Anatolian Journal of Emergency Medicine 2026;9(3):157-162

INVITED REVIEW / DAVETLİ DERLEME

Sepsis in the Emergency Department: An Evidence-Based Reappraisal of the "Golden Hour"

Acil Serviste Sepsis: "Altın Saat" Kavramının Kanıta Dayalı Yeniden Değerlendirmesi

Faruk Danış[1], Emre Kudu[2]

ABSTRACT

Sepsis affects approximately 49 million people and causes about 11 million deaths worldwide each year, with first medical contact frequently occurring in the emergency department (ED). Over the past decade, the practical meaning of sepsis "time sensitivity" has evolved, and the traditional "golden hour" has shifted from a single bundle toward several distinct evidence streams. We synthesize post-2014 randomized trials, individual-patient-data meta-analyses, and large observational cohorts identified through a structured search of PubMed, Scopus, and Web of Science from 1 January 2014 to 31 May 2026. The search combined controlled-vocabulary and free-text terms related to sepsis, the ED setting, and the review's clinical themes, while landmark earlier trials were identified through hand-searching. Timely recognition and administration of appropriate antibiotics are consistently associated with mortality. In a 49,331-patient New York State cohort, each hour of delay in completing the 3-hour bundle was associated with a 4% relative increase in mortality, whereas the timing of the initial fluid bolus was not. The CLASSIC and CLOVERS trials showed similar mortality with restrictive and liberal fluid strategies in average patients, although initial resuscitation remains necessary in patients with hypoperfusion. Early norepinephrine in CENSER accelerated shock control, while ANDROMEDA-SHOCK supported capillary refill time as a reasonable adjunct to lactate-guided resuscitation. For ED clinicians, the evidence supports three priorities: timely recognition and appropriate antibiotic administration, individualized titration of fluids and vasopressors, and transition to structured post-sepsis follow-up. The "golden hour" is therefore best understood as a debated and evolving construct rather than a single fixed bundle.

Keywords: Antibacterial agents, emergency service, hospital, norepinephrine, resuscitation, sepsis, septic shock

ÖZ

Sepsis, dünya genelinde her yıl yaklaşık 49 milyon kişiyi etkilemekte ve yaklaşık 11 milyon ölüme neden olmaktadır. İlk tıbbi başvuru sıklıkla acil servise yapılmaktadır. Son on yılda sepsiste "zamana duyarlılık" kavramının pratik anlamı değişmiş, geleneksel "altın saat" yaklaşımı tek bir tedavi paketinden farklı kanıt alanlarına doğru evrilmiştir. Bu derlemede, 1 Ocak 2014 ile 31 Mayıs 2026 tarihleri arasında PubMed, Scopus ve Web of Science veri tabanlarında yapılandırılmış bir aramayla belirlenen randomize çalışmalar, bireysel hasta verilerine dayalı meta-analizler ve geniş gözlemsel kohortlar sentezlenmiştir. Aramada sepsis, acil servis ortamı ve derlemenin klinik temalarıyla ilişkili kontrollü sözlük terimleri ile serbest metin terimleri birlikte kullanılmış, daha eski döneme ait dönüm noktası niteliğindeki çalışmalar ise elle tarama yoluyla belirlenmiştir. Sepsisin zamanında tanınması ve uygun antibiyotiklerin uygulanması, mortaliteyle tutarlı biçimde ilişkilidir. New York Eyaleti'nde 49.331 hastayı kapsayan bir kohortta, 3 saatlik tedavi paketinin tamamlanmasındaki her bir saatlik gecikme mortalitede %4'lük göreceli artışla ilişkiliyken, başlangıç sıvı bolusunun uygulanma zamanı mortaliteyle ilişkili bulunmamıştır. CLASSIC ve CLOVERS çalışmaları, genel hasta popülasyonunda kısıtlayıcı ve liberal sıvı stratejilerinin benzer mortalite sonuçlarına sahip olduğunu göstermiştir. Bununla birlikte, hipoperfüzyonu bulunan hastalarda başlangıç resüsitasyonu gerekliliğini korumaktadır. CENSER çalışmasında erken norepinefrin uygulanması şok kontrolünü hızlandırırken, ANDROMEDA-SHOCK çalışması kapiller geri dolum süresinin laktat rehberli resüsitasyona makul bir yardımcı yöntem olarak kullanılmasını desteklemiştir. Acil servis klinisyenleri açısından kanıtlar üç önceliğe işaret etmektedir: zamanında tanıma ve uygun antibiyotik uygulanması, sıvı ve vazopressör tedavilerinin bireyselleştirilerek titre edilmesi ve yapılandırılmış sepsis sonrası izleme geçiş. Bu nedenle "altın saat", tek ve sabit bir tedavi paketi yerine tartışmalı ve gelişmekte olan bir kavram olarak değerlendirilmelidir.

Anahtar Kelimeler: Antibakteriyel ajanlar, acil servis, hastane, norepinefrin, resüsitasyon, sepsis, septik şok

Received: 16 June 2026 Accepted: 10 September 2026

[1]Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Emergency Medicine, Bolu, Türkiye

[2]Marmara University, Faculty of Medicine, Department of Emergency Medicine, İstanbul, Türkiye.

Corresponding Author: Faruk Danış, Assistant Professor. **Address:** Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Emergency Medicine, Gölköy Yerleşkesi, 14030 Merkez/Bolu, Türkiye. **Telephone:** +90 374 254 10 00 **e-mail**: farukdanis@gmail.com.

Atıf için/Cited as: Danis F, Kudu E. Sepsis in the Emergency Department: An Evidence-Based Reappraisal of the "Golden Hour". Anatolian J Emerg Med 2026;9(3):157-162. https://doi.org/10.54996/anatolianjem.1972015.

Introduction

Sepsis accompanies roughly one in five deaths worldwide and is among the syndromes whose conceptual framework has changed most over the past decade; the 2017 Global Burden of Disease estimates put the annual figure at 48.9 million cases and 11.0 million deaths (1). For a large share of these patients, the first medical contact occurs in the ED, where the early trajectory of care is shaped.

That decade reorganized the mental map of sepsis. The 2016 Sepsis-3 consensus moved the definition from systemic inflammatory physiology to organ dysfunction (2). Between 2014 and 2017, three independent randomized trials and their patient-level meta-analysis showed that protocolized early goal-directed therapy (EGDT), derived from the 2001 Rivers protocol, conferred no benefit over contemporary usual care (3). The CLASSIC, CLOVERS, and ANDROMEDA-SHOCK trials then reopened the question of how early, with what, and for whom (4-6).

In emergency practice the “golden hour” has long evoked a single treatment package. This review argues that the construct is best understood not as discarded but as a debated and evolving idea that has fragmented into separable evidence streams: the time component remains strongly supported for recognition and antibiotics, while fixed timetables for fluid volume and hemodynamic targets have given way to individualized, heterogeneity-aware decisions. The sections that follow re-read current evidence in that frame, from the ED point of view. Figure 1 summarizes the resulting ED pathway across its clinical time windows.

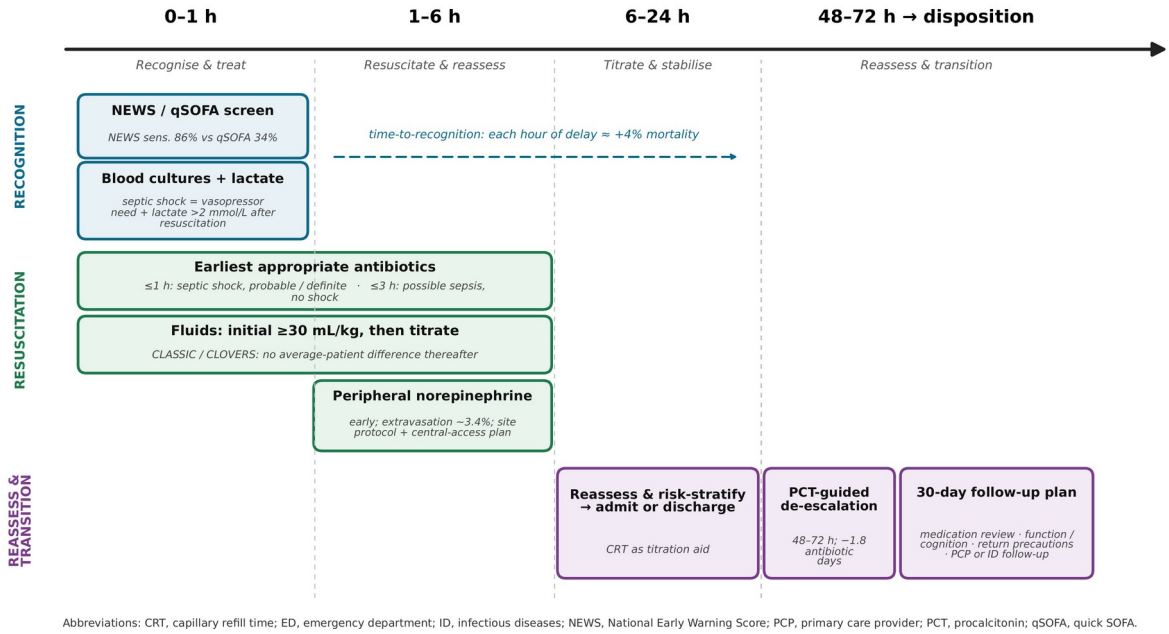


Figure 1. Emergency-department sepsis care mapped onto its true clinical time windows. Each item is placed along the time axis (0–1 h, 1–6 h, 6–24 h, and a 48–72 h reassessment leading to disposition) at the interval in which it actually occurs, in three lanes. Recognition (first hour): NEWS or qSOFA screening (NEWS sensitivity 86% versus qSOFA 34%) and blood cultures with lactate, with septic shock defined as a vasopressor requirement plus lactate greater than 2 mmol/L persisting after adequate fluid resuscitation; the dashed arrow denotes the continuing time-to-recognition risk (each hour of delay ≈ 4% relative mortality increase). Resuscitation: earliest appropriate antibiotic (≤1 h for septic shock and probable/definite sepsis; ≤3 h for possible sepsis without shock), initial fluids ≥30 mL/kg then dynamic titration (CLASSIC and CLOVERS: no average-patient difference thereafter), and peripheral norepinephrine with site and extravasation safeguards (extravasation ≈3.4%). Reassessment and transition: reassessment and risk stratification leading to admission or discharge (capillary refill time as a titration aid); procalcitonin-guided de-escalation at 48–72 h (≈1.8 fewer antibiotic days); and a structured 30-day follow-up plan (medication review, functional and cognitive assessment, return precautions, primary-care or infectious-diseases follow-up). CRT, capillary refill time; NEWS, National Early Warning Score; PCT, procalcitonin; qSOFA, quick Sequential Organ Failure Assessment.

Evidence sources and selection

The invited review was designed as an interpretive narrative synthesis rather than as an exhaustive systematic review. To make the synthesis transparent, we searched PubMed, Scopus, and Web of Science Core Collection for 1 January 2014–31 May 2026, combining MeSH and free-text terms across three axes: sepsis or septic shock; the ED or prehospital setting; and the review's clinical themes (recognition, antibiotic timing, fluids, vasopressors, biomarkers, phenotypes and machine-learning alerts, EGDT, adjuncts, and post-sepsis care). Landmark pre-2014 trials were added by hand-searching. We prioritized post-2014 randomized trials, individual-patient-data meta-analyses, and large observational cohorts; clinical

guidelines, including the 2026 SSC recommendations, were used as context rather than as the evidentiary spine. Final inclusion reflected the authors' judgment of methodological quality and direct bearing on early ED sepsis care.

Defining sepsis and its heterogeneity

Sepsis-3 proposed life-threatening organ dysfunction caused by a dysregulated host response to infection, adopted an increase of 2 or more points in the Sequential Organ Failure Assessment (SOFA) score as the operational criterion, and defined septic shock as a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg plus a lactate above 2 mmol/L in the absence of hypovolemia, a combination with reported hospital mortality above 40% (2). In the same document, qSOFA was positioned as a prompt to consider sepsis rather than a screening or diagnostic test; that caveat was widely overlooked, and qSOFA was later criticized for the low sensitivity it shows when used for a purpose it was not designed for. Table 1 summarizes how the sepsis definition evolved from the 1991 consensus to the 2024 Phoenix criteria.

The operational boundaries of Sepsis-3, drawn from retrospective electronic health record data, do not transfer directly to real-time ED triage (2). The authors themselves noted that systemic inflammatory response syndrome criteria remain useful for recognizing infection, a nuance lost in practice. Sepsis-3 answers “who is septic?” more firmly than it answers “who needs which protocol?”

Iteration	Year	Core concept	Operational criteria
Sepsis-1	1991	Infection + SIRS	Temperature, heart rate, respiratory rate, leukocyte count
Sepsis-2	2001	SIRS-based, expanded	Additional markers (PIRO concept)
Sepsis-3	2016	Life-threatening organ dysfunction from a dysregulated host response	SOFA increase ≥2; septic shock = vasopressor + lactate >2 mmol/L
Phoenix (pediatric)	2024	Organ-dysfunction-based childhood definition	Phoenix Sepsis Score ≥2

Table 1. Historical evolution of the sepsis definition (1991–2024).

SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; PIRO, predisposition–infection–response–organ dysfunction.

The clearest illustration of that gap is the 2019 phenotype derivation by Seymour and colleagues. Consensus k-means clustering of routine variables in 20,189 ED sepsis patients identified four phenotypes: alpha, beta, gamma, and a delta group with hepatic dysfunction and shock (mortality 32%), validated externally (7). In a post hoc simulation of EGDT trial data, the phenotype mix could shift the apparent direction of treatment effect, with delta-predominant groups trending toward harm from aggressive fluids (7). These hypothesis-generating observations offer a plausible mechanism for why uniform resuscitation protocols have so often been neutral.

Pediatric sepsis followed a parallel path: the 2024 Phoenix criteria, derived from 3.05 million encounters, moved childhood sepsis onto an organ-dysfunction basis (Phoenix score ≥2 marking substantially higher mortality); the same “single definition, many phenotypes” tension recurs in children (8,9).

Recognition: The first meaning of time

ED recognition turns on three linked questions: which score sorts patients with adequate sensitivity, what time-to-antibiotics means, and whether time-to-fluid carries the same meaning.

The choice of score moved toward qSOFA in the mid-2010s but was unsettled by subsequent observational data. In an ED cohort of 556 patients with suspected infection (54% meeting Sepsis-3 criteria), the sensitivity for detecting sepsis was 86% for the National Early Warning Score (NEWS; cut-off ≥5) versus 34% for qSOFA (≥2), although qSOFA was the more specific of the two (90% versus 55%) (10). When a screening tool captures only about a third of cases relative to a more sensitive alternative, using it as a primary filter risks systematic misses; ED practice has accordingly settled on treating qSOFA as a late alarm and a more sensitive early warning score as the first-pass sorting instrument.

The evidence for antibiotic timing has, by contrast, strengthened. In the New York State mandated-protocol cohort of 49,331 patients, each hour of delay in completing the 3-hour bundle was associated with a 4% relative increase in hospital mortality (odds ratio 1.04 per hour; 95% CI 1.02–1.05; p<0.001), with a parallel dose–response for antibiotics alone (11). In the 21-hospital Kaiser Permanente cohort, the per-hour effect was larger in the septic-shock subgroup (12). Rothrock and colleagues, however, found that the evidence base for a strict “first-hour” mandate is weaker outside septic shock (13). The 2026 SSC recommendations reconcile these observations through a tiered scheme keyed to the probability and severity of infection: for septic shock and for probable or definite sepsis, antibiotics should be given immediately, ideally within one hour; for possible sepsis without shock, a rapid diagnostic assessment with antibiotics within three hours is advised; and where infection is judged unlikely, antibiotics may be deferred under close monitoring. The operative principle for the ED is therefore the earliest appropriate antibiotic matched to that assessment, rather than the broadest possible agent given reflexively within one hour.

A counterpoint comes from the same New York cohort: the time to completion of the initial fluid bolus was not associated with mortality (odds ratio 1.01 per hour; 95% CI 0.99–1.02; P=0.21) (11). Resting on a single observational cohort, this should be read cautiously, but it suggests that the causal basis for completing a 30 mL/kg bolus within a fixed window is shallower than the time-dependence that holds for antibiotics.

On the biomarker side, the role of procalcitonin has clarified since the 2018 individual-patient-data meta-analysis. Pooling 4,482 patients from 11 randomized ICU trials, Wirz and colleagues found that procalcitonin-guided antibiotic management shortened treatment by 1.19 days (9.3 versus 10.4 days) and lowered 30-day mortality (21.1% versus 23.7%; adjusted odds ratio 0.89; 95% CI 0.80–0.99) (14). The ED implication is deliberately narrow: procalcitonin does not inform the decision to start antibiotics and should not be used to withhold empirical therapy; its value is as a de-escalation tool, opening a discontinuation window at 48–72 hours after admission in patients whose course allows it.

Early resuscitation: The second meaning of time

The negative EGDT trials are the conceptual backdrop. ProCESS, ARISE, and ProMISe compared EGDT with usual care in 1,341, 1,600, and 1,260 patients respectively, with no survival difference; the patient-level PRISM meta-analysis of 3,723 patients reached the same conclusion while EGDT increased central-line placement and intensive care use (3). This is the historical break that splits the "golden hour" from a single bundle into separable evidence streams. Table 2 summarizes these trials and the other landmark studies discussed in this section.

Trial	Year	n	Population	Intervention	Primary outcome
ProCESS / ARISE / ProMISe	2014–15	4,201	ED-based, Septic shock	EGDT vs usual care	60–90-day mortality: no difference
CENSER	2019	310	ED-based, Early septic shock	Early norepinephrine	6-h shock control +27.7%
ANDROMEDA-SHOCK	2019	424	ED/ICU, Septic shock	CRT vs lactate target	28-day mortality HR 0.75 (P=0.06)
CLASSIC	2022	1,554	ICU-based, Septic shock (ICU)	Restrictive fluids	90-day mortality: no difference
LOVIT	2022	872	ICU-based, Sepsis	IV vitamin C	Composite: trend toward harm
CLOVERS	2023	1,563	ED-based, Sepsis-induced hypotension (ED)	Restrictive fluids	90-day mortality: no difference

Table 2. Key randomized trials in ED-relevant sepsis care (2014–2023). The Population column flags each trial's clinical setting (ED-based, ICU-based, or ED/ICU) so that ICU-derived evidence (notably CLASSIC and LOVIT) is not read directly as ED evidence.
CRT, capillary refill time; ED, emergency department; EGDT, early goal-directed therapy; HR, hazard ratio; ICU, intensive care unit; IV, intravenous.

The fluid-volume debate follows directly. CLASSIC (2022) randomized 1,554 ICU patients with septic shock to restrictive versus standard fluids, with 90-day mortality of 42.3% versus 42.1% (5). The later ED-based CLOVERS trial (2023) randomized 1,563 patients with sepsis-induced hypotension to a restrictive (vasopressor-first) or liberal (fluid-first) strategy; despite a 24-hour separation of about 2,100 mL, death before discharge by day 90 was 14.0% versus 14.9% (p=0.61), and the trial stopped for futility (4). These trials do not abolish initial resuscitation: the SSC continues to suggest at least 30 mL/kg of intravenous crystalloid within the first three hours for hypoperfusion or shock, and both trials delivered substantial early volume before diverging. What they show is that beyond that initial resuscitation there is no average-patient advantage to either an aggressive or a conservative subsequent strategy, so that fluids are best reassessed dynamically and titrated to the individual rather than fixed by protocol, which leaves the "which patient benefits from which" question open while granting the clinician latitude.

For fluid type, a small and inconsistent signal favors balanced crystalloids: SMART (15,802 patients) showed a marginal reduction in major adverse kidney events versus saline, while PLUS (5,037 patients) found no difference (15,16). Balanced crystalloid is thus a reasonable default, particularly when high-volume resuscitation risks hyperchloremic acidosis, rather than a strong recommendation.

Vasopressor timing, site, and route are shaped by three evidence streams. In the double-blind CENSER trial, early fixed-dose norepinephrine in 310 patients improved shock control at 6 hours (76.1% versus 48.4%; p<0.001) (17). In ANDROMEDA-SHOCK, 424 patients with septic shock were randomized to capillary refill time (CRT)- or lactate-targeted resuscitation; 28-day mortality was 34.9% versus 43.4% (hazard ratio 0.75; 95% CI 0.55–1.02; p=0.06), with a lower 72-hour SOFA score in the CRT arm and a Bayesian reanalysis favoring CRT (6). Peripheral safety data have accumulated: a systematic review of 1,382 patients across seven studies estimated an extravasation incidence of about 3.4% (95% CI 2.5 to 4.7%), with no reported tissue necrosis or limb ischemia (18). The ED synthesis is that norepinephrine can be started through a peripheral line without waiting for central access or for hypotension to become refractory, provided operational safeguards are in place: a large-bore catheter in a proximal upper-limb vein, frequent inspection of the infusion site, an institutional extravasation protocol with a defined antidote pathway, a plan for timely transition to central access if vasopressor need persists, and continuous hemodynamic monitoring. Within that framework CRT can serve as a bedside titration aid alongside lactate.

Adjuncts remain mixed. Hydrocortisone did not alter 90-day mortality in ADRENAL but, with fludrocortisone in the sicker APROCCHSS population, lowered mortality (relative risk 0.88), so it remains an option in refractory shock (19,20). Intravenous vitamin C trended toward harm in LOVIT, which stopped early, and has no role in routine sepsis care (21).

Where ED evidence is thin: Crowding, mandates, and algorithms

The move from trial result to bedside is constrained by the ED itself, through three independent mechanisms: crowding, bundle mandates, and algorithmic alerts.

Prolonged ED boarding is associated with higher mortality and plausibly degrades the time-sensitive processes that sepsis care depends on (22). In high-volume systems such as Türkiye, how architectural and staffing limits shape bundle adherence is a question awaiting locally grounded data. One concrete evidence gap sits here: the discriminative performance of NEWS2 at the ED door has not been validated in multi-center prospective cohorts, and no such data exist from Türkiye, a tractable target for emergency-medicine research.

The "evidence–action gap" of bundle mandates is visible in the US SEP-1 measure. Pepper and colleagues found SEP-1 compliance was not consistently linked to mortality while pushing broad-spectrum antibiotic use and "sepsis" coding upward, and Rhee and colleagues found coding-based incidence trends inconsistent with the clinical picture (23,24). Institution-level compliance and patient-level outcome are not the same currency.

Algorithmic alerts have generated the highest expectations and the thinnest validation. External validation of the Epic Sepsis Model in 38,455 patients returned an area under the curve of 0.63, with 67% of sepsis cases not flagged (25). The gap between developer-reported and independent performance is the reason machine-learning alerts belong beside, not in place of, clinical judgment in the ED.

After the ED: The post-sepsis syndrome

Sepsis care does not end at discharge, and the ED is the starting point of that continuity. Prescott and Angus reported that roughly one-third of survivors die within a year, about 30% live with cognitive or functional sequelae, and readmission within 90 days approaches 40% (26). Patients discharged from the ED with low-severity sepsis (even under the appearance of a simple urinary infection) belong to this risk pool, so early follow-up planning, medication review, and reassessment of functional capacity should be part of the ED discharge note.

Conclusion

The "golden hour" is best understood not as refuted but as a debated construct that has fragmented into separable evidence streams. Time remains strongly evidenced for recognition and antibiotics, while fixed timetables for fluid volume, hemodynamic target, and adjunctive therapy have yielded to patient-based, heterogeneity-aware decisions. Three priorities organize ED practice: time, for recognition and antibiotics; titration, for fluids and vasopressors; and transition, as the first step of the post-sepsis pathway. The open gaps cluster around prospective phenotype-based triage, safe integration of machine-learning alerts, and protocols that are feasible in low- and middle-income settings. The 2026 SSC update (27) is best used here as one reference point in a continuing debate rather than as an evidentiary spine; reading the primary evidence critically is the precondition for turning any guideline into practice.

Key clinical take-home messages

- Recognize early: in ED cohorts NEWS is more sensitive than qSOFA for sepsis screening; treat time-to-recognition as a modifiable driver of mortality.
- Antibiotics, tiered: immediate (≤1 h) for septic shock and probable/definite sepsis; within 3 h for possible sepsis without shock; defer under monitoring when infection is unlikely: earliest appropriate, not broadest reflexive.
- Fluids: give initial resuscitation (≥30 mL/kg for hypoperfusion/shock), then reassess dynamically and titrate; no average-patient benefit to fixed aggressive or restrictive strategies thereafter.
- Vasopressors: start peripheral norepinephrine early with site and extravasation safeguards and a central-access transition plan; use CRT alongside lactate for titration.
- Procalcitonin is a de-escalation tool at 48–72 h, not a trigger to start or withhold empirical antibiotics.
- Transition matters: discharge planning includes a structured 30-day follow-up (medication review, functional/cognitive assessment, return precautions, primary-care/ID follow-up).

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' Contribution: FD: Conceptualization; defined the ED focused scope; primary literature retrieval, source organization, and reference verification; interpretation of the evidence base; preparation and critical revision of the

original draft; final approval; accountability for all aspects of the work. **EK:** Contributed to the conception and to the framing of the ED-specific synthesis; reviewed the selected literature; contributed to data interpretation and verification of cited evidence; critical revision for important intellectual content and structural/editorial recommendations; final approval; accountability for all aspects of the work. Both authors read and approved the final submitted version of the manuscript and agreed to be accountable for all aspects of the work.

Artificial Intelligence Usage Statement: No generative artificial intelligence tool was used to produce the scientific content, arguments, or conclusions of this manuscript. Basic language, grammar, and spell-checking software was used during preparation. All literature retrieval, source organization, drafting, and the verification of every numerical and definitional statement against the primary sources were carried out by the authors, who take full responsibility for the content.

Ethical Approval: This is an invited review article that does not involve human or animal subjects; ethics committee approval is therefore not required. The review draws exclusively on previously published literature, all of which is appropriately cited in the manuscript.

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