Modern Intensive Care in Sepsis and Septic Shock: Early Recognition, Hemodynamic Resuscitation, and Assessment of Organ Perfusion

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Abstract. *Sepsis remains a leading cause of death in intensive care units worldwide, accounting for an estimated 48.9 million cases and 11 million deaths annually. Outcomes depend critically on the speed of recognition and the quality of early hemodynamic resuscitation.*

To synthesize current evidence on three pillars of modern intensive care for sepsis and septic shock: early identification, hemodynamic resuscitation, and bedside assessment of organ perfusion.

Narrative review of randomized controlled trials, international guidelines (Surviving Sepsis Campaign 2021), and major observational studies published between 2001 and 2025, identified through PubMed, Scopus, and the Cochrane Library.

Screening instruments (qSOFA, NEWS2, SIRS) each trade sensitivity against specificity, and guidelines now favor sensitive multi-parameter scores supported by lactate measurement and, increasingly, machine-learning surveillance. Resuscitation has shifted from protocolized early goal-directed therapy toward individualized, fluid-conservative strategies: balanced crystalloids, early norepinephrine, adjunctive vasopressin and hydrocortisone in refractory shock, and a default mean arterial pressure target of 65 mm Hg. Perfusion assessment combines serial lactate, capillary refill time, central venous oxygen saturation, the veno-arterial CO2 gap, and point-of-care ultrasound; peripheral perfusion-targeted resuscitation proved at least equivalent to lactate-targeted therapy in ANDROMEDA-SHOCK.

Modern sepsis care is time-critical, individualized, and multimodal. Bundled early recognition, judicious fluids with early vasopressors, and repeated multimodal perfusion assessment form the current standard; artificial intelligence and microcirculation-guided therapy are the most promising frontiers.

Keywords: *sepsis; septic shock; early recognition; hemodynamic resuscitation; organ perfusion; lactate; capillary refill time; vasopressors.*

Introduction

Sepsis is defined by the Third International Consensus (Sepsis-3, 2016) as life-threatening organ dysfunction caused by a dysregulated host response to infection, operationalized as an acute increase of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score [1]. Septic shock is the subset in which circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality: vasopressor requirement to maintain a mean arterial pressure (MAP) ≥65 mm Hg and serum lactate >2 mmol/L despite adequate volume resuscitation [1]. Hospital mortality in

septic shock still exceeds 35–40% in most registries.

The Global Burden of Disease analysis estimated 48.9 million incident sepsis cases and 11.0 million sepsis-related deaths in 2017 — approximately 19.7% of all global deaths — with a disproportionate burden in low- and middle-income countries [2]. Sepsis is therefore recognized by the World Health Organization (resolution WHA70.7, 2017) as a global health priority.

Three interdependent clinical problems determine outcome in the first hours of sepsis. First, recognition: sepsis has no single diagnostic test, presents heterogeneously, and every hour of delay in adequate treatment is associated with a measurable increase in mortality [3]. Second, hemodynamic resuscitation: the field has moved from rigid protocolized "early goal-directed therapy" toward individualized strategies balancing fluids against earlier vasopressor use [4, 5]. Third, assessment of organ perfusion: macrohemodynamic normalization (blood pressure, cardiac output) does not guarantee adequate tissue perfusion, so modern intensive care relies on multimodal perfusion monitoring — lactate kinetics, capillary refill time (CRT), venous oxygen saturation, CO2-derived indices, and point-of-care ultrasound [6, 7].

The aim of this review is to summarize the contemporary evidence base and guideline recommendations — principally the Surviving Sepsis Campaign (SSC) 2021 guidelines [4] and landmark trials published through 2025 — for each of these three pillars, and to outline unresolved controversies and future directions.

2. Materials and Methods

This article is a narrative (non-systematic) review. We searched PubMed/MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials for publications from January 2001 to October 2025 using combinations of the terms: *sepsis*, *septic shock*, *early recognition*, *screening*, *qSOFA*, *NEWS2*, *biomarkers*, *fluid resuscitation*, *vasopressors*, *norepinephrine*, *mean arterial pressure*, *lactate clearance*, *capillary refill time*, *microcirculation*, *tissue perfusion*, and *hemodynamic monitoring*.

Inclusion criteria: (1) randomized controlled trials (RCTs), systematic reviews and meta-analyses of adult patients (≥18 years) with sepsis or septic shock; (2) international consensus definitions and guidelines (Sepsis-3; Surviving Sepsis Campaign 2016 and 2021); (3) large multicenter observational cohorts (>1,000 patients) addressing recognition, resuscitation, or perfusion monitoring; (4) English-language full-text publications.

Exclusion criteria: pediatric and neonatal populations, single-center studies with fewer than 100 patients (unless methodologically unique, e.g., first-in-human physiological studies), case reports, and animal studies.

Priority was given to landmark multicenter RCTs (ProCESS, ARISE, ProMISe, SEPSISPAM, the "65" trial, VASST, ATHOS-3, ADRENAL, APROCCHSS, SMART, BaSICS, PLUS, CLASSIC, CLOVERS, ANDROMEDA-SHOCK) and to the most recent guideline iterations. Evidence was synthesized thematically into three domains corresponding to the aims of the review: early recognition, hemodynamic resuscitation, and organ perfusion assessment. Because this is a narrative review of published aggregate data, ethics committee approval was not required.

3. Results

3.1. Early recognition of sepsis

Screening tools. No single score is both sensitive and specific. The quick SOFA (qSOFA: respiratory rate ≥22/min, systolic blood pressure ≤100 mm Hg, altered mentation; positive at ≥2 criteria) is specific for poor outcome but insensitive as a screening instrument — pooled sensitivity around 60% outside the ICU. The SSC 2021

guidelines therefore issue a strong recommendation **against** using qSOFA as a single screening tool, favoring continuous multi-parameter screening with SIRS, NEWS/NEWS2, or MEWS embedded in hospital-wide protocols [4]. NEWS2 ≥5 is currently the most widely adopted ward-level trigger in Europe, combining acceptable sensitivity with an actionable escalation pathway.

Biomarkers. Serum lactate >2 mmol/L identifies cryptic hypoperfusion even with normal blood pressure and is a mandated element of the Hour-1 bundle [4, 8]. Procalcitonin (PCT) is more useful for antibiotic de-escalation than for diagnosis: PCT-guided discontinuation shortens antibiotic exposure without harming survival, but a low PCT must never delay empirical therapy in suspected sepsis [4]. Emerging markers — presepsin, proadrenomedullin (MR-proADM), interleukin-6, and transcriptomic host-response signatures (e.g., SeptiCyte, IMX-BVN) — improve risk stratification but have not yet changed guideline practice.

The time factor and bundles. Retrospective analysis of 49,331 patients in the New York State mandate showed that each hour of delay in completing the 3-hour bundle (cultures, broad-spectrum antibiotics, lactate) increased the odds of in-hospital death by approximately 4% per hour [3]. The SSC Hour-1 bundle (2018) consolidates five actions to begin within the first hour of recognition: measure lactate, obtain blood cultures before antibiotics, administer broad-spectrum antibiotics, start 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L, and apply vasopressors if MAP remains <65 mm Hg [8]. SSC 2021 nuances antibiotic timing: within 1 hour for probable sepsis or shock, and within 3 hours when sepsis is possible but unconfirmed, to limit antibiotic overuse [4].

Machine-learning surveillance. Real-time electronic sepsis alerts based on machine learning have moved from research to deployment. In a prospective multisite evaluation of the TREWS system, alerts confirmed by clinicians within 3 hours were associated with reduced mortality and earlier antibiotics [9]. Alert fatigue and external validity remain the principal implementation barriers.

3.2. Hemodynamic resuscitation

From EGDT to individualized therapy. Rivers' single-center trial (2001) of early goal-directed therapy targeting CVP 8–12 mm Hg, MAP ≥65 mm Hg, and ScvO2 ≥70% reduced mortality by 16 absolute percentage points and shaped a decade of practice [10]. However, the three multicenter trials ProCESS (2014), ARISE (2014) and ProMISe (2015), and their 3,723-patient pooled PRISM meta-analysis, found no survival benefit of protocolized EGDT over modern usual care that already included early antibiotics and fluids [5]. The legacy of EGDT is urgency, not its catheter-based targets.

Fluid choice and volume. Balanced crystalloids (Ringer's lactate, Plasma-Lyte) are preferred over 0.9% saline: SMART (n=15,802) showed fewer major adverse kidney events with balanced fluids, and while BaSICS and PLUS were individually neutral, updated meta-analyses suggest a high probability of a small mortality benefit [4, 11]. Hydroxyethyl starches are contraindicated (increased renal failure and death); albumin is a reasonable adjunct in patients who have received large crystalloid volumes [4]. The guideline 30 mL/kg initial bolus is a weak recommendation; after it, further fluid should be given only for demonstrated fluid responsiveness, assessed dynamically (passive leg raising with cardiac output measurement, pulse pressure or stroke volume variation, end-expiratory occlusion test) rather than by static pressures such as CVP [4, 7]. Restrictive strategies proved safe: CLASSIC (2022) and CLOVERS (2023) found no mortality difference between restrictive (vasopressor-first) and liberal fluid

strategies after initial resuscitation, legitimizing fluid-sparing practice [12, 13].

Vasopressors. Norepinephrine is the unequivocal first-line agent; dopamine causes more arrhythmias and higher mortality in cardiogenic subgroups [4]. Early norepinephrine — started during, not after, fluid loading — achieved faster shock control in the CENSER trial and is increasingly standard, including via peripheral venous access for limited periods [14]. Vasopressin (up to 0.03 U/min) is the recommended second agent to reduce norepinephrine requirements (VASST); angiotensin II (ATHOS-3) is an option in catecholamine-refractory vasodilatory shock [4]. Low-dose hydrocortisone (200 mg/day) is suggested when norepinephrine exceeds approximately 0.25 μg/kg/min for ≥4 hours: ADRENAL and APROCCHSS showed faster shock reversal, with a survival benefit in APROCCHSS (combined with fludrocortisone) [4, 15].

Pressure targets. SEPSISPAM found no overall mortality difference between MAP targets of 65–70 versus 80–85 mm Hg (higher targets caused more atrial fibrillation but less renal replacement therapy in chronically hypertensive patients); the "65" trial showed that permissive hypotension (60–65 mm Hg) in patients ≥65 years was not inferior [16, 17]. The default target remains MAP 65 mm Hg, individualized upward for selected hypertensive patients with renal dysfunction [4].

3.3. Assessment of organ perfusion

Lactate kinetics. A ≥10–20% lactate decrease over 2 hours ("lactate clearance") predicts survival, and lactate-guided resuscitation reduced mortality in meta-analysis; SSC 2021 suggests resuscitation guided by decreasing lactate [4]. Its limitations are kinetic (slow, hepatically cleared) and etiologic: hyperlactatemia also reflects adrenergic glycolysis, liver dysfunction, and metformin, not only anaerobic metabolism.

Capillary refill time. ANDROMEDA-SHOCK (2019, n=424) compared CRT-targeted (normal ≤3 s, checked every 30 min) versus lactate-targeted resuscitation: 28-day mortality was 34.9% vs 43.4% (p=0.06), with significantly less organ dysfunction at 72 h and less fluid in the CRT arm; Bayesian re-analysis indicated >90% probability of benefit [6]. CRT is free, fast, and repeatable, making it attractive far beyond high-resource ICUs; the follow-up ANDROMEDA-SHOCK-2 trial is testing a CRT-centered hierarchical algorithm.

Oxygen-derived and CO2-derived indices. ScvO2 <70% suggests inadequate oxygen delivery, while supranormal values in late sepsis may indicate mitochondrial dysfunction and carry poor prognosis. The central venous–arterial CO2 difference (Pcv-aCO2 gap) >6 mm Hg indicates flow insufficient to wash out tissue CO2 even when ScvO2 appears adequate, and the Pcv-aCO2/Ca-vO2 ratio helps unmask anaerobic metabolism [7]. These indices are best used in combination to answer the operational question: will increasing cardiac output help this patient?

Ultrasound and advanced monitoring. Point-of-care echocardiography identifies sepsis-induced cardiomyopathy (present in 10–40% of septic shock), severe vasoplegia, right-ventricular failure, and unexpected causes of shock, and should be the first-line advanced assessment [7]. Invasive calibrated monitors (transpulmonary thermodilution: PiCCO, VolumeView) are reserved for refractory shock or sepsis with ARDS, providing extravascular lung water and preload indices. Venous congestion scoring (VExUS) adds the "backward" dimension: systemic venous hypertension predicts acute kidney injury and argues for decongestion rather than more fluid.

Microcirculation. Handheld sublingual videomicroscopy demonstrates that microcirculatory flow abnormalities predict mortality independently of blood pressure and cardiac output — the phenomenon of

hemodynamic incoherence [18]. Routine clinical use awaits automated, validated analysis; for now the microcirculation is monitored indirectly through CRT, mottling score, and CO2-derived indices.

4. Discussion

The evidence reviewed points to a single unifying principle: modern sepsis care is **time-critical in its first hour and individualized thereafter**. Early recognition and bundle delivery are where the largest, most consistent survival gains lie; beyond the initial bundle, one-size-fits-all protocols have repeatedly failed to outperform skilled, physiology-guided usual care.

Recognition: sensitivity first, then confirmation. The rejection of qSOFA as a stand-alone screening tool reflects a pragmatic hierarchy. Screening must be sensitive (NEWS2, SIRS, electronic alerts) so that patients are not missed; confirmation and prognostication can then rely on SOFA, lactate, and clinical judgment. The tension between speed and stewardship is real: aggressive time targets increase broad-spectrum antibiotic use in patients who are ultimately not infected. The SSC 2021 stratification — 1 hour for probable sepsis, 3 hours for possible sepsis without shock — is a reasonable compromise, but it requires reliable re-assessment systems, which many hospitals, including those in resource-limited settings, still lack.

Resuscitation: from "more" to "enough". The collapse of the EGDT paradigm, together with the neutrality of CLASSIC and CLOVERS, shifts the burden of proof: additional fluid must now be justified by demonstrated fluid responsiveness and evidence of persistent hypoperfusion, not by a number on a protocol sheet. Fluid overload is independently associated with mortality, prolonged ventilation, and acute kidney injury, and the de-resuscitation phase deserves the same attention as the initial phase. A practical framework is the four-phase ROSE model (Rescue, Optimization, Stabilization, Evacuation), in which goals change as the patient progresses. Early, even peripheral, norepinephrine treats vasoplegia — the dominant mechanism of septic hypotension — more directly than additional volume. Remaining uncertainty concerns the optimal timing of vasopressin and corticosteroids, and whether some phenotypes benefit from higher MAP targets.

Perfusion: multimodal and repeated. No single perfusion variable is sufficient. Lactate is sensitive but slow and non-specific; CRT is rapid and reflects the skin's sympathetic response to flow; ScvO2 and the CO2 gap characterize the adequacy of global flow; ultrasound reveals the mechanism. We suggest that clinicians integrate them in a structured sequence: (1) CRT and mottling every 30–60 minutes as the bedside "trigger"; (2) lactate every 2–6 hours as the metabolic "trend"; (3) echocardiography and fluid-responsiveness testing to decide *how* to intervene (fluid, inotrope, vasopressor, or nothing); and (4) venous congestion assessment to recognize when fluid has become harmful. Normal CRT with persistent hyperlactatemia should prompt the search for non-hypoperfusion causes of lactate rather than reflexive further fluid loading, a strategy supported by ANDROMEDA-SHOCK.

Heterogeneity and precision medicine. Sepsis is a syndrome, not a disease. Latent class analyses have identified reproducible clinical phenotypes (e.g., the α, β, γ, δ phenotypes) and biological endotypes (hyperinflammatory vs hypoinflammatory; immunoparalysis) with different responses to fluids, corticosteroids, and immunomodulators. Future trials are likely to be enrichment-based, testing interventions in biomarker-defined subgroups rather than in the heterogeneous whole.

Limitations. This is a narrative, not a systematic, review; study selection may reflect author judgment, and no formal risk-of-bias assessment or meta-analysis was

performed. Most cited trials were conducted in high-income countries, limiting generalizability to settings with fewer ICU beds, delayed presentation, and different microbiological profiles — a gap particularly relevant to Central Asia, including Uzbekistan, where locally generated data on sepsis epidemiology and outcomes remain scarce.

Future directions. Priorities include prospective validation of machine-learning early-warning systems with outcome endpoints; results of ANDROMEDA-SHOCK-2 and similar perfusion-targeted algorithms; personalized vasopressor and MAP strategies; automated microcirculatory analysis; and implementation research adapting bundles to low- and middle-income health systems.

5. Conclusion

Sepsis and septic shock remain among the most lethal conditions in intensive care, but outcome is strongly modifiable in the first hours. Current evidence supports:

Early recognition using sensitive multi-parameter screening (NEWS2, SIRS, electronic alerts) rather than qSOFA alone, with immediate lactate measurement and delivery of the Hour-1 bundle.

Individualized hemodynamic resuscitation with balanced crystalloids, an initial bolus followed by fluid only for demonstrated responsiveness, early norepinephrine to a MAP of 65 mm Hg, and vasopressin plus hydrocortisone for escalating vasopressor needs.

Multimodal, repeated assessment of organ perfusion combining capillary refill time, lactate kinetics, ScvO2 and the venous–arterial CO2 gap, and point-of-care ultrasound, including recognition of venous congestion.

Integrating these elements into institutional protocols, staff education, and quality-improvement programs is the most immediate opportunity to reduce sepsis mortality, including in settings with limited resources.

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