Antimicrobial Therapy for Sepsis: How Does It Affect Survival?

Harbarth S, Garbino J, Pugin J, et al. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med 2003;115:529–35.

Study Overview

Objective. To assess the impact of antibiotic choice on subsequent survival in patients with sepsis syndrome.

Design. Retrospective cohort study (nested in a placebo-controlled clinical trial).

Settings and participants. Adults with severe sepsis or early septic shock who were enrolled in a clinical trial of an immunomodulating agent. The patients were recruited from 108 hospitals in the United States, Canada, and Europe.

Main outcome measures. Main outcome was survival at 28 days after study enrollment. Inappropriate therapy was defined as the receipt of at least 1 antimicrobial agent within 24 hours of diagnosis of sepsis.

Main results. Of the 1342 patients enrolled in the initial trial, 904 had microbiologically documented sepsis and were used in the analysis. Of these 904 patients, 211 (23%) received inappropriate therapy either because the agent used was not effective against all causative microorganisms or the agent was not administered in a timely manner. Patients who did not receive appropriate initial antimicrobial treatment had higher mortality than those who received appropriate treatment (39% versus 24%; $P < 0.001$). When adjusting for the numerous baseline differences between the 2 groups, higher mortality persisted for patients who initially received inappropriate antibiotics (odds ratio, 1.8 [95% confidence interval, 1.2–2.6]; $P < 0.05$).

Conclusion. Among patients with sepsis syndrome, those who receive appropriate antimicrobial therapy have approximately 80% lower odds of dying compared with those patients who receive inappropriate antimicrobial treatment.

Commentary

Sepsis syndrome is a major cause of morbidity and mortality in the United States and is the common end pathway by which many patients die of infections [1].

Given the high rates of mortality associated with sepsis, finding both novel agents to treat sepsis and appropriate treatments to avoid sepsis are critical. Using data from a clinical trial to evaluate a novel agent for sepsis, Harbarth and colleagues tried to ascertain if choosing the correct antibiotic early improves outcomes in patients with sepsis. Several issues surrounding both the methodology and the clinical relevance should be considered when trying to understand this study.

First, all patients in this study had severe sepsis or septic shock. Therefore, to some extent, they all represented either late presentation with an infection or inadequate early treatment of their infection. It is difficult to know how this study might generalize to other hospitalized patients with infections. Second, patients who were treated adequately may have been different from patients who were treated inappropriately—in ways that could potentially account for the results. The authors do try to account for this by carefully measuring and adjusting for severity of illness at the time of enrollment.

Finally, there is a clinical issue that needs to be better understood. When treating patients with sepsis, it is difficult to know which antibiotic is appropriate since the causative agent usually is unknown. Given that the authors studied appropriateness retrospectively, they had the benefit of hindsight that clinicians do not have. Further, there is a potentially important downside to these findings. If clinicians try to prescribe more appropriate antibiotics by using more broad-spectrum agents, this practice is likely to lead to more antimicrobial resistance against antibiotics [2]. Therefore, any attempt to improve appropriateness must be weighed against the potential harm of increasing resistance.

Applications for Clinical Practice

It seems likely that Harbarth and colleagues' findings are accurate; however, it is unclear how to apply these findings. If attempts to improve the treatment of patients with severe sepsis lead to greater use of broad-spectrum antibiotics, as it

is likely to do, this may increase antimicrobial resistance. The risks and benefits of such efforts must be weighed before any changes in clinical practice are implemented.

–Review by Ashish K. Jha, MD

References

1. Minino AM, Arias E, Kochanek KD, et al. Deaths: final data for 2000. Natl Vital Stat Rep 2002;50:1–119.
2. Neuhauser MM, Weinstein RA, Rydman R, et al. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA 2003;289:885–8.