Surviving Sepsis Campaign Research Priorities 2023

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OBJECTIVES: To identify research priorities in the management, epidemiology, outcome, and pathophysiology of sepsis and septic shock.

DESIGN: Shortly after publication of the most recent Surviving Sepsis Campaign Guidelines, the Surviving Sepsis Research Committee, a multiprofessional group of 16 international experts representing the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, convened virtually and iteratively developed the article and recommendations, which represents an update from the 2018 Surviving Sepsis Campaign Research Priorities.

METHODS: Each task force member submitted five research questions on any sepsis-related subject. Committee members then independently ranked their top three priorities from the list generated. The highest rated clinical and basic science questions were developed into the current article.

RESULTS: A total of 81 questions were submitted. After merging similar questions, there were 34 clinical and ten basic science research questions submitted for voting. The five top clinical priorities were as follows: 1) what is the best strategy for screening and identification of patients with sepsis, and can predictive modeling assist in real-time recognition of sepsis? 2) what causes organ injury and dysfunction in sepsis, how should it be defined, and how can it be detected? 3) how should fluid resuscitation be individualized initially and beyond? 4) what is the best vasopressor approach for treating the different phases of septic shock? and 5) can a personalized/precision medicine approach identify optimal therapies to improve patient outcomes? The five top basic science priorities were as follows: 1) How can we improve animal models so that they more closely resemble sepsis in humans? 2) What outcome variables maximize correlations between human sepsis and animal models and are therefore most appropriate to use in both? 3) How does sepsis affect the brain, and how do sepsis-induced brain alterations contribute to organ dysfunction? How does sepsis affect interactions between neural, endocrine, and immune systems? 4) How does the microbiome affect sepsis pathobiology? 5) How do genetics and epigenetics influence the development of sepsis, the course of sepsis and the response to treatments for sepsis?

CONCLUSIONS: Knowledge advances in multiple clinical domains have been incorporated in progressive iterations of the Surviving Sepsis Campaign guidelines, allowing for evidence-based recommendations for short- and long-term management of sepsis. However, the strength of existing evidence is modest with significant knowledge gaps and mortality from sepsis remains high. The priorities identified represent a roadmap for research in sepsis and septic shock.

KEYWORDS: fluids; organ failure; precision medicine; sepsis management; sepsis recognition; vasopressors

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Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). Sepsis affected nearly 50 million people per year worldwide before the COVID pandemic and continues to be associated with a high risk of death (2, 3).

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DOI: 10.1097/CCM.0000000000006135

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KEY POINTS

Question: The Surviving Sepsis Research Committee aimed to identify clinical and basic science research priorities in sepsis and septic shock.

Findings: An international multiprofessional panel of sepsis experts identified five top clinical and five top basic and translational science research priorities that, if answered, should provide insight into the pathobiology of sepsis, and identify novel treatment approaches to improve patient outcomes.

Meaning: The priorities identified represent a roadmap for research in sepsis and septic shock.

The Surviving Sepsis Campaign (SSC) is dedicated to reducing mortality from sepsis. Over the last 17 years, the SSC has released five sets of guidelines for the management of sepsis in adults, with the most recent being published in 2021 (4, 5). Despite knowledge gained from multiple important studies and clinical trials, many issues remain unaddressed or insufficiently resolved by the available data. Also, there remain fundamental gaps in the understanding of the pathobiology of sepsis-induced organ dysfunction and failure and the processes that prevent and/or lead to the resolution of sepsis and its complications, and it is extraordinarily difficult to fully recapitulate the human response to and basic management of sepsis in animal models. These latter issues hinder the ability to develop sepsis-directed therapies. Accordingly, gaps in the evidence frequently exist, leading to insufficient clarity on many elements of sepsis management and precluding recommendations on many topics. In fact, of 93 statements, only 15 strong recommendations were issued in the most recent SSC guidelines. In comparison, there were 54 weak recommendations, 15 best practice statements, and nine questions for which no recommendation could be made. In addition to knowledge gaps on clinical care, there are also significant gaps in the basic understanding of sepsis, which, if answered, would help focus the design of new trials and lead to possible substantial changes in bedside therapy of septic patients.

To determine priorities for research within the field of sepsis, the SSC created a research committee that was explicitly charged with developing a list of research priorities related to sepsis. The intention was to address all aspects of sepsis instead of being constrained solely to topics covered within the guidelines. The SSC research committee published a list of 26 priorities, including the top six clinical priorities and five basic science priorities in 2018 (6, 7), and more detailed descriptions of the priorities (8–13) and COVID research priorities (14). Since then, multiple trials and basic science articles have been published, addressing some of these questions, generating new knowledge but also further gaps in knowledge. After the most recent SSC guidelines were published, a new research committee was appointed to determine updated research priorities for improving understanding, management, and outcomes from sepsis.

METHODS

Sponsorship

Funding for the committee was provided by Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM). No outside funding was received for any portion of the committee's work.

Selection and Organization of the Committee

The presidents of ESICM and SCCM appointed six committee members each (including one co-chair [D.D.B., C.M.C.], respectively). Committee members were chosen based on expertise in a diverse array of sepsis-related subjects. In addition, diversity (broadly defined and including geography, sex, profession, and specialty) was expressly considered when populating the committee. The co-chairs of the SSC adult (M.A., H.C.P.) and children (N.K., P.T.) guidelines also served as committee members. Unlike the SSC guidelines where all endorsing organizations appoint a representative to the panel before its work, no societies outside of SCCM and ESICM nominated any members.

Determination of Research Questions and Priorities

Each committee member was asked to submit approximately five research questions on any subject they felt would improve their understanding of sepsis pathobiology, epidemiology, management, or outcome. Respondents were instructed to pick their top

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priorities, explicitly not restricting this to any particular area with the expectation that this open-ended approach would lead to research questions spanning a broad spectrum of unanswered essential questions related to sepsis. A total of 81 questions were submitted. When questions covering very similar topics were independently submitted by different committee members, they were grouped together into a single question by the Committee Chairs and validated by panel members before voting. The newly created grouping questions encompassed the original questions of the panel as subquestions. No question was deleted during that process. As a result, the list was narrowed to 34 clinical questions and ten basic research questions (**Fig. 1**). It was decided in a pre hoc manner that the article would detail five clinical and five basic research questions deemed to be of highest priority. Committee members were independently asked to rank their top three priorities. Choices were weighted so that each respondent's first choice was worth three points, the second choice was worth two points, and the third choice was worth one point. The votes were collected and aggregated by a SCCM staff member. The votes of each panel member were not known by other members, including committee co-chairs. Only the final results of the votes were communicated to the panel. Prioritization yielded the top five most important clinical questions (**Table 1**), some having several subquestions. We note that the questions are not listed in priority order as they are all felt to be of equal importance. Rather, they are presented in the order of sequence in the clinical management of septic patients.

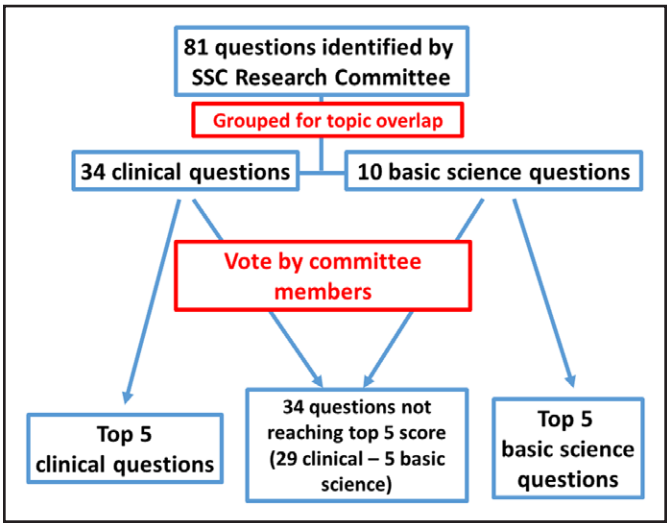

Figure 1. Selection process of the top clinical and basic science questions. SSC = Surviving Sepsis Campaign.

Additionally, basic and translational science (BTS) questions were prioritized in a separate vote, as the committee did not feel it was possible to directly compare these with more immediately clinically relevant questions. Prioritization yielded the top five most important BTS questions (Table 1). All questions that were submitted by at least one committee member but not judged as being a top five clinical or basic science question are shown in **Table 2**. A pre hoc decision was made to have a standardized method of describing clinical questions with distinct sections comprising "what is known," "gaps in knowledge/critique of evidence," and "future directions." While basic science questions also have a standardized description, the method used was distinct. Thus, we used a holistic approach, which was required because the voluminous knowledge might itself fill an article. In addition, we recognized that gaps in knowledge and future directions might incorporate techniques and/or intellectual advances that do not yet exist. We acknowledge that significantly less is known about sepsis management in resource-limited environments. While each priority includes questions that are applicable regardless of location, different approaches and experimental designs may be required to answer research questions in resource-limited settings, and this should be a topic for a separate working group.

Conflict of Interest

The process of conflict of interest (COI) reporting relied on personal disclosure identical to the approach used in the SSC guidelines, and both of the co-chairs of COI in the most recent SSC guidelines (M.A., C.M.C.) were members of the research committee. No industry input was obtained for any portion of the process.

RESULTS

Each research priority was felt to be highly significant, so the committee did not attempt to distinguish the relative importance of each.

Question 1:

What is the best strategy for screening and identification of patients with sepsis? Can predictive modeling be used in real-time to assist recognition of sepsis?

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TABLE 1.
Top Research Priorities

Top Clinical Priorities
What is the best strategy for screening and identification of patients with sepsis? Can predictive modeling be used in real-time to assist recognition of sepsis?
Organ injury and dysfunction in sepsis: what cause it, how to define, how to detect?
How should fluid resuscitation be individualized? (Initial and beyond)?
What is the best vasopressor approach for treating the different phases of septic shock?
Can a personalized/precision medicine approach identify optimal therapies to improve patient outcomes?
Top Basic Science Priorities
How can we improve animal models so that they more closely resemble sepsis in humans?
What outcome variable maximizes correlations between animal models and human sepsis and is therefore most appropriate to use in both?
How does sepsis affect specific regions of the brain that modulate pulmonary, cardiovascular, hepatic, renal, and gastrointestinal function? And how do sepsis-induced alterations in these regions contribute to organ dysfunction? How does sepsis affect interactions between neural, endocrine and immune systems?
How does the microbiome affect sepsis pathobiology? How does sepsis pathobiology contribute to the "pathobiome," which may also be affected by the use of antibiotics?
How do genetics and epigenetics influence the development of sepsis, the course of sepsis and the response to treatments for sepsis?

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What Is Known. The 2021 SSC guidelines strongly recommend that health systems have a performance improvement program for sepsis, including screening for sepsis (4). Timely identification is crucial since delays in treatment are associated with worse outcomes (15–18). However, the guidelines were unable to recommend any approach to screening.

Identification of sepsis requires recognition of infection and acute organ dysfunction and determination that the acute organ dysfunction is due to a dysregulated host response (1). In practice, however, many screening tools have been developed and validated for predicting clinical deterioration (transfer to ICU) or poor outcomes (mortality). Before publication of the most recent definitions of sepsis (1), the criteria that comprise the systemic inflammatory response syndrome (SIRS) were used to identify patients with a high likelihood of having the disorder. SIRS criteria for sepsis diagnosis were implemented in several improvement quality initiatives for many years (15, 19, 20). However, SIRS criteria failed to identify one in eight cases of sepsis (21). With the new definitions of sepsis, several other sepsis identifiers were proposed. Initially, the quick Sequential Organ Failure Assessment (qSOFA) was proposed to predict hospital mortality or ICU length of stay greater than 3 days (22). In a retrospective study of 500,000 hospitalizations, the National Early Warning Score (NEWS) outperformed Modified Early Warning Score, qSOFA, and SIRS for predicting in-hospital mortality among both emergency department (ED) and ward patients with suspected infections (23). In contrast, a meta-analysis of 26 studies demonstrated that qSOFA had higher prognostic accuracy than NEWS or SIRS (24). However, while these tools are simple and help to identify risk for clinical deterioration or poor outcomes, they are not specific to sepsis. These tools may increase suspicion with varying sensitivity and specificity but cannot make a diagnosis (25).

There has been strong interest in leveraging the electronic health record (EHR) to implement more sophisticated algorithms for identifying sepsis. Several algorithms have been developed and assessed in retrospective data, showing strong discriminative ability (26–29). However, these were based on coding and/or clinical data suggestive of sepsis, which depend on accuracy of the underlying definition in the absence of gold standard. These reference data were also retrospectively obtained after several hours of evolution, and algorithms may fail to match the criteria for prospective timely diagnosis, especially when the full pattern is not

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TABLE 2.
Other Research Priorities

Other Clinical Priorities
Should immunosuppressed patients be included in surviving sepsis campaign recommendations?
Does obesity affect sepsis outcomes? Obese patients can be subclassified based on their metabolic health. Does metabolic health (obese healthy/obese not healthy) affect outcomes?
What is the ideal hemodynamic monitoring tool (or association of tools/clinical signs/biomarkers) to apply to septic shock patients (beyond mean arterial pressure)?
How to better define right ventricular failure, for which therapeutic consequence (fluids, vasopressors, respiratory settings)?
How to better characterize LV systolic dysfunction? Do we need to treat LV systolic dysfunction, and if so, for which subgroups of patients and which treatment (dobutamine, norepinephrine, other inotropes, ECMO venoarterial…)?
Can epinephrine be used as an inotropic agent?
How is bacterial sepsis different than viral, fungal or parasitic sepsis?
What mechanisms underlie sepsis-induced cellular and subcellular dysfunction?
Are there methods to determine the status of the immune response (pro vs. anti-inflammatory) to guide precision therapy?
How to induce immunity after sepsis? Can the immune system be modulated post-sepsis to reduce risk for recurrent sepsis?
How do sepsis-induced changes in endocrine activity affect inflammation? Do they contribute to a state of excessive inflammation? To immunosuppression?
Does reversing immunosuppression improve sepsis outcomes?
Can we diagnose infection rapidly upon presentation? What is the role of molecular testing in the early phase and beyond?
Should new antibiotics be reserved for targeted treatment of empiric therapy?
Should antifungal drugs be included in the treatment of patients with multiple organ failure without clinical improvement and negative cultures?
Does any O_2 saturation target to be achieved in patients with sepsis/septic shock exist?
Should the use of ECMO be indicated in patients with acute respiratory distress syndrome with sepsis and MOF?
What are the indications for noninvasive (noninvasive ventilation or high-flow oxygen therapy) and invasive respiratory support in patients with sepsis/septic shock? Does it affect outcome?
What are the optimal targets/endpoints for resuscitation? How to determine the time point where individual organs have reached their capacity (to cope) and organ support is needed?
What is the global burden of morbidity and mortality from sepsis?
Should sepsis definition operationalization be different depending on resources?
What is the role of multilevel omics and other biomarkers in the diagnosis and treatment of sepsis?
How to monitor vascular permeability in clinical practice?
Do racial and socioeconomic inequities contribute to sepsis outcomes? If so, how?
Is there a room for antagonist of interleukin-6 receptor?
Is there a room for systematic corticosteroids in sepsis-related pneumonia?
Is Grading of Recommendations Assessment, Development, and Evaluation still the best system to evaluate the evidence and to produce guidelines?
What interventions in the ICU/hospital will lead to better long-term sepsis outcomes? How do therapies during the acute phase of sepsis affect intermediate and long-term outcomes (morbidity and mortality)? What are the best tools to screen for new morbidity (functional impairment, cognitive impairment) after sepsis? What should be the ideal rehabilitation program after hospital discharge of a severe episode of sepsis or septic shock?
Should studies “about sepsis” actually demonstrate organ dysfunction?

(*Continued*)

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TABLE 2. (*Continued*)
Other Research Priorities

Other Basic Science Priorities
Why do infections sometimes progress to sepsis? What defines a "dysregulated" host response to infection?
What factors predict mortality or recovery from sepsis? Are there modifiable risk factors for bad outcomes of sepsis that can be identified at or shortly after the time of sepsis diagnosis?
How to promote repair after sepsis induced organ injury without stimulating fibrosis? What determines activation of repair vs. stimulation of fibrosis? Can it be manipulated?
What are the roles of exosomes and extracellular vesicles in promoting, or conversely, protect against the septic shock and organ failure? Extracellular vesicles serve as vehicles for transfer of proteins, lipids, and RNA between cells and are a means of intercellular communication
How do fixed cell populations (e.g., neurons, endothelial cells, epithelial cells, tissue leukocytes) contribute to beneficial and pathologic responses in sepsis?

ECMO = extracorporeal membrane oxygenation, LV = left ventricular.

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yet developed. Ultimately, algorithms must lead to better or faster treatment than would have been provided without decision support. Several pre-post and observational cohort studies have shown improved care processes and outcomes following the implementation of sepsis screening algorithms (30, 31). However, delayed and false alarms remain problematic. In a recent evaluation of a widely used proprietary sepsis prediction model, 93% of patients identified as having sepsis were already receiving antibiotics by the time of the alarm (32). Further, the model did not identify 67% of patients with sepsis despite generating alerts in nearly 20% of hospitalized patients, thus creating a large burden of alert fatigue while having poor discrimination and calibration in predicting the onset of sepsis.

Gaps in Knowledge/Critique of Evidence. The best screening tool(s) for sepsis is unknown. Without standards for diagnosing infection, sepsis, dysregulated host response, or organ dysfunction that are both accurate and generalizable, it will be difficult to create them. Despite the interest and growth in automated sepsis screening models, high-quality evidence of benefit over routine care is lacking (33). A Cochrane review of automated monitoring vs. standard care identified only very low-quality evidence that precluded drawing any meaningful conclusions (34). While two randomized controlled trial (RCT) have suggested benefit of automated sepsis screening, they were relatively small (19, 35) and should be viewed as exploratory.

Future Directions. Studies are required to determine sepsis algorithms that are generalizable to different EHRs, have adequate sensitivity, specificity, and positive predictive value to be incorporated into clinical workflow. Further, studies are required to test if automated sepsis algorithms improve outcomes compared with routine care. These studies should not solely include large-scale observational studies allowing to ensure external validity of the algorithms but also RCTs evaluating prospectively the added value of the algorithms. These RCTs should ideally be designed as cluster RCTs that randomize units or hospitals to having the alert in "live mode" vs. "silent mode" and then comparing outcomes (including not only patient-related outcomes but also the impact on the healthcare system). Algorithms should accelerate sepsis recognition, trigger timely treatment, and be tuned to minimize alarm fatigue driven by erroneous or unneeded triggering. Questions to be addressed in future studies include: 1) what defines a dysregulated host response to infection? 2) how should sepsis algorithms be trained, and what should be used as gold standard against which to train sepsis algorithms? 3) how is automated sepsis screening best implemented into clinical workflow? 4) when implemented well, can automated sepsis screening algorithms improve care processes and outcomes compared with usual care? and 5) how is sepsis screening best implemented in lower resourced settings?

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Question 2: What Causes Organ Injury and Dysfunction in Sepsis, How Should It Be Defined and How Can It Be Detected?

2A: What Causes Organ Injury and Dysfunction in Sepsis?

What is known. Immune and endothelial cell dysfunction, impaired neural mechanisms, cellular and metabolic dysregulation, microvascular dysfunction, compromised oxygen delivery or utilization, endocrinopathy, mitochondrial dysfunction, and abnormalities in transcellular signal transduction have all been implicated in the pathobiology of sepsis-induced organ injury and dysfunction (multiple organ dysfunction score [MODS]) (36–39). Studies in cells, animals, and humans suggest that endothelial cells contribute to the host response to sepsis and that sepsis induces endothelial dysfunction that promotes organ injury and failure (40, 41). Animal and human data support roles for cellular metabolic block in organ dysfunction and failure (42–46). Numerous studies have implicated mitochondrial dysfunction in the pathogenesis of sepsis-induced organ dysfunction (42, 47–49), even though this has been challenged by others (50). Studies have identified roles for cytochrome C oxidase dysfunction in sepsis and promising roles for the restoration of cytochrome C oxidase activation in improving sepsis-induced mitochondrial dysfunction (47, 51). Differences in metabolomic profiles of patients are predictive of sepsis outcomes, and studies have demonstrated associations between metabolic profiles, the immune status, the endothelium, and the development of MODS (52, 53). Finally, there has been progress in identifying the roles of the CNS and peripheral nervous system in regulating inflammation and organ responses to sepsis (54–59).

Gaps in knowledge/critique of evidence. The roles of noncirculating cells (e.g., endothelial cells, pericytes, marginated leukocytes, tissue macrophages, neurons, microglia, astrocytes, etc.) are not well understood. These are mainly being studied in vitro and in animal models, whereas human studies use blood biomarkers as proxies of organ functions (40, 41). Much of the work to date has used reductionistic systems, studying individual cell lineages, and focusing primarily on immune cells. The role of inadequate communication/interaction between organ systems, through circulating (immune, endocrine, microparticles) and noncirculating (neuronal, endothelial) cells, requires clarification.

After 2 decades of experimental research supporting an important role for the vagus nerve in regulating inflammatory responses and outcomes of sepsis (54, 56, 60), the role of vagal nerve stimulation in patients with sepsis remains largely unaddressed. In a pilot RCT, transcutaneous auricular vagus nerve stimulation decreased inflammatory cytokines but did not affect organ function (61). Similarly, direct interventions on peripheral nervous system failed to improve kidney function (58, 59).

The relationship between organ injury and dysfunction is poorly understood, and there is a lack of understanding of what constitutes an adaptive vs. a maladaptive response to sepsis. Clarity is lacking about the role of sepsis vs. host comorbidities in organ dysfunction. We do not fully understand what represents adequate organ function. This makes it difficult to study the pathobiology of organ injury and dysfunction.

Future directions. The development of methods to study human cellular and tissue responses to sepsis in real time would be enormously helpful to our understanding of how sepsis affects organs individually and collectively. There is a need to devise better methods to explore the organ and tissue specific pathophysiology and to improve our understanding of the role of noncirculating cells. Additionally, work is needed to determine how sepsis affects cells within organs, what constitutes an adaptive vs. maladaptive cellular and organ response to sepsis, and how organ and systems interactions contribute to healthy and maladaptive responses during sepsis.

2B: How Do We Identify Organ Dysfunction?

What is known. Patients with sepsis develop a constellation of laboratory and physiologic indices that track with disease severity and outcomes. Currently, the diagnoses of organ injury and/or dysfunction rely on proxies, such as commonly obtained laboratory tests (e.g., arterial blood gases, liver function tests, creatinine, and coagulation markers) and radiographic findings. In 2016, the Sepsis-3 task force revised and clarified the definitions of sepsis and septic shock (1). In addition to clarifying that sepsis is defined as "life threatening organ dysfunction caused by a dysregulated host response to infection," they focused on the use of the SOFA, which incorporates laboratory variables and interventions (62), to identify sepsis at the bedside. Baseline elevations or increasing SOFA scores positively correlate with mortality (1).

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Gaps in knowledge/critique of evidence. There remains a lack of clarity regarding the line separating adaptive and maladaptive function, in large part because of a lack of gold standard criteria. Clinical research relies on organ failure proxies rather than the direct measurements of organ function. Differentiating organ injury from organ dysfunction remains problematic.

It should be noted that some elements of the SOFA score are no longer used clinically, alternative vasopressor agents are used, and some organs are not included in the SOFA score, which altogether suggests that the SOFA score should be revised (63).

Future directions. The definitions of organ injury and dysfunction need to be further clarified. Methods to assess organ function, either through biologic activity or closer proxies to function-related activities, would help to then identify dysfunction. As organs usually have several metabolic pathways (e.g., kidneys, liver), the question is whether one functional or multiple pathways should be investigated, and how to prioritize these? If such endpoints are to be helpful, they would need to be understood in the context of pathobiology, whether they are intrinsic or extrinsic, how they are elicited, and by what mechanisms. The development of practical methods to directly assess organ function in humans, without relying on surrogate measurements, would help to drive forward the understanding of organ injury and dysfunction.

2C: Can Blood Biomarkers (e.g., Cytokines, Chemokines, Lipid Mediators, Metabolites) and/or Activation Profiles of Circulating Leukocytes and Platelets Be Used to Understand What Is Happening Within Specific Organs?

What is known. Biomarkers may be used to identify organ injury and dysfunction and to track responses to treatments. Some may roughly reflect the magnitude of the organ pathology—for example, liver injury (increasing transaminases levels), liver dysfunction (e.g., modestly increased bilirubin levels), liver failure (high bilirubin, profound coagulopathy), but there are, admittedly, many confounders. Human studies have demonstrated alterations in levels of numerous biomarkers in sepsis, and their correlation with organ failure and mortality, including markers of endothelial activation and injury, long noncoding RNAs, cancer protein biomarkers, and brain natriuretic peptide (64–68). Markers of leukocyte activation and function also associate with sepsis outcomes (67, 69–72). RBC and platelet parameters may predict sepsis severity and outcomes (73–75).

Gaps in knowledge/critique of evidence. The utility of using biomarkers, cells and platelets to understand the pathobiology of sepsis at the tissue and organ levels remains unclear. Circulating microparticles are increased in sepsis but their protective or detrimental effects should be clarified. An important limitation of many biomarkers is that they do not inform on the exact process explaining the rise in biomarker. Some markers may be more specific or more informative of the process but direct mechanistic links between most biomarkers and organ pathologies have yet to be characterized. There continues to be a lack of data confirming that circulating biomarkers reflect what is going on at the tissue level (e.g., nervous system, adipose tissue, vasculature, interstitial spaces). Accordingly, there remains a lack of clarity in their utility in identifying and tracking organ dysfunction or directing therapies.

Future directions. Continued innovation in methods to use combination of clinical features, functional measurements, and laboratory endpoints (e.g., imaging, biomarkers, physiologic, neurocognitive) is required to understand the pathobiology and progression of organ injury and dysfunction and to guide human sepsis studies. Further delineation of the relationship between specific biomarkers or patterns of biomarkers, single or multiple organ injury or dysfunction is needed.

Question 3: How Should Fluid Resuscitation Be Individualized, Initially and Beyond?

3A: What Is the Optimal Fluid Management in the First 24 Hours of the Septic Patient With Hypotension or Hypoperfusion?

What is known. The initial fluid management of patients with sepsis is an important aspect of therapy that has been debated for years. Despite being one of the most common interventions in the critically ill, evidence to guide fluid resuscitation in patients with sepsis is scant. The current SSC guidelines suggest a fixed early resuscitation of 30 mL/kg bolus of balanced crystalloids for septic patients with hypotension (mean arterial pressure [MAP] < 65 mm Hg) or hypoperfusion (lactate > 4 mmol/L). This volume of fluid recommended is based on retrospective studies (76) and observations from RCTs of hemodynamic management of sepsis (77, 78)

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showing that, on average, patients received 30 mL/kg of fluid before randomization, suggesting this is standard clinical practice. Evidence to guide fluid management of septic shock after initial fluid resuscitation is sparse (79–81). The present SSC guidelines suggest additional fluid infusion be guided by dynamic hemodynamic variables and issue no recommendation regarding liberal or restrictive fluid strategy due to insufficient data (4). Since publication of the SSC guidelines, two large multicenter RCTs failed to demonstrate a difference in outcome using either a liberal or restrictive fluid strategy (79, 80); furthermore, no difference was detected in mortality, health-related quality of life, or cognitive function 1 year after randomization (82).

Gaps in knowledge/critique of evidence. There is a need for studies to determine the optimal regimen of fluid resuscitation during sepsis with hypotension and hypoperfusion, not only for initial but also ongoing resuscitation. The current recommendation of fixed volume resuscitation is loosely supported, and while this approximate value may be beneficial in many patients, it is difficult to believe this precise amount of resuscitation is needed or beneficial in all patients regardless of individual factors such as comorbidities, severity of illness, and perhaps source of sepsis (83). In quality improvement studies, fluid resuscitation is part of a bundle that includes early recognition and antibiotics and that is associated with improved mortality (15, 84–86). However, the relative contribution of each element of the bundle is unknown. Additionally, studies that assessed the appropriate timing for fluid resuscitation were confounded by their observational design.

Early administration of vasopressors may help to limit fluid resuscitation volume (87) and even improve the response to a fluid bolus (88).The approach of modest fluid resuscitation and early initiation of vasopressors during initial management of sepsis with hypotension or hypoperfusion has gained attention in the last years (87). While no difference was seen with liberal vs. restrictive fluids in two RCTs (79, 80), approximately one-third of the patients in the trial conducted in the ED did not require ICU management (80). There was approximately a 2 L fluid difference between groups in both studies, which may not be enough to generate outcome differences. Finally, approximately 20% of patients in both arms of the ED study were already receiving vasopressors at randomization (80) and 100% in the ICU study (79); therefore, these trials do not directly inform on early introduction of vasopressors. While the results were similar in the studies, it does not imply that both approaches can be used indifferently depending on clinician preference. These studies do not provide an answer on best fluid management for septic patients, and especially on individualization of fluid management as all patients in a given group received the same approach. It is likely that some patients with specific conditions benefit from more restrictive or more liberal approaches and others come to harm, but these cohorts still need to be identified.

Future directions. The hemodynamic treatment of sepsis patients clearly would benefit from studies on early fluid resuscitation. One possible approach could include the comparison of a fixed volume of 30 mL/kg crystalloids to less or more fluid based on clinical context. This would be important in settings where the availability of hemodynamic monitoring to guide fluid infusion is scarce. Alternatively, an individualized management integrating clinical context and using dynamic variables or passive leg raising test (PLR) for the prediction of fluid responsiveness should be studied and compared with fixed volume initial resuscitation. Also, strategies of early norepinephrine infusion to limit fluid administration would be important to study and determining whether to start hypotensive patients on fluids first, vasopressors first or both simultaneously.

3B: What Is the Best Hemodynamic Tool to Predict Fluid Responsiveness in the Septic Patient in the Early Resuscitation Phase?

What is known. The proportion of patients responding to fluids rapidly decreases over the course of resuscitation, even though perfusion abnormalities are still observed (89). Repeated fluid boluses increase the risk of fluid overload and are associated with worse outcomes in patients with septic shock (90). Therefore, after initial resuscitation, predicting fluid responsiveness should allow restriction of fluid administration to patients likely to respond to fluids (91). Dynamic indices and PLR better predict fluid responsiveness than static parameters (92). Dynamic indices are based on heart-lung interaction (93) and include respiratory variations of pulse pressure or stroke volume (94), respiratory variations in vena cava size (95), end-expiratory pause (96), tidal volume (Vt) challenge (97), and sigh (98) or positive end-expiratory pressure

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test (99). The common limitations of these indices are spontaneous breathing, low lung compliance, ventilation using low Vt, right ventricular dysfunction, and arrhythmias (92, 100, 101). PLR induced changes in cardiac output (CO) may be an alternative to reliably predict fluid responsiveness, can be used in patients under spontaneous or mechanical ventilation, and can overcome most of the limitations of the tests using heart-lung interactions (102),.

Gaps in knowledge/critique of evidence. While PLR is attractive, it requires measurement of CO, which may not always be available (102). The use of plethysmography (103) or capillary refill time (CRT) (104) during PLR appears promising but needs to be evaluated further. In ventilated patients, changes in end-tidal CO_2 may be used to reflect changes in CO, but these changes are usually relatively small (105). Ventilation using low Vt is the most common limitation of the tests predicting fluid responsiveness using heart-lung interactions (100). Although the Vt challenge has conceptual appeal and is evidence-based (92, 97, 106), its value in unselected populations remains to be evaluated. Each test assessing fluid responsiveness is associated with an indeterminate/gray zone (107), making clinical decision-making challenging much of the time. While the different dynamic variables have different diagnostic capacities (95), whether combining different tests improves diagnostic accuracy is unknown. In post-surgical patients, incorporating dynamic assessment of fluid responsiveness into goal-directed therapy has shown improved outcomes including reduced mortality (108). However, the impact on outcome in patients with septic shock is less clear, even though studies have shown a reduction in the amount of fluid (81, 109).

Future directions. Large studies comparing the diagnostic accuracy of the different tests and indices to predict fluid responsiveness are required. In addition, it is important to explore which tests are most valuable in specific settings, such as spontaneous breathing, low lung compliance, and right ventricular dysfunction, and whether a combination of tests provides added value. Finally, studies assessing the impact on outcomes of resuscitative strategies using fluid responsiveness prediction should be performed.

3C: What Measures Predict Optimal Fluid Resuscitation?

What is known. Optimal fluid resuscitation is usually based on improvement in tissue perfusion in a fluid-responsive patient without signs of poor fluid tolerance. Clinical variables, such as urine output, level of consciousness, mottling of the skin, or CRT, are easy means to assess tissue perfusion, especially in resource-constrained settings. During the early phase of septic shock, peripheral perfusion-guided resuscitation is likely associated with lower mortality, faster recovery of organ dysfunction, and reduced use of therapeutic interventions compared with lactate-targeted resuscitation (89). Using assessment of peripheral perfusion with CRT to guide resuscitation resulted in a significant reduction in the fluids administered (110).

Biological indices, such as mixed venous oxygen saturation (Svo_2)/central venous oxygen saturation ($Scvo_2$), blood lactate, and venoarterial carbon dioxide ($Pvaco_2$), are presently used at the bedside to assess adequacy of CO (111). A low $Scvo_2$ (used as a surrogate for Svo_2) suggests inadequate oxygen delivery and that increasing CO is an option when shock persists although the appropriate treatment depends upon type of shock and if a mixed shock state is present. In shock states, high $Pvaco_2$ values (> 6 mm Hg) are associated with poor outcome (112). Microcirculatory abnormalities are common in patients with septic shock (113), and their duration and severity are associated with organ failure and mortality (37). Persistent hyperlactatemia can be a signal of tissue hypoperfusion in patients with septic shock and therefore lactate measurements can be used to guide resuscitation (4). Following initial resuscitation, the correlation between the sublingual microcirculation and systemic hemodynamics is often poor, and fluid administration improves the microcirculation only in early sepsis (114). Additionally, apart from $Pvaco_2$, surrogate markers for assessing tissue perfusion correlate poorly with sublingual microcirculatory changes (115).

Evaluating fluid intolerance is even more complex. It usually relies on a combination of clinical signs (edema), biologic (Pao_2/Fio_2), hemodynamic, and echographic variables (91). Of note, none can be taken in isolation. As an example, patients with edema may still be fluid responsive (116), as intravascular volume and total volume may not be in equilibrium in patients

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with significant capillary leak, while patients with signs of dehydration may not be fluid-responsive.

Gaps in knowledge/critique of evidence. While hypotension is often used to trigger fluid administration (117), the effects of fluids on MAP are highly variable. More importantly, fluid administration aims to increase tissue perfusion but MAP is a poor index of tissue perfusion. The response of the various tissue perfusion indices (e.g., $ScVO_2$, blood lactate, $PvaCO_2$, microcirculation) to fluid administration remains poorly defined. Urine output may be altered by many other factors and may thus fail to represent tissue hypoperfusion.

The different perfusion variables have different time to normalization (118, 119). Accordingly, there is uncertainty about the optimal value for a patient at a given time. Although $PvaCO_2$ has shown good prognostic value, it is uncertain whether resuscitation should reduce or normalize $PvaCO_2$, and whether resuscitation therapies based on the $PvaCO_2$ can improve outcome. Additionally, hyperlactatemia is a nonspecific marker of hypoperfusion, and lactate decrease is slow. Therefore, pursuing lactate normalization without evaluating simultaneously tissue perfusion may lead to fluid overload, potentially increasing mortality or morbidity (110). Microcirculation-targeted resuscitation is appealing (120) but clinical trials are lacking. Which (if any) specific microcirculatory variables should be used, what their target values should be and what level of improvement in the microcirculation should be considered optimal during fluid resuscitation is unknown. These essential questions should be addressed before investigating whether microcirculation-targeted therapy improves outcomes. A microcirculation-targeted therapy trial was recently published, but clinicians failed to follow microcirculation-based recommendations in two thirds of the cases (121).

CRT targeted resuscitation appears promising but there is no standardization of the technique yet, which could decrease inter-rater reliability. Outcome studies compared CRT to lactate based strategies, but no other head-to-head comparisons have been performed.

Future directions. While different perfusion variables are currently used to trigger fluid administration, studies should better characterize the response of these variables to fluids. More studies are required to determine the thresholds of the various indices to define optimal fluid resuscitation (any improvement? Or normalization?). Studies should determine whether there is a benefit of combining various markers of tissue perfusion on optimal fluid resuscitation and outcomes. Outcome studies using CRT-targeted resuscitation should be performed in various subphenotypes of septic shock.

3D: Which Is the Best Fluid for Initial Resuscitation of Sepsis-Induced Hypoperfusion?

What is known. Crystalloid fluid administration is recommended for initial fluid therapy during sepsis resuscitation in the most recent SSC guidelines (4). Additionally, SSC suggests using balanced crystalloids over saline. There has been a long-standing debate about whether balanced crystalloids are superior to saline 0.9% for resuscitation, owing to the risk of inducing hyperchloremic acidosis with saline. The suggestion for balanced crystalloids was based upon a single center pragmatic, cluster-randomized multiple-crossover trial demonstrating improvement in a composite outcome of mortality, need for renal replacement therapy (RRT) and acute kidney injury (AKI) in critically ill patients randomized to receive balanced crystalloids vs. saline 0.9% (122). However, new evidence has arisen since publication of the SSC guidelines. A multifaced implementation program including preferential use of balanced crystalloids over saline 0.9% was associated with a reduction of major kidney events (123), confirming the results of another sequential period interventional study (124). Two large multicenter RCTs failed to demonstrate a benefit with balanced crystalloids (125, 126). A post hoc analysis of these trials suggested some benefit in septic shock patients receiving only balanced crystalloids already from the preenrollment period (127, 128). A meta-analysis including six low risk of bias RCTs and reaching nearly 35,000 critically ill patients, demonstrated a high probability (89.5%) of decreased 90-day mortality using Bayesian analysis, with an estimated effect ranging from a 9% reduction to a 1% increase in mortality with the use of balanced solutions (129). However, the authors acknowledge that using frequentist statistics (which have a dichotomized yes/no answer); the CIs would lead to a conclusion that balanced solutions do not decrease mortality.

Separately, a meta-analysis including 69 studies with over 30,000 patients compared colloids to crystalloids in critical illness (not sepsis specifically) (130). This demonstrated that using starches, dextrans,

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or albumin (moderate-certainty evidence), or gelatins (low-certainty evidence) probably makes little or no difference in mortality compared with crystalloids. However, additional effects may be considered. Starches slightly increase the need for blood transfusion and RRT (moderate-certainty evidence), whereas albumin does not change the need for RRT (low-certainty evidence). Accordingly, the SSC guidelines recommend against using starches for resuscitation while suggesting using albumin in patients who received large volumes of crystalloids (4). Human albumin has pleiotropic properties (including antioxidant and anti-inflammatory effects, glycocalyx stabilization, positive inotropic effect), which make it a fluid of potential interest for initial resuscitation of patients with sepsis and septic shock (131). Small volumes of 20% human albumin can improve hemodynamics with lower daily fluid balance (132).

Gaps in knowledge/critique of evidence. The optimal crystalloid to use in resuscitation is unclear. While saline 0.9% should clearly be avoided in patients with hyperchloremia and may be avoided in patients who will require multiple liters of resuscitation, it is unclear if there is a difference between balanced crystalloids in septic patients without hyperchloremia requiring only a modest amount of resuscitation fluids (133, 134). Admittedly, it is sometimes difficult to predict which patient may require large volumes, but stopping administration of saline 0.9% when chloride levels rise is easy. Beneficial effects of balanced crystalloids were observed in septic patients who received balanced crystalloids already in the preenrollment period, but many factors may confound these nonstratified subgroup analyses (127, 128). Additionally, the composition of nonresuscitative fluid may also be considered (125), as these often constitute the majority of the infused fluids (135). Use of albumin as fluid therapy of choice in comparison with balanced solutions in early sepsis and septic shock is, however, still controversial with mixed results. Some studies suggest that administration of human albumin for resuscitation in septic shock may improve survival (132, 136), while larger most recent meta-analyses in critically ill patients (not sepsis specific) do not show a benefit (130). Of note, these studies did not focus on initial resuscitation, some of the studies included in the meta-analysis are old, and most did not focus on mortality as a primary endpoint (130). Related to this, there are other open questions concerning the cost and equity of choosing human albumin instead of crystalloid.

Future directions. Further studies comparing balanced crystalloids to saline 0.9% in patients without hyperchloremia or acidosis should be performed. Additionally, although the overall ALBumin Italian Outcome Septic Shock (ALBIOS) trial showed no impact of albumin on survival, post hoc subset analysis suggested that albumin administration may improve outcome in septic shock (132). Future trials enrolling only patients in septic shock should be performed. The ALBumin Italian Outcome Septic Shock 2-Balanced study (NCT03654001) comparing albumin, balanced crystalloids and saline 0.9% in a 2×2 factorial design, is one of these. The study has concluded the enrollment of 1272 patients with septic shock and may offer a better insight on the impact of albumin on mortality. Trials should also evaluate what the best time/indicators for introduction of albumin are (early resuscitation? after given volume of crystalloids? according to albumin levels? and if so at which level? in patients with edema?).

Question 4: What Is the Best Vasopressor Approach for Treating the Different Phases of Septic Shock?

4A: What Should Be the Target of Vasopressor Therapy (e.g., Mean Arterial Pressure, Organ-Specific Perfusion Pressure, Diastolic Blood Pressure)?

What is known. The optimal hemodynamic targets to preserve or restore microcirculatory blood flow and improve organ perfusion remain controversial (137). The SSC guidelines recommend an initial MAP target of 65 mm Hg over higher MAP targets (4). However, observational data showed that the risks for mortality and AKI progressively increased as MAP thresholds decreased from 85 to 55 mm Hg (138). Other studies reported similar link between MAP and mortality, with MAP thresholds largely above 65 mm Hg (139, 140). In selected patients with strictly normal perfusion indices, mild hypotension (MAP 60–65 mm Hg) may be tolerated (141). RCTs evaluated different MAP thresholds at the stabilization phase but not at the initial phase. All failed to report improved survival rates with higher compared with lower MAP thresholds (142–144). In all these trials, the actual MAP achieved in the lower MAP group was much higher than the

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target MAP, so that MAP targets lower than 65 mm Hg have not really been tested.

Further, organ blood flow depends on organ-specific perfusion pressure, which is determined by the difference between inflow and either outflow pressure (central venous pressure [CVP]), interstitial or surrounding pressure, whichever is the highest. The autoregulation threshold—the MAP value at which blood flow in the organ is directly dependent on perfusion pressure—varies across organs and is also influenced by preexisting chronic organ damage. Finally, receptor type and density vary between organs, making a uniform approach to vasodilatory shock challenging.

In patients with septic AKI, a mean perfusion pressure (MPP) deficit (defined as the difference between premorbid MPP and MPP achieved during resuscitation) was associated with severe AKI (145). In a pilot study, individualizing MPP targets based on patients' preillness MPP decreased the incidence of AKI (146). Patients with chronic hypertension and patients with naturally low blood pressure (BP) may benefit from adjusted BP targets. In some RCT patients with chronic hypertension benefited from higher MAP targets (142, 143), but another trial failed to reproduce these results (144).

Sepsis is also associated with increased endothelial permeability, leukocyte adhesion, and microvascular blood flow heterogeneity. Microcirculatory dysfunction may persist even when reaching MAP greater than 65 mmg Hg (113, 147).

The primary markers of global tissue perfusion that have been used clinically are $Scvo_2$ or Svo_2, lactate, and $Pvaco_2$ gap. Three RCTs comparing $Scvo_2$-driven protocols to usual care did not support using $Scvo_2$ as a resuscitation endpoint, although importantly, $Scvo_2$ was already within target at inclusion in most patients (148, 149). Lactate is used as a marker of tissue hypoxia, but there are several other causes of hyperlactatemia in sepsis (150, 151). Nevertheless, tissue hypoxia predominates at early stages (152). Further, lactate kinetics typically lags behind other metrics such as $Scvo_2$ and $Pvaco_2$ (89, 119). Last, skin perfusion parameters such as mottling score or CRT have been recognized as essential markers of hypoperfusion. The ANDROMEDA-SHOCK trial did not detect a significant difference in 28-day mortality between CRT and lactate-targeted resuscitations but less organ dysfunction at 72 hours in the CRT-guided cohort (89). This nonsignificant difference in 28-day mortality using frequentist analysis became significant using Bayesian reanalysis (153).

In contrast, in an RCT including patients with shock requiring vasopressors and elevated lactate concentrations, those allocated to incorporation of microcirculatory perfusion monitoring into the therapeutic plan did not show a change in mortality compared with those receiving routine care (121). Attending physicians, however, did not implement therapeutic interventions suggested by microcirculatory analysis in 60% of the cases. Importantly, neither $Scvo_2$, Svo_2, lactate, $Pvaco_2$, CRT, nor sublingual microcirculation monitoring inform about organ-specific perfusion nor indicate a required intervention (154). Indeed, normal values of these variables do not prevent occurrence of perfusion alterations in splanchnic area, kidneys or brain. In addition, when abnormal, these do not indicate which intervention should be favored.

Gaps in knowledge/critique of evidence. Targeting MAP without taking into account other indices of perfusion or vasopressor adverse effects has led to ambiguous results (142–144), so that MAP threshold should not be considered in isolation. There is a need to identify reliable indicators of microcirculatory health that are easily measured at the bedside and organ-specific perfusion targets that can guide physiology-based resuscitation. Trials are ongoing with a targeted tissue perfusion-guided strategy (NCT02579525, NCT05057611). However, the relationship between skin perfusion and organ-specific microcirculation remains unclear. Whether there is a role for specific biomarkers of microcirculation to guide vasopressor therapy is unknown.

Different subphenotypes of sepsis have been identified, but whether they warrant specific vasopressor support or other perfusion targets has yet to be discovered (155). Often the response to vasopressor agents is not taken into account when defining these subphenotypes, even though different trajectories are associated with different outcomes (156). Selecting patients responding to vasopressin may be achieved with the use of a loading dose (157), but this is less likely to occur with other vasopressor agents. It also needs to be determined whether perfusion targets should be adjusted to the phase of sepsis (158). Last, hypotension with a low diastolic arterial pressure (DAP) (e.g., < 40 mm Hg) indicates reduced vascular tone. The role

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of DAP and diastolic shock index (calculated as heart rate divided by DAP) (159, 160) as targets of vasopressor therapy has yet to be investigated.

Future directions. Research is needed comparing currently used hemodynamic variables with a direct evaluation of the perfusion of different key organs (if possible including microvascular within the organ itself) to understand the value and limitations of other techniques. These studies should consider different sepsis subphenotypes, patient comorbidities and phases of resuscitation. Whether direct (i.e., sublingual videomicroscopy) or indirect (e.g., CRT and $Pva{CO_2}$) assessment of microcirculation could be used to individualize BP targets still needs to be evaluated. Knowledge about receptor type and density in different organs may also guide the choice of vasopressor(s), avoiding medications unlikely to improve organ function. Further, studies focusing on preventing specific types of organ dysfunction (i.e., AKI) need to consider the impact on other organs. It is plausible that strategies used to achieve organ-specific perfusion targets may cause unintended dysfunction or harm in other organs. Finally, there is a need for tools (e.g., imaging, biomarkers) that indicate early perfusion/microcirculatory dysfunction and "organ stress" before organ failure occurs to provide opportunities for timely modification and adjustment of the resuscitation strategy.

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4B: What Strategies Optimize Vasopressor Therapy Outcomes?

4B1: When Should Vasopressors Be Initiated?

What is known. Delay in correcting hypotension is associated with increased mortality (161). While some patients may respond to fluid therapy alone, others need vasopressor support. The SSC guidelines do not indicate timing nor guide prioritization of fluids vs. vasopressors. Experimental studies suggest early vasopressor introduction decreases the need for resuscitative fluids (162, 163) and improves tissue perfusion (163). In an observational study using propensity matching, early initiation of norepinephrine was associated with lower fluid volumes administered, a less positive fluid balance and a lower 28-day mortality (87). A small RCT demonstrated that the early use of a fixed dose of norepinephrine after the initial 30 mL/kg of crystalloids was associated with more shock control and less cardiogenic pulmonary edema and arrhythmia (164).

Gaps in knowledge/critique of evidence. There are no reliable tools to determine which patients require immediate vasopressor initiation and those who should receive fluid therapy first. Low DAP or low arterial elastance (165) suggests that the patient would fail to respond to fluid alone. Further, it is unclear which patient-specific characteristics are most important to determine timing and whether any other factors (i.e., type of sepsis including offending pathogen, site of infection, or organ dysfunction patterns) contribute.

Future directions. It is crucial to develop tools (e.g., imaging techniques, biomarkers) that are readily available to identify patients who benefit from immediate vasopressor initiation and patients in whom vasopressor support can be deferred safely. Future vasopressor timing studies should include the comparison of different subphenotypes of sepsis, evaluate the impact of vasopressor timing in patients with variable acute and chronic comorbidities, and evaluate the role of early vasopressor support in patients with sepsis-induced "organ stress."

4B2: In What Circumstances Can Vasopressors Be Delivered Peripherally?

What is known. Vasopressors have been traditionally administered via central venous access. However, securing a central venous permit can be time-consuming, leading to delayed initiation of vasopressors (166). Studies exploring the safety of vasopressors via peripheral catheters have shown variable results related to feasibility and adverse effects (167–171). Several patients initially receiving vasopressors via peripheral access never subsequently required a central line during their ICU stay. However, failure rates for peripheral vein insertion reached 15%, and infectious complications were more frequent with peripheral access (167). There are concerns about extravasation when giving vasopressors through a peripheral vein, but the incidence seems relatively low and the consequences are usually minimal when peripheral line are used for less than 6–12 hours (168–170). Based upon this, the SSC guidelines concluded that administering vasopressors for a short period of time via a well-placed peripheral catheter proximal to the antecubital fossa is unlikely to cause local tissue injury (4). However, it should be noted that information derived from central venous catheters (i.e., $Scv{O_2}$, $P{CO_2}$ gradients, and CVP) cannot be accurately measured peripherally.

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Gaps in knowledge/critique of evidence. Although vasopressors are initiated earlier when given peripherally rather than centrally, studies evaluating the comparative safety of various agents, as well different dose ranges and concentrations, still need to be performed. Further, there is some evidence that larger catheters placed more proximal are safer, but the ideal caliber and preferable site of the peripheral catheter has yet to be discovered. The administration of more than one vasopressor via a peripheral line has yet to be studied.

Future directions. Adequately powered prospective studies are needed to provide better evidence on the adequacy and safety of peripheral lines for administering vasopressors in sepsis. In particular, the maximum dose and duration of vasopressor therapy that can be safely administered peripherally and the characteristics of patients benefiting most need to be identified. Future studies should also include specific analyses of high-risk groups.

4B3: What Is the Role of Epinephrine/Adrenaline in Septic Shock?

What is known. Epinephrine may be administered for two main reasons: its vasopressor effect (as first-line or as salvage) and its inotropic properties. Epinephrine is a catecholamine vasopressor with greater β1- and β2-adrenergic activity than norepinephrine. This differential pharmacology leads to a higher heart rate and lactate levels with epinephrine (172). Interestingly, CO may not be higher with epinephrine (173), perhaps due to the limited diastolic time. Two RCTs compared first-line epinephrine to norepinephrine in patients with shock (174, 175). Both trials demonstrated similar increases in MAP with the two agents, but tachycardia, hyperlactatemia and lower pH were observed on the first day with epinephrine. There was no difference in 90-day mortality (174, 175), but in one trial 13% of patients allocated to epinephrine were switched to open-label norepinephrine due to more frequent adverse effects (174). In the other trial, patients with septic shock were assigned to epinephrine monotherapy or norepinephrine with the mandatory addition of dobutamine that could be progressively weaned (175). In a RCT including 67 septic children comparing norepinephrine plus dobutamine to epinephrine, time to shock resolution was shorter and fewer children developed refractory shock with norepinephrine/dobutamine (176).

Regarding inotropic properties, observational studies have shown an association between adjunctive dobutamine, levosimendan, or epinephrine and higher mortality in septic shock (177, 178). However, patients receiving these inotropes had higher doses of norepinephrine and lactate levels (177). Indirect evidence from cardiogenic shock also suggests possible harm associated with epinephrine compared with norepinephrine (179).

Gaps in knowledge/critique of evidence. Although epinephrine has been used as a norepinephrine adjunct or replacement in individual patients with septic shock and cardiac dysfunction, trials have not evaluated epinephrine for this patient subset, and it remains unclear how to identify individual patients who may benefit from inotropic support. Further, it is unknown how individual catecholamines impact specific organ function differentially and whether improvement of one organ is potentially associated with impairment of the microcirculation in other organs. It is also unknown if the transient effects of epinephrine on lactate concentration and arterial pH lead to differences in major outcomes.

Future directions. Because epinephrine is commonly available in low-resource settings and because of uncertainty arising from available studies, an adequately powered trial should compare first-line epinephrine to norepinephrine without the mandatory addition of dobutamine. Additional trials are needed to evaluate treatment strategies, specifically in patients with septic shock and cardiac dysfunction, as detected with tools such as echocardiography. Additionally, these trials should incorporate measurement of organ-specific biomarkers and (in)direct evaluation of the microcirculation of vital organs. Further, studies should evaluate if epinephrine is beneficial, particularly compared with dobutamine or inodilators (e.g., milrinone), in the subset of patients with cardiac dysfunction facing escalating norepinephrine dosages or persistent hypoperfusion. Finally, future trials may consider clinical endpoints different from 30- to 60-day mortality, such as days alive and free of organ dysfunction and improvement in organ function (180) in addition to quality of life and duration of rehabilitation before return to baseline function.

4B4: For Patients With Septic Shock Receiving Norepinephrine and Vasopressin, Which Drug Should Be Weaned First and How?

What is known. The addition of vasopressin to norepinephrine (adjunctive vasopressin) is suggested for patients with inadequate MAP levels with norepinephrine alone (4). Vasopressin can function both as

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a vasopressor and as "endocrine replacement therapy." Endogenous plasma vasopressin concentrations rise in early septic shock but rapidly decrease to normal range within 48 hours from shock onset, resulting in a "relative vasopressin deficiency" (181, 182). Further, vasopressin secretion may be inhibited by corticosteroids. In the only trial specifically evaluating cessation order of concomitant norepinephrine and vasopressin, tapering norepinephrine first more frequently caused hypotension (183).

In contrast, in an individual patient data meta-analysis, including the sole randomized trial and several observational studies, the cessation or tapering of norepinephrine first was associated with less frequent hypotension without affecting short-term mortality (184). However, other studies reported similar rates of hypotension occurrence (185). It might be attractive to evaluate endogenous release of vasopressin to predict hypotension occurrence after cessation of exogenous vasopressin infusion. Unfortunately, vasopressin measurements are difficult to perform. Copeptin is a stable peptide that is released together with vasopressin (186) and measurement of copeptin reflects endogenous release of vasopressin (186–189). Decreased copeptin levels were associated with hypotension after vasopressin discontinuation (183). No RCT has evaluated vasopressin cessation strategies. Observational studies comparing vasopressin down-titration to abrupt cessation did not detect a between-group difference in hypotension rates (190) nor in time to ICU discharge (191).

Gaps in knowledge/critique of evidence. The optimal cessation order for patients receiving norepinephrine and vasopressin is uncertain, as opposite results were observed between studies. It is unclear if hypotension after the first vasoactive agent cessation affects outcome. Preliminary data suggest that copeptin, a marker of vasopressin deficiency, may help identify patients prone to develop hypotension at the vasopressin cessation (183). Further, the optimal vasopressin cessation strategy (i.e., down-titration vs. abrupt cessation, speed of weaning if weaning is used) and whether the cessation strategy influences the optimal cessation order have yet to be determined.

Future directions. Future trials should evaluate the best time for decision-making regarding combination vasopressor cessation. This includes norepinephrine dosage decrement below a particular threshold, duration of combination vasopressor therapy, and restoration of the endogenous vasopressin axis, in addition to evaluation of the effects of vasopressor cessation order and cessation strategies, possibly in a two-by-two factorial trial, on essential endpoints such as mortality, organ function, and cardiovascular support-free days. Tools (e.g., organ-specific biomarkers, imaging, etc.) that indicate "readiness for vasopressor cessation" in individual patients need to be identified. The role of biomarkers like copeptin for predicting hypotension after vasopressin discontinuation should also be investigated further.

Question 5: Can a Personalized/Precision Medicine Approach Identify Optimal Therapies to Improve Patient Outcomes?

What Is Known. Personalized medicine offers the opportunity to optimize therapy to the patient's baseline characteristics, actual clinical condition, and trajectory. Yet, because it is challenging to predict treatment response at the individual patient level (personalized medicine), current efforts focus on elucidating effective approaches in groups of patients with similar characteristics (precision medicine) (192). Precision may be based on several aspects, including (but not limited to), the source of sepsis, comorbidities, and the patient's immune status related to past medical history or response to the insult (69), organ dysfunction or hemodynamic profile (83, 193).

Sepsis is associated with an altered immune response to infection (194). Historically, sepsis has been considered a cytokine-mediated hyper-inflammatory phase related to stimulating innate or adaptive immunity (195). However, immune hyporesponsiveness has also been simultaneously reported (196, 197). This disordered immune response may play an important role in developing hemodynamic compromise and organ dysfunction and may thus be a target for therapy (198, 199).

Hemodynamic compromise is common in sepsis and septic shock. Randomization to specific drugs (200) or treatment algorithms (79, 80, 148) has failed to improve outcomes. However, these trials did not precisely assess the cardiovascular status for predictive enrichment. Specific cardiovascular subphenotypes are identified by echocardiography in both sepsis (201) and acute respiratory distress syndrome (202). Different subphenotypes of septic patients have been characterized based

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on several approaches, including baseline characteristics, hemodynamics, genomics, RNA sequencing, and evolution of vital signs (203–211). These subphenotypes are associated with varying risks of poor outcomes but may also affect response to therapy. Using latent class analysis of clinical and inflammatory/endothelial biomarker data in patients with sepsis-associated AKI, two AKI subphenotypes were identified with different short-term renal recovery and 90-day mortality rates (212). Applying a parsimonious subphenotyping strategy to participants in the Vasopressin and Septic Shock Trial, differences in treatment effect were observed across the two groups, with patients with AKI subphenotype 1 showing a survival benefit with the administration of low-dose vasopressin, in contrast to AKI subphenotype II (213).

Gaps in Knowledge/Critique of Evidence: The complex interaction of the immune and hemodynamic responses with subsequent organ failure still needs to be more adequately understood. While a hyperimmune reaction is a hallmark of sepsis, immune exhaustion also occurs. Patients with minimal inflammatory response have the highest mortality risk from the lack of immune response and delayed recognition (214). Most therapies tested in sepsis over the last decades have focused on blocking sepsis's cytokine-mediated initial hyper-inflammatory phase (215, 216). These trials failed to demonstrate an improvement in 28-day mortality. However, the absence of short-term survival benefits in an indiscriminate septic population does not imply a lack of clinical efficacy in specific populations. While many approaches to identifying subsets of septic patients have been proposed, ranging from vital signs to multiscale omics, these have yet to be generalized or enter wide-scale clinical usage. Application of different subphenotype categorization in the same dataset failed to identify comparable patient populations (217). Accordingly, the respective value of subphenotype categorization remains to be determined. Furthermore, although conceptually appealing, it has yet to be discovered whether the ability to discriminate specific patient populations will result in better patient outcomes.

Tools to identify the onset of early organ dysfunction before the development of organ failure still need to be improved. Organ-specific biomarkers are often measured in biological fluids, but whether they reflect the condition within tissues and organs is unknown. Organ support therapies are, hence, currently applied when overt organ dysfunction is demonstrated, but preventive interventions are often not feasible. Appropriate hemodynamic support is required to allow time for recovery. The response of the various hemodynamic subphenotypes to therapies may vary. Prospective studies applying fluid, inotropic and vasopressor therapies targeting different hemodynamic subphenotypes are being conducted (218).

Future Directions: There is an urgent need to identify biomarkers that indicate early stages of sepsis-associated "organ stress" at the bedside before dysfunction occurs. The role of targeted interventions to prevent organ failure in these high-risk patients should be explored.

There is also an urgent need to identify patients with sepsis-associated organ dysfunction who are more likely to benefit from optimally timed and selectively targeted specific interventions and those who are unlikely to respond or potentially harmed.

Defining the target population for specific interventions is crucial. The response to some therapeutic interventions has been shown to vary according to the proportion of specific sepsis subphenotypes (207, 213, 219). Accordingly, defining which therapy best suits which specific subphenotype is crucial. Better definition of the pro and anti-inflammatory state is essential to better identify which patients may benefit from anti-inflammatory agents or immune stimulation. Whether this should be based on cytokine profile and evaluation of blood markers of immune status or clinical subphenotypes remains to be determined. Development of bedside diagnostics to support this approach will be essential. At some point, artificial intelligence may also aid to better define these profiles (220, 221). Ideally, studies investigating specific approaches should take into consideration different sepsis subphenotypes, the phase of sepsis and patient comorbidities and evaluate not only 28-day mortality but also other important patient-centered outcomes, including mental well-being and quality of life. Similar considerations apply to hemodynamic and organ support.

Basic and Translational Science Questions

BTS.1: How Can We Improve Animal Models So That They More Closely Resemble Sepsis in Humans? The profound complexity of sepsis, which affects virtually

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every organ and system in the body, makes it difficult to understand and challenging to treat. Identifying and treating abnormalities at the cellular or subcellular level may be the most effective way to prevent sepsis-induced organ dysfunction. Unfortunately, direct evaluation of organ function in patients is limited by logistics, even in an experimental setting. In some limited cases, direct physiologic findings (e.g., CO to assess cardiac function) or leukocyte surface markers or responses (e.g., stimulated cytokine production) are available. However, function is most often inferred from plasma biomarkers that serve as proxies for organ function. Further complicating matters, sepsis alters interactions between organ systems. Finally, we do not yet understand what constitutes a "regulated host response"—that is, what responses to infection are normal/adaptive, what responses are maladaptive, and at what point do the two diverge. Thus, identification of the maladaptive "dysregulated host response" in sepsis is exceedingly problematic. What is needed is an approach that permits the study of both normal and sepsis-induced responses in multiple tissues and examination of interactions between organ systems. Emerging technologies may identify direct, noninvasive approaches to tissue and cellular analysis including multiomic approaches from accessible human samples, functional MRI scanning, or in silico modeling. Ultimately, animal models are likely to provide accessible and applicable data, consistent with approaches taken in multiple disease states where animal models have led to fundamental changes in therapeutic approaches (222). Unfortunately, currently used animal models of sepsis have limitations and strengths that require careful consideration when performing preclinical studies of sepsis (222–224).

BTS.2: What Outcome Variables Maximize Correlations Between Human Sepsis and Animal Models and Are Therefore Most Appropriate to Use in Both? A second global concern in both human and animal interventions involves the choice of appropriate outcome variables. While mortality is easily measured, it is a narrow endpoint that does not in isolation account for other host factors such as quality of life. Further, organ support systems make it possible to stave off death in septic humans almost indefinitely, while many regulatory bodies prohibit use of death as an outcome variable in animal experiments. Additionally, mortality fails to address adverse but potentially modifiable outcomes in sepsis survivors (e.g., neurocognitive dysfunction, respiratory insufficiency, malnutrition, weakness) (225).

BTS.3: How Does Sepsis Affect Specific Regions of the Brain That Modulate Pulmonary, Cardiovascular, Hepatic, Renal, and Gastrointestinal Function? And How Do Sepsis-Induced Alterations in These Regions Contribute to Organ Dysfunction? How Does Sepsis Affect Interactions Between Neural, Endocrine, and Immune Systems? Many cellular/extracellular processes—cell cycle arrest, neutrophil extracellular traps, autophagy/mitophagy, release of vesicles into the extracellular space, changes in the endothelium and glycocalyx, etc.—likely contribute to or are altered by sepsis pathobiology in humans (226–229). However, an inability to identify the differences between "normal" and "dysregulated" host responses limits our ability to address many important questions. Thus, to identify and modify sepsis-induced cellular activities and responses, we require a better understanding of what is adaptive/reversible and what is pathologic (and perhaps irreversible). Examination of both normal and abnormal cellular activity/responses, in turn, underscores the need to develop better animal models.

Sepsis impairs organ-organ interaction. Three basic systems facilitate the transfer of information from one organ to another—the immune system, the endocrine system, and the neural system. We can study white cells and hormone levels in septic patients, and both the endocrine and the immune systems have been investigated extensively. However, both the endocrine and immune system have compartmentalization, and there is not a single immune system response as there are marked differences in the blood, spleen, gut, lymph nodes, and bone marrow, and most of these are not amenable to sampling in patients. In addition, while much less is known about neural responses in sepsis (57), exciting new data document interactions between the nervous and the immune systems (55, 230).

BTS.4: How Does the Microbiome Affect Sepsis Pathobiology? How Does Sepsis Pathobiology Contribute to the "Pathobiome," Which May Also Be Affected by the Use of Antibiotics? Reports in animal models of sepsis indicate that microbiota metabolites modulate outcomes (231–233) and implicate the gut microbiome in injury in multiple organs (234, 235). Further, targeting the microbiome for therapeutic

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gain—by probiotics, prebiotics, synbiotics, microbial spores, fecal microbial transplantation, or selective decontamination of the digestive system—has been helpful in disorders such as dementia and cognitive disorders, inflammatory bowel disease, and lupus (236–240) and may have therapeutic benefit in sepsis (232, 233, 241). However, the contribution of the microbiome to sepsis pathobiology is underexplored (242), and the therapeutic potential of microbiota manipulation is untapped.

BTS.5: How Do Genetics and Epigenetics Influence the Development of Sepsis, the Course of Sepsis and the Response to Treatments for Sepsis? While studies support a role for genetic (243–248) and epigenetic (249–255) factors in sepsis, the topic remains relatively unexplored. Despite years of research in this domain, we do not yet fully understand the link between genetic factors and susceptibility, severity and evolution of sepsis. Some cohort data or post hoc analyses of intervention studies suggest a link between genetic or metabolomic factors and response to therapy (206, 219, 256–258). Epigenetic factors play a crucial role in various processes in sepsis from the coordination of the response to infection to inflammatory response (259, 260) but also particularly contributes to the induction of immunoparalysis (249, 250, 252, 261). The pattern (predominantly affecting immune state, coagulation or other genes) may vary on a daily basis after admission, suggesting that repeated measurements may be required (257). Unfortunately, we are still at a very preliminary level of understanding of what the key players are and how to intervene in this domain.

PROGRESS SINCE PRIOR RESEARCH PRIORITIES ARTICLE

Continuing to ask "big picture" questions that will guide the future of sepsis care necessitates that every time one question is answered, many more will follow. The SSC Research Committee published its first set of research priorities in 2018 (6). A total of 26 priorities were identified. Of these, the top six clinical priorities were: 1) can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times? 2) what are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated? 3) should rapid diagnostic tests be implemented in clinical practice? 4) should empiric antibiotic combination therapy be used in sepsis or septic shock? 5) what are the predictors of sepsis long-term morbidity and mortality? and 6) what information identifies organ dysfunction? Significant progress has been made on each of these questions. However, it is notable that four of the current top five clinical priorities in this article were also identified as priorities in 2018. This is not surprising as even when multiple studies have been performed and clinicians have a better idea how to manage sepsis at the bedside, the concept of precision medicine (a priority in 2018 and now) means with near certainty that one size will not fit all in sepsis, which is a heterogeneous syndrome. Interestingly, although few basic science insights have translated into improved outcomes, the majority of the basic science priorities have changed since 2018 with a question related to the microbiome being the only repeat priority. We suspect that this change is due to a combination of questions answered over time and subjective priorities of a committee whose roster has evolved significantly between the previous iteration of the research priorities and the current version.

LIMITATIONS

The current questions are those provided by the individuals included in the panel, as selected by the two societies (SCCM and ESICM), and the process used was inherently subjective. As such, we freely acknowledge that other experts may have selected other research priorities and suggest that readers also read similar manuscripts published by other professional societies and groups that cover topics not included in our article. Interestingly, even though the panel somewhat differed from the previous panel reporting the first set of priorities (6), several questions identified in 2018 are again considered as top priorities.

Additionally, even though multiprofessional, the panel was mostly composed of intensivists. While these came from a variety of backgrounds (anesthesia, internal medicine, surgery) with a variety of expertise, not all physician or nonphysician specialties that manage septic patients were included. We thus acknowledge that we do not have representation from all possible stakeholders, and incorporating valuable feedback from those not on the panel may have resulted in different prioritization. Also, even though the panel was clearly intercontinental, Africa was not represented, and some continents had more panel members than others. Nevertheless, the panel members tried to

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include topics that were perceived equally important for resource limited and other settings. While many of these questions are independent of practice setting, there will also assuredly be differences depending upon whether a patient is in a high or low resource setting. This needs to be incorporated into future research efforts. Next, while we only detail the top five clinical and BTS questions, we do not wish to imply that these are the only important research questions related to sepsis. The remaining questions listed in Table 2 are assuredly worth pursuing. These questions should be considered important for future research in the field sepsis and should require attention from investigators in the future. Finally, we acknowledge that, in order for some elements of the research agenda to ultimately reach the patient, there are pragmatic elements to its success that need to be considered including explicitly linking research performed to implementation science so it can be optimally translated to bedside practitioners.

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CONCLUSIONS

Each successive version of the SSC guidelines is based upon the most up-to-date data available to the panel. Increases in knowledge have allowed for upgrading and downgrading guideline recommendations using GRADE methodology and evidence to decision framework (262–264). Nevertheless, multiple knowledge gaps remain precluding the possibility of strong recommendations in most domains, and at times preventing any recommendation at all. Our hope is that this document will spur international research on sepsis—both to change clinical guidelines in the near future and also to answer more basic questions that will hopefully spur discovery and innovation that can be translated to fundamental breakthroughs in sepsis.

ACKNOWLEDGMENTS

Surviving Sepsis Research Subgroup Heads: Clifford Deutschman (basic science), Judith Hellman (organ injury and dysfunction), Sheila N. Myatra (resuscitation), Marlies Ostermann (vasopressors), Hallie Prescott (screening and identification), and Daniel Talmor (precision medicine).

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Drs. De Backer, Pontes Azevedo, and Tissieres received funding from Baxter. Dr. De Backer received funding from Edwards Lifesciences, Phillips, and Viatris Pharmazz. Dr. Deutschman received funding from Elsevier, Siemens Healthcare Diagnostics (Tarrytown, NY), Enliven (Jerusalem, Israel), The Society of Critical Care Medicine, the National Institute of General Medical Sciences, and La Jolla Pharmaceuticals; he received support for article research form the National Institutes of Health (NIH); he received Giapreza (angiotensin II infusion) for experimental use from La Jolla Pharmaceuticals (La Jolla, CA); and he received honorarium for serving as Scientific Editor of the journal Critical Care Medicine*. Dr. Ostermann received research funding from Baxter, Fresenius Medical, bioMerieux, and La Jolla Pharma. Dr. Talmor received funding from NIH, Clew Medical, Mindray, and STIMIT. Dr. Prescott's institution received funding from the NIH, U.S. Department of Veterans Affairs, the Agency for Healthcare and Research and Quality, the U.S. Centers for Disease Control and Prevention, and Blue Cross Blue Shield Michigan; she disclosed government work. Dr. Antonelli received funding from General Electrics, Fisher & Paykel, Menarini, and*

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Pfizer. Dr. Pontes Azevedo received funding from Merck Sharp Dohme (MSD) and Nestle. Dr. Loeches received funding from ThermoFisher, Polyphor, MSD, Fresenius Kabi, Gilead, Clinigen, Biotest, Accelerate, and bioMérieux. Dr. Tissieres received funding from Sanofi, bioMerieux, Abionic, Sedana, and ThermoFisher. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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