

DR EMILY L. HEIL (Orcid ID : 0000-0002-6644-6684)

DR SAMUEL LAWRENCE AITKEN (Orcid ID : 0000-0002-8659-4238)

DR SUSAN DAVIS (Orcid ID : 0000-0001-7521-9486)

Article type : Invited Commentary

Insights from the Society of Infectious Diseases Pharmacists

Recommended Revisions to the National SEP-1 Sepsis Quality Measure: A commentary by the Society of Infectious Diseases Pharmacists on the Infectious Diseases Society of America Position Paper

Emily L. Heil¹, Samuel L. Aitken², David E. Nix³, Richard Drew⁴, Warren E. Rose⁵, Susan L. Davis⁶, Julie Ann Justo⁷, Douglas N. Fish⁸, Jason M. Pogue⁹, on Behalf of the Society of Infectious Diseases Pharmacists

¹ Department of Pharmacy Practice and Science, School of Pharmacy, University of Maryland, Baltimore, MD, USA

² Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

³ Department of Pharmacy Practice and Science, College of Pharmacy, The University of Arizona, Tucson, AZ, USA

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/PHAR.2384](https://doi.org/10.1002/PHAR.2384)

This article is protected by copyright. All rights reserved

⁴ Department of Pharmacy Practice, College of Pharmacy & Health Sciences, Campbell University. Buies Creek, NC, USA

⁵ School of Pharmacy, University of Wisconsin-Madison, Madison, WI, USA

⁶ Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA

⁷ Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina College of Pharmacy, Columbia, SC, USA

⁸ Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA

⁹ Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI

Key words: Sepsis, infectious diseases, septic shock

Running Head: Recommended Revisions to SEP-1

Conflict of Interest Statement: EH received research grant funding from ALK-Abello; JJ serves on the speakers bureau for Biomerieux; WR serves as a consultant for Visante, Achaogen, Melinta, Paratek, received grant funding for Merck, Theravance, NIH, and serves as a speaker for Melinta; SD serves as a consultant for Allergan, Spero, Tetrphase, Melinta, Nabriva, Achaogen, Zavante and research contracts with Merck, CDC. RD serves as a consultant for Paratek and has received royalties from Wolters-Kluwer; JP serves as a consultant for Merck, Shionogi, QPex, Summit Therapeutics, Accelerate Diagnostics.

Other authors report no conflicts of interest to disclose.

Corresponding Author:

Emily L. Heil

Department of Pharmacy Practice and Science

University of Maryland School of Pharmacy

20 N. Pine St,

Baltimore, MD 21201, USA

Following recent revisions to the United States Centers for Medicare and Medicaid Services (CMS) Sepsis and Septic Shock Early Management Bundle (SEP-1) reporting requirement, the Infectious Diseases Society of America (IDSA) led a group of invested stakeholder organizations to develop a position paper of recommended revisions to further improve SEP-1. The goals of these recommendations from IDSA were primarily to improve the balance between early and aggressive treatment of life-threatening infections and antibiotic overuse. Specifically, these recommendations sought to enhance SEP-1 by focusing it as an evidence-based mandate only for the populations where evidence was the strongest and, secondarily, to limit unnecessary antibiotic exposure for patients without true infection but presenting with sepsis-mimicking syndromes. Prior to publication of the guidance document, IDSA engaged the Society of Infectious Diseases Pharmacists (SIDP) by including a representative on the working group (EH) and provided an opportunity for SIDP to review and comment on these recommendations with an opportunity for endorsement. Per SIDP policy the IDSA recommendations were forwarded to the SIDP Guidelines Committee and Board of Directors to review and provide comment. After extensive review and discussion, SIDP endorsed the recommended revisions from IDSA on the new SEP-1 reporting requirement. In this *Insights from SIDP*, we highlight the main points of the IDSA position statement on recommended revisions to SEP-1 and offer suggestions to further clarify and strengthen the recommendations. We emphasize SIDP's perspective regarding opportunities for improved clarity and best practices toward patient care and antimicrobial use in this setting, as well as highlight potential unintended consequences of the IDSA recommendations for consideration.

The Society of Infectious Diseases Pharmacists agrees that the revisions suggested by IDSA are important improvements to the SEP-1 measure, and readers are encouraged to review the entire recommendation and rationale¹. Important highlights of the recommendations from IDSA are as follows. First, IDSA emphasized that the current SEP-1 measures combine the entities of septic shock and sepsis without shock to address in the urgency for immediate antibiotic administration. However, compared to septic shock, sepsis without shock requires alternative management strategies and has dramatically different outcomes. Thus, consolidating these two separate syndromes into one metric is not appropriate. This is illustrated in the references that accompany the IDSA recommendation, which demonstrate the change in risk-benefit ratio for rapid antibiotic administration within these two entities. The Society of Infectious Diseases Pharmacists believes the current evidence supports timely administration of antibiotics in patients with severe sepsis as an urgent priority and that stewardship programs should prioritize minimizing time to appropriate therapy in these patients as well. However, since severe sepsis is a more nebulous definition and there are many syndromes that mimic this presentation, we agree this metric is unsuitable for a core measure bundle. The second key statement from the IDSA is the recommendation that obtaining blood cultures before antibiotics should remain part of SEP-1. Although SIDP recognizes there may be potential downstream consequences of having to expedite blood culture collection before antibiotic administration (including potential contamination and processing issues), we agree that this recommendation is backed by sound scientific evidence to improve appropriate pathogen-directed therapy. In addition, microbiologic testing is critical for antimicrobial stewardship programs to inform antibiotic optimization, either escalation or de-escalation, and to identify the optimal duration of therapy. Therefore, we believe the risk of negative consequences associated with obtaining a culture are outweighed by the benefits of directed therapy. An additional laboratory-based recommendation in the IDSA document advocates for removal of lactate measurements from SEP-1. The IDSA document clearly describes the lack of evidence for using lactate as an appropriate marker to initiate antibiotic therapy and otherwise guide management of septic shock.

The other three recommendations from the IDSA are interrelated. The first states the need to more clearly define time zero in patients with shock based on clear and reproducible objective clinical data. The next two focus on administration strategies and recommend that the window for administration of antimicrobials from time zero be narrowed from 3 hours to 1 hour, and that SEP-1 should require hospitals to report the time interval between when antibiotics were ordered and the time when the first antibiotic infusion began in patients with septic shock.

Although SIDP agrees with the critical importance of these definitions and management strategies to optimize patient care, we emphasize additional areas of consideration with these recommendations in our commentary below.

As stated, the IDSA recommends that the interval from septic shock time zero to initiation of broad-spectrum antibiotics should be 1 hour or less. Although we agree with the clinical benefit of this timing, SIDP has significant concerns with this timing being used as a quality metric as currently framed in the IDSA document. Although IDSA recommends septic shock time zero be clearly defined and reproducible, the recommendation is currently not paired with a defined time zero. Although the IDSA suggests potential time zero definitions, SIDP feels an appropriate time zero must be defined simultaneously with a change in antibiotic timing recommendations. Should time zero remain unchanged but the timing of administration be reduced, haste to administer antibiotics to meet this metric could result in an unintentional rise in antibiotic overuse. Furthermore, without careful consideration for time zero, practical considerations might make compliance with the measure impossible for certain institutions. This would include, but is not limited to, issues such as the inability to achieve rapid vascular access and provider burden in hospitals with multiple emergent patients. These logistic issues can easily push antibiotic administration beyond this 1-hour window. In situations with diagnostic uncertainty, this delay becomes increasingly more likely.

In order to overcome these challenges, SIDP advocates for a definition of time zero that is immediately evident to the treating clinicians at the point-of-care, which, ideally, could trigger an electronic medical record notification or other means of communication to identify the need to administer antibiotics under the SEP-1 measure. The Society of Infectious Diseases Pharmacists believes the most practical and rational suggestion for time zero is to define this as the time of initiation of vasopressors. This time point could be easily abstracted from an electronic medical record and typically coincides with persistent hypotension following an adequate fluid challenge. In the absence of such a clearly defined time zero that assures the ability to provide antimicrobials immediately, SIDP asserts that the original 3-hour goal, or even 2 hours depending on institution type and/or resources, would be a more realistic goal for antibiotic administration for a quality metric.

In addition to a consensus time zero, IDSA recommends that in patients with septic shock, SEP-1 should require hospitals to report “antibiotic delivery time”, defined as the time interval between when antibiotics are first ordered and when they are administered. The Society of Infectious Diseases Pharmacists recognizes the importance of prompt antibiotic

administration in order to facilitate the best possible clinical outcomes in patients with septic shock. While this concept is laudable, SIDP is concerned that requiring hospitals to report this time interval could possibly lead to an easily manipulated quality metric. This could, in turn, further promote inappropriate ordering of standard antibiotic(s) that are readily and quickly available in emergency departments or general floor medicine cabinets. Such practice would counteract the message of thoughtful empiric antibiotic selection currently advocated by antimicrobial stewardship programs and could exacerbate inappropriate antibiotic use. In addition, reporting of time intervals between antibiotic orders and drug administration disregards potentially legitimate reasons for relative delays such as, but not limited to, allergy verification, assessment of antimicrobial spectrum relative to prior cultures, performance of diagnostic testing in venues that preclude antibiotic administration, and drug preparation and delivery. Nevertheless, SIDP recognizes the importance of prompt antibiotic administration in order to facilitate best possible clinical outcomes in patients with septic shock. Rather than implementing required reporting of this time interval, SIDP recommends specifically calling on hospital pharmacies to increase accountability for the drug distribution process from order verification to delivery to patient bedside. Furthermore, SIDP sees this as an opportunity for pharmacy operations to contribute in a directly measurable way in order to improve patient care without the need for an additional reporting requirement.

In addition to these specific comments on the recommendations from IDSA, SIDP also recommends general improvements in broad-spectrum antibiotic administration in patients with septic shock. Although septic shock may be caused by a variety of bacterial pathogens, the greatest proportion of sepsis episodes and sepsis-related mortality are attributable to gram-negative bacteria². Therefore, a broad-spectrum β -lactam empirically targeting gram-negative and gram-positive pathogens is the backbone of treatment in the absence of compelling arguments against their use (e.g., multiple true allergies, unusual resistance patterns). Accordingly, SIDP recommends that a broad-spectrum β -lactam or appropriate alternative therapy be administered as the first component of a potential multidrug antibiotic regimen for septic shock and, furthermore, that administration of this agent serve as the index time for initiation of antibiotics. Combination antimicrobial therapy targeting other select pathogens (e.g., methicillin-resistant *Staphylococcus aureus*, anaerobes, or fungi) are often used appropriately in patients with septic shock but should not be considered in “time to initiation” for SEP-1 due to their longer infusion times and the essentiality of β -lactam therapy. In addition, SIDP recommends the term “delivery” not be used when recommending that broad-spectrum antibiotics be administered within a given time frame. Delivery is an imprecise term that could

refer to delivery of the antibiotic from the pharmacy, initiation of administration, or completion of the intravenous infusion. Therefore, SIDP instead recommends consistent use of the term “initiation” and that this term should refer exclusively to the start of intravenous antibiotic infusion, such as “antibiotic initiation time.”

In summary, SIDP supports the recommendations provided by IDSA on the SEP-1 CMS Sepsis Quality Measure. The Society of Infectious Diseases Pharmacists also strongly advocates for clarification and/or further consideration of several key issues within the recommendations in order to more effectively operationalize the revisions within the existing framework of institutional workflow and patient care. Similar to IDSA, we strongly recommend core measures should be founded on strong evidence-based principles to improve the quality, delivery, and outcomes of care. Finally, though not the focus of this document, SIDP believes it will be of utmost importance that changes to SEP-1 be paired with extensive education about the importance of timing of antibiotic administration. The Society of Infectious Diseases Pharmacists appreciates the opportunity to review and endorse these important recommendations and will continue to collaborate with IDSA to improve patient care and antimicrobial use.

Acknowledgements. We would like to thank the SIDP Guidelines Committee for their thoughtful review and commentary on the IDSA position paper.

References:

1. Rhee C, Chiotos KM Cosgrove SE, et.al. Infectious Diseases Society of America Position Paper: Recommended Revisions to the National SEP-1 Sepsis Quality Measure. Clin Infect Dis (manuscript in press)
2. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence*. 2014;5(1):4–11.