THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 7

RESEARCH ARTICLE

Stewardship and Sepsis: Are They Compatible?

Edward J. Septimus, MD [1]

[1] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA

OPEN ACCESS

PUBLISHED
31 July 2025

CITATION
Septimus, EJ., 2025. Stewardship and Sepsis: Are They Compatible? Medical Research Archives, [online] 13(7).
https://doi.org/10.18103/mra.v13i7.6746

DOI
https://doi.org/10.18103/mra.v13i7.6746

ISSN
2375-1924

ABSTRACT

Sepsis is a leading cause of death and disability globally. Sepsis affects millions of individuals per year and carries high morbidity and mortality rates even if appropriate care is provided. In the United States, sepsis is considered the most common cause of inpatient death, affecting 1.7 million adults per year and contributing to 270 000 deaths. Globally, there were an estimated 49 million cases of sepsis in 2017. The annual economic burden from sepsis hospitalizations and post-acute care exceeds $60 billion. Despite advances in care, short-term mortality rates continue to exceed 15%.

Combining antimicrobial stewardship with diagnostic stewardship enhances sepsis management by improving recognition, treatment, and outcomes. Key factors include early detection of sepsis leading to optimal timing and initial choice of antimicrobials. Getting proper cultures and diagnostics improves de-escalation opportunities. Antimicrobial de-escalation reduces unnecessary broad-spectrum antimicrobials when the pathogen(s) and their susceptibilities are identified. Lastly, determining the optimal duration of antibiotic therapy based on diagnosis and clinical response. Over the past two decades, numerous randomized controlled trials (RCTs) have evaluated antibiotic durations for common clinical syndromes generally demonstrating that shorter courses are as effective as longer ones. Shorter treatment duration lowers risks of adverse drug reactions, multidrug resistance, and *Clostridioides difficile* infection. In conclusion, stewardship is not only compatible with sepsis care but also vital for better patient outcomes.

Keywords: Sepsis, diagnostic stewardship, antimicrobial stewardship, rapid diagnostics, biomarkers, de-escalation

Introduction

Sepsis is a leading cause of death and disability globally. [1] Sepsis is defined as a dysregulated immune response to infection affecting millions of individuals per year and carries high morbidity and mortality rates even if appropriate care is provided.[2,3] In the United States(US), sepsis is considered the most common cause of inpatient death, affecting 1.7 million adults per year and contributing to 270 000 deaths.[4] Globally, there were an estimated 49 million cases of sepsis in 2017.[1] The annual economic burden from sepsis hospitalizations and post-acute care exceeds $60 billion.[5] Despite advances in care, short-term mortality rates continue to exceed 15%.[6]

Sepsis incidence and mortality rates varied significantly by region. Furthermore, sepsis can be difficult to accurately diagnose, is a diverse clinical syndrome, and there is no gold standard for diagnosis. Assessing infection and related organ dysfunction can be difficult due to subjectivity.

Survivors are also at high risk for recurrent sepsis, readmission, cognitive and functional impairment. [7] After hospitalization, survivors can be too ill to return to their homes or work and may require ongoing care in venues such as skilled nursing facilities. In addition, cognitive impairment and functional disability can be major consequences, adding significantly to societal health care costs and productivity. Iwashyna et al demonstrated that severe sepsis in this older population was independently associated with substantial and persistent new cognitive impairment and functional disability among survivors.[8]

Over the past 3 decades, the Surviving Sepsis Campaign (SSC) has released several guidelines aimed at standardizing and improving the management of patients with severe sepsis and septic shock. [9]These guidelines have helped raise sepsis awareness and triggered numerous quality improvement initiatives around the world. In 2013, the New York State Department of Health began a mandatory state-wide initiative to improve early recognition and treatment of severe sepsis and septic shock.[10] The initiative led to increased compliance with sepsis-performance measures across hospitals, which correlated with a decline in risk-adjusted sepsis mortality. These results highlight the potential impact of policy-driven quality improvement programs in enhancing patient outcomes. The United States (US) Centers for Medicare & Medicaid Services'(CMS) SEP-1 measure has also established sepsis as a national priority for quality improvement. SEP-1 was first implemented in October 2015 and requires hospitals to report their bundled performance rates to CMS as part of the Inpatient Quality Reporting Program. Initially a pay-for-reporting measure, SEP-1 is now shifting to pay-for-performance under CMS's Value-Based Purchasing program.

Although early antimicrobial therapy can be lifesaving in patients with sepsis, unnecessary exposure to broad-spectrum antimicrobials has been associated with adverse effects and worse patient outcomes. [11] In addition, ~1/3 of patients with suspected sepsis are ultimately diagnosed with a non-infectious or viral condition. [12] Antimicrobial resistance (AMR) poses an important global health challenge in the 21st century which can be accelerated by overuse and misuse of antimicrobial agents. [13] Given the growing AMR burden, it is important that interventions combine infection prevention, vaccination, and antimicrobial-diagnostic stewardship to reduce inappropriate antimicrobial use. The purpose of this paper is to review literature on the role of early antimicrobial administration in sepsis combined with effective antimicrobial and diagnostic stewardship to improve outcomes and reduce unintended consequences of overuse of broad-spectrum antimicrobial agents.

Sepsis Definitions

An objective surveillance definition is crucial in making meaningful comparisons, tracking quality improvement efforts and outcomes. The recent task force proposed Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection".[2] The Sepsis-3 task force proposed criteria for sepsis that clinicians can use for patients who may have sepsis defined as the combination of suspected infection plus organ dysfunction, quantified as an increase in Sequential Organ Failure Assessment (SOFA) score by ≥2 points. Many clinicians have now adopted Sepsis-3 operational criteria for identifying sepsis. Others, however, including CMS(SEP-1)(Table 1) still use the Second International Consensus Definition (Sepsis-2), which defined severe sepsis as suspected infection, at least 2 systemic inflammatory response signs, and acute organ dysfunction, quantified using specific thresholds per organ.[14] Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. The challenge is that both Sepsis-2 and Sepsis-3 capture a heterogenous set of patients that vary widely in their presentations, severity, and prognosis. In addition clinicians have to determine if the dysregulation was due to infection versus some other cause.[15]

Table 1: The CMS Severe Sepsis/Septic Shock Management Bundle (SEP-1)

Severe Sepsis Bundle:	Septic Shock Bundle:
1. Measure lactate level within 3 h 2. Blood cultures (prior to antibiotics) within 3 h 3. Broad spectrum antibiotics within 3 h 4. Remeasure lactate if initial lactate elevated (>2.0 mmol/L) within 6 h	5. 30 cc/kg crystalloid bolus (normal saline or lactated ringers) within 3 h of hypotension, initial lactate ≥4.0 mmol/L, or clinician documentation of septic shock 6. Vasopressors to target mean arterial pressure ≥65 mmHg within 6 h if there is persistent hypotension after ≥30 cc/kg crystalloid bolus 7. Document repeat volume status and tissue perfusion assessment within 6 h: • Repeat focused exam: vital signs, cardiopulmonary, capillary refill, pulse and skin findings, OR

	• 2 of the following: Measure central venous pressure, central venous oxygen saturation, bedside cardiovascular ultrasound, or passive leg raise or fluid challenge

Hospital discharge diagnosis codes using administrative data are commonly used to track sepsis outcomes within hospitals.[16,17] Sepsis diagnosis codes are also used for quality analyses and reporting, including screening cases to review for adherence to the CMS Severe Sepsis/ Septic Shock Early Management Bundle (SEP-1). The accuracy of administrative definitions relative to medical record reviews also varies substantially.[18] In addition the use of administrative data for tracking sepsis trends is highly susceptible to bias from changing diagnosis and coding practices over time.[19]

Recognizing the need for a more objective measure to track sepsis incidence and outcomes, in 2018 the US Centers for Disease Control and Prevention (CDC) created an adult sepsis event (ASE) tool kit, which includes a validated definition that can be implemented using electronic health record (EHR) data and supporting materials to help hospitals create and maintain a robust, EHR-based sepsis surveillance operation.[4] (Table 2) The ASE definition was based on the Sepsis-3 framework of suspected infection with concurrent organ dysfunction but optimized for simplicity and reproducibility across institutions. An ASE is defined as (1) presumed serious infection, signified by obtained blood cultures and ≥4 consecutive days of antibiotics (or up until 1 day before death, discharge to hospice, transfer to another acute care hospital, or transition to comfort measures) starting within 2 calendar days of when blood cultures were obtained, plus (2) evidence of concurrent organ dysfunction, signified by any of 6 binary indicators of cardiovascular, pulmonary, renal, hepatic, coagulation, or perfusion dysfunction.

Table 2: CDC Adult Sepsis Event Criteria

Presumed Serious Infection

Blood Culture Order

+

New Antibiotic (within ±2 days)

+

Antibiotics Continued for ≥4 Days*

+

Acute Organ Dysfunction (eSOFA)

- **Vasopressor initiation**
- **Mechanical ventilation initiation**
- **Lactate ≥ 2.0 mmol/L**
- **↑2x in Creatinine, or ↓50% in eGFR**
- **↑2x in Bilirubin to ≥2.0 mg/dL**
- **↓50% in Platelets to <100**

**<4 antibiotic days allowed if patient dies, is made CMO, or is discharged to hospice or another hospital*

Baseline laboratory values defined as best during hospitalization (or during +/-2 day infection window for hospital-onset infection)

Hospital-Onset Adult Sepsis Event = All Criteria Met on Hospital Day ≥3

www.cdc.gov/sepsis/clinicaltools

The ASE definition was developed by a CDC Prevention Epicenters Program funded consortium that estimated the US national burden of sepsis by applying these criteria to EHR data from a large and diverse set of hospitals. The definition was validated using medical record reviews and found to have superior sensitivity and similar positive predictive value compared with sepsis diagnosis codes for identifying cases meeting Sepsis-3 criteria.[6]

The very wide spectrum of illnesses captured by current sepsis operational criteria are problematic because clinicians and regulators have been taught to treat all sepsis patients in a common fashion with immediate broad-spectrum antibiotics, and for those with hypotension and/or elevated lactates, high volume intravenous fluids. Regulators and quality improvement advocates reinforce and accelerate this perception through public reporting and pay-for-performance metrics that penalize clinicians and hospitals for failing to administer these interventions within 3 hours of recognizing possible sepsis. The rest of this paper will focus on diagnostic and antimicrobial stewardship and how together they can improve sepsis care.

Diagnostic and Antimicrobial Stewardship

The goals of diagnostic stewardship is to ensure the selection of the right test for the right patient at the right time.(Table 3 and Figure 1) In addition, excellence in diagnostic stewardship should reduce unnecessary testing and overdiagnosis/misdiagnoses and reduce delays. Both underutilization and overutilization of diagnostic tests are important as well as optimizing the timing of test ordering and reporting. Underutilization of appropriate diagnostic testing can lead to unnecessary diagnostic delays, diagnostic uncertainty, increased unnecessary empirical antimicrobial use, longer hospitalization or worse patient outcomes due to missed diagnoses.[20] The goals of antimicrobial stewardship on the other hand is to ensure the right interpretation to guide the prescription for the right antimicrobial therapy at the right time.(Table 3) Both diagnostic and antimicrobial stewardship are required to optimize use of resources and outcomes.

Table 3:

Goals of

Diagnostic Stewardship

- Select the right test for the right patient
- Generate accurate, clinically relevant results at the right time
- Improve clinical outcomes
- Reduce costs

Antimicrobial Stewardship

- Right interpretation
- Right antimicrobial selection
- Right time
- Improve patient outcomes
- Reduce unnecessary antimicrobial use

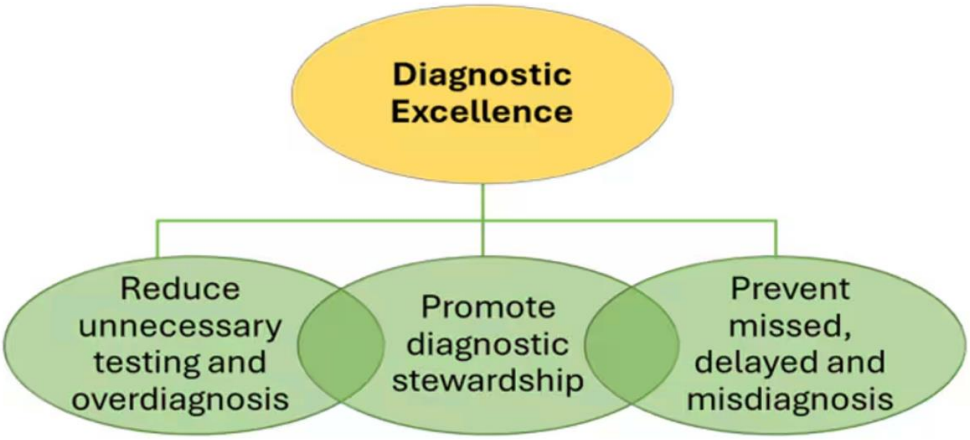

Figure 1: The Agency for Healthcare Research and Quality (AHRQ) Safety Program for Improving Antibiotic Use was convened to improve antibiotic prescribing practices by combining adaptive change theories and evidence-based diagnostic and antimicrobial practices. The program incorporated what was called the 4 moments of antibiotic decision making to improve antibiotic prescribing. [21] (Figure 2)

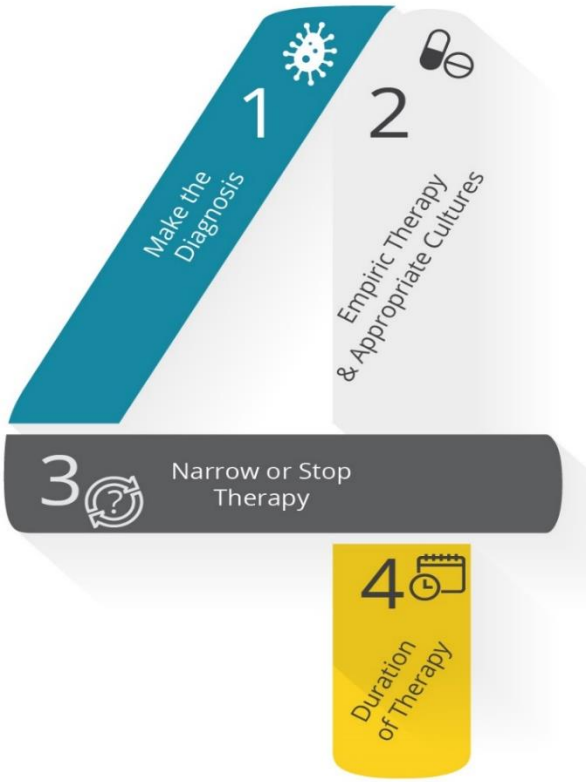

Figure 2

Moment 1 inquires whether the patient has an infection necessitating antibiotic treatment. This moment is designed to counter the knee jerk tendency in clinical settings to prescribe antibiotics in response to nonspecific symptoms—such as fever or altered mental status—without first fully assessing whether the patient's condition is due to an infection or a noninfectious cause.

Timely and appropriate antibiotic administration is the intervention most likely to improve outcomes in patients with bacterial sepsis and are thus strongly emphasized by practice guidelines and quality improvement initiatives. [22] The necessity of timely antibiotics for patients with possible sepsis needs to be balanced against their potential adverse effects including adverse drug effects and selection for antibiotic-resistant organisms, particularly for patients who turn out to have non-bacterial or non-infectious conditions that present similarly to sepsis.[11,23] In fact approximately one third of patients treated with an antibacterial antibiotic for possible sepsis are later found to have a viral infection or a non-infectious condition.[12,24] This challenge is potentiated by the difficulty in accurately diagnosing sepsis when patients first present because the signs and symptoms of sepsis are often non-specific and clinicians may need time to make an accurate diagnosis.[12,24,25]

Moment 2 asks has the clinician ordered appropriate cultures and other diagnostics before starting antibiotics and what empiric therapy should I initiate? Recommendations to immediately treat all patients with sepsis with broad-spectrum antibiotics are controversial. The most recent surviving sepsis guidelines recommend immediate broad-spectrum antibiotics for all patients with possible sepsis.[9] They recommend for adults with possible septic shock or a high likelihood of sepsis to administer antimicrobials immediately, ideally within one hour of recognition. The guidelines go on to say for adults with possible sepsis without shock the administration of antimicrobials should be administered within 3 hours from the time of sepsis recognition. In a recent study, Pak et al found in an adjusted model that each hour in antimicrobial administration from 1–6 hours was associated with significantly higher mortality in patients with suspected septic shock, but not in patients with suspected sepsis or infection alone. Another recent study reported on treating 600 patients with broad-spectrum antibiotics for possible sepsis. After review 1 in 3 most likely did not have a bacterial infection, 80% with bacterial infections treatment were overly broader than necessary, and 1 in 6 developed antibiotic-associated complications. In a previous study with large electronic datasets, researchers found that fewer than 10% of patients treated for suspected sepsis were infected with resistant organisms. [11] In addition, this study also found that both inadequate and unnecessarily broad empiric antibiotics were associated with higher mortality. Clinical decision support has been shown to reduce empiric broad-spectrum antimicrobial use in hospitalized patients with urinary tract infections and pneumonia by estimating multi-drug-resistant organism (MDRO) risk at order entry.[26,27] Until widely available clinicians should use the site of infection, the expected pathogen(s), local antibiograms, and history of MDROs in selecting empiric antimicrobials for patients with sepsis.

The interval between antibiotic order and administration is also a clinically meaningful and objective measure associated with sepsis outcomes independent of overall time-to-antibiotics.[28,29] β-lactam and vancomycin are often used for empiric sepsis treatment, despite MRSA being a rare cause of sepsis.[30] Vancomycin administration delays β-lactam administration especially in patients with limited IV access due to its prolonged infusion time. β-lactams, by contrast, are rapidly infused or given IV push, are active against more pathogens than vancomycin, and better tolerated. Two recent observational studies demonstrated that administering β-lactams before vancomycin is associated with improved outcomes.[30,31]

Moment 2 also emphasizes diagnostic testing which includes blood cultures, biomarker testing and rapid assays to identify pathogens and antimicrobial genes if available as well as appropriate imaging. Appropriate and timely specimen collection is critical. Failing to obtain appropriate cultures if accessible—such as blood or urine cultures—before starting antibiotics can create diagnostic uncertainty which can lead to prolonged unnecessary broad spectrum antimicrobial therapy. Poor quality specimens should be rejected and recollected. Optimizing blood culture use is important both to ensure true bacteremia is identified, particularly in patients with sepsis, and to reduce harms associated with unnecessary blood cultures, which can lead to treatment of false positive results(contaminants) and false-negative if drawn after starting antibiotics. This will result in delays in hospital discharge and increased healthcare costs.[32] Two blood culture sets should be obtained by separate venipunctures to optimize adequate volume and yield. The American Society for Microbiology (ASM) panel suggests using molecular diagnostics to rapidly identify the organism and antibiotic resistance markers which can inform more targeted therapy in combination with active communication by antimicrobial stewardship personnel. [33]

Perhaps the most common site of overdiagnosis and overtreatment occurs in the setting of asymptomatic bacteriuria (ASB). The incidence of ASB varies significantly from 5–15% in healthy individuals to 30–60% amongst elderly patients. [34]Antimicrobial therapy for ASB is exceedingly common, occurring in upwards of 50% of cases documented in clinical literature.[35] In a 43-hospital cohort study of patients presenting to the emergency department(ED) with positive urine cultures but no documented signs or symptoms of a UTI, 74.4% received antimicrobial therapy.[36] Once antimicrobials are started, they often continued into patients' hospital stay for at least 3 days; this was associated with longer hospitalization and adverse drug events. Therefore, urine should only be collected for patients with urinary symptoms such as dysuria and flank pain. Replace standalone urine culture with a urinalysis with reflex culture only if urine has significant pyuria (>10 WBC per high power field [hpf]). Both together have been shown to reduce unnecessary urine cultures and inappropriate treatment especially for patients with asymptomatic bacteriuria. Inappropriate practices include standard orders for urine for emergency department (ED) evaluation, hospital admission, inpatient preoperative screening, and assessment of altered mental or falls

without systemic signs of infection. Lastly, you should not order a urine culture due to changes in urine characteristics alone such as cloudy urine or odor.[37]

Biomarker-guided approaches have attracted great interest as potential tools for reducing antimicrobial use. Procalcitonin (PCT) has been the most extensively studied in both critically ill and noncritically ill patients, both for initiation and discontinuation of therapy. In 2019 an international expert consensus on optimized clinical use was published. [38]The group agreed that there is strong evidence that PCT-guided antimicrobial stewardship supports decisions on initiation and duration of antibiotic treatment in patients with sepsis. Levels of PCT can help to discriminate bacterial from viral disease and have been shown to lead to decreased rates of antibiotic prescriptions safely and early discontinuation of therapy. PCT expression is upregulated with bacterial pathogens and PCT expression is downregulated in patients with viral infections. PCT also decreases once the bacterial infection is controlled and thus provides information about response to infection (see Moment 4). Because sepsis patients have a high risk and time to treatment is crucial, PCT has mainly been used for early discontinuation of treatment, rather than for guiding initial empiric treatment.

A rapid test often overlooked is the gram stain. It is used to differentiate two large groups of bacteria based on their different cell wall components. Gram stain can distinguish between Gram-positive and Gram-negative groups by coloring these cells violet or pink. Gram-positive bacteria stain violet due to the thick peptidoglycan layer in the cell wall. Whereas Gram-negative bacteria stain pink due to the thin peptidoglycan layer. This technique also allows the determination of cell morphology, size, and cell arrangement. If you have body fluid from an infected site, a gram stain can provide useful preliminary information. An example would be from a patient who comes in with a draining leg abscess. If the gram stain shows gram-positive cocci in clusters that would indicate the patient probably has a *Staphylococcus(S) aureus* infection. The clinician would start an antibiotic empirically which covers both methicillin-resistant *S aureus* (MRSA) and methicillin sensitive S aureus (MSSA) until sensitivities are available; however, if the gram stain showed gram-positive cocci in chains the most likely organism would be a *Streptococcal* species so you would start with a penicillin or first-generation cephalosporin.

A detailed discussion on the role of molecular diagnostics in the management of sepsis is beyond the scope of this paper, but a detailed discussion can be found in the papers by Candel et al. and Eubank et al [39] [40]

Lastly, it should not be forgotten that approximately one-third of sepsis patients require procedural source control, and early intervention is associated with lower mortality.[41] Source control may include drainage of an abscess, debriding infected necrotic tissue, or removal of a potentially infected device.

Movement 2 underscores the important role of antimicrobial and diagnostic stewardship to guide more judicious use of broad-spectrum antibiotics for empiric sepsis treatment.

Moment 3 emphasizes the importance of daily review to reassess therapy. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy? Once the pathogen(s) and susceptibilities are known, antimicrobial de-escalation-i.e., stopping an antimicrobial that is no longer necessary (in case of combination therapy) or changing an antimicrobial to narrow the spectrum is critical. Studies have demonstrated that discontinuing anti-MRSA or antipseudomonal agents by day 3 in patients whose cultures are positive for organisms that do not require these agents is associated with similar or better outcomes compared to continued broad-spectrum use.[42] Improved outcomes result from reduced antibiotic-associated toxicities, decrease antimicrobial resistance, and less gut microbiome disruption.

Moment 4 focuses on determining the optimal duration of antibiotic therapy based on diagnosis and clinical response. Traditionally, antimicrobial durations have been longer than necessary—often based more on opinion rather than evidence. Determining the optimal duration of antimicrobial therapy in patients with sepsis is a complex decision that must account for multiple factors. These include infecting pathogen, infection site, illness severity, host immune status, source control, drug choice, renal and hepatic function, and clinical trajectory. Over the past two decades, numerous randomized controlled trials (RCTs) have evaluated antibiotic durations for specific infections including pneumonia, intra-abdominal infections, urinary tract infections, and bacteremia, generally demonstrating that shorter courses are as effective as longer ones.[43] (Table 4)These infections account for over half of inpatient antibiotic use, so tailoring duration has significant implications for patient safety.

Table 4: Infections Where Short-Course Therapy is Equivalent to Longer Course

	Days of Treatment	
	Short-Course	Long-Course
Community-acquired pneumonia	3-5	7-10
Ventilator-associated Pneumonia	≤8	10-15
Pyelonephritis	-7	10-14
Intraabdominal infection*	4	10
Acute exacerbation COPD	≤5	≥7
Cellulitis	5-6	10
Gram-negative bacteremia	7	10-14

* with source control

If optimal duration of therapy is unclear and if PCT is available using PCT along with clinical evaluation to decide when to discontinue antimicrobials in adults with an initial diagnosis of sepsis or septic shock can be very useful. PCT results protocol strongly support stopping antibiotics if PCT <0.5 ug/l or based on PCT fall >80% from baseline. The SAPS trial (2016) enrolled 1,546 ICU patients with suspected infection in 15 hospitals in the Netherlands and used a similar threshold for stopping antibiotics (<0.5 µg/L or >80% decrease from peak). The SAPS investigators reported that PCT use led to a significant reduction in antibiotic duration (5 vs 7 days, p<0.0001) and significantly lower 28-day (20% vs 25%) and 1-year mortality.[44] The recently published ADAPT-Sepsis trial provides additional data on use PCT guided antimicrobial duration. [45] The ADAPT-Sepsis trial found that PCT-guided care significantly reduced the duration of antibiotic therapy within 28 days of randomization compared to standard care (mean duration 9.8 vs 10.7 days(p=0.01), while 28-day mortality was non-inferior based on a 5.4% safety margin (20.9% for PCT-guided care vs 19.4% for standard care, absolute difference 1.6%, 95% CI -2.2-5.3%). CRP is less effective than PCT for guiding antibiotic discontinuation. If hospitals choose to implement PCT-guided strategies in patients with sepsis, I recommend focusing on antibiotic discontinuation rather than initiation. Successful implementation should be supported by clinician education, ideally integrated with clinical decision support tools and oversight and integration with antimicrobial stewardship programs.

Combining diagnostic and antimicrobial stewardship programs using the four moments helps clinicians make evidence-based decisions, crucial for evaluating and treating septic patients.

Conclusion

There is an urgent need to improve recognition and treatment of patients with sepsis. Effective sepsis management and antimicrobial stewardship are essential to optimize patient outcomes and minimize adverse events in patient with sepsis. Effective sepsis treatment should consider the potential risk of overuse and misuse of antimicrobial therapy balancing to quickly respond to patients with suspected sepsis, especially septic shock. Timely effective antimicrobial treatment has been shown to reduce morbidity and mortality. Integrating an effective antimicrobial stewardship approach enables: (1) optimal timing and appropriate antimicrobials in patients with sepsis; (2) antimicrobial de-escalation reducing unnecessary broad-spectrum antimicrobials when the pathogen(s) and their susceptibilities are identified-antimicrobial de-escalation or modification to narrow the spectrum should be implemented if appropriate; (3) appropriate duration of therapy in patients with sepsis-every extra dose and day of antimicrobial therapy increases adverse events; and (4) if available use of rapid diagnostics and biomarkers to improve diagnostic accuracy and treatment duration. Therefore, stewardship is not only compatible with sepsis care but vital for better patient outcomes.

References

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet (London, England)*. Jan 18 2020;395(10219):200-211. doi:10.1016/s0140-6736(19)32989-7
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama*. Feb 23 2016;315(8):801-10. doi:10.1001/jama.2016.0287
3. Liu V, Escobar GJ, Greene JD, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. *Jama*. Jul 2 2014;312(1):90-2. doi:10.1001/jama.2014.5804
4. Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *Jama*. Oct 3 2017;318(13):1241-1249. doi:10.1001/jama.2017.13836
5. Buchman TG, Simpson SQ, Sciarretta KL, et al. Sepsis Among Medicare Beneficiaries: 2. The Trajectories of Sepsis, 2012-2018. *Critical care medicine*. Mar 2020;48(3):289-301. doi:10.1097/CCM.0000000000004226
6. Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *JAMA*. Oct 3 2017;318(13):1241-1249. doi:10.1001/jama.2017.13836
7. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. May 2010;38(5):1276-83. doi:10.1097/CCM.0b013e3181d8cc1d
8. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Jama*. Oct 27 2010;304(16):1787-94. doi:10.1001/jama.2010.1553
9. Evans L, Rhodes A, Alhazzani W, et al. Executive Summary: Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021. *Crit Care Med*. Nov 1 2021;49(11):1974-1982. doi:10.1097/ccm.0000000000005357
10. Levy MM, Gesten FC, Phillips GS, et al. Mortality Changes Associated with Mandated Public Reporting for Sepsis. The Results of the New York State Initiative. *American journal of respiratory and critical care medicine*. Dec 1 2018;198(11):1406-1412. doi:10.1164/rccm.201712-2545OC
11. Rhee C, Kadri SS, Dekker JP, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. *JAMA Netw Open*. Apr 1 2020;3(4):e202899. doi:10.1001/jamanetworkopen.2020.2899
12. Shappell CN, Klompas M, Ochoa A, Rhee C, Program CDCPE. Likelihood of Bacterial Infection in Patients Treated With Broad-Spectrum IV Antibiotics in the Emergency Department. *Crit Care Med*. Nov 1 2021;49(11):e1144-e1150. doi:10.1097/CCM.0000000000005090
13. Kariuki S. Global burden of antimicrobial resistance and forecasts to 2050. *The Lancet*. 2024;404(10459):1172-1173. doi:10.1016/S0140-6736(24)01885-3
14. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. Apr 2003;31(4):1250-6. doi:10.1097/01.Ccm.0000050454.01978.3b
15. Biebelberg B, Rhee C, Chen T, McKenna C, Klompas M. Heterogeneity of Sepsis Presentations and Mortality Rates. *Annals of internal medicine*. Jul 2024;177(7):985-987. doi:10.7326/m24-0400
16. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. Jul 2001;29(7):1303-10. doi:10.1097/00003246-200107000-00002
17. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med*. Mar 2012;40(3):754-61. doi:10.1097/CCM.0b013e318232db65
18. Jolley RJ, Sawka KJ, Yergens DW, Quan H, Jetté N, Doig CJ. Validity of administrative data in recording sepsis: a systematic review. *Critical care (London, England)*. Apr 6 2015;19(1):139. doi:10.1186/s13054-015-0847-3
19. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care--reasons for caution. *The New England journal of medicine*. May 1 2014;370(18):1673-6. doi:10.1056/NEJMp1400276
20. Hueth KD, Prinzi AM, Timbrook TT. Diagnostic Stewardship as a Team Sport: Interdisciplinary Perspectives on Improved Implementation of Interventions and Effect Measurement. *Antibiotics*. 2022;11(2):250.
21. Tamma PD, Miller MA, Cosgrove SE. Rethinking How Antibiotics Are Prescribed: Incorporating the 4 Moments of Antibiotic Decision Making Into Clinical Practice. *JAMA*. 2019;321(2):139-140. doi:10.1001/jama.2018.19509
22. Seymour CW, Gesten F, Prescott HC, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. *The New England journal of medicine*. Jun 8 2017;376(23):2235-2244. doi:10.1056/NEJMoa1703058
23. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. *JAMA internal medicine*. Sep 1 2017;177(9):1308-1315. doi:10.1001/jamainternmed.2017.1938
24. Klein Klouwenberg PM, Cremer OL, van Vught LA, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. *Critical care*. 2015;19:319. doi:10.1186/s13054-015-1035-1
25. Rhee C, Chen T, Kadri SS, et al. Trends in Empiric Broad-Spectrum Antibiotic Use for Suspected Community-Onset Sepsis in US Hospitals. *JAMA Netw Open*. Jun 3 2024;7(6):e2418923. doi:10.1001/jamanetworkopen.2024.18923

26. Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection: The INSPIRE Randomized Clinical Trial. *JAMA*. 2024;doi:10.1001/jama.2024.6259
27. Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA*. 2024;doi:10.1001/jama.2024.6248
28. Kashiouris MG, Zemore Z, Kimball Z, et al. Supply Chain Delays in Antimicrobial Administration After the Initial Clinician Order and Mortality in Patients With Sepsis. *Critical care medicine*. Oct 2019;47(10):1388-1395. doi:10.1097/CCM.0000000000003921
29. Taylor SP, Anderson WE, Beam K, Taylor B, Ellerman J, Kowalkowski MA. The Association Between Antibiotic Delay Intervals and Hospital Mortality Among Patients Treated in the Emergency Department for Suspected Sepsis. *Critical care medicine*. May 1 2021;49(5):741-747. doi:10.1097/CCM.0000000000004863
30. Kondo Y, Klompas M, McKenna CS, et al. Association Between the Sequence of beta-lactam and Vancomycin Administration and Mortality in Patients with Suspected Sepsis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Dec 5 2024;doi:10.1093/cid/ciae599
31. Amoah J, Klein EY, Chiotos K, Cosgrove SE, Tamma PD. Administration of a beta-Lactam Prior to Vancomycin as the First Dose of Antibiotic Therapy Improves Survival in Patients With Bloodstream Infections. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Aug 24 2022;75(1):98-104. doi:10.1093/cid/ciab865
32. Fabre V, Klein E, Salinas AB, et al. A Diagnostic Stewardship Intervention To Improve Blood Culture Use among Adult Nonneutropenic Inpatients: the DISTRIBUTE Study. *Journal of clinical microbiology*. Sep 22 2020;58(10)doi:10.1128/jcm.01053-20
33. Wolk DM, Parrott JS, Babady NE, et al. The American Society for Microbiology's evidence-based laboratory medicine practice guidelines for the diagnosis of bloodstream infections using rapid tests: a systematic review and meta-analysis. *Clinical Microbiology Reviews*. 0(0):e00137-24. doi:doi:10.1128/cmr.00137-24
34. Ipe DS, Sundac L, Benjamin WH, Jr, Moore KH, Ulett GC. Asymptomatic bacteriuria: prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection. *FEMS Microbiology Letters*. 2013;346(1):1-10. doi:10.1111/1574-6968.12204
35. Spivak ES, Burk M, Zhang R, et al. Management of Bacteriuria in Veterans Affairs Hospitals. *Clinical Infectious Diseases*. 2017;65(6):910-917. doi:10.1093/cid/cix474
36. Petty LA, Vaughn VM, Flanders SA, et al. Assessment of Testing and Treatment of Asymptomatic Bacteriuria Initiated in the Emergency Department. *Open forum infectious diseases*. 2020;7(12)doi:10.1093/ofid/ofaa537
37. Claeys KC, Trautner BW, Leekha S, et al. Optimal Urine Culture Diagnostic Stewardship Practice—Results from an Expert Modified-Delphi Procedure. *Clinical Infectious Diseases*. 2021;75(3):382-389. doi:10.1093/cid/ciab987
38. Schuetz P, Beishuizen A, Broyles M, et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2019;57(9):1308-1318. doi:doi:10.1515/cclm-2018-1181
39. Candel FJ, Salavert M, Cantón R, et al. The role of rapid multiplex molecular syndromic panels in the clinical management of infections in critically ill patients: an experts-opinion document. *Critical care (London, England)*. Dec 30 2024;28(1):440. doi:10.1186/s13054-024-05224-3
40. Eubank TA, Long SW, Perez KK. Role of Rapid Diagnostics in Diagnosis and Management of Patients With Sepsis. *The Journal of infectious diseases*. Jul 21 2020;222(Suppl 2):S103-s109. doi:10.1093/infdis/jiaa263
41. Reitz KM, Kennedy J, Li SR, et al. Association Between Time to Source Control in Sepsis and 90-Day Mortality. *JAMA Surg*. Sep 1 2022;157(9):817-826. doi:10.1001/jamasurg.2022.2761
42. Kam KQ, Chen T, Kadri SS, et al. Epidemiology and Outcomes of Antibiotic De-escalation in Patients With Suspected Sepsis in US Hospitals. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Feb 5 2025;80(1):108-117. doi:10.1093/cid/ciae591
43. Spellberg B. The New Antibiotic Mantra—"Shorter Is Better". *JAMA internal medicine*. 2016;176(9):1254-1255. doi:10.1001/jamainternmed.2016.3646
44. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *The Lancet Infectious diseases*. Jul 2016;16(7):819-827. doi:10.1016/s1473-3099(16)00053-0
45. Dark P, Hossain A, McAuley DF, et al. Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis: The ADAPT-Sepsis Randomized Clinical Trial. *Jama*. Feb 25 2025;333(8):682-693. doi:10.1001/jama.2024.26458

