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MAJOR ARTICLE

Infectious Diseases Society of America Position Paper: Recommended Revisions to the National Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Sepsis Quality Measure

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(See the Editorial Commentary by Townsend et al on pages 553–5 and the Major Article by Pakyz et al on pages 556–65.)

The Centers for Medicare & Medicaid Services' Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) measure has appropriately established sepsis as a national priority. However, the Infectious Diseases Society of America (IDSA and five additional endorsing societies) is concerned about SEP-1's potential to drive antibiotic overuse because it does not account for the high rate of sepsis overdiagnosis and encourages aggressive antibiotics for all patients with possible sepsis, regardless of the certainty of diagnosis or severity of illness. IDSA is also concerned that SEP-1's complex "time zero" definition is not evidence-based and is prone to inter-observer variation. In this position paper, IDSA outlines several recommendations aimed at reducing the risk of unintended consequences of SEP-1 while maintaining focus on its evidence-based elements. IDSA's core recommendation is to limit SEP-1 to septic shock, for which the evidence supporting the benefit of immediate antibiotics is greatest. Prompt empiric antibiotics are often appropriate for suspected sepsis without shock, but IDSA believes there is too much heterogeneity and difficulty defining this population, uncertainty about the presence of infection, and insufficient data on the necessity of immediate antibiotics to support a mandatory treatment standard for all patients in this category. IDSA believes guidance on managing possible sepsis without shock is more appropriate for guidelines that can delineate the strengths and limitations of supporting evidence and allow clinicians discretion in applying specific recommendations to individual patients. Removing sepsis without shock from SEP-1 will mitigate the risk of unnecessary antibiotic prescribing for noninfectious syndromes, simplify data abstraction, increase measure reliability, and focus attention on the population most likely to benefit from immediate empiric broad-spectrum antibiotics.

Keywords. sepsis; septic shock; SEP-1; severe sepsis; IDSA

The US Centers for Medicare & Medicaid Services (CMS) implemented the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) in October 2015. SEP-1 requires hospitals to report their compliance with a rigidly defined sepsis bundle to CMS as part of the Inpatient Quality Reporting (IQR) program. SEP-1 is an "all-or-nothing" measure in the IQR that requires adherence to all bundle elements to receive any credit. Hospitals that participate in the IQR receive additional payments for submitting data to CMS. SEP-1 results are publicly reported [1].

The Infectious Diseases Society of America (IDSA) applauds CMS for emphasizing the importance of improving sepsis management and outcomes. IDSA has several major concerns about SEP-1, however, including its failure to address the high rate of sepsis overdiagnosis, its conflation of sepsis and septic shock in the urgency of antibiotics, and its potential to contribute to a rush to judgement for stable patients, some of whom could be diagnosed with noninfectious syndromes if physicians are permitted a small amount of time for investigation and observation.

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IDSA is also concerned about the reliability of SEP-1 abstraction in view of its complicated rules for identifying "time zero."

CMS made several changes to SEP-1 following its initial release in order to simplify the measure and improve its clinical credibility [2, 3]. In the spirit of constructive dialogue, IDSA would like to provide concrete suggestions to further improve SEP-1. Our primary aim is to help promote a better balance between immediate and aggressive treatment for patients who truly stand to benefit from early antibiotics versus limiting antibiotic overuse for uninfected patients presenting with sepsis-mimicking syndromes. We also seek to align SEP-1 with the strongest available evidence and to reduce the burden of documentation and abstraction, in order to make it a more trusted and accepted quality metric.

IDSA acknowledges that concerns have been expressed about SEP-1's fluid resuscitation requirement, including their potential to contribute to fluid overload and worse outcomes in some patients [4–11]. However, we believe other professional societies should lead discussion of the hemodynamic aspects of SEP-1. IDSA is also aware of the ongoing controversy regarding new versus old definitions of sepsis, but believes this is outside the scope of this document. We refer here to infection with organ dysfunction as "sepsis," per Sepsis-3 and use this term interchangeably with SEP-1's "severe sepsis" [12].

REGULATORY MEASURES VERSUS CLINICAL GUIDELINES

IDSA believes that national quality measures should be limited to clearly beneficial interventions with strong supporting evidence that can be objectively measured and readily extracted from electronic medical records. Interventions that might be credible but are not clearly evidence-based or require nuanced judgements that vary between patients do not belong in regulatory measures; such recommendations are more appropriate for clinical practice guidelines, where the strengths and limitations of the supporting evidence can be delineated, the recommendations can be graded, and providers have flexibility to determine whether and how each recommendation applies to their specific patients. Hospitals may elect to augment the actions stipulated by federal or state mandates with additional interventions, including those recommended by guidelines. However, such additions should be their prerogative based on local needs assessments and opportunities.

INFECTIOUS DISEASES SOCIETY OF AMERICA'S MAJOR CONCERNS WITH THE SEVERE SEPSIS AND SEPTIC SHOCK EARLY MANAGEMENT BUNDLE

SEP-1's Requirement to Immediately Administer Antibiotic Therapy for All Patients with Possible Sepsis Risks Increasing Excessive and Unwarranted Antibiotic Administration

Mandatory quality measures can have unintended and harmful consequences. There are important lessons in this regard from the 2002 CMS core pneumonia measure, which required clinicians to administer antibiotics to patients with community-acquired pneumonia within 4 hours of hospital arrival. This measure was recommended on the basis of retrospective analyses of patients with pneumonia discharge diagnosis codes, rather than randomized trials of early intervention versus usual care for patients with possible pneumonia [13]. When the measure was applied prospectively and clinicians had to contend with the complexity of rapidly differentiating bacterial pneumonia from viral pneumonia and noninfectious conditions with similar presentations, it led to more antibiotic prescribing for uninfected patients and a rise in *Clostridioides difficile* infections, but had no impact on pneumonia mortality rates [13–16]. Clinicians admitted that they felt compelled to prescribe potentially unnecessary antibiotics to patients with ambiguous syndromes rather than risk being penalized for failing to prescribe antibiotics for the subset of patients later found to have pneumonia [17].

Sepsis quality measures carry similar risks, since the signs and symptoms of sepsis, like those of pneumonia, are nonspecific and often subjective, especially in the first hours after presenting for care [18]. Sepsis is even more complicated and challenging than pneumonia, however, because it includes a heterogeneous mix of infections and organ dysfunctions, all of which have many noninfectious mimics (Table 1). Up to 40% of patients initially treated for sepsis have a low post hoc probability of bacterial infection; hence, a forced rush to treatment will expose many patients to the risks of antibiotics without any benefit [19–21]. A regulatory emphasis on sepsis may also predispose clinicians to prematurely favor infectious diagnoses and, thus, delay the identification of serious, noninfectious conditions [19, 22].

The risks of unnecessary antibiotics are often overlooked in the context of the high mortality rate associated with sepsis. However, antibiotic over-prescribing has contributed to the global crisis of antibiotic resistance and antibiotic resistance–related deaths [23]. Failure to de-escalate empiric broad-spectrum therapy is common, even when cultures are negative [24]. Up to 20% of hospitalized patients who receive antibiotics suffer an adverse effect, and each day of antibiotic use increases the risk of *C. difficile* infection, acute kidney injury, antibiotic resistance, and disruption of the gut microbiome [25–31]. Multiple hospitals have reported an increase in both broad-spectrum antibiotic use and *C. difficile* rates after instituting aggressive screening and treatment protocols for sepsis [32, 33]. Indeed, aggressive antibiotic prescribing in critically ill patients has been associated with higher mortality rates compared to more conservative practices in some studies [34–36].

Conflating the Urgency of Antibiotic Administration for Sepsis and Septic Shock

SEP-1 stipulates the same time-to-antibiotic goal for both sepsis and septic shock, but the association between time-to-antibiotics and mortality is much stronger for septic shock than

Table 1. Conditions That Can Mimic Sepsis

Category	Examples
Cardiac disease	Arrhythmias
	Heart failure
	Myocardial infarction
Pulmonary disease	Acute respiratory distress syndrome
	Aspiration pneumonitis
	Asthma exacerbation
	Bronchiectasis exacerbation
	Chronic obstructive pulmonary disease exacerbation
	Interstitial lung disease flare
	Hypersensitivity pneumonitis
	Pulmonary embolism
Gastrointestinal disease	Acute liver failure
	Bowel obstruction
	Gastrointestinal hemorrhage
	Inflammatory bowel disease
	Mesenteric ischemia
	Pancreatitis
	Volvulus
Central nervous system disease	Autonomic dysfunction
	Seizure
	Stroke/intracranial hemorrhage
Endocrine disease	Adrenal insufficiency
	Diabetic ketoacidosis
	Myxedema coma
	Thyroid storm
Hematologic/oncologic disease	Antiphospholipid syndrome
	Malignancy
	Hemophagocytic syndrome
	Tumor lysis syndrome
Rheumatologic/autoimmune disease	Gout
	Rheumatoid arthritis
	Still's disease
	Systemic lupus erythematosus
	Vasculitis
Drugs/toxins	Drug overdose
	Drug/alcohol withdrawal
	Hypersensitivity drug reaction
	Medication toxicity
	Malignant hyperthermia
	Neuroleptic malignant syndrome
	Serotonin syndrome
Other	Allograft rejection (solid organ transplant recipients)
	Anaphylaxis
	Compartment syndrome
	Heat stroke
	Hemorrhage
	Hypovolemia
	Postoperative period
	Severe burns
	Tissue ischemia

it is for sepsis without shock (Table 2) [37–45]. IDSA believes the perception that any delays in antibiotic therapy lead to worse outcomes for patients with sepsis, regardless of the severity of illness, contributes to inappropriate antibiotic prescribing and is the wrong message to communicate to providers.

The studies cited by the 2016 Surviving Sepsis Campaign guidelines that showed an association between time-to-antibiotics and mortality were all limited to critically ill patients, most or all of whom had septic shock [37–40, 46]. The 2 studies cited by the guidelines that did include patients without shock were nonetheless still restricted to intensive care unit patients, were dominated by septic shock, and did not report on the association between time-to-antibiotics and mortality in the nonshock subpopulation [37, 40].

More data have emerged since the publication of the 2016 Surviving Sepsis Campaign Guidelines. There are 2 very large studies of the impact of timely sepsis care in New York State and Northern California that provide new data on outcomes in sepsis with versus without shock [41, 43]. Both of these studies found little or no association between time-to-antibiotics and mortality in sepsis without shock, but strong associations for sepsis with shock [41, 43]. A third large study, which was limited almost exclusively to patients without shock, found that the risk for hospital death only clearly and consistently increased after intervals of ≥5 hours from presentation [44].

A recent analysis did report that each hour delay in antibiotics in sepsis without shock was associated with an increased risk of progression to septic shock [42]. However, the hourly estimate was based on averaging hourly rates of progression over a 24-hour period; the raw data only indicated higher rates of progression to septic shock with delays of ≥5 hours.

It must be noted that almost all the data we have on the association between the time-to-antibiotics and mortality come from observational studies that often fail to account for important potential confounders, such as the severity of illness, adequacy of the antibiotic choice and dose, source control, presenting signs and symptoms, and the presence of concurrent illnesses. In addition, many of the observational studies only analyze patients with sepsis discharge diagnosis codes. This creates a bias towards individuals with more severe illnesses (since sepsis codes tend to be preferentially applied to sicker patients) and ignores the possible harms caused to patients initially treated for possible sepsis but subsequently found to have noninfectious diagnoses [47]. To date, the only randomized trial that has examined differential timing of antibiotics in sepsis compared prehospital antibiotic administrations versus antibiotics in the emergency department [48]. The vast majority of patients in this study had infection alone or sepsis without shock. The investigators found no difference in mortality rates despite >90-minute differences between arms in the time-to-antibiotics.

Recognizing that the importance of the time-to-antibiotics is much greater in septic shock than in sepsis without shock is critical, because it dramatically changes the risk-benefit ratio for immediate antibiotics versus rapid investigation followed by antibiotics only if suspicion for bacterial infection persists. In patients without shock, if the evidence for an infection is

Table 2. Major Observational Studies Assessing Time-to-Antibiotics and Mortality in Adult Patients With Sepsis

Reference	Study Design and Setting	Sample Size	% ICU Patients	% Septic Shock	Main Findings: Time-To-Antibiotics and Mortality (or Other Outcome)	Effect Estimate: Septic Shock	Effect Estimate: Sepsis Without Shock	Comments
Barie et al, Surg Infect (Larchmt), 2005 [37]	Prospective: 1 surgical ICU in New York	356	100%	Not reported	OR 1.021 [1.003–1.038] for in-hospital death with each 30-minute delay	Not reported	Not reported	Time zero based on suspected infection rather than any physiologic criteria
Kumar et al, Crit Care Med, 2006 [38]	Retrospective: 14 ICUs in 10 hospitals in Canada	2154	100%	100%	OR 1.119 [1.103–1.136] for in-hospital death with each hr delay	Same as primary finding (all patients had septic shock)	N/A	Time-to-antibiotics measured after onset of persistent or recurrent hypotension
Gaieski et al, Crit Care Med, 2010 [39]	Retrospective: 1 university hospital ED	261	100%	100%	OR 0.30 [0.11–0.83] for in-hospital death if antibiotics given <1 hr from triage; OR 0.50 [0.27–0.92] if given <1 hr from qualifying for EGDT	Same as primary finding (all patients had septic shock)	N/A	No significant association between time-to-antibiotics and mortality at different hourly cutoffs other than <1 hr
Ferrer et al, Crit Care Med, 2014 [40]	Retrospective: 165 ICUs in the Surviving Sepsis Campaign database	17 990	100%	64%	OR for in-hospital death: hr 1–2, 1.07 [0.97–1.18]; hr 2–3, 1.14 [1.02–1.26]; hr 3–4, 1.19 [1.04–1.35]; hr 4–5, 1.24 [1.06–1.45]; hr 5–6, 1.47 [1.22–1.76]; hr > 6, 1.52 [1.36–1.70]	Not reported	Not reported	Statistically significant signal for mortality only seen after hr 2
Liu et al, Am J Resp Crit Care Med, 2017 [41]	Retrospective: 21 EDs in Northern California	35 000	21%	13%	OR 1.09 [1.05–1.13] for in-hospital death with each hr delay	OR 1.14 [1.06–1.23]	OR 1.07 [1.01–1.24]	Cohort identified by sepsis billing codes; ORs represented linearized estimates across 6 hrs but increase in mortality was not linear; increase in absolute mortality per hr delay much higher with septic shock (1.8%, vs severe sepsis [0.4%] and sepsis [0.3%])
Whiles et al, Crit Care Med, 2017 [42]	Retrospective: 1 ED in Kansas	3929	59%	0%	OR 1.08 [1.06–1.10] for progression from severe sepsis to septic shock with each hr delay; OR 1.05 [1.03–1.07] for in-hospital death with each hr delay	N/A	Same as primary finding (all patients had no shock on presentation)	Cohort identified by sepsis billing codes; ORs represented linearized estimates across 24 hrs but no change in proportion of severe sepsis patients progressing to septic shock with antibiotic delays until after hr 5
Seymour et al, N Engl J Med, 2017 [43]	Retrospective: 149 hospitals in New York	49 331	Not reported	45%	OR 1.04 [1.03–1.06] for in-hospital death with each hr delay	OR 1.07 [1.05–1.09] for patients who required vasopressors	OR 1.01 [0.99–1.04] for no vasopressors	Risk-adjustment model had modest performance (AUROC = 0.77); ORs represented linearized estimates across 12 hrs but increase in mortality was not linear

Table 2. Continued

Reference	Study Design and Setting	Sample Size	% ICU Patients	% Septic Shock	Main Findings: Time-To-Antibiotics and Mortality (or Other Outcome)	Effect Estimate: Septic Shock	Effect Estimate: Sepsis Without Shock	Comments
Peltan et al, Chest, 2019 [44]	Retrospective: 4 hospitals in Utah	10 811	29%	8%	OR 1.10 [1.05–1.14] for 1-year mortality with each hr delay OR 1.12 [1.06–1.18] for in-hospital death with each hr delay	OR 1.13 [1.00–1.28] for patients with hypotension	OR 1.09 [1.05–1.13] for no hypotension	ORs represented linearized estimates across >15 hrs but increase in mortality was not linear; No significant increase in 1-year mortality seen until hr 3; no increase in in-hospital mortality until hr 5
Ko et al, Am J Med, 2019 [45]	Prospective: 10 EDs in South Korea	2229	Not reported	100%	OR for in-hospital death: hr 1–2, 1.248 [1.053–1.478]; hr 2–3, 1.186 [0.999–1.408]; hr > 3, 1.419 [1.203–1.675]	Same as primary finding (all patients had septic shock)	N/A	No clear linear association between each hour delay and in-hospital mortality

Abbreviations: AUROC, area under the receiver operating characteristic curve; ED, emergency department; EGDT, early goal-directed therapy; hr, hour; ICU, intensive care unit; N/A, not applicable; OR, odds ratio; pts, patients.

ambiguous, in many cases clinicians can safely take additional time to obtain laboratory and imaging results and assess the impact of nonantibiotic therapies; even a few short hours can be highly informative in helping determine whether antibiotics are indicated [49, 50]. If the balance of clinical evidence favors infection, then antibiotics should be given expeditiously.

Our focus on septic shock should not be misconstrued to suggest that antibiotics should be withheld from patients with suspected infection until hypotension develops or until an infection is fully confirmed. Some normotensive patients with infections can be quite severely ill; worrisome signs can include an altered mental status, severe lactic acidosis, respiratory distress, multiple organ dysfunction, or a general toxic appearance. The decision of whether and when to start empiric antibiotics in patients without shock, however, is a nuanced and complicated matter that requires balancing the patient's likelihood of infection, site of infection, severity of illness, and possible benefits versus the risks of antibiotics. This calculus is too nuanced for a national quality measure and, thus, is more appropriately addressed by clinical guidelines and educational initiatives and then left to individual clinicians' discretion.

Bundle Studies are at High Risk for Bias and Likely Overestimate Benefits

There are 2 major lines of evidence that are used to support the mandated roll-out of bundled sepsis care: (1) before/after studies that demonstrate a reduction in sepsis mortality after bundle implementation [51–56]; and/or (2) studies of association that report lower mortality rates in sepsis patients who received bundle-compliant care versus those who did not [41, 43, 55, 57]. Both of these types of observational studies, however, are at high risk for bias.

Before/After Analyses

Before/after studies are at high risk for ascertainment bias because sepsis bundle rollouts typically include educational initiatives and new screening protocols designed to enhance sepsis recognition. This leads to the increased detection of patients with milder forms of sepsis and, thus, an increase in the overall number of sepsis cases and a parallel decrease in mortality [58]. The risk of ascertainment bias is particularly high in studies that use administrative data, given that coding for sepsis tends to increase over time in response to new policies, financial incentives, and campaigns to improve documentation [59–61].

A recent study using administrative data to study the impact of mandated sepsis care in New York State underscores the problem of ascertainment bias [56]. This study reported a greater decrease in sepsis mortality rates in New York State after mandatory sepsis protocols were introduced, compared to control states without mandates, but the study also documented a 34% increase in patients with sepsis codes during the intervention period: an increase that more likely represents changing documentation and coding strategies rather than an expansion

in patients meeting consistent criteria for sepsis, given that the change took place over a period of less than 5 years [56]. Ironically, sepsis mortality rates were still higher in New York State at the end of the intervention period, compared to control states, which may reflect variation in coding practices rather than true differences in mortality and, thus, underscores the difficulty of using administrative data to evaluate sepsis initiatives and to compare outcomes between health-care systems or regions [62].

Furthermore, many before/after studies only analyzed outcomes in patients diagnosed with sepsis and did not report on the outcomes and potential adverse effects of aggressive fluids and antibiotics in patients ultimately diagnosed with noninfectious conditions [56]. The rush to treatment for patients who initially appear septic but are subsequently found to have noninfectious conditions needs to be included in SEP-1 evaluations in order to determine the full spectrum of benefit and harm from the measure.

Analyses Associating Higher Bundle Compliance with Lower Sepsis Mortality

Several studies, including analyses of the Surviving Sepsis Campaign database and New York State cohort, have reported associations between higher bundle compliance or time-to-bundle completion and lower risk-adjusted mortality rates [41, 43, 55, 57]. However, in addition to ascertainment bias from enhanced sepsis detection, there may be important differences in patients who receive bundle-compliant versus noncompliant care.

Clinicians are less likely to administer bundle-compliant fluid volumes to patients with heart failure, chronic kidney disease, or cirrhosis, thus raising the question of whether higher mortality rates in bundle–noncompliant patients are due to noncompliance with the bundle or these patients' underlying comorbidities [63]. Similarly, patients who develop sepsis while in the hospital are less likely to receive bundle-compliant care but are also more severely ill and at higher risk of death [64]. Furthermore, most analyses have not adjusted for patients' presenting signs, even though patients with explicit signs of infection, such as fever, are recognized more rapidly, treated sooner, have fewer comorbidities, and experience better outcomes, compared to patients with vague presenting signs and symptoms who may have confounding acute illnesses and comorbidities [65–67]. Adjusting for these confounders can diminish or eliminate the association between sepsis bundle completion rates and mortality [63, 68].

Definition for Time Zero is Complex, Subjective, and Not Evidence-based

SEP-1's time zero definition requires documentation of suspected infection, systemic inflammatory response syndrome criteria, and 1 or more of 8 potential organ dysfunction criteria (Table 3). These criteria were adapted from the 2012 Surviving Sepsis Campaign Guidelines, but there is no clear evidence supporting the specific organ dysfunctions or thresholds chosen [69, 70]. In particular, we are not aware of any high-quality studies demonstrating the benefit of immediate antibiotics in patients whose only signs of organ dysfunction are abnormal creatinine, bilirubin, a marker of coagulopathy, or mildly elevated lactate.

The complexity of SEP-1's time zero criteria means it can take chart abstractors several hours per chart to identify this moment [5]. Abstractors must comb through multiple notes to identify when an infection was first suspected, how this moment aligned with vital sign and laboratory abnormalities, and whether any organ dysfunction criteria were present and related to the infection. Calculating the time of fluid bolus completion to identify persistent hypotension requires adding up multiple flow sheet entries and, often, making assumptions about flow rates. Defining septic shock as persistent hypotension after a 30 cc/kg fluid challenge is particularly difficult and error-prone because it further requires weight-based calculations [5]. Given these challenges, it is unsurprising that abstractors frequently disagree on time zero [71, 72]. For example, abstractors in 1 study only agreed on time zero in 36% of cases; this led to an almost 2-fold difference in perceived SEP-1 bundle compliance rates [72]. Retraining and central adjudication by experienced abstractors can mitigate this variability, but this may not be available or achievable in all hospitals [71]. Notably, SEP-1 time zero can also be triggered by clinician documentation of suspected severe sepsis or septic shock even if the patient does not have objective clinical findings associated with sepsis. This is problematic, because sepsis is part of the differential diagnosis for a wide range of conditions, and SEP-1 does not consider clinicians' level of suspicion. Requiring bundled care when the suspicion of sepsis is low is counterproductive and might lead providers to prescribe unnecessary antibiotics, or avoid appropriately documenting that they have considered the diagnosis of sepsis.

Mandating Lactate Measurements for all Patients with Possible Sepsis

Lactate levels have prognostic significance, but there is very limited evidence that measuring lactate or serial lactates improves outcomes compared with clinical evaluations alone [73–75]. A retrospective analysis found that delays in initial lactate measurement were associated with longer times to antibiotics and higher mortality rates, but this study was subject to similar risks of confounding and bias as studies of the time-to-bundle completion [76]. In a 2-year observational study conducted at 7 hospitals, failure to measure lactate levels was the most common reason for SEP-1 noncompliance, yet failing SEP-1 for this reason alone was not associated with higher mortality [68]. A meta-analysis of 4 small randomized trials on early lactate clearance–guided

Table 3. Infectious Diseases Society of America's Proposed Changes to the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Measure

Current SEP-1 Measure	IDSA Recommendations and Rationale	IDSA Proposed SEP-1
Definitions		
Severe sepsis •Documentation of suspected or confirmed infection, AND •≥2 SIRS criteria, AND •≥1 organ dysfunction (8 possible criteria)[a] •OR documentation of suspected severe sepsis (regardless of clinical criteria)	•Eliminate from SEP-1 (weak evidence for necessity of immediate antibiotics in sepsis without shock; many potential noninfectious mimickers may be treated with antibiotics unnecessarily and lead to promoting widespread unnecessary antibiotic prescribing; complex and heterogeneous criteria lead to variability in abstraction)	…
Septic shock •Documentation of suspected or confirmed infection, AND •≥2 SIRS criteria, AND •Persistent hypotension after 30 cc/kg of fluids, or lactate ≥4.0 mmol/L •OR documentation of suspected septic shock (regardless of clinical criteria)	•Eliminate SIRS requirement (shock and suspected infection are sufficient evidence of septic shock; SIRS criteria add complexity to time zero abstraction) •Modify persistent hypotension definition to more objective and reproducible clinical criteria (30 cc/kg not evidence-based and difficult to abstract) •Eliminate documentation of possible or suspected septic shock as potential trigger (poor proxy for clinical recognition; does not take into account level of suspicion)	•Documentation of suspected or confirmed infection, AND •Objective and reproducible clinical criteria for shock (precise "time zero" definition warrants discussion with other expert task forces)
Management bundles		
3-hour bundle		
•Measure lactate level	•Eliminate (not specific for infection; clear evidence of clinical benefit is lacking)	…
•Blood cultures (prior to antibiotics)	•Agree	•Blood cultures (prior to antibiotics)
•Broad-spectrum antibiotics	•Agree but decrease time requirement for septic shock (strong evidence that each hour delay increases risk of death)	•Administer broad-spectrum antibiotics within 1 hour of septic shock "time zero" •Report time interval between antibiotic order and delivery for the first broad-spectrum antibiotic
•30 cc/kg intravenous fluids for hypotension or lactate ≥4.0 mmol/L	•Defer to other expert task forces	…
6-hour bundle		
•Remeasure lactate if initial level >2.0 mmol/L	•Eliminate (evidence of clinical benefit is lacking)	…
•Vasopressors to target mean arterial pressure ≥65 mmHg for persistent hypotension after 30 cc/kg fluids	•Defer to other expert task forces	…
•Document repeat volume status and perfusion assessment for septic shock	•Defer to other expert task forces	…

Abbreviations: IDSA, Infectious Diseases Society of America; SEP-1, Severe Sepsis and Septic Shock Early Management Bundle; SIRS, systemic inflammatory response syndrome.
[a]Time zero organ dysfunction criteria for severe sepsis include: systolic blood pressure <90 mmHg or decrease by >40 mmHg or mean arterial blood pressure <65 mmHg; lactate >2.0 mmol/L; initiation of mechanical ventilation or noninvasive positive pressure ventilation; creatinine >2.0 mg/dL, or urine output <0.5 mL/kg/hour for 2 hours; total bilirubin >2 mg/dL; platelet count <100 000 × 10^9/L; international normalized ratio >1.5; or activated partial thromboplastin time >60 seconds.

therapy reported a possible benefit for measuring lactate [77], but a recent randomized trial found that resuscitation informed by the physical examination of peripheral perfusion was associated with similar 28-day mortality as compared to lactate-guided resuscitation and was associated with less organ dysfunction at 72 hours [78].

Importantly, hyperlactatemia is not specific for sepsis. Lactate can be elevated in any condition that causes shock, as well as in malignancies, renal or liver disease, drug or toxin ingestions, and congenital enzyme deficiencies [79]. Requiring clinicians to measure lactate levels in all patients presenting with any syndrome resembling sepsis, and then requiring immediate antibiotics for those with mildly elevated lactate levels who may otherwise be clinically well, risks driving further antibiotic overuse.

INFECTIOUS DISEASES SOCIETY OF AMERICA'S RECOMMENDATIONS TO MODIFY THE SEVERE SEPSIS AND SEPTIC SHOCK EARLY MANAGEMENT BUNDLE

Sepsis Without Shock Should be Removed from SEP-1

The evidence supporting the impact of immediate antibiotics on survival is strong for septic shock and weak for sepsis without shock. IDSA therefore recommends focusing SEP-1 on septic shock alone. While early empiric antibiotics are appropriate for some patients with suspected sepsis who are not in shock, there is too much heterogeneity in this population and uncertainty about the presence or absence of infection to support one mandatory treatment standard for all patients. Removing sepsis without shock from SEP-1 will mitigate the risk of indiscriminate prescribing for patients who present with signs and

symptoms resembling sepsis but with a low likelihood of infection. The impact on unnecessary prescribing could be large because many more patients present with sepsis without shock than sepsis with shock [80]. Limiting SEP-1 to septic shock alone will also simplify the time zero abstraction (see below).

Note again that this recommendation is in no way intended to detract from the importance of immediate antibiotics in rapidly progressive, life-threatening infections without shock, such as acute meningitis, necrotizing soft tissue infections, acute epiglottitis, and others. However, these syndromes account for a minority of patients and are better dealt with through targeted clinical education and guidelines, rather than through blunt regulatory measures that compel a single treatment pathway for all conditions.

Obtaining Blood Cultures Before Antibiotics Should Remain Part of SEP-1

Obtaining blood cultures before versus after antibiotics doubles the rate of pathogen recovery [81–83]. While drawing blood cultures has not been directly linked to patient outcomes, blood cultures provide important diagnostic information to help guide both immediate patient treatment and long-term population management. Positive blood cultures facilitate targeted, pathogen-specific therapy and antibiotic de-escalation, which may result in fewer adverse effects. In addition, the resistance profiles of organisms detected in blood cultures provide crucial data to create hospital antibiograms and inform empiric prescribing guidelines.

The Interval from Septic Shock Time Zero to Initiation of Broad-spectrum Antibacterial Therapy Should be 1 Hour or Less

IDSA believes a 1-hour treatment target is plausible and justifiable, compared to 3 hours, given the urgency of septic shock [10, 38, 41, 43]. When septic shock is a possibility, emergent evaluation and initiation of broad-spectrum empiric antibiotic coverage are warranted even if the diagnosis of infection is unclear based on the information available at that point. The potential benefit of timely antibiotics in this case outweighs the risk of unnecessary antibiotics in the subset of patients who turn out to be uninfected [50]. IDSA acknowledges, however, that the feasibility of a 1-hour antibiotic measure depends on the precise time zero definition used (see below).

SEP-1 Should Use a Clear and Reproducible Definition of Septic Shock Time Zero

Limiting SEP-1 to septic shock alone will simplify time zero by eliminating the heterogeneous and complicated organ dysfunction criteria required to identify sepsis without shock. The current SEP-1 definition for septic shock, however, still requires identifying the moment when infusing 30cc/kg of intravenous fluids has been completed: a subjective and onerous task [5].

We therefore recommend simplifying SEP-1's criteria for septic shock. Possible options to consider include serial blood pressure measurements below a certain threshold, failure to respond to fixed volumes of crystalloids, very high lactate levels, and/or the time of vasopressor initiation. Refractory hypotension after a fixed-volume challenge (eg, 1 or 2 liters) or an initial lactate $\geq$4.0 mmol/L would mirror the entry criteria for recent randomized controlled trials of early septic shock care [84–86]. The time of vasopressor initiation is a relatively late indicator of shock but has the advantages of being objective, being easily extractable from electronic health record systems, and avoiding the complexity of accounting for patients' baseline blood pressure or totaling up fluid administrations.

IDSA does not have 1 firm recommendation for defining septic shock time zero; instead, all SEP-1 stakeholders should be invited to comment on the merits and limitations of different time zero options in order to reach consensus on the best balance between clinical validity and ease of abstraction in the variety of clinical settings where patients with sepsis and septic shock are recognized and managed. Prospective studies on the feasibility, reproducibility, and meaningfulness of different options to define time zero are warranted.

IDSA notes that emergency department triage time has been proposed as a potential time zero for sepsis [87]. Defining time zero as triage time, however, ignores the fact that diagnosing sepsis requires a constellation of clinical signs and laboratory findings that are rarely all present on arrival and may evolve over time. More than 50% of septic patients do not meet SEP-1 criteria until more than an hour after arriving in the emergency department, and even patients admitted with septic shock often do not have hypotension or explicit signs of infection at triage [88, 89]. While early recognition and treatment are important goals, setting expectations for treating all patients with possible sepsis within 1 or even 3 hours of triage time, when most patients are still undifferentiated, risks driving antibiotic overuse.

Similarly, using the time of sepsis recognition is also problematic because it is subjective and difficult to identify through retrospective chart reviews. Furthermore, time zero should not be triggered merely by clinician documentation of suspected or possible sepsis, since the time of documentation is a poor proxy for the time of recognition; this could penalize clinicians and hospitals for including sepsis within their preliminary differential diagnoses in patients presenting with undifferentiated syndromes that turn out to be noninfectious.

SEP-1 Should Require Hospitals to Report Time Intervals

Optimizing the time to recognition of possible septic shock is only part of the equation when it comes to delivering timely and appropriate antibiotics. Hospitals also need to be attentive to their systems for delivering antibiotics once they have been ordered [90, 91]. All health-care systems should, therefore, work to streamline their antibiotic delivery systems to minimize the time interval between each stat antibiotic order for septic

shock and initiation of the infusion. IDSA hopes that reporting this time interval will help draw hospitals' attention to this important aspect of timely care and drive improvements in drug delivery systems. Operationally, hospitals could be required to report this interval for either the first antibiotic or for each antibiotic ordered for septic shock within a certain time window.

Lactate Measurements Should be Removed from SEP-1

Including lactate measurements in a national quality measure may promote indiscriminate testing that risks unnecessary fluids, diagnostic evaluations for infection, and antibiotic prescribing for noninfected patients. IDSA acknowledges that lactate values can add important clinical information in certain patients, but believes guidance on the appropriate role of lactate testing in sepsis diagnosis, risk stratification, and resuscitation is nuanced and, thus, better left to clinical discretion informed by clinical guidelines rather than compelled by a single, homogeneous quality measure for all patients.

OTHER IMPORTANT INFECTION-RELATED CONSIDERATIONS

IDSA recognizes that there are many other critical aspects to the infectious disease care of septic patients beyond those discussed above. For example, IDSA encourages the use of rapid diagnostic tests; the targeted selection of culture sites, depending upon patients' presenting signs and symptoms; and the targeted selection of empiric antibiotics [92]. Given the variability in patient presentations and the rapidly evolving availability of diagnostic assays, specific testing cannot be reduced to simple rules within a national quality measure.

Mandates for source control are similarly problematic, due to the variability in patient presentations [46]. Source control requires considerable judgement as to when, whether, and how best to intervene, depending upon a patient's clinical stability, comorbidities, suspected or known pathogens, site of infection, presence and type of prosthetic material, procedural safety and feasibility, and more. Studies examining the association between the time to source control and outcomes have been limited by small numbers of patients, heterogeneous sites of infection, and different thresholds for timeliness, but most have reported benefits [93–98]. Thus, IDSA believes that timely source control should be strongly recommended in guidelines but is not suitable to include in mandatory quality metrics.

Lastly, IDSA encourages the use of daily antibiotic "time-outs" to assess the appropriateness of currently prescribed antibiotics and whether they can be de-escalated or stopped [92]. This practice has been associated with reductions in *C. difficile* rates, antibiotic resistance, and costs, and could potentially help counterbalance the antibiotic overuse spurred by SEP-1 [99–101]. However, implementing antibiotic time-outs so that they are effective and not unduly burdensome requires further evaluation and testing before incorporation into a national mandate.

CONCLUSION

National quality measures have the potential to substantially improve patient outcomes. However, they should be limited to clearly beneficial interventions with strong supporting evidence while being attentive to the possibility of unintended, harmful consequences. IDSA therefore recommends focusing SEP-1 on drawing blood cultures and administering antibiotics within 1 hour of septic shock recognition, since the evidence best supports the urgency and benefit of immediate antibiotics in this population. IDSA acknowledges that prompt empiric antibiotics are often appropriate for suspected sepsis without shock, but believes this should be an individual clinical determination based on varied and sometimes nuanced patient factors that cannot be adequately addressed by a regulatory mandate. IDSA believes that direction on managing suspected sepsis without shock is more appropriate for guidelines, where the subtleties of the supporting evidence can be delineated and clinicians have more room for discretion about whether and how to apply recommendations to their patients. Removing sepsis without shock from SEP-1 will diminish the pressure on clinicians to prescribe antibiotics to uninfected patients presenting with sepsis-mimicking syndromes, simplify data abstraction, increase measure reliability, and allow hospitals to focus their resources on the patients most likely to benefit from aggressive care.

IDSA and its partner stakeholders are pleased to be meeting with the Quality Measurement and Value-Based Incentives Group in the Center for Clinical Standards and Quality at CMS to discuss the recommendations outlined in this position paper, review currently available data and gaps in the literature, and present additional perspectives of providers from several disciplines. These discussions will hopefully lead to an improved measure that all parties can embrace and will further enhance the goal that CMS and all stakeholders share: to improve patient outcomes.

Notes

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