

Surviving Sepsis: Importance of Timely Antibiotic Administration

Twisha S. Patel¹, Keith S. Kaye²

¹Department of Pharmacy Services and Clinical Sciences, Michigan Medicine and the University of Michigan College of Pharmacy, Ann Arbor, Michigan

²Department of Internal Medicine, Division of Infectious Diseases, University of Michigan Medical School, Ann Arbor, MI

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, remains a significant cause of in-hospital mortality in healthcare centers across the world [1-3]. Several public health campaigns endorsed by large national organizations are focused on improving the management of patients with sepsis and septic shock (defined as those with circulatory and cellular and/or metabolic dysfunction) [1]. The Society of Critical Care Medicine and the European Society of Intensive Care Medicine have worked to develop the “Surviving Sepsis Campaign” which aims to reduce sepsis-related mortality by educating healthcare professionals and improving diagnosis and treatment, as outlined in a comprehensive set of guidelines available for clinicians [4]. The Centers for Disease Control and Prevention’s (CDC) “Get Ahead of Sepsis” campaign emphasizes early recognition and timely initiation of treatment for sepsis [5]. Furthermore, the Centers for Medicare and Medicaid Services (CMS) requires hospitals to report compliance with the core sepsis measures – termed “SEP-1” [6]. Although differences exist between societal recommendations and required quality metrics, bundled interventions to improve the care of patients with sepsis are universally recommended, including the timely initiation of antibiotics. Antibiotics are widely recognized as a life-saving intervention in the management of patients with sepsis and septic shock and

appropriate, prompt initiation of effective antibiotics should be prioritized.

Several studies have been conducted to evaluate the impact of early antibiotic administration on outcomes in patients with sepsis and septic shock. Kumar and colleagues demonstrated that, among patients with septic shock, each hour of delayed administration of effective antibiotics over the first 6 hours after the onset of hypotension was associated with a decrease in survival of 7.6%. The significant impact of time to effective antibiotic administration on reducing mortality persisted in an adjusted analysis after controlling for severity of illness [7]. Furthermore, in a larger, multi-center, prospective, observational cohort study of 17,990 patients with severe sepsis and septic shock, adjusted hospital mortality was associated with delays in antibiotic administration. In this study, the odds ratio (OR) for mortality increased in a linear fashion from 1.00 to 1.52 as time to antibiotic administration increased from 0 to >6 hours [8]. Overall in-hospital mortality was high in both studies (58% in the Kumar et al study and 30% in the Ferrer et al study) indicating that both included a severely ill patient population.

The positive impact of early initiation of effective antibiotic therapy has also been demonstrated in other studies of more diverse populations [9, 10]. In a study of 35,000 patients with sepsis, severe sepsis, and septic shock, hospital mortality was lower than the previously

described studies and varied between groups (3.9%, 8.8% and 26%, respectively). In adjusted analysis, hospital mortality increased with each hour of delay in antibiotics after presentation (OR 1.09 [95% confidence interval [CI], 1.00–1.19] for sepsis, OR 1.07 [95% CI, 1.01-1.24] for severe sepsis, and OR 1.14 [95% CI, 1.06-1.23] for septic shock [9]. Lastly, in a recent large retrospective cohort study of 10,811 adult patients presenting to the emergency department with sepsis, 30-day mortality was 8.2%. Using an adjusted analysis, each additional hour from presentation to antibiotic initiation was associated with increased mortality risks: in-hospital mortality risk OR 1.16 (95% CI, 1.07-1.26), 30-day mortality risk OR 1.12 (95% CI, 1.06-1.18), 90-day mortality risk OR 1.09 (95% CI, 1.04-1.15), and 1-year mortality risk OR 1.10 (95% CI, 1.05-1.14) [10]. The results of these studies and others have culminated in the final “Surviving Sepsis Campaign” guideline recommendation of targeting administration of antibiotics as early as possible, ideally within the first hour of diagnosis [4]. The CMS SEP-1 measure calls for antibiotic administration to occur within the first 3 hours of diagnosis [6]. Although the exact time window differs, prompt initiation of effective antibiotics is a key component to promoted bundled interventions.

Studies with conflicting results to those described above exist and the differences in findings may be due to one or more of the following: varying definitions of sepsis, heterogeneous study populations, lack of

adjusted analyses, and a variety of different outcome variables [11]. Thus, although literature with conflicting results exists, timely administration of antibiotics in patients with sepsis and especially those in shock remains a cornerstone of clinical management.

As a part of the CDC’s “Get Ahead of Sepsis” campaign, a number of clinical resources (including toolkits) are available to help institutions in the management of patients with sepsis and septic shock [5]. Institutions have implemented quality improvement programs to recognize signs and symptoms of sepsis earlier with subsequent earlier initiation of effective therapy. Antimicrobial stewardship programs can play an important role in developing effective treatment guidelines and including order sets integrated into the electronic health record. Pharmacy departments can provide quick access to relevant antibiotics in both the emergency department and intensive care unit settings. A multi-disciplinary effort is needed to maximize the efficacy of these types of sepsis initiatives.

In summary, the timely initiation of effective antibiotics is universally recognized as a key intervention in the management of patients with sepsis and septic shock. Institutions should work with key stakeholders, including intensivists, the antimicrobial stewardship team, pharmacy, infectious diseases, nursing, the quality department, and health informatics, to guarantee the success of sepsis management initiatives.

References:

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315:801-10.
2. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority—a WHO resolution. *N Engl J Med* 2017; 377:414–7.
3. Epstein L, Dantes R, Magill S, Fiore A. Varying Estimates of Sepsis Mortality Using Death Certificates and Administrative Codes — United States, 1999–2014. *MMWR Morb Mortal Wkly Rep* 2016; 65:342–345.
4. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock. *Crit Care Med*. 2017; 45(3):486-552.
5. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Healthcare Quality Promotion (DHQP). Get Ahead of Sepsis. Last updated: August 21, 2017.

6. QualityNet: Inpatient Hospitals Specifications Manual, version 5.2 (November 1, 2016). Available at: <https://www.qualitynet.org>.
7. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006; 34(6):1589-1596.
8. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42(8):1749-1755.
9. Liu VX, Fielding-Singh V, Greene JD, et al. The Timing of Early Antibiotics and Hospital Mortality in Sepsis. *Am J Respir Crit Care Med*. 2017 Oct 1; 196(7):856-863.
10. Peltan ID, Brown SM, Bledsoe JR, et al. ED Door-to-Antibiotic Time and Long-term Mortality in Sepsis. *Chest*. 2019;155(5):938-946.
11. Sterling SA, Miller WR, Pryor J, Puskarich MA, Jones AE. The impact of timing of antibiotics on outcomes in severe sepsis and septic shock: a systematic review and meta-analysis. *Crit Care Med*. 2015;43(9):1907-1915.