Timing and Spectrum of Antibiotic Treatment for Suspected Sepsis and Septic Shock

Why so Controversial?

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KEYWORDS

• Sepsis • Evidence-based medicine • Retrospective studies • time-to-antibiotics • antibiotic stewardship • quality improvement

KEY POINTS

- A third or more of patients treated for possible sepsis or septic shock have noninfectious conditions or nonbacterial infections.
- The literature on the association between time-to-antibiotics and mortality is almost exclusively observational and at high risk of bias. Sources of bias include failure to differentiate between sepsis and septic shock, insufficient adjustment for potential confounders, and blending together the high increases in mortality associated with very long delays until antibiotics with the small or absent effects associated with short delays until antibiotics, thus generating a misleading impression that every hour until antibiotics increases mortality and does so equally.
- Choosing appropriate empiric antibiotics for patients with possible sepsis or septic shock is a balancing act: both failure to cover the active pathogen and treating with unnecessarily broad regimens are associated with increased mortality.
- Clinicians are advised to tailor the timing and breadth of antibiotics for each patient with possible sepsis and septic shock to each individual's likelihood of infection, risk factors for resistant pathogens, and severity of illness.

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BACKGROUND

Sepsis, defined as a dysregulated host response to infection leading to acute organ dysfunction, affects millions of patients per year. It is associated with 850,000 visits to US emergency departments (EDs) annually[1] and one-third of US hospitalizations that end in death or discharge to hospice.[2] Guidelines on sepsis management have long emphasized that early recognition and treatment are key to lowering mortality. Many observational studies have attempted to quantify the association between delays in antibiotics and mortality risk. One of the earliest studies analyzed 2,731 cases of septic shock and estimated that mortality increased by 7.6% for every hour until effective antimicrobials were administered after the onset of recurrent or persistent hypotension.[3] Subsequent studies have not replicated as dramatic a result,[4] but associations of about 1% absolute increase in mortality risk per hour have been reported by several large studies that included tens of thousands of patients.[5–7]

Based in part upon these data, the Surviving Sepsis Campaign (SSC), the Centers for Medicaid and Medicare Services (CMS), the New York State Department of Health, and other state regulators have promoted 1-h or 3-h bundles of care for sepsis that include requirements to give empiric broad-spectrum antibiotics within brief time windows.[8–11] In 2016, SSC guidelines reaffirmed a target of less than 1 h to deliver antibiotics for all patients with sepsis (per Sepsis-3 definitions) or septic shock.[10,12,13] The Severe Sepsis and Septic Shock Management (SEP-1) bundle by CMS was implemented in 2015 and modeled on SSC guidelines.[14] It requires lactate measurements, blood cultures, and broad-spectrum antibiotics within 3 h of meeting specific physiologic criteria for severe sepsis with or without shock (per Sepsis-2 definitions).

These recommendations stirred considerable controversy. The Infectious Diseases Society of America (IDSA), for example, withheld their endorsement from the 2016 SSC guidelines.[15] One of their primary concerns was the SSC guidelines' failure to acknowledge the high levels of uncertainty inherent to the diagnosis of sepsis. Up to 40% of patients treated with antibacterials for possible sepsis turn out to have noninfectious conditions or nonbacterial infections.[16,17] These patients risk suffering the potential harms of antibacterial treatments without their potential benefits. These potential harms are not insignificant; a growing body of literature associates unnecessary antibiotics and unnecessarily broad antibiotics with higher rates of *Clostridioides difficile* infections, acute kidney injury, selection for resistant pathogens, and in some studies higher mortality rates.[18–20] IDSA feared that 1-h or even 3-h time-to-treatment requirements would perpetuate or exacerbate the problem of overtreatment given the difficulty of establishing a clear diagnosis within this timeframe, and thus inadvertently cause more harm than benefit to patients.

Moreover, IDSA noted substantial weaknesses in the data being used to support sepsis management bundles and their strict time-to-antibiotic deadlines, finding that nearly all studies on the association between time-to-antibiotics and mortality were at substantial risk of bias.[4,15] As such, the premise driving strict time-to-treatment mandates was potentially flawed. Finally, the 2016 SSC guidelines equated patients with *suspected sepsis* and *suspected septic shock* for the purposes of recommending the 1 h time-to-treatment, even though these groups have very different associations between time-to-antibiotics and mortality.[7,9] Studies published after the 2016 guidelines were released have reported that the association between time-to-antibiotics and mortality for sepsis without shock is much weaker than that for septic shock, and when present, the signal suggesting increased mortality in sepsis without shock only becomes apparent after delays of three to 5 h, not 1 h.[21,22]

Challenges in Interpreting Evidence on Antibiotic Delays and Associated Outcomes

How has the evidence regarding timing of antibiotics for sepsis patients led to such a wide range of conclusions? First, most of the evidence available for this question is from retrospective observational studies, given the difficulty of performing prospective trials that randomize patients to different antibiotic strategies during emergency care. We are only aware of two randomized controlled trials (RCTs) specifically examining the impact of faster time-to-antibiotics for sepsis on patient outcomes. One was a randomized trial of antibiotics in the prehospital setting versus the ED for patients with suspected sepsis.[23] Despite a 96-min difference in median time to antibiotics between groups there were no significant differences in mortality. The second study was a randomized trial comparing a multifaceted set of interventions focusing on reducing time-to-antibiotics versus conventional continuous medical education.[24] Unfortunately, this study did not achieve a significant difference in time-to-antibiotics between groups and thus was uninformative on this specific question. All the other evidence for the existence of an association between time-to-antibiotics and increased mortality is from observational studies, which carry inherent risks of confounding and are more difficult to interpret as causal evidence.

Second, most early observational studies (particularly those cited by SSC in 2016) were limited to intensive care unit (ICU) populations and thus enriched with a high proportion of patients with septic shock, potentially introducing unintended bias when formulating guidelines for all sepsis patients, including those without shock. Most of these studies did not perform subgroup analyses comparing sepsis with and without shock, and the few studies that included subgroup analyses found smaller associations or no significant association for sepsis without shock.[21] For example, in 35,000 presentations of sepsis to California EDs, there was an absolute increase in mortality of 1.8% (95% confidence interval [CI], 0.8%–3.0%; adjusted odds ratio [aOR], 1.14; aOR 95% CI, 1.06 to 1.23) associated with each hour of delay in antibiotics for patients with septic shock, whereas for severe sepsis patients without shock, this association shrank to 0.4% (95% CI, 0.1%–0.8%; aOR, 1.07; aOR 95% CI, 1.01–1.24).[7] Similarly, a study of 49,331 patients triggering sepsis protocols in New York EDs found a significant association between in-hospital death and hourly delays in completing a bundle that included antibiotics among patients that required vasopressors (aOR, 1.07; 95% CI, 1.05–1.09), but the association was not significant for patients not requiring vasopressors (aOR, 1.01; 95% CI, 0.99–1.04).[9] So too, in a study of 10,811 adult ED patients in Utah with sepsis predominantly without shock (92% did *not* have septic shock) there was no impact on 30-day mortality until $\geq$5 h had elapsed from ED triage until antibiotics were given.[5] And in a study of 74,114 adult ED patients with suspected infection without shock, there was an association between time-to-antibiotics and progression to shock (aOR 1.03 per hour, 95% CI 1.02–1.04) but no association between time-to-antibiotics and hospital mortality (aOR 1.02, 95% CI 0.99–1.04).[25] Most recently, a *prospective* non-randomized study of 178 Japanese ICU patients with sepsis found an association between decreased in-hospital mortality and completion of a 1-h bundle including antibiotics (aOR, 1.28; 95% CI, 1.04–1.57).[26] But once more, in risk-adjusted subgroup analyses comparing patients with and without shock, the association between in-hospital mortality and hourly bundle delays was only significant for the 55% of patients with septic shock (aOR, 1.25; 95% CI, 1.03–1.52), there was no significant association for the 45% of patients without shock (aOR, 1.17; 95% CI, 0.73–1.87).[26]

Third, most studies have linearized the relationship between time-to-antibiotics and mortality and reported a single blended estimate of the effect of each hour interval until

antibiotics. This is highly problematic because inspection of the data underlying these studies shows clear nonlinear relationships.[21] Generally, very long intervals until antibiotics (typically >5 or 6 h) are associated with increased mortality but shorter intervals are not. Blending the effects of long intervals with the effects of shorter intervals gives the misimpression that each hour until treatment is associated with a clear and consistent increase in mortality. A very recent analysis of the impact of time-to-antibiotics in 4,792 patients with sepsis, for example, found that each additional hour until time-to-antibiotics was associated with a statistically significant 0.42% increase in 28-day mortality when combining data from all patients with time-to-antibiotic intervals ranging from <1 h to 48 h.[27] When the investigators compared intervals of 1 to 3 h versus <1 h and intervals of 3 to 6 h versus <1 h, however, there was no significant difference in 28-day mortality rates; only intervals of >6 h were associated with significantly higher mortality rates.[27]

Fourth, the timing of antibiotic administration in real-world practice is not random. Sicker patients with more obvious presentations of sepsis tend to be treated sooner. Confounders must be carefully controlled to disentangle the effects of time-to-antibiotics from patients' underlying mortality risk attributable to their preexisting comorbidities, presenting signs and symptoms, and severity of illness, all of which may influence the timing of antibiotics. Clinicians tend to order antibiotics more immediately for more ill-appearing patients and for those with higher baseline mortality risk, whether because of their demographics, medical history, or other data available at presentation, and for patients with more obvious clinical signs of infection (eg, fever).[28,29] Consequently, even in the largest observational studies, results change drastically when including different confounders in the model, going so far as to shift negative associations (earlier antibiotics paradoxically associated with greater mortality) to positive associations (earlier antibiotics associated with lower mortality).[7] Despite the clear importance of rigorously adjusting for potential confounders, studies vary widely in the number, breadth and granularity of the variables they use for this process; some do not even include age or comorbid diseases.[21] When medical history is included as a confounder, it is via simplifying rubrics such as Charlson or Elixhauser indices,[30,31] which conflate conditions with vastly different severities (eg, "mild intermittent asthma, uncomplicated" and "chronic obstructive pulmonary disease" incur equivalent risk in the Elixhauser Comorbidity Index).[32] Furthermore, these indices are not comprehensive; they omit key comorbidities (such as cystic fibrosis and some congenital immunodeficiencies) that may be uncommon but nonetheless clearly increase the risk of sepsis and death.[33] Few of the studies incorporate patients' prior infection-related data (culture results, recent antibiotic exposures, and recent infections) as confounders, even though these are often important determinants of clinicians' prescribing behavior and likely correlate with patients' likelihood of true sepsis and risk of death.

2016 to 2020: Conflicting Guidelines on a Time-To-Antibiotics Target

The net effect of these weaknesses and inconsistencies in source evidence as well as the controversy stirred by various sepsis guidelines and mandates is that guidelines on expected antibiotic timing for sepsis have changed frequently in the last 6 years, with contradictory recommendations between different professional societies. As described above, IDSA did not endorse the SSC 2016 guidelines, citing concerns regarding the promotion or perpetuation of antibiotic overuse, overdiagnosis of sepsis, weaknesses of the data supporting time-to-antibiotic goals, conflation of suspected sepsis and septic shock, and disagreement on specific recommendations regarding antimicrobial selection, blood cultures, procalcitonin, and treatment

duration.[15] The concurrent release of the Third International Consensus definitions for sepsis ("Sepsis-3") sowed further confusion, partly because of terminology changes (redefining severe sepsis as sepsis)[34] and partly because different groups variably adopted the new definitions. SSC 2016 did adopt Sepsis-3 terminology but cited data using the old definitions to support their recommendations. Meanwhile, CMS continues to use the old definitions for their SEP-1 reporting requirement.

In 2018, the SSC released a "bundle update" combining its 3 h and 6 h bundles into a single 1 h bundle, which included lactate levels, blood cultures, volume resuscitation, vasopressors if fluid-refractory, and broad-spectrum antibiotics, all within 1 h of ED triage.[35] As more than 80% of sepsis is diagnosed on admission and initially managed in the ED,[1,2] concerns over the lack of evidence to support such a significant change to emergency medicine workflow were quickly raised.[36–38] In response to these concerns, the Society of Critical Care Medicine (SCCM) and American College of Emergency Physicians (ACEP) published a joint statement saying: "We recommend that hospitals not implement the Hour-1 Bundle in its present form in the United States at this time," whereas the authors of the SSC bundle update acknowledged that it was intended as a facilitative tool and not as a potential quality indicator.[39] "Time-zero" for bundle initiation was also revised from ED triage to time of sepsis recognition. Collectively, the net result was substantial confusion and/or disagreement among frontline providers, hospitals, and regulators on which components of the 2016 guidelines and the 2018 bundle update were in fact appropriate for implementation. Finally, in 2020, IDSA recommended revisions to the SEP-1 bundle created by CMS, again citing the lack of evidence supporting early antimicrobials for suspected sepsis without shock, concerns over the potential to drive antibiotic overuse, and the high complexity of SEP-1's "time-zero" definition.[22]

The Optimal Breadth of Broad-Spectrum Antibiotics

A parallel controversy has been determining the appropriate spectrum of empiric antibiotic coverage for sepsis, given similar mismatches between evolving guidelines and the level of evidence supporting them. In practice, just as important as *when* antibiotics are needed for sepsis is the corollary question of *which* antibiotics must be given. Antibiotic coverage is ideally tailored to causative pathogens and their susceptibility profiles, but these data are rarely available when antibiotics are started.

In 2016, SSC specified a number of overlapping terms for antimicrobial selection in sepsis ("empiric", "targeted/definitive", "broad-spectrum", "multidrug", and "combination").[10] IDSA felt that these terms were confusing, because differences between most of them would not be obvious even to experts in the field, and the terms were ultimately used inconsistently within the guidelines.[15] For example, SSC 2016 recommended "combination" therapy for septic shock—which they defined as the use of two or more antibiotics active against the patient's causative pathogen—"for several days." This recommendation was controversial for two reasons. First, many clinicians use "combination therapy" to refer to the empiric use of two agents active against gram-negative bacteria in order to increase the probability that the patient receives at least one agent active against their causative pathogen(s), that is, to broaden coverage. On the contrary, SSC defined it as two agents active against the same pathogen "to accelerate pathogen clearance rather than broaden antimicrobial coverage."[15] Second, the evidence supporting sustained use of two active agents for septic shock is very weak. Two large and rigorous randomized trials fail to support this approach, one focused on patients with sepsis in general[40] and one focused on patients with VAP.[41] Similarly, a meta-analysis of 13 randomized trials found no

difference between empiric mono-versus combination antibiotic therapy on length-of-stay, mortality, or any other objective outcome among patients with sepsis.[42]

There is increasing evidence that the use of overly broad empiric antibiotics is not only unnecessary but may in fact cause harm.[43] A retrospective, propensity-weighted study of methicillin-resistant *Staphylococcus aureus* (MRSA) coverage in 88,605 Veterans' Affairs (VA) patients treated for community-acquired pneumonia (CAP) showed that the addition of anti-MRSA therapy was associated with increased adjusted risk of 30-day mortality and secondary infections including *Clostridioides difficile*, vancomycin-resistant *Enterococcus* (VRE), and gram-negative bacilli.[44] Counterintuitively, even when restricting to patients with MRSA found on cultures, there was no mortality benefit to adding anti-MRSA therapy, belying the complexity of diagnosing certain infections (did these patients have true pneumonias or mimicking conditions?) and the inconsistent relationships between antibiotic utilization and outcomes. Similar retrospective studies of 2,198 CAP patients in four US EDs, and a second VA cohort of 15,071 nonsevere pneumonia patients, showed increased mortality associated with broad-spectrum antibiotics.[45,46] A prospective cohort study of 303 ICU patients at risk for multidrug-resistant (MDR) pneumonia noted that guideline-directed (broader) therapy was associated with increased mortality.[47]

Regarding infections other than pneumonia, a 2-year quasi-experimental before-and-after observational cohort study of surgical ICU admissions at one hospital found that implementation of a conservative strategy for antimicrobial treatment, where antibiotics were started only after cultures or gram stain supported an infection, was associated with reduced mortality when compared with an aggressive strategy where broad empiric antimicrobials were started upon clinical suspicion and then stopped if cultures and gram stains were negative.[48] A retrospective study of 17,430 patients admitted to 104 US hospitals with sepsis and positive cultures (primarily blood, urine, or respiratory) found that unnecessarily broad empiric antibiotics, defined as including coverage of MRSA, VRE, *Pseudomonas*, or other MDR organisms when none of these were ultimately isolated on cultures, were independently associated with increased in-hospital mortality after adjusting for baseline characteristics and illness severity.[18] Identifying causes of these increases in mortality was outside the scope of these studies, but antibiotics have many known risks, including acute kidney injury, liver toxicity, cytopenias, selection for drug-resistant flora, mitochondrial toxicity, and disruption of the gut microbiome (an important modulator of the immune system).

On the contrary, empiric treatment of sepsis with a regimen that fails to cover the causative pathogen is also independently associated with increased mortality. Studies on this are limited to those with positive cultures so that antibiotic appropriateness can be determined, and therefore may not be representative of all suspected sepsis, for which a substantial fraction have negative cultures. Acknowledging this limitation, the aforementioned study of 17,430 patients with positive cultures did also show an association between inadequate empiric coverage and higher in-hospital mortality.[18] Similarly, a retrospective study of 21,608 patients from 131 US hospitals with bloodstream infections (about 20% of all sepsis cases)[2] found that among the 19% that received an inadequate initial regimen (failure to cover the bloodstream isolate), there was an independent association with increased mortality that was not affected by the presence or absence of drug resistance, sepsis, or septic shock.[49]

Therefore, the optimal "breadth" of broad-spectrum antibiotics for sepsis faces a Goldilocks problem[50]: evidence supports harms of both overly broad and overly narrow therapy, so in the face of diagnostic uncertainty, practical compromises have to be struck. As with time-to-antibiotics, the high rate of overdiagnosis of sepsis needs

to be taken into account, as well as the variability in the signal between time-to-appropriate-antibiotics and mortality depending on patients' clinical syndrome and severity-of-illness. For conditions such as septic shock with less room for error, it is appropriate to use broader antibiotics up front, whereas ideally a stable patient with lower probability of infection should receive narrower or no antibiotics until a causative pathogen is confirmed.

2021 and Beyond: Toward Consensus in Sepsis Antimicrobial Guidelines

In July 2021, ACEP released its own set of guidelines on early sepsis care in the ED, which were endorsed by IDSA, SCCM, and 10 other professional societies. Taking a different tone from SSC 2016, ACEP's guidelines acknowledged the "inherent difficulty in establishing the early diagnosis of sepsis" in the ED.[51] Although prompt antibiotic administration is encouraged once sepsis is diagnosed, the authors concluded "there are insufficient data to recommend a specific time threshold for administration of antibiotics."[51] Regarding antibiotic spectrum, the guidelines avoided endorsing two-agent or "combination" therapy, instead recommending "initiation of broad-spectrum antibiotics with activity against gram-negative and gram-positive bacteria according to local susceptibility patterns."[51]

In November 2021, SSC published a new version of their guidelines that responded to much of the feedback from IDSA, ACEP, and other professional societies on antimicrobial management recommendations.[52] This update was endorsed by IDSA, signaling a shift back toward consensus. Although the general outline of antimicrobial-related recommendations remained similar, the evidence for many recommendations was downgraded from "moderate" quality evidence to "low" or "very low", and several crucial changes were made.

First, the new guidelines emphasize "the challenge of diagnostic uncertainty early in a patient's presentation," and now advise clinicians to "stratify antimicrobial timing recommendations based on the likelihood of sepsis and presence of shock."[53] Specifically, the cohort targeted for antimicrobials within 1 h has been narrowed from all patients with suspected sepsis or septic shock to just those patients with septic shock and possible sepsis "where likelihood of infection is high." For patients with an intermediate likelihood of infection, the guidelines now suggest a time-limited course of rapid investigation to determine a diagnosis, concluding with the administration of antimicrobials within 3 h only if concern for infection persists; the guidelines categorize evidence for this timeframe as weak instead of strong. Finally, the 2021 guidelines define an entirely new group of patients, "adults with low likelihood of infection and without shock," who explicitly do not need antimicrobials unless and until they are proven to have an infection. This recommendation will hopefully reinforce that many patients initially suspected of sepsis do not have a bacterial infection, and therefore it can be appropriate to do a diagnostic workup before starting antibiotics.

Second, a subtle but important change was added to the language of the SSC 2021 guidelines regarding time to antibiotics. The 2016 guidelines used durations of "within X hours" with the starting point left unnamed, leaving open an implication that this referred to the onset of sepsis. As the time of sepsis onset is not known for many patients entering the hospital, and could have occurred hours to days before admission, this is difficult to incorporate into metrics for hospital performance or observational studies, setting aside the minority case of hospital-onset sepsis.[2] Therefore, when creating bundles and cohort definitions, SSC, CMS, and sepsis researchers have all chosen different "time-zero" definitions—ranging from ED triage time in SSC's 2018 bundle update,[35] a combination of documentation and physiologic data within a sliding 6 h window in SEP-1,[8] and variations on these themes among the time-to-

antibiotics studies.[21] By contrast, the SSC 2021 guidelines now explicitly refer to the clock on antibiotics starting "from the time when sepsis was first recognized," acknowledging the reality of a clinician needing time to evaluate the patient and consider other diagnoses before management can begin. Some time-to-antibiotics studies have also tried to use clinical recognition as their time-zero, although it is a labor-intensive and subjective concept to abstract from charts. Even time-zero definitions based on vital signs and laboratory measures are subject to high interobserver variability. Manual abstractors of SEP-1's time-zero, for example, disagree over half of the time on when time-zero occurred.[54] Nevertheless, by including a conceptual time-zero (sepsis recognition) for the first time, the 2021 guidelines helped narrow down potential interpretations of time-to-antibiotics and may encourage future researchers to build consensus on an operational definition.

Finally, the SSC 2021 guidelines made significant changes to recommendations on spectrum of coverage. The artificial terminology of "empiric", "targeted/definitive," "combination," "multidrug," etc., was eliminated. Instead, the new guidelines frame spectrum of coverage around specific categories of pathogens that should be considered when starting antimicrobials. For instance, there is a new best practice statement on including empiric MRSA coverage for sepsis only when the patient is judged to have "high risk of MRSA infection," and a similar "weak" suggestion for antifungal coverage only if the patient is at "high risk for fungal infection." There still is a "weak" suggestion for using two antimicrobial agents (previously called "combination therapy") to cover gram-negative bacteria, but instead of applying to all patients with suspected sepsis, it is aimed at patients specifically with high risk for MDR organisms. There is a parallel recommendation to narrow this regimen to a single agent once the causative pathogen(s) and susceptibilities are known, and the evidence categorization for these suggestions has been downgraded to "very low quality." Overall, although evidence ratings for the new antimicrobial spectrum recommendations are modest, by framing them around categories with specific microbiologic correlates such as "MRSA coverage," they have increased clarity and adaptability to local data, such as the use of community prevalence of MRSA and MDR organisms to help determine the appropriateness of broader empiric coverage.

DISCUSSION

Overall, the 2021 SSC and ACEP guidelines have made significant progress in building consensus recommendations for antimicrobial timing and breadth, balancing the importance of rapid treatment for potentially septic patients with bona fide infections against the potential harms associated with antibiotics for those who are not infected. By casting a more critical light upon the limitations of existing evidence, they also forecast several areas where higher quality evidence is needed. For instance, although the 2021 SSC guidelines now emphasize concepts intrinsic to the early clinical evaluation and management of sepsis, including "sepsis where the likelihood of infection is high," "the time when sepsis was first recognized," "high risk for MDRs," and "high risk for fungal infection," the onus is on researchers to characterize these probabilities and timepoints more concretely so that clinicians may leverage them for decision-making.

The fundamental challenge in sepsis management remains: how might we better identify which patients along the spectra of sepsis risk and severity benefit most from earlier antibiotics, and which merit broader versus narrower coverage? One approach might be to raise the standard for large observational studies on time-to-antibiotics, which are increasingly robust in terms of sample size but have been less

rigorous about the methods used to control for confounders. Future studies can and should expand their input variables to incorporate more of the richness and breadth of the data available in electronic medical records (EMRs). For example, studies rarely use data from prior encounters to formulate confounders and the likelihood for a patient's subsequent presentation of suspected sepsis. Incorporating more detailed measures of current and prior clinical markers of organ dysfunction as well as their trajectories could improve differentiation and quantification of acute changes catalyzed by infection vs chronic underlying conditions—something that clinicians do routinely when evaluating patients, but has been left out of cohort definitions and adjustment models underlying nearly all time-to-antibiotics studies. In addition, machine-learning techniques may disentangle the vast heterogeneity in EMR data from sepsis populations by identifying distinct sub-phenotypes of sepsis using clustering and similar techniques.[55–59] Future work could integrate machine-learning sub-phenotyping with data on antibiotic timing, breadth, and outcomes to generate predictive models of the sub-phenotypes that most likely benefit from earlier antibiotics or broader-spectrum coverage.

Translational research on rapid diagnostics for sepsis may also permit a more tailored approach. After decades of research, likely due to the biological heterogeneity of the syndrome,[60] there still are no gold-standard diagnostic tests or biomarkers for sepsis, which remains a clinical diagnosis based on the same kinds of data that were first used to describe the "systemic inflammatory response syndrome" in 1992.[61] Nonetheless, earlier accurate identification of sepsis caused by bacteria and their susceptibility profiles could both accelerate the time-to-antibiotics and mitigate antibiotic overuse. Over 200 biomarkers for sepsis have been investigated,[62] with C-reactive protein and procalcitonin among the most popular, but as these two markers are both upregulated in noninfectious inflammation, neither is sensitive nor specific enough to reliably guide initial sepsis treatment. Procalcitonin has shown more promise as a longitudinal marker of antibiotic response in serious infections, permitting shortened antibiotic courses that are associated with lower in-hospital mortality in meta-analyses.[63,64] Of the other biomarkers, only 26 have been investigated in samples of at least 300 patients, and it seems increasingly unlikely that any single host biomarker will "break through" and significantly alter early sepsis diagnosis or management.[62]

Other researchers have focused on molecular diagnostics targeting bacterial nucleic acids, such as polymerase chain reaction (PCR) of 16S ribosomal RNA and microarrays. In principle, these may yield equally accurate and slightly faster results compared with blood cultures,[65,66] but their utility is less clear for non-bloodstream infections. Similarly, mass spectrometry is increasingly integrated into culturing workflows, providing the greatest speed benefit when identifying slow growing and less common organisms.[67] Recent methods have attempted to decrease turnaround time for mass spectrometry on blood culture isolates by replacing subculturing with centrifugation and protein extraction, although this still requires waiting for growth in the initial blood culture bottle.[68,69] Whole-genome sequencing of pathogens provides high-resolution data useful for genotyping and molecular epidemiology, but is unlikely to usurp culturing and mass spectrometry on turnaround time for species identification, except for pathogens that are difficult to culture.[70] Researchers have also directed omics assays toward the host immune response, finding potential sepsis sub-phenotypes in meta-analysis of microarray data from 600 patients,[71] and more recently, a unique $CD14^+$ monocyte state distinguishing 29 sepsis patients from 36 controls using single-cell RNA sequencing.[72] New diagnostics leveraging these insights are still undergoing development and validation for potential clinical applications.

SUMMARY

From 2016 to 2020, sepsis guidelines and regulatory mandates encouraged increasingly brief targets—as short as 1 h—for initiating broad-spectrum antimicrobials for patients with suspected sepsis or septic shock. This sparked considerable controversy due to weaknesses in the underlying evidence and concern that strict antibiotic deadlines cause inadvertent harm by perpetuating or accelerating overtreatment at the expense of diagnostic inquiry. A third or more of patients treated for sepsis and septic shock have noninfectious or nonbacterial conditions. These patients risk harm from unnecessary antibiotics. New guidelines from both ACEP and SSC in 2021 now emphasize the importance of tailoring treatment to each patient's likelihood of infection, risk for drug-resistant pathogens, and severity of illness. These guidelines will benefit from future research that raises the standards for evidence derived from observational studies of time-to-antibiotics and associated outcomes. New diagnostics that rapidly quantify the likelihood of infection by bacteria, MDR organisms, fungi, and other pathogen groups relevant to antimicrobial selection could also have a major clinical impact, given the emphasis on these concepts in the latest guidelines.

CLINICS CARE POINTS

- A third or more of patients treated for sepsis turn out to have noninfectious conditions or nonbacterial infections.
- When evaluating a patient for possible sepsis, tailor the urgency of antibiotics to the patient's likelihood of infection and severity of illness.
- In patients with possible septic shock, administer antibiotics immediately. In patients with less severe illness, undertake a rapid course of diagnostics (eg, lab studies, imaging, microbiological assays, etc.) and treat for noninfectious possibilities if present (eg, fluids, diuretics, bronchodilators, heart rate control, etc.). Continually reevaluate the likelihood of infection based on the results of diagnostic studies and response to treatments for noninfectious conditions. If high concern for infection persists at 3 h from when sepsis was first suspected, then administer antimicrobials.
- Choose the spectrum of antibiotics according to severity of illness (as critically ill patients have less margin for error) and the local distribution of organisms and their resistance patterns as well as each patient's individual risk factors for antibiotic-resistant organisms.

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