Executive Summary: Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021

Laura Evans[1]
Andrew Rhodes[2]
Waleed Alhazzani[3]
Massimo Antonelli[4]
Craig M. Coopersmith[5]
Craig French[6]
Flávia R. Machado[7]
Lauralyn Mcintyre[8]
Marlies Ostermann[9]
Hallie C. Prescott[10]
Christa Schorr[11]
Steven Simpson[12]
W. Joost Wiersinga[13]
Fayez Alshamsi[14]
Derek C. Angus[15]
Yaseen Arabi[16]
Luciano Azevedo[17]
Richard Beale[18]
Gregory Beilman[19]
Emilie Belley-Cote[20]
Lisa Burry[21]
Maurizio Cecconi[22]
John Centofanti[23]
Angel Coz Yataco[24]
Jan De Waele[25]
R. Phillip Dellinger [26]
Kent Doi[27]
Bin Du[28]
Elisa Estenssoro[29]
Ricard Ferrer[30]
Charles Gomersall[31]
Carol Hodgson[32]

The Surviving Sepsis Campaign (SSC) International Guidelines for the Management of Sepsis and Septic Shock provide guidance on the care of hospitalized adult patients with (or at risk for) sepsis, based on systematic summary and assessment of relevant literature. This executive summary reviews the history, scope, methodology, and major recommendations of the guidelines, focusing on aspects that are new or different compared with the 2016 guidelines that were published in 2017. Full description of the guidelines process and recommendations are provided in the complete guidelines document.

KEY WORDS: adults; evidence-based medicine; guidelines; sepsis; septic shock

HISTORY AND SCOPE OF THE GUIDELINES

The SSC first published guidelines for the management of severe sepsis and septic shock in 2004. Updates were published in 2008, 2012, and 2017. The guidelines are sponsored by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), with methodological support by the Guidelines in Intensive Care Development and Evaluation (GUIDE) group, and endorsement by 24 additional societies. There is no funding from any industry partner. Panel membership, patient involvement, and conflict of interest management are discussed in the complete guidelines document.

The guidelines provide recommendations on the management of sepsis, focusing on aspects of care specific to sepsis and limiting duplication with other guidelines wherever possible. It is not intended to replace clinical judgement, which must account for the unique circumstances of an individual patient. Following the recommendation of SCCM and ESICM, there are now separate guidelines for sepsis in children (1). The SSC also published separate guidelines specific to the management of COVID (2, 3).

The 2021 guidelines largely apply to high-resource settings but discuss applicability of the recommendations to lower-resource settings as data allow. The SSC also creates sepsis bundles (4) (a selected set of interventions or processes of care distilled from evidence-based practice guidelines) to facilitate quality improvement and implementation of guidelines recommendations. However, the bundles are developed via a separate process and published separately from the guidelines.

Definitions

The guidelines recognize sepsis as *life-threatening organ dysfunction secondary to a dysregulated host response to infection* consistent with the Sepsis-3 consensus

DOI: 10.1097/CCM.0000000000005357

definition (5). However, studies were not required to use a particular sepsis definition to be considered as relevant evidence for the guidelines.

Question Development and Outcome Prioritization

Guidelines questions were selected based on panel rating, clinical practice variability, and inclusion in prior SSC guidelines, and then assigned to one of six SSC adult guidelines working groups: screening and initial resuscitation; infection; hemodynamics; ventilation; additional therapies; and goals of care and long-term outcomes. Clinical practice variation was identified through a global survey of SCCM and ESICM members regarding their current practice and how it related to previous recommendations. All questions were structured in the Population, Intervention, Control, and Outcomes (PICO) format. For each question, relevant outcomes were enumerated and ranked prior to the literature search.

Search Strategy and Evidence Summation

Professional librarians drafted and executed the search strategy for each PICO question (or group of similar questions), with input from subgroup members. Only English language studies published before May 2019 were included (the lag was the result of the guideline review and approval process coupled with the COVID-19 pandemic). For PICO questions addressed in the 2016 guidelines, the search strategy was revised and updated. Reviewers in the systematic review team, with input from methodologists and experts, screened article titles and abstracts to identify the highest quality evidence, particularly recent randomized controlled trials and high-quality systematic reviews. When new or updated meta-analyses were required, relevant data were abstracted with emphasis on intention-to-treat data where possible and conventional meta-analytic techniques were used to produce pooled estimates.

Quality of Evidence and Formulation of Recommendations

Using the GRADE approach, methodologists and panelists assessed the quality of evidence for each PICO question as high, moderate, low, or very low. Using the Evidence-to-Decision (EtD) framework (6), each subgroup drafted preliminary recommendations for their assigned PICO questions. The EtD framework took into account not only the magnitude of effect and quality of evidence, but also patient values, resources and cost, equity, acceptability, and feasibility (6).

The strength of each recommendation was informed by the quality of the evidence and other components of the EtD framework. Strong recommendations (signified by "we recommend") reflect high confidence that the desirable effects of adhering to a recommendation clearly outweigh undesirable effects. Weak recommendations (signified by "we suggest") indicate that desirable effects likely outweigh undesirable effects. Best practice statements (BPSs) reflect ungraded strong recommendations and are used sparingly when benefit or harm is unequivocal, but evidence is difficult to summarize or assess according to GRADE methodology (7).

Morten Hylander Møller[33]
Theodore Iwashyna[34]
Shevin Jacob[35]
Ruth Kleinpell[36]
Michael Klompas[37]
Younsuck Koh [38]
Anand Kumar[39]
Arthur Kwizera[40]
Suzana Lobo[41]
Henry Masur[42]
Steven McGloughlin[43]
Sangeeta Mehta[44]
Yatin Mehta[45]
Mervyn Mer[46]
Mark Nunnally[47]
Simon Oczkowski[48]
Tiffany Osborn[49]
Elizabeth Papathanassoglou[50]
Anders Perner[51]
Michael Puskarich[52]
Jason Roberts[53]
William Schweickert[54]
Maureen Seckel[55]
Jonathan Sevransky[56]
Charles L. Sprung[57]
Tobias Welte[58]
Janice Zimmerman[59]
Mitchell Levy[60]

Voting Progress

Preliminary recommendations were discussed during face-to-face meetings and revised based on panel feedback prior to electronic voting by panel members who had no conflicts of interest. The *a priori* threshold for acceptance was having votes cast by at least 75% of the panel and 80% agreement among those who cast a vote. Up to three rounds of voting were allowed per PICO question.

RECOMMENDATIONS

The recommendations of the SSC 2021 guidelines update are summarized in Table 1 of the full guidelines document. There are 93 total statements, which address screening and initial resuscitation (n = 10 statements), infection (n = 21), hemodynamics (n = 14), ventilation (n = 12), additional therapies (n = 16), and goals of care and long-term outcomes (n = 20). Of the 93

TABLE 1.
Selected New and/or Revised Recommendations in the 2021 Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock

2016 Recommendation	2021 Recommendation	Rationale for Change
We recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours.	For patients with sepsis-induced hypoperfusion or septic shock we suggest that at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hours of resuscitation.	This panel downgraded this recommendation from a strong recommendation to a weak recommendation based on the low quality of the evidence. There are no prospective intervention studies comparing different volumes for initial resuscitation in sepsis or septic shock. However, a retrospective analysis of adults presenting to an emergency department with sepsis or septic shock showed that failure to receive 30mL/kg of crystalloid fluid therapy within 3 hours of sepsis onset was associated with higher in-hospital mortality (10). Furthermore, the average volume of fluid received pre-randomization the PROCESS (11), PROMISE (12), and ARISE (13) trials was in the range of 30 mL/kg, suggesting this fluid volume has been adopted in routine clinical practice (14).
We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock.	For adults with sepsis or septic shock, we suggest using balanced crystalloid instead of normal saline for resuscitation.	There are many, increasingly recognized potential adverse effects of normal saline including hyperchloremic metabolic acidosis. A network meta-analysis showed in an indirect comparison that balanced fluids were associated with decreased mortality compared with saline (15). In the 2018 SMART single-center cluster-randomized RCT comparing saline to balance fluid, the pre-specified subgroup of patients admitted with sepsis experienced lower 30-day mortality when randomized to balanced fluids versus saline (OR, 0.90; 95% CI, 0.67, 0.94) (16).
Not addressed	For adults with septic shock, we suggest starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured.	Prompt initiation of vasopressors is an integral component of septic shock management. Vasopressors have been traditionally administered via central venous access due to concerns of extravasation and local tissue injury and ischemia. However, placement of central venous access requires specialized expertise and is time consuming, potentially leading to delays in administration. A recent systematic review showed that peripheral administration of vasopressors is generally safe, particularly if infused distally to the antecubital fossa and for short periods of time (< 6 hr) (17, 18). Peripheral administration of vasopressors is associated with shorter time to administration and faster time to achieving a MAP > 65 mm Hg (19).

(*Continued*)

TABLE 1. (*Continued*).
Selected New and/or Revised Recommendations in the 2021 Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock

2016 Recommendation	2021 Recommendation	Rationale for Change
Not addressed	For adults with sepsis or septic shock we suggest against using IV vitamin C.	A 2017 single center before and after study reported reduced mortality with administration of high-dose Vitamin C, hydrocortisone, and thiamine among patients with sepsis and sepsis shock (20). However, an updated meta-analysis by the guideline panel found no association between vitamin C and reduced mortality.
We suggest against using IV hydrocortisone to treat patients with septic shock if adequate fluid resuscitation and vasopressor therapy can restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg/day.	For adults with septic shock and an ongoing requirement for vasopressor therapy we suggest using IV corticosteroids.	Since the 2016 guideline, three large RCTs have been published (21–23). An updated meta-analysis found systemic corticosteroid to accelerate resolution of shock (MD, 1.52 days; 95% CI, 1.71 to 1.32) and increase vasopressor-free days (MD, 1.5 days; 95% CI, 0.8 to 3.11 days) (24). However, corticosteroid use increased neuromuscular weakness (RR, 1.21; 95% CI, 1.01 to 1.45), without a clear effect on short- or long-term mortality (24). The overall quality of evidence was moderate. The panel judged the desirable effects (shock resolution, vasopressor-free days) to outweigh the undesirable effects. This observation, combined with consideration of the resources required, cost of the intervention, and feasibility supported a weak recommendation in favor of using low-dose corticosteroid therapy in septic shock.
Not addressed	For adult survivors of sepsis or septic shock, we recommend assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge.	Given the prevalence of new and worsening physical, cognitive, and emotional problems experienced by sepsis survivors, we recommend assessment and follow-up of these problems after discharge.

statements, 15 are strong (16%) and 54 are weak (58%) recommendations, 15 are best practice statements (16%), and 9 are statements declaring 'no recommendation' (10%). Of the 15 strong recommendations, all but one are based on moderate or high-quality evidence. Selected recommendations that are new or revised from the 2016 guidelines are shown in **Table 1**.

Screening and Initial Resuscitation

The guidelines recommend that hospitals use a performance improvement program for sepsis, including screening of high-risk patients and standard operating procedures for management. The guidelines recognize sepsis as a medical emergency and recommend that treatment and resuscitation begin immediately. For initial resuscitation in patients with sepsis-induced hypoperfusion or septic shock, the guidelines suggest 30 mL/kg IV crystalloid. This recommendation was downgraded from a strong recommendation to a weak recommendation based on the low quality of evidence. Additionally, the guidelines suggest resuscitation be guided by dynamic over static measures, target a decrease in serum lactate, and use capillary refill as an adjunct measure of perfusion. New to this update, the guidelines recommend against qSOFA as a sole screening tool and suggest that patients who are determined to need intensive care be admitted to an ICU within 6 hours.

Infection

As in the 2016 guidelines, the 2021 guidelines again recommend delivering antimicrobials as soon as possible, ideally within 1 hour of sepsis recognition. The 2021 guidelines provide additional guidance on initiation of

antimicrobials, recognizing the challenge of diagnostic uncertainty early in a patient's presentation. The guidelines now stratify antimicrobial timing recommendations based on the likelihood of sepsis and presence of shock (**Figure 1**). For patients with probable sepsis or with shock resulting from possible or probable sepsis, the guidelines recommend administering antimicrobials immediately, ideally within 1 hour of recognition. For patients with possible sepsis but without shock, the guidelines recommend rapid assessment of the likelihood of infection versus non-infectious illness. If concern for infection persists after a time-limited course of rapid investigation, then antimicrobials should be administered within 3 hours from when sepsis was first recognized. Finally, for patients with a low likelihood of infection and without shock, the guidelines suggest deferring antimicrobials while continuing to closely monitor the patient.

The guidelines include several additional recommendations regarding antimicrobial therapy for sepsis. Given the heterogeneity of infectious pathogens, sites of infection, severity of illness, local resistance patterns, and other patient and contextual factors, specific treatment recommendations are beyond the scope of the guidelines. However, the guidelines provide a framework for approaching antimicrobial therapy. They suggest that use of empiric coverage for methicillin-resistant *Staphylococcus aureus* (MRSA), empiric double-coverage for gram-negative pathogens, and empiric coverage for fungal pathogens be determined based on patient and contextual risk factors. The guidelines provide several recommendations for optimizing antibiotic dosing, addressing source control, and determining duration of antimicrobial therapy.

Hemodynamics

The guidelines recommend crystalloid fluids as a first line for resuscitation, and new in this update, suggest balanced crystalloids over normal saline. For patients with septic shock, the guidelines recommend norepinephrine as the first-line vasopressor and suggest that vasopressors be started peripherally to avoid delays in administration in the absence of central venous access. There was insufficient evidence to make a recommendation regarding the use of a restrictive versus liberal fluid strategy after the initial fluid resuscitation, and this remains an important area for future research. As in the 2016 guidelines, albumin is suggested in patients who have received large volumes of crystalloid.

Ventilation

The guidelines recommend a low tidal volume ventilation strategy with limitation of plateau pressure for patients with sepsis-associated ARDS and the use of prone positioning in moderate-to-severe ARDS, and suggest a low tidal volume approach for all patients with sepsis-induced respiratory failure. The guidelines

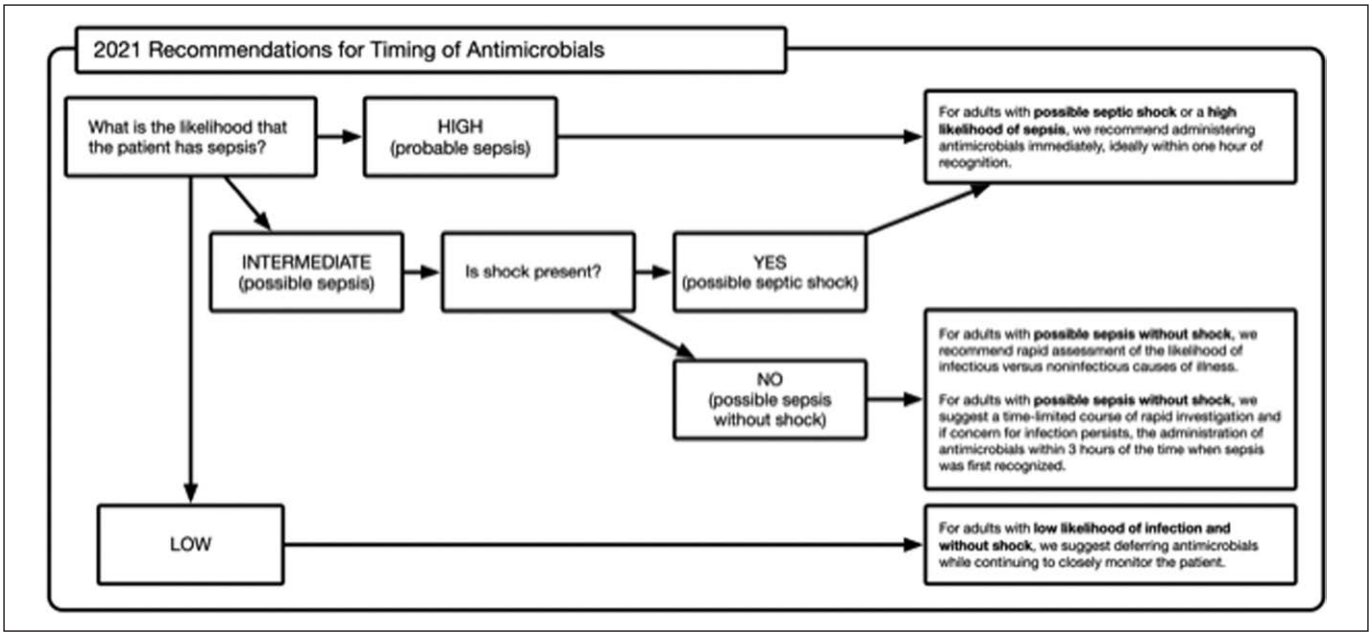

Figure 1. 2021 Recommendations of the initiation of antimicrobials.

suggest using traditional recruitment maneuvers but recommend against an incremental PEEP strategy. There was insufficient evidence to make a recommendation regarding use of liberal versus conservative oxygen targets; this remains an important area for future research.

Additional Therapies

To limit overlap with other guidelines and create space for a new section focused on long-term outcomes, PICOs on additional therapies were reduced from prior SSC guidelines. However, there are some noteworthy new recommendations regarding adjunctive therapies. In contrast to the 2016 guidelines, the 2021 guidelines suggest the use of IV corticosteroids for patients with an ongoing need for vasopressor therapy based on newer clinical trial data. Additionally, the guidelines suggest against using IV vitamin C for sepsis or septic shock based on recent randomized controlled trials and an updated meta-analysis showing no impact on mortality.

Goals of Care and Long-Term Outcomes

As acute survival from sepsis has improved, a growing number of sepsis survivors leave the hospital alive—many of whom experience long-term morbidity and a heightened risk for adverse health outcomes including mortality in the months and years following sepsis (8). Indeed, the 2017 World Health Organization resolution on sepsis called for improving outcomes of sepsis survivors and addressing survivors' access to rehabilitation (9). Given the burden of long-term morbidity and mortality stemming from sepsis, the SSC guidelines now include a section dedicated to the longer-term recovery from sepsis. To enhance recovery, the guidelines recommend screening for economic and social support for patient and families, involving patients and families in shared decision-making regarding discharge planning, reconciling medications at both ICU and hospital discharge, including information about sepsis and common impairment after sepsis in the discharge summary, and assessing for physical, cognitive, and emotional problems after hospital discharge. The guidelines suggest having a critical care transitional program during ICU stay to floor transitions, using a handoff process during transitions of care, offering verbal and written sepsis education, and referring patients to peer support programs, post-critical illness follow-up programs (if available), and post-hospital rehabilitation programs (for selected survivors). There was insufficient evidence to make a recommendation regarding early cognitive rehabilitation or timing of post-hospital follow up. While many of these recommendations are generally applicable to critically ill and hospitalized patients, the panel deemed them necessary to include in the sepsis guidelines given the burden of long-term morbidity and mortality due to sepsis.

CONCLUSIONS

This executive summary highlights the most novel aspects of the Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock 2021 that clinicians and stakeholders should consider when caring for adult patients with (or at risk for) sepsis. The recommendation rationales, informed by rigorous data evaluation, discussion by panelists, and input from patients, provide deeper insight into each recommendation. We believe that the 2021 SSC guidelines will foster the delivery of best practices for sepsis evaluation and management, as well as highlight aspects of management where additional evidence is needed most urgently.

1 *Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, Washington, USA.*

2 *Adult Critical Care, St. George's University Hospitals NHS Foundation Trust & St. George's University of London, London, United Kingdom.*

3 *Department of Medicine, McMaster University, Canada & Department of Medicine, McMaster University, Hamilton, Ontario, Canada.*

4 *Dipartimento di Scienze dell' Emergenza Anestesiologiche e della Rianimazione, Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.*

5 *Emory University School of Medicine, Atlanta, Georgia, USA*

6 *Western Health, Melbourne, Australia.*

7 *Anesthesiology, Pain, and Intensive Care Department, Federal University of São Paulo, São Paulo, Brazil.*

8 *Ottawa Hospital, Ottawa, Ontario, Canada.*

9 *Guy's & St Thomas' Hospital, London, United Kingdom.*

10 *University of Michigan and VA Center for Clinical Management Research, Ann Arbor, Michigan, USA.*

11 *Cooper Health System, Camden, New Jersey, USA.*

12 *University of Kansas Medical Center, Kansas City, Kansas, USA.*

13 *Division of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis.*

14 *Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates.*

15 *University of Pittsburgh Critical Care Medicine CRISMA Laboratory, Pittsburgh, Pennsylvania, USA.*

16 *Intensive Care Department, Ministry of National Guard Health Affairs, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Kingdom of Saudi Arabia.*

17 *University of São Paulo, School of Medicine, São Paulo, Brazil.*

18 *Guy's & St Thomas' Hospital, London, United Kingdom.*

19 *University of Minnesota, Minneapolis, Minnesota, USA.*

20 *Population Health Research Institute, Hamilton, Ontario, Canada.*

21 *Mount Sinai Hospital & University of Toronto (Leslie Dan Faculty of Pharmacy), Toronto, Ontario, Canada.*

22 *Department of Anesthesia and Intensive Care, Humanitas Clinical and Research Center, Rozzano, Milan, Italy.*

23 *Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada.*

24 *Lexington Veterans Affairs Medical Center/University of Kentucky College of Medicine, Lexington, Kentucky, USA.*

25 *Ghent University Hospital, Ghent, Belgium.*

26 *Cooper Health System, Camden, New Jersey, USA.*

27 *The University of Tokyo, Tokyo, Japan.*

28 *Medical ICU, Peking Union Medical College Hospital, Beijing, China.*

29 *Hospital Interzonal de Agudos San Martin de La Plata, Buenos Aires, Argentina.*

30 *Intensive Care Department, Vall d'Hebron University Hospital, Vall d'Hebron Institut de Recerca, Barcelona, Spain.*

31 *Prince of Wales Hospital, Hong Kong, China.*

32 *Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia.*

33 *Copenhagen University Hospital Rigshospitalet, Department of Intensive Care, Copenhagen, Denmark.*

34 *University of Michigan Health System, Ann Arbor, Michigan, USA.*

35 *Liverpool School of Tropical Medicine, Liverpool, United Kingdom.*

36 *Vanderbilt University, Nashville, Tennessee, USA.*

37 *Department of Medicine, Brigham and Women's Hospital, Boston MA; Department of Population Medicine, Harvard Medical School, and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA.*

38 *ASAN Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.*

39 *University of Manitoba, Winnipeg, Manitoba, Canada.*

40 *Makerere University College of Health Sciences, Kampala, Uganda.*

41 *Intensive Care Division. Faculdade de Medicina de São José do Rio Preto, São Paulo, Brazil.*

42 *Critical Care Medicine Department, NIH Clinical Center, Bethesda, Maryland, USA.*

43 *Alfred Health, Melbourne, VIC, Australia.*

44 *Mount Sinai Hospital, Toronto, Ontario, Canada.*

45 *Medanta The Medicity, Gurugram, Haryana, India.*

46 *Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.*

47 *New York University School of Medicine, New York, New York, USA.*

48 *Department of Medicine, McMaster University, Hamilton, Ontario, Canada.*

49 *Washington University School of Medicine, St. Louis, Missouri, USA.*

50 *Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada.*

51 *Rigshospitalet, Copenhagen, Denmark.*

52 *University of Minnesota/Hennepin County Medical Center, Minneapolis, Minnesota, USA.*

53 *University of Queensland Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, Australia, Departments of Pharmacy and Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia, Division of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes, France.*

54 *University of Pennsylvania, Philadelphia, Pennsylvania, USA.*

55 *ChristianaCare, Newark, Delaware, USA.*

56 *Emory University School of Medicine, Atlanta, Georgia, USA.*

57 *Faculty of Medicine, Hebrew University of Jerusalem, Israel; Department of Anesthesiology, Critical Care and Pain Medicine, Hadassah Medical Center, Jerusalem, Israel.*

58 *Medizinische Hochschule Hannover and German Center of Lung Research (DZL), Hannover, Germany.*

59 *World Federation of Intensive and Critical Care, Brussels, Belgium.*

60 *Warren Alpert School of Medicine at Brown University, Providence, Rhode Island & Rhode Island Hospital, Providence, Rhode Island, USA.*

Dr. Alhazzani is the Chair of the Guidelines Chapter for the Saudi Critical Care Society and is the chair of the guidelines in intensive care, development and evaluation (GUIDE) Group, McMaster University Canada. Dr. Antonelli received funding from GE, Toray-Estor, Baxter, Pfizer, Orion, Maquet, and Fisher and Paykel; he was on the board of Baxter and Pfizer, and is a member of the executive committee and past president of Società Italiana di Anestesia Rianimazione e Terapia Intensiva (SIAARTI). Dr. French contributed to the ANZICS Guidelines and the National COVID-19 Guidelines. Dr. Machado is a member of the Executive Committee for the Basics Study (for which Baxter provided the drugs and logistics) and AMIB. Dr. McIntyre is a member of the Canadian Critical Care Society and serves on the Surviving Sepsis Campaign Steering Committee. Dr. Ostermann is a council member of the Intensive Care Society UK and member of the Renal Association UK and World Sepsis Alliance. Dr. Prescott is a member of the ATS Critical Care Program Committee. Dr. Simpson is the president-elect and Chair of CHEST, is a member of the board of directors and medical

director of Sepsis Alliance, and Chair of the Sepsis Institute Advisory Board. Dr. Wiersinga is a member of ISF, ESCIMID, and SWAB. Dr. Angus received funding from Ferring Pharmaceuticals, Inc and ALung Technologies, Inc. Dr. Beale provides consultancy services for Philips Healthcare with his time billed by his institution. Dr. Beilman is the president of the Surgical Infection Society. Dr. Belley-Cote received grants from Roche and Bayer and is a panel member on the Saudi Critical Care Society COVID-19 Thrombosis Guidelines. Dr. Cecconi is a consultant for Edwards Lifesciences, Cheetah Medical, and Directed Systems and is President of the European Society of Intensive Care Medicine. Dr. Coz is a board member of the American College of Chest Physicians. Dr. De Waele consulted for Accelerate, Bayer, Grifols, Pfizer, and MSD with all honoraria paid to Ghent University; he is a Senior Clinical Investigator with the Research Foundation Flanders. Dr. Dellinger serves as an expert witness on occasional medical legal case reviews. Dr. Doi is a member of the Japanese Society of Intensive Care Medicine. Dr. Du is a member of the Chinese Society of Critical Care Medicine and the Chinese College of Intensive Care Medicine. Dr. Ferrer received funding from Grifols, MSD, Pfizer, Shionogi, Toray, Jafron, and Cytosorbents; he is a member of SEMICYUC. Dr. Gomersall is a member of an educational subgroup of the International Forum of Acute Care Trialists. Dr. Hodgson is a member of the Australian National Health and Medical Research Council guidelines (COVID-19) and leading funded trials in early rehabilitation and ECMO. Dr. Møller contributed to guideline work for DASAIM, SSAI, GUIDE, and ESA. Dr. Iwashyna is a member of the ATS, the NIH, and an informal (unincorporated) organization called the Critical and Acute Illness Recovery Organization. Dr. Jacob co-directs the African Research Collaboration on Sepsis (ARCS, funded by UK National Institute for Health Research, sponsored by Liverpool School of Tropical Medicine), he is Secretary General for the African Sepsis Alliance, and is a technical expert for the World Health Organization panels. Dr. Kleinpell is a board member of the World Federation of Intensive and Critical Care, American Nurses Credentialing Center, and the Tennessee Nurses Association Political Action Committee. Dr. Klompas received funding from Up-to-Date; he is a member of the guidelines committees of the Infectious Disease Society of America (IDSA) and Society of Healthcare Epidemiologists of America (SHEA). Dr. Koh is a member of The Korean Society of Critical Care Medicine, The Korean Academy of Tuberculosis and Respiratory Diseases, The Korean Society of Medical Ethics, and the Asia Ventilation Forum. Dr. Kumar served as an expert witness regarding a lethal dose of narcotics. Dr. Kwizera is president of the Intensive Care Society of Uganda and PRO for the Association of Anesthesiologists of Uganda. Dr. Lobo received funding from Pfizer, MSD, Edwards, and Nestle; she is the principal investigator in new antibiotics research led by CROs/industry; she is a member of the AMIB Executive Board and was elected president for 2020-2021. Dr. McGloughlin is a member of ANZICS (Australian New Zealand Intensive Care Society). Dr. Mehta participated in two non-interventional studies by ISCCM-Hermes and Indicaps. Dr. Mer has been an invited speaker for educational talks in industry-sponsored symposia for which honoraria was received; he is the current Vice President of the Southern African Society of Thrombosis and Haemostasis (SASTH), and is involved in annual congress organization; he is an invited author of the Global guidelines for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Dr. Nunnally is the treasurer of SOCCA, committee member of ASA, NYSSA, IARS, AUA, and SAAAPM and serves on the American College of Critical Care Medicine Board of Regents. Dr. Oczkowski is a member of the European Respiratory Society, and contributed to the High Flow Nasal Cannula Guidelines, the Non-Invasive Ventilation in COPD Guidelines. Dr. Osborn received funding from Viven Inc, Inflammatrix, Beckman, and the Foundation for Barnes Jewish Hospital; she is on the advisory board for Beckman, Inflammatix, and Viven; she is a member of the American College of Emergency Physicians, American College of Chest Physicians, American Medical Association, Society of Academic Emergency Medicine, and American Academy of Emergency Physicians; she served as an expert witness in a case related to viral as compared to bacterial sepsis. Dr. Papathanassoglou is a member of the World Federation of Critical Care Nurses (Editor of Journal) and the Canadian Association of Critical Care Nurses. Dr. Perner received a research grant from Pfizer Denmark. Dr. Puskarich is the co-inventor of a patent to assess L0carnitine drug responsiveness in sepsis (USPO 10330685); he is a member of the Society for Academic Emergency Medicine, American College of Emergency Physicians (ACEP); he was invited to a recently gathered ACEP early sepsis treatment policy task force asked to develop specialty recommendations for early sepsis treatment. Dr. Roberts received funding from MSD, The Medicines Company, Cardeas Pharma, Biomerieux, QPEX, Cipla, and Pfizer; he consulted for MSD, QPEX, Discuva Ltd, Accelerate Diagnostics, Bayer, Biomerieux, UptoDate, and Australian Therapeutic Guidelines; he is a member of the Society of Hospital Pharmacists of Australia Leadership Committees for Critical Care and Infectious Diseases and the Lead of Sepsis Working group for the International Society of Anti-infective Chemotherapy. Dr. Schweickert is a paid consultant to the American College of Physicians (last performed in Spring, 2019). Dr. Seckel volunteers for AACN and is a paid consultant to revise online Critical Care Orientation. Dr. Sevransky received funding from the Marcus Foundation- PI VICTAS Trial and serves on the American College of Critical Care Medicine Board of Regents. Dr. Welte received funding from Astellas, AstraZeneca, Boehringer, Basilea, Bayer, Berlin-Chemie, Grifols, Infectopharm, Mundipharma, MSD, Novartis, Pfizer, DFG, EU, BMBF, and Insmed; he is on the advisory board for AstraZeneca, Boehringer, Bayer, Gilead, GSK, Insmed, Novartis, Pfizer, Roche; he is a member of the European Respiratory Society, German Society of Pneumology, and Paul Ehrlich Gesellschaft. Dr. Zimmerman is a member of the ACP, AACP, and WFPICCS. Dr. Levy is a legal consultant for a few cases involving sepsis and serves as co-chair of the Surviving Sepsis Campaign Steering Committee. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, Email: leevans@uw.edu

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