Journal of Intensive Medicine 3 (2023) 144–146

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Perspective

How to improve the care of septic patients following "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021"?

Baoji Hu[1], Wentao Ji[2], Lulong Bo[2,*], Jinjun Bian[2,*]

[1] *Department of Anesthesiology, Shanghai Pudong Hospital, Fudan University Pudong Medical Center, Shanghai 201399, China*
[2] *Faculty of Anesthesiology, Changhai Hospital, Naval Medical University, Shanghai 200433, China*

The updated global adult sepsis guidelines (guideline-2021), released in October 2021 by the Surviving Sepsis Campaign (SSC), place increased emphasis on improving the care of patients with sepsis. These evidence-based guidelines, published in *Critical Care Medicine* [1] and *Intensive Care Medicine*,[2] reflect practices and recommendations for the treatment of sepsis and septic shock in adults and are revised regularly to account for new research. Guideline-2021 should be applauded for its comprehensive and global perspective, with emphasis placed on the following sections: sepsis screening and early treatment, infection, hemodynamic management, mechanical ventilation, additional therapies, and goals of care and long-term outcomes. In this viewpoint, however, we would like to address some special and controversial points that might deserve consideration in clinical practice.

First, the concept of sepsis used in guideline-2021 follows the definition of sepsis-3;[3] however, eligible evidence in guideline-2021 was not screened following the definition of sepsis-3. The definition of sepsis-3 was updated in 2016, which may not have allowed adequate research to be performed, and studies from databases were screened only up to July 2019. Thus, clinical studies based on the latest definition of sepsis are not included. We identified four other studies published in *Chest* [4–6] and *Critical Care Medicine* [7] since guideline-2021 was released. Further studies conducted according to sepsis-3 are warranted and will aid our understanding of guideline-2021, which will eventually contribute new evidence for sepsis management in the future.

Second, the SSC laudably employs the Grading of Recommendations, Assessment, Development, and Evaluation approach in its guideline development, and all available evidence at the time the guidelines were developed was observational. Importantly, the quality of evidence of the included observational studies should be considered as low, yet it is treated as moderate in guideline-2021. It is axiomatic that patients with life-threatening illnesses, such as sepsis or septic shock, should not be randomized in a prospective study to a treatment that is riskier than the prevailing standard of care. As a result, great caution should be taken when generalizing or interpreting the evidence of guideline-2021. In addition, clinicians should be encouraged to understand the meaning and difference between "strong" and "weak" recommendations.[8]

Third, guideline-2021 was released late, probably because of the coronavirus disease 2019 pandemic. Updated studies in recent years were not included in guideline-2021, which may have lessened the timeliness and advancement of the guideline. Moreover, guideline-2021 is conservative to some extent and does not assess novel therapies and technologies, including broad-spectrum genome sequencing for pathogenic microorganisms, diaphragm-protected pulmonary ventilation, thresholds of continuous renal-replacement therapy for acute kidney injury, endotoxin adsorption, and the role of electronic health and telemedicine for long-term outcomes.

Fourth, most contributors to guideline-2021 were from the specialty of intensive care medicine and may have focused mainly on the anaphase of sepsis, septic shock, or multiple organ dysfunction syndrome (MODS). Importantly, existing organ failures cannot be effortlessly reversed at the phase of MODS, and the cost of treatment is high. Potential guidelines should focus on the early phase of sepsis and emphasize septic shock or MODS prevention; in other words, they should endeavor to recognize and prevent sepsis in the emergency department (ED) or general family medicine practice, not just in the intensive care unit (ICU). This is because different departments have their own diagnostic and therapeutic strategies at different stages of each disease. Guideline-2021, developed using intensive care viewpoints, focuses on the systematic inflammatory response and

* Corresponding authors: Lulong Bo and Jinjun Bian, Faculty of Anesthesiology, Changhai Hospital, Naval Medical University, Shanghai 200433, China.
E-mail addresses: bartbo@smmu.edu.cn (L. Bo), jinjunbicu@163.com (J. Bian).

https://doi.org/10.1016/j.jointm.2022.08.001
Received 13 June 2022; Received in revised form 20 July 2022; Accepted 5 August 2022. Managing Editor: Jingling Bao
Available online 31 October 2022

MODS, whereas the ED focuses on its early recognition and diagnosis and the specialty of infectious diseases focuses on the pathogen and its clearance.[9] Societies should implement positive cooperation and merge the best strategies for diagnosing and treating sepsis in the future for the benefit of patients with sepsis.

Fifth, the logical arrangement of the content should be discussed. Fluid resuscitation and hemodynamic management interact during sepsis, but these were discussed independently of one another. One previous study has demonstrated an association between poor outcomes and the volume of positive fluid balance in patients with septic shock.[10] A 2019 meta-analysis found no difference in outcomes when comparing fluid administration approaches.[11] Vasopressors should be administered if a patient with sepsis remains hypotensive despite initial fluid administration. Early vasopressors can be considered, given that protocol-based peripheral vasopressor use is safe during initial resuscitation.[12] The first procedure to control infection should ascertain the infection sources, but this was mentioned when discussing the antibacterial agents in guideline-2021. Signs of infection or sepsis are often nonspecific and sometimes do not indicate that an infection exists, so the benefit of early antibiotic administration should be balanced against the risk of adverse effects of antimicrobials such as hypersensitivity reactions, renal failure, *Clostridioides difficile* infection, and antimicrobial resistance.[13] For patients with septic shock, it is particularly important to use antibiotics in the early period (1 h) to control the primary infection. It may be difficult to accurately identify the exact source of infection in the early stages of sepsis, but this should not be a reason to delay antibiotic use. The guidelines also state "for adults with a low likelihood of infection and without shock, we suggest deferring antimicrobials while continuing to closely monitor the patient." It should be noted that we do not deny the value of administering antibiotics within 1 h to control the primary infection but seek to raise clinical concern that early identification of the source of infection is of equal importance. With advances in molecular diagnostic techniques, more sensitive and rapid clinical testing will be of value to and will impact the management of patients with sepsis. The guideline also points out "for adults with possible sepsis without shock, we suggest a time-limited course of rapid investigation and, if concern for infection persists, the administration of antimicrobials within 3 h from the time when sepsis was first recognized." We believe that the 3-h period mentioned here is clinically unreasonable given that most patients with septic shock are severe hemodynamically unstable.

Sixth, guideline-2021 suggests optimizing the measurement and management of the blood lactate level, which should be incorporated into the resuscitation process. It is now believed that simply normalizing the blood lactate while ignoring the systemic overall responses might lead to excessive resuscitation with inherent fluid and vasopressor overload.

Finally, the eligible studies for consideration were only those published in the English language, thus covering only countries or regions with abundant medical resources. However, the characteristics and treatment of sepsis are affected by territory and geodemographics. Thus, guildeline-2021 should be followed with caution in individual regions. In addition, detailed treatment procedures were deleted or simplified in guideline-2021 compared to in the previous version, which may make compliance difficult for users. We believe that the guideline seeks to teach readers "to fish," not to "give them fish." It should assess and summarize the available evidence, focusing on a specific medical subject.

Various clinical characteristics, complex pathophysiological reactions, and high heterogeneity of the clinical syndrome add to the difficulty of clinical research on sepsis. A meta-analysis that included multicenter randomized controlled trials revealed no conclusive evidence of any pharmacologic intervention that has consistently reduced mortality in patients with sepsis.[14] Results from some positive randomized controlled trials were not replicated in subsequent randomized controlled trials.[14] However, this may lead to a "making bricks without straw" dilemma because guidelines should be based on solid evidence.

To avoid following the "standard" recommendation, we believe that the study of sepsis should be divided into different subgroups and focus on patient diversity. Dr. Jean-Louis Vincent, the chief editor of *Critical Care*, put forth 20 recommendations to individualize interventions in the early resuscitation of patients with sepsis. Dr. Vincent recommended individualizing the timing and decision of ICU admission, the timing of antibiotic therapy, respiratory settings in mechanically ventilated patients and oxygenation targets, fluid resuscitation, vasopressor therapy, arterial blood pressure levels, and so on.[15] These 20 recommendations, in our opinion, deserve further consideration.

Guideline-2021 facilitates global researchers to study sepsis treatment exactly according to setting orientation and frame. It should be emphasized that offering our viewpoints herein is not intended to deny the value of guideline-2021 but instead to raise concern and highlight issues for further consideration. Researchers will constantly endeavor to practice, innovate, query, break, and explore the optimum treatment for individual patients with sepsis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med 2021;49(11):e1063–143. doi:10.1097/CCM.0000000000005357.

[2] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Intensive Care Med 2021;47(11):1181–247. doi:10.1007/s00134-021-06506-y.

[3] Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):775–87. doi:10.1001/jama.2016.0289.

[4] Schinkel M, Paranjape K, Kundert J, Nannan Panday RS, Alam N, Nanayakkara P. Towards understanding the effective use of antibiotics for sepsis. Chest 2021;160(4):1211–21. doi:10.1016/j.chest.2021.04.038.

[5] Bisarya R, Song X, Salle J, Liu M, Patel A, Simpson SQ. Antibiotic timing and progression to septic shock among patients in the ED with suspected infection. Chest 2022;161(1):112–20. doi:10.1016/j.chest.2021.06.029.

[6] Townsend SR, Phillips GS, Duseja R, Tefera L, Cruikshank D, Dickerson R, et al. Effects of compliance with the early management bundle (SEP-1) on mortality changes

among Medicare beneficiaries with sepsis: a propensity score matched cohort study. Chest 2022;161(2):392–406. doi:10.1016/j.chest.2021.07.2167.
[7] Tarabichi Y, Cheng A, Bar-Shain D, McCrate BM, Reese LH, Emerman C, et al. Improving timeliness of antibiotic administration using a provider and pharmacist facing sepsis early warning system in the emergency department setting: a randomized controlled quality improvement initiative. Crit Care Med 2022;50(3):418–27. doi:10.1097/CCM.0000000000005267.
[8] Oczkowski S, Alshamsi F, Belley-Cote E, Centofanti JE, Hylander Møller M, Nunnaly ME, et al. Surviving sepsis campaign guidelines 2021: highlights for the practicing clinician. Pol Arch Intern Med 2022;132:16290. doi:10.20452/pamw.16290.
[9] de Groot B, Jessen MK, Nickel CH. The new 2021 surviving sepsis guidelines: an emergency department perspective may be more effective. Eur J Emerg Med 2022;29(1):5–6. doi:10.1097/MEJ.0000000000000898.
[10] Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009;76(4):422–7. doi:10.1038/ki.2009.159.
[11] Pepper DJ, Sun J, Cui X, Welsh J, Natanson C, Eichacker PQ. Antibiotic- and fluid-focused bundles potentially improve sepsis management, but high-quality evidence is lacking for the specificity required in the Centers for Medicare and Medicaid Service's Sepsis Bundle (SEP-1). Crit Care Med 2019;47(10):1290–300. doi:10.1097/CCM.0000000000003892.
[12] Patel S, Puri N, Dellinger RP. Sepsis management for the nephrologist. Clin J Am Soc Nephrol 2022;17(6):880–9. doi:10.2215/CJN.14381121.
[13] Mushtaq A, Kazi F. Updates in sepsis management. Lancet Infect Dis 2022;22(1):24. doi:10.1016/S1473-3099(21)00773-8.
[14] Santacruz CA, Pereira AJ, Celis E, Vincent JL. Which multicenter randomized controlled trials in critical care medicine have shown reduced mortality? A systematic review. Crit Care Med 2019;47(12):1680–91. doi:10.1097/CCM.0000000000004000.
[15] Vincent JL, Singer M, Einav S, Moreno R, Wendon J, Teboul JL, et al. Equilibrating SSC guidelines with individualized care. Crit Care 2021;25(1):397. doi:10.1186/s13054-021-03813-0.