VIEWPOINT

Antibiotics for Sepsis—Finding the Equilibrium

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Sepsis is medicine's last remaining preserve for unrestrained antibiotic prescribing. The Surviving Sepsis Campaign guidelines recommend empirical broad-spectrum therapy within one hour of triage for both sepsis and septic shock.[1] This recommendation, and mandates that compel it, encourage clinicians to adopt an approach of "treat first, ask questions later" for patients with any possibility of serious infection. This approach fails to account for the difficulties clinicians face with diagnosing infection, especially when patients initially present to care, and the high rate of overdiagnosis of sepsis, and thus risks promoting excess antibiotic use and causing unintended harm.

The recommendation to treat quickly and aggressively may seem sensible because sepsis and septic shock are potentially deadly conditions. Delays in appropriate antimicrobial therapy have been associated with higher mortality rates, and quality improvement initiatives that encouraged earlier prescribing have reported substantial decreases in mortality. Many of the studies supporting these assertions, however, may be biased. Most of these investigations failed to account for confounding by indication. Delays in appropriate therapy are more likely to occur in complex patients who are more likely to harbor resistant organisms and present in atypical ways whether they are infected or not. Other studies may have failed to adjust adequately for changes in patients' characteristics over time; most sepsis quality improvement initiatives try to improve sepsis detection as well as time to treatment and thus tend to include patients with less severe illness over time. The inclusion of less severely ill patients lowers overall mortality rates and makes it difficult to know whether better outcomes over time were due to improvements in care, changes in patient mix, or a combination of both. In addition, many studies that examined sepsis quality improvement initiatives only reported outcomes for patients with a final diagnosis of sepsis and thus failed to account for misdiagnoses of sepsis at presentation and any potential harm that antibiotics might have caused in patients who were initially diagnosed with sepsis but subsequently diagnosed with other conditions.

> The time has come to balance the recommendation for early and aggressive antibiotics for all patients with possible sepsis with the diagnostic uncertainty regarding sepsis and the possible harm associated with unnecessary antibiotics.

Three key issues require consideration. First, diagnosing sepsis and septic shock can be challenging. Sepsis is defined as infection leading to organ dysfunction, but both diagnosing infection and attributing organ dysfunction to infection are often subjective. Fever and leukocytosis are neither sensitive nor specific signs for infection. Deciding whether organ dysfunction is due to infection or some other factor (eg, volume depletion, cardiomyopathy, inflammatory or autoimmune diseases, toxic ingestions, medication adverse effects, drug withdrawal) is often arbitrary. Experienced clinicians frequently disagree on whether sepsis is present. Occasional missed diagnoses of sepsis culminating in tragic outcomes have been highly publicized, but overdiagnosis is far more common. Less than 60% of patients admitted to intensive care units with a diagnosis of sepsis are confirmed to have definite or probable infection,[2] and of these patients, only a subset have infections caused by bacteria. Pneumonia is the most common source of sepsis, but one-third of pneumonia cases that require hospitalization are caused by viruses. Uninfected patients and patients with viral infections alone are subjected to antibiotic-related risks without any of the benefits.

Second, antibiotic use in critically ill patients can have adverse consequences. Withholding antibiotics from patients with serious bacterial infections can increase mortality risk, but unnecessary exposure to antibiotics, either because a patient does not have a bacterial infection or because antibiotics are continued beyond the minimum duration necessary, is also potentially harmful. Multiple studies have associated more aggressive antibiotic regimens and longer treatment courses with higher mortality rates.[3-5] Antibiotic-related risks, such as *Clostridium difficile* infection, acute kidney injury, hepatitis, cytopenias, severe rash, and selection for drug-resistant pathogens, have been well described, but more insidious effects, including mitochondrial toxicity and altering the microbiome, are less well appreciated. A recent study that demonstrated diminished effectiveness of checkpoint inhibitors in treating different cancers during concurrent antibiotic use highlights a potential off-target antibiotic-related adverse effect.[6]

Third, conflating sepsis and septic shock is a mistake. Time to instituting effective treatment is important for patients with septic shock, but the data are less clear for patients with possible sepsis alone who are not in shock. For example, 2 recent retrospective analyses that examined time to treatment and mortality risk in almost 50 000 patients in New York State hospitals and 35 000 patients admitted to Kaiser Permanente hospitals in California reported significant associations between delays in antibiotic administration and higher mortality rates in patients with septic shock, but little or no association in patients

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without shock.[7,8] Similarly, in a randomized trial that examined the effect of antibiotics administered in the out-of-hospital setting vs antibiotics administered in the emergency department on 2672 patients with suspected sepsis, mortality rates were the same for both groups even though the emergency department treatment group received antibiotics a median of 96 minutes after the out-of-hospital treatment group.[9] More than 95% of patients in the study had infection alone or sepsis without septic shock, suggesting that it may be safe to take some time to gather data in cases of patients without septic shock to inform whether antibiotics are necessary. Further trials are needed that randomize patients without shock to either receive immediate antibiotics or to undergo immediate diagnostics and close observation followed by antibiotics only if warranted.

Clinicians should take a nuanced approach to treating patients with possible sepsis or septic shock. The need to treat patients rapidly and aggressively ought to reflect on the severity of illness and certainty of diagnosis rather than applied uniformly to all patients. If a patient clearly has a bacterial infection, prompt treatment is indicated. If there is diagnostic uncertainty, however, clinicians should calibrate their response to severity of illness and probability of infection. Immediate antibiotics are warranted if the patient has shock or rapid deterioration and if there is even a small possibility that their condition is due to infection. In many instances of patients with shock or rapid deterioration, bacterial infection will not be borne out (at which point antibiotics can be discontinued promptly), but preemptive treatment is nonetheless worthwhile to ensure coverage for the subset of patients who do have infections.

Conversely, if a patient does not have shock and has a lower probability of infection, then a reasonable approach may be to gather more data from biochemical tests, imaging, microbiologic and molecular assays, clinical observation, and/or specialty consultation before prescribing antimicrobials. Assays to differentiate infectious from noninfectious etiologies, and bacterial from nonbacterial pathogens, may be particularly helpful. There is also much to be learned from observing the patient's clinical trajectory and response to initial therapies, such as fluids, diuretics, vasodilators, or bronchodilators. Some patients improve substantially with these treatments alone and do not require antibiotics.

The time has come to balance the recommendation for early and aggressive antibiotics for all patients with possible sepsis with the diagnostic uncertainty regarding sepsis and the possible harm associated with unnecessary antibiotics. The Surviving Sepsis Campaign and similar quality improvement initiatives have helped improve quality of care by focusing much-needed attention on sepsis and emphasizing the importance of early diagnosis and optimal management. The good that these initiatives have done could be further enhanced by encouraging and permitting clinicians to gather more data to confirm infection in patients without shock before prescribing antibiotics when the evidence for infection is equivocal.

In coming years, innovative technologies may help accelerate time to diagnosis and optimal treatment selection for patients with possible sepsis. Until then, studies that have documented high rates of sepsis overdiagnosis and the possibility that overtreatment may increase mortality rates compel caution.[2-5] Titrating the timing and breadth of treatment to each patient's likelihood of infection and severity of illness should be considered rather than treating all patients with sepsis and septic shock homogeneously.

ARTICLE INFORMATION

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