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Is Severe Sepsis Associated With New-Onset Atrial Fibrillation and Stroke?

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Severe sepsis is a major health problem in the United States and around the world, with hospital mortality rates ranging from 18% to 50%.^{1,2} Patients with severe sepsis are defined as a subset of patients with sepsis who have acute organ dysfunction in the setting of a systemic inflammatory response due to an infection.³ Severe sepsis has an estimated incidence between 50 and 300 cases per 100 000 individuals annually, depending on the study.^{4–7} The prevalence of severe sepsis increases with age and with the number of comorbidities (eg, liver disease and diabetes).^{8,9} Arrhythmias are common in the intensive care unit, occurring in 12% of all patients (with supraventricular arrhythmias occurring in 8% of all patients).¹⁰ Arrhythmias are more likely to occur in older patients and those with severe sepsis or septic shock.

Despite the prevalence of arrhythmia, controversy persists regarding the effect of atrial fibrillation on clinical outcome, with studies showing both increased mortality associated with atrial fibrillation^{11,12} and no association with mortality.^{10,13,14} When treating a patient with severe sepsis and new-onset atrial fibrillation, the goals of the intensive care unit clinician are likely short-term—controlling heart rate or performing cardioversion if the patient is hemodynamically unstable. Initiating anticoagulation to prevent long-term sequelae in a patient who may already be coagulopathic poses a challenging risk-benefit assessment. Better data are needed to refine the understanding of the implication of this common complication in the setting of sepsis.

In this issue of *JAMA*, Walkey and colleagues¹⁵ address this important question. The authors used administrative claims data from California in 2007 to address the clinical significance of new-onset atrial fibrillation in the setting of severe sepsis. The authors report that patients with severe sepsis and new-onset atrial fibrillation had an increased odds of in-hospital stroke (adjusted odds ratio, 2.70; 95% CI, 2.05–3.57) and increased hospital mortality (adjusted relative risk, 1.07; 95% CI, 1.04–1.11). The authors performed a number of key sensitivity analyses to demonstrate the robustness of their findings. One of the key sensitivity analyses tried to unravel the temporal relationship between the occurrence of stroke and the onset of severe sepsis. By restricting the analysis to patients who had severe

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sepsis on admission and for whom atrial fibrillation was not present on admission, the associated risk of stroke was reduced but remained significant. The authors also evaluated the risk of rehospitalization for new-onset stroke following hospitalization with severe sepsis; patients with new-onset atrial fibrillation in the setting of severe sepsis had a nonsignificant increased risk of readmission for acute stroke compared with patients with prior history of atrial fibrillation or no atrial fibrillation.

Additional sensitivity analyses included using increasingly narrow *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes to define the primary outcome of interest, embolic stroke, showing that the risk of stroke increased as the code was refined. The results were robust to the use of alternative *ICD-9-CM* codes to define the patient cohort, those with severe sepsis. Overall, these analyses support the authors' primary findings: atrial fibrillation in the setting of severe sepsis is associated with an increased risk of stroke and increased hospital mortality.

Administrative databases like the one used by Walkey et al will be key to advancing the evidence base in the management of critically ill patients as well as patients with chronic illnesses. Such databases have been previously used to assess the incidence of sepsis in the United States^{2,7} and have been instrumental in bringing the study of sepsis to the forefront of clinical investigation in the intensive care unit. Martin et al² used validated *ICD-9-CM* codes to show that the incidence of sepsis and the number of sepsis-related deaths were increasing while the overall mortality rate due to sepsis was declining. Additional studies have used similar methods to assess the epidemiology of severe sepsis in children¹⁶ and the role of comorbidities in outcome in severe sepsis.⁸ These large administrative databases have also enabled researchers to estimate the outcome and costs of severe sepsis in the United States (an estimated annual cost of \$16.7 billion in 1995).⁷ These studies have been invaluable in generating novel clinical questions and assessing the disease burden of sepsis on a national scale.

The challenges inherent to any study using administrative data are to understand the weaknesses of the data. Validation and quality of administrative data may depend heavily on the diagnosis of interest: for example, a recent study of administrative data found that misclassification was common for gout.¹⁷ In contrast, a study of severe sepsis demonstrated high agreement between the medical record and the administrative database.⁷ The supporting data for use of administrative data to identify new-onset atrial fibrillation are less clear (*ICD-9-CM* code 427.3x). The authors reported a $\kappa=0.74$ when reviewing their own hospital discharge data. However, with anonymized billing data, the authors were unable to validate a subset of the data used for their analyses, as has been done in other studies of sepsis using administrative data.²

An elemental component of the analysis by Walkey et al was the timing of events during hospitalization. Being able to clearly define the date of onset of a diagnosis can enrich such administrative data analyses. However, the only key covariate available was whether the diagnosis was "present on admission." This can pose some clear challenges to the analysis in defining the period at risk for the event and the temporal sequence of events. For example, a patient in the intensive care unit who is admitted for a surgical intervention might have a later complication of postoperative atrial fibrillation and then a stroke. These events could subsequently lead to aspiration pneumonia and severe sepsis. Without being able to precisely determine the temporal relationship among sepsis, atrial fibrillation, and stroke, it is possible that the study by Walkey et al merely showed that atrial fibrillation occurring during a hospitalization that also involved an episode of sepsis was associated with stroke and increased mortality. Moreover, the authors may not have been able to control for all potential confounders. For example, the dose and type of vasopressors used to treat septic

shock could predispose to atrial fibrillation and may be an indicator of more severe shock, cerebral underperfusion, and higher risk of death.

Does this mean that the findings from such analyses should be disregarded? The answer is that it depends. Several factors can help determine whether causal inferences can be drawn from observational data, including assessment of biological plausibility, evidence that supports that the predictor (in this case, new-onset atrial fibrillation) precedes the outcome (in hospital stroke), magnitude of the effect, direction of potential biases, and robustness of the association to sensitivity analyses. Given the limitations of the data analyzed, Walkey et al have shown that the association of new-onset atrial fibrillation with both in-hospital stroke and death persisted through a number of key sensitivity analyses. This association is plausible and represents an important finding (particularly in relation to the association with stroke) that is potentially relevant to intensivists.

An important question is whether this association of new-onset atrial fibrillation with acute stroke should lead clinicians to intervene with the hope of preventing this complication, such as with acute cardioversion, anticoagulation, or both. It is difficult to maintain successful cardioversion as long as severe sepsis persists, perhaps because acute risk factors such as high catecholamine states have not yet resolved. Anticoagulation presents additional risks for patients with severe sepsis due to coagulation abnormalities and frequent invasive procedures. Given the limitations of these observational data, current practice should not change in favor of interventions that could involve additional risk. Given the small event rate, a randomized trial of anticoagulation for new-onset atrial fibrillation in severe sepsis would be logically difficult. However, further observational studies with large databases assessing how interventions might modify the risk of stroke could provide more useful information.

In summary, Walkey et al have presented observational data from a large administrative database demonstrating that new-onset atrial fibrillation in the setting of severe sepsis appears associated with an increased risk of stroke and hospital mortality. The authors are appropriately cautious about their interpretation and implications of their data. If these findings are replicated in another large cohort study of patients with severe sepsis that could also assess potential interventions, the next step would be to conduct a clinical trial to evaluate different approaches to management. As survival in sepsis continues to improve, clinical investigators must look for potentially modifiable factors that influence long-term patient-centered outcomes. New-onset atrial fibrillation may represent one of those factors.

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