*Clinical Infectious Diseases*

IDSA FEATURES

# IDSA/ACEP/ASM/PIDS/SCCM/SHEA/SHM/SIDP Multisociety Position Paper: Hospital Strategies to Improve Sepsis Outcomes

**Chanu Rhee,[1,2,a] Henry Masur,[3,a] Michael Klompas,[1,2,b] Taison Bell,[4,a] Lindsay M. Busch,[5,a] Kathleen Chiotos,[6,c] David Classen,[7,a] David Gilbert,[8,a] Emily L. Heil,[9,d] Cindy Hou,[10,e] Sameer S. Kadri,[3,a] Andre C. Kalil,[11,a] Elizabeth L. Palavecino,[12,f] Sameer J. Patel,[13,c] Edward J. Septimus,[1,14,a] Jonathan Sevransky,[15,g] Steven Q. Simpson,[16,e] Jeffrey R. Strich,[3,a] Daniel A. Sweeney,[17,a] Preetham Talari,[18,h] Stephanie P. Taylor,[19,i] Dean Winslow,[20,a] Donald M. Yealy,[21,j] Frances A. Griffin,[22,a] and Sara E. Cosgrove[23,a]**

[1]Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA; [2]Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [3]Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA; [4]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia, USA; [5]Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine; Emory Critical Care Center, Atlanta, Georgia, USA; [6]Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [7]Division of Epidemiology, Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA; [8]Division of Infectious Diseases, Department of Medicine, Oregon Health & Science University, Portland, Oregon, USA; [9]Department of Practice, Sciences, and Health Outcomes Research, University of Maryland School of Pharmacy, Baltimore, Maryland, USA; [10]Division of Infectious Diseases, Department of Medicine, Jefferson Health-New Jersey, Cherry Hill, New Jersey, USA; [11]Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA; [12]Department of Pathology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA; [13]Division of Infectious Diseases, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern Feinberg School of Medicine, Chicago, Illinois, USA; [14]Department of Internal Medicine, Texas A&M Health Science Center College of Medicine, Houston, Texas, USA; [15]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Emory University School of Medicine, Atlanta, Georgia, USA; [16]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Kansas School of Medicine, Kansas City, Kansas, USA; [17]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California San Diego School of Medicine, San Diego, California, USA; [18]Center for Clinical Transformation, Ballad Health, Johnson City, Tennessee, USA; [19]Department of Internal Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan, USA; [20]Division of Infectious Diseases, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA; [21]Department of Emergency Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [22]Infectious Diseases Society of America, Arlington, Virginia, USA; and [23]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Sepsis remains a leading cause of morbidity and mortality in US hospitals despite extensive efforts to improve early recognition and treatment, particularly through implementation of the Centers for Medicare & Medicaid Services (CMS) SEP-1 quality measure. Recognizing the need for broader approaches to sepsis improvement, CMS and the Centers for Disease Control and Prevention are advancing new sepsis quality measures focused on outcomes and hospital programmatic capacity, while the Surviving Sepsis Campaign guidelines continue to provide evidence-based recommendations for bedside clinical management. However, there remains a need for practical, actionable guidance that complements existing guidelines and quality frameworks by addressing hospital-based strategies across the continuum of sepsis care. To address this gap, the Infectious Diseases Society of America convened a multidisciplinary, multisociety expert panel to develop a consensus-based position paper outlining evidence-informed recommendations for hospital-based sepsis improvement. The recommendations focus on infection-related aspects of sepsis management and span 6 domains: diagnostic testing and pathogen detection, antimicrobial management and delivery, surveillance and performance metrics, adjunctive therapy, program infrastructure and organizational support, and infection prevention. Examples include implementing multiplex nucleic acid amplification tests for positive blood cultures paired with active stewardship support; optimizing workflows for timely antibiotic delivery in septic shock; using clinical decision support to prioritize β-lactam administration before vancomycin when both are ordered; defaulting antipseudomonal β-lactams to prolonged infusion in critically ill patients; adopting EHR-based sepsis surveillance; tracking rates of inadequate empiric therapy, unnecessarily broad empiric therapy, antibiotic de-escalation, and timeliness of source control; establishing protocols for appropriate corticosteroid use in severe community-acquired pneumonia; and standardizing daily tooth brushing to prevent

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[a]C.R., H.M., T.B., L.M.B., D.C., D.G., S.S.K., A.C.K., E.J.S., J.R.S., D.A.S., D.W., F.A.G., and S.E.C. are representatives of the Infectious Diseases Society of America

[b]M.K. is a representative of the Society for Healthcare Epidemiology of America

[c]K.C. and S.J.P. are representatives of the Pediatric Infectious Diseases Society

[d]E.L.H. is a representative of the Society of Infectious Diseases Pharmacists

[e]C.H. and S.Q.S are representatives of the Sepsis Alliance

[f]E.L.P is a representative of the American Society for Microbiology

[g]J.S. is a representative of the Society of Critical Care Medicine

[h]P.T. is a representative of the Society of Hospital Medicine

[i]S.P.T. is a representative of the American Thoracic Society

[j]D.M.Y. is a representative of the American College of Emergency Physicians

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Correspondence: Chanu Rhee, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401, Boston, MA 02215, USA (crhee@bwh.harvard.edu).

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hospital-acquired pneumonia. The panel also highlights emerging approaches, particularly novel diagnostic strategies, that show promise but require further validation before widespread adoption. Collectively, these recommendations provide a pragmatic framework for hospitals to strengthen infection-related sepsis management and improve patient outcomes.

**Keywords.** sepsis; quality improvement; health care delivery; antimicrobial stewardship; diagnostic stewardship; performance measurement.

Sepsis is a leading cause of death, disability, and healthcare costs [1, 2]. Most efforts to improve sepsis outcomes have emphasized early recognition and initial treatment, with the Centers for Medicare & Medicaid Services (CMS) SEP-1 measure serving as the principal US policy initiative in this domain since 2015 [3]. However, the association between SEP-1 compliance and outcomes has been inconsistent, and large multicenter studies have not demonstrated clear reductions in sepsis mortality following implementation [4–13].

In 2023, IDSA and partnering societies called for greater emphasis on outcome-focused quality measurement to promote more comprehensive approaches to sepsis improvement beyond early treatment bundles alone [14]. CDC and CMS have since advanced complementary measures assessing sepsis mortality, readmissions, and hospital sepsis program capacity, while the Surviving Sepsis Campaign (SSC) continues to provide evidence-based recommendations spanning early recognition, critical illness, and recovery [15–18].

Although these initiatives are broadening the scope of sepsis improvement efforts, there remains a need for more consolidated, actionable guidance on hospital-based approaches to strengthen sepsis management across the continuum of care. The SSC guidelines provide foundational guidance for bedside clinical management and the CDC Hospital Sepsis Program Core Elements serve as a "manager's guide" outlining key hospital-level program principles [19, 20], but neither were designed to identify, prioritize, and operationalize specific system-level strategies most likely to reduce sepsis-related morbidity and mortality.

To address this gap, IDSA convened a multidisciplinary, multisociety expert panel to develop this consensus-based position paper outlining practical, evidence-informed recommendations for hospital-based sepsis improvement, with a focus on infection-related aspects of sepsis care. The panel's central position is that achieving better sepsis outcomes requires implementation of complementary strategies spanning diagnosis, early management, reassessment, and prevention, supported by effective measurement and feedback, coordinated care processes, and the infrastructure needed to implement and sustain these practices.

## METHODS

### Panel Composition

The multidisciplinary panel included representatives from IDSA, 8 other professional societies—the American College of Emergency Physicians (ACEP), Pediatric Infectious Diseases Society (PIDS), Society for Healthcare Epidemiology of America (SHEA), Society of Hospital Medicine (SHM), Society of Infectious Diseases Pharmacists (SIDP), Society of Critical Care Medicine (SCCM), American Thoracic Society (ATS), and American Society for Microbiology (ASM)—and the Sepsis Alliance, a national patient advocacy organization. The voting panel comprised 24 members with multidisciplinary expertise spanning adult and pediatric infectious diseases, critical care, emergency medicine, hospital medicine, antimicrobial stewardship, infection prevention, microbiology, pharmacy, quality improvement, health systems leadership, and patient advocacy (Supplementary Table 1). All panel members completed disclosure review in accordance with IDSA policy. The panel chair (C.R.) reviewed all disclosures, and none precluded participation in the development of this position paper.

### Scope and Intended Setting

The panel identified 6 domains for hospital-based sepsis improvement: diagnostic testing and pathogen detection, antimicrobial management and delivery, surveillance and performance metrics, adjunctive therapy, program infrastructure and organizational support, and infection prevention. Interventions focused on optimizing ventilatory or hemodynamic support and other general critical care practices—while essential to high-quality sepsis care—were considered out of scope for this document given its focus on infection-related care.

This document was developed primarily for US healthcare settings. Many of the broader principles and strategies described may also be relevant in other well-resourced health systems, although applicability will vary depending on local resources, infrastructure, workflows, and healthcare delivery context.

The strategies described are intended to complement—not replace—existing sepsis guidance and quality initiatives, including the SSC's patient-level clinical guidelines, SEP-1, and emerging CDC/CMS sepsis measures. Figure 1 illustrates how these recommendations relate to established sepsis guidance and US sepsis quality measurement frameworks.

### Target Population and Special Considerations

The recommendations address hospital-level structures, workflows, and practices relevant to patients evaluated and managed under commonly used clinical and operational definitions of sepsis and septic shock. This includes both patients with



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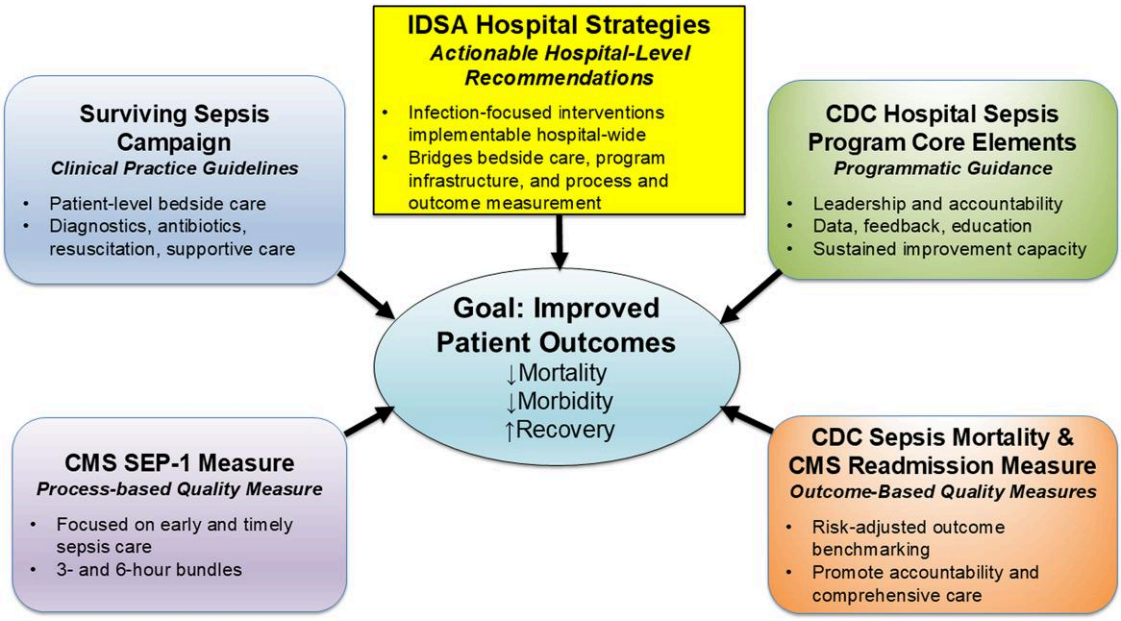


**Figure 1.** Positioning of IDSA hospital-level strategies within a patient-centered sepsis quality framework. Conceptual framework illustrating how IDSA Hospital Strategies fit within the broader landscape of sepsis guidance and US sepsis quality measurement. Patient outcomes are depicted as the shared goal of improvement. Existing sepsis resources address complementary domains, including patient-level clinical guidelines, programmatic guidance, and process- and outcome-based quality measures. IDSA Hospital Strategies are intended to complement these existing frameworks by providing actionable, infection-focused, hospital-level recommendations that bridge bedside care, program infrastructure, and measurement to support implementation of high-value practices and improve sepsis outcomes.

established sepsis and those with suspected sepsis who may ultimately be found to have noninfectious causes of illness [21].

This document is intended to inform sepsis care in both adult and pediatric settings, recognizing that many hospital-based sepsis programs span both populations. Because much of the supporting evidence derives from adult populations and care settings, pediatric-specific considerations related to differences in epidemiology, physiology, and care delivery are noted where relevant. Recommendations without explicit pediatric-specific caveats were considered broadly applicable to pediatric hospital settings, although implementation may require age-specific adaptation. Neonatal sepsis was considered out of scope because of its distinct pathophysiology, care environment, and established neonatal-specific approaches to surveillance, prevention, and management. Many of the overarching principles are also relevant to maternal and postpartum sepsis, although physiologic and pharmacologic considerations in pregnancy and the peripartum period may warrant tailored implementation in obstetric settings.

#### Consensus Process

The panel used a modified Delphi process combined with structured discussions to identify and prioritize practical, evidence-informed hospital-level strategies. Panelists first proposed candidate recommendations via a structured electronic survey, including supporting rationale and key references. The chair consolidated overlapping submissions into a preliminary recommendation set, which was refined through structured virtual meetings during which supporting evidence, operational feasibility, and potential unintended consequences were discussed. Recommendations were informed by targeted review of relevant guidelines and studies identified by panelists and supplemented by focused literature review; a formal systematic review was not undertaken.

Panelists independently scored each recommendation on a 1–5 scale across predefined domains, including potential impact on outcomes, opportunity size, feasibility (including resource and cost considerations), risk of unintended consequences, and overall priority for hospital implementation. Aggregate scores were reviewed and refined through an additional iterative round of anonymous voting followed by structured discussion.

Recommendations were categorized into 2 tiers: high priority (Tier 1) and moderate priority (Tier 2) (definitions in Box 1) based on aggregated scoring patterns and panel consensus rather than a single numerical cutoff. The tiered structure is intended to help hospitals prioritize implementation efforts, particularly where resources are limited, rather than imply that all recommendations are expected to have equivalent effects on outcomes, cost, or operational burden. A small subset of conceptually promising strategies with insufficient evidence or implementation experience to support broad recommendation was designated as emerging

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**Box 1. Definitions of Recommendation Tiers**

**Tier 1—High Priority**

Interventions judged by the panel to have the strongest overall combination of potential to improve outcomes, feasibility for hospital implementation, and supportive evidence and rationale. Recommended For Broad Implementation.

**Tier 2—Moderate Priority**

Interventions judged likely to provide benefit but with greater uncertainty regarding impact, feasibility, cost, unintended consequences, or implementation readiness. Selective or phased implementation may be appropriate.

**Emerging and Promising Strategies (Not Recommended for Routine Implementation)**

Conceptually compelling approaches with evolving evidence or limited real-world implementation experience. Not recommended for broad adoption at this time but highlighted to inform future research, innovation, and future policy development.

**Table 1. Summary of Recommended Hospital Strategies to Improve Sepsis Outcomes**

| |
|---|
| A. Diagnostic Testing and Pathogen Detection |
| 1. Implement multiplex nucleic acid amplification tests for positive blood cultures, paired with active antimicrobial stewardship program support to ensure timely interpretation, treatment optimization, and follow-up. [Tier 1—High Priority] |
| 2. Use clinical decision support strategies to optimize blood culture ordering practices, including appropriate indications for initial and follow-up cultures. [Tier 2—Moderate Priority] |
| B. Antibiotic Management and Delivery |
| 1. Implement hospital workflows and performance monitoring to optimize time from recognition of septic shock to first antibiotic administration, with a target of <1 h. [Tier 1—High Priority][a] |
| 2. Monitor and minimize time from antibiotic order to infusion start in patients with septic shock, with a pragmatic target of <30 min. [Tier 1—High Priority] |
| 3. Establish institutional policies that default antipseudomonal β-lactam antibiotics to prolonged infusion, after an initial loading dose, when these agents are ordered for critically ill patients with sepsis. [Tier 1—High Priority][a] |
| 4. Implement clinical decision support and multidisciplinary education to prioritize β-lactam administration before vancomycin when both agents are ordered in patients with suspected sepsis. [Tier 1—High Priority] |
| 5. Implement standardized workflows and clinical decision support to ensure timely administration of second antibiotic doses with frequent dosing intervals in patients with suspected sepsis. [Tier 2—Moderate Priority] |
| 6. Develop protocols and clinical decision support to guide antibiotic selection for patients who report penicillin or other β-lactam allergies. [Tier 2—Moderate Priority] |
| 7. Implement EHR-based clinical decision support tools that provide infection site-specific MDRO risk estimates to guide empiric antibiotic selection in suspected sepsis. [Tier 2—Moderate Priority] |
| C. Surveillance and Performance Metrics |
| 1. Adopt the CDC's Adult Sepsis Event definition to monitor sepsis incidence, outcomes, and care processes, stratified by community-onset and hospital-onset sepsis. [Tier 2—Moderate Priority][a] |
| 2. Monitor both inadequate and unnecessarily broad empiric antibiotic therapy in patients with suspected sepsis, using automated methods where feasible. [Tier 2—Moderate Priority] |
| 3. Measure de-escalation of anti-MRSA and antipseudomonal therapy among patients with suspected sepsis. [Tier 2—Moderate Priority] |
| 4. Monitor time from sepsis onset to definitive source control in patients requiring procedural intervention, and track timeliness of transfers when on-site source control is unavailable. [Tier 2—Moderate Priority][a] |
| D. Adjunctive Therapy |
| 1. Implement protocols and clinical decision support to promote timely corticosteroid use for appropriately selected patients with severe community-acquired pneumonia. [Tier 2—Moderate Priority][a] |
| 2. Implement protocols and clinical decision support to promote corticosteroid use for patients with refractory septic shock. [Tier 2—Moderate Priority][a] |
| E. Program Infrastructure and Organizational Support |
| 1. Establish a multidisciplinary sepsis governance structure that includes infectious diseases, antimicrobial stewardship, and clinical microbiology expertise and engages infection-prevention teams through structured collaboration. [Tier 2—Moderate Priority] |
| 2. Integrate antimicrobial stewardship participation into routine ICU rounds to support real-time optimization of antibiotic therapy in critically ill patients. [Tier 2—Moderate Priority] |
| 3. Support the application of pharmacokinetic/pharmacodynamic principles in antimicrobial dosing for critically ill patients, including access to infectious diseases and critical care pharmacists, clinician and nursing education, and laboratory capacity for therapeutic drug monitoring where appropriate. [Tier 2—Moderate Priority] |
| F. Infection Prevention |
| Primary recommendation: Ensure high adherence to the SHEA/IDSA Compendium for HAI prevention. In addition, the panel identified the following additional high-opportunity interventions: |
| 1. Implement universal chlorhexidine gluconate bathing with either universal or targeted MRSA nasal decolonization for all ICU patients and for non-ICU patients with invasive devices. [Tier 2—Moderate Priority] |
| 2. Implement structured programs to ensure daily toothbrushing for all hospitalized patients. [Tier 2—Moderate Priority] |
| G. Emerging and Promising Strategies (Not Recommended for Routine Implementation) |
| 1. Automated sepsis prediction tools |
| 2. Host immune response–based sepsis diagnostics |
| 3. Culture-independent rapid diagnostics for bloodstream infection |
| 4. Multiplex nucleic acid amplification test panels for lower respiratory samples |
| 5. Procalcitonin-guided antibiotic duration |

[a]See text for pediatric-specific considerations.

and promising. Table 1 summarizes the final recommendations and selected emerging strategies. Some candidate strategies were judged to have limited incremental value, insufficient evidence, low feasibility, or redundancy with existing practices and were therefore not included in the final recommendation set. Additional details regarding the modified Delphi process, voting framework, recommendation refinement, and final prioritization are provided in the Supplementary Methods, with detailed voting results shown in Supplementary Table 2.

### Implementation Context

Implementation of the strategies recommended in this document is best situated within existing hospital quality and patient

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safety infrastructure. Responsibility for implementation, performance monitoring, and accountability should reside within a clearly defined multidisciplinary sepsis governance structure supported by institutional leadership. Successful implementation also requires engagement of nursing, pharmacy, and frontline clinical teams, given their central role in protocol execution, workflow integration, patient monitoring, and education.

#### Manuscript Development

The panel chair drafted the manuscript. The full panel reviewed and revised the document before formal review by designated IDSA committees and external reviewers. Revisions were incorporated before circulation to participating societies for review and endorsement. Additional revisions were made in response to feedback from endorsing societies before final approval by the IDSA Board of Directors.

## RECOMMENDATIONS

### A. Diagnostic Testing and Pathogen Detection

This domain focuses on hospital-based strategies to improve timely pathogen identification, support pathogen-directed therapy, and reduce unnecessary antibiotic use. Only 2 diagnostic strategies were prioritized as Tier 1 or Tier 2 recommendations. Several additional promising approaches that currently lack sufficient evidence or implementation experience for recommendation are discussed in the Emerging and Promising Strategies section.

**1. Implement multiplex nucleic acid amplification tests (NAATs) for positive blood cultures, paired with active antimicrobial stewardship program support to ensure timely interpretation, treatment optimization, and follow-up. [Tier 1]**

#### Key Considerations

Blood cultures remain an important diagnostic test in suspected sepsis, identifying bloodstream pathogens in 10–20% of patients overall and up to 40% of those with septic shock [1, 22, 23]. Conventional laboratory workflows for species identification and susceptibilities typically require 48–72 hours after the blood culture becomes positive, during which clinicians frequently continue inadequate empiric coverage or unnecessarily broad regimens. When performed directly on positive blood cultures as soon as they signal growth, multiplex NAAT panels can identify ~90% of common bloodstream pathogens and key resistance genes within hours of culture positivity, enabling far earlier optimization of therapy [24].

The broader literature on rapid diagnostic tests for bloodstream infection—including multiplex NAATs, direct-from-positive-blood-culture MALDI-TOF, and other rapid organism identification approaches—supports the principle that earlier microbiologic information can improve care. In a meta-analysis of 88 studies (25 682 encounters), rapid diagnostic tests paired with active antimicrobial stewardship programs were associated with reduced mortality (OR 0.72 [95% CI, 0.59–0.87]), shorter time to optimal therapy, and reduced length of hospitalization compared with conventional blood culture workflows alone [25]. Importantly, in network meta-analysis, rapid diagnostic tests combined with antimicrobial stewardship were also associated with lower mortality compared with conventional blood culture workflows that already included stewardship (OR 0.78 [95% CI, 0.63–0.96]), supporting their benefit beyond stewardship alone [25]. Notably, no observed survival benefit existed when rapid diagnostics were used without stewardship involvement, underscoring the need for structured antimicrobial stewardship engagement—including guidance on interpretation, escalation and de-escalation pathways, and follow-up—to translate faster results into improved patient outcomes. These findings are also consistent with ASM's recent systematic review, meta-analysis, and practice guideline, which strongly recommend rapid diagnostics for positive blood cultures in conjunction with active antimicrobial stewardship support [26].

The panel acknowledged important limitations in this literature, including heterogeneity in study populations, diagnostic platforms, and stewardship models, as well as the predominance of quasi-experimental study designs [25]. The evidence is strongest and most consistent for improvements in time to optimal therapy and antibiotic optimization, whereas evidence for mortality reduction is more indirect and less certain. However, the panel judged this strategy to merit a Tier 1 designation based on the overall concordance of the evidence, strong biological and clinical plausibility, minimal downside when paired with stewardship, and suitability for hospital-wide implementation.

The panel intentionally prioritized multiplex NAATs for positive blood cultures over other rapid diagnostic tests in this recommendation. Although other rapid diagnostic approaches applied to positive blood cultures may provide benefit and have often been grouped together with NAATs in prior meta-analyses, multiplex NAATs currently offer the most immediately actionable combination of rapid organism identification and key resistance gene detection within a clinically relevant timeframe, enabling earlier and more confident optimization of antibiotic therapy. In contrast, culture-independent rapid diagnostics performed directly on whole blood represent a distinct category with different implementation challenges and a more limited evidence base and are therefore addressed separately in the Emerging and Promising Strategies section.

**2. Use clinical decision support strategies to optimize blood culture ordering practices, including appropriate indications for initial and follow-up cultures. [Tier 2]**

#### Key Considerations

Blood culture practices are variable across providers and institutions and often suboptimal [27]. In patients with suspected

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sepsis, blood cultures are sometimes not obtained, obtained with inadequate blood volume, or are drawn after initiation of empiric antibiotics, which is associated with an ~50% reduction in culture yield [28, 29]. Conversely, blood cultures are frequently obtained in patients at very low risk of bacteremia, and follow-up cultures after antibiotics are common in patients unlikely to have persistent infection [30]. Unnecessary blood cultures increase the risk of growth of contaminants, which can precipitate additional testing, inappropriate antibiotics, central line removals, and prolonged length of stay [31].

Clinical decision support (CDS) tools can both promote timely blood culture collection with adequate blood volume when indicated while also improving the appropriateness of blood culture testing [32]. Given the workflow pressures and time-sensitive nature of care in settings such as the emergency department or during urgent resuscitation, system-level CDS strategies are particularly important to facilitate pre-antibiotic culture collection without delaying antibiotic therapy. Strategies include EHR-based tools, standardized order sets or institutional guidelines, audit-and-feedback mechanisms, and stewardship- or microbiology-led interventions, depending on local resources and workflows. Electronic prompts linked to broad-spectrum antibiotic orders can increase appropriate pre-antibiotic blood culture collection without increasing low-value testing [33]. During the recent national blood culture bottle shortage, many institutions used CDS to curtail unnecessary blood cultures [34]. Across both pediatric and adult ICUs, CDS-supported blood culture optimization initiatives have consistently improved the appropriateness of blood culture draws and antibiotic prescribing, often resulting in fewer unnecessary blood cultures and reduced antibiotic use without adverse effects on patient outcomes such as mortality, readmissions, or length of stay [35–37]. Similar principles apply to other microbiologic testing in patients with suspected sepsis, underscoring the importance of aligning diagnostic stewardship with time-sensitive antibiotic decisions.

Although optimized blood culture practices have not been shown to reduce sepsis mortality, they improve diagnostic stewardship and support safer, more effective antimicrobial decision-making by enhancing diagnostic yield and minimizing contamination-related cascades. While no single national guideline provides explicit, comprehensive criteria for initial or follow-up blood culture indications, existing stewardship resources, professional society guidance, and expert consensus consistently emphasize targeted, indication-based use and provide a solid foundation for CDS implementation [30, 32, 38].

### B. Antimicrobial Management and Delivery

Effective antimicrobial therapy—encompassing timely initiation, appropriate spectrum, and optimized dosing and administration—is a powerful lever to improve sepsis outcomes, yet hospital processes are highly variable. This section outlines organizational strategies to optimize antimicrobial delivery for the highest-risk patients, reduce inappropriate or unnecessarily broad empiric therapy, and standardize dosing and infusion practices.

**1. Implement hospital workflows and performance monitoring to optimize time from recognition of septic shock to first antibiotic administration, with a target of <1 hour. [Tier 1]***

#### Key Considerations

Prompt, appropriate antimicrobial therapy is consistently linked to improved sepsis outcomes, underpinning its central role in clinical guidelines and hospital performance initiatives. However, the effect is not uniform across illness severity. Multiple large observational studies show that, in patients with septic shock, each hour of delay in antibiotic administration is associated with increased mortality, with reported adjusted odds ratios ranging from ~1.07 to 1.14 per hour of delay [39–42]. In contrast, the evidence supporting strict time-to-antibiotic targets for sepsis without shock is inconsistent, with several well-conducted studies showing no increase in mortality even if antibiotics are given up to 6 hours after recognition [41–44]. Unlike SEP-1, which applies a uniform 3-hour target to both sepsis and septic shock, prioritizing a <1-hour target specifically for septic shock focuses urgent therapy on the subgroup most likely to benefit while allowing clinicians more time to clarify the diagnosis and limit overtreatment in others.

Hospitals should routinely monitor the interval from recognition of septic shock to first antibiotic administration as a core process metric to identify delays, diagnose workflow barriers, and guide targeted quality-improvement efforts. Improvement strategies may include clinician education, electronic alerts when shock criteria are met, rapid triage pathways, optimized order sets, and close collaboration among nursing, pharmacy, and frontline clinical teams. These efforts can be further strengthened by also tracking and improving the time from antibiotic order to infusion start, a complementary operational metric addressed in the subsequent recommendation (B.2). Together, these system-level supports can reduce delays and improve timely delivery of antibiotics to the highest-risk patients.

An important consideration is the lack of consensus on a pragmatic, operational definition of septic shock. Definitions used in practice range from highly sensitive but nonspecific criteria (eg, any hypotension), to more restrictive definitions requiring persistent hypotension after fluid resuscitation and/or elevated lactate levels (eg, ≥4.0 mmol/L, as used in SEP-1 and early goal-directed therapy trials), to the Sepsis-3 criteria, which require vasopressor-dependent hypotension and a lactate level >2 mmol/L despite adequate fluid resuscitation [42, 45, 46].

For the purpose of operational measurement, hospitals may consider using objective, electronically documented indicators



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of shock recognition—such as vasopressor initiation—as pragmatic anchors for monitoring, while recognizing that these are imperfect surrogates and should not substitute for clinical judgment. This approach may improve feasibility and comparability across institutions by avoiding some of the complexity involved in accounting for baseline blood pressure, fluid responsiveness, or variable bedside documentation. The panel recognizes that vasopressor initiation may occur late in the course of shock physiology and that some high-risk patients, such as those with markedly elevated lactate levels (eg, ≥4.0 mmol/L), may warrant similarly urgent treatment even before vasopressors are started [42]. However, vasopressor initiation provides a reproducible and feasible reference point for monitoring time to antibiotic administration across diverse settings. Additional work is needed to refine and standardize operational definitions that balance sensitivity, specificity, feasibility, and reproducibility.

Importantly, prompt treatment remains appropriate for patients with a high clinical probability of sepsis even in the absence of shock, whereas patients with more uncertain presentations may benefit from a brief period of rapid diagnostic reassessment before antibiotic initiation. This general principle is reflected in the SSC guidelines, which recommend immediate antibiotic therapy for adults with probable or definite sepsis without shock, and a time-limited evaluation with antibiotic initiation within 3 hours if concern for infection persists in those with possible sepsis [18].

#### *Pediatric Considerations

In children, the evidence supporting a specific 1-hour threshold for antibiotic delivery is more limited than in adults, and similar challenges exist related to heterogeneity in pediatric septic shock definitions [47–52]. Nevertheless, substantial delays in antibiotic administration are associated with worse outcomes, particularly in children with higher-risk presentations [47–51]. Consistent with current pediatric SSC guidance, prompt antibiotic administration—ideally within 1 hour—remains appropriate for children with suspected septic shock, and hospitals should develop workflows and monitoring strategies to facilitate timely recognition and treatment of these higher-risk patients [53]. Children without shock, however, may warrant a brief period of rapid diagnostic evaluation to clarify the likelihood of sepsis and competing diagnoses before treatment is initiated [53].

### 2. Monitor and minimize time from antibiotic order to infusion start in patients with septic shock, with a pragmatic target of <30 minutes. [Tier 1]

#### Key Considerations

Order-to-infusion time is a critical operational metric as improving shock-to-antibiotic time requires prompt shock recognition and optimized antibiotic delivery. Observational studies suggest that longer delays between antibiotic orders and initial administration are associated with increased mortality [43, 54]. This metric has practical advantages: once a clinician determines that a patient with septic shock requires antibiotics, there is broad consensus that administration should occur as rapidly as possible, and both order and infusion timestamps are objective, routinely captured data elements in most electronic health records.

Improvement efforts typically depend on coordinated workflows and may include placing key antibiotics in automated dispensing cabinets in EDs and ICUs, implementing "code sepsis" response pathways, and developing pathways to expedite pharmacist review for stat antibiotic orders [55]. For clarity, this recommendation refers specifically to time to initiation (not completion) of intravenous antibiotic infusion and does not endorse alternative routes of administration (eg, intramuscular, oral) or methods (eg, IV push) solely to meet time-based metrics. Efforts to reduce order-to-infusion start time may require workflow redesign and safeguards to prevent unsafe shortcuts, dosing errors, or inappropriate administration practices.

The panel recognizes that the available literature does not define a specific evidence-based threshold for this interval. In observational studies of sepsis populations, administration delays associated with increased mortality have generally been longer (eg, ~1 to 1.5 hours), although these studies were not focused specifically on septic shock [43, 54]. The proposed <30-minute target should therefore be viewed as a pragmatic hospital benchmark to support antibiotic administration within <1 hour of septic shock recognition, since hospitals are unlikely to reliably achieve that broader goal without minimizing postorder delays. The panel also prioritized this recommendation because it is especially well suited to hospital-level quality improvement, as it can be measured objectively and directly targeted through workflow redesign.

Importantly, this metric should be limited to patients with septic shock. Extending aggressive infusion-time expectations to all antibiotic orders may consume resources, introduce operational strain, and could inadvertently encourage unnecessary broad-spectrum antibiotic use with little expected benefit.

### 3. Establish institutional policies that default antipseudomonal β-lactam antibiotics to prolonged infusion, after an initial loading dose, when these agents are ordered for critically ill patients with sepsis. [Tier 1]*

#### Key Considerations

Multiple randomized trials and observational studies suggest that prolonged infusions of β-lactam antibiotics improve outcomes in critically ill patients with sepsis, including higher clinical cure rates and a possible reduction in mortality. The largest individual trial to date (BLING III) enrolled more than 7200 ICU patients treated with piperacillin-tazobactam or

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meropenem for sepsis and compared continuous infusion after an initial loading dose with standard intermittent infusion [56]. Although the trial did not demonstrate a statistically significant reduction in 90-day mortality in its primary analysis, point estimates favored the continuous infusion group (24.9% vs 26.8%; $P = .08$), clinical cure was significantly higher, and mortality was significantly lower in a prespecified adjusted analysis (OR 0.89, 95% CI, 0.79–0.99). A meta-analysis published concurrently that incorporated BLING III and 16 other randomized controlled trials reported a 99.1% posterior probability that prolonged infusions reduce 90-day mortality compared with intermittent dosing (RR 0.86), corresponding to an estimated number needed to treat of ∼26 to prevent 1 death, along with increased clinical cure and lower ICU mortality [56, 57].

For purposes of this recommendation, prolonged infusion refers to administration strategies that extend drug exposure beyond standard intermittent dosing, including extended infusions (eg, 3–4 hours) and continuous infusions. This approach is most appropriate for antipseudomonal β-lactams, which benefit from extended time above the minimum inhibitory concentration, whereas agents with long half-lives (eg, ceftriaxone, ertapenem) achieve adequate exposure with standard intermittent dosing [58]. Available data do not include robust direct comparisons between extended and continuous β-lactam infusion strategies. Rather, both approaches are generally considered under the broader concept of prolonged infusion and are supported by the same pharmacokinetic/pharmacodynamic principles [59]. Selection should therefore be guided by local workflows, feasibility, and patient-specific factors.

All patients who receive prolonged β-lactam infusions should receive an initial loading dose via standard (short) infusion to achieve rapid therapeutic levels [60]. Because the strongest evidence derives from critically ill populations, hospitals should prioritize implementation in ICU settings, where patients' altered pharmacokinetics may increase benefit and established nursing workflows and vascular access facilitate reliable administration. This approach can also be extended to other units that frequently care for patients with sepsis, but hospitals should tailor adoption based on feasibility, resource availability, and vascular access constraints. Operationalizing prolonged infusion protocols in the emergency department should be done with caution to avoid missed loading doses and need for additional intravenous access during early resuscitation efforts. Hospital protocols should also allow for reversion to intermittent dosing when limited vascular access or specific clinical circumstances warrant. In patients with substantially altered pharmacokinetics—such as those receiving renal replacement therapy, extracorporeal membrane oxygenation, or with severe obesity—dosing and infusion strategies should be guided by established institutional protocols and pharmacy oversight.

***Pediatric considerations**

The benefits of extended infusion β-lactam antibiotics in children with sepsis have not clearly been demonstrated in the available literature [61]. If hospitals elect to use extended infusion β-lactam strategies in children, these efforts may be most appropriately focused on patients at higher risk of suboptimal target attainment in whom this strategy is feasible based on access and compatibility considerations [62].

**4. Implement clinical decision support and multidisciplinary education to prioritize β-lactam administration before vancomycin when both agents are ordered in patients with suspected sepsis. [Tier 1]**

**Key Considerations**

Many patients with suspected sepsis are empirically treated with both broad-spectrum β-lactam antibiotics and vancomycin, despite methicillin-resistant *Staphylococcus aureus* (MRSA) being identified from any clinical culture site in fewer than 4% of patients treated for suspected community-onset sepsis overall and in ∼12% of those with culture-confirmed community-onset sepsis [21, 63]. Due to its prolonged infusion time (≥60 minutes), vancomycin administration can delay timely β-lactam delivery, particularly in patients with limited vascular access. This delay is consequential because β-lactam antibiotics provide both high clinical effectiveness and broad coverage of common sepsis pathogens not covered by vancomycin, particularly Gram-negative organisms.

Two retrospective studies found that administering β-lactams before vancomycin was associated with lower mortality among patients with bloodstream infections and those with suspected sepsis, regardless of bacteremia status [64, 65]. Although these studies are subject to residual confounding, the findings are consistent with the central role of β-lactams in empiric sepsis therapy and support prioritizing their administration when both agents are indicated.

CDS and targeted education can facilitate implementation of this practice. Examples of CDS include default antibiotic order sets that sequence β-lactams before vancomycin and EHR prompts recommending β-lactam-first administration when both agents are ordered for suspected sepsis. Education for physicians, pharmacists, and nursing staff can reinforce the rationale for β-lactam prioritization and support coordinated implementation. Importantly, this recommendation is intended to guide default workflow when both agents are used as part of broad empiric sepsis coverage and is not intended to override clinical judgment when vancomycin-first administration or targeted anti-MRSA therapy alone may be appropriate.

The panel debated whether this recommendation should be Tier 1 or Tier 2 given that the evidence is observational. Ultimately, a Tier 1 designation was selected given the biological and clinical plausibility of the association, its minimal risk, feasibility through modest workflow adjustments, and



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strong suitability as an objective, measurable hospital quality metric.

**5. Implement standardized workflows and clinical decision support to ensure timely administration of second antibiotic doses with frequent dosing intervals in patients with suspected sepsis. [Tier 2]**

**Key Considerations**

Hospitals often focus on timely administration of the first antibiotic dose in sepsis, yet delays in second or later doses occur in at least a quarter of patients with suspected sepsis and are associated with worse outcomes, likely due to inadequate maintenance of therapeutic drug concentrations during the critical early treatment period [66–69]. These delays commonly arise when clinicians order 1-time doses or when care handoffs and patient transportation disrupt scheduled dosing (eg, ED-to-inpatient handoffs). System-level factors such as ED crowding and boarding—which are increasingly common and associated with worse outcomes—may further exacerbate these delays [70].

Standardized workflows can reduce delays by embedding second-dose planning into routine care processes. Examples include defaulting ED antibiotic orders to scheduled dosing rather than 1-time dosing, ensuring scheduled doses are active before patient transfer, incorporating antibiotic dose–timing checks into handoff protocols or transfer checklists, and using EHR-based CDS. In a randomized quality improvement study of 420 ED patients treated with cefepime or piperacillin-tazobactam, an alert prompting clinicians to reorder antibiotics before the next dose was due significantly reduced second-dose delays, although the study was not powered to detect differences in clinical outcomes [71]. Timely administration of second doses is straightforward to measure using EHR timestamps for scheduled and actual administration times, enabling routine monitoring and iterative improvement.

**6. Develop protocols and clinical decision support to guide antibiotic selection for patients who report penicillin or other β-lactam allergies. [Tier 2]**

**Key Considerations**

About 10% of US patients report penicillin and cephalosporin allergies but over 90% of these patients do not have true allergies and can safely receive β-lactams [72]. Furthermore, most patients with reported penicillin allergies can safely receive key cephalosporins commonly used in sepsis care (eg, cefepime, ceftazidime) without test dosing or other precautions, even after prior IgE-mediated reactions [73]. In the absence of clear guidance and protocols, these patients are often treated with agents that may be less effective, more toxic, or unnecessarily broad compared with first-line β-lactams [74]. This is particularly problematic in patients with possible sepsis where timely and effective treatment is critical [75].

Standardized protocols and CDS tools that stratify patients based on their reaction history and outline when direct challenges, test doses, skin testing, or alternative β-lactams are appropriate can safely increase β-lactam use [76–79]. Although confirmatory testing may be impractical before the initial antibiotic dose in unstable patients with suspected sepsis, it can be valuable for optimizing therapy after stabilization.

Penicillin allergy delabeling programs are an important complementary strategy and have been associated with increased use of preferred β-lactams and reduced reliance on broad-spectrum alternatives [80]. While delabeling is rarely feasible during acute sepsis management, integrating systematic allergy reassessment into inpatient workflows can reduce inappropriate allergy labels and improve empiric antibiotic selection over time. Such efforts should include appropriate safeguards, including careful review of reaction history, avoidance of direct challenges in patients with severe delayed hypersensitivity reactions, and involvement of clinicians with relevant expertise when needed.

Although data on CDS tools specifically for patients with sepsis who report β-lactam allergies are limited, benefit is plausible, implementation is feasible, and embedding structured allergy-assessment pathways into CDS may help standardize practice and improve timely access to optimal therapy [81, 82]. Effective β-lactam allergy protocols require multidisciplinary collaboration, including antimicrobial stewardship programs, pharmacy support to assist with risk stratification and test-dose procedures, and access to allergy expertise (in person or virtual) for complex cases.

**7. Implement EHR-based clinical decision support tools that provide infection site-specific MDRO risk estimates to guide empiric antibiotic selection in suspected sepsis. [Tier 2]**

**Key Considerations**

Empiric coverage for multidrug resistant organisms (MDROs), particularly MRSA and *Pseudomonas aeruginosa*, is frequently used in suspected sepsis, even though most community-onset sepsis is not caused by these pathogens [63]. The INSPIRE trials were large pragmatic randomized trials that evaluated EHR-integrated, infection site-specific MDRO risk prediction tools using routinely available patient-level data—including prior microbiology results, recent healthcare exposures, prior antibiotic exposure, comorbidities, and infection-specific clinical variables—in conjunction with local microbiologic epidemiology to generate patient- and pathogen-specific risk estimates embedded within ordering workflows [83–86]. These tools safely reduced unnecessary broad-spectrum empiric therapy for patients with suspected pneumonia, urinary tract infections, skin and soft-tissue infections, and intra-abdominal infections without increasing mortality, treatment failure, or other adverse outcomes [83–86]. These findings support implementation of

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similar EHR-integrated risk prediction tools to guide empiric antibiotic selection in patients with suspected sepsis.

The INSPIRE trials excluded critically ill patients; use in ICU populations should therefore be approached cautiously pending further studies. However, many hospitalized patients with suspected sepsis are managed outside the ICU, representing a substantial opportunity to reduce unnecessary broad-spectrum therapy in a population for whom safety and effectiveness are supported by available data [87, 88]. Because these models require local validation, institution-specific data inputs, customized EHR integration, and strong stewardship oversight, the panel judged this a Tier 2 recommendation.

### C. Surveillance and Performance Metrics

Objective measures of sepsis incidence, outcomes, and care processes are essential for quality improvement. This section highlights EHR-based approaches to sepsis surveillance and performance measurement, including metrics that track under- and over-treatment and the timeliness of critical interventions.

**1. Adopt the CDC adult sepsis event definition to monitor sepsis incidence, outcomes, and care processes, stratified by community-onset and hospital-onset sepsis. [Tier 2]***

#### Key Considerations

Accurate surveillance is essential to inform sepsis prevention and quality improvement. Traditionally, sepsis surveillance has relied on administrative diagnosis codes, but ICD-based approaches are unreliable because sepsis-specific codes miss many cases, while indirect estimation using infection and organ dysfunction codes introduces substantial heterogeneity between providers and hospitals and is prone to variation due to changes in diagnosis, documentation, and coding practices over time [89–92]. CDC developed the Adult Sepsis Event (ASE) definition as an alternative method to track sepsis using objective clinical criteria extracted from EHR records (eg, blood culture orders, sustained antimicrobial therapy, and evidence of concurrent organ dysfunction) instead of codes to identify sepsis in a standardized and reproducible manner [93]. A recently proposed update to the ASE definition (version 2.0) incorporates modifications intended to improve clinical credibility and better capture the spectrum of organ dysfunction [94].

Compared to ICD code-based approaches, ASE provides more objective estimates of changes in sepsis incidence over time, enables fairer comparisons across institutions, and may support more accurate evaluation of quality-improvement interventions. It also offers consistent differentiation between community-onset and hospital-onset sepsis, which can help hospitals better characterize where sepsis is occurring and where additional review or improvement efforts may be warranted [95]. Early adoption of ASE surveillance may also facilitate participation in emerging CDC and CMS sepsis reporting initiatives.

Although ASE provides a strong foundation for sepsis surveillance, important considerations remain for its use in quality measurement. Changes in ASE incidence or mortality may reflect differences in case mix and illness severity in addition to care quality, underscoring the need for robust risk adjustment. In addition, although hospital-onset sepsis is associated with particularly high mortality, its preventability remains incompletely defined [95]. Accordingly, at present, ASE is best used to track sepsis burden and trends over time, distinguish community-onset from hospital-onset sepsis, and identify priorities for local review and quality improvement.

Other EHR-based approaches—including electronic implementations of Sepsis-3 and hybrid methods combining diagnosis codes with objective clinical data—can be used for internal surveillance when ASE implementation is not yet feasible, but they introduce greater variability and limit comparisons across institutions [96, 97]. For example, SOFA-based surveillance depends on locally available data elements, baseline assumptions, and site-specific calculation rules, and Sepsis-3 criteria were developed to predict mortality among patients with suspected infection rather than for surveillance or quality monitoring.

#### *Pediatric Considerations

This recommendation does not apply to pediatric sepsis surveillance at this time. However, building on prior CDC-supported consensus recommendations and pilot surveillance work [98, 99], an electronic Pediatric Sepsis Event surveillance definition has recently been developed, validated, and applied to national datasets to estimate the US burden of pediatric sepsis [100]. This framework provides a scalable approach for pediatric sepsis surveillance, although experience with real-world implementation and use for quality monitoring remains limited.

**2. Monitor both inadequate and unnecessarily broad empiric antibiotic therapy in patients with suspected sepsis, using automated methods where feasible. [Tier 2]**

#### Key Considerations

Empiric therapy turns out to be inadequate—defined as lacking activity against the ultimately identified pathogen—in 1 of 5 patients with bloodstream infections [101, 102]. At the same time, about two-thirds of patients with suspected community-onset sepsis are treated with anti-MRSA or antipseudomonal antibiotics despite <10% harboring these pathogens, resulting in unnecessarily broad empiric therapy [21, 63]. Both under-treatment and over-treatment are associated with worse outcomes: inadequate empiric therapy is linked to increased mortality, whereas unnecessarily broad therapy is associated with acute kidney injury, *C. difficile* infection, antimicrobial resistance, and increased mortality [103].

Hospitals should monitor both inadequate and unnecessarily broad empiric antibiotic therapy to balance the competing



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goals of ensuring timely adequate coverage while minimizing unnecessary broad-spectrum antibiotic use, using automated EHR-based methods where feasible. Useful measures include the proportion of bacteremic patients whose empiric regimen lacks activity against the recovered pathogen and the proportion of patients started on anti-MRSA or antipseudomonal agents who ultimately have no microbiologic evidence of MRSA, *Pseudomonas aeruginosa*, or other ceftriaxone-resistant organisms. These data can inform targeted stewardship and quality-improvement efforts, such as refining local empiric therapy guidelines, updating risk-factor–based MRSA or pseudomonal coverage criteria, incorporating EHR-based risk-stratification prompts for resistant organisms (see Recommendation B.7), enhancing de-escalation workflows, or providing feedback to clinicians at the individual or service level.

**3. Measure de-escalation of anti-MRSA and antipseudomonal therapy among patients with suspected sepsis. [Tier 2]**

**Key Considerations**

De-escalation of empiric MRSA and antipseudomonal therapy is highly variable across hospitals and often does not occur even when cultures and clinical data support narrowing [104]. Although randomized trial data are limited, observational studies consistently associate de-escalation with equivalent or improved outcomes [104–108].

Hospitals can operationalize a de-escalation metric by identifying patients with suspected sepsis who receive empiric anti-MRSA or antipseudomonal therapy, lack evidence of MRSA or ceftriaxone-resistant gram-negative infection within 3–4 days, and have these agents discontinued or narrowed accordingly. This approach was used in a large US-based cohort analysis that demonstrated substantial interhospital variation and better patient outcomes with de-escalation even after detailed risk adjustment [104]. Alternative approaches, such as antibiotic spectrum scores, have been described but are more complex to implement and limit interhospital comparability because no consensus exists regarding which score to use [109]. Hospitals may also choose to track de-escalation of carbapenems in patients without documented carbapenem-resistant organisms.

Tracking and feeding back de-escalation rates at the hospital, service, or clinician level can inform local stewardship efforts. Strategies to improve de-escalation include CDS prompts, pharmacist-led outreach, structured antibiotic time-outs, and selective use of MRSA nasal surveillance testing to facilitate earlier discontinuation of empiric anti-MRSA therapy in patients with suspected pneumonia [110]. Importantly, this metric should be interpreted in the context of clinical stability and source control. Continued broad-spectrum therapy may be appropriate in select cases, including patients with persistent hemodynamic instability, suspected deep-seated or uncontrolled infection due to resistant pathogens, or severe immunocompromise. The intent is not to mandate de-escalation in every culture-negative case, but to identify opportunities where narrowing is supported by available microbiologic and/or clinical data.

**4. Monitor time from sepsis onset to definitive source control in patients requiring procedural intervention, and track timeliness of transfers when on-site source control is unavailable. [Tier 2]***

**Key Considerations**

Timely source control is a foundational principle of sepsis management because persistent infected foci can drive ongoing immune dysregulation, organ dysfunction, and treatment failure. Approximately one-third of hospitalized patients with sepsis require a procedure for source control, such as abscess drainage, debridement of infected or necrotic tissue, or removal of an infected device [111–113]. Although observational studies evaluating the association between source control timing and outcomes remain limited and susceptible to confounding, the most rigorous evaluation to date—a retrospective cohort study of 4962 adults with community-onset sepsis at UPMC—found that source control within 6 hours of sepsis onset was associated with lower risk-adjusted 90-day mortality, with the strongest associations observed in gastrointestinal, abdominal, and soft-tissue infections [113].

Although the optimal timing of source control varies by clinical context—including illness severity, infection site, pathogen, procedural options, and technical feasibility—hospitals currently have limited visibility into how often delays occur. Electronic identification of patients with sepsis who undergo source control, using procedure-code lists similar to those developed in the UPMC study, could help quantify performance and identify workflow barriers such as delays in consultation, operating room or interventional radiology availability, imaging, or cross-service coordination. Because many hospitals lack full-time procedural capabilities, monitoring the timeliness of transfers for source control is equally important.

The panel recognizes that many hospitals currently lack the technical expertise and resources to implement this recommendation and that operationalizing source control timing metrics presents definitional and analytic challenges, including variability in defining sepsis onset, procedural initiation, and transfer intervals. Standardized analytic code, implementation toolkits, and interpretive guidance are therefore needed to support consistent measurement across settings and represent important priorities for future work.

***Pediatric Considerations**

Timely transfer for definitive source control is a particularly important consideration in pediatric sepsis care and is

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emphasized in the pediatric SSC guidelines, as many children with sepsis initially present to hospitals without on-site pediatric subspecialty, surgical, or interventional radiology capabilities [53, 114]. Monitoring transfer timeliness may therefore be especially relevant for identifying delays and opportunities to improve regional care coordination for pediatric patients requiring source control.

### D. Adjunctive Therapy

This section focuses on corticosteroid use in clinical contexts where evidence suggests benefit but practice remains variable, highlighting opportunities for standardized implementation. Despite overlap with broader critical care management, adjunctive immunomodulatory therapies were considered within the scope of this multidisciplinary initiative.

**1. Implement protocols and clinical decision support to promote timely corticosteroid use for appropriately selected patients with severe community-acquired pneumonia. [Tier 2]***

#### Key Considerations

The role of corticosteroids in community-acquired pneumonia (CAP) is an area of longstanding controversy. In the US Veterans Affairs ESCAPe trial, corticosteroids were not associated with a mortality benefit, and the REMAP-CAP steroid domain was stopped early for futility with numerically higher mortality in the corticosteroid arm [115, 116]. In contrast, the CAPE-COD trial demonstrated that hydrocortisone 200 mg IV daily initiated within 24 hours of ICU admission substantially reduced progression to mechanical ventilation and 28-day mortality among patients with severe CAP [117]. Differences in patient selection, baseline severity, and timing of corticosteroid initiation may explain inconsistent findings across studies.

Despite heterogeneity across trials, several meta-analyses suggest a mortality benefit [118–120]; accordingly, guidelines from SCCM and ATS now recommend corticosteroid therapy for adults with severe CAP [121, 122]. Because severe CAP with acute hypoxemic respiratory failure meets sepsis criteria even in the absence of shock, and pneumonia is the most common cause of sepsis, improving outcomes in severe CAP represents an important opportunity to reduce overall sepsis mortality [123, 124].

Implementation tools such as order sets, local guidance, and CDS can promote timely and consistent uptake, while EHR-based monitoring of corticosteroid use can support adherence and iterative improvement. Importantly, CDS and educational efforts should ensure that corticosteroid use is generally limited to patients approximating populations for which trials have demonstrated benefit (eg, severe CAP with acute hypoxemic respiratory failure requiring ICU-level care), while recognizing that emerging evidence suggests benefit may be concentrated among patients with elevated C-reactive protein (CRP) levels [125]. Local protocols should therefore specify inclusion criteria and align contraindications and cautions with prior trial populations (ie, excluding suspected or confirmed influenza pneumonia, chemical pneumonitis from aspiration of gastric contents, invasive fungal or mycobacterial infection, or other conditions in which corticosteroid risks may outweigh potential benefits). Hospitals may further consider incorporating CRP-informed stratification into local protocols to help identify patients most likely to benefit, while balancing potential risks.

Although the overall balance of evidence supports early corticosteroid administration for patients with severe CAP, the panel designated this Tier 2 recommendation because of inconsistent efficacy findings across clinical trials and because successful implementation requires careful attention to patient selection, contraindications, and CDS design to avoid inappropriate corticosteroid use. Notably, the panel did not specifically recommend protocols to support routine initiation in the emergency department, given diagnostic uncertainty early in the clinical presentation and the risk of unnecessary steroid exposure. However, corticosteroid initiation in the ED may be reasonable when diagnostic certainty is high, particularly in settings of prolonged boarding where delays in ICU transfer may postpone therapy.

#### *Pediatric considerations

There are no high-quality pediatric trials evaluating the impact of corticosteroids in children with severe CAP, so the potential benefits versus harms of implementing tools to facilitate steroid administration in pediatric settings are unknown.

**2. Implement protocols and clinical decision support to promote corticosteroid use for patients with refractory septic shock. [Tier 2]***

#### Key Considerations

The role of corticosteroids in septic shock has been debated for decades, but several large trials and meta-analyses suggest a mortality benefit, particularly in adults with persistent vasopressor-dependent shock [126, 127]. Recent SCCM and SSC guidelines suggest administering corticosteroids to adults with persistent septic shock, reflecting the balance of current evidence [18, 121].

Despite these recommendations, corticosteroid use in septic shock varies widely across US hospitals, underscoring an implementation gap [128]. Standardized protocols, order sets, and CDS can help ensure timely and consistent use of corticosteroids in patients most likely to benefit, and monitoring compliance rates can help identify workflow barriers and guide iterative improvements. Such protocols should clearly define refractory septic shock, commonly operationalized as a requirement for norepinephrine or epinephrine at ≥0.25 mcg/kg/min for at least 4 hours to maintain target mean arterial pressure, and



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specify the recommended regimen of intravenous hydrocortisone 200 mg daily [60]. Although debate persists regarding adjunctive fludrocortisone, protocolized hydrocortisone administration remains the core recommended approach [129].

This recommendation was designated Tier 2 because, although current guidelines support corticosteroid use in persistent septic shock, uncertainty remains regarding the magnitude of benefit and some trials have reported neutral findings. Nevertheless, corticosteroid therapy is supported by contemporary guidelines, is low-cost and operationally straightforward, and has a favorable benefit-risk profile when used at recommended doses and durations.

#### *Pediatric Considerations

Available pediatric data do not clearly demonstrate a mortality benefit associated with corticosteroid use in children with refractory septic shock, and small retrospective studies raise concern for possible harm [130–132]. In alignment with the SSC guidelines for children [53], and pending results from an ongoing randomized trial (NCT03401398), either administering or withholding corticosteroids is considered acceptable in children. Implementation of tools to promote corticosteroids should therefore be limited to those with suspected adrenal insufficiency.

### E. Program Infrastructure and Organizational Support

Effective sepsis care depends not only on clinical protocols but also on strong organizational infrastructure. Multidisciplinary governance, stewardship integration, and pharmacologic expertise are essential components of high-functioning sepsis programs and may support reliable implementation of the recommendations in this document. The panel designated all recommendations in this section as Tier 2 because, although supported by expert consensus, observational data, and national frameworks such as CDC's Hospital Sepsis Program Core Elements, direct evidence linking these structures to improved patient outcomes is limited, and implementation often requires dedicated personnel, institutional commitment, and resources that vary across hospitals.

**1. Establish a multidisciplinary sepsis governance structure that includes infectious diseases, antimicrobial stewardship, and clinical microbiology expertise and engages infection-prevention teams through structured collaboration. [Tier 2]**

#### Key Considerations

Effective sepsis care requires coordination across multiple disciplines. Sepsis governance has traditionally been driven by critical care, emergency medicine, hospital medicine, nursing, pharmacy, and other clinical and operational teams whereas infectious diseases, antimicrobial stewardship, clinical microbiology, and infection prevention have often been absent from (or only peripherally engaged in)program leadership. Findings from the 2022 National Healthcare Safety Network survey underscore this gap: only 55% of hospital sepsis committees reported antimicrobial stewardship participation [133]. This gap is important because many of the most impactful opportunities to improve sepsis outcomes depend on optimizing infection diagnosis, antimicrobial management, and prevention.

Infectious disease, antimicrobial stewardship, and clinical microbiology specialists provide essential expertise in diagnostic stewardship, development of institutional antibiograms, empiric antibiotic guidelines, antibiotic dosing, and structured de-escalation strategies. These activities help ensure that antimicrobial management is tailored to infection source, host factors, prior healthcare exposures, microbiologic history, and local resistance patterns.

Infection preventionists and hospital epidemiologists provide complementary expertise in healthcare-associated infection (HAI) surveillance and prevention. Their engagement is particularly valuable for sepsis program activities focused on preventing HAIs and hospital-onset sepsis, including implementation of the strategies outlined in the Section "Infection Prevention Considerations."

Integrating these disciplines into formal sepsis governance structures, whether through standing membership or structured collaboration, strengthens both acute sepsis management and upstream prevention efforts aimed at reducing sepsis incidence and improving outcomes. As with other hospital-wide quality initiatives, sepsis governance is most effective when aligned with existing quality and patient safety structures, supported by clearly defined leadership, led by a designated individual accountable for program oversight and performance, and appropriately resourced to achieve its mandate [19].

**2. Integrate antimicrobial stewardship participation into routine ICU rounds to support real-time optimization of antibiotic therapy in critically ill patients. [Tier 2]**

#### Key Considerations

Embedding antimicrobial stewardship expertise into daily ICU rounds enables real-time review of antibiotic selection, dosing, de-escalation opportunities, and duration. This collaborative approach improves the appropriateness of antibiotic therapy during the highest-risk phase of sepsis care and provides ongoing education for ICU clinicians [134]. Both observational studies and randomized trials demonstrate that ICU-focused stewardship rounds can decrease antibiotic utilization and reduce costs, though mortality benefits have not been consistently shown [135, 136]. Despite this, ICU-based antimicrobial stewardship engagement aligns with best practices and helps ensure coordinated, appropriate care for critically ill patients with suspected or confirmed sepsis. Implementation may be constrained by stewardship staffing and resource availability,

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particularly in smaller hospitals, but participation can often be achieved through flexible models tailored to local resources.

3. **Support the application of pharmacokinetic/pharmacodynamic (PK/PD) principles in antimicrobial dosing for critically ill patients, including access to infectious diseases and critical care pharmacists, clinician and nursing education, and laboratory capacity for therapeutic drug monitoring where appropriate. [Tier 2]**

#### Key Considerations

Critically ill patients often have altered and rapidly changing pharmacokinetics due to fluid shifts, organ dysfunction, augmented renal clearance, or extracorporeal therapies. Standard antibiotic dosing regimens may therefore provide suboptimal drug exposure in this population. Applying PK/PD principles of individualized dosing, loading doses, optimized infusion strategies, and selective therapeutic drug monitoring can help ensure adequate and sustained antimicrobial concentrations. A recent meta-analysis of 10 randomized trials found that individualized antimicrobial dose optimization strategies, including therapeutic drug monitoring and related PK/PD-guided approaches, were associated with significantly improved target attainment and lower treatment failure, with numerically favorable but not statistically significant improvements in mortality and clinical cure [137].

Surveys of ICU clinicians note gaps in PK/PD knowledge, suggesting a need for clinician and nursing education plus enhanced access to infectious diseases and critical care pharmacists (including those with pediatric training in relevant settings) with expertise in antimicrobial dosing [138]. Laboratory infrastructure to support therapeutic drug monitoring for selected agents (eg, aminoglycosides, vancomycin, and potentially β-lactams as capacity expands) can further enhance antimicrobial optimization in critically ill patients.

### F. Infection Prevention Considerations

Hospital-onset sepsis is often precipitated by HAIs, many of which are likely preventable [139]. Crude and adjusted mortality rates for hospital-onset sepsis are approximately twice as high as those for community-onset sepsis [140]. Patients with sepsis are also particularly vulnerable to secondary HAIs because of sepsis-induced immune dysfunction [141]. In a large prospective ICU cohort from the Netherlands, more than 1 in 8 patients admitted with sepsis developed a HAI, most commonly CLABSI (26%), pneumonia (25%), and intra-abdominal infections (16%), and these events were strongly associated with higher mortality [142].

Infection prevention is therefore integral to improving sepsis outcomes, both by reducing hospital-onset sepsis and by preventing secondary infections in patients with community-onset sepsis. The panel emphasizes that the SHEA/AHA/APIC/IDSA Joint Commission Compendium remains the essential, evidence-based foundation for preventing CLABSI, CAUTI, VAP, and other HAIs; improving adherence to these established best practices is a core infection-prevention recommendation for any sepsis program [143].

In addition to reinforcing the Compendium, the panel identified 2 further high-opportunity, evidence-supported interventions that have particular relevance to reducing sepsis morbidity and mortality and that remain suboptimally implemented nationwide.

1. **Implement universal chlorhexidine gluconate bathing and either universal or targeted MRSA nasal decolonization for all ICU patients and for non-ICU patients with invasive devices. [Tier 2]**

#### Key Considerations

Universal decolonization with daily chlorhexidine gluconate (CHG) bathing and nasal mupirocin reduces healthcare-associated bloodstream infections in high-risk hospitalized patients. The REDUCE-MRSA trial demonstrated an ~43% reduction in all-pathogen bloodstream infections in ICU patients using daily CHG baths + nasal mupirocin compared with standard care [144]. Despite these data, national implementation remains incomplete: a 2021 national survey revealed that only 63% of US hospitals provide routine CHG bathing for ICU patients, and fewer than 40% routinely provide nasal decolonization [145]. In non-ICU settings, the ABATE trial showed similar reductions in bloodstream infections in non-ICU patients with invasive devices such as central lines, midlines, and lumbar drains—an important risk group for hospital-onset sepsis [146].

Effective implementation requires structured staff education, periodic reinforcement of best practices, and routine monitoring with feedback to promote consistent and high-quality chlorhexidine treatment delivery [147]. Although a mortality benefit of universal decolonization has not been demonstrated, reductions in healthcare-associated bloodstream infections provide a strong rationale for implementation as part of a comprehensive sepsis prevention program.

2. **Implement structured programs to ensure daily toothbrushing for all hospitalized patients. [Tier 2]**

#### Key Considerations

Hospital-acquired pneumonia is the most common HAI and the leading cause of hospital-onset sepsis, making it a major contributor to sepsis-related morbidity [139, 148]. A recent meta-analysis of 15 randomized trials showed that daily tooth brushing, as a core component of oral care, reduces HAP incidence—particularly among mechanically ventilated patients—and is associated with shorter duration of mechanical ventilation, shorter ICU stays, and lower ICU mortality [149]. Because non-ventilator HAP is far more common than ventilator-associated pneumonia, extending daily tooth



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brushing across all inpatient units represents a practical, low-cost intervention with substantial potential to reduce both community-onset sepsis complications and hospital-onset sepsis. Standardized workflows, staff education, and routine monitoring can help ensure consistent and reliable implementation. The panel designated this recommendation as Tier 2 because, although daily tooth brushing reduces HAP and related morbidity, the strongest evidence comes from ICU and mechanically ventilated populations, with more limited evidence in other hospitalized patients, and its impact on sepsis-specific outcomes has not been directly established.

### G. Emerging and Promising Strategies (Not Recommended for Routine Implementation)

The panel identified several emerging strategies and technologies with potential to improve sepsis recognition and management but judged that current evidence, feasibility, or generalizability is insufficient to support broad implementation. Hospitals may reasonably pilot these approaches in selected settings with clear protocols, antimicrobial stewardship support, and well-defined evaluation plans.

#### 1. Automated sepsis prediction tools

Automated sepsis prediction models, often using machine learning or artificial intelligence techniques applied to routinely collected EHR data, aim to identify clinical deterioration or evolving sepsis earlier than manual screening or clinician recognition. Examples include commercially available systems such as the Epic Sepsis Predictive Model, TREWS, and Sepsis ImmunoScore, which continuously integrate vital signs, laboratory results, and other EHR data to estimate sepsis risk and prompt clinician evaluation [150, 151]. Unlike established bedside clinical screening scores (eg, NEWS/NEWS2, MEWS, SIRS, and qSOFA), these systems continuously analyze evolving EHR data to generate automated risk estimates rather than relying on simpler rule-based criteria. Several observational and quasi-experimental studies suggest these systems may improve process measures such as bundle adherence and time to antibiotic administration [152, 153].

Despite these encouraging findings, important uncertainties remain that precluded Tier 1 or 2 designations. Although several studies have demonstrated improvements in process measures, there is no convincing evidence from rigorous randomized trials that currently available automated prediction tools improve patient outcomes. Additional concerns include uncertain generalizability outside development settings, limited model transparency, risk of alert fatigue, and imperfect performance characteristics that may promote overdiagnosis and unnecessary broad-spectrum antibiotic use. Hospitals choosing to deploy these systems should do so selectively, with rigorous local validation (particularly for externally developed models), clearly defined clinical response pathways, and ongoing monitoring of model performance.

#### 2. Host immune response–based sepsis diagnostics

A growing number of host-response–based diagnostic tests may assist with evaluating patients who may have sepsis, especially when infection is uncertain or presentations are nonclassic. These assays stratify patients into risk categories using different biological signals, including white blood cell characteristics (such as monocyte distribution width [MDW] and IntelliSep) or gene-expression signatures (such as SeptiCyte Rapid and TriVerity) [154–157]. MDW is notable because it can be reported automatically as part of a routine complete blood count with differential, without requiring a separate test order or platform.

Although these tools may improve diagnostic discrimination in select situations, evidence supporting their clinical impact remains limited. Existing studies focus almost entirely on diagnostic accuracy, and no rigorous randomized evaluations have demonstrated improvements in mortality, antibiotic use, or other clinically meaningful outcomes. Several assays have received FDA authorization, but authorization reflects analytical or diagnostic performance rather than proven clinical effectiveness. Moreover, abnormal results may prompt unnecessary antibiotic use unless interpreted within the broader clinical context and paired with strong stewardship oversight.

Given this uncertainty, along with cost, workflow complexity, and the potential for unintended consequences, the panel does not recommend broad adoption at this time. Health systems interested in these technologies should limit use to structured pilot programs with clear action pathways and rigorous monitoring to determine whether they offer measurable improvements in sepsis care and outcomes.

#### 3. Culture-independent rapid diagnostics for bloodstream infection

Direct-from-blood molecular assays offer the promise of faster, sensitive detection of bloodstream pathogens without waiting for culture growth, potentially enabling earlier optimization of therapy. Unlike multiplex nucleic acid amplification tests performed on positive blood cultures (Recommendation A.1), which are applied to patients with microbiologically confirmed bloodstream infection, direct-from-blood testing is performed in a much broader population in whom most patients with suspected sepsis are ultimately not bacteremic. Consequently, thepotential benefits must be weighed against substantially higher testing costs, uncertain impact on clinical outcomes, and the risk of detecting organisms of unclear clinical significance [158].

Notably, a recent pragmatic randomized trial demonstrated that direct-from-blood bacterial testing significantly shortened time to pathogen identification but did not reduce

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empiric broad-spectrum antibiotic exposure or improve clinical outcomes compared with usual care [159]. At present, given limited evidence of patient benefit, targeted use within research settings or pilot programs—coupled with strong antimicrobial stewardship oversight—remains the most appropriate approach.

#### 4. Multiplex NAAT panels for lower respiratory samples

Syndromic multiplex NAAT panels for lower respiratory tract specimens can accelerate pathogen identification and improve detection of bacterial and viral pathogens in patients with suspected pneumonia, particularly after antibiotic exposure, when conventional culture-based diagnostics become less sensitive. However, these assays are costly, operationally complex, and may detect organisms that represent colonization rather than the cause of pneumonia, increasing the risk of unnecessary broad-spectrum antibiotic use. Although several randomized trials have demonstrated earlier pathogen-directed or otherwise appropriate antibiotic therapy, none have shown consistent improvements in clinical outcomes such as length of stay or mortality [160–169].

Accordingly, it remains unclear whether routine, widespread use provides sufficient benefit to justify the cost and complexity of these assays. If deployed, these assays should be restricted to carefully selected high-risk populations (such as ICU patients, immunocompromised hosts, or patients with suspected hospital-acquired pneumonia) and paired with strong antimicrobial stewardship support to guide appropriate interpretation and antibiotic management.

#### 5. Procalcitonin-guided antibiotic duration

Meta-analyses of randomized controlled trials suggest that procalcitonin-guided antibiotic cessation can shorten antibiotic courses and may potentially offer a mortality benefit, but most contributing trials were unblinded and at high risk of bias, which limits the certainty of these conclusions [170, 171]. The largest and most rigorous evaluation to date, ADAPT-sepsis, demonstrated a 1-day reduction in antibiotic exposure but no impact on 28-day mortality [172]. In contrast to some adult studies, a recent pediatric randomized trial did not demonstrate benefit from procalcitonin-guided antibiotic duration strategies in hospitalized children with suspected bacterial infection in settings with established antimicrobial stewardship programs [173].

Beyond differences across patient populations, real-world experience has been inconsistent. Many clinicians use procalcitonin as a single diagnostic test rather than as part of the serial, algorithm-based discontinuation rules evaluated in trials, and centers reporting success typically relied on intensive stewardship support that may not be feasible in high-volume settings [174, 175]. Given modest benefits under ideal conditions, inconsistent real-world impact, and cost and complexity, the panel did not support universal deployment of procalcitonin but recognizes a potential role for selective use within structured protocols and robust stewardship programs.

More recently, the PRONTO trial, published after completion of the panel's formal review and voting process, raised the possibility that early point-of-care procalcitonin testing at presentation may improve outcomes in adult patients with suspected sepsis [176]. However, the mechanism of benefit remains uncertain, as antibiotic initiation and duration were similar between study arms. One hypothesis is that early procalcitonin testing improves diagnostic confidence, prompting more timely escalation of sepsis-directed care when values are elevated and earlier reconsideration of alternative diagnoses when values are low [177]. Because the trial did not evaluate these potential pathways, the findings should be considered hypothesis-generating and warrant further study before broader implementation can be recommended.

#### Implementation Considerations for Resource-Limited Hospitals

The panel recognizes that hospitals vary substantially in size, infrastructure, and available resources. Small, rural, and safety-net hospitals may face barriers to implementing certain recommendations, including advanced diagnostic testing, informatics support, and real-time performance monitoring. The tiered framework is intended to help hospitals prioritize interventions and adopt them incrementally based on local capacity. While implementation should be tailored to available resources, these recommendations may also serve as a framework for engaging institutional leadership and advocating for investments in sepsis care infrastructure. Regional collaboration, referral networks, shared laboratory services, tele-infectious diseases, tele-stewardship, and tele-critical care support, partnerships with EHR vendors to integrate sepsis CDS and reporting tools, and external quality-improvement initiatives may help resource-constrained hospitals access capabilities that are not available on-site.

## CONCLUSION

Improving sepsis outcomes requires sustained commitment, multidisciplinary collaboration, and a focus on strengthening systems of care across the continuum of sepsis management. The strategies outlined in this position paper reflect a synthesis of available evidence and multidisciplinary expert consensus, identifying high-value, evidence-informed approaches to the infection-related aspects of sepsis care that hospitals can implement today while also highlighting promising strategies that warrant further evaluation. As evidence, technologies, and implementation experience continue to evolve, these recommendations should be revisited and refined to help hospitals continue advancing sepsis care and improving patient outcomes.



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## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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