POINT:
Should the Surviving Sepsis Campaign Guidelines Be Retired? Yes

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PODCAST

ABBREVIATIONS: COI = conflict of interest; ESICM = European Society of Intensive Care Medicine; IDSA = Infectious Disease Society of America; IHI = Institute for Healthcare Improvement; ISF = International Sepsis Forum; RCT = randomized controlled trial; SSC = Surviving Sepsis Campaign; SCCM = Society of Critical Care Medicine

Concern regarding the Surviving Sepsis Campaign (SSC) guidelines dates to their inception. Guideline development was sponsored by Eli Lilly and Edwards Life Sciences as part of a commercial marketing campaign.[1] Throughout its history, the SSC has a track record of making strong recommendations based on weak evidence and being poorly responsive to new evidence.[2-4] The original backbone of the guidelines was a single-center trial by Rivers et al[5] defining a protocol for early goal-directed therapy. Even after key elements of the Rivers protocol were disproven (eg, targeting a central venous oxygen saturation >70%, blood transfusions for hemoglobin >7 g/dL), the SSC continued to recommend them.

The cornerstone of the SSC guidelines has always been completion of specific bundles of treatment within specific periods; however, it has become increasingly clear that these bundles are not evidence-based. Apart from the timely administration of antibiotics, multiple studies have demonstrated that all the other elements of the 3- and 6-h resuscitation bundle are devoid of supporting scientific evidence and do not positively influence patient outcomes.[2-4,6,7] Indeed, the 30 mL/kg fluid bolus mandate is likely harmful.[8,9] Measurement of serum lactate within 3 h and repeated measurement after 6 h is the most common reason for noncompliance with the "bundle"[7]; yet, it is unproven that measurement of blood lactate will improve patient outcomes.[10]

Despite waning evidence to support these bundles, the 2018 SSC guidelines have doubled down, by combining the 3- and 6- h bundles into a single 1-h bundle (Table 1).[11] This would require obtaining blood cultures, administering antibiotics, initiating 30 mL/kg fluid, and initiating vasopressors for ongoing hypotension: all within an hour of triage. This major policy shift has been made despite the lack of any prospective evidence that supports it.

Well-intentioned policies may inadvertently cause harm. One example of this is the 2002 Centers for Medicare & Medicaid Services' quality measure mandating that all patients admitted for pneumonia must receive blood cultures and antibiotics within 4 h of ED triage.[12] As with the 2018 SSC guidelines, this initiative was based on retrospective data *correlating* rapid treatment with better outcomes. Pressure to comply with this metric caused harm by promoting premature diagnoses and the liberal use of antibiotics. Eventually, it was recognized that forcing ED to work faster actually worsened patient care, prompting the removal of the 4-h mandate.

Compared with the 4-h pneumonia mandate, a 1-h sepsis mandate would cause much greater harm. Achieving the 3-h treatment bundle is challenging enough for most EDs.[13] Complying with a 1-h bundle would require diagnosing any ill patient with possible infection as septic, which would immediately trigger fluid and antibiotic administration.[14] Such issues with overdiagnosis have

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TABLE 1] Bundle Elements With Strength of Recommendations

Bundle Element	Grade of Recommendation and Level of Evidence
Measure lactate level. Remeasure if initial lactate >2 mmol/L	Weak recommendation; low-quality evidence
Obtain blood cultures before administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive	Strong recommendation, moderate quality of during or after fluid resuscitation to maintain evidence
Mean arterial pressure ≥65 mm Hg	

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previously been documented, even with less demanding sepsis protocols.[15] For example, this would expose many nonseptic patients to iatrogenic volume overload, the risk of *Clostridium difficile* infection, and promote bacterial resistance. The Infectious Disease Society of America (IDSA) chose not to endorse the 2016 guidelines largely because of concerns regarding excessive antibiotic use and overly rigid timelines for antibiotic initiation: problems that would be dramatically exacerbated by the new 2018 guidelines.[16] Additional collateral damage would potentially result from attention being diverted from other patients in the ED with high-acuity illness of noninfectious etiology.

The SSC has long assumed that protocolized care is superior to individualized treatment guided by the bedside clinician. This hypothesis has its roots in the original trial of Early Goal-Directed Therapy by Rivers et al.[5] This protocol has subsequently been shown to be no better than usual care in three large randomized controlled studies.[17] Although guidelines should summarize evidence and provide evidence-based recommendations, the SSC recommends prescribing a rigid set of bundles that mandate specific interventions within fixed time frames[18]; these recommendations are mostly unsupported by evidence. Nonetheless, they have been adopted by the Centers for Medicare & Medicaid Services as a core quality measure (Severe Sepsis/Septic Shock Early Management Bundle). This pressures physicians to administer treatments despite their best medical judgment. It is noteworthy that in response to the publication of the 2016 SSC guidelines, Timothy Buchman and Elie Azoulay, the Editors of *Critical Care Medicine* and *Intensive Care Medicine*, respectively, stated that "As clinicians, we are bound to deviate from guidelines when such deviation is reasonably expected to improve an individual patient outcome… We therefore caution against any quality metric or reimbursement policy that mandates slavish adherence to a particular recommendation."[19] This statement is clearly at odds with the stated goals of the 2016 and 2018 SSC guidelines.[11,18] For example, these guidelines slavishly mandate a fluid bolus to *all* patients with sepsis-induced hypotension or a lactate >4 mmol/L regardless of the patients clinical status.[11,18] Indeed, the 2016 SSC guidelines advocate that patients with pneumonia or acute lung injury be intubated specifically so that they can receive the 30 mL/kg fluid bolus.[20]

Early antibiotic therapy is sensible; however, a recent randomized controlled trial of prehospital administration of antibiotics did not demonstrate an improvement in patient outcomes with the earlier administration of antibiotics.[21] We therefore do not agree with mandating antibiotic initiation within an hour of triage, because in most instances this is unlikely to improve patient outcomes, and in many instances this may be logistically impossible. Instead, we endorse the concept as expressed by the IDSA that "each antibiotic ordered should be initiated promptly, with health care systems working to reduce that time to as short a duration as feasible."[16] Remarkably, the authors of the 2016 SSC guidelines have stated that the…recommendation for antibiotic administration within an hour of diagnosis of sepsis is a lofty goal of care… Despite the best intentions of the healthcare team, antibiotic administration within one hour from time of diagnosis may be difficult due to the complexity of the hospital environment and essential care being delivered to other patients during the same time period by the same healthcare practitioners and health system.[20] This statement undermines the very core of the 2018 SSC guideline that requires that antibiotics be administered within an hour of triage.[11]

We have waited patiently for years in hope that the guidelines would improve, but they have not. The 2018 SSC update appears to have deviated from evidence-based

medicine more than the 2016 version. These recommendations will likely cause hasty management decisions, inappropriate fluid administration, and indiscriminate use of broad-spectrum antibiotics, which are impediments to providing the best possible care to our septic patients. We believe therefore that the SSC guidelines should be retired. In its place, we suggest that trustworthy evidence-based sepsis guidelines be developed and based upon high-quality systematic reviews conducted by a global group of stakeholder societies.

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COUNTERPOINT:

Should the Surviving Sepsis Campaign Guidelines Be Retired? No

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To address the question at the core of this Point/Counterpoint, the Surviving Sepsis Campaign (SSC) guidelines must be considered separately from the SSC bundles because they are distinctly different entities. We will explain why neither the guidelines nor the bundles should be abandoned based on the clear published data that demonstrate the benefit to patient care of both applying the guidelines and adhering to the bundles. Further, because the history of SSC has been marked by controversy, we will attempt to distinguish between academic debate and clinical impact on patient care and outcomes.

History of the SSC

SSC was initiated as a collaboration among the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum (ISF) in 2002 as a call to action to reduce mortality from sepsis.[1] In 2008, the ISF withdrew and SSC remained a partnership between the two critical care societies. Initially, SSC was funded by industry (Eli Lilly and Company and Edwards Lifesciences) and the professional society partners (SCCM, ESICM, ISF). After 2006, SSC has been completely free of industry funding and has been supported primarily by SCCM and ESICM, and grants from The Gordon and Betty Moore Foundation (Palo Alto, CA).[1] The most important tools from the SSC's 16-year effort to reduce sepsis mortality have been the SSC Guidelines, the SSC bundles, and the sepsis education and recognition efforts that have gone alongside them.

SSC Guidelines

Clinical practice guidelines are an important tool to promote evidence-based medicine; the SSC published the first sepsis guidelines in 2004.[2] Revisions have subsequently been published every 4 years to ensure they reflect the latest published evidence.[3-5] The importance and relevance of the SSC guidelines is demonstrated by the growing number of citations for each iteration: in 2004 (2,265); 2008 (3,846); 2012 (4,583); and 2016 (648 to date). The SSC guideline development process is rigorous. Panelists are selected and potential conflicts of interest (COIs) are disclosed and managed if necessary. Development of patient, problem, or population; intervention; comparison, control, or comparator; and outcome questions, along with search strategies, systematic reviews, formulation and grading of recommendations, and voting on recommendations were all done using Grading of Recommendations Assessment, Development, and Evaluation methodology with methodologic expertise provided by the Grading of Recommendations Assessment, Development, and Evaluation working group.[5]

Because SSC was initially funded by industry, questions of potential COI in the development of the first set of guidelines arose, although a disclosure and recusal process was enforced. SSC has developed a rigorous method for determining and adjudicating COI to minimize the potential influence of both financial and intellectual COI on guideline development. In 2008, as part of the guidelines process, SSC published the process of determining COI of panel members.[6] This process remains an essential aspect of the SSC guidelines.

Over time, the number of professional societies participating in the development has increased. The most recent SSC guidelines (2016) were sponsored by 35 international professional medical societies and have emerged as the global standard for sepsis management such that some randomized clinical trials now use the SSC guidelines to standardize sepsis care across the control and intervention groups.[7-10]

Even with the success of the SSC guidelines, one of the challenges common to all guideline development is implementation at the bedside. For that purpose, the sepsis bundles were developed and introduced by the SSC.

SSC Sepsis Bundles

The SSC bundles were first released in 2005 in partnership with the Institute for Healthcare Improvement (IHI).[11] The bundles were developed in concert with a separate group convened by IHI and tested in IHI-related hospitals. Bundle revisions continue through a separate process from the guidelines. The first bundles were 6- and 24-h bundles, also known as the resuscitation and management bundles. Over the next 7.5 years, SSC introduced a performance improvement initiative into 225 hospitals in Europe, North America, and Latin America. The results of this study demonstrated an 11.6% and 5.2% improvement in 6- and 24-h bundle compliance, respectively, which was associated with a 27.3% improvement in survival.[12] More important, hospitals with higher compliance with the bundles had an even steeper decline in mortality when compared with hospitals that had lower overall compliance. These data support the close link between compliance with the sepsis bundles and improved survival in

patients with sepsis and septic shock. In addition to this study, the SSC bundles were used in performance improvement initiatives in many other countries, with several national networks demonstrating improved survival associated with implementation.[13-16] A meta-analysis of 44 studies revealed a significant reduction in mortality associated with improved compliance with the sepsis bundle, with an OR for mortality of 0.58 (95% CI, 0.51-0.66).[17] Since that time, numerous papers have been published that have also demonstrated a significant reduction in mortality associated with improved compliance with the bundles.[18,19]

In 2015, based on recently published results of randomized trials and data analysis from the published SSC dataset, the SSC bundles were revised to 3- and 6-h bundles. The results of compliance have been recently published and reflect the New York State Department of Health's mandated public reporting of hospital-based protocols based on these revised bundles.[20] They demonstrated a significant reduction in mortality (4.4% absolute risk reduction and 15.2% relative risk reduction; $P < .001$) associated with timely completion of the revised SSC bundles. A significant increase in mortality was shown to be associated with each hour of delay in completion of the 3-h bundle.[21]

Further, in 2015 the Centers for Medicare and Medicaid Services adopted the SSC bundles for mandatory reporting in all hospitals in the United States.[22] Early results of this initiative (Severe Sepsis/Septic Shock Early Management Bundle) demonstrated a significant reduction in mortality associated with completion of all elements of the bundles.

In 2018, the revised SSC bundle was released.[23] This bundle combined the 3- and 6-h bundle into a single Hour-1 bundle, which was developed to ensure that continuous improvements in performance are realized and to emphasize that sepsis and septic shock should be viewed as medical emergencies that require rapid diagnosis and immediate intervention. These interventions should be *started* within the first hour from sepsis recognition. The bundle is intended as a tool to facilitate the prompt diagnosis and treatment rather than a quality indicator to be adopted by national regulatory agencies.

As a result of discussions among leaders of the SCCM and the American College of Emergency Physicians (ACEP), the following (excerpted) joint statement was issued on the SSC website.

SCCM and ACEP acknowledge concerns expressed about the recently released Surviving Sepsis Campaign (SSC) Hour-1 Bundle and the appropriateness of implementation in the United States. Both organizations understand the importance of prompt and optimal sepsis diagnostics and treatment. We recommend that hospitals not implement the Hour-1 Bundle in its present form in the United States at this time.

Summary

The SSC guidelines have become widely quoted and supported by researchers, bedside clinicians, and professional societies. The SSC bundles, derived from the guidelines, have been tested in multiple international studies in multicultural environments and in a wide range of hospital types. All the published studies have demonstrated a clear message: changing clinical behavior so that sepsis management is consistent with the guidelines and the bundles is associated with a statistically significant improvement in survival for patients with sepsis and septic shock. The strength and consistency of the evidence make it difficult to fully understand why the question in this Point/Counterpoint is being asked at all. If every initiative using the SSC bundles is tied to improved patient outcomes, do any of us really believe that there is any reason to retire them? It seems that we would all want our loved ones to be cared for in institutions that can consistently and reliably meet these continuously evolving performance metrics, because they have been repeatedly associated with delivering better care and driving improved outcomes.

A better question might be to ask ourselves honestly why they are still not being achieved everywhere. Our families and our patients deserve nothing less.

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Rebuttal From Drs Marik, Farkas, Spiegel et al

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Levy et al[1] referenced 13 studies to support the Surviving Sepsis Campaign (SSC). On careful review, none of these studies provide robust scientific evidence that SSC has improved mortality.[2] In fact, they highlight the *lack* of solid evidence supporting the SSC.

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Some studies used a quasiexperimental design to compare outcomes before vs after implementation of sepsis guidelines.[3] Although improved outcomes are an optimistic sign, this may easily be explained by greater attention and energy for sepsis therapy (the Hawthorne Effect).

Several articles *correlate* the receipt of various interventions with mortality.[4] Such correlations are laden with confounding factors; for example, compliance with the sepsis bundle is a surrogate marker for a patient receiving more aggressive management overall. Prompt receipt of interventions could reflect that the patient is otherwise healthy and thus more rapidly diagnosed with sepsis. Quite simply, correlational studies cannot prove causation.

Decreasing sepsis mortality over several years has been interpreted as evidence to support the success of the SSC, but parallel mortality reductions have been noted in Australia and New Zealand despite *rejection* of SSC by those countries.[5] Improving outcomes therefore likely reflect gradual improvements in critical care over time.

In addition to these observational data, four multicenter randomized clinical trials (RCTs) were referenced. None support the SSC. Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis in Adult Patients With Septic Shock disproved the utility of activated protein C, which was recommended by the SSC at that time.[6] The Protocolized Care for Early Septic Shock, Australasian Resuscitation in Sepsis Evaluation, and Protocolised Management in Sepsis trials uniformly disproved the necessity of invasive early goal-directed therapy, a cornerstone of the SSC treatment bundles at that point. When components of SSC were subjected to rigorous scientific testing, they were therefore found to be therapeutically ineffective.

Overall, these studies show a dramatic schism between multicenter RCTs (which have consistently *disproven* SSC guidelines) vs observational trials (which seem to *support* the SSC guidelines). This disconnect is remarkable because most of the observational trials supporting SSC were performed using invasive early goal-directed therapy, a treatment that has currently been discarded. Overall, this demonstrates that no matter how optimistic observational studies may seem, rigorous RCTs are required to provide truly scientific evidence. Guideline-driven health care policy should never be based upon retrospective, correlational studies.

No evidence seems to exist supporting the 1-h cutoff recommended in the 2018 revised SSC bundle. Collapse of the 3- and 6-h bundles into a single 1-h bundle is an enormous change, which appears to be completely arbitrary. No data are provided to show that implementing a 1-h bundle is either feasible or beneficial.

We agree with Levy et al[1] that sepsis is a medical emergency warranting immediate and aggressive management; however, we also believe that strong recommendations by international guidelines must be based upon robust, validated scientific evidence. The SSC guidelines openly admit failure to do so (eg, recommendations for fluid management are listed as a *strong* recommendation based upon *weak* evidence). We therefore support the moratorium placed upon the 2018 SCC bundles by the SCCM and ACEP.

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Rebuttal From Drs Levy, Rhodes, and Evans

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In their piece suggesting the Surviving Sepsis Campaign (SSC) guidelines be retired, Marik et al[1] make several misleading statements. First, it is important to understand the differences between guidelines, bundles, clinical protocols, and performance measures, which are conflated as equivalent. Clinical practice guidelines follow a clearly defined methodology to make evidence-based recommendations. Bundles, which are derived from guidelines, are tools to facilitate implementation at the bedside with defined targets. Protocols are tools for putting guidelines or bundles into operation. Measures are ways to track and report performance. All are important quality improvement tools.

Second, it was stated that SSC has not been responsive to new evidence. SSC has responded to new, published evidence with each iteration of the guidelines: tight glucose control, drotrecogin alfa, and the recommendation for central lines for protocol-based resuscitation were all removed in response to strong published evidence that failed to confirm earlier trials. The cornerstone of the SSC guidelines has always been the evidence-based review of the literature that supports guideline development. Because the bundles are derived from the guideline recommendations, they are also evidence-based.

There are robust and consistent published studies and meta-analyses supporting the association between implementation of sepsis bundles and improved survival.[2-4] Furthermore, there has *never* been harm demonstrated with bundle implementation.

Nothing in the SSC bundles "pressures physicians to administer treatments despite their best medical judgment." If a physician, based on his or her bedside assessment, feels an element of the bundle is inappropriate, that physician should document that assessment and decision and act accordingly.

Regarding specific elements of the SSC bundle, additional statements require rebuttal. The claim that the administration of 30 mL/kg of crystalloid fluid for patients with hypotension and/or an elevated lactate is likely harmful is not founded in evidence and fails to consider data from published trials using the bundles and the use of 30 mL/kg as the median amount of fluid administered *before randomization* in the three large international randomized clinical trials that evaluated Early Goal Directed Therapy. SSC bundles do not recommend 30 mL/kg for any ill patient with suspected infection, but for hypotension and/or an elevated lactate.[5] As for antibiotics, multiple studies have consistently demonstrated increased mortality associated with every hour an institution delays antibiotic therapy in sepsis and septic shock.[6,7] There is also evidence linking lactate to improved outcomes.[8]

The Hour-1 bundle was introduced based on two concepts: First, time to initiation of therapy is a critical determinant of outcome; and, second, a recognition that most clinicians faced with a critically ill patient with sepsis-induced hypotension will choose to commence (not necessarily complete) implementation of *all* aspects of the 3- and 6-h bundle immediately, rather than delay treatment.

In conclusion, we end our rebuttal with the same statement with which we ended our first statement: It seems that we would all want our loved ones to be

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cared for in institutions that can consistently and reliably meet these continuously evolving performance metrics. Our families and our patients deserve nothing less.

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