationship has been postulated in which sepsis can impair cardiovascular function but in turn cardiovascular disease may predispose to sepsis. One of the inherent challenges with sepsis is that it is a heterogenous and nebulous syndrome and often challenging to diagnose compared with clearly defined disease processes, such as myocardial infarction. Although there have been some investigations into postdischarge cardiovascular complications in patients with sepsis, a recent meta-analysis highlighted that the overall quality of data is low because of the various methodologic limitations of previously available studies.[4]

See Article by Jentzer et al.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Jentzer et al provide the largest study to date evaluating the association between sepsis and postdischarge adverse events, specifically highlighting cardiovascular complications with more than a decade of nationwide follow-up data.[5] Using an impressive cohort composed of ≈2.3 million hospitalized individuals, the researchers found that patients with sepsis had an elevated risk of all-cause mortality, all-cause rehospitalization, and cardiovascular rehospitalization in the early and late discharge periods. Patients with sepsis were at higher risk for atherosclerotic and nonatherosclerotic cardiovascular events postdischarge compared with patients without sepsis. Of note, they report that the incidence of postdischarge cardiovascular events was increased in both patients with and without existing cardiovascular disease. Rehospitalization for heart failure following an admission for sepsis was the most common cardiovascular event identified. Interestingly, the authors found that younger patients without comorbidities had a higher relative rate of postdischarge cardiovascular complications than older patients with comorbid conditions. The authors used multiple definitions of sepsis,

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and the results were robust across these categories, suggesting generalizability of the findings.

As is true of most studies, important limitations exist to the current report. The study was retrospective and observational and used an administrative database, the accuracy of which could not be precisely verified. Causal inferences and biologic mechanisms were outside of the scope of this investigation. It is unfortunate that the authors were unable to stratify patients according to the standard atherosclerotic cardiovascular disease risk algorithm derived from pooled studies. It is possible that sepsis would not add significantly to the risk of cardiovascular disease over and above the factors in that algorithm. However, the conclusions provided, although correlative, provide evidence that sepsis may be an important risk factor for cardiovascular complications across a broad group of patients.

Many critical questions remain for postsepsis care that require further research to answer and ultimately improve patient-centered outcomes. This is increasingly important as the number of survivors of sepsis has increased in the past decade.[6] First, the underlying biological mechanism of why some patients with sepsis experience an adverse cardiovascular event after discharge and others do not remains unanswered. It is well accepted that inflammation, endothelial dysfunction, and neurohormonal activation are present in certain patients with sepsis, and these factors are likely responsible for accelerated thrombotic conditions.[7,8] Identifying those patients at high risk of endothelial dysfunction and persistent inflammation while in the hospital or shortly after could allow for more personalized care and improved risk stratification. Second, characterizing patients with genetic predispositions for adverse cardiovascular events after sepsis could allow for interventions in patients at high risk for postdischarge complications. Recent data have described novel sepsis phenotypes that are associated with treatment response and outcomes.[9] We believe that the development of clinical and biological phenotypes represents an attractive approach and a future avenue for research to help answer these questions, which is increasingly possible with advanced analytic approaches.[10] Third, clinical researchers should use these data to explore interventions to decrease long-term postdischarge cardiovascular complications. Prior data have demonstrated no short-term benefit to statin use in the setting of sepsis; however, there are no data to guide long-term preventive therapies in this patient population to our knowledge.[11] Antiplatelet and anti-inflammatory agents are additional possibilities. Development of postdischarge programs such as those described by Taylor et al represent attractive options to prevent postdischarge sepsis complications, although they have not been specifically studied in patients with cardiovascular disease.[12] The additive value of including the social determinants of health may also help identify patients at high risk for postdischarge cardiovascular complications.[13] Given the huge economic burden of postdischarge sepsis complications, trials focusing on low-cost interventions and strategies to address the persistent inflammation, prothrombotic milieu, and endothelial dysfunction in this population are indicated to improve postdischarge care.[14]

How should clinicians use these new findings to improve patient care? To begin, as Jentzer et al suggest, sepsis may be a nontraditional risk factor for cardiovascular disease. Next, the association between sepsis and cardiovascular complications in this study was present both in early (within 6–12 months of admission) and long-term time periods (years after discharge), each of which may serve as targets for intervention. In the immediate postdischarge phase, prompt follow-up for patients with preexisting cardiovascular disease after a sepsis hospitalization is imperative. This approach may allow providers to ensure potentially avoidable reasons for readmission, such as incomplete or inadequate cardiovascular medication reconciliation. This problem is particularly important for patients with preexisting heart failure as medication deprescription in the hospital is easily remedied. Recent data have shown that intense early follow-up of patients with sepsis, including proper medication reconciliation, can reduce postdischarge complications.[8] In addition, clinicians should consider that survivors of sepsis may benefit from cardiovascular risk factor stratification early in the postdischarge period. This time frame may be an ideal time to reevaluate preventive measures in patients with risk factors for cardiovascular disease—or screen otherwise healthy younger patients for cardiovascular disease. Finally, long-term risk stratification and modification after a sepsis hospitalization may prevent the development—or mitigate the progression—of cardiovascular disease.

Moving forward, as Jentzer et al suggest, clinicians might consider that sepsis is a nontraditional risk factor for short- and long-term cardiovascular disease. Although many questions remain, the findings of this article should alert providers to the importance of an episode of sepsis as a major event in their patient's medical history. Prompt attention and recognition of the postdischarge burden of sepsis coupled with meticulous postdischarge care and cardiovascular risk stratification may potentially improve patient-centered outcomes. Future clinical investigations should include diverse groups of individuals and assess whether sepsis is truly an independent cardiovascular risk factor and how interventions impact these outcomes.

ARTICLE INFORMATION

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