Antimicrobial Stewardship in the Management of Sepsis

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KEYWORDS

• Antimicrobial stewardship • Antibiotics • Sepsis • Clinical decision support
• Biomarkers • Rapid pathogen identification assays • Quality measures
• Emergency medicine

KEY POINTS

- Antimicrobial stewardship refers to efforts aimed at enhancing judicious prescribing of these unique therapeutic agents in health care settings.
- Inappropriate use of antimicrobials represents a global threat to public health and a direct threat to individual patient safety.
- Sepsis is a life-threatening, complex clinical syndrome without a gold standard diagnostic test and thus represents a unique clinical dilemma with regard to antimicrobial stewardship.
- Recent literature questioning the clinical impact of time to antimicrobials in sepsis before the onset of shock and improving the definition of sepsis may have a positive impact on antimicrobial stewardship.
- Electronic health record clinical decision support, biomarkers, and rapid pathogen identification assays have tremendous potential to enhance antimicrobial stewardship in sepsis care and should be a focus of future research efforts.

INTRODUCTION

The term antimicrobial stewardship is often mistakenly considered to only include efforts to reduce or restrict use of these agents. A more comprehensive view includes a focus on the "4 Ds" of optimal antimicrobial therapy coined by

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Joseph and Rodvold[1] in 2008: drug, dose, de-escalation, and duration. The focus here is on getting the right antimicrobial in the right dose to the right patient for the right amount of time. The opposite of optimal antimicrobial therapy is often referred to as inappropriate or overuse. These terms can refer to a range of practices, such as prescribing when no antimicrobial was indicated, prescribing an overly broad-spectrum agent, or prescribing an excessive length of therapy. In some instances, such as bronchitis, the right antimicrobial is no antimicrobial. In cases of septic shock, the right antimicrobial is broad-spectrum coverage of all likely pathogens. Both of these scenarios represent widely accepted approaches to antimicrobial stewardship. Unfortunately, when it comes to suspected sepsis in the emergency department (ED) setting, the ideal approach to the antimicrobial management is less clear.

The timely administration of antimicrobial agents with activity against the causative pathogen has been a cornerstone of sepsis management long before it was included in the original Surviving Sepsis consensus guidelines.[2] Based on the literature linking time and appropriateness of antimicrobials to mortality in sepsis,[3–7] the ED implementation of this concept has been to rapidly cover all potential pathogens with broad-spectrum agents. De-escalation of therapy is left to occur days later after the patient has stabilized or when pathogen information is available.

The problem with this approach stems from a lack of a true gold standard for diagnosing the complex syndrome that is sepsis and the corresponding inaccuracy of widely used diagnostic criteria. The Sepsis 2.0 definition of 2 systemic inflammatory response syndrome (SIRS) criteria plus suspected infection suffers from poor discriminant validity due to a lack of specificity for both infection and the occurrence of adverse outcomes.[8–10] The combination of flawed diagnostic criteria with incredible time pressure to provide broad-spectrum antimicrobial therapy is troubling from the stewardship perspective, as it is not uncommon for patients with otherwise uncomplicated cases of common infections (eg, influenza, pneumonia, or pyelonephritis) to meet this widely used definition of sepsis.

Emerging literature that questions the optimal timing and clinical impact of antimicrobial agents in sepsis before the onset of shock may relax some of the pressure on emergency providers and allow more judicious and targeted administration in response to clinical judgment and patient trajectory rather than rigid definitions.[11–14] Also, recently updated definitions of sepsis and septic shock appear to offer an improved ability to identify septic patients at risk for adverse outcomes and thus most likely in need of early broad-spectrum antimicrobials.[9,15] As these definitions were developed with hospital mortality as the primary outcome variable,[15] their value as broad screening tools for sepsis in the ED and impact on antimicrobial stewardship will require further study. Unfortunately, these promising developments for antimicrobial stewardship in sepsis exist in sharp contrast to the recently implemented Centers for Medicare and Medicaid Services (CMS) ED Sepsis Quality Measure, which codifies poor performing and outdated definitions of sepsis and links them to mandated use of a specific list of broad-spectrum agents.

The discussion around more judicious use of antimicrobials in sepsis also must include data that suggest that up to 30% of patients diagnosed with sepsis in US EDs do not receive antibiotics before admission.[16] There is clearly much work to be done in both defining what constitutes optimal antimicrobial use in sepsis and the development of implementation strategies that facilitate their appropriate administration. The aim of this article was to provide an overview of

antimicrobial resistance, evidence-based antimicrobial stewardship interventions for the ED, and potential future directions with regard to antimicrobial use in sepsis care. Due to a paucity of interventional research aimed at improving antimicrobial use in sepsis, aside from enhancing time to administration, much of this information is gleaned from interventional ED stewardship research involving other types of infection.

PUBLIC HEALTH IMPLICATIONS OF ANTIMICROBIAL OVERUSE

Antimicrobial resistance is a naturally occurring phenomenon in which antimicrobials exert selective pressure on pathogens that, in turn, develop defense mechanisms against that antimicrobial agent's mode of attack.[17] Overuse and misuse of antimicrobials has accelerated this natural process, resulting in multidrug-resistant organisms or "super bugs," as well as a general trend toward antimicrobial resistance outpacing humankind's ability to develop novel, effective antimicrobials.[18]

Although the root causes of antimicrobial resistance are multifold and include antimicrobial overuse in the agricultural and veterinary sectors; the use of antimicrobials in human medicine is a key cause of nosocomial-resistant organisms like *Clostridium difficile,* methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus.*[19] Worldwide there are 700,000 annual deaths attributable to nosocomial-resistant organisms.[20] If the trend continues at the current rate, antimicrobial resistance will have cost the global economy more than $100 *trillion* by 2050.[20] A 2014 review commissioned by the prime minister of the United Kingdom warns of "a return to the dark age of medicine" in which routine medical care like childbirth and outpatient surgery are risky undertakings and cancer chemotherapy or organ transplantation is no longer possible.[20]

In the United States, conservative estimates of morbidity and mortality attributable to antimicrobial resistance place the annual number of illnesses at 2,049,442 and the annual number of deaths at 23,000.[19] Regarding resource management, sequelae of antimicrobial resistance costs the United States between $21 and $34 billion annually and subjects US citizens to more than 8 million additional patient-days in the hospital.[17] The World Health Organization, US Centers for Disease Control and Prevention (CDC), European Medicines Agency, Institute of Medicine, World Economic Forum, Society for Healthcare Epidemiology of America, the Infectious Diseases Society of America, and most recently the White House have identified antimicrobial resistance as a pressing threat to global public health.[21–23] The CDC's *Get Smart for Healthcare Campaign* calls the improved use of antimicrobials "an important patient safety and public health issue as well as a national priority" and encourages a shift toward more judicious antimicrobial use.[24] In an effort to support public health agencies, hospitals, and clinicians in the fight against antimicrobial-resistant organisms, the CDC provides a variety of resources to promote stewardship activities, including assessment tools for antimicrobial use and a workshop on the core elements of hospital antimicrobial stewardship programs.[25]

PATIENT SAFETY IMPLICATIONS OF ANTIMICROBIAL OVERUSE

Although much of the emphasis around antimicrobial stewardship is related to the public health concerns of increasing resistance, it also should be regarded as a means of enhancing individual patient safety.[26,27] Examples of negative sequelae related to antimicrobials are pervasive in the medical literature and include adverse reactions,

drug-drug interactions, and nosocomial-resistant pathogens (ie, *C difficile*). Although evidence-based infection control practices are firmly established within the lexicon of patient safety,[28] antimicrobial stewardship has only recently begun to garner similar institutional attention and support.[27]

Adverse drug events are injuries resulting from drug-related medical interventions and are estimated to account for more than 700,000 annual ED visits in the United States.[29] Shehab and colleagues[26] found that approximately 20% of ED visits for adverse drug events (more than 140,000 ED visits per year) were related to antimicrobial use. In an 11-year national data analysis, antimicrobials by category accounted for the highest number (27.5%) of all pediatric adverse drug events occurring in the outpatient setting.[30] Most of these visits were allergic reactions with clinical presentations ranging from mild rash to life-threatening anaphylaxis. The incidence of adverse drug events related to antimicrobials is likely underestimated, as many patients may not seek out medical attention for less severe episodes. For example, antimicrobial-associated diarrhea is estimated to occur in 30% of outpatient courses and is a contributing factor in nonadherence.[31,32] Additional serious adverse drug reactions associated with antimicrobials include retinal detachment,[33] tendon injury,[34] and encephalopathy.[35] Observational studies have also found an association between the macrolide class of antimicrobials and an increased risk of arrhythmias and sudden cardiac death.[36,37]

Drug-drug interactions with antimicrobials are common and, in many cases, related to changes in the activity of the cytochrome P450 isoenzymes, especially CYP3A.[38] Symptoms of drug interactions can range from disruptive (unwanted pregnancy resulting from an interaction with oral contraceptives)[39] to life-threatening (arrhythmias with amiodarone, QT prolongation with antipsychotics, and coagulopathies with warfarin).[40–43] Concurrent use of warfarin and antimicrobials deserves special mention, as these interactions are common and can result in intracranial hemorrhage or fatal gastrointestinal bleeding. Warfarin-antimicrobial interactions are particularly risky in the elderly population and can result in a sixfold increase in the odds of being hospitalized for bleeding complications.[42] Of the antimicrobials that interact with warfarin, common medications like trimethoprim/sulfamethoxazole, metronidazole, fluconazole, ciprofloxacin, levofloxacin, azithromycin, and clarithromycin are the most significant.[44]

Nosocomial-resistant pathogens are increasingly prevalent in hospitals throughout the United States. *C difficile* is widely recognized as one of the more virulent of these pathogens, infecting more than 500,000 patients annually and causing 15,000 annual deaths.[41,45] In the elderly, 1 in 11 patients older than 65 dies within a month of being diagnosed.[19] *C difficile* is classified by the CDC as an "urgent threat" to patient safety and is 7 to 10 times more likely to be found in patients who have recently taken antimicrobials.[19]

ANTIMICROBIAL STEWARDSHIP IN THE EMERGENCY DEPARTMENT

The ED is increasingly recognized as the nexus of the US health care system, serving as a 24/7 diagnostic center and entry point for most hospital admissions.[46] As such, the ED is also increasingly viewed as playing a strategic role in public health initiatives, such as curbing antimicrobial resistance.[47] As plans for outpatient care, facility-based long-term care, and inpatient care often begin in the ED, careful decisions about antimicrobial use are crucial in the ED.[48] Emergency providers (EPs) have 2 key opportunities to practice antimicrobial stewardship. First, the seemingly simple choice of whether or not to prescribe antimicrobials requires

significant clinical judgment. Given the lack of diagnostic tests that can rapidly distinguish bacterial from viral infections, as well as logistical barriers to using a watch-and-wait strategy in the ED, EPs must rely heavily on clinical gestalt and evidence-based guidelines in making this determination. Second, after deciding to prescribe an antimicrobial, the choices of drug, dose, and duration represent additional opportunities for stewardship and require careful consideration of factors such as infection type, local resistance patterns, patient allergies, and cost.

As a proactive response to the epidemic of antimicrobial resistance, many EDs have implemented evidence-based care pathways[49–51] or antimicrobial stewardship intervention bundles.[52–58] Furthermore, basic antimicrobial stewardship principles are appearing as either optional or required performance measures for state and/or federal quality metric reporting.[59] For example, the American College of Emergency Physicians recently highlighted the 2016 CMS Physician Quality Reporting System (PQRS), which includes 2 antimicrobial stewardship measures: #93, avoidance of inappropriate systemic antibiotic therapy for acute otitis externa, and #116, avoidance of antibiotic treatment in adults with acute bronchitis.[60] At the hospital level, the Joint Commission promotes 16 standards and 1 National Patient Safety Goal related to antimicrobial stewardship.[59]

As antimicrobial stewardship becomes increasingly tied to ED quality reporting and value-based payment, it is imperative that these quality metrics are based on high levels of evidence. The desire to reduce the trend of global antimicrobial resistance and enhance patient safety with quality metrics must be balanced by acknowledging diagnostic uncertainty and inadequate access to follow-up care; 2 factors EPs cite as primary drivers of antimicrobial overuse.[61,62]

ANTIMICROBIAL STEWARDSHIP INTERVENTIONS FOR SEPSIS IN THE EMERGENCY DEPARTMENT

The available literature involving antimicrobial stewardship interventions in the ED is scant when compared with what is reported for inpatient and ambulatory care settings.[63,64] It is also highly fragmented in terms of intervention type(s), target disease, and antimicrobial stewardship outcome of interest. Although guidelines exist regarding optimal selection of initial antimicrobials based on the most likely source of sepsis, local resistance patterns, and patient-level risk factors for multidrug-resistant infections,[65–71] we were able to find only a handful of interventional studies targeting this outcome.

Intervention Bundles

The 4 identified studies, which included appropriateness of empiric antimicrobials for sepsis as an outcome measure, each used intervention bundles and were published between 2006 and 2010.[54,55,72,73] As there is considerable overlap between these studies in terms of design (pre-post), elements included in the intervention bundle (eg, provider education, standardized order sets, and care pathways) and overarching objective (improved adherence to Surviving Sepsis Campaign guidelines), we have selected the largest US-based and international studies for detailed discussion. From a practical perspective, when interpreting the results of these studies, it is impossible to determine the impact of each intervention bundle element on the observed outcomes. Knowing which bundle elements are highest yield would be of great value to those tasked with implementation of antimicrobial stewardship programs but unfortunately this information is not readily available. On

the contrary, one could also argue that education is a foundational part of any new health care intervention and that the similar approaches used in each study combined with a shared goal (improved standardization of sepsis care) make them easily adoptable.

Micek and colleagues[72] examined the impact of an educational program and standardized paper-based order set for 120 patients (60 pre, 60 post) with septic shock at a single US academic medical center. The order set included a detailed list of recommended antimicrobials divided by probable source of infection, and appropriate initial antimicrobial treatment in the ED was a primary outcome measure. Appropriate therapy was defined by positive culture results being treated based on in vitro susceptibility results at the time of identification. This metric improved from 72% to 87% ($P = .043$) after implementation of the intervention bundle.

Levy and colleagues[73] published results from an international, bundle-based approach to improve adherence with the initial Surviving Sepsis Campaign guidelines.[74] The intervention targeted patients with severe sepsis (2 SIRS plus organ dysfunction)[8] and included the creation and dissemination of educational materials and sepsis care bundles, recruitment of clinician site champions, and the creation of a secure database for tracking outcomes. This study involved 165 sites in Europe, North America, and South America, and included more than 15,000 subjects. Among the various pre/post outcomes measures tracked was administration of broad-spectrum antibiotics within 6 hours, which improved from 60.4% to 67.9% ($P = .0002$). As there is no information provided on how broad spectrum was defined and no assessment of the appropriateness of antimicrobial selection based on the source of sepsis or culture results, it is difficult to gauge the exact impact of this intervention on stewardship beyond time to administration.

In summary, bundle-based interventions to enhance compliance with guidelines (Surviving Sepsis Campaign) appear to have a positive impact on the appropriateness of empiric antimicrobial therapy. The studies from Micek and colleagues[72] and Francis and colleagues are particularly informative due to the use of prespecified definitions of appropriate use, which were based on objective criteria (culture results, published guidelines, and local susceptibility patterns). As electronic health records (EHR) and computerized physician order entry have become ubiquitous in the time since the last of these studies was published (2010), we anticipate future studies examining bundle interventions to enhance the appropriateness of empiric antimicrobials for sepsis will focus on clinical decision support (CDS) within the EHR.

Emergency Department–Specific Antibiograms

The Surviving Sepsis Campaign guidelines recommend that empiric antimicrobial therapy is based on likely pathogen and local/hospital resistance patterns.[66] It is important to note that hospital antibiograms generated from inpatient cultures may not reflect the ED population. One study found that the susceptibility pattern of *Escherichia coli* in ED patients requiring admission for urinary tract infections did not match information on the hospital antibiograms.[75] EPs should advocate that an ED-specific antibiogram be generated and maintained to guide empiric antimicrobial selection in septic patients.

Emergency Department Pharmacist Programs

Based on their unique knowledge of pharmacologic therapies, pharmacists can offer significant contributions toward antimicrobial stewardship programs. The American

Society of Health-System Pharmacists has issued a statement that defines the prominent role hospital pharmacists should play in antimicrobial stewardship efforts.[76] Specifically, they can promote appropriate selection, provide consultation and feedback, and identify potential drug-drug interactions.[77] Although the presence of ED-based pharmacists has been demonstrated to reduce medication errors and facilitate optimal therapy in discharged patients,[78] there is a paucity of interventional research examining their direct impact on antimicrobial stewardship. Two studies have demonstrated an improvement in appropriateness of antimicrobial therapy for ED patients with a pharmacist-led culture review process.[79,80] However, the direct applicability of these findings is questionable, as patients diagnosed with sepsis in the ED are universally admitted and cultures are typically reviewed by the inpatient care team.

Cultures in the Emergency Department

The Surviving Sepsis Guidelines recommend obtaining any appropriate cultures in patients with suspected sepsis before administration of antimicrobial therapy, as long as these cultures do not cause a significant delay in the administration of appropriate antibiotic therapy. This recommendation also includes obtaining 2 sets of blood cultures, as well as obtaining any other cultures of appropriate sites (urine, cerebrospinal fluid [CSF], wounds, respiratory secretions, or other body fluids).[66] These recommendations have become generally accepted as typical practice and were also incorporated as part of the recent CMS SEP-1 sepsis quality measure.

Identification of a causative organism is essential in allowing inpatient providers to de-escalate antibiotics, which in turn has the potential to reduce costs, decrease the length of hospital stays, and help to control development of antibiotic resistance. Several studies have demonstrated the positive impact of culture review programs on antibiotic prescribing.[79–83] The benefit derived from tailored antimicrobial therapy in the case of true-positive blood cultures must be balanced with the potential for overuse due to frequent false positives resulting from bacterial contamination.[84] This concern, combined with multiple reports indicating blood cultures obtained in the ED are rarely positive (and typically do not impact management) in immunocompetent patients with uncomplicated bacterial infections,[85–89] has led to calls for culture use guidelines that are based on objective markers of infection severity.

Once a decision has been made to obtain blood cultures, every effort should be made to obtain the samples before the initiation of antimicrobial therapy. Failure to do so can result in sterilization of the blood and subsequent negative culture results even when bacteremia was present. Although 2 separate 15-mL sets of blood cultures have been shown to detect the pathogen in 80% to 99% of bloodstream infections,[90,91] a much lower sensitivity has been demonstrated after antibiotics are initiated.[92] Similarly, CSF sterilization has been shown to occur anywhere from 2 to 4 hours after administration of antibiotics.[93,94]

Electronic Health Record Alerts and Clinical Decision Support (CDS)

Delays in the recognition and initiation of treatment of septic shock have been associated with increased mortality.[13] The most recent Surviving Sepsis Guidelines recommend the routine screening of "seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy."[66]

Operational barriers including ED crowding and increasing ED volumes, combined with the potential for occult presentations of sepsis, can make the prompt recognition and delivery of effective ED sepsis care difficult. When surveyed, 18.2% of physicians

and 15.8% of nurses rated the lack of sepsis recognition in ED triage as the greatest cause of delay to sepsis treatment.[95]

Recent attention has turned toward the use of CDS for sepsis recognition and treatment in the ED. Although historically this was in the form of paper-based algorithms and protocols, it is increasingly electronically integrated, as EHRs are ubiquitous throughout health care. By constantly assessing available data in a "digital screening," this has the potential to facilitate early sepsis detection or patient deterioration, as well as encouraging and facilitating optimal sepsis care.

CDS tools for the detection and treatment of sepsis have been studied in the ED,[96–101] as well as general care/medical units.[73,102–104] Many of the ED electronic CDS systems describe the predictive value of such applications on process measures, such as time to antibiotics or intravenous fluids. One study evaluating an electronic CDS system in the ED did find increased ordering of chest radiographs and blood cultures after the electronic CDS was implemented, but no statistically significant increase in the number of patients receiving antibiotics.[96] Another study found an increased number of sepsis diagnoses with a higher percentage of obtaining blood cultures.[105]

There also has been research evaluating CDS with antimicrobial prescribing. This has been shown to successfully assist with antimicrobial prescribing in a variety of care settings,[106,107] such as the intensive care unit[108] and outpatient clinics.[109]

As electronically integrated CDS for sepsis care becomes increasingly used in EDs throughout the country, further study will be needed to determine its effect on utilization of antibiotics (decision to treat and spectrum). Additional work also may be merited to evaluate how to best integrate antimicrobial prescribing support within the CDS systems currently being implemented in the ED so as to achieve a balance between improved sepsis detection and antibiotic stewardship.

Biomarkers and Rapid Pathogen Diagnostic Assays

The greatest potential for a major breakthrough in antimicrobial stewardship for sepsis management exists within the rapidly advancing field of molecular diagnostics. From an antimicrobial stewardship perspective, the ideal assay is one that rapidly and accurately rules out bacterial infection as the cause of illness. For cases of suspected sepsis in the ED, an assay with performance characteristics that allowed discrimination between infectious and noninfectious causes of SIRS would be incredibly valuable. Additionally, the ability to rapidly identify viral or bacterial pathogens and susceptibility patterns would assist EPs with the decision to treat and optimal antimicrobial selection.[110]

C-reactive protein (CRP) and procalcitonin (PCT) are the 2 most extensively studied acute phase protein biomarkers in sepsis. CRP is produced in the liver and upregulated in response to inflammatory conditions via cytokines (primarily interleukin-6). It is widely available and frequently used in a clinical context to determine the likelihood of infection.[111] PCT, the prohormone of calcitonin, is ubiquitously produced in response to bacterial infection.[111]

Although there are sufficient data to support an adverse prognostic implication of elevated CRP and PCT in patients with sepsis,[112,113] the clinical utility of these biomarkers in the management of sepsis in the ED is an area of considerable controversy.[114,115]

Likely due to a superior kinetic profile and specificity for bacterial infections as compared with CRP,[116–122] PCT is the only biomarker that has been studied extensively as an antimicrobial stewardship intervention in the ED. A Cochrane review concluded that PCT has demonstrated efficacy in reducing antimicrobial use for respiratory tract

infections in the ED without increasing adverse outcomes.[123] The 2012 Surviving Sepsis Guidelines include a recommendation for the use of low PCT levels to guide antimicrobial de-escalation in the intensive care unit when no evidence of infection is found. PCT has recently received Food and Drug Administration approval for use as a prognostic assay for ED patients with sepsis.[66,124] However, when discussing the utilization of PCT in the ED to guide antimicrobial management in sepsis, it is important to note that PCT performed only moderately well in identifying ED patients with bacteremia (area under the curve of 0.84, 95% confidence interval [CI] 0.75–0.90)[125] and distinguishing infectious from noninfectious SIRS (0.85, 95% CI 0.81–0.88).[126]

The bottom line is that despite some promising candidates, there is no single biomarker that has demonstrated adequate individual diagnostic performance characteristics to rule in or rule out sepsis.[127] This is likely because sepsis is a complex syndrome that evolves as it progresses rather than a measurable, single pathologic process.

The impact of pathogen identification on antimicrobial stewardship for suspected sepsis in the ED is currently bound by the limited number of relevant, rapidly available assays. Rapid influenza assays have been extensively studied in the pediatric ED population in terms of impact on antimicrobial prescribing. Unfortunately, we were unable to identify any study specifically examining impact on patients who met sepsis criteria. In addition to influenza assays, there are several studies examining the feasibility and impact of rapid MRSA identification assays on antimicrobial stewardship for purulent skin and soft tissue infections treated in the ED. These assays are capable of reliably identifying MRSA in purulent drainage in approximately 1 hour and feasibility studies indicate they can be incorporated into ED workflow without impacting important flow metrics.[128–130] Although not yet studied for this indication, these assays may have a role in helping to tailor initial antimicrobial therapy in cases of sepsis due to skin and soft tissue infections.

IMPACT OF CENTERS FOR MEDICARE AND MEDICAID SERVICES EMERGENCY DEPARTMENT SEPSIS QUALITY MEASURE ON ANTIMICROBIAL STEWARDSHIP

On October 1, 2015, CMS began to require reporting of the Severe Sepsis/Septic Shock Early Management Bundle (SEP-1).[131] Although this measure has the potential to reduce the mortality, morbidity, and hospital length of stay for patients with sepsis, there is also potential for an impact on antibiotic utilization and antibiotic stewardship in the ED.

SEP-1 requires the administration of broad-spectrum antibiotics from a prespecified list within the first 3 hours of care to patients with severe sepsis/septic shock. The SEP-1 definition of severe sepsis/septic shock includes a "suspected source of clinical infection, 2 or more manifestations of systemic infection (SIRS criteria), and the presence of sepsis-induced organ dysfunction," including a lactate greater than 2.[66] This more inclusive definition of severe sepsis has the potential to lead to reflexive overuse of broad-spectrum antibiotics without room for application of clinical discretion. For a detailed discussion on SEP-1, see Jeremy S. Faust and Scott D. Weingart's article, "The Past, Present, and Future of the Centers for Medicare and Medicaid Services Quality Measure SEP-1, the Early Management Bundle for Severe Sepsis/Septic Shock," in this issue.

Many groups have expressed their concern over potential for overutilization of antibiotics due to SEP-1. In a letter sent to CMS, the American Hospital Association, America's Essential Hospitals, Association of American Medical Colleges, and Federation of American Hospitals expressed concern that the measure will "promote the overuse of the antibiotics that are our last line of defense against drug-resistant

bacteria" and that requiring reporting on this measure "runs counter to the tenets of effective antimicrobial stewardship."[132]

Given the high level of concern among professional societies about the impact of SEP-1 on antibiotic stewardship, it is useful to reexamine lessons from another antibiotic-prescribing, process-based quality measure that had unanticipated consequences. In 2002, the Joint Commission and CMS endorsed PN-5b as one of their initial "core measures." PN-5b required that the first dose of antibiotics for pneumonia be administered within 4 hours of presentation to the ED. This was based on 2 large retrospective studies that demonstrated an association between the timing of antibiotic administration and improved outcomes in patients with community-acquired pneumonia.[133,134] However, subsequent studies began to demonstrate the unintended negative impact of PN-5b on antibiotic stewardship, including the administration of antibiotics to many patients who ultimately did not have pneumonia or any other infectious process.[135,136] One such study revealed that that more than half of ED physicians who were surveyed endorsed prescribing antibiotics to patients who they did not believe had pneumonia so as to comply with the CMS guideline (almost half of these more than 3 times a month).[137] Medical directors of academic medical centers surveyed had instituted operational responses to this measure that included policies for administration of antibiotics before chest radiograph if pneumonia was suspected (37%).[138] A variety of pressures including financial and social pressures likely led to adoption of this "shoot first and ask questions later" mentality of giving antibiotics to any patient who "might have" pneumonia. The timeline was first loosened to a 6-hour window and then ultimately withdrawn completely.

Quality measures are an important vehicle to improve health care. Process of care measures, such as SEP-1 or PN-5b, are much easier to identify and measure than clinical outcomes. Unfortunately, these are often shown to generate unanticipated consequences. Similar to the PN-5b measure, we will need to closely monitor the effect that the SEP-1 measure has on antibiotic utilization, especially because it involves the use of broad-spectrum antibiotics.

SUMMARY

Sepsis management in the ED is an incredibly dynamic landscape with massive implications for antimicrobial stewardship. This is an important issue both from a public health (ie, increasing global bacterial resistance) and patient safety perspective (eg, adverse drug reactions, *C difficile*). The broad-spectrum agents used in suspected cases of sepsis make it absolutely essential that we continue to refine the definitions of sepsis such that we can more accurately identify who is in need of immediate antimicrobials and who might be safely observed for clinical progression. Definitions aside, investing in new rapid biomarkers and organism identification assays is worthwhile, as they provide EPs with objective data regarding the presence and severity of bacterial illness while also allowing optimal pathogen targeting. Intelligent CDS tools embedded in the EHR that can synthesize patient-level clinical data, the ED antibiogram, and best practice guidelines also possess great potential for improving stewardship. Ultimately, the most effective antimicrobial stewardship intervention for sepsis will likely be a bundle composed of traditional quality improvement strategies (eg, education, audit, and feedback) combined with rapid diagnostics and CDS (**Table 1**). Recently implemented quality measures targeting ED sepsis management have the potential to adversely impact antimicrobial stewardship in the ED and need to be closely monitored.

Table 1
Summary of antimicrobial stewardship interventions in the emergency department

Intervention	Rationale
Emergency department antibiogram	Resistance patterns observed in the emergency department may differ from that observed in inpatient units
Educational and audit/feedback programs	• Ensure baseline level of awareness among clinical staff regarding antimicrobial stewardship for condition of interest (eg, sepsis) • Tailoring individual feedback based on specific cases or practice patterns as compared with group may encourage behavior change
Standardized care pathways	• Assist providers in optimizing the use of antimicrobials using available best practice, evidence-based guidelines • Decreases variability of antimicrobial prescribing and selection decisions among various providers
Cultures before antimicrobial therapy	• Yield of clinical cultures (eg, blood, urine, cerebrospinal fluid) declines rapidly following antimicrobial therapy • Culture results are a primary tool for antimicrobial stewardship after emergency department care (eg, de-escalation of broad-spectrum agents started for suspected sepsis)
Clinical decision support embedded in the electronic health record	• Enhance early detection of sepsis • Support compliance with quality measures • Assist with optimal antimicrobial selection
Biomarkers and organism identification assays	• Procalcitonin to guide antimicrobial therapy in respiratory tract infections (nonseptic) • Rapid influenza assays to identify potential viral etiology for the presence of systemic inflammatory response syndrome criteria

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