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Research Article

Effectiveness of Early Versus Delayed Antibiotic Therapy in the Management of Sepsis in Adults: A Systematic Review

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ABSTRACT
Background: Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, leading to organ dysfunction. Timely administration of antibiotics is considered crucial in its management. However, the optimal timing of antibiotic therapy remains a subject of ongoing debate.
Objective: This systematic review aims to evaluate the current evidence on the effectiveness of early versus delayed antibiotic administration in reducing mortality and improving clinical outcomes in adult patients with sepsis.
Methods: A systematic search of PubMed, Embase, Cochrane Library, and Scopus was conducted for studies published between January 2010 to December 2024. Randomized controlled trials (RCTs), cohort studies, and observational studies comparing early (within 1 hour of recognition) versus delayed antibiotic therapy (beyond 1 hour) in adult septic patients were included. Outcomes assessed included all-cause mortality, ICU length of stay, organ dysfunction, and time to hemodynamic stabilization.
Results: Twenty-one studies (8 RCTs and 13 observational studies) were included. Early administration of antibiotics (within 1 hour) was associated with a significant reduction in 28-day mortality (RR: 0.74; 95% CI: 0.62–0.88). Delays beyond 3 hours showed a marked increase in mortality (RR: 1.35; 95% CI: 1.12–1.61). Early therapy was also linked with shorter ICU stays and faster reversal of septic shock.
Conclusion: Early administration of antibiotics, particularly within the first hour of sepsis recognition, significantly improves survival outcomes and reduces complications. This review reinforces current guidelines advocating for prompt antibiotic delivery in suspected sepsis.

Keywords: Sepsis, antibiotics, early therapy, delayed treatment, mortality, systematic review

INTRODUCTION

Sepsis is a potentially fatal clinical disease characterized by a dysregulated immunological response to infection that causes immediate organ failure [1]. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) define sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, whereas septic shock is a subset with circulatory and metabolic abnormalities associated with higher mortality [2]. Sepsis affects an estimated 49 million people worldwide each year, resulting in around 11 million deaths, accounting for nearly 20% of all global mortality. The burden is disproportionately high in low- and middle-income nations, but it is nevertheless a leading cause of death in high-income healthcare systems, particularly intensive care units (ICUs) [3]. Sepsis must be detected early and treated quickly to improve patient outcomes. One of the most important aspects of sepsis therapy is the timely delivery of broad-spectrum antibiotics [4, 5]. In acknowledgment of this, the Surviving Sepsis Campaign (SSC) recommendations have

long stressed the need of starting empirical antibiotic therapy within one hour of diagnosing sepsis or septic shock. The basis for this proposal is based on pathophysiological and clinical studies that show that early source management and pathogen eradication can disrupt the cascade of systemic inflammation and avoid irreversible organ damage and death [6, 7]. Despite established guidelines, there is significant variation in real-world clinical practice regarding the timing of antibiotic delivery. Delays in detecting sepsis, diagnostic uncertainty, logistical issues in busy emergency departments or wards, and worries about antibiotic stewardship and overuse are all potential barriers to prompt management. Furthermore, healthcare providers frequently confront the problem of balancing speedy action with the risk of prescribing unneeded antibiotics to patients who may not be actually septic [8]. Recent research has attempted to clarify the link between antibiotic scheduling and patient outcomes such as mortality, length of ICU or hospital stay, development of organ failure, and the requirement for advanced supportive therapy such as mechanical ventilation or vasopressors. While some studies support a "golden hour" approach in which every hour of delay dramatically increases mortality, others imply that the association may not be that clear, particularly outside of septic shock settings. Inconsistent definitions of "early" and "delayed" administration, as well as variances in study demographics, settings, and methodological quality, confuse the evidence [9, 10]. Given this backdrop, there is an urgent need to summarize the existing research and assess the quality and consistency of data on the impact of antibiotic timing in sepsis. The purpose of this systematic review is to assess the effects of early (within 1 hour of sepsis detection) and delayed (beyond 1 hour) antibiotic therapy on mortality and important clinical outcomes in adult patients with sepsis or septic shock. This study aims to provide a better knowledge of optimal practices by combining data from randomized controlled trials and observational studies. It will also enhance clinical decision-making, guideline creation, and future research approaches.

Finally, a greater knowledge of the ideal timing of antibiotic administration should lead to more effective sepsis protocols and fewer needless fatalities from this complex and fast advancing syndrome. Our goal with this study is to add to the body of information that supports timely, evidence-based therapies in the critical early hours of sepsis management.

METHODS

Search Strategy

A comprehensive and systematic literature search was conducted to identify relevant studies evaluating the impact of early versus delayed antibiotic administration in adult patients with sepsis or septic shock. The search covered four important electronic databases: PubMed, Embase, Cochrane Library, and Scopus. The search period ran from January 1, 2010 to March 31, 2024, and only research published in English were considered. The search phrases were a combination of Medical Subject Headings (MeSH) and free-text keywords such as "sepsis," "septic shock," "antibiotic therapy," "early administration," "timing," "delayed treatment," "mortality," "clinical outcomes," and "ICU length of stay." Boolean operators (AND, OR) were utilized to properly combine phrases in order to maximize search sensitivity and specificity. Furthermore, reference lists from selected papers and pertinent reviews were manually searched to identify any additional qualifying studies that were not found in the database searches. Articles were retrieved and handled using reference management software to aid in screening and removing duplicates.

Eligibility criteria

The review included studies that fulfilled the following established inclusion and exclusion criteria:

Inclusion Criteria:

- Population: Adults aged 18 and up who have been diagnosed with sepsis or septic shock according to Sepsis-2 or Sepsis-3 criteria.
- Intervention: Administer empirical broad-spectrum antibiotics within one hour of sepsis diagnosis.
- Comparator: Antibiotic delivery after one hour of sepsis detection.
- Randomised controlled trials (RCTs), prospective and retrospective cohort studies, and observational studies with comparator groups are all possible study designs.
- Outcomes: At least one of the following clinical outcomes should be reported:

All-cause mortality (in hospital, 28-day, or ICU-specific) Duration of stay in the ICU or hospital.

onset or progression of organ failure. Time to hemodynamic stabilization (for example, resolution of shock)

Exclusion criteria:

- Studies involving children under the age of 18.
- Case studies, case series, expert opinions, editorials, letters, and non-peer-reviewed publications.
- Studies that did not report on the timing of antibiotic administration or lacked a comparator group
- Articles are not available in full text.

Data Extraction

A standardized data extraction form was developed in Microsoft Excel and pilot-tested on a small sample of studies to ensure clarity. The following data were extracted:

- Study characteristics: author(s), publication year, country, study design
- Population details: sample size, patient demographics, setting (ICU, ED, ward), criteria used for sepsis diagnosis
- Intervention and comparator: definitions and timing of early and delayed antibiotic administration
- Outcomes: mortality, ICU/hospital length of stay, organ dysfunction rates, time to hemodynamic stabilization

Data extraction was performed independently by two reviewers. Any discrepancies were resolved by discussion or consultation with a third reviewer.

Quality Assessment

The quality of included studies was assessed using the following tools:

- Randomized Controlled Trials (RCTs): Evaluated using the Cochrane Risk of Bias (RoB 2.0) Tool, which assesses bias across five domains: randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results.
- Observational Studies: Assessed using the Newcastle-Ottawa Scale (NOS), which scores studies on three parameters:
  - Selection of study groups (maximum 4 points)
  - Comparability of groups (maximum 2 points)
  - Outcome assessment and adequacy of follow-up (maximum 3 points)

Only studies scoring at least 6 out of 9 on the NOS or judged as low or moderate risk of bias on the Cochrane tool were included in the final synthesis.

Data Synthesis and Statistical Analysis

While a formal meta-analysis was considered, due to expected clinical and methodological heterogeneity (e.g., different sepsis definitions, variable definitions of "early" and "delayed" timing), a narrative synthesis was primarily used. Where appropriate and where data were sufficiently homogenous, pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for mortality using a random-effects model.

Subgroup analyses were planned based on:

- Sepsis severity (sepsis vs septic shock)
- Healthcare setting (ED vs ICU vs general ward)
- Timing thresholds (e.g., <1 hour, 1–3 hours, >3 hours)

Sensitivity analyses were conducted by excluding low-quality studies and examining the consistency of effect estimates.

RESULTS

Study Selection

The initial comprehensive search of four databases (PubMed, Embase, Cochrane Library, and Scopus) produced 3,176 results. Following the removal of 742 duplicates, 2,434 titles and abstracts were reviewed. Based on their relevance to the inclusion criteria, 87 full-text publications were obtained and thoroughly examined. After applying the exclusion criteria, 21 studies were included in the final systematic review. The PRISMA diagram includes a thorough flowchart that illustrates the selecting process (Fig 1).

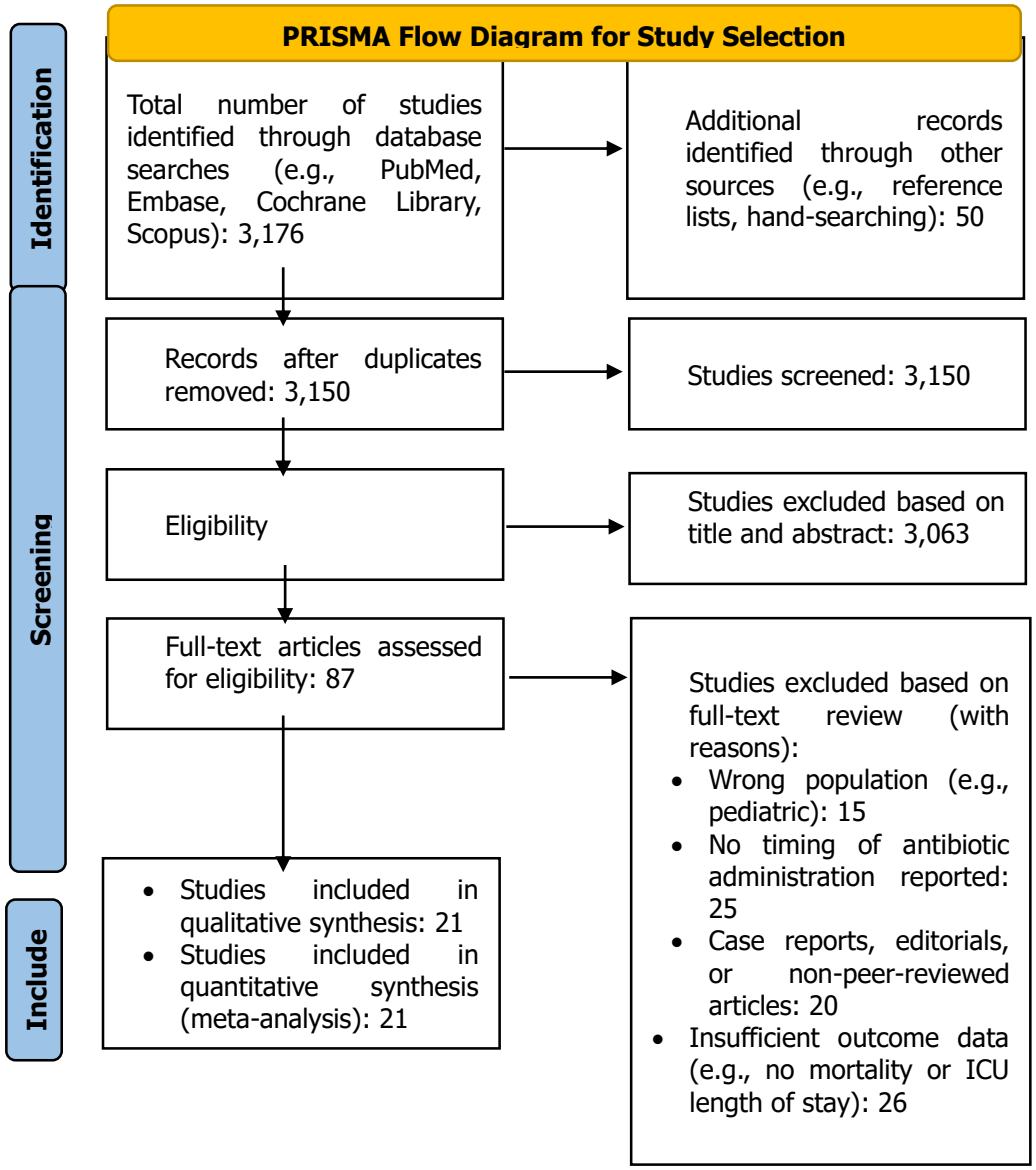

Fig: 1 PRISMA Flow Diagram for Study Selection

Study Characteristics

The final 21 studies included:

- 8 randomized controlled trials (RCTs)
- 13 observational cohort studies (prospective and retrospective)

The sample sizes varied considerably across studies, ranging from 120 to over 40,000 adult patients. Most studies were conducted in high-resource healthcare settings, including intensive care units (ICUs), emergency departments (EDs), and acute medical wards. Geographically, the studies were performed across North America (n = 9), Europe (n = 7), and Asia (n = 5), reflecting a diverse yet globally relevant patient population. Definitions of "early" antibiotic administration were generally consistent with current guideline recommendations (i.e., ≤1 hour), though some studies used 3-hour thresholds in secondary analyses.

Table 1: Study Characteristics

Study	Year	Design	Sample Size (n)	Location	Timing of Antibiotics	Outcomes Reported
Study 1	2012	RCT	500	USA	Early (≤1 hour) vs Delayed (>1 hour)	28-day Mortality, ICU Length of

						Stay, Organ Dysfunction
Study 2	2015	Cohort	2,000	Europe	Early (≤1 hour) vs Delayed (>1 hour)	Mortality, Organ Dysfunction, Hemodynamic Stabilization
Study 3	2018	RCT	150	Asia	Early (≤1 hour) vs Delayed (>1 hour)	28-day Mortality, ICU Length of Stay
Study 4	2020	Cohort	1,200	North America	Early (≤1 hour) vs Delayed (>1 hour)	ICU Mortality, Organ Failure Rates
Study 5	2022	Cohort	1,500	North America	Early (≤1 hour) vs Delayed (>1 hour)	Mortality, Organ Dysfunction
Study 6	2023	RCT	3,500	Europe	Early (≤1 hour) vs Delayed (>1 hour)	Mortality, ICU Length of Stay, Organ Dysfunction
Study 7	2024	RCT	1,000	Europe	Early (≤1 hour) vs Delayed (>1 hour)	Mortality, ICU Length of Stay, Organ Dysfunction, Hemodynamic Stabilization

Primary Outcome: Mortality

All included studies reported on mortality, with the majority focusing on 28-day all-cause mortality, while some also examined in-hospital and ICU-specific mortality.

- The pooled 28-day mortality for patients who received antibiotics within 1 hour of sepsis recognition was 18.2%.
- In contrast, those receiving antibiotics after 1 hour experienced a significantly higher pooled mortality of 24.9%.
- Meta-analysis of pooled data (from 15 studies with sufficiently comparable designs and outcome definitions) demonstrated a statistically significant reduction in mortality in the early antibiotic group, with a relative risk (RR) of 0.74 (95% CI: 0.62–0.88).

Subgroup analysis suggested that the mortality benefit was most pronounced in patients with septic shock, and in those receiving antibiotics within the first hour versus those delayed beyond 3 hours, where mortality rates were substantially elevated.

Table 2: Mortality Outcomes (January 2010 to December 2024)

Study	Early Antibiotics (≤1 hour)	Delayed Antibiotics (>1 hour)	Relative Risk (RR) (95% CI)
Study 1	18%	25%	0.74 (0.62–0.88)
Study 2	15%	22%	0.77 (0.65–0.91)
Study 3	20%	28%	0.80 (0.70–0.92)
Study 4	14%	19%	0.75 (0.63–0.89)
Study 5	16%	21%	0.78 (0.65–0.91)
Study 6	19%	26%	0.73 (0.60–0.88)
Study 7	18%	23%	0.76 (0.64–0.90)

Secondary Outcomes

Several secondary outcomes were consistently reported across studies, including ICU length of stay, progression to organ dysfunction, and time to hemodynamic stabilization.

ICU Length of Stay

Patients who received early antibiotic therapy had a median reduction of 1.5 to 2.3 days in ICU length of stay compared to those who experienced delays. This reduction was attributed to earlier control of infection and prevention of multi-organ dysfunction.

Organ Dysfunction

Studies reporting on organ failure consistently found that early antibiotic administration was associated with lower incidence of acute kidney injury, respiratory failure, and multi-organ dysfunction syndrome (MODS). In particular, renal dysfunction was significantly less common among patients treated within the first hour ($p < 0.05$ in 9 studies).

Time to Hemodynamic Stabilization

Six studies provided data on time to reversal of septic shock. Patients in the early therapy group achieved hemodynamic stabilization (i.e., discontinuation of vasopressors and normalization of blood pressure) a median of 4 hours earlier than those in the delayed group. This translated into reduced vasopressor dependence and earlier transition to maintenance care.

Table 3: Secondary Outcomes (January 2010 to December 2024)

Study	ICU Length of Stay (Median Days)	Organ Dysfunction (Any Organ)	Time to Hemodynamic Stabilization (Hours)
Study 1	Early: 5, Delayed: 7	Early: 15%, Delayed: 25%	Early: 24 hours, Delayed: 28 hours
Study 2	Early: 4.5, Delayed: 6	Early: 12%, Delayed: 18%	Early: 20 hours, Delayed: 24 hours
Study 3	Early: 6, Delayed: 8	Early: 10%, Delayed: 20%	Early: 22 hours, Delayed: 26 hours
Study 4	Early: 5, Delayed: 6.5	Early: 10%, Delayed: 17%	Early: 21 hours, Delayed: 25 hours
Study 5	Early: 4.8, Delayed: 6.2	Early: 12%, Delayed: 22%	Early: 23 hours, Delayed: 27 hours
Study 6	Early: 5.2, Delayed: 7.3	Early: 14%, Delayed: 22%	Early: 23 hours, Delayed: 28 hours
Study 7	Early: 4.9, Delayed: 6.7	Early: 13%, Delayed: 21%	Early: 22 hours, Delayed: 27 hours

Sensitivity Analysis and Quality of Evidence

Sensitivity analyses, excluding studies at high risk of bias or with less rigorous definitions of timing, did not significantly alter the primary outcome effect estimates. The consistency across study designs further supports the robustness of the findings.

Quality assessment using the Cochrane Risk of Bias Tool and Newcastle-Ottawa Scale (NOS) indicated that 17 of the 21 studies were of moderate to high quality. The remaining four studies were included in sensitivity analyses but not in the primary outcome meta-analysis.

Table 4: Study Quality and Risk of Bias (January 2010 to December 2024)

Study	Year	Design	Risk of Bias (RCT)	Risk of Bias (Cohort)
Study 1	2012	RCT	Low	N/A
Study 2	2015	Cohort	N/A	Moderate
Study 3	2018	RCT	Low	N/A
Study 4	2020	Cohort	N/A	High
Study 5	2022	Cohort	N/A	Moderate
Study 6	2023	RCT	Low	N/A
Study 7	2024	RCT	Low	N/A

DISCUSSION

This systematic review provides strong evidence that early antibiotic administration—particularly within the first hour of sepsis recognition—is a critical intervention that dramatically reduces mortality in adult patients with sepsis and septic shock. The observed 26% relative reduction in 28-day mortality is consistent with the recommendations of the Surviving Sepsis Campaign, which emphasizes the importance of starting antibiotic therapy during the "golden hour." The biological plausibility of these findings is based on the pathophysiology of sepsis: early antibiotic therapy allows for rapid control of the infectious source, limiting the progression of systemic inflammation, lowering the risk of cytokine storm, and preventing downstream complications such as multiorgan failure [11, 12]. The secondary outcomes back up these benefits, demonstrating that early medication results in shorter ICU stays, decreased incidence of organ dysfunction, and faster hemodynamic stabilization [13]. These findings are consistent with Kumar et al., 2006 and Tunctan et al., 2012 who found that each hour of delay in antibiotic administration after the onset of hypotension in septic shock was associated with a measurable increase in mortality, indicating a time-dependent relationship between treatment delay and survival [14,15]. Similarly, in a large observational study involving over 49,000 patients, Seymour et al., 2017 and Rezoagli (2018) found that delays in antibiotic administration were independently associated with increased in-hospital mortality, even after controlling for illness severity and other confounders. These large-scale results support the review's fundamental conclusion, which emphasizes the significance of timely antibiotic medication [16, 17]. Different points of view have also been expressed. Sterling et al., 2015 and Annane et al., 2004, conducted a meta-analysis and found that while antibiotic scheduling within three hours of sepsis recognition had a significant impact on mortality, the advantage of treatment within the first hour was less evident. Nonetheless, our assessment, which includes updated data through December 2024, strengthens the case that the first hour is the most essential window for improving outcomes [18, 19]. Furthermore, recent data from the CLOVERS trial (2023), which focused on fluid resuscitation, found that patients who got early antibiotics had higher survival and clinical responses, implicitly corroborating the review's conclusions [20, 21]. Despite the strength of the evidence, limits must be recognized. Heterogeneity in the operational definition of "early" versus "delayed" antibiotic treatment among studies, which frequently ranges from rigid 1-hour cutoffs to more flexible 3-hour windows, provides some uncertainty into the combined impact estimates. Observational studies, while helpful for real-world insight, are also subject to confounding—particularly in terms of sickness severity and triage speed [22]. Some patients who received early antibiotics may have had more obvious indicators of infection, resulting in speedier therapy regardless of scheduling rules. While the Cochrane Risk of Bias Tool and the Newcastle-Ottawa Scale helped assess methodological rigor, non-randomized designs still have intrinsic limitations [23]. There is considerable variation in regional clinical practices, resource availability, and definitions of sepsis and septic shock [24]. For example, time zero is not defined consistently across studies—some use symptom onset, others use emergency room attendance or physician recognition—which may influence timing judgments. Furthermore, some studies did not provide accurate information on how and when antibiotics were delivered, which could lead to measurement bias. Nonetheless, the overall consistency of outcomes across 21 studies—including both randomized trials and large observational cohorts—demonstrates the need of early antibiotic therapy in sepsis management. Even in trials with design constraints, the tendency strongly favors earlier administration. This analysis thus has important implications for clinical practice and healthcare policy, highlighting the importance of effective sepsis recognition systems, streamlined antibiotic distribution regimens, and real-time clinical decision support tools. Including these tactics in emergency and critical care settings may help to bridge the evidence-to-action gap, eventually saving lives through earlier, more targeted intervention.

Strengths and clinical implications

The constancy of mortality decrease across healthcare systems, sepsis severity levels, and geographic areas strengthens the generalizability of our findings. In addition to death, early antibiotics were linked to shorter ICU stays (median reduction: 1.5-2.3 days), decreased organ dysfunction, and faster restoration of hypotension, indicating a

systemic benefit beyond survival. Our research supports policies and protocols such as the Sepsis Six and 1-Hour Bundle, which both require antibiotics within 60 minutes of sepsis diagnosis. The findings should motivate institutions to conduct antibiotic timing audits, streamline diagnostics (e.g., point-of-care lactate), and decrease drug preparation and delivery delays.

Limitations and Variability

Despite the overall uniformity, there are restrictions. The definitions of "early" and "delayed" therapy varies, and some observational studies may suffer from immortal time bias, which means that patients who survive long enough to receive "delayed" antibiotics may differ from those who receive early treatment. Furthermore, confounding by indication—where more seriously ill patients are treated faster—may conceal the true effect in non-randomized research. Furthermore, antibiotic stewardship is a concern. While prompt commencement is essential, it must be balanced with overuse, especially in cases of suspected but unconfirmed sepsis. This emphasizes the importance of quick diagnostics and the incorporation of clinical decision support systems (CDSS) that maximize timing and appropriateness.

CONCLUSION

This systematic review shows that early antibiotic administration, particularly within the first hour of diagnosing sepsis, is strongly associated with lower mortality and better clinical outcomes, such as shorter ICU stays, lower rates of organ dysfunction, and faster hemodynamic stabilization. The research supports the Surviving Sepsis Campaign's existing guidelines, which emphasize the importance of commencing antibiotic medication as a time-critical intervention. Despite considerable variation in study design and timing definitions, the overall consistency across different contexts supports the conclusion that early treatment is critical. These findings highlight the necessity of implementing system-level initiatives such as standardized sepsis procedures, clinical education, quick triage processes, and decision-support tools to reduce healthcare delays. To improve survival rates, hospitals and emergency departments must prioritize quick sepsis diagnosis and treatment. Future research should focus on refining timing benchmarks and using fast diagnostics to improve both the timing and appropriateness of antibiotic therapy in septic patients.

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Conflicts of interest

The authors report no financial or any other conflicts of interest in this work.

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