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LOST IN TRANSLATION: SEPSIS BUNDLE IMPLEMENTATION GAPS IN MEDICAL WARDS AND IMPLICATIONS FOR A HOSPITL-WIDE SEPSIS TEAM

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1 Abstract

Background:

Early recognition and prompt management of sepsis are essential to improve patient outcomes. While evidence-based sepsis bundles are widely recommended, their implementation in non-critical care settings remains challenging. This study aimed to assess adherence to the sepsis bundle across medical wards identify barriers to implementation, and provide evidence supporting the development of a hospital-wide multidisciplinary Sepsis Team.

Methods:

We conducted a cross-sectional point-prevalence study at the University Hospital of Modena between April and May 2025. Adult patients admitted to medical wards with sepsis or septic shock were included. The sepsis bundle was defined as completion of serum lactate measurement, blood cultures before antibiotic administration, timely empirical antimicrobial therapy, and intravenous fluid resuscitation. Bundle completion within 3 and 6 hours from sepsis recognition was evaluated. The primary composite outcome was 30-day all-cause mortality and/or unplanned hospital readmission within 90 days. Secondary outcomes included hospital length of stay, intensive care unit (ICU) admission, length of stay, 90-day mortality and readmission.

Results:

Seventy-one patients were included; 68.6% presented with sepsis and 22.5% with septic shock. The median Charlson Comorbidity Index was 5 and clinical outcomes were poor, with 32 in-hospital deaths (44.4%), 6 ICU admissions (8.3%), and 20 readmissions (27.8%) during the study period. Overall, the sepsis bundle was completed in 47.1% of cases, while only 37.1% and 45.7% achieved bundle completion within 3 and 6 hours, respectively. Lactate measurement represented the major implementation gap, being performed in only 57.7% of patients. Bundle completion occurred more frequently in patients with greater illness severity, including hypotension, septic shock, higher NEWS2 scores, and elevated SOFA scores. Internal Medicine and Infectious Diseases wards demonstrated higher adherence compared

with oncological and surgical settings. Bundle completion was not independently associated with improved clinical outcomes, likely reflecting confounding by indication. Multivariable analysis identified age ≥75 years (aOR 15.6, p=0.006) and culture-negative sepsis (aOR 9.37, p=0.006) as independent predictors of the composite outcome, whereas urinary tract infection was protective (aOR 0.13, p=0.028).

Conclusions:

Sepsis bundle implementation in medical wards was suboptimal and heterogeneous, with significant diagnostic and organizational gaps, particularly lactate measurement. Performance was largely driven by clinical severity rather than standardized processes. The high mortality and readmission rates underline the clinical impact of delayed or incomplete management. These findings support the establishment of a hospital-wide Sepsis Team to promote early recognition, improve bundle adherence, standardize sepsis management, and strengthen collaboration between emergency, medical, microbiology, intensive care, and infectious diseases services.

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2 Introduction

2.1 Definition of Sepsis

According to a recent review in the New England Journal of Medicine, sepsis is defined fundamentally as a life-threatening acute organ dysfunction due to a dysregulated host response to infection.[1] The key biologic features of this complex syndrome extend far beyond simple inflammation, including dysregulated systemic inflammation, immunosuppression, and vascular injury.[1]

This contemporary definition, established by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016, represents a significant conceptual shift from earlier diagnostic frameworks.[2] The clinical and pathophysiological conceptualization of sepsis has undergone a profound evolution over the past three decades. The first modern definition, retrospectively known as Sepsis-1 (established in 1992), characterized sepsis as an overabundant inflammatory response to infection.[3] Clinically, this early framework recognized sepsis by the presence of the systemic inflammatory response syndrome (SIRS), which required two or more abnormalities in temperature, heart rate, respiratory rate, or white-cell count.[1]

However, as clinical understanding advanced, the limitations of defining sepsis purely through an inflammatory lens became apparent. SIRS is no longer included in the current core definition of sepsis, since it may frequently reflect a proportionate and noninjurious host response to an invading pathogen.[1] While the recognition of the SIRS syndrome remains helpful as a bedside tool for initially identifying the presence of an infection, it lacks the specificity required to diagnose a lethal pathophysiological cascade.[1]

Importantly, this conceptual evolution also overhauled the clinical lexicon. The historical terms “severe sepsis” and “sepsis syndrome” have been officially retired.[1]

Under the current framework, the diagnostic continuum is simplified into distinct, mutually exclusive categories: uncomplicated infection (an infection without acute organ dysfunction), sepsis (an infection accompanied by organ dysfunction), and septic shock.[2]

Septic shock is defined as a particularly severe subset of sepsis characterized by circulatory and cellular or metabolic abnormalities profound enough to substantially alter the clinical trajectory and increase illness severity.[1]
Clinically, this profound subset is identified by the strict need for ongoing vasopressor therapy to maintain a mean arterial pressure (MAP) ≥65 mm Hg, alongside a persistent serum lactate level ≥2 mmol/L after adequate intravenous fluid resuscitation.[1]

Despite these robust consensus criteria, sepsis remains a clinical syndrome without a single confirmatory diagnostic test.[1] The diagnosis strictly requires astute clinical judgment based on the concurrent evidence of infection and new-onset organ failure[1]. Particularly in general medical and surgical wards, the differential diagnosis for acute organ dysfunction is often broad, and an accurate diagnosis frequently necessitates continuous clinical observation, alongside repeated laboratory testing.[4] Acknowledging the clinical reality of the bedside, this pragmatic framework categorizes cases as definite, probable, possible, or unlikely sepsis.[4] This standardized terminology ensures that multidisciplinary inpatient teams can communicate effectively and initiate appropriate, life-saving interventions even when the diagnosis remains presumptive.

2.2 Epidemiology and Global Burden

Sepsis is universally recognized as one of the most pervasive and challenging global health crises of the modern era. Historically, accurately capturing the true epidemiological burden of the syndrome has been fraught with methodological difficulties. Discrepancies in clinical diagnostic criteria, variations in administrative coding practices (such as the transition from ICD-9 to ICD-10), and a historical reliance on hospital-level data derived almost exclusively from high-income countries have traditionally skewed both incidence and mortality estimates.[5] However, the advent of comprehensive, systematic global analyses has recently illuminated the staggering true scale of the disease.

The most robust contemporary assessments of the global burden of sepsis are derived from the Global Burden of Disease (GBD) studies. The epidemiology of sepsis has

evolved substantially over the past three decades, defined by two markedly different trajectories.[6,7]

Prior to the COVID-19 pandemic (1990-2017), global public health initiatives demonstrated significant progress. During this period, the age-standardized incidence of sepsis decreased by approximately 37%, and mortality fell by 53%, driven largely by advancements in infection prevention, maternal and neonatal care, and vaccination programs.[6] By 2017, the pre-pandemic global burden was estimated at 48.9 million incident cases and 11.0 million sepsis-related deaths annually, representing approximately 19.7% of all global deaths.[6]

However, the emergence of SARS-CoV-2 severely disrupted this positive epidemiological trajectory. According to the updated GBD 2021 systematic analysis, the pandemic precipitated a massive global surge in viral sepsis and exacerbated underlying vulnerabilities. In 2021, an estimated 166 million incident cases of sepsis occurred globally, resulting in 21.4 million sepsis-related deaths.[7] Astoundingly, this indicates that sepsis was associated with 31.5% of all global deaths that year, effectively reversing decades of prior progress.[7]

The global distribution of sepsis reveals profound health inequities, with the burden overwhelmingly concentrated in low- and middle-income countries (LMICs). Epidemiological data indicate that approximately 85% of all sepsis cases, and a disproportionate share of the resulting mortality, occur in LMICs.[1] Sub-Saharan Africa alone accounts for nearly 40% of the global case burden.[1]

The highest age-standardized mortality rates are heavily concentrated in geographical regions characterized by a low Socio-demographic Index (SDI).[6] In these vulnerable regions, disparities in healthcare access, limited critical care infrastructure, and delayed hospital admissions significantly exacerbate the lethality of the syndrome.[1,6] Furthermore, etiology varies significantly by socioeconomic status: in low-SDI settings, the vast majority of sepsis deaths are driven by primary communicable diseases, whereas in high-SDI nations, non-communicable underlying diseases predominate.[6]

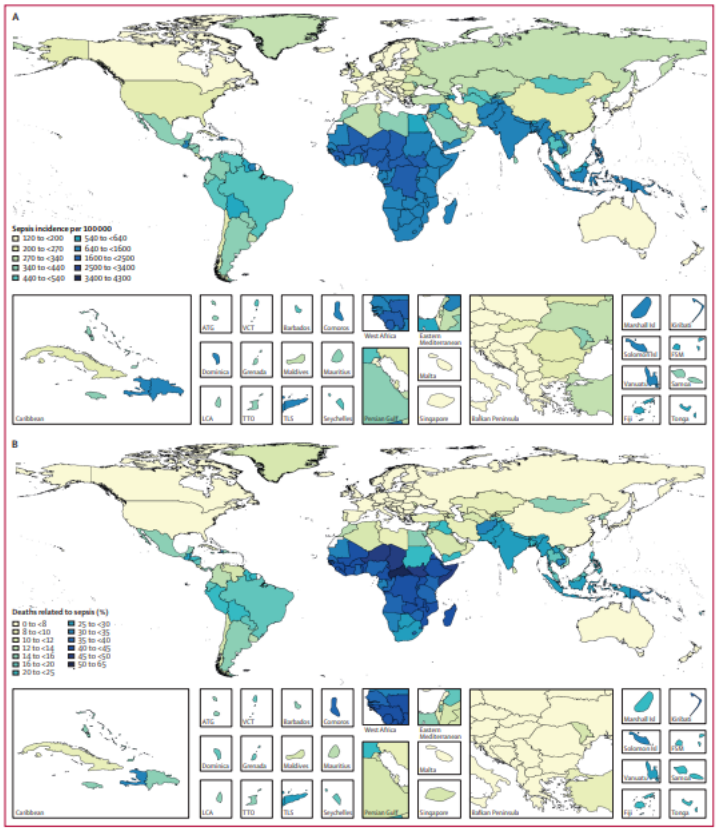

Figure 1. Geographical distribution of the global sepsis burden in 2017. Panel (A): age-standardized incidence per 100,000 population. Panel (B): age-standardized percentage of total deaths related to sepsis. Adapted from Rudd et al.

In high-income countries, sepsis represents a massive, escalating strain on modern inpatient hospital systems. Sepsis is currently the most common cause of in-hospital death, implicated in more than one-third of all inpatient mortalities.[1] Beyond its acute lethality, it is also the most expensive cause of hospitalization. This immense economic burden is driven by prolonged lengths of stay in both intensive care units and medical wards, extensive medical resource utilization, and the exceptionally high readmission rates associated with post-sepsis morbidity and chronic critical illness.[1,4]

The incidence of sepsis does not affect all demographics equally; rather, it follows a characteristic J-shaped curve across the human lifespan.[1] There is a remarkably high incidence in young children (under 5 years of age), a vulnerable cohort that accounted for 26%of all sepsis deaths in 2017.[1] . Incidence reaches a nadir during middle childhood and adolescence before climbing exponentially beginning around 60 years of age.[1] Consequently, older adults face the greatest absolute mortality burden, with adults aged 70 years and older accounting for 9.28 million sepsis-related deaths in

2021.[7] Furthermore, demographic analyses consistently demonstrate that males have a higher age-standardized sepsis-related mortality rate compared to females (164.2 versus 134.1 per 100,000, respectively).[6]

Certain clinical subpopulations are exceptionally susceptible to developing life-threatening organ dysfunction. Key risk factors for sepsis include baseline immunocompromise, underlying active malignancies, and end-stage kidney disease requiring hemodialysis, which carries a staggering 40-fold increased incidence of sepsis.[1]

In modern ward-based settings, sepsis increasingly complicates non-infectious underlying chronic conditions. Notably, sepsis-related mortality arising from non-infectious baseline etiologies - such as stroke, chronic obstructive pulmonary disease (COPD), and cirrhosis - rose from 4.69 million deaths in 1990 to 5.81 million in 2021.[7]

Regarding the primary anatomical source of infection triggering the dysregulated host response, epidemiological data consistently demonstrate that pulmonary infections are the most frequent culprit, accounting for 40% to 60% of all cases.[1] This is followed by intra-abdominal infections (15-30%) and genitourinary tract infections (15-30%). [1] Across all clinical presentations, primary bloodstream infections and lower respiratory tract infections remain the most prominent and lethal infectious syndromes complicating fatal sepsis cases.[7]

2.3 Antimicrobial Resistance and Sepsis

Antimicrobial resistance (AMR) represents a critical and escalating determinant of adverse outcomes in patients presenting with sepsis and septic shock. A comprehensive global meta-analysis encompassing over 20,000 patients across 34 studies demonstrated a pooled nosocomial AMR prevalence of 36.5%.[8] Furthermore, infections caused by resistant organisms are associated with an 58% increased mortality risk compared to susceptible strains, yielding an adjusted pooled Risk Ratio (RR) of 1.58.[8] In cohorts of Gram-negative severe sepsis and septic shock, multidrug resistance (MDR) is strongly associated with administration of inappropriate initial

antibiotic therapy (non-IAAT), which is independently associated with an approximately threefold increase in hospital mortality.[9]

The clinical impact of delayed optimal therapy due to resistance is profound. Systematic review data indicate that inadequate empiric antibiotic coverage in sepsis is associated with an adjusted Odds Ratio (OR) for mortality of 1.60, translating to a number needed to harm of 10, or one additional death for every ten patients undertreated.[10] Resistance to the most frequently utilized empiric agents (specifically third-generation cephalosporins, beta-lactam/beta-lactamase inhibitors, and carbapenems) drives the highest associations with 90-day mortality.[10] At the population level, epidemiological surveillance demonstrates that fluoroquinolone resistance in Escherichia coli exhibits the strongest correlation with both septicemia hospitalization rates in adults over 50 years of age and sepsis mortality rates in adults aged 18 to 84.[11]

Key MDR pathogens of concern in sepsis include ESBL-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant Acinetobacter baumanii, MDR Pseudomonas aeruginosa, MRSA, and vancomycin-resistant Enterococcus.[4,12]

The imperative to avoid the mortality risks associated with inadequate coverage frequently results in a complex clinical tension, leading to significant overtreatment. An extensive analysis of 17,430 patients with culture-positive community-onset sepsis illustrated that empiric therapy targeted resistant organisms in 67.0% of cases.[13]. However, the actual net prevalence of these pathogens was markedly lower, recorded at only 13.6% for resistant Gram-positive organisms (e.g., methicillin-resistant Staphylococcus aureus [MRSA] or vancomycin-resistant Enterococcus [VRE]) and 13.2% for resistant Gram-negative organisms (e.g., extended-spectrum beta-lactamase [ESBL] producers or carbapenem-resistant Enterobacterales [CRE]).[13] This mismatch highlights a severe overtreatment phenomenon occurring routinely in community-onset sepsis, exacerbating the selective pressures that drive further resistance.

To address this imbalance, the 2026 Surviving Sepsis Campaign (SSC) guidelines explicitly caution against universal overtreatment, stating that universal MDR

coverage in every adult with sepsis or septic shock results in increased net harm, particularly as a minority of global sepsis cases are caused by MDR organisms.[4] Consequently, the guidelines emphasize rigorous risk stratification. For adults with sepsis or septic shock categorized at high risk for a specific MDR pathogen, empirical antimicrobial therapy with coverage for that pathogen is conditionally recommended based on very low certainty evidence.[4] Risk factors necessitating MDR coverage are defined strictly as: colonization or previous infection with the MDR pathogen within the past year, prolonged use of broad-spectrum antibiotics, and prolonged hospitalization in a unit with a high local prevalence of MDR organisms.[4]

Mitigating the adverse effects of empirical broad-spectrum therapy relies heavily on structured de-escalation. Target trial emulation data confirm that systematically de-escalating broad-spectrum coverage (e.g., anti-MRSA or anti-pseudomonal agents) on day 4 following negative cultures is clinically safe, resulting in fewer antibiotic days and shorter hospitalizations without increasing mortality.[14] Furthermore, recent clinical reviews and the 2026 SSC guidelines highlight the detrimental impact of unnecessary anti-anaerobic antibiotics, which have been shown to increase the risk of adverse clinical outcomes in critically ill populations.[1,4] It is recommended to utilize empiric regimens devoid of anaerobic coverage in patients lacking specific risk factors, expressly to spare the protective anaerobic microbiota and prevent secondary complications such as Clostridioides difficile infection.[1,4]

Optimizing the initial phase of sepsis care in the era of AMR necessitates a multifaceted institutional approach. Current evidence supports the early integration of the following strategic interventions:

- Systematic Risk Stratification: Routine implementation of clinical pathways that restrict MDR empirical coverage exclusively to adult patients exhibiting the defined high-risk criteria.[4]
- Rapid Molecular Diagnostics: The deployment of rapid diagnostic platforms, such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) or multiplex polymerase chain reaction (PCR) directly from positive blood cultures, to significantly improve the time to optimal targeted therapy and facilitate safe, early de-escalation.[12]

- Antimicrobial Stewardship Programs (AMS): Adherence to the strong recommendations outlined by the 2026 SSC guidelines, which mandate the systematic de-escalation of antimicrobial therapy as soon as a confirmed microbiological diagnosis and susceptibility profile become available, linked directly to hospital-wide AMS protocols to reduce unnecessary broad-spectrum exposure.[4]

3 Pathophysiology of Sepsis

3.1 Host Immune Response

Sepsis represents a fundamentally dysregulated host immune response to infection, characterized by the simultaneous manifestation of hyperinflammation and immunosuppression driving acute organ dysfunction.[1,15] This heterogeneous state severely disrupts the physiological balance between immune hyperactivation and hyporesponsiveness. Both pro-inflammatory and immunosuppressive trajectories fluctuate dynamically throughout the clinical course.[15]

The innate immune response begins when pattern recognition receptors (PRRs) detect pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), peptidoglycan, and viral nucleic acids.[16] Concurrently, these receptors recognize damage-associated molecular patterns (DAMPs) released by injured host tissues, including high-mobility group box 1 (HMGB1), extracellular histones, and mitochondrial DNA.[17] This surveillance is primarily mediated by Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), C-type lectin receptors (CLRs), and retinoic acid-inducible gene I (RIG-I)-like receptors.[17] PRR engagement triggers intracellular signaling cascades- specifically nuclear factor-kappa B (NF-κB) and activator protein 1 (AP-1) - which upregulate pro-inflammatory gene transcription.[18]

Following PRR activation, the systemic release of cytokines - including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-12, IL-17, IL-8, and interferons - drives a profound hyperinflammatory state, often called “cytokine storm”.[18] These molecules are pleiotropic immunoregulators that coordinate the initial host defense.[19]

However, in sepsis, this response often exceeds the threshold required for pathogen containment, leading to widespread cellular activation and the recruitment of innate immune cells.[16,19]

Simultaneously, the host initiates powerful counter-regulatory mechanisms.

- Innate Immune Suppression: sepsis initiates emergency myelopoiesis, releasing immature and hypofunctional neutrophils.[15,20] Monocytes develop endotoxin tolerance (characterized by impaired pro-inflammatory cytokine secretion upon re-stimulation) and an expansion of the immunosuppressive CD14+ monocyte subset (MS1) is observed.[15] Concurrently, dendritic and natural killer (NK) cells exhibit enhanced apoptosis and reduced pathogen clearance capabilities.[15,21] A critical reduction in human leukocyte antigen (HLA)-DR expression on circulating monocytes compromises antigen presentation.[15]
- Adaptive Immune Suppression: the host experiences a rapid, apoptosis-driven depletion of B and T lymphocytes, exacerbated by reduced lymphopoiesis. The resulting persistent lymphopenia is associated with increased mortality.[1,15,20] Surviving T cells manifest an exhausted phenotype, characterized by sustained upregulation of inhibitory checkpoint molecules like programmed cell death protein-1 (PD-1) and reduced production of immunostimulatory mediators such as interferon-gamma (IFN-γ).[15] Simultaneously, a relative expansion of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) actively suppresses effector T cell responses, further dampening adaptive immunity.[15,20]

The clinical trajectory of sepsis is modulated by baseline host factors, including age, sex, genetic predispositions, and pre-existing comorbidities such as diabetes, chronic obstructive pulmonary disease, obesity, and prior immunosuppressive therapy.[20,21] The gut microbiome also plays a critical regulatory role; microbial metabolites like gut-derived short-chain fatty acids (e.g., butyrate) and tryptophan derivatives (e.g., indoles) imprint antimicrobial programming in macrophages.[21] Molecular profiling has identified distinct clinical subphenotypes, such as

macrophage activation-like syndrome (MALS), with differential responses to therapies, driving interest in precision immunotherapy.[15,21]

3.2 Dysregulated Inflammation and Organ Dysfunction

The progression of sepsis is characterized by a loss of homeostatic control over inflammatory and coagulatory pathways, resulting in systemic tissue injury.

The so called "cytokine storm" initiates widespread collateral tissue damage during the early stages of sepsis.[18] This process is amplified by the uncontrolled activation of the complement system, which generates anaphylatoxins such as C3a and C5a that promote systemic inflammation and vascular injury.[21] Endothelial activation represents the critical junction where inflammatory signaling and coagulation converge, a process termed "immunothrombosis".[21]

Endothelial injury and the expression of tissue factor, paired with the suppression of endogenous anticoagulant mechanisms (e.g., antithrombin and the protein C system), establish a procoagulant state.[21] This systemic dysregulation frequently progresses to disseminated intravascular coagulation (DIC), which acts as an intravascular effector of innate immunity.[21]

Cytokine-mediated injury disrupts homeostatic endothelial functions, causing the loss of barrier integrity and the breakdown of the endothelial glycocalyx, which result in capillary leak, interstitial edema, and compromised microvascular perfusion, which directly contribute to organ disfunction.[17,21]

Activated neutrophils release neutrophil extracellular traps (NETs) to trap circulating microorganisms. On the other hand, it promotes microvascular thrombosis and actively exacerbate endothelial injury.[1,20]

The dysregulated immune response exerts protracted physiological effects well beyond the acute phase. A substantial proportion of sepsis survivors develop Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS), a distinct chronic critical illness phenotype.[15] This prolonged immunocompromised state confers severe vulnerability to secondary infections and the reactivation of latent viruses.[15,16] Furthermore, survivors encounter increased risks of long-term morbidities, including a threefold increase in moderate-to-severe cognitive impairment,

psychological sequelae such as post-traumatic stress disorder (PTSD), and incident cardiovascular events.[22] Clinical data further associate post-sepsis immune suppression with accelerated solid tumor growth and increased cancer incidence.[16]

3.3 Septic Shock and Multiorgan Failure

Septic shock represents a severe subset of sepsis where underlying cellular and metabolic abnormalities substantially increase mortality. Clinical criteria define this state by profound circulatory collapse associated with hospital mortality rates exceeding 40%.[2] Current models consistently validate this paradigm of dysregulated host immune response.[17]

Organ failure in sepsis is fundamentally driven by cellular dysoxia and metabolic reprogramming, often independent of macroscopic blood flow.[1] It is the result of the convergence of multiple insults:

- Endothelial dysfunction and coagulopathy: inflammatory cytokines and reactive oxygen species activate enzymes that damage the protective glycocalyx coating the microvascular endothelium.[23] Loss of barrier function impairs systemic tissue oxygenation. This permeability increase stems from vascular endothelial cadherin dysfunction and altered endothelial tight junctions.[17] Disruption of the vascular endothelial cadherin and p120-catenin complex directly drives profound vascular leak [24]. Coagulation pathways precipitate widespread thrombus formation in the microcirculation. Tissue factor action and impaired anticoagulant mechanisms drive this microvascular thrombosis.[17] Dying neutrophils release extracellular traps that facilitate immunothrombosis.[17]
- Cardiovascular dysfunction: generalized arterial vasodilatation with an associated decrease in systemic vascular resistance represents the hemodynamic hallmark of sepsis.[25] Decreased intracellular adenosine triphosphate during septic shock activates ATP-sensitive potassium channels. Subsequent potassium efflux causes hyperpolarization of vascular smooth-muscle cells. This electrical shift induces severe vascular resistance to endogenous and exogenous pressor hormones.[25] Inflammatory mediators

induce direct myocardial depression, manifesting as profound systolic or diastolic dysfunction.[23] This septic cardiomyopathy severely impairs systemic tissue perfusion and precipitates severe hypotension.[23] Myocardial edema exacerbates this state by impairing both systolic contraction and diastolic relaxation.[23]

- Mitochondrial impairment and metabolic reprogramming: cellular dysoxia and profound metabolic reprogramming fundamentally drive organ failure in sepsis, acting largely independent of macroscopic blood flow alterations.[1] Intrinsic bioenergetic failure occurs rapidly. Evidence identifies this phenomenon as cytopathic hypoxia.[26] Reactive oxygen species produced during the inflammatory cascade damage mitochondrial respiratory chain components.[23] This oxidative injury induces severe adenosine triphosphate depletion. Prolonged inflammation suppresses mitochondrial activity through nitric oxide and peroxynitrite formation. Persistent S-nitrosylation of complex I triggers persistent electron transport chain dysfunction.[26] Sepsis forces a critical metabolic shift from oxidative phosphorylation to aerobic glycolysis, known as the Warburg effect.[1] This transition drives significant hyperlactatemia, representing a definitive hallmark of metabolic stress and impaired cellular oxygen.[23] Injured mitochondria ultimately release damage-associated molecular patterns, including fragmented mitochondrial DNA. Extruded mitochondrial DNA triggers intracellular inflammasome activation via NLRP3 and remote organ injury through Toll-like receptor 9 binding.[26]

In the end, the pathological convergence of uncontrolled inflammation, microvascular thrombosis, loss of barrier function, vasodilatation, and mitochondrial dysfunction creates a self-perpetuating cycle of cellular injury, ultimately manifesting as multiorgan failure.[17]

3.4 Biomarkers in Sepsis

Sepsis remains a clinical diagnosis. Current guidelines emphasize that clinicians should not definitively rule sepsis in or out using a single diagnostic test.[4] Researchers have evaluated over 250 biomarkers over the past decades. No single molecule perfectly differentiates sepsis from non-infectious systemic inflammatory

syndromes.[27] Evidence indicates that biomarker kinetics provide greater diagnostic and prognostic utility than isolated static values.[27]

Procalcitonin (PCT) is the most extensively studied sepsis biomarker. It is a calcitonin precursor synthesized by parafollicular thyroid cells and neuroendocrine cells following bacterial invasion. Serum levels rise within 3 to 4 hours and peak at 6-8 hours.[28] A 2025 meta-analysis of 38 observational studies reports a pooled sensitivity of 78%, a specificity of 77%, and an area under the receiver operating characteristic curve (AUROC) of 0.84 for sepsis detection.[29] In emergency department patients presenting with a qSOFA score ≥1, applying a PCT cutoff of 0.25 μg/L improved net risk reclassification by 35.2% compared to relying on clinical scores alone.[30] The 2026 Surviving Sepsis Campaign conditionally suggests incorporating PCT to guide antimicrobial discontinuation.[4] Clinical algorithms target a PCT level <0.5 μg/L or an ≥80% decline from peak concentration.[28] The ADAPT-Sepsis randomized clinical trial confirmed that daily PCT monitoring safely reduced antibiotic duration by a mean of 0.88 days while maintaining noninferior 28-day mortality.[31]

C-reactive protein (CRP) is a hepatic acute-phase protein. Concentrations increase 12 to 24 hours post-insult and peak at 48 hours.[28] Meta-analyses indicate lower diagnostic accuracy compared to PCT, yielding an AUROC of 0.73.[28] The ADAPT-Sepsis trial demonstrated that CRP-guided protocols do not reduce antibiotic duration compared to standard care.[31] Neutropenia, immunodeficiencies, and nonsteroidal anti-inflammatory drugs (NSAIDs) easily alter CRP levels, limiting its isolated diagnostic value.[28]

Presepsin (sCD14-ST) is a soluble fragment of CD14 released during monocyte activation by bacterial pathogens. Serum concentrations surge within 2-3 hours. Recent meta-analyses report an AUROC of 0.87, demonstrating comparable statistical sensitivity and specificity to PCT for early infection detection.[29]

Lactate serves as an essential prognostic marker and resuscitation guide. Tissue hypoxia and sepsis-associated accelerated aerobic glycolysis drive early hyperlactatemia. Sepsis-3 criteria define septic shock partially through a serum lactate >2 mmol/L despite adequate fluid resuscitation.[32] Persistently elevated 6-hour

concentrations (≥3.5 mmol/L) strongly predict 30-day mortality. The SSC 2026 Guidelines recommend targeting a ≥10% lactate reduction rate every 2 hours during initial resuscitation rather than pursuing static normalization.[4]

Routine hematological and biochemical indices offer auxiliary prognostic value. The neutrophil-to-lymphocyte ratio (NLR) yields an AUROC of 0.68 for bacterial sepsis diagnosis, performing comparably to PCT in less severe patient cohorts . Interleukin-6 (IL-6), combined with NT-proBNP, and INR achieves an AUROC of 0.890 for 28-day mortality prediction.[34]

The SSC 2026 guidelines note "insufficient evidence" to recommend novel rapid host-response diagnostics for routine bedside care.[4] Emerging tools include monocyte distribution width (MDW), which quantifies circulating monocyte size characteristics. Transcriptomic tests, such as SeptiCyte Rapid and TriVerity, analyze host mRNA expression profiles associated with sepsis. Flow-based systems like IntelliSep assess the physical deformability of neutrophils.[4]

Table 1. Summary of Biomarker Kinetics and Diagnostic Accuracy

Biomarker	Onset of Rise	Peak Concentration	AUROC for Sepsis	Primary Clinical Role
Procalcitonin (PCT)	3-4 hours	6-24 hours	0.84-0.86	Diagnosis, antibiotic stewardship
Presepsin (P-SEP)	2-3 hours	3-6 hours	0.87	Diagnosis, prognosis
C-reactive protein (CRP)	12-24 hours	48 hours	0.73	Inflammation monitoring
Lactate	Minutes	Variable	Prognostic	Prognosis, resuscitation guidance
Interleukin-6 (IL-6)	1-2 hours	6 hours	Variable	Prognosis, severity assessment

4 Diagnosis and Early Recognition in the Ward

4.1 Clinical Presentation

The clinical presentation of sepsis is highly heterogeneous.[1] This variability reflects the complex combinations of the initial infection site, the causative pathogen, acute organ dysfunction, and baseline health status.[1] Pneumonia represents the most

common underlying infection.[35] Genitourinary, gastrointestinal, and skin or soft tissue infections follow in incidence.[35]

Initial assessments typically reveal general systemic signs.[1] Documented manifestations include:

- General signs of infection: fever above 38.3ºC, hypothermia below 36.0ºC, malaise, tachycardia, and hyperglycemia.[17]
- Site-specific symptoms: cough, dysuria, erythema, or abdominal pain.[1,17]
- Signs of organ dysfunction: altered mentation or delirium, hypotension, tachypnea, oliguria, dyspnea, and mottled skin.[1,17]

Timely recognition remains challenging due to the dynamic evolution of the disease.[1] Early in the disease process, clinical manifestations often present subtly and are not specific to sepsis.[1] Routine pharmacological agents, such as beta-blockers or antipyretics, frequently mask standard diagnostic signs.[1] Diagnostic algorithms necessitate a high index of suspicion even without localizing infection signs, because their absence does not rule out sepsis.[1] Sepsis requires consideration in patients presenting with isolated altered mentation, unexplained hypotension, or new-onset dyspnea.[1] Acute decompensation of chronic conditions frequently serves as the primary indicator of underlying sepsis.[1] Common examples include acute presentations of diabetic ketoacidosis or decompensated cirrhosis.[1]

Progression to severe disease involves distinct, organ-specific failure patterns.[17] Respiratory compromise classically manifests as acute respiratory distress syndrome (ARDS).[17] This syndrome features hypoxemia alongside bilateral noncardiac infiltrates.[17] Cardiovascular dysfunction primarily presents as refractory hypotension and elevated serum lactate levels.[17] Hypotension frequently persists despite adequate volume expansion, necessitating continuous vasopressor support and myocardial dysfunction regularly accompanies vascular collapse.[17] Neurologic impairment typically emerges as obtundation, delirium, or nonfocal encephalopathy.[17] Critical illness polyneuropathy and myopathy frequently complicate prolonged intensive care admissions.[17] Renal involvement typically demonstrates decreasing urine output and escalating serum creatinine levels.[17] This decline in renal function often necessitates

renal-replacement therapy.[17] Additional systemic manifestations include paralytic ileus, elevated aminotransferases, and disseminated intravascular coagulation.[17] Adrenal dysfunction, altered glycemic control, and euthyroid sick syndrome also occur frequently.[17]

4.2 Screening Tools (SIRS, qSOFA, SOFA, NEWS)

The Sepsis-3 consensus established the Sequential Organ Failure Assessment (SOFA) score as the diagnostic standard. Sepsis requires an acute increase in the total SOFA score of ≥2 points consequent to infection.[2] The SOFA score evaluates dysfunction across six organ systems (respiratory, coagulation, hepatic, cardiovascular, neurologic, renal) on a 0-4 scale each, for a total range of 0-24.[36] The tool demonstrates strong predictive validity for in-hospital mortality. Evidence shows an AUROC of 0.74 in the ICU and 0.79 outside the ICU.[36] Its requirement of laboratory data limits its routine utility as a rapid bedside screen.[36]

The quick SOFA (qSOFA) score was introduced with the Sepsis-3 definitions in 2016 as a bedside prompt for evaluation outside the ICU.[2] It uses three criteria: altered mental status (GCS < 15), systolic blood pressure ≤100 mmHg, and respiratory rate ≥22 breaths per minute; a score ≥2 indicates high risk. It requires no laboratory tests and can be assessed rapidly.[2] Clinical studies demonstrate that qSOFA provides high specificity (82-99%) but low sensitivity (28-46%) for sepsis identification.[37] A recent meta-analysis confirms a low pooled qSOFA sensitivity of 37%.[38] The Sepsis-3 framework introduced qSOFA specifically for prognostication rather than initial screening.[2,39] The 2021 Surviving Sepsis Campaign (SSC) guidelines recommend against using qSOFA as a single diagnostic screening tool, though a positive qSOFA should still alert clinicians to possible sepsis and clinical deterioration.[39]

The Systemic Inflammatory Response Syndrome (SIRS) criteria define sepsis as infection plus 2 of the following: temperature >38°C or <36°C, heart rate >90 bpm, respiratory rate >20 or PaCO2 <32 mmHg, and WBC >12,000 or <4,000/mm³ or >10% bands.[2] SIRS yields high sensitivity (82-86%) and low specificity (24-41%) for sepsis detection, meaning it captures most septic patients but also flags many with non-infectious inflammation.[37,40] Studies consistently show SIRS superiority over qSOFA

for initial sepsis diagnosis.[40] The Sepsis-3 consensus removed SIRS from the formal disease definition, yet institutional performance improvement programs continue to utilize SIRS for general infection screening.[2,4]

The National Early Warning Score (NEWS) incorporates seven vital sign parameters: heart rate, respiratory rate, temperature, systolic blood pressure, oxygen saturation, supplemental oxygen use, and level of consciousness (AVPU).[37] The Royal College of Physicians published the updated National Early Warning Score 2 (NEWS2) in 2017. This revision introduced two primary modifications to the original instrument: an alternative oxygen saturation scale (SpO_2 Scale 2) for patients experiencing hypercapnic respiratory failure, and the expansion of the consciousness evaluation from the standard AVPU scale to ACVPU to systematically capture new-onset confusion.[41] Both versions evaluate the same seven physiological parameters. Risk stratification thresholds remain consistent across both scores, defining clinical risk as low (0-4 points), medium (5-6 points), or high (≥7 points).[41] A NEWS or NEWS2 score of ≥5 demonstrates intermediate-high sensitivity (71-84%) and specificity (52-85%) for sepsis identification [38]. This tool is designed to identify patients at risk of clinical deterioration from any cause, and performs well for sepsis identification; it provides an optimal combined AUROC of 0.91 for severe sepsis detection during emergency triage.[37]

The 2026 SSC guidelines prioritize high screening sensitivity to minimize false negative results. The document issues a strong recommendation to use NEWS, NEWS2, or SIRS over qSOFA as a single screening tool for hospitalized patients.[4] Current evidence supports a practical ward-based approach that involves using NEWS/NEWS2 ≥5 or SIRS ≥2 as initial triggers for possible sepsis evaluation.[38] Sepsis remains a clinical diagnosis. Screening alerts must be followed by clinical assessment and immediate point-of-care lactate measurement.[4] Importantly, no single tool replaces clinical judgment.[4] The 2026 SSC guidelines mandate the integration of validated screening tools into sepsis performance improvement programs that include education, bundle compliance, and outcome measurement.[4]

Table 2. Diagnostic and Predictive Performance of Sepsis Clinical Tools

Scoring System	Sensitivity (95% CI)	Specificity (95% CI)	Clinical Application & Predictive Validity
SIRS (≥2)	70% (49-85%)	62% (41-80%)	High sensitivity but lower specificity. It captures most septic patients but flags many with non-infectious inflammation.[38]
qSOFA (≥2)	37% (20-59%)	94% (86-98%)	High specificity but poor sensitivity. Inadequate as a standalone screening tool; better suited to identify high risk of poor outcomes.[38]
NEWS / NEWS2 (≥5)	65% (56-72%)	77% (59-88%)	Provides a balanced performance for early sepsis identification in wards and emergency departments.[38]
SOFA (≥2)	*N/A (Reference Standard)*	*N/A (Reference Standard)*	Diagnostic standard for sepsis (Sepsis-3). Strong predictive validity for in-hospital mortality: AUROC 0.74 (ICU) and 0.79 (outside ICU).[36]

4.3 Microbiological Diagnosis

Establishing a microbiological diagnosis represents a critical pillar in the management of sepsis and septic shock, providing the necessary data to transition from empiric to targeted pathogen-directed antimicrobial therapy. The SSC 2026 guidelines strongly recommend to collect blood cultures as soon as possible, ideally prior to the initiation of antimicrobial therapy, for all adults with possible, probable, or definite sepsis or septic shock.[4]

While a specific pathogen is identified through various modalities in 60% to 70% of sepsis patients overall, standard blood cultures demonstrate positivity in approximately 10% to 20% of cases, though this diagnostic yield rises to ≥50% in patients presenting with septic shock.[4] Key technical factors in recovering viable pathogens from blood specimens are:

- Blood volume: guidelines dictate a target volume of 10 mL of blood directly inoculated into each culture bottle.[4,42]
- Number of sets: collecting two blood culture sets from distinct venipuncture sites increases pathogen detection sensitivity from 91.5% to 99.3% compared to a single set.[4] A systematic review involving 18,901 patients demonstrated that single-site blood culture collection may achieve a higher proportion of adequate-volume samples, improve overall pathogen detection, and minimize contamination risks compared to fragmented practices.[4]

- Anaerobic bottles: approximately 15% of positive blood cultures isolate pathogens exclusively within anaerobic bottles, although this specific finding rarely alters empiric therapy unless anaerobic infection is strongly suspected on clinical grounds.[4]
- The timing of specimen collection relative to antimicrobial administration: this significantly modulates diagnostic yield. Multicenter data indicate that blood culture positivity decreases from 31.4% pre-antimicrobial administration to 19.4% post-antimicrobial administration, representing a 38.2% relative reduction in pathogen recovery.[4] Cultures should be drawn before antibiotics, but must not delay the initiation of antimicrobial therapy, particularly in hemodynamically unstable patients or those exhibiting explicit signs of septic shock.[4]

Following initial resuscitation, routine repeat blood cultures are not universally required but are recommended to confirm the clearance of bacteremia or fungemia specifically for Staphylococcus aureus, Staphylococcus lugdunensis, and Candida species.[4]

In addition to systemic venipuncture, guidelines advise sampling suspected localized anatomical sites to clarify the primary source of infection.[4] Diagnostic testing choices should rely systematically on patient medical history, clinical symptoms, and physical examination findings. Given that pneumonia and urinary tract infections represent the two most common primary sources of infection in sepsis, urine cultures are recommended when no clear source is identified.[43] Depending on clinical signs, source-directed cultures may encompass urine, cerebrospinal fluid, peritoneal fluid, deep wound swabs, or sputum.[43] For the vast majority of common etiologic agents, conventional continuous-monitoring blood culture systems deliver positive identification within a 24-to-48-hour incubation window, meaning that extended incubation exceeding 5 days is rarely necessary for routine diagnostic workflows.[42]

To overcome the inherent delays of conventional culture systems, modern molecular and phenotypic diagnostic assays have been integrated into clinical pathways. Pathogen-specific rapid diagnostic tests (e.g. Streptococcal and Legionella urinary antigens) are recommended in selected patients, based on localized pathogen

distribution, specific antimicrobial resistance patterns, clinical presentation, and seasonal epidemiological factors.[4] Systematic reviews demonstrate that the isolation of rapid diagnostic tests without concurrent clinical interventions results in little to no difference in short-term mortality.[4] Conversely, demonstrable mortality benefits emerge when these rapid diagnostic technologies are coupled structurally with effective antimicrobial stewardship programs.[4] Generalized, unrestricted use across all hospitalized populations is discouraged, as it inflates healthcare expenditures without delivering clear clinical utility.[4]

Multiplex PCR panels (e.g. respiratory viral PCR panels) allow rapid pathogen detection and maintain clinical utility when prior antimicrobial therapy has suppressed standard culture growth.[42] For rapid identification from positive cultures, Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) identifies bacterial and fungal species directly from positive culture bottles within 1 to 3 hours, significantly shortening the time to targeted therapy.[42]
These emerging diagnostic technologies fail to improve patient outcomes unless actively integrated into formal antimicrobial stewardship interventions.[4]

4.4 Laboratory and Imaging Investigations

The laboratory workup serves two purposes: detecting organ dysfunction and identifying the infectious source and pathogen. Elevated serum lactate exceeding 2 mmol/L formally defines septic shock under Sepsis-3 criteria.[1,4] Bedside lactate testing rapidly identifies tissue hypoperfusion.[44]

Complete blood counts quantify inflammatory and hematologic responses. Core diagnostic variables include leukocytosis above 12,000/μL, leukopenia below 4,000/μL, bandemia exceeding 10%, and thrombocytopenia below 100,000/μL, which represent severe disease markers.[45]

Basic metabolic panels detect acute kidney injury and metabolic alterations. Serum creatinine increases exceeding 0.5 mg/dL reflect acute renal dysfunction.[45] Sepsis-induced insulin resistance causes hyperglycemia [44], defined as a plasma glucose above 140 mg/dL independent of diabetes status.[45]

Hepatic impairment presents as hyperbilirubinemia, with total bilirubin concentrations exceeding 4 mg/dL defining hepatic organ dysfunction.[45]

Coagulation studies evaluate disseminated intravascular coagulation risk. An international normalized ratio (INR) exceeding 1.5 indicates systemic coagulation abnormalities.[45] PT/INR, D-dimer, and fibrinogen require immediate measurement upon coagulopathy suspicion.[44]

Arterial blood gas analyses quantify respiratory failure, where arterial hypoxemia requires a PaO_2/FiO_2 ratio below 300. [45] Pulse oximetry provides a noninvasive SpO_2/FiO_2 approximation, but shock states significantly reduce the accuracy of peripheral oximetry measurements.[4]

Procalcitonin levels rise four hours after bacterial exposure, and concentrations peak within six to eight hours.[28] Effective antibiotic therapy induces a rapid procalcitonin decline.[28] Severe viral illnesses like influenza and COVID-19 also elevate procalcitonin, limiting its diagnostic utility for isolated bacterial sepsis, and major guidelines recommend against routine procalcitonin use for initial sepsis diagnosis.[28] However, serial procalcitonin measurements effectively guide antimicrobial de-escalation.[4,28]

Hepatic synthesis of C-reactive protein occurs during systemic inflammation.[28] Single biomarkers demonstrate limited capacity to differentiate bacterial sepsis from non-infectious inflammatory states, but composite biomarker panels improve diagnostic accuracy.[33] A three-biomarker variation achieved an area under the curve of 0.85 for diagnosing severe bacterial sepsis, while a model combining all four markers (procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate) yielded an area under the curve of 0.86.[33]

Imaging modalities must target specific clinical signs, and untargeted whole-body screening lacks clinical utility.[46] Bedside chest radiographs represent the standard initial imaging step when no clear source is identified.[28,46] Pneumonia constitutes the most frequent source of infection.[44,46]

Targeted computed tomography (CT) follows nonspecific chest radiographs. CT with intravenous contrast identifies a septic focus in 76.5% of cases. The positive predictive value for locating a septic source reaches 81.82%. Common infectious sources include the chest (38.6%), abdomen (22.0%), and pelvis (20.5%). Radiological findings alter clinical management in 45% of surgical intensive care patients.[46]

Point-of-care ultrasound (POCUS) expedites source identification. Standard clinical assessment yields a diagnostic sensitivity of 48%, and ultrasound integration improves diagnostic sensitivity to 73%. Bedside imaging yields diagnoses within ten minutes.[45]

Lung ultrasound exhibits 88% sensitivity and 86% specificity for pneumonia detection. Cardiac ultrasound evaluates ventricular function and sepsis-induced cardiomyopathy. Abdominal ultrasound reliably identifies cholelithiasis, hydronephrosis, and abscesses. The Rapid Ultrasound in Shock (RUSH) protocol provides a systematic framework for hemodynamic assessment.[47]

Hospitals must implement structured sepsis response systems. The Surviving Sepsis Campaign 2026 guidelines recommend establishing a bedside "code sepsis" or "sepsis huddle".[4] Multidisciplinary teams execute rapid, parallel investigations: blood cultures require immediate collection prior to antimicrobial administration, lactate measurements and organ dysfunction labs must be sent simultaneously to direct targeted resuscitation, and imaging needs to target the most likely source based on clinical assessment.[4]

4.5 Challenges of Sepsis Recognition Outside the ICU

Sepsis recognition in general medical wards presents distinct diagnostic challenges compared to the intensive care unit. Diverse combinations of infection site, pathogen type, organ dysfunction, and baseline health create substantial clinical heterogeneity.[1] Early clinical signs evolve over time and frequently appear subtle.[1] Common signs (fever, tachycardia, tahcypnea) are nonspecific, which leads up to one-third of patients initially treated for presumed bacterial sepsis to ultimately receive a noninfectious diagnosis.[1] Sepsis can present without fever or localizing signs. Sepsis-induced

hypothermia and afebrile presentations occur predominantly in older adults or immunocompromised individuals.[35]

Lower monitoring intensity outside the intensive care unit complicates early detection. Ward patients typically have vital signs checked every 4-8 hours, in contrast to the continuous monitoring available in the ICU. Because of this intermittent assessment, clinical deterioration can go undetected. Comprehensive tools like SOFA require laboratory variables, which may frequently be missing or difficult to obtain rapidly in ward settings. This lack of data increases the measurement burden for clinicians.[36] The qSOFA model bypasses laboratory requirements by utilizing only bedside clinical variables, but has poor sensitivity (54%).[36,48] Evidence indicates that no single screening tool achieves optimal sensitivity and specificity simultaneously on the wards.[38] The 2026 Surviving Sepsis Campaign guidelines strongly recommend against using qSOFA as a standalone screening tool.[4] SIRS criteria display low specificity (13%), which means that nearly half of general ward patients trigger SIRS criteria without progressing to organ dysfunction.[48] NEWS currently offers a superior balance. NEWS yields the highest area under the curve (AUC 0.77) for predicting in-hospital mortality among infected ward patients.[48] Guidelines currently recommend NEWS, NEWS2, or SIRS over qSOFA for ward-based screening.[4]

Electronic sepsis alerts generate a high volume of false-positives. These inaccurate notifications induce “alert fatigue”.[49] Survey data indicate 62.5% of medical trainees experience alert fatigue. An additional 46.3% cite limited clinical utility as a primary concern regarding electronic sepsis tools.[49]

Workload constraints and nurse staffing level directly influence ward-based recognition. Nurse workload represents the primary mechanism preventing rapid initiation of antimicrobial therapy. Effective nurse-physician communication remains a necessary component for expediting sepsis care.[50] Each additional patient assigned to a nurse correlates with a 9% to 12% increase in sepsis-related mortality. Evidence suggests nurse staffing exerts a stronger effect on patient outcomes than baseline compliance with sepsis protocols.[51]

Hospital-onset sepsis constitutes a distinct, high-risk clinical entity. These cases account for approximately 12% of sepsis encounters, and carry a 33% in-hospital mortality rate compared to 17% for community-onset sepsis.[52] Ward-onset sepsis correlates with substantially lower adherence to the SEP-1 bundle (RR 0.33 for overall adherence).[53]

5 Medical Management of Sepsis

5.1 Early Resuscitation and Hemodynamic Support

Immediate recognition of sepsis-induced hypoperfusion necessitates immediate hemodynamic resuscitation. Current guidelines recommend an initial intravenous crystalloid volume of 30 mL/kg administered within three hours.[4] For patients with a body mass index exceeding 30, providers must calculate this volume using adjusted body weight. Clinicians should also consider fluid resuscitation for intermediate lactate elevations between 2 and 4 mmol/L. Balanced crystalloids (e.g. lactated Ringer's) are currently suggested over normal saline to reduce mortality. Guidelines strongly recommend against using starches or gelatins for initial volume expansion. Both underresuscitation and overresuscitation are associated with harm.[1] For example, the SSSP-- trial demonstrated significant harm when administering a median fluid volume of 3.5 liters (exceeding 30 mL/kg) during the first six hours.[1]

To assess fluid responsiveness and to guide ongoing resuscitation clinicians use dynamic parameters like stroke volume variation, passive leg raise, pulse pessure variation or echocardiography.[4] Liberal and restrictive fluid strategies demonstrate similar overall clinical outcomes. The FRESH trial showed stroke volume-guided resuscitation reduced renal replacement therapy to 5.1% compared to 17.5% under usual care.[1] This individualized approach also decreased invasive mechanical ventilation rates from 34.1% to 17.7%.

Vasopressor therapy targets persistent hypotension despite initial fluid administration. The 2026 guidelines recommend an initial mean arterial pressure (MAP) of 65 mm Hg. A lower MAP target of 60-65 mm Hg is conditionally suggested for patients aged 65 years or older.[4] This targeted reduction decreases mortality risk (RR 0.89) and

minimizes atrial fibrillation incidence in this age group. Norepinephrine represents the first-line vasopressor. Clinicians can initiate norepinephrine via central IV access or a high-quality peripheral catheter to prevent delayed hemodynamic support. Escalating vasopressor requirements necessitate arterial blood pressure monitoring. Vasopressin is the preferred adjunctive agent for escalating norepinephrine doses between 0.25 and 0.5 μg/kg/min. Epinephrine serves as a third-line therapy for refractory shock.[4]

Concomitant cardiac dysfunction requires tailored pharmacological support. Norepinephrine or epinephrine act as first-line agents depending on the presence of, respectevely, tachyarrhythmias or bradyarrhythmias. Dobutamine addition remains a viable option for persistent hypoperfusion. Levosimendan is explicitly suggested against in this clinical scenario.[4]

The 2026 guidelines also suggest intravenous corticosteroids for adult with septic shock, with a standard regimen of 200 mg of hydrocortisone per day. The addition of fludrocortisone is debated: most panelists do not routinely add it, though evidence suggest a benefit in mortality with the combination. Corticosteroids do not confer clinical benefit in sepsis without concurrent shock.[4]

5.2 Antimicrobial Therapy

Prompt antimicrobial administration is a cornerstone of early sepsis management. Evidence indicates a strong inverse relationship between time-to-antibiotics and patient survival. The Surviving Sepsis Campaign 2026 guidelines risk-stratify the urgency of antimicrobial initiation based on shock presence and infection probability.[4] Patients with possible, probable, or definite septic shock require immediate antimicrobial therapy within one hour of recognition.[4] Immediate administration within one hour is equally indicated for patients with probable or definite sepsis without shock.[4] A meta-analysis of 42 observational studies associates antibiotic administration within one, three, or six hours with reduced short-term mortality.[4] Guidelines suggest a time-limited rapid investigation course for patients presenting with possible sepsis without shock.[4] Antimicrobials should follow within three hours if infection concerns persist.[4] For patients with a low likelihood of infection without

shock, deferring therapy while providing close clinical monitoring remains appropriate.[4]

Clinical protocols mandate obtaining appropriate cultures before initiating antimicrobial therapy. On the other hand, blood and site-specific cultures must not delay antibiotic administration, especially in hypotensive patients.[4] Empiric regimens must target the most probable pathogens based on suspected infection site, patient-specific risk factors, and local resistance.[1] Guidelines restrict broad-spectrum coverage targeting Methicillin-resistant Staphylococcus aureus or multidrug-resistant Gram-negative pathogens to high-risk patients.[39] Once the causative pathogen is identified, double Gram-negative coverage is not generally necessary.[39] For patients demonstrating a high risk for invasive fungal infections, empiric antifungal therapy is suggested.[4] Furthermore, prolonged intravenous infusions of beta-lactam antibiotics, after an initial loading dose, are recommended to optimize pharmacodynamic targets.[4] Data indicate this administration strategy reduces short-term mortality in patients with sepsis and septic shock.[4]
Antimicrobial stewardship principles dictate tailoring empiric therapy to local antibiograms to mitigate resistance emergence.

5.3 Source Identification and Monitoring

Rapid localization of the anatomical infection site and pathogen isolation represent diagnostic pillars in sepsis management. Serial clinical and laboratory reassessments provide the necessary physiological data to guide ongoing resuscitation and treatment response.

The 2026 Surviving Sepsis Campaign guidelines strongly recommend collecting blood cultures prior to antimicrobial administration.[4] Antimicrobial exposure rapidly degrades diagnostic yield. A multicenter trial of 325 patients demonstrated a blood culture positivity decrease from 31.4% pre-antibiotics to 19.4% post-antibiotics.[4] Diagnostic collection protocols must never delay antimicrobial initiation in hemodynamically unstable patients presenting with hypotension. [4] Clinicians must obtain repeat cultures to confirm bacteremia clearance for specific high-risk pathogens.[4]

Pneumonia and urinary tract infections remain the most frequent sepsis sources.[43] Site-directed clinical evaluation dictates chest imaging and urinalysis when alternative sources remain obscure.[43] Physical examination findings direct the sampling of cerebrospinal, joint, pleural, or peritoneal fluids.[35] Targeted CT imaging provides superior diagnostic utility for source localization compared to untargeted whole-body imaging.[43] Cryptic infection origins require targeted clinical reassessment of the genitourinary tract, the perianal region, and indwelling medical devices.[43] Suspected vascular catheter infections necessitate simultaneous peripheral and catheter-drawn blood cultures to facilitate differential time-to-positivity testing.[28] Rapid antigen testing and multiplex PCR panels provide commercial diagnostic options, though these molecular tools currently reside outside routine standard practice.[1]

Anatomical diagnoses qualifying for intervention require rapid source control within six hours of clinical recognition.[4] Early surgical or percutaneous intervention may reduce short-term mortality, yielding a relative risk of 0.70 based on observational data.[4] Common targetable foci include intra-abdominal abscesses, gastrointestinal perforations, cholangitis, necrotizing soft tissue infections, empyema, septic arthritis, and infected devices.[39] Dynamic hemodynamic measures predict fluid responsiveness with greater accuracy than static variables. Fluid management protocols guided by dynamic measures reduce mortality (RR 0.91) and renal replacement therapy requirements (RR 0.75) across 18 randomized controlled trials.[4] The European Society of Intensive Care Medicine delineates hemodynamic monitoring into distinct phases: salvage (arterial pressure, clinical exam, lactate, echocardiography), optimization (tissue perfusion markers, cardiac output monitoring), stabilization, and de-escalation, specifically structured to prevent deleterious fluid overload.[4]

Serial serum lactate measurements guide initial resuscitation intensity. A targeted lactate reduction of 10% every two hours improves clinical outcomes and shortens intensive care unit length of stay compared to static normalization goals.[4] Lactate functions as a biomarker of cellular stress and hypoxia rather than a direct index of systemic tissue perfusion. Continuous fluid administration aimed exclusively at absolute lactate normalization may lead to harmful volume overload.[4]

Capillary refill time (CRT) serves as a physiologically robust, non-invasive alternative for tissue perfusion monitoring. The ANDROMEDA-SHOCK trial demonstrated numerical reductions in 28-day mortality for the CRT-guided cohort (34.9%) compared to the lactate-guided cohort (43.4%).[4] A statistical reanalysis confirms a probability exceeding 90% for mortality reduction utilizing this specific clinical parameter.[4]

Biomarker kinetics provide actionable physiological data for antimicrobial stewardship. The 2021 guidelines issue a weak recommendation against initiating antibiotic therapy based solely on procalcitonin levels coupled with clinical evaluation.[39] Conversely, substantial evidence supports procalcitonin utility for guiding antimicrobial de-escalation. The 2025 ADAPT-Sepsis multicenter trial confirms that daily procalcitonin protocols successfully reduce total antibiotic duration without elevating patient risk.[31]

C-reactive protein increases rapidly following infectious insults, but lacks specific diagnostic capability for bacterial etiologies.[27] Serial biomarker tracking consistently yields higher clinical prognostic value than isolated baseline measurements.[27]

Finally, systematic organ function monitoring relies on the SOFA score. Serial clinical evaluation tracks mental status, urine output, serum creatinine, mean arterial pressure, oxygen saturation, bilirubin, and platelet count to objectively quantify progressive multiorgan dysfunction.[43]

5.4 Antimicrobial Stewardship in Sepsis Care

Early antimicrobial administration determines sepsis survival. Guidelines advocate a three-hour administration window for patients lacking shock.[39] Delays escalate mortality risks. Each hour of delay from emergency department arrival increases in-hospital mortality odds by 1.07 for patients requiring vasopressors.[39] Unnecessary antimicrobial administration induces allergic reactions, kidney injury, Clostridioides difficile infection, and antimicrobial resistance.[39]

Antimicrobial de-escalation mitigates resistance and toxicity. The 2026 Surviving Sepsis Campaign strongly recommends de-escalation upon pathogen identification.[4]

Guidelines conditionally suggest de-escalation even when no pathogen is identified.[4] A meta-analysis of 26 studies demonstrates that de-escalation reduces short-term mortality hospital length of stay, and antimicrobial resistance.[4] Targeted therapy challenges empirical broad-spectrum regimens. Discontinuing anti-methicillin-resistant Staphylococcus aureus (MRSA) and antipseudomonal therapies on day four yields a similar or improved 90-day mortality compared to continued broad-spectrum therapy. In particular, this is demonstrated among clinically stable patients at day three.[14] Clinicians must strictly avoid unnecessary antianaerobic agents. These drugs deplete healthy enteric gut microbiota and drive adverse clinical outcomes.[1]

The SSC guidelines recommend shorter antimicrobial courses, especially for patients achieving adequate source control.[1] The BALANCE trial confirms the efficacy of 7-day regimens for bloodstream infections. 90-day all-cause mortality reached 14.5% in the 7-day group versus 16.1% in the 14-day group.[54] This establishes a non-inferiority risk difference of -1.6 %.[54] The trial extends this benefit to critically ill populations, consisting of 55% ICU patients.[54] Biomarkers safely guide therapy discontinuation. The 2026 guidelines conditionally recommend procalcitonin integration with clinical evaluation.[4] The ADAPT-Sepsis trial and large meta-analyses prove procalcitonin-guided protocols reduce antibiotic exposure by approximately two days without compromising survival.[4]

Early transition from intravenous to oral therapy optimizes resource utilization. A 2025 meta-analysis of 38 studies confirms transition safety across 11,566 patients.[55] Six randomized trials demonstrate non-inferiority for treatment failure (OR 0.89) alongside a significant reduction in hospital stay.[55] Optimal review timing occurs 48 to 72 hours after intravenous initiation.[56] Modern protocols evaluate earlier transitions within 24 hours for appropriate uncomplicated candidates.[56] Transition occurs safely at 3 to 5 days for Enterobacterales and 3 to 7 days for Streptococcus species.[55] Patient eligibility demands specific clinical criteria: clinical stability (afebrile and hemodynamically stable for more than 48 hours), source control achieved within five days, functional gastrointestinal absorption (able to tolerate oral medications), and clinical improvement.[57] Pharmacological barriers regarding oral bioavailability appear perceived rather than real. Retrospective data reveal equivalent outcomes among

highly bioavailable agents (fluoroquinolones, trimethoprim-sulfamethoxazole) and low-bioavailability oral β-lactams.[57]

5.5 Supportive Care in Medical Wards

Ward septic patients require continuous monitoring for signs of clinical deterioration, that may warrant ICU transfer. Delayed admission to the intensive care unit correlates directly with adverse clinical outcomes. Data indicate ICU mortality increases by 1.5% for every hour of delay from the emergency department to ICU.[39] Emergency department stays exceeding six hours elevate mortality significantly.[39] Clinical guidelines mandate that patient location must not delay regular assessment and appropriate treatment.[39]

Rigourous monitoring of septic patients in the ward is fundamental, as patients often necessitate additional supportive measures:

- Venous thromboembolism (VTE) prophylaxis: given that sepsis induces a procoagulant state, VTE is often needed. The 2026 Surviving Sepsis Campaign guidelines strongly recommend pharmacologic prophylaxis unless specific contraindications exist.[4] Low-molecular-weight heparin demonstrates superior efficacy and is explicitly preferred over unfractionated heparin.[4] Evidence suggests utilizing pharmacological prophylaxis alone rather than combining it with mechanical devices.[4]
- Glucose control: sepsis frequently precipitates stress-induced hyperglycemia. Clinical protocols dictate initiating insulin therapy when blood glucose levels equal or exceed 180 mg/dL.[4] Following initiation, standard care targets a blood glucose range between 144 and 180 mg/dL.[39] Strict glycemic control below this range offers no additional survival benefit and increases hypoglycemia risk.
- Stress ulcer prophylaxis: critical illness predisposes patients to gastrointestinal mucosal ischemia. Stress ulcer prophylaxis with proton-pump inhibitors is exclusively indicated for patients exhibiting specific risk factors for gastrointestinal bleeding.[4]

- Nutrition: guidelines suggest early initiation of enteral nutrition within 72 hours for eligible patients, as it preserves intestinal barrier integrity.[39] Aggressive early parenteral nutrition fails to demonstrate mortality benefits.[35] Current protocols recommend against initiating parenteral nutrition within the first seven days of sepsis management.[35]
- Sedation and immobility: sedation management requires careful calibration to minimize prolonged immobility. Patients requiring neuromuscular blocking agents for moderate-to-severe acute respiratory distress syndrome should receive intermittent boluses rather than continuous infusions.[4] Early mobilization on the medical ward accelerates functional recovery. Post-critical illness physical rehabilitation programs improve physical recovery and quality of life for sepsis survivors.[39]

Sepsis survivors experience profound long-term physical, cognitive, and emotional sequelae, as approximately 40% of sepsis survivors require hospital readmission within 90 days of discharge.[4] Medical teams must discuss goals of care and prognosis with patients and families within the first 72 hours of admission.[4] Hospital discharge plans require structured assessments and post-critical illness follow-up programs are conditionally recommended to mitigate long-term morbidity.[4]

6 Surgical Management of Sepsis

6.1 Source Control Principles

The 2026 Surviving Sepsis Campaign guidelines recommend rapid evaluation for specific anatomical diagnoses requiring emergent source control, in patients with sepsis or septic shock.[4] Guidelines suggest early source control over late interventions, with optimal execution within six hours of diagnosis.[4] A meta-analysis of 11 observational studies indicates early source control reduces short-term mortality and one-year mortality.[4]

Source control includes surgical and procedural interventions to remove the infection source, reduce pathogen burden, or correct anatomical issues that hinder infection clearance.[4,39] Common foci include intra-abdominal abscesses, gastrointestinal

perforation, and ischemic bowel.[4,39] Other foci involve cholangitis, cholecystitis, pyelonephritis with obstruction, and necrotizing soft-tissue infections.[4,39] Empyema, septic arthritis, and implanted device infections also require evaluation.[4,39]

Source control requires implementation as soon as medically and logistically practical.[4,39] Prolonged efforts at medical stabilization without source control frequently fail among severely ill patients, especially those with septic shock.[4,39] The selection of optimal source control methods weighs benefits, risks, and patient preference.[39] Clinician expertise, availability, potential delays, and probability of success also dictate the approach.[39] Clinicians generally pursue the least invasive option that achieves effective source control.[39]

Source control is highly time-sensitive, and delays are associated with an increase in mortality risk, particularly among patients in shock.[1] A cohort study of 4,962 patients demonstrates that source control within six hours is associated with decreased risk-adjusted 90-day mortality odds.[58] Gastrointestinal and abdominal interventions yield the greatest mortality benefits (aOR 0.56), while soft tissue debridements also show significant survival advantages (aOR 0.72).[58]

6.2 Intra-Abdominal Infections

The Surgical Infection Society (SIS) 2024 update recommends source control within 12 hours for lower-risk patients, whereas higher-risk patients with septic shock require intervention within 6 hours.[59] Patients with septic shock secondary to gastrointestinal perforation exhibit zero survival with operative delays exceeding six hours.[59]

The SIS provides key operative principles for patients with intra-abdominal infections. Percutaneous drainage of localized fluid collections represents the least invasive approach. This technique yields success rates ranging from 82% to 91%.[60] For patients with exhausted physiologic reserves (including pH below 7.2, temperature below 35ºC, or coagulopathy), damage control laparotomy is indicated.[60] Other indications include intra-abdominal hypertension risk, inadequate source control, or planned second-look for mesenteric ischemia.[60] Furthermore, the on-demand re-laparotomy strategy demonstrates superiority over routine planned re-laparotomy, which increases

resource utilization without mortality benefit.[60] Finally, peritoneal lavage is mainly considered for removal of gross contamination; evidence does not support continuous postoperative lavage or antibiotic-containing lavage.[60]

Open abdomen management is endorsed in severe peritonitis with septic shock, when physiological derangements require abbreviated laparotomy, source control is incomplete, or there is a concern for abdominal compartment syndrome.[61]
The preferred temporary abdominal closure technique is negative pressure wound therapy (NPWT), which improves open abdomen outcomes.[61]

6.3 Surgical Site Infections

The Infectious Diseases Society of America (IDSA) classifies surgical site infections into superficial incisional, deep incisional, and organ/space infections.[62]

Suture removal paired with incision and drainage constitutes the primary intervention for superficial infections.[62] Uncomplicated superficial infections do not routinely require systemic antibiotics, but their addition is recommended when systemic signs are present.[62] These signs include erythema extending beyond 5 cm from the wound edge, temperature above 38.5ºC, heart rate exceeding 110 bpm, or leukocyte count above 12,000/µL.[62] In surgical site infections following clean operations, the suggested antibiotics for methicillin-susceptible Staphylococcus aureus (MSSA) are first-generation cephalosporins or antistaphylococcal penicillins.[62] Alternatively, options for patients at risk of methicillin-resistant Staphylococcus aureus (MRSA) include vancomycin, linezolid, daptomycin, telavancin, or ceftaroline.[62] Operations involving the gastrointestinal tract, perineum, or genital tract necessitate gram-negative and anaerobic coverage.[62] Regimens combine a cephalosporin or fluoroquinolone with metronidazole.[62]

Deep incisional and organ/space infections causing sepsis demand urgent operative exploration.[39,62] These deeper infections require extensive debridement and drainage for adequate source control.[4,62]

6.4 Necrotizing Soft Tissue Infections

Necrotizing soft tissue infections represent a significant diagnostic challenge. Initial clinical evaluations misdiagnose approximately 50% of cases.[63] To distinguish necrotizing fasciitis from cellulitis, the LRINEC score utilizes C-reactive protein, leukocyte count, hemoglobin, sodium, creatinine, and glucose. This score exhibits limited sensitivity and cannot definitively rule out necrotizing infections.[64] CT visualizing fascial gas provides superior diagnostic accuracy, yielding 88.5% sensitivity and 93.3% specificity.[64] Ultimately, clinical suspicion dictates the operative decision.[64,65]

Disease management requires urgent and repeated surgical source control. Early surgical debridement within 6 hours of presentation improves survival.[65] Patients typically require a mean of three surgical debridements to remove all necrotic tissue.[66] Surgeons must perform second-look re-explorations every 12 to 24 hours after the initial operation until necrotic tissue ceases to develop.[65]

Empiric antimicrobial therapy requires broad-spectrum coverage. First line regimens typically include piperacillin-tazobactam combined with vancomycin or linezolid.[67] Unstable patients receive adjunct clindamycin to suppress streptococcal exotoxin production.[65] Therapy continues for 2-4 days after the final debridement under specific favorable conditions: clinical improvement, afebrile status for 48 hours, and negative blood cultures. Treatment extends to 5-7 days if sepsis criteria persist or blood cultures remain uncollected.[67]

6.5 Timing and Strategies of Surgical Intervention

Early source control dictates survival outcomes across varied anatomical sources. Gastrointestinal interventions and soft tissue debridements exhibit the greatest mortality risk reductions.[58] The 2026 Surviving Sepsis Campaign emphasizes that initial resuscitation must not delay source control efforts in patients with septic shock.[4] Severe illness precludes successful medical stabilization in the absence of surgical source control.[4]

Minimally invasive approaches are preferred when adequate source control can be achieved. However, open surgery is reserved for diffuse peritonitis, failed percutaneous approaches, or hemodynamic instability.[60]

Multidisciplinary consultation between critical care and procedural teams facilitates rapid logistical coordination and urgent intervention execution.[1]

7 Ward-Based Sepsis Pathways and Multidisciplinary Care

7.1 Rapid Response Systems

Clinical architecture for inpatient deterioration relies on rapid response systems (RRS). An RRS consists of three interrelated components: the afferent arm provides crisis detection through early warning scores, the efferent arm delivers specialist teams to the bedside, and a governance and audit process evaluates and coordinates system resources.[68] International nomenclature describes these units as medical emergency teams (METs) in Australia, critical care outreach teams (CCOTs) in the United Kingdom, and rapid response teams (RRTs) in the US.[68]

These systems operate within the "Sepsis Chain of Survival" framework. This model adapts sudden cardiac arrest protocols to sepsis, emphasizing an interconnected continuum of time-critical interventions.[69] Key steps include early recognition, prompt clinical activation, timely antimicrobial administration, and appropriate fluid resuscitation.[69] Effective implementation requires coordinated efforts across the entire healthcare spectrum.[69]

Effective RRS deployment depends on accurate screening tools. The 2026 SSC guidelines recommend using NEWS, NEWS2, MEWS, or SIRS over qSOFA for initial screening.[4]

Data suggest qSOFA maintains utility for detecting general clinical deterioration despite lower diagnostic sensitivity for sepsis.[4] Electronic alerts linked to screening tools improve clinical outcomes. The SCREEN trial evaluated an electronic qSOFA-based alert across 60,055 ward patients.[70] Alert implementation coupled with staff education yielded a lower 90-day in-hospital mortality.[70] Real-world effectiveness

remains limited by human factors.[71] High-level evidence highlights substantial heterogeneity in intervention success due to alert fatigue and local contextual variables.[71]

The efferent response involves targeted multidisciplinary evaluation. The 2026 SSC guidelines issue a conditional recommendation for implementing "code sepsis" or "sepsis huddle" protocols, which mandate a multidisciplinary bedside huddle following a positive screen that triggers an alert.[4] Rapid bedside evaluation accelerates diagnosis and therapy. Evidence indicates these protocols lower mortality, reduce mechanical ventilation odds, and shorten time to antibiotic delivery.[4] Response team composition varies depending on institutional resources. Teams range from dedicated multidisciplinary sepsis units to general rapid response teams or ad hoc assemblies of existing unit staff.[4]

Long-term RRS sustainability requires robust governance and continuous operation. A 10-year retrospective cohort study analyzed 976 patients with septic shock managed through an RRS.[72] Overall sepsis bundle compliance increased from 26.5% to 70% over the study period, while 28-day mortality decreased from 50% to 32.1%.[72] Bundle completion independently correlated with lower mortality.[72] Furthermore, operating hours directly impact clinical efficacy. This is demonstrated in a prospective multicenter study that showed that 24-hour RRT availability significantly reduced in--hospital mortality compared to part-day coverage.[73] Incremental clinical benefits of code sepsis implementation vary across hospitals. Less resourced institutions derive greater relative benefit than hospitals with robust existing rapid treatment infrastructure.[4]

7.2 Role of Infectious Diseases Specialists

Evidence indicates infectious disease (ID) consultation significantly improves clinical outcomes in sepsis.[74] A retrospective analysis of 248 patients completing the 3-hour sepsis bundle demonstrated substantial survival benefits: early ID evaluation within 12 hours correlated with a 40% reduction in in-hospital mortality.[74] The same cohort showed a higher likelihood of alive discharge.[74] Dedicated multidisciplinary teams enhance clinical protocol adherence.[75] Implementation of a dedicated ID team for early

sepsis management in the ED improved SSC bundle compliance from 4.6% to 32%.[75] The administration of an appropriate initial empiric antibiotic therapy rose from 30% to 79%, and was associated with decreased 14-day all-cause mortality.[75]

The need for rapid and sustained specialist input extends beyond sepsis to bloodstream infections.[76] A cohort study of 995 patients with bloodstream infections indicated that multiple ID consultations reduce mortality risk.[76] Single consultations did not demonstrate this protective effect.[76] In streptococcal bacteremia, ID consultation within 48 hours improved 14-day survival.[77]

Antimicrobial stewardship represents a core ID function. The 2021 SSC guidelines recommend broad-spectrum empiric therapy followed by daily clinical reassessment.[39] Culture data availability must trigger timely antimicrobial de-escalation.[4] Systemic stewardship integration remains incomplete across health systems.[78] A 2022 CDC report identified major structural gaps in acute care hospitals. Only 55% of facilities provided dedicated time for sepsis program leaders to conduct daily activities.[78] The report emphasizes the necessity of integrating sepsis committees with formal antimicrobial stewardship programs.[78]

7.3 Role of Surgeons and Intensivists

The surgeon's role in sepsis care centers on timely source control.[59] A meta-analysis of 3,373 patients with intra-abdominal infections confirmed that early surgical exploration reduces both mortality and hospital length of stay.[59] Survival decreases rapidly with operative delay.[59] A cluster-randomized trial of 4,792 patients demonstrated that delayed surgical intervention sequentially increases death risk in septic shock.[59] Prolonged medical stabilization without physical source control fails in severely ill cohorts.[39]

All procedural interventions carry inherent physiological risks.[1] Since all interventions come with risks, consultation between critical care and procedural teams is important to determine the benefit and urgency of procedural source control.[1]

Intensivist expertise extends beyond the ICU via Rapid Response Systems, triage and delivery of ICU-level care when needed.[79] A multicenter study evaluating RRS interventions found no overall survival difference across the general ward population.[79] Meanwhile, a subgroup analysis isolated patients with sepsis or septic shock and found that the presence of dedicated RRS doctors significantly improved survival for this specific subset.[79] Dedicated intensivist evaluation also lowered intensive care admission rates in this group.[79]

The SSC 2021 guidelines suggest admitting adults requiring critical care to the ICU within six hours of diagnosis.[39] Delayed transfer produces adverse clinical outcomes. Ward-to-ICU transfer delays of four hours or more significantly increase mortality risk.[80] The Society of Critical Care Medicine recommends treating patients with complex life-threatening conditions like sepsis directly in the ICU.[80] Key intensivist-driven criteria for ICU admission include:

- Invasive mechanical ventilation: general medical wards demonstrate worse-than-predicted survival for critically ill patients requiring mechanical ventilation.[80] The ICU environment provides superior monitoring, active ventilator management, and fewer endotracheal tube complications.[80]
- Vasopressor requirement to maintain MAP ≥65 mmHg, which is included in the Sepsis-3 definition of septic shock, alongside serum lactate >2 mmol/L following adequate fluid resuscitation.[1] In cases of unstable septic shock, clinicians may initiate simultaneous administration of vasopressors (norepinephrine is the first-line vasopressor) and intravenous crystalloids.[4]
- Renal replacement therapy (RRT): current SSC recommendations suggest against utilizing RRT for sepsis-associated acute kidney injury lacking definitive indications.[4] Absolute indications for dialysis initiation include uremic complications, refractory metabolic acidosis, refractory fluid overload/pulmonary edema, and refractory hyperkalemia.[39] Clinicians may use either continuous or intermittent renal replacement modalities when therapy is warranted.[4]

Intensivists play a crucial role also in leading goals-of-care discussion to ensure proportionality of care, including activation of palliative care for end-stage patients.

The SSC 2021 guidelines recommend to discuss goals of care and prognosis with patients and families, preferably within 72 hours of ICU admission.[39] This is based on evidence that a multicomponent family support intervention conducted 48 hours after ICU admission significantly improved communication quality and reduced ICU length of stay.[39] The SSC 2026 guidelines found insufficient evidence to recommend standardized criteria to trigger goals of care discussions.[4] The SSC suggests integration of palliative principles into treatment plan when it is appropriate, without routinely mandating formal palliative care consultations for all sepsis patients.[39] In particular, palliative care can be helpful for patients not responding to treatment or for whom sepsis represents an end-stage manifestation of chronic illness.[39] Intensivists can deliver palliative care principles without necessarily requiring a formal palliative care consult.[39]

7.4 Nursing Management and Early Warning Scores

Ward nurses function as frontline clinicians to monitor clinical deterioration and activate sepsis protocols. Vital signs constitute the simplest and most accessible indicators of clinical deterioration.[81] Standard practice requires monitoring of heart rate, respiratory rate, systolic blood pressure, level of consciousness, oxygen saturation, and temperature, at a minimum of 12-hours intervals.[68] The SSC 2026 guidelines recommend the NEWS2 over qSOFA for initial sepsis screening.[4] NEWS2 utilizes continuous surveillance of seven physiological parameters to detect early clinical decline.[41] It is demonstrated that NEWS provides superior diagnostic sensitivity compared to qSOFA.[38] Objective scoring requires integration with subjective nursing intuition.[41] Because nurses spend the most hours performing routine bedside monitoring, sepsis screening tools have been integrated into nurses's routine patient assessment to facilitate early identification.[38,82] Electronic screening systems significantly improve outcomes when coupled with mandated nurse-to-physician communication.[70]

Nurses also hold primary responsibility for executing initial sepsis bundles. The SSC 2026 guidelines mandate antimicrobial administration within 1 hour for septic shock, and within 3 hours for patients with possible sepsis.[4] Nurses must draw blood cultures

before administering antibiotic therapy, because antimicrobial administration significantly reduces subsequent blood culture sensitivity.[4] Immediate nursing interventions also include measuring serum lactate and administering intravenous crystalloids.[4] Structured nursing reassessment utilizing dynamic hemodynamic parameters guides ongoing fluid resuscitation.[4]

Structural barriers frequently impede optimal ward-based sepsis management. Missed nursing care represents a critical factor delaying necessary interventions and vital sign monitoring. High nurse-to-patient ratios directly compromise clinical outcomes. Data indicate each additional patient per nurse increases the odds of in-hospital sepsis mortality by 12%.[83] Furthermore, knowledge deficits among ward nurses regarding sepsis recognition and management are reported.[82] A multi-site study found that while over 75% of nurses reported confidence in knowing when to escalate to physicians, only about 50% expressed confidence in identifying sepsis symptoms.[82]

7.5 Clinical Decision Support Systems and Digital Tools

The 2021 and 2026 SSC guidelines support electronic screening within performance improvement programs.[4,39] The guidelines prioritize structured screening processes over specific screening modalities.[39] Artificial intelligence (AI) tools require further comparative studies before widespread implementation.[4]

Electronic alert systems integrated into the Electronic Health Record (EHR) are frequently studied for ward-based sepsis management. Electronic alert systems continuously process routine clinical data to identify sepsis according to predetermined diagnostic thresholds.[84] Automated notifications prompt clinical evaluation and potential therapy initiation.[84] A meta-analysis of 36 studies demonstrated these systems reduce overall mortality.[85] Mortality reductions appear more pronounced in emergency departments and medical wards compared to ICUs.[85]

The SCREEN trial evaluated a qSOFA-based electronic alert across 60,055 ward patients.[70] Electronic screening reduced 90-day in-hospital mortality by 15%.[70] Alerted patients experienced increased 12-hour testing for serum lactate and intravenous fluid administration.[70] A separate meta-analysis focused on ED sepsis alert

systems confirmed electronic alerts improve sepsis bundle adherence and reduce mortality in emergency departments.[86] Non-electronic alert systems showed no comparable clinical benefit.[86]

Machine learning (ML) models demonstrate superior predictive accuracy compared to traditional rule-based algorithms, as it is shown in a meta-analysis reported in the SSC 2021 guidelines.[39] Traditional screening tools yielded lower predictive values.[39] Data suggest machine learning predictions drive larger mortality reductions than rule-based methods.[85]

The Targeted Real-time Early Warning System (TREWS) is the most rigorously evaluated ML-based sepsis alert in clinical deployment. TREWS achieved 82% sensitivity in a multi-site cohort study monitoring patients across five hospitals.[87] Provider confirmation of the alert within 3 hours conferred an 18.7% relative mortality reduction and decreased time to first antibiotic administration.[88] Conversely, the Epic Sepsis Model (ESM) version 1 demonstrated poor discrimination, identifying only 7% of sepsis cases missed by clinicians.[89] The updated version 2 showed improved performance.[90] However, positive predictive values remained low, maintaining a high alert burden across clinical settings.[90]

Continuous wearable devices offer non-invasive vital sign tracking to detect early clinical deterioration. A randomized trial of surgical patients utilizing wireless patches observed faster antibiotic administration, shorter length of stay, and lower 30-day admission rates, even though differences were not statistically significant.[91] Telemedicine applications provide remote specialist expertise to resource-limited settings.[92] Telehealth use correlates with higher survival rates in hospitals with low baseline survival.[92]

High false-positive rates generate significant alert fatigue among clinical staff. Survey data indicate 62.5% of medical trainees report alert fatigue, making it one of the most significant barriers to effective clinical decision support systems implementation for sepsis.[49] Over half of surveyed trainees find current digital tools unhelpful.[49] Effective mitigation strategies include transitioning alerts to non-interruptive formats and the suppression of redundant alerts when patients are already being treated and a sepsis

workup is underway.[49] High inter-institutional variability mandates local model validation before clinical deployment.[90]

8 Special Populations and Clinical Settings

8.1 Elderly Patients

Sepsis in older adults presents significant diagnostic challenges due to age-related atypical clinical manifestations. Older patients frequently present with nonspecific symptoms such as acute confusion, falls, incontinence, and functional decline instead of classical symptoms.[93] Fever is frequently absent in older populations.[94] The absence of fever in bacteriemia independently predicts in-hospital mortality.[93]

Standard screening tools demonstrate poor sensitivity in this demographic. SIRS criteria exhibit low sensitivity for identifying severe infection and organ failure in the elderly.[93] qSOFA shows poor diagnostic performance in patients aged 65 years and older. Procalcitonin provides significantly greater diagnostic accuracy for sepsis in this group.[95] Lactate levels of 2 mmol/L or higher and elevated PCT significantly correlate with in-hospital mortality.[95]

Fluid resuscitation in the elderly requires careful individualization, because of higher risk for fluid overload for patients with cardiac or renal comorbidities.[94] Evidence supports dynamic assessment of fluid responsiveness over static measures for frail older patients.[94]

Age-related decline in renal function also affects antimicrobial pharmacokinetics and complicates antibiotic dosing. Protocols mandate systematic dosage adjustments for renally cleared antimicrobials.[94] Early detection and management of decompensated comorbidities, such as heart failure or diabetes, represent core geriatric priorities during acute infections.[94] Sepsis severity and comprehensive geriatric evaluations must guide early goals-of-care discussions. ICU admission decisions depend heavily on baseline functional status, comorbidities, and expected quality of life.[94]

8.2 Immunocompromised Patients

Immunosuppression substantially blunts the host inflammatory response during sepsis. Highly immunocompromised hosts, including solid organ transplant (SOT) recipients, hematopoietic stem cell transpant recipients, patients on high-dose corticosteroids, and those receiving biologic response modifiers, display diminished symptoms and attenuated radiologic findings.[96,97] In particular, solid organ transplant recipients exhibit fewer instances of fever and leukocytosis.[96] Classic sepsis features may remain completely absent.[97]

The SSC 2021 guidelines recommend broad empiric antimicrobial coverage for these patients. Protocols explicitly recommend empiric antifungal therapy for individuals at high risk of fungal infection. Neutropenia, SOT, hematopoietic stem cell transplantation, and high-dose corticosteroid therapy represent specific high-risk factors for Candida and endemic fungal infections.[39] Biomarker assays like Beta-D-glucan and galactomannan aid the early detection of invasive aspergillosis and fungal infections.[96,97]

The management of immunosuppressive therapies during severe sepsis lacks universal consensus. Dose reduction or withdrawal often improves the host immunological response. Clinicians must balance this strategy against the risk of precipitating acute graft rejection or immune reconstitution syndrome.[96]

Intravenous fluid resuscitation requires rigorous monitoring in SOT recipients. Elevated central venous pressure levels and fluid overload cause particular harm in this population.[96]

Transplant recipients also face significant risks for opportunistic viral infections. Cytomegalovirus (CMV) acts as an immunomodulator and increases the risk of subsequent bacterial and fungal sepsis.[97] Diagnostic profiling for immunocompromised septic patients must actively screen for opportunistic viruses, including CMV, Epstein-Barr virus (EBV), and Human herpesvirus 6 (HHV-6).[98]

8.3 Oncology and Hematology Wards

Cancer patients account for more than 20% of all sepsis-related hospitalizations. This demographic faces an increased risk of sepsis-related death in both medical wards and ICUs.[98] Febrile neutropenia constitutes a severe medical emergency. Current guidelines mandate the administration of empiric antibacterial therapy within one hour of triage for febrile neutropenia.

Risk stratification is fundamental and relies on precise clinical scoring systems. High-risk classification includes a MASCC (Multinational Association for Supportive Care in Cancer) score below 21 or a CISNE (Clinical Index of Stable Febrile Neutropenia) score of 3 or higher, and inpatient status at fever onset. Absolute neutrophil counts below 100/mL for seven or more days also indicate high risk. Impaired hepatic or renal function, pneumonia symptoms, severe mucositis, and allogeneic stem cell transplantation also categorize patients into high-risk groups.[99,100]

Initial empiric therapy consists of monotherapy with an antipseudomonal beta-lactam agent. Cefepime, meropenem, or piperacillin-tazobactam represent standard options. Routine vancomycin inclusion is not recommended, and it is reserved for specific indications, including suspected catheter-related infections, soft-tissue infections, or hemodynamic instability. Tailored coverage targets resistant organisms based on colonization history. Protocols dictate the early addition of vancomycin, linezolid, or daptomycin for MRSA. Linezolid or daptomycin provides coverage for vancomycin-resistant Enterococci (VRE), and early carbapenem use targets ESBLs. Polymyxin-colistin or novel beta-lactam combinations cover Klebsiella pneumoniae carbapenemase (KPC) producers.[100]

Antimicrobial stewardship is critical and requires timely de-escalation to narrower-spectrum agents once susceptibility profiles return. Protocols endorse shorter antibiotic courses and rapid discontinuation when infection is ruled out.[39] Systemic guidelines stratify cancer patients into low, intermediate, and high overall infection risk categories to guide precise bacterial, fungal, and viral prophylaxis.[99] Non-neutropenic cancer patients face distinct infectious challenges. Chemotherapy and radiation disrupt the mucosal barrier, allowing local flora invasion.[101] Targeted

therapies, including kinase inhibitors, compromise host immunity.[98] Central venous catheters serve as primary portals of entry for skin flora and biofilm formation.[97] Source control demands the prompt removal of infected intravascular access devices, which is essential among cancer patients presenting with shock.[101]

8.4 Postoperative Patients

The adjusted overall incidence of postoperative sepsis is 1.84%, but risk varies depending on procedure type and patient factors.[102] Early recognition in surgical wards remains difficult due to overlapping clinical signs. The normal postoperative systemic inflammatory response mimics early infectious sepsis.[103] Patient-related risk factors for postoperative sepsis include male gender, pre-existing heart failure, diabetes, and chronic kidney disease. Surgery-related factors include emergency surgery, peri-operative blood transfusion, and open surgery.[102]

Biomarker monitoring aids postoperative diagnosis. Procalcitonin measurement on postoperative day one provides strong diagnostic utility. A PCT cut-off of 1.1 ng/Ml yields 81% sensitivity and 72% specificity for septic complications. Combining this PCT cut-off with clinical SIRS criteria on day one achieves 100% sensitivity.[103]

Rapid source control is crucial and dictates survival outcomes. Early source control within 6 hours significantly reduces 90-day mortality. This survival benefit is most pronounced for gastrointestinal interventions and soft tissue debridement.[58] Delaying exploratory laparotomy steadily increases mortality risk with each passing hour.[58]

Fluid management in septic perioperative patients requires a balanced approach. SSC guidelines recommend dynamic measures like stroke volume assessment to guide fluid resuscitation. Balanced crystalloids are preferred over normal saline.[39,104]

Antimicrobials should be selected based on the surgical site, healthcare-associated pathogen risk, and antibiogram.[1] Finally, patients with prior broad-spectrum antibiotic exposure or prolonged healthcare contact require tailored, broad empiric coverage for multidrug-resistant pathogens.[4]

9 Outcomes and Quality Improvement

9.1 Mortality and Morbidity

Global epidemiological data highlight an escalating burden of sepsis. The 2021 Global Burden of Disease study estimates 166 million incident cases and 21.4 million sepsis-related deaths globally in 2021, accounting for 31.5% of total global deaths.[7] Earlier 2017 estimates reported 48.9 million cases and 11.0 million deaths, which shows an increase of sepsis cases from 2017 to 2021.[6] United States hospital data attribute more than one third of inpatient mortality to sepsis.[1]

Quality improvement programs significantly reduce sepsis mortality. A meta-analysis of 50 observational studies demonstrates a reduction in mortality associated with performance improvement initiatives.[105] Compliance with the Early Management Bundle (SEP-1) yields a 4.06% to 5.67% reduction in 30-day mortality among Medicare beneficiaries.[106]. The large SCREEN cluster randomized trial reports lower 90-day in-hospital mortality following electronic alerts combined with staff education.[4]

Sepsis survivors experience severe long-term morbidity. Older adults demonstrate an increase in moderate-to-severe cognitive impairment from 6.1% before hospitalization to 16.7% after sepsis.[1] Hospital readmission within 90 days affects approximately 40% of sepsis survivors.[1] Occupational disability is substantial, with 40% of a Norwegian cohort failing to return to work at 6 months.[1] Neurologic complications often occur during hospitalization, with septic encephalopathy complicating initial hospitalization in 36% of cases. Cognitive impairment persists in 30% of patients at 12 months.[107]

9.2 Length of Stay and Healthcare Costs

Sepsis generates substantial resource utilization and financial strain. United States healthcare costs for sepsis exceeded $38 billion in 2017. Sepsis represents the most expensive cause of hospitalization.[1]

Adherence to clinical pathways optimizes resource utilization. Complete SEP-1 bundle compliance shortens median hospital length of stay to 5 days compared to 6

days for non-compliant cases.[106] A single-center quality improvement program demonstrates an accelerated time to discharge of 25% after implementation, showing a hazard ratio of 1.25.[108]

Protocol adherence generates quantifiable financial benefits. A systematic review indicates sepsis bundle implementation decreases hospital costs in 66.7% of evaluated studies.[109] Compliance with a 3-hour bundle produces adjusted cost savings between $1,423 and $2,851 per patient.[110] Implementation of comprehensive multidisciplinary quality improvement programs demonstrates an absolute cost-saving of $272,646 for patients with suspected infection.[108]

9.3 Sepsis Bundles and Guideline Adherence

The SSC 2026 guidelines strongly recommend systematic performance improvement programs. These frameworks require sepsis screening for high-risk patients, standard operating procedures, and continuous quality improvement strategies. The guidelines conditionally suggest implementing “code sepsis” or “sepsis huddle” protocols, consisting of rapid bedside multidisciplinary responses triggered by positive sepsis screens.[4]

Standardized bundle execution directly impacts clinical outcomes. SEP-1 compliance requires lactate measurement, blood culture collection, broad-spectrum antibiotics, fluid administration, vasopressors, and clinical reassessment. Full SEP-1 compliance is associated with lower 30-day mortality.[106] Performance improvement programs significantly enhance protocol adherence. Such initiatives increase compliance with 6-hour bundles (OR 4.12) and 24-hour bundles (OR 2.57).[105]

Electronic health record interventions also reinforce bundle adherence. Electronic early warning flags combined with pharmacist notifications reduce time to antimicrobial therapy from 3 to 2.3 hours. This strategy increases days alive and out of the hospital at 28 days.[4] Dedicated sepsis response teams elevate bundle adherence from 4.6% to 32% and improve initial antibiotic appropriateness from 30% to 79%. Such rapid-response teams correlate with a hazard ratio of 0.64 for 14-day mortality.[71]

9.4 Training and education strategies for improving adherence to sepsis bundles

Effective bundle implementation requires structured multidisciplinary education. A systematic review of 32 studies indicates active learning approaches, such as simulation and game-based learning, yield superior knowledge gains compared to didactic teaching. Improvements in patient care and outcomes are associated with the existence of a hospital sepsis care bundle, which suggests that education and bundles based on protocols act synergistically.[111]

Simulation-based training accelerates clinical responses. The integration of mind mapping and in-situ simulation increases Hour-1 Bundle completion rates from 58.3% to 85.7%. This dual training approach significantly reduces diagnostic time and improves non-technical team skills among nurses.[112] Virtual telesimulation also builds robust interprofessional collaboration. Medical and nursing students demonstrate significant immediate improvements in sepsis knowledge and communication strategies following virtual training. Nursing students retain these educational gains at a 2-month follow-up evaluation.[113]

9.5 Future Perspectives and Innovative Approaches

Technological integration and targeted therapies shape the future of sepsis care. Artificial intelligence and machine learning improve early recognition capabilities. A meta-analysis of 42,623 patients reports a pooled AUROC of 0.89 for machine learning screening tools, outperforming traditional SIRS (0.70) and SOFA (0.78) models.[4] TREWS demonstrates that prompt provider confirmation of electronic alerts reduces mortality and shortens hospital stays.[71] However, algorithmic bias, false-positive rates, and limited external validation remain substantial barriers to widespread clinical implementation.[114]

Precision immunotherapy targets specific biological endotypes. The ImmunoSep clinical trial investigated anakinra for macrophage activation-like syndrome and recombinant interferon-gamma for sepsis-induced immunoparalysis. Precision immunotherapy improved organ dysfunction by day 9 compared with placebo. Target SOFA score reductions occurred in 35.1% of the treatment group versus 17.9% in the

placebo group.[115] This marks a transition toward precision medicine, where treatments are tailored to specific biomarkers, and clinical phenotypes.

Furthermore, resuscitation strategies continue to evolve toward customized physiologic targets. Evidence suggests a clinical shift toward fluid-sparing and less-invasive approaches, including early peripheral vasopressor administration, lower MAP targets of 60 to 65 mmHg in older patient demographics.[116]

Table 3. Summary of Key Gaps and Potential Solutions for sepsis care in medical wards

Gap	Evidence of Impact	Potential Solution
Delayed recognition	Ward-onset sepsis mortality 33-38% vs. 17-29% for ED-onset	NEWS/NEWS2 screening, "code sepsis" protocols
Low bundle compliance	SEP-1 adherence RR 0.33 for hospital-onset vs. community-onset	Multidisciplinary sepsis huddles, critical care outreach
Delayed lactate measurement	Only 32% timely on wards; delayed lactate → 29% mortality	Point-of-care lactate on wards, automated order sets
Alert fatigue	ESM: 18% alert rate, misses 67% of sepsis cases; 62.5% report fatigue	Machine learning models (AUROC 0.89), workflow-integrated alerts
Delayed ICU escalation	1.5% mortality increase per hour delay; ward-to-ICU HRR 1.35	SOFA-based triage thresholds, rapid response integration
Antibiotic timing	Median 3.5 hr on wards vs. 2.0 hr in ED	Pre-mixed antibiotics on ward floors, nurse-initiated protocols
Hemodynamic monitoring	Static measures poorly predict fluid responsiveness	POCUS training, dynamic measure protocols

10 Background

Despite major advances in critical care medicine, sepsis remains one of the leading causes of preventable death worldwide.[4] In 2021, an estimated 166 million incident cases of sepsis and more than 21 million sepsis-related deaths were reported globally, accounting for nearly one-third of all deaths worldwide.[7] Increasingly, sepsis occurs in patients with chronic non-infectious conditions, such as cardiovascular disease,

chronic obstructive pulmonary disease, liver cirrhosis, cancer, and other complex comorbidities, making its recognition and management more challenging than ever.[7]

Over the last two decades, substantial efforts have been devoted to improving sepsis care in emergency departments (EDs) and intensive care units (ICUs).[39] The implementation of protocolized management strategies and the Surviving Sepsis Campaign (SSC) bundles has significantly improved the timeliness of diagnosis and treatment in these settings.[4,39] Consequently, the greatest opportunity for further improvement in sepsis outcomes may no longer reside in critical care environments but rather in general medical wards, where most hospitalized patients with sepsis are managed and where important implementation gaps persist.[53]

Recognition of sepsis in medical wards is intrinsically challenging.[94] Patients are often older, frail, and affected by multiple chronic diseases, while clinical manifestations may be subtle, atypical, or masked by ongoing therapies.[94] Compared with EDs and ICUs, vital signs are monitored less frequently, access to advanced hemodynamic assessment is limited, and deterioration may go unrecognized for prolonged periods.[53] As a result, hospital-onset sepsis is consistently associated with delayed diagnosis, lower adherence to evidence-based interventions, and worse clinical outcomes. [52,53]

Several studies have demonstrated that patients developing sepsis in hospital wards are substantially less likely to receive timely bundle-compliant care than those diagnosed in the ED.[53] Delays affect virtually every component of sepsis management, including lactate measurement, blood culture collection, early antimicrobial administration, fluid resuscitation, and escalation to higher levels of care.[53] Consequently, hospital-onset sepsis is associated with significantly higher mortality, with reported in-hospital mortality rates of 33.4%, compared with 16.8% among patients presenting from the community.[52]

The 2026 SSC guidelines emphasize the importance of early recognition systems, multidisciplinary sepsis response pathways, and prompt implementation of a structured sepsis bundle.[4] However, evidence regarding real-world adherence to these recommendations in non-critical care settings remains limited.[4,53] In particular, few

studies have comprehensively evaluated sepsis bundle implementation across medical wards while simultaneously examining its relationship with patient outcomes.

The present study was designed to address this knowledge gap by assessing adherence to the SSC sepsis bundle among patients with sepsis or septic shock admitted to medical wards of a tertiary-care university hospital. We evaluated compliance with individual bundle components, identified factors associated with bundle completion, and explored the impact of bundle adherence on clinically relevant outcomes, including mortality and hospital readmission. By identifying the principal barriers to timely sepsis management in medical wards, this study aims to provide the foundation for the development of a hospital-wide Sepsis Team and a standardized sepsis pathway capable of improving early recognition, accelerating treatment, and reducing sepsis-related morbidity and mortality.

11 Methods

11.1 Study Design and Setting

This cross-sectional prevalence study was conducted between April and June 2025 at the University Hospital Policlinico of Modena, Italy. The study aimed to evaluate the recognition and management of sepsis and septic shock among patients admitted to medical wards. Data were collected retrospectively from electronic health records and included cases of sepsis occurring either at hospital admission or during hospitalization.

11.2 Study Population

Adult patients (≥18 years) admitted to medical wards with a diagnosis of sepsis or septic shock according to contemporary international definitions were eligible for inclusion. The study population comprised patients managed in the General Internal Medicine Ward, Sub-Intensive Care Unit, Infectious Diseases Unit, Geriatric Ward, Oncology Ward, and Otorhinolaryngology Ward.

11.3 Data Collection and Definitions

Demographic characteristics included age, sex, dates of hospital admission and discharge, date of sepsis diagnosis, and vital status. Clinical parameters recorded at the time of sepsis recognition included heart rate, respiratory rate, body temperature, systolic and diastolic blood pressure, oxygen saturation (with or without supplemental oxygen), Glasgow Coma Scale score, serum lactate concentration, and mean arterial pressure (MAP).

The National Early Warning Score 2 (NEWS2) was calculated to assess the risk of clinical deterioration, while the Sequential Organ Failure Assessment (SOFA) score was calculated whenever sufficient data were available. Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI).

Data regarding limitations of care and proportionality-of-care decisions, when available, were collected from intensivist consultations.

Risk factors for multidrug-resistant (MDR) organisms were recorded, including chronic dialysis, presence of a central venous catheter, prosthetic joint, prosthetic heart valve, vascular graft, residence in a long-term care facility, previous MDR colonization or infection, immunosuppression, surgery within the preceding 30 days, indwelling urinary catheter, hospitalization within the previous 3 months, and antibiotic exposure during the previous 3 months.

Laboratory parameters collected at sepsis diagnosis included white blood cell count, neutrophil count, hemoglobin, platelet count, C-reactive protein (CRP), procalcitonin (PCT), serum glucose, creatinine, and bilirubin. Arterial blood gas parameters, when available, included pH, lactate concentration, PaO_2, $PaCO_2$, bicarbonate levels, and PaO_2/FiO_2 ratio.

Diagnostic and therapeutic interventions were assessed, including collection of blood and urine cultures, timing of blood culture acquisition in relation to antibiotic administration, imaging studies (chest radiography, abdominal ultrasound, and computed tomography), administration and timing of antimicrobial therapy, fluid

resuscitation, vasopressor support, cardiopulmonary resuscitation, and consultation by infectious diseases and intensive care specialists.

The suspected and subsequently confirmed source of infection was recorded. Microbiological data included pathogen identification from blood cultures and other clinical specimens, blood culture contamination, and antimicrobial susceptibility testing results.

Empirical antimicrobial therapy was evaluated according to local institutional guidelines. Antimicrobial treatment was classified as guideline-concordant or non-concordant and further categorized as appropriate, overtreatment, or undertreatment based on microbiological findings and local recommendations.

The sepsis bundle was considered completed when all of the following interventions were performed: serum lactate measurement, blood culture collection before antibiotic administration, initiation of empirical antimicrobial therapy, and administration of intravenous fluids when indicated. Bundle completion within 3 hours and within 6 hours from sepsis recognition was also assessed. The location of bundle implementation (Emergency Department versus medical ward) was recorded.

11.4 Outcomes

The primary composite outcome was defined as all-cause mortality within 30 days from sepsis diagnosis and/or unplanned hospital readmission for clinical reasons within 90 days after discharge from the index hospitalization.

Secondary outcomes included bundle completion, hospital length of stay, intensive care unit (ICU) admission, ICU length of stay, all-cause mortality within 90 days, and hospital readmission within 90 days.

11.5 Statistical Analysis

Categorical variables were summarized as frequencies and percentages, whereas continuous variables were reported as medians and interquartile ranges (IQRs). The distribution of continuous variables was assessed using the Shapiro–Wilk test.

Baseline characteristics were compared between patients who completed the sepsis bundle and those who did not. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate, whereas continuous variables were compared using the Mann–Whitney U test.

Univariable logistic regression analyses were performed to identify factors associated with the primary composite outcome. Variables with a p-value <0.05 in univariable analyses, together with variables considered clinically relevant based on previous evidence and expert judgment, were entered into a multivariable logistic regression model after assessment for collinearity. All selected variables were simultaneously entered using the enter method.

A second set of univariable and multivariable logistic regression analyses was conducted to identify factors independently associated with sepsis bundle completion. Variable selection and model construction followed the same approach described above.

Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs). All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA).

12 Results

12.1 Comparison between bundle completed and bundle not completed groups

Seventy-one patients were included, of whom 48 (68.6%) presented with sepsis at admission and 16 (22.5%) with septic shock. 56.3% of patients studied were males. The majority of patients (81.7%) were 65 or older, while only 18.3% were between 18-64 years old. 38 patients (53.5%) were managed in the internal medicine ward, 11 (15.5%) in the sub-intensive care unit, 8 (11.3%) in the infectious disease unit, 7 (9.9%) in the geriatric ward, 5 (7%) in the oncology unit, and 2 (2.8%) in the otorhinolaryngology ward. 8.6% of patients had a proportionality of care plan. Patients had a Charlson Comorbidity index (CCI) with a median of 5 (IQR 4-7), with 77.1% of

the total sample presenting with a CCI index ≥4. 42.3% of patients presented with 2 or more MDR risk factors, and 21.1% with more than 3 MDR risk factors. Data related to patients' characteristics can be observed in *Table 4*.

Table 4. Patient characteristics according to sepsis bundle completion

Characteristics		**Total (n=71)**	**Bundle completed n= 33 (47.1)**	**Bundle not completed n= 37 (52.9)**	**p-value**
Demographics. n (%)	**Age (years)**				
	18- 64	13 (18.3)	4 (12.1)	9 (24.3)	0.425
	65-84	42 (59.2)	21 (63.6)	21 (58.6)	
	85+	16 (22.5)	7 (18.9)	8 (24.2)	
	Gender				
	Male	40 (56.3)	19 (57.6)	21 (56.8)	1.00
Sepsis Care Setting, n (%)	Internal Medicine Ward	38 (53.5)	19 (57.6)	18 (48.6)	0.478
	Infectious Disease Unit	8 (11.3)	5 (13.5)	5 (13.5)	
	Geriatric ward	7 (9.9)	3 (9.1)	4 (10.8)	
	Oncology Unit	5 (7.0)	**1 (3.0)**	**4 (10.8)**	
	Surgery	2 (2.8)	0	2 (5.4)	
	Sub-Intensive care Unit	11 (15.5)	7 (21.2)	4 (10.8)	
Sepsi at admission, n (%)		48 (68.6)	22 (66.7)	26 (70.3)	0.800
Proportionality of care patients, n (%)		13 (8.6)	7 (21.9)	6 (16.2)	0.759
Charlson Comorbidity index, median [IQR]		5.0 [4 -7]	5 [2]	5 [5]	0.771
Charlson Comorbidity index ≥4, n (%)		54 (77.1)	29 (87.9)	25 (67.6)	**0.051**
Extrinsic Risk factors	Dialysis	2 (2.8)	0	2 (5.4)	0.494
	Central venous catheter	5 (7.0)	2 (6.1)	3 (8.1)	1.00
	Prosthetic joint	8 (11.3)	5 (15.2)	3 (8.1)	0.462
	Vascular graft	8 (11.3)	4 (12.1)	4 (10.8)	1.00
	Nursing home resident	2 (2.8)	1 (3.0)	1 (2.7)	1.00
	Prosthetic valve	5 (7.0)	2 (6.1)	3 (8.1)	1.00
	MDR colonization	4 (5.6)	2 (6.1)	2 (5.4)	1.00
	Immunocompromised	18 (25.4)	7 (21.2)	11 (29.7)	0.585
	Recent surgery (<30 days)	6 (8.5)	2 (6.1)	4 (10.8)	0.677
	Urinary Catheter	7 (9.9)	4 (12.1)	3 (8.1)	0.699
2+ Risk MDR		30 (42.3)	13 (39.4)	17 (45.9)	0.713
3+ Risk MDR		15 (21.1)	5 (15.2)	10 (27)	0.258

**MDR: multi-drug resistance; IQR: interquartile range*

The sepsis bundle was completed in 33 patients (47.1%) and not completed in 37 patients (52.9%). Age and gender distributions showed no statistically significant differences between the two groups, with the 65-84 age bracket being the most represented overall (59.2%). The most represented care setting in the cohort was the Internal Medicine ward, which accounted for more than half of all cases (38/71; 53.5%). This setting also contributed the largest proportion of patients in whom the sepsis bundle was completed (19/33; 57.6%), confirming its central role in the implementation of sepsis management protocols within medical wards. The Infectious Diseases Unit represented a smaller but still relevant proportion of the cohort (8/71; 11.3%), with a relatively balanced distribution between bundle completion and non-completion.

The remaining care settings contributed less frequently to the overall population. The Geriatric and Oncology wards accounted for 9.9% and 7.0% of cases, respectively, while surgical wards represented a marginal proportion (2.8%). Across these settings, bundle completion appeared less consistent, particularly in oncological and surgical patients, where a higher proportion of cases did not achieve full bundle implementation. Overall, these findings highlight a heterogeneous pattern of sepsis bundle adherence across hospital wards, with higher performance observed in Internal Medicine and Infectious Diseases units compared with surgical and oncological settings. A Charlson Comorbidity Index ≥4 was more prevalent in the bundle completed group (87.9% vs 67.6%, p=0.051). Data regarding clinical presentation can be observed in *Table 5*.

Table 5. Clinical presentation according to sepsis bundle completion

Characteristics		**Total (n=71)**	**Bundle completed n= 33 (47.1)**	**Bundle not completed n= 37 (52.9)**	**p-value**
Vitals at sepsis presentation	Heart rate, median [IQR]	97 [84.5 - 111.3]	100 [28]	94.5 [28]	0.847
	Respiratory rate, median [IQR]	18 [18 - 18]	18 [0]	18 [0]	0.219
	Body Temperature, median [IQR]	37.6 [36.2 - 38.2]	38 [2.3]	37.4 [2.1]	0.316
	Febrile (≥37.5°C)	38 (54.3)	21 (63.6)	17 (47.2)	0.227

	Mean arterial pressure,	88.3 [70 - 102.8]	73.3 [33]	94 [21]	**<0.001**
	Hypotension, n (%)	23 (32.9)	19 (57.6)	4 (11.1)	**<0.001**
	Septic Shock, n (%)	16 (22.5)	16 (48.1)	0	**<0.001**
	SpO2, median [IQR]	94 [92 - 96]	93 [4]	95 [3]	**0.004**
	GCS, median [IQR]	15 [12 - 15]	15 [6]	15 [1]	0.157
	Serum lactate > 2 mmol/l, n (%)	18 (43.9)	16/31 (51.6)	2 / 10 (20)	0.142
Emato-Chemistry values, median [IQR]	WBC (× 10^3/µL),	10.3 [7.6 - 16.7]	19.0 [11.3]	7.9 [18.7]	0.782
	Neutrophils (× 10^3/µL)	8.8 [6.1 - 14.8]	16.9 [10.3]	6.5 [18.7]	0.941
	Haemoglobin (g/dl)	11.9 [10 -13.2]	12.8 [2.2]	10.7 [2.2]	0.902
	Platelet (× 10^3/µL)	187 [114 - 295]	228 [405]	145 [195]	0.819
	Procalcitonin (ng/ml)	2.9 [0.8 - 11.7]	196.5 [486]	1.05 [2.8]	**0.024**
	CRP (mg/dl)	2.9 [5.9 - 21.3]	35.8 [28.6]	16.1 [10.4]	0.335
	Blood glucose (mg/dl),	126 [99 -161]	134 [100]	100 [60]	0.484
	Creatinine (mg/dl),	1.2 [0.9 - 2]	1.29 [1.2]	1.05 [0.75]	**0.025**
	Bilirubin (mg/dl)	1.3 [0.7 - 3.9]	1.05 [0.8]	0.93 [0.47]	0.709
Severity score	NEWS2 score, median [IQR]	5 [4 - 7.3]	6.5 [3]	4 [2]	**<0.001**
	NEWS2 ≥7	22 (31.4)	18 (54.5)	4 (11.1)	**<0.001**
	SOFA score available, n (%)	44 (62.9)	22 (66.7)	22 (59.5)	0.623
	SOFA score, median [IQR]	4 [3.0 - 5.8]	4 [4]	3 [1]	**0.026**
	SOFA score ≥4	26/45 (57.8)	16 / 22 (72.7)	10/23 (43.5)	**0.071**
Infection type	Lung, n (%)	14 (19.7)	5 (15.2)	9 (24.3)	0.384
	Urinary tract, n (%)	32 (45.1)	20 (60.6)	11 (29.7)	**0.015**
	Biliary, n (%)	3 (4.2)	1 (3.0)	2 (5.4)	1.00
	Abdominal, n (%)	7 (9.9)	2 (6.1)	5 (13.5)	0.434
	Bone and Joint, n (%)	2 (2.8)	1 (3.0)	1 (2.7)	1.00
	Skin and soft tissue, n (%)	8 (11.3)	4 (12.1)	4 (10.8)	1.00
	Other, n (%)	5 (7.0)	2 (6.1)	3 (8.1)	1.00
	Unknown, n (%)	4 (5.6)	1 (3.0)	3 (8.1)	0.616

**GCS: Glasgow Coma Scale; WBC: White Blood Cells; CRP: C-reactive protein; NEWS: National Early Warning Score; SOFA: Sequential Organ Failure Assessment.*

Vital signs at presentation varied significantly between the two cohorts. The median mean arterial pressure (MAP) was 73.3 mmHg (IQR 33) in the bundle completed group compared to 94 mmHg (IQR 21) in the non-completed group ($p<0.001$). Hypotension was observed in 57.6% of the bundle completed group versus 11.1% of the non-completed group ($p<0.001$), and septic shock was present in 48.1% of the completed group compared to 0% in the non-completed group ($p<0.001$).

The median NEWS2 score was higher in the bundle completed group (6.5 IQR 3 versus 4.0 IQR 2, $p<0.001$), with a NEWS2 score ≥7 recorded in 54.5% of the completed group compared to 11.1% of the non-completed group ($p<0.001$).

Serum lactate was measured in 57.7% of patients, with lactate >2 mmol/L observed more frequently among bundle-completed patients (51.6% vs. 20.0%; $p=0.142$). Haemato-chemistry values from *Table 5* showed a higher median procalcitonin (PCT) in the completed group (196.5 ng/ml IQR 486 vs 1.05 ng/ml IQR 2.8, $p=0.024$) and a higher median creatinine level (1.29 mg/dl IQR 1.2 vs 1.05 mg/dl IQR 0.75, $p=0.025$). With the data collected, it was possible to calculate the SOFA score for 44 patients (62.9%). The median SOFA score was higher in the completed group (4 IQR 4 vs 3 IQR 1, $p=0.026$). Specifically, of the 26 patients (57.8% of the total sample) presenting a SOFA score ≥4, 16 were among the sepsis bundle completed (making up 72.7% of this group), and 10 among the not completed group (50%) ($p=0.071$).

Regarding the source of infection, the most frequent site was the urinary tract (32 patients, 45.1%), followed by lungs (14 patients, 19.7%). Urinary tract infections were more frequent in the bundle completed group (60.6% vs 29.7%, $p=0.015$).

Bundle performance outcomes

Table 6. Sepsis care process adherence according to sepsis bundle completion

Characteristics		**Total (n=71)**	**Bundle completed n=33 (47.1)**	**Bundle not completed n=37 (52.9)**	**p-value**
Sepsis bundle performance	Bundle completed within 3 hours, n (%)	26 (37.1)			-
	Bundle completed within 6 hours, n (%)	32 (45.7)			-
Location of sepsis bundle execution n (%)	Sepsis bundle started in the ED	15 (25.9)			-
	Sepsis bundle performed in medical ward,	43 (74.1)			-
Sepsis performance	Respiratory rate recorded	19 (26.8)			-
	Lactate measured	41 (57.7)	31 (93.9)	10 (27)	**<0.001**
	Arterial blood gas (ABG) performed	37 (52.1)	29/29 (100)	8 / 8 (100)	-
	SOFA score calculated	44 (62)	22 (66.7)	22 (59.5)	0.623
	Procalcitonin (PCT) measured	14 (19.7)	4 (12.1)	10 (27)	0.144
	Bilirubin measured	54 (76.1)	23 (69.7)	30 (81.1)	0.403
	Blood cultures	68 (95.8)	33 (100)	34 (91.9)	0.242
	Blood cultures pre-antibiotic therapy	66 (93)			
	Urine cultures	55 (75.0)	29 (87.9)	25 (67.6)	**0.051**
	Chest X-Ray	52 (73.2)	28 (84.8)	23 (62.2)	**0.058**
	Abdominal ultrasound	28 (39.4)	11 (33.3)	16 (43.2)	0.465
	CT scan	11 (15.5)	4 (12.1)	7 (18.9)	0.522
	Antibiotic administered	71 (100)	33 (100)	37 (100)	-
	Antibiotic given within 1 hour	30 (42.9)	17 (51.5)	13 (35.1)	0.227
	Antibiotic given within 3 hours	49 (70)	26 (78.8)	23 (62.2)	0.192
	Antibiotic given within 6 hours	64 (91.4)	32 (97)	32 (86.5)	0.203
	Fluid challenge	54 (76.1)	33 (100)	21 (56.7)	**<0.001**

	Vasopressors		9 (12.7)	8 (24.2)	1 (2.7)	**0.010**
	Intensivist evaluation		14 (19.7)	9 (27.3)	5 (13.5)	0.231
	ID evaluation		40 (56.3)	15 (45.5)	25 (67.6)	0.090
Antibiotic administration	Type of antibiotic	Amoxicillin/ clavulanate	4 (5.7)	1 (3.0)	3 (8.1)	0.616
		Ampicillin	2 (2.9)	1 (3.0)	1 (2.7)	1.00
		Ceftriaxone	13 (18.6)	3 (9.1)	10 (27)	**0.069**
		Piperacillin/tazobactam	44 (62.9)	28 (84.8)	16 (43.2)	**<0.001**
		Meropenem	5 (7.1)	2 (6.1)	3 (8.1)	1.00
		Carbapenems	6 (8.6)	2 (6.1)	4 (10.8)	0.677
		Azithromycin	7 (10)	2 (6.1)	5 (13.5)	0.434
		Clindamycin	1 (1.4)	0	1 (2.7)	1.00
		Vancomycin	2 (2.9)	1 (3.0)	1 (2.7)	1.00
		Daptomycin	6 (8.6)	2 (6.1)	4 (10.8)	0.677
		Tigecycline	1 (1.4)	0	1 (2.7)	1.00
		Teicoplanin	1 (1.4)	0	1 (2.7)	1.00
		Fosfomycin	1 (1.4)	0	1 (2.7)	1.00
		Linezolid	4 (5.7)	3 (9.1)	1 (2.7)	0.337
	Antibiotic association		23 (32.4)	10 (30.3)	13 (35.1)	0.800
	Antibiotic therapy appropriate according to guidelines		55/65 (84.6)	23/29 (79.3)	32/36 (88.9)	0.321
	Microbiologic isolate cultured		60 (84.5)	28 (84.8)	31 (83.8)	1.00
	Blood culture isolated pathogen, n (%)	E. coli	16 (23.2)	6/ 33 (18.2)	10/35 (28.6)	0.396
		Klebsiella pneumoniae	10 (14.5)	5 / 33 (5.3)	5/35 (14.3)	1.00
		Other Enterobacteriaceae	3 (4.3)	4/ 33 (12.1)	0	**0.047**
		Staphylococcus aureus	6 (8.5)	3 / 33 (9.1)	3 / 35 (8,1)	1.00
		Streptococcus spp.	4 (5.6)	2 / 33 (6.1)	2 / 35(5.7)	1.00
		CoNs	3 (4.2)	0	3 / 35 (8.1)	0.240
		Enterococcus spp	1 (1.4)	0	1 / 35 (1.5)	1.00
		Others	2 (2.8)	1 /33 (3.0)	1 / 35 (1.5)	1.00
		None	25 (36.2)	13 (39.4)	12 (34.3)	0.802

		Polymicrobial	3 (4.3)	1 / 33 (3.0)	2 /35 (5.6)	1.00
	Other sample isolated pathogens, n (%)	E. coli	13 (24.5)	5/ 24 (20.8)	8/27 (29.6)	0.534
		Klebsiella pneumoniae	15 (30.6)	7/ 24 (29.2)	8/27 (29.6)	1.00
		Other Enterobacteriaceae	6 (11.5)	4 /24 (16.7)	1 /27 (3.7)	0.175
		Pseudomonas aeruginosa	5 (11.7)	2 /24 (8.3)	3/27 (11.1)	1.00
		Staphylococcus aureus	3 (5.8)	2 /24 (8.3)	1 /27 (3.7)	0.595
		Enterococcus spp	5 (9.6)	2 /24 (8.3)	3/27 (11.1)	1.00
		Other	3 (5.8)	3/24 (12.5)	0 /27 (0)	0.097
		Polymicrobials	14 (26.9)	7/24 (29.2)	6/27 (22.2)	0.749
		None, n (%)	11 (21.2)	3/24 (12.5)	8/27 (29.6)	0.182
	Resistance mechanism	MRSA	5 (8.5)	1 (3.6)	4 (12.1)	0.363
		ESBL	11 (18)	6 (21.4)	5 (15.2)	0.740
		None	45 (73.8)	21 (75)	24 (72.7)	1.00
	Effective therapy according to antibiogram		45/55 (81.8)	20/26 (80.8)	25/29 (86.2)	0.490
	Effective therapy within 1 hour		22/55(40)	13 /26 (50)	9 / 29 (31)	0.178
	Effective therapy within 3 hours		35/55 (63.6)	17/26 (65.4)	18/29 (62.1)	1.00
	Effective therapy within 6 hours		42/55 (76.4)	20/26 (76.9)	22/29 (75.9)	1.00
	Appropriate therapy according to antibiogram		23/55(41.8)	6 (23.1)	17 (58.6)	**0.013**
	Correct identification of infective focus		55/67 (82.1)	27/31 (87.1)	28/36 (77.8)	0.359
	Contaminated blood cultures		7/ 67 (10.4)	2 / 31 (6.5)	5/35 (14.3)	0.433
	Undertreatment based on guidelines		8/ 55 (14.5)	5/26 (19.2)	3/29 (10.3)	0.455
	Overtreatment based on guidelines		23/55 (41.8)	14/26 (53.8)	9 / 29 (31)	0.107

**ABG: Arterial Blood Gas; SOFA: Sequential Organ Failure Assessment; PCT: Procalcitonin; CT: Computed Tomography; ID: infectious diseases; CoNs: Coagulase-Negative Staphylococci; MRSA:Methicillin-resistant Staphylococcus aureus; ESBL: Extended.spectrum beta-lactamase.*

Overall, adherence to recommended sepsis care processes was heterogeneous and only partially achieved across the cohort (*Table 6*). Regarding bundle implementation, 37.1% of patients achieved full bundle completion within 3 hours, while 45.7% completed the bundle within 6 hours. Bundle execution was predominantly initiated in medical wards (74.1%) rather than in the emergency department (25.9%).

Lactate measurement was significantly more frequent among patients in whom the sepsis bundle was completed (93.9% vs. 27.0%; $p<0.001$). Similarly, fluid challenge and vasopressor use was higher in the bundle-completed group ($p=0.010$ and <0.001, respectively), reflecting a greater proportion of patients with more severe clinical presentations in this subgroup. In contrast, no significant differences were observed for most other diagnostic and therapeutic interventions, including SOFA score calculation, biomarker use (PCT, bilirubin), imaging studies, and timing of antibiotic administration within 1, 3, or 6 hours.

Microbiological evaluation was overall high across the cohort, with blood cultures obtained in 95.8% of cases and a high rate of pathogen identification from blood and other clinical samples. Antibiotic therapy was universally administered, most commonly piperacillin/tazobactam, which was significantly more frequently used in the bundle-completed group (84.8% vs. 43.2%; $p<0.001$). No major differences were observed in microbiological yield and resistance patterns.

Among the 55 patients for whom microbiological susceptibility data were available, effective antimicrobial therapy according to the antibiogram was administered in 81.8% of cases, with no significant difference between the bundle-completed and bundle-not-completed groups (80.8% vs. 86.2%, $p=0.490$). Similarly, the proportion of patients receiving effective therapy within 1 hour (50.0% vs. 31.0%, $p=0.178$), 3 hours (65.4% vs. 62.1%, $p=1.00$), and 6 hours (76.9% vs. 75.9%, $p=1.00$) did not differ significantly between groups. In contrast, appropriate antimicrobial therapy according to the antibiogram was significantly less frequent in patients who completed the bundle compared with those who did not (23.1% vs. 58.6%, $p=0.013$). Correct identification of the infective focus was achieved in 82.1% of evaluable patients and was comparable between groups (87.1% vs. 77.8%, $p=0.359$). Blood culture contamination occurred in

10.4% of cases, with no significant difference between bundle-completed and bundle-not-completed patients (6.5% vs. 14.3%, p=0.433).

Guideline-discordant antimicrobial prescribing was common. Undertreatment occurred in 14.5% of patients and did not differ significantly between groups (19.2% vs. 10.3%, p=0.455). Overtreatment was observed in 41.8% of patients overall, occurring more frequently among bundle-completed patients (53.8% vs. 31.0%), although this difference did not reach statistical significance (p=0.107).

Clinical outcomes

Bundle completion was not associated with statistically significant differences in hospital length of stay, ICU utilization, or mortality outcomes in this cohort (*Table 7*).

Overall, the median duration of hospital stay was 18 days (IQR 9-18). 6 patients (8.5%9 were admitted to the ICU, with a median length of stay of 6 (IQR 2-10).

Table 7. Clinical outcomes according to sepsis bundle completion status

Characteristics		**Total (n=71)**	**Bundle completed n= 33 (47.1)**	**Bundle not completed n= 37 (52.9)**	**p-value**
Outcomes	Duration of hospital stay, median [IQR]	18 [9 -28]	18 [15]	17 [24]	0.916
	ICU admission, n (%)	6 (8.5)	3 (9.1)	3 (8.1)	1.00
	ICU days, median [IQR]	5.5 [2 -10]	18 [15]	17 [24]	0.837
	All cause 30-day mortality	11 (15.5)	5 (15.2)	6 (16.2)	1.00
	All cause 90-day mortality	22 (31)	11 (33.3)	11(29.7)	0.800
	New hospital admission within 90 days	19 (26.8)	7 (21.2)	12 (32.4)	0.420

**IQR: interquartile range; ICU: intensive care unit.*

Clinical outcomes were overall comparable between patients with completed and non-completed sepsis bundles. The median length of hospital stay was similar in the two groups (18 [IQR 15–28] days overall), with no significant difference observed between patients who completed the bundle and those who did not (p=0.916). Rates of ICU

admission were low and did not differ between groups (9.1% vs. 8.1%; p=1.00), as well as ICU length of stay, which showed no significant variation between cohorts. Similarly, short- and medium-term mortality outcomes were comparable: 30-day all-cause mortality was 15.2% in the bundle-completed group versus 16.2% in the non-completed group (p=1.00), while 90-day mortality was 33.3% and 29.7%, respectively (p=0.800).

No significant differences were also observed in post-discharge outcomes, with a 90-day hospital readmission rate of 21.2% in patients with completed bundle compared with 32.4% in those withPout bundle completion (p=0.420).

12.2 Predictors of primary outcome

Table 8. Predictors of the composite outcome (30-day mortality and 90-day readmission): univariable and multivariable analysis

Characteristics		**Univariate**		**Multivariate**	
		OR	**p-value**	**aOR**	**p-value**
Demographics	**Age ≥75 years**	2.89 (1.05 - 8.0)	**0.041**	15.6 (2.2 - 110.5)	**0.006**
	Gender (male)	1.49 (0.57 - 3.9)	0.419		
Sepsis Care Setting	Internal Medicine	0.86 (0.34 - 2.29)	0.801		
	Infectious Diseases	1.52 (0.35 - 6.64)	0.578		
	Geriatric	1.1 (0.23 - 5.31)	0.909		
	Oncology	0.96 (0.15 - 6.16)	0.968		
	Surgery	1.46 (0.09 - 24.4)	0.790		
	Sub-Intensive Care Unit	0.80 (0.21 - 3.03)	0.743		
Sepsi at admission		0.66 (0.24 - 1.79)	0.409		
Proportionality of care patients		4.16 (1.14 - 15.2)	**0.031**	3.68 (0.44 - 30.7)	0.229
Charlson Comorbidity index		1.24 (0.996 - 1.54)	**0.054**	1.14 (0.79 - 1.63)	0.483
2+ Risk MDR		3.16 (1.18 - 8.5)	**0.022**		
3+ Risk MDR		3.9 (1.16 - 13.03)	**0.027**	3.2 (0.52 - 20.1)	0.208
Vitals at sepsis presentation	Heart rate	0.99 (0.97 - 1.01)	0.367		
	Respiratory rate	1.42 (0.87 - 2.31)	0.159		

	Febrile (≥37.5°C)	0.6 (0.23 - 1.55)	0.283		
	Mean arterial pressure	1.01 (0.98 - 1.03)	0.542		
	Hypotension	1.24 (0.45 - 3.41)	0.678		
	Septic Shock	1.17 (0.38 - 3.6)	0.788		
	SpO2	1.01 (0.88 - 1.16)	0.900		
	GCS	0.89 (0.76 - 1.03)	0.106		
	Serum lactate > 2 mmol/l	0.55 (0.15 - 1.96)	0.352		
Emato-Chemistry values	WBC (× 10^3/μL), median [IQR]	0.96 (0.9 - 1.03)	0.259		
	Neutrophils (× 10^3/μL), median [IQR]	0.96 (0.9 - 1.04)	0.325		
	Platelet (× 10^3/μL) , median [IQR]	1.0 (0.99 - 1.01)	0.341		
	Procalcitonin (PCT) (ng/ml), median [IQR]	0.86 (0.59 - 1.26)	0.439		
	CRP (mg/dl), median [IQR]	0.96 (0.91 - 1.0)	**0.059**	0.95 (0.9 - 1.02)	0.152
	Blood glucose (mg/dl), median [IQR]	0.99 (0.98 - 1.00)	0.203		
	Creatinine (mg/dl), median [IQR]	0.89 (0.56 - 1.4)	0.609		
	Bilirubin (mg/dl), median [IQR]	1.0 (1.0 - 1.01)	0.160		
Severity score	NEWS2 score	1.1 (0.9 - 1.3)	0.308		
	NEWS2 ≥7	1.34 (0.5 - 3.86)	0.529		
	SOFA score	0.98 (0.77 - 1.24)	0.849		
	SOFA score ≥4	0.96 (0.3 - 3.45)	0.954		
Infection type	Lung	2.29 (0.7 - 7.49)	0.172		
	Urinary tract	0.29 (0.1 - 0.79)	**0.016**	0.13 (0.02 - 0.8)	**0.028**
	Biliary	-	0.999		
	Abdominal	0.548 (0.1 - 3.04)	0.492		
	Other	0.96 (0.15 - 6.16)	0.968		
	Unknown	4.73 (0.47 - 47.9)	0.188		
Sepsis performance	Lactate measured	1.06 (0.41 - 2.77)	0.901		
	SOFA score calculated	0.37 (0.14 - 1.0)	**0.051**	0.84 (0.22 - 3.25)	0.797

	Procalcitonin (PCT) measured	0.63 (0.19 - 2.04)	0.439		
	Bilirubin measured	0.52 (0.17 - 1.57)	0.248		
	Blood cultures	0.33 (0.03 - 3.81)	0.374		
	Blood cultures pre-antibiotic therapy	0.43 (0.07 - 2.77)	0.377		
	Urine cultures	0.86 (0.28 - 2.64)	0.788		
	Chest X-Ray	0.69 (0.24 - 2.00)	0.500		
	Abdominal ultrasound	0.55 (0.2 - 1.47)	0.231		
	CT scan	0.8 (0.21 - 3.03)	0.743		
	Antibiotic given within 1 hour	0.55 (0.21 - 1.47)	0.236		
	Antibiotic given within 3 hours	0.53 (0.19 - 1.49)	0.226		
	Antibiotic given within 6 hours	0.68 (0.13 - 3.66)	0.657		
	Fluid challenge	1.92 (0.59 - 6.21)	0.276		
	Vasopressors	2.0 (0.48 - 8.11)	0.343		
	Intensivist evaluation	2.27 (0.7 - 7.49)	0.172		
	ID evaluation	1.9 (0.72 - 5.04)	0.197		
	Absence of microbiological isolates	4.53 (1.63 -12.6)	**0.04**	9.37 (1.9 - 45.5)	**0.006**
	Sepsis bundle completed	0.67 (0.26 - 1.76)	0.417		
	Effective therapy according to antibiogram	2.2 (0.42 - 11.7)	0.352		
	Effective therapy within 1 hour	0.45 (0.13 - 1.53)	0.202		
	Effective therapy within 3 hours	0.85 (0.27 - 2.72)	0.786		
	Effective therapy within 6 hours	1.143 (0.29 - 4.3)	0.863		
	Appropriate therapy according to antibiogram	1.17 (0.38 - 3.7)	0.783		
	Correct identification of infective focus	0.41 (0.11 - 1.46)	0.167		
	Undertreatment	0.25 (0.03 - 2.23)	0.215		
	Overtreatment based on guidelines	1.17 (0.38 - 3.6)	0.783		

**MDR: multi-drug resistance; GCS: Glasgow Coma Scale; WBC: White Blood Cells; IQR: interquartile range; PCT: Procalcitonin; CRP: C-reactive protein; NEWS: National Early Warning Score; SOFA: Sequential Organ Failure Assessment; CT: Computed Tomography; ID: infectious diseases.*

In univariable analysis, age ≥75 years (OR 2.89, 95% CI 1.05–8.00; p=0.041), proportionality-of-care status (OR 4.16, 95% CI 1.14–15.2; p=0.031), the presence of ≥2 MDR risk factors (OR 3.16, 95% CI 1.18–8.50; p=0.022), and ≥3 MDR risk factors (OR 3.90, 95% CI 1.16–13.03; p=0.027) and absence of microbiological isolates (OR 4.53, 95% CI 1.63-12.6, p=0.04) were associated with an increased risk of the composite endpoint. Conversely, urinary tract infection and SOFA score calculated (OR 0.37, 95% CI 0.14-1.0, p=0.051) was associated with a significantly lower risk of adverse outcome (OR 0.29, 95% CI 0.10–0.79; p=0.016). No significant associations were observed for sepsis severity indicators, physiological parameters at presentation, laboratory biomarkers, SOFA score, or care setting.

In the multivariate analysis, age ≥75 years remained a strong, independent risk factor (aOR 15.6; 95% CI 2.2-110.5, p=0.006). Similarly, having no pathogen isolated in blood cultures (culture-negative sepsis) independently increased the risk of the composite outcome (aOR 9.37; 95% CI 1.9-45.5, p=0.006). A urinary tract infection was confirmed an independent protective factor for the composite outcome (aOR 0.13; 95% CI 0.02-0.8, p=0.028).

12.3 Predictors of bundle completion

A second univariate analysis (*Table 9*) was performed assessing predictors of successful sepsis bundle completion identified several clinically relevant variables. Hemodynamic and severity markers were significantly associated with bundle completion, including lower mean arterial pressure (OR 0.95, 95% CI 0.93–0.98; p=0.001), hypotension (OR 10.86, 95% CI 3.12–37.8; p<0.001), and a NEWS2 score ≥7 (OR 9.60, 95% CI 2.70–33.30; p<0.001). A SOFA score ≥4 showed a borderline association (OR 3.47, 95% CI 0.99–12.10; p=0.051), while serum lactate >2 mmol/L did not reach statistical significance (OR 4.27, 95% CI 0.78–23.40; p=0.095).

Regarding infection characteristics and diagnostic workup, urinary tract infection was significantly associated with higher odds of bundle completion (OR 3.64, 95% CI 1.39–9.81; p=0.011). Similarly, performance of urine cultures (OR 3.48, 95% CI 0.99–12.20; p=0.051) and chest X-ray (OR 3.41, 95% CI 1.07–10.80; p=0.038) were positively associated with bundle adherence in the univariate model.

However, in the subsequent multivariable analysis, these associations were attenuated and no longer retained statistical significance, suggesting that the observed univariate relationships were largely influenced by confounding clinical severity and presentation patterns.

Table 9. univariate and multivariate analysis: sepsis bundle completed

Characteristics		**Univariate**		**Multivariate**	
		OR	**p-value**	**aOR**	**p-value**
Demographics	**Age ≥75 years**	1.03 (0.4 - 2.67)	0.945	2.36 (0.1 - 55.9)	0.595
Vitals at sepsis presentation	Mean arterial pressure	0.95 (0.93 - 0.98)	**0.001**	0.97 (0.88 - 1.07)	0.507
	Hypotension	10.86 (3.12 - 37.8)	**< 0.001**		
	Serum lactate > 2 mmol/l	4.27 (0.78 - 23.4)	**0.095**	3.9 (0.08 - 185.6)	0.487
Severity score	NEWS2 score	1.55 (1.21 - 1.9)	**<0.001**		
	NEWS2 ≥7	9.6 (2.7 - 33.3)	**<0.001**	6.39 (0.17 - 245.2)	0.319
	SOFA score	1.47 (1.05 - 2.06)	**0.027**		
	SOFA score ≥4	3.47 (0.99 - 12.1)	**0.051**	0.41 (0.02 - 10.1)	0.585
Infection type	Urinary tract	3.64 (1.39 - 9.81)	**0.011**	10.4 (0.53 - 206)	0.123
Sepsis performance	Urine cultures	3.48 (0.99 - 12.2)	**0.051**		
	Chest X-Ray	3.41 (1.07 - 10.8)	**0.038**	-	0.99

13 Discussion

The main findings of this study highlight significant implementation gaps in the early management of sepsis within non-critical care medical wards. The primary objective of this research was to systematically evaluate adherence to the 2026 Surviving

Sepsis Campaign (SSC) and analyze its impact on clinical outcomes to inform the development of a hospital-wide Sepsis Team.[4]

This study's results reveal dramatically low overall adherence to standardized sepsis protocols in the medical wards. Out of the total cohort of 71 patients, complete sepsis bundle execution was achieved in only 33 patients (47.1%), and a mere 26 patients (37.1%) received the full bundle within the recommended 3-hour window *(Table 6).* Timing in antimicrobial administration proved to be a critical bottleneck: antibiotics were administered within the crucial 1-hour window in only 30 cases (42.9%), although 64 patients (91.4%) eventually received them within 6 hours *(Table 6).* Furthermore, the most glaring diagnostic omission was the failure to measure serum lactate in 42.3% of the cohort, meaning it was performed only for 41 patients (57.7%) *(Table 6).*

These findings confirm existing literature evaluating hospital-onset and ward-based sepsis, which consistently demonstrates that medical wards struggle to deliver protocolized care. This study's 47.1% bundle completion rate, while suboptimal, is actually higher than some international reports; for instance, a multi-year point-prevalence study across Wales reported a "Sepsis Six" bundle completion rate of only 14.0% in ward environments.[117] The severe delays in our cohort align closely with studies comparing community-onset to hospital-onset sepsis. A multicenter cohort study demonstrated that hospital-onset sepsis cases are 67% less likely to receive SEP-1-adherent care compared to community-onset cases, with significant delays in blood cultures, lactate measurement, and antibiotic delivery.[53] Similarly, research comparing admission sources found that ward-presenting sepsis patients have less than half the odds of receiving 3-hour bundle-compliant care and timely antibiotics compared to patients presenting in the Emergency Department.[118] Furthermore, delays in lactate measurements, which were observed in almost half of our cohort, have been strongly associated with increased mortality and prolonged hospital stays.[119]

A comparative analysis of the "Bundle completed" (n=33) versus "Bundle not completed" (n=37) groups unveils a strong "severity paradox", suggesting that ward clinicians react primarily to overt physiological deterioration rather than acting

proactively on early warning signs. Bundle completion was strongly associated with higher disease severity. Patients in the completed group exhibited significantly lower median MAP (73.3 mmHg IQR 33 vs 94 mmHg IQR 21, p<0.001) and substantially higher rates of active hypotension (57.6% vs 11.1%, p<0.001), and septic shock (48.1% vs 0%, p<0.001) compared to the non-completed group *(Table 5).* Additionally, 54.5% of the completed cohort presented with a NEWS2 score ≥7, compared to only 11.1% in the incomplete group (p<0.001) (*Table 5*). Crucially, serum lactate measurement was almost universally performed in the completed group (93.9%), but was largely omitted in the non-completed group (27%, p<0.001) (*Table 4).*This reactive application of the bundle confirms observations in recent machine learning-driven comparisons, which note that hospital-onset sepsis often presents with atypical, subtle features, such as lower white blood cell counts and less pronounced vital sign abnormalities, that may not aggressively trigger traditional clinical suspicion until the patient decompensates.[120] Because ward-onset sepsis develops gradually in already hospitalized patients, clinicians may falsely attribute early signs of deterioration to the patient's underlying conditions.[53]

The severe clinical outcomes observed in this cohort, including an all-cause 30-day mortality of 15.5%, a 90-day mortality of 31%, and a 90-day readmission rate of 26.8%, underscore the lethality of ward-based sepsis when management is delayed *(Table 7).* The multivariate analysis further identified advanced age ≥75 years (aOR 15.6; 95% CI 2.2-110.5, p=0.006) *(Table 8)* and culture-negative sepsis (aOR 9.37; 95% CI 1.9-45.5, p=0.006) *(Table 8)* as powerful independent risk factors for the composite outcome of 30-day mortality and 90-day readmission. These findings are particularly relevant given that the cohort was predominantly elderly, with 42 patients (59.2%) aged 65-84 years and 16 patients (22.5%) aged 85 or older *(Table 2).* Sepsis in older adults presents significant diagnostic challenges due to atypical clinical manifestations; as noted in a study, elderly patients frequently present with nonspecific symptoms like acute confusion or functional decline rather than classic signs.[94] Moreover, another research demonstrates that the absence of fever, which is a common occurrence in the elderly, independently predicts higher in-hospital mortality, delaying early recognition and life-saving interventions.[93] Furthermore, the failure to isolate a pathogen prolongs diagnostic uncertainty and severely limits the

ability to transition from broad empiric antibiotics to targeted, pathogen-directed therapy. The 2026 SSC guidelines strongly emphasize the importance of microbiological diagnosis to facilitate rapid de-escalation, as prolonged broad-spectrum exposure without a known source drives adverse clinical outcomes and antimicrobial resistance.[4]

The high mortality burden among ward patients is consistently reflected in current literature; an observational cohort study demonstrated that patients admitted to the ICU from hospital wards have significantly higher mortality hazard ratios (HR 1.35) compared to those admitted from the ED.[121]

These poor outcomes and the failure to execute the bundle prior to hemodynamic collapse provide a robust clinical rationale for establishing a multidisciplinary Rapid Response System (RRS) or Sepsis Team. While automated electronic health record (EHR) alerts are frequently proposed as a solution, recent studies highlight that automated sepsis prediction models often generate massive alert fatigue, poor positive predictive values, and limited clinical utility.[49,89] Therefore, a dedicated human Sepsis Team is critical. Kopczynska et al. demonstrated that patients reviewed by a critical care outreach team were nearly three times more likely to receive complete sepsis bundle care (32.0% vs 11.6%, $p<0.001$).[117]

Deploying intensivists and infectious disease specialists directly to the bedside bridges the implementation gap, ensuring that critical interventions are executed swiftly and targeted antimicrobial stewardship is optimized. Research indicates that ID bedside evaluation improves SSC bundle compliance (from 4.6% to 32%, $p<0.001$), directly optimizing the appropriateness of initial empiric antibiotic therapy (from 30% to 79%, $p<0.001$).[75] Moreover, a 10-year retrospective study demonstrated that an intensivist-led RRS independently correlated with a significant improvement in overall sepsis bundle compliance, increasing from 26.5% to 70.0%. This improved compliance directly translated to enhanced survival, with 28-day mortality continuously decreasing from 50% to 32.1% over the study period.[72]

A major strength of this study is its granular focus on sepsis performance stratified by specific non-critical clinical areas (e.g., Internal Medicine, Infectious Diseases, Geriatrics, Oncology). Most existing literature either groups all hospital wards

together or compares them solely to the ED and ICU. By detailing the exact origin of patients (e.g., 53.5% from Internal Medicine, 11.3% from ID, 7.0% from Oncology, from *Table 4*), this study provides unique insights into how performance and patient acuity vary across diverse medical specialties, highlighting specific bottlenecks in settings where continuous monitoring is absent.

However, the study also carries several limitations that must be acknowledged. First, the relatively small sample size (n=71) and the point-prevalence, cross-sectional design limit the statistical power and the ability to draw definitive causal links between interventions and mortality outcomes. Second, the distribution of patients across the clinical areas was highly heterogeneous: the vast majority of the cohort was drawn from Internal Medicine while areas like Oncology contributed very low numbers. Finally, surgical wards were almost entirely excluded from this analysis, representing a marginal proportion of the cohort (2.8%). Consequently, these findings reflect the management of medical sepsis and cannot be generalized to postoperative sepsis patients, who often exhibit different pathophysiological trajectories and distinct barriers to bundle compliance. Despite these limitations, the systematic quantification of missed lactate measurements and the reactive nature of bundle application provide a highly actionable, evidence-based foundation to justify the clinical implementation of a proactive, hospital-wide Sepsis Team.

14 Conclusions

Advanced age (≥75 years) and culture-negative sepsis were identified as significant independent risk factors for the composite outcome in patients with sepsis or septic shock admitted to medical wards, whereas urinary tract infection was associated with a protective effect, likely reflecting higher bundle compliance in this syndrome.The data demonstrate a “severity paradox” where protocol-driven care is disproportionately reserved for patients already exhibiting overt signs of hemodynamic collapse. Given the low overall adherence to the 2026 SSC bundle, highlighted by the frequent omission of lactate measurement and delayed 1-hour antibiotic administration, a structural intervention will be urgently needed to reduce high mortality and readmission rates. The establishment of a proactive, hospital-wide

Sepsis Team, incorporating the expertise of both intensivists and infectious disease specialists and supported by continuous staff education, is essential to bypass current ward-level organizational bottlenecks. Moreover, further studies are needed to confirmed and investigate the independent clinical impact of such dedicated Rapid Response Systems on time-to-treatment, bundle compliance, and overall patient survival across non-critical care settings.

15 Bibliography

1. Meyer NJ, Prescott HC. Sepsis and Septic Shock. Hardin CC, editor. N Engl J Med. 2024 Dec 5;391(22):2133–46. doi:10.1056/NEJMra2403213

2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801. doi:10.1001/jama.2016.0287

3. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. Chest. 1992 Jun;101(6):1644–55. doi:10.1378/chest.101.6.1644

4. Prescott HC, Antonelli M, Alhazzani W, Møller MH, Alshamsi F, Azevedo LCP, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2026. Critical Care Medicine. 2026 Mar 23. doi:10.1097/CCM.0000000000007075

5. Fleischmann C, Scherag A, Adhikari NKJ, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis: Current Estimates and Limitations. American Journal of Respiratory and Critical Care Medicine. 2016 Feb 1;193(3):259–72. doi:10.1164/rccm.201504-0781OC

6. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan;395(10219):200–11. doi:10.1016/S0140-6736(19)32989-7

7. Gray AP, Chung E, Hsu RL, Araki DT, Gershberg Hayoon A, Davis Weaver N, et al. Global, regional, and national sepsis incidence and mortality, 1990–2021: a systematic analysis. The Lancet Global Health. 2025 Dec;13(12):e2013–26. doi:10.1016/S2214-109X(25)00356-0

8. George NA, Pan D, Silva L, Baggaley RF, Irizar P, Divall P, et al. The prevalence and risk of mortality associated with antimicrobial resistance within nosocomial settings—a global systematic review and meta-analysis of over

20,000 patients. eClinicalMedicine. 2025 Sep;87:103384. doi:10.1016/j.eclinm.2025.103384

9. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study.

10. Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, MacFadden DM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2023 Feb;56:101781. doi:10.1016/j.eclinm.2022.101781

11. Goldstein E, MacFadden DR, Karaca Z, Steiner CA, Viboud C, Lipsitch M. Antimicrobial resistance prevalence, rates of hospitalization with septicemia and rates of mortality with sepsis in adults in different US states. 2020.

12. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections.

13. Rhee C, Kadri SS, Dekker JP, Danner RL, Chen HC, Fram D, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Netw Open. 2020 Apr 16;3(4):e202899. doi:10.1001/jamanetworkopen.2020.2899

14. Gupta AB, Heath M, Walzl E, Ratz D, Munroe E, Vaughn VM, et al. Antibiotic De-Escalation in Adults Hospitalized for Community-Onset Sepsis. JAMA Intern Med. 2026 Feb 1;186(2):192. doi:10.1001/jamainternmed.2025.6919

15. Cajander S, Kox M, Scicluna BP, Weigand MA, Mora RA, Flohé SB, et al. Profiling the dysregulated immune response in sepsis: overcoming challenges to achieve the goal of precision medicine. The Lancet Respiratory Medicine. 2024 Apr;12(4):305–22. doi:10.1016/S2213-2600(23)00330-2

16. Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunological Reviews. 2016 Nov;274(1):330–53. doi:10.1111/imr.12499

17. Angus DC. Severe Sepsis and Septic Shock. n engl j med. 2013.

18. You W. Roles of cytokine storm in sepsis progression: biomarkers, and emerging therapeutic strategies. Front Immunol. 2025 Nov 4;16:1696366. doi:10.3389/fimmu.2025.1696366

19. Schulte W, Bernhagen J, Bucala R. Cytokines in Sepsis: Potent Immunoregulators and Potential Therapeutic Targets—An Updated View. Mediators of Inflammation. 2013;2013:1–16. doi:10.1155/2013/165974

20. Rubio I, Osuchowski MF, Shankar-Hari M, Skirecki T, Winkler MS, Lachmann G, et al. Current gaps in sepsis immunology: new opportunities for translational

research. The Lancet Infectious Diseases. 2019 Dec;19(12):e422–36. doi:10.1016/S1473-3099(19)30567-5

21. Wiersinga WJ, Van Der Poll T. Biological drivers of the host response in sepsis. Thorax. 2026 Apr;81(4):396–403. doi:10.1136/thorax-2024-222012

22. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. JAMA. 2018 Jan 2;319(1):62. doi:10.1001/jama.2017.17687

23. Fan D, Wu R. Mechanisms of the septic heart: From inflammatory response to myocardial edema. Journal of Molecular and Cellular Cardiology. 2024 Oct;195:73–82. doi:10.1016/j.yjmcc.2024.08.003

24. Russell JA, Rush B, Boyd J. Pathophysiology of Septic Shock. Critical Care Clinics. 2018 Jan;34(1):43–61. doi:10.1016/j.ccc.2017.08.005

25. Schrier RW. Acute Renal Failure and Sepsis. The New England Journal of Medicine. 2004.

26. Maestraggi Q, Lebas B, Clere-Jehl R, Ludes PO, Chamaraux-Tran TN, Schneider F, et al. Skeletal Muscle and Lymphocyte Mitochondrial Dysfunctions in Septic Shock Trigger ICU-Acquired Weakness and Sepsis-Induced Immunoparalysis. BioMed Research International. 2017;2017:1–12. doi:10.1155/2017/7897325

27. Póvoa P, Coelho L, Dal-Pizzol F, Ferrer R, Huttner A, Conway Morris A, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. Intensive Care Med. 2023 Feb;49(2):142–53. doi:10.1007/s00134-022-06956-y

28. O'Grady NP, Alexander E, Alhazzani W, Alshamsi F, Cuellar-Rodriguez J, Jefferson BK, et al. Society of Critical Care Medicine and the Infectious Diseases Society of America Guidelines for Evaluating New Fever in Adult Patients in the ICU. Critical Care Medicine. 2023 Nov;51(11):1570–86. doi:10.1097/CCM.0000000000006022

29. Chairaj T, Mongkhon P, Leewongsakorn P, Saensongkwae K, Nangola S, Saoin S, et al. Diagnostic performance of procalcitonin and presepsin in sepsis: a systematic review and meta-analysis. BMC Emerg Med. 2025 Dec 4;26(1):9. doi:10.1186/s12873-025-01433-3

30. Bolanaki M, Winning J, Slagman A, Lehmann T, Kiehntopf M, Stacke A, et al. Biomarkers Improve Diagnostics of Sepsis in Adult Patients With Suspected Organ Dysfunction Based on the Quick Sepsis-Related Organ Failure Assessment (qSOFA) Score in the Emergency Department*. Critical Care Medicine. 2024 Jun;52(6):887–99. doi:10.1097/CCM.0000000000006216

31. Dark P, Hossain A, McAuley DF, Brealey D, Carlson G, Clayton JC, et al. Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis: The ADAPT-Sepsis Randomized Clinical Trial. JAMA. 2025 Feb 25;333(8):682. doi:10.1001/jama.2024.26458

32. Lee SG, Song J, Park DW, Moon S, Cho H jin, Kim JY, et al. Prognostic value of lactate levels and lactate clearance in sepsis and septic shock with initial hyperlactatemia: A retrospective cohort study according to the Sepsis-3 definitions. Medicine. 2021 Feb 19;100(7):e24835. doi:10.1097/MD.0000000000024835

33. Ljungström L, Pernestig AK, Jacobsson G, Andersson R, Usener B, Tilevik D. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. Azevedo LCP, editor. PLoS ONE. 2017 Jul 20;12(7):e0181704. doi:10.1371/journal.pone.0181704

34. Liu J, Bai C, Li B, Shan A, Shi F, Yao C, et al. Mortality prediction using a novel combination of biomarkers in the first day of sepsis in intensive care units. Sci Rep. 2021 Jan 14;11(1):1275. doi:10.1038/s41598-020-79843-5

35. Gauer R, Forbes D, Boyer N. Sepsis: Diagnosis and Management.

36. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):762. doi:10.1001/jama.2016.0288

37. Usman OA, Usman AA, Ward MA. Comparison of SIRS, qSOFA, and NEWS for the early identification of sepsis in the Emergency Department. The American Journal of Emergency Medicine. 2019 Aug;37(8):1490–7. doi:10.1016/j.ajem.2018.10.058

38. Chua WL, Rusli KDB, Aitken LM. Early warning scores for sepsis identification and prediction of in-hospital mortality in adults with sepsis: A systematic review and meta-analysis. Journal of Clinical Nursing. 2024 Jun;33(6):2005–18. doi:10.1111/jocn.17061

39. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine. 2021 Nov;49(11):e1063–143. doi:10.1097/CCM.0000000000005337

40. Serafim R, Gomes JA, Salluh J, Póvoa P. A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality. Chest. 2018 Mar;153(3):646–55. doi:10.1016/j.chest.2017.12.015

41. Hwang J, Chin HJ. Relationships between the National Early Warning Score 2, clinical worry and patient outcome at discharge: Retrospective observational study. Journal of Clinical Nursing. 2020 Oct;29(19–20):3774–89. doi:10.1111/jocn.15408

42. Miller JM, Binnicker MJ, Campbell S, Carroll KC, Chapin KC, Gonzalez MD, et al. Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2024 Update by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). Clinical Infectious Diseases. 2024 Mar 5;ciae104. doi:10.1093/cid/ciae104

43. Yealy DM, Mohr NM, Shapiro NI, Venkatesh A, Jones AE, Self WH. Early Care of Adults With Suspected Sepsis in the Emergency Department and Out-of-Hospital Environment: A Consensus-Based Task Force Report. Annals of Emergency Medicine. 2021 Jul;78(1):1–19. doi:10.1016/j.annemergmed.2021.02.006

44. Gauer RL, Center WAM, Bragg F, Carolina N. Early Recognition and Management of Sepsis in Adults: The First Six Hours.

45. Cortellaro F, Ferrari L, Molteni F, Aseni P, Velati M, Guarnieri L, et al. Accuracy of point of care ultrasound to identify the source of infection in septic patients: a prospective study. Intern Emerg Med. 2017 Apr;12(3):371–8. doi:10.1007/s11739-016-1470-2

46. Brixey AG, Fung A, De Leon AD, Walker CM, Porter KK, Khatri G, et al. ACR Appropriateness Criteria® Sepsis. Journal of the American College of Radiology. 2024 Jun;21(6):S292–309. doi:10.1016/j.jacr.2024.02.029

47. Sweeney DA, Wiley BM. Integrated Multiorgan Bedside Ultrasound for the Diagnosis and Management of Sepsis and Septic Shock. Semin Respir Crit Care Med. 2021 Oct;42(05):641–9. doi:10.1055/s-0041-1733896

48. Churpek MM, Snyder A, Han X, Sokol S, Pettit N, Howell MD, et al. Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. American Journal of Respiratory and Critical Care Medicine. 2017 Apr 1;195(7):906–11. doi:10.1164/rccm.201604-0854OC

49. Hijjawi S, Ssentongo P. Evaluation of sepsis CDS tool knowledge and utilization among graduate medical trainees: insights to inform redesign in an academic health system. Front Med. 2026 Jan 5;12:1660390. doi:10.3389/fmed.2025.1660390

50. Cimiotti JP, Becker ER, Li Y, Sloane DM, Fridkin SK, West AB, et al. Association of Registered Nurse Staffing With Mortality Risk of Medicare Beneficiaries Hospitalized With Sepsis. JAMA Health Forum. 2022 May 27;3(5):e221173. doi:10.1001/jamahealthforum.2022.1173

51. Dierkes AM, Aiken LH, Sloane DM, Cimiotti JP, Riman KA, McHugh MD. Hospital nurse staffing and sepsis protocol compliance and outcomes among patients with sepsis in the USA: a multistate cross-sectional analysis. BMJ Open. 2022 Mar;12(3):e056802. doi:10.1136/bmjopen-2021-056802

52. Rhee C, Wang R, Zhang Z, Fram D, Kadri SS, Klompas M. Epidemiology of Hospital-Onset Versus Community-Onset Sepsis in U.S. Hospitals and Association With Mortality: A Retrospective Analysis Using Electronic Clinical Data. Critical Care Medicine. 2019 Sep;47(9):1169–76. doi:10.1097/CCM.0000000000003817

53. Baghdadi JD, Wong MD, Uslan DZ, Bell D, Cunningham WE, Needleman J, et al. Adherence to the SEP-1 Sepsis Bundle in Hospital-Onset v. Community-Onset Sepsis: a Multicenter Retrospective Cohort Study. J GEN INTERN MED. 2020 Apr;35(4):1153–60. doi:10.1007/s11606-020-05653-0

54. The BALANCE Investigators. Antibiotic Treatment for 7 versus 14 Days in Patients with Bloodstream Infections. N Engl J Med. 2025 Mar 13;392(11):1065–78. doi:10.1056/NEJMoa2404991

55. Li Q, Zhou Q, Fan J, Huang S, Chen Y, Song F, et al. Oral switch vs. continued intravenous antibiotic therapy in patients with bacteraemia and sepsis: a systematic review and meta-analysis. Clinical Microbiology and Infection. 2025 Apr;31(4):551–9. doi:10.1016/j.cmi.2024.11.035

56. Harvey EJ, McLeod M, De Brún C, Ashiru-Oredope D. Criteria to achieve safe antimicrobial intravenous-to-oral switch in hospitalised adult populations: a systematic rapid review. BMJ Open. 2023 Jul;13(7):e068299. doi:10.1136/bmjopen-2022-068299

57. Tamma PD, Conley AT, Cosgrove SE, Harris AD, Lautenbach E, Amoah J, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med. 2019 Mar 1;179(3):316. doi:10.1001/jamainternmed.2018.6226

58. Reitz KM, Kennedy J, Li SR, Handzel R, Tonetti DA, Neal MD, et al. Association Between Time to Source Control in Sepsis and 90-Day Mortality. JAMA Surg. 2022 Sep 1;157(9):817. doi:10.1001/jamasurg.2022.2761

59. Huston JM, Barie PS, Dellinger EP, Forrester JD, Duane TM, Tessier JM, et al. The Surgical Infection Society Guidelines on the Management of Intra-Abdominal Infection: 2024 Update.

60. Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surgical Infections. 2017 Jan;18(1):1–76. doi:10.1089/sur.2016.261

61. Coccolini F, Roberts D, Ansaloni L, Ivatury R, Gamberini E, Kluger Y, et al. The open abdomen in trauma and non-trauma patients: WSES guidelines. World J Emerg Surg. 2018 Dec;13(1):7. doi:10.1186/s13017-018-0167-4

62. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America.

63. Hua C, Urbina T, Bosc R, Parks T, Sriskandan S, De Prost N, et al. Necrotising soft-tissue infections. The Lancet Infectious Diseases. 2023 Mar;23(3):e81–94. doi:10.1016/S1473-3099(22)00583-7

64. Fernando SM, Tran A, Cheng W, Rochwerg B, Kyeremanteng K, Seely AJE, et al. Necrotizing Soft Tissue Infection: Diagnostic Accuracy of Physical Examination, Imaging, and LRINEC Score: A Systematic Review and Meta-Analysis. Annals of Surgery. 2019 Jan;269(1):58–65. doi:10.1097/SLA.0000000000002774

65. McDermott J, Kao LS, Keeley JA, Grigorian A, Neville A, De Virgilio C. Necrotizing Soft Tissue Infections: A Review. JAMA Surg. 2024 Nov 1;159(11):1308. doi:10.1001/jamasurg.2024.3365

66. Hua C, Bosc R, Sbidian E, De Prost N, Hughes C, Jabre P, et al. Interventions for necrotizing soft tissue infections in adults. Cochrane Skin Group, editor. Cochrane Database of Systematic Reviews. 2018 May 31;2018(5). doi:10.1002/14651858.CD011680.pub2

67. Nohra E, Appelbaum RD, Farrell MS, Carver T, Jung HS, Kirsch JM, et al. Fever and infections in surgical intensive care: an American Association for the Surgery of Trauma Critical Care Committee clinical consensus document. Trauma Surg Acute Care Open. 2024 Jun;9(1):e001303. doi:10.1136/tsaco-2023-001303

68. McGaughey J, Fergusson DA, Van Bogaert P, Rose L. Early warning systems and rapid response systems for the prevention of patient deterioration on acute adult hospital wards. Cochrane Central Editorial Service, editor. Cochrane Database of Systematic Reviews. 2021 Nov 22;2025(1). doi:10.1002/14651858.CD005529.pub3

69. Hidalgo JL, Kumar VK, Akech SO, Myatra SN, Jacob ST, Kortz T, et al. The Sepsis Chain of Survival: A Comprehensive Framework for Improving Sepsis Outcomes. Critical Care Medicine. 2025 Oct;53(10):e1886–92. doi:10.1097/CCM.0000000000006796

70. Arabi YM, Alsaawi A, Alzahrani M, Al Khathaami AM, AlHazme RH, Al Mutrafy A, et al. Electronic Sepsis Screening Among Patients Admitted to Hospital Wards: A Stepped-Wedge Cluster Randomized Trial. JAMA. 2025 Mar 4;333(9):763. doi:10.1001/jama.2024.25982

71. Lafon T, Weingart M, Vaidie J, Calfee CS, Jacob ST, Freund Y, et al. Challenges in early detection and prognostication of sepsis: new approaches

from the emergency department and intensive care unit. eClinicalMedicine. 2026 Apr;94:103864. doi:10.1016/j.eclinm.2026.103864

72. Choi S, Son J, Oh DK, Huh JW, Lim CM, Hong SB. Rapid Response System Improves Sepsis Bundle Compliances and Survival in Hospital Wards for 10 Years. JCM. 2021 Sep 18;10(18):4244. doi:10.3390/jcm10184244

73. Hyun D gon, Lee SY, Ahn JH, Huh JW, Hong SB, Koh Y, et al. Mortality of patients with hospital-onset sepsis in hospitals with all-day and non-all-day rapid response teams: a prospective nationwide multicenter cohort study. Crit Care. 2022 Sep 16;26(1):280. doi:10.1186/s13054-022-04149-z

74. Madaline T, Wadskier Montagne F, Eisenberg R, Mowrey W, Kaur J, Malik M, et al. Early Infectious Disease Consultation Is Associated With Lower Mortality in Patients With Severe Sepsis or Septic Shock Who Complete the 3-Hour Sepsis Treatment Bundle. Open Forum Infectious Diseases. 2019 Oct 1;6(10):ofz408. doi:10.1093/ofid/ofz408

75. Viale P, Tedeschi S, Scudeller L, Attard L, Badia L, Bartoletti M, et al. Infectious Diseases Team for the Early Management of Severe Sepsis and Septic Shock in the Emergency Department. Clinical Infectious Diseases. 2017 Oct 15;65(8):1253–9. doi:10.1093/cid/cix548

76. Tang G, Huang L, Zong Z. Impact of Infectious Disease Consultation on Clinical Management and Outcome of Patients with Bloodstream Infection: a Retrospective Cohort Study. Sci Rep. 2017 Oct 10;7(1):12898. doi:10.1038/s41598-017-13055-2

77. Fourre N, Zimmermann V, Senn L, Aruanno M, Guery B, Papadimitriou-Olivgeris M. Predictors of Mortality of Streptococcal Bacteremia and the Role of Infectious Diseases Consultation: A Retrospective Cohort Study. Clinical Infectious Diseases. 2024 Jun 14;78(6):1544–50. doi:10.1093/cid/ciae168

78. Dantes RB, Kaur H, Bouwkamp BA, Haass KA, Patel P, Dudeck MA, et al. Sepsis Program Activities in Acute Care Hospitals — National Healthcare Safety Network, United States, 2022. Vol. 72. 2023;72(34).

79. Kim HJ, Jeon K, Kang BJ, Ahn JJ, Hong SB, Lee DH, et al. Relationship between the presence of dedicated doctors in rapid response systems and patient outcome: a multicenter retrospective cohort study. Respir Res. 2021 Dec;22(1):236. doi:10.1186/s12931-021-01824-7

80. Nates JL, Nunnally M, Kleinpell R, Blosser S, Goldner J, Birriel B, et al. ICU Admission, Discharge, and Triage Guidelines: A Framework to Enhance Clinical Operations, Development of Institutional Policies, and Further Research. Critical Care Medicine. 2016 Aug;44(8):1553–602. doi:10.1097/CCM.0000000000001856

81. Honarmand K, Wax RS, Penoyer D, Lighthall G, Danesh V, Rochwerg B, et al. Society of Critical Care Medicine Guidelines on Recognizing and Responding to Clinical Deterioration Outside the ICU: 2023. Critical Care Medicine. 2024 Feb;52(2):314–30. doi:10.1097/CCM.0000000000006072

82. Chua WL, Teh CS, Basri MABA, Ong ST, Phang NQQ, Goh EL. Nurses' knowledge and confidence in recognizing and managing patients with sepsis: A multi-site cross-sectional study. Journal of Advanced Nursing. 2023 Feb;79(2):616–29. doi:10.1111/jan.15435

83. Lasater KB, Sloane DM, McHugh MD, Cimiotti JP, Riman KA, Martin B, et al. Evaluation of hospital nurse-to-patient staffing ratios and sepsis bundles on patient outcomes. American Journal of Infection Control. 2021 Jul;49(7):868–73. doi:10.1016/j.ajic.2020.12.002

84. Warttig S, Alderson P, Evans DJ, Lewis SR, Kourbeti IS, Smith AF. Automated monitoring compared to standard care for the early detection of sepsis in critically ill patients. Cochrane Emergency and Critical Care Group, editor. Cochrane Database of Systematic Reviews. 2018 Jun 25;2019(1). doi:10.1002/14651858.CD012404.pub2

85. Zhang Z, Chen L, Xu P, Wang Q, Zhang J, Chen K, et al. Effectiveness of automated alerting system compared to usual care for the management of sepsis. npj Digit Med. 2022 Jul 19;5(1):101. doi:10.1038/s41746-022-00650-5

86. Kim HJ, Ko RE, Lim SY, Park S, Suh GY, Lee YJ. Sepsis Alert Systems, Mortality, and Adherence in Emergency Departments: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024 Jul 22;7(7):e2422823. doi:10.1001/jamanetworkopen.2024.22823

87. Henry KE, Adams R, Parent C, Soleimani H, Sridharan A, Johnson L, et al. Factors driving provider adoption of the TREWS machine learning-based early warning system and its effects on sepsis treatment timing. Nat Med. 2022 Jul;28(7):1447–54. doi:10.1038/s41591-022-01895-z

88. Adams R, Henry KE, Sridharan A, Soleimani H, Zhan A, Rawat N, et al. Prospective, multi-site study of patient outcomes after implementation of the TREWS machine learning-based early warning system for sepsis. Nat Med. 2022 Jul;28(7):1455–60. doi:10.1038/s41591-022-01894-0

89. Wong A, Otles E, Donnelly JP, Krumm A, McCullough J, DeTroyer-Cooley O, et al. External Validation of a Widely Implemented Proprietary Sepsis Prediction Model in Hospitalized Patients. JAMA Intern Med. 2021 Aug 1;181(8):1065. doi:10.1001/jamainternmed.2021.2626

90. Wong A, Currey D, Schwinne M, Park-Egan B, Meyer S, Gutting A, et al. Multicenter Prospective Validation of an Updated Proprietary Sepsis Prediction Model. JAMA Netw Open. 2026 Feb 27;9(2):e260181. doi:10.1001/jamanetworkopen.2026.0181

91. Downey C, Randell R, Brown J, Jayne DG. Continuous Versus Intermittent Vital Signs Monitoring Using a Wearable, Wireless Patch in Patients Admitted to Surgical Wards: Pilot Cluster Randomized Controlled Trial. J Med Internet Res. 2018 Dec 11;20(12):e10802. doi:10.2196/10802

92. Tu KJ, Wymore C, Tchangalova N, Fuller BM, Mohr NM. The impact of telehealth in sepsis care: A systematic review. J Telemed Telecare. 2025 Jan;31(1):3–13. doi:10.1177/1357633X231170038

93. Wester AL, Dunlop O, Melby KK, Dahle UR, Wyller TB. Age-related differences in symptoms, diagnosis and prognosis of bacteremia. BMC Infect Dis. 2013 Dec;13(1):346. doi:10.1186/1471-2334-13-346

94. Putot A, Prendki V. New horizons in sepsis management in older patients. Age and Ageing. 2023 Feb 1;52(2):afad016. doi:10.1093/ageing/afad016

95. Devia Jaramillo G, Ibáñez Pinilla M. Quick Sequential Organ Failure Assessment, Sequential Organ Failure Assessment, and Procalcitonin for Early Diagnosis and Prediction of Death in Elderly Patients with Suspicion of Sepsis in the Emergency Department, Based on Sepsis-3 Definition. Gerontology. 2022;68(2):171–80. doi:10.1159/000515851

96. Bafi AT, Tomotani DYV, De Freitas FGR. Sepsis in Solid-Organ Transplant Patients. Shock. 2017 Jan;47(1S):12–6. doi:10.1097/SHK.0000000000000700

97. McCreery RJ, Florescu DF, Kalil AC. Sepsis in Immunocompromised Patients Without Human Immunodeficiency Virus. The Journal of Infectious Diseases. 2020 Jul 21;222(Supplement_2):S156–65. doi:10.1093/infdis/jiaa320

98. Deinhardt-Emmer S, Chousterman BG, Schefold JC, Flohé SB, Skirecki T, Kox M, et al. Sepsis in patients who are immunocompromised: diagnostic challenges and future therapies. The Lancet Respiratory Medicine. 2025 Jul;13(7):623–37. doi:10.1016/S2213-2600(25)00124-9

99. Baden LR, Bensinger W, Angarone M, Casper C, Dubberke ER, Freifeld AG, et al. Prevention and Treatment of Cancer-Related Infections. Journal of the National Comprehensive Cancer Network. 2012;10(11).

100. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. JCO. 2018 May 10;36(14):1443–53. doi:10.1200/JCO.2017.77.6211

101. Nates JL, Pène F, Darmon M, Mokart D, Castro P, David S, et al. Septic shock in the immunocompromised cancer patient: a narrative review. Crit Care. 2024 Aug 30;28(1):285. doi:10.1186/s13054-024-05073-0

102. Plaeke P, De Man JG, Coenen S, Jorens PG, De Winter BY, Hubens G. Clinical- and surgery-specific risk factors for post-operative sepsis: a systematic

review and meta-analysis of over 30 million patients. Surg Today. 2020 May;50(5):427–39. doi:10.1007/s00595-019-01827-4

103. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. British Journal of Anaesthesia. 2005 Jun;94(6):767–73. doi:10.1093/bja/aei143

104. Nasa P, Wise R, Malbrain MLNG. Fluid management in the septic peri-operative patient. Current Opinion in Critical Care. 2024 Dec;30(6):664–71. doi:10.1097/MCC.0000000000001201

105. Damiani E, Donati A, Serafini G, Rinaldi L, Adrario E, Pelaia P, et al. Effect of Performance Improvement Programs on Compliance with Sepsis Bundles and Mortality: A Systematic Review and Meta-Analysis of Observational Studies. Efron PA, editor. PLoS ONE. 2015 May 6;10(5):e0125827. doi:10.1371/journal.pone.0125827

106. Townsend SR, Phillips GS, Duseja R, Tefera L, Cruikshank D, Dickerson R, et al. Effects of Compliance With the Early Management Bundle (SEP-1) on Mortality Changes Among Medicare Beneficiaries With Sepsis. CHEST. 2022 Feb;161(2):392–406. doi:10.1016/j.chest.2021.07.2167

107. Fan TH, Premraj L, Roberts J, Lydston M, Robba C, Hager D, et al. In-Hospital Neurologic Complications, Neuromonitoring, and Long-Term Neurologic Outcomes in Patients With Sepsis: A Systematic Review and Meta-Analysis. Critical Care Medicine. 2024 Mar;52(3):452–63. doi:10.1097/CCM.0000000000006096

108. Afshar M, Arain E, Ye C, Gilbert E, Xie M, Lee J, et al. Patient Outcomes and Cost-Effectiveness of a Sepsis Care Quality Improvement Program in a Health System*. Critical Care Medicine. 2019 Oct;47(10):1371–9. doi:10.1097/CCM.0000000000003919

109. Ladbrook E, Bouchoucha S, McDonall J, Hutchinson AF. A systematic review of the cost impact of sepsis care bundles. Journal of Hospital Infection. 2025 Dec;166:170–82. doi:10.1016/j.jhin.2025.08.006

110. Leisman DE, Doerfler ME, Ward MF, Masick KD, Wie BJ, Gribben JL, et al. Survival Benefit and Cost Savings From Compliance With a Simplified 3-Hour Sepsis Bundle in a Series of Prospective, Multisite, Observational Cohorts. Critical Care Medicine. 2017 Mar;45(3):395–406. doi:10.1097/CCM.0000000000002184

111. Choy CL, Liaw SY, Goh EL, See KC, Chua WL. Impact of sepsis education for healthcare professionals and students on learning and patient outcomes: a systematic review. Journal of Hospital Infection. 2022 Apr;122:84–95. doi:10.1016/j.jhin.2022.01.004

112. Zhao L, Wu C, Su J, Bai H, Xia Q, Ma W, et al. Integration of mind mapping and In-Situ Simulation training to enhance the implementation of sepsis Hour-1 Bundle treatment. BMC Med Educ. 2025 Mar 4;25(1):331. doi:10.1186/s12909-025-06918-0

113. Chua WL, Ooi SL, Chan GWH, Lau TC, Liaw SY. The Effect of a Sepsis Interprofessional Education Using Virtual Patient Telesimulation on Sepsis Team Care in Clinical Practice: Mixed Methods Study. J Med Internet Res. 2022 Apr 18;24(4):e35058. doi:10.2196/35058

114. Papareddy P, Lobo TJ, Holub M, Bouma H, Maca J, Strodthoff N, et al. Transforming sepsis management: AI-driven innovations in early detection and tailored therapies. Crit Care. 2025 Aug 19;29(1):366. doi:10.1186/s13054-025-05588-0

115. Giamarellos-Bourboulis EJ, Kotsaki A, Kotsamidi I, Efthymiou A, Koutsoukou V, Ehler J, et al. Precision Immunotherapy to Improve Sepsis Outcomes: The ImmunoSep Randomized Clinical Trial. JAMA. 2026 Mar 3;335(9):775. doi:10.1001/jama.2025.24175

116. Munroe ES, Hyzy RC, Semler MW, Shankar-Hari M, Young PJ, Zampieri FG, et al. Evolving Management Practices for Early Sepsis-induced Hypoperfusion: A Narrative Review. American Journal of Respiratory and Critical Care Medicine. 2023 May 15;207(10):1283–99. doi:10.1164/rccm.202209-1831CI

117. Kopczynska M, Unwin H, Pugh RJ, Sharif B, Chandy T, Davies DJ, et al. Four consecutive yearly point-prevalence studies in Wales indicate lack of improvement in sepsis care on the wards. Sci Rep. 2021 Aug 10;11(1):16222. doi:10.1038/s41598-021-95648-6

118. Leisman DE, Angel C, Schneider SM, D'Amore JA, D'Angelo JK, Doerfler ME. Sepsis Presenting in Hospitals versus Emergency Departments: Demographic, Resuscitation, and Outcome Patterns in a Multicenter Retrospective Cohort. Journal of Hospital Medicine. 2019 Jun;14(6):340–8. doi:10.12788/jhm.3188

119. Han X, Edelson DP, Snyder A, Pettit N, Sokol S, Barc C, et al. Implications of Centers for Medicare & Medicaid Services Severe Sepsis and Septic Shock Early Management Bundle and Initial Lactate Measurement on the Management of Sepsis. Chest. 2018 Aug;154(2):302–8. doi:10.1016/j.chest.2018.03.025

120. Verma R, Elhance A, Marsh TJ, Baudier RL, Sherry SP, Reddy R, et al. Timing matters: a machine learning–driven comparison of community and hospital-onset sepsis. BMC Med Inform Decis Mak. 2026 Jan 31;26(1):56. doi:10.1186/s12911-026-03353-z

121. Motzkus CA, Chrysanthopoulou SA, Luckmann R, Rincon TA, Lapane KL, Lilly CM. ICU Admission Source as a Predictor of Mortality for Patients With

Sepsis. J Intensive Care Med. 2018 Sep;33(9):510–6.
doi:10.1177/0885066617701904