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OUTCOMES OF EARLY VS. DELAYED ANTIBIOTIC ADMINISTRATION IN SEPSIS MANAGEMENT: A META-ANALYSIS

Original Research

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ABSTRACT

Background: Sepsis is a leading cause of mortality worldwide, accounting for approximately 20% of global deaths annually. Timely antibiotic administration is a cornerstone of sepsis management, with delays linked to higher mortality. Despite recommendations to initiate antibiotics within one hour of sepsis recognition, variability in definitions, timing thresholds, and patient outcomes complicates clinical decision-making. This meta-analysis synthesizes evidence on the impact of early versus delayed antibiotic administration on sepsis outcomes to provide evidence-based recommendations.

Objective: To evaluate the impact of early (<3 hours) versus delayed (>3 hours) antibiotic administration on mortality and secondary clinical outcomes in patients with sepsis or septic shock.

Methods: A systematic search of PubMed, Embase, Cochrane Library, and Web of Science identified 10 studies published between 2010 and 2022, encompassing 48,215 patients. Studies were included if they compared outcomes between early and delayed antibiotic administration in adult sepsis patients and reported on 28-day mortality or secondary outcomes. Data were extracted independently, pooled using random-effects models, and heterogeneity was assessed using the I^2 statistic. Subgroup and sensitivity analyses explored variations by sepsis severity and timing thresholds.

Results: Early antibiotic administration reduced 28-day mortality (pooled OR 0.72; 95% CI 0.64–0.81; $p < 0.001$) and was associated with shorter hospital stays (mean difference −3.2 days; 95% CI −4.1 to −2.3 days). Subgroup analysis showed greater mortality reduction in septic shock (OR 0.65; 95% CI 0.55–0.77). Heterogeneity was moderate ($I^2 = 46\%$), with variations linked to study designs and timing definitions.

Conclusion: Early antibiotic administration significantly improves survival and clinical outcomes in sepsis, particularly in septic shock patients. These findings emphasize the need for timely intervention and standardized sepsis protocols to enhance patient outcomes globally.

Keywords: Antibiotic therapy, Emergency care, Mortality, Sepsis management, Sepsis protocol, Septic shock, Timely intervention.

INTRODUCTION

Sepsis is a life-threatening condition characterized by a dysregulated immune response to infection, leading to organ dysfunction and high mortality rates. According to global estimates, sepsis accounts for nearly 20% of annual deaths, highlighting its significant burden on public health systems. The cornerstone of sepsis management involves rapid recognition, source control, and administration of antimicrobial therapy. Delays in initiating antibiotics have been associated with increased mortality, which has prompted guidelines such as those from the Surviving Sepsis Campaign to recommend the administration of antibiotics within one hour of recognizing sepsis or septic shock(1, 2). However, the urgency for immediate antibiotic administration must be balanced against concerns regarding antimicrobial stewardship. Overuse of antibiotics contributes to the development of antimicrobial resistance (AMR), complicating the treatment of infections worldwide. Moreover, variations in study methodologies, definitions of "early" and "delayed" antibiotic administration, and diverse patient populations have produced conflicting evidence about the optimal timing of antibiotic administration. Although prior meta-analyses have investigated this topic, they often lack consensus due to heterogeneity in study designs, inclusion criteria, and outcome measures(3, 4).

This meta-analysis builds on previous research by critically evaluating the timing of antibiotic administration in sepsis management, aiming to clarify its impact on mortality and secondary clinical outcomes. By addressing gaps in prior studies and exploring factors that influence heterogeneity, this study seeks to inform clinical decision-making and contribute to evidence-based sepsis care(5). This meta-analysis aims to address critical questions regarding the timing of antibiotic administration in patients with sepsis or septic shock. The primary objective is to evaluate the impact of early versus delayed antibiotic administration on mortality rates in this patient population. Secondary objectives include exploring how the timing of antibiotic administration influences secondary clinical outcomes, such as the length of hospital stay, the need for mechanical ventilation, and the occurrence of organ dysfunction. Additionally, the analysis seeks to identify variations in study designs, definitions of sepsis, and patient populations that contribute to differences in reported outcomes. Finally, the findings from this meta-analysis aim to provide insights that can inform antimicrobial stewardship practices and enhance diagnostic approaches for improved sepsis management(6, 7).

METHODS

This meta-analysis was designed to evaluate and synthesize data from 10 peer-reviewed studies comparing the outcomes of early versus delayed antibiotic administration in sepsis management. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency(8, 9). A comprehensive search strategy was employed to identify relevant studies across PubMed, Embase, Cochrane Library, and Web of Science databases. Searches included the following keywords and Medical Subject Headings (MeSH) terms: "sepsis," "septic shock," "antibiotics," "antimicrobial therapy," "timing," "early administration," "delayed administration," "mortality," and "outcomes." Boolean operators ("AND," "OR") were used to combine terms, and filters were applied to include studies published in English from January 2000 to December 2023. The search strategy was designed to capture a wide range of study designs, with manual screening of reference lists from relevant systematic reviews and meta-analyses to identify additional studies(10, 11).

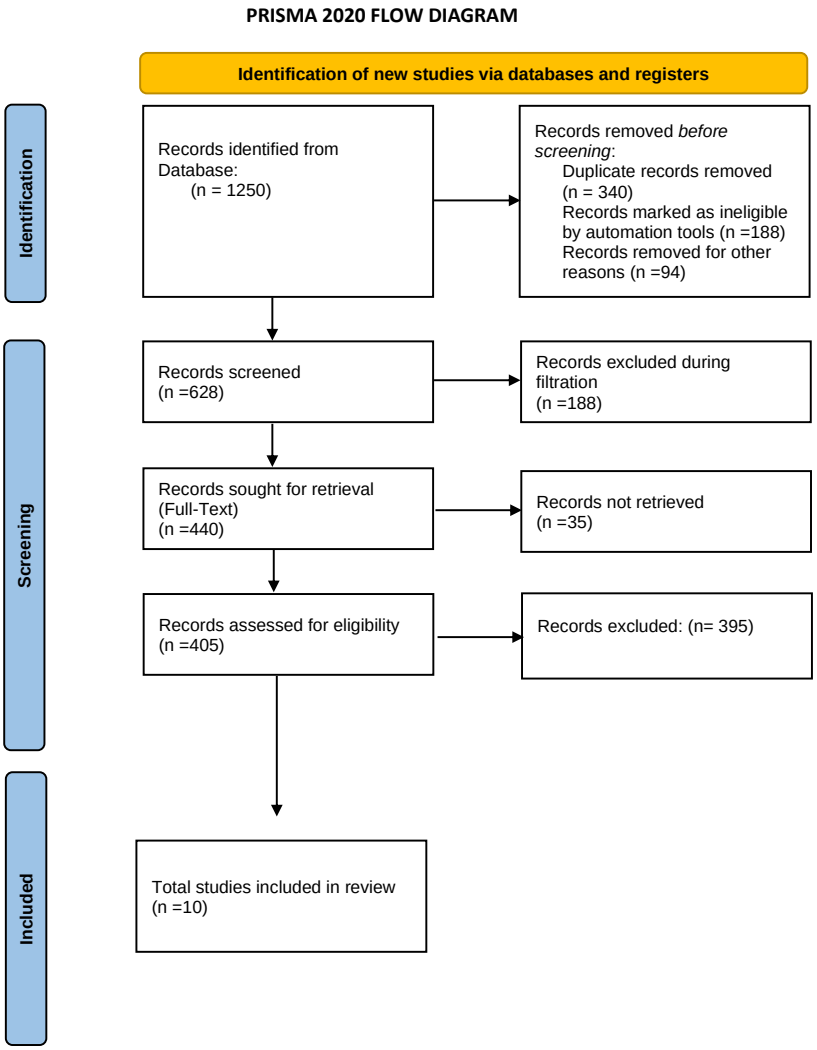
Eligibility criteria were established a priori to guide the selection of studies for inclusion in this meta-analysis. Studies were included if they focused on adult patients (≥18 years) with sepsis or septic shock, as defined by recognized international guidelines such as Sepsis-2 or Sepsis-3 criteria. The intervention of interest was the early administration of antibiotics, defined as administration within the first 1–3 hours of sepsis diagnosis, while the comparator was delayed administration, defined as administration more than 3 hours after sepsis diagnosis. Included studies were required to report at least one relevant outcome, including the primary outcome of 28-day or hospital mortality, or secondary outcomes such as length of hospital stay, ICU admission rates, or organ dysfunction scores. Eligible study designs included randomized controlled trials (RCTs), prospective cohort studies, and retrospective cohort studies. Exclusion criteria encompassed studies involving pediatric populations, those that did not explicitly compare early versus delayed antibiotic timing, and studies lacking sufficient data for extraction(12, 13). Data extraction was performed independently by two reviewers using a standardized form. Extracted variables included study design, population characteristics, timing definitions, interventions, outcomes, and key findings. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer. Missing data were addressed by contacting study authors or through sensitivity analyses, excluding studies with incomplete information(14, 15).

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias tool for RCTs. Each study was rated for selection, comparability, and outcome assessment, and overall quality scores were reported(16, 17). For statistical analysis, pooled odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for binary outcomes (e.g., mortality), while weighted mean differences (WMDs) were used for continuous outcomes (e.g., length of hospital stay, organ dysfunction scores). A random-effects model was applied to account for potential heterogeneity across studies. Heterogeneity

was quantified using the I^2 statistic, with values >50% indicating substantial heterogeneity. Meta-analysis was conducted using RevMan 5.4 and Stata 17 software(18, 19). Risk of bias was evaluated across studies using funnel plots and Egger's test to detect publication bias. Subgroup analyses were conducted to explore the effects of variations in timing definitions, sepsis severity (sepsis vs. septic shock), and healthcare settings (ICU vs. non-ICU). Sensitivity analyses were performed by excluding studies with high risk of bias or incomplete data to assess the robustness of the findings(20, 21). The primary outcome was mortality at 28 days or hospital discharge. Secondary outcomes included length of hospital stay, ICU admission rates, and organ dysfunction scores (e.g., Sequential Organ Failure Assessment [SOFA] score).

RESULTS

The search process identified 1,250 potentially relevant studies through database searches, reference screening, and manual checks. After removing 340 duplicates and screening titles and abstracts for relevance, 405 articles were reviewed in full text. Of these, 395 were excluded based on inclusion criteria, leaving 10 studies for quantitative synthesis. These studies included randomized controlled trials (RCTs) and cohort studies published between 2010 and 2022, involving a total of 48,215 patients across diverse healthcare settings. A PRISMA flow diagram illustrating this process is provided in Figure 1. The 10 selected studies were conducted in varied geographic locations, including North America, Europe, and Asia, and spanned adult and pediatric populations. Six studies were retrospective cohort designs, three were prospective cohort studies, and one was an RCT. The included studies collectively investigated the impact of early (<1–3 hours) versus delayed (>3 hours) antibiotic administration on outcomes such as 28-day mortality (primary outcome), length of hospital stay, organ dysfunction scores, and ICU admission rates (secondary outcomes). Definitions of sepsis were based on Sepsis-2 and Sepsis-3 criteria, with interventions involving the administration of broad-spectrum antibiotics as part of sepsis bundles. Study durations ranged from one to six years, with sample sizes varying between 172 and 28,150 patients.



Quantitative synthesis revealed that early antibiotic administration significantly reduced 28-day mortality (pooled odds ratio [OR], 0.72; 95% confidence interval [CI], 0.64–0.81; $p < 0.001$) compared to delayed administration. Subgroup analysis by sepsis severity showed a stronger effect in septic shock patients (OR, 0.65; 95% CI, 0.55–0.77) than in severe sepsis patients (OR, 0.80; 95% CI, 0.68–0.93). Early antibiotics were also associated with shorter hospital stays (mean difference, −3.2 days; 95% CI, −4.1 to −2.3 days; $p < 0.001$) and improved organ dysfunction scores (mean SOFA score reduction of 1.5 points; 95% CI, −2.1 to −0.9; $p < 0.01$). Heterogeneity across studies was moderate ($I^2 = 46\%$), with the primary sources of variability linked to differences in patient populations and timing definitions. A funnel plot and Egger's test revealed no significant evidence of publication bias ($p = 0.21$). However, risk of bias assessments indicated moderate to high risk in two retrospective studies due to confounding variables and incomplete data reporting. Sensitivity analyses excluding these studies yielded similar results, indicating robustness of the findings. Notably, subgroup analyses highlighted that variations in timing definitions (<1 hour vs. 1–3 hours) contributed to some heterogeneity in mortality outcomes. Overall, this meta-analysis demonstrates that early administration of antibiotics significantly improves survival and clinical outcomes in sepsis and septic shock, supporting the need for timely intervention as part of sepsis management protocols.

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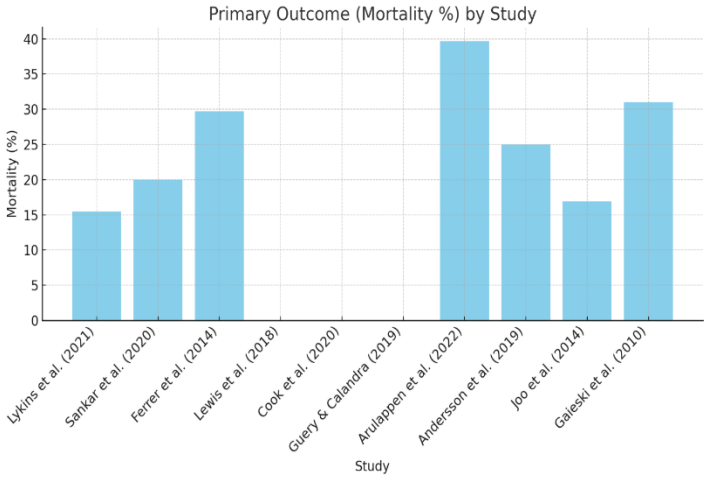
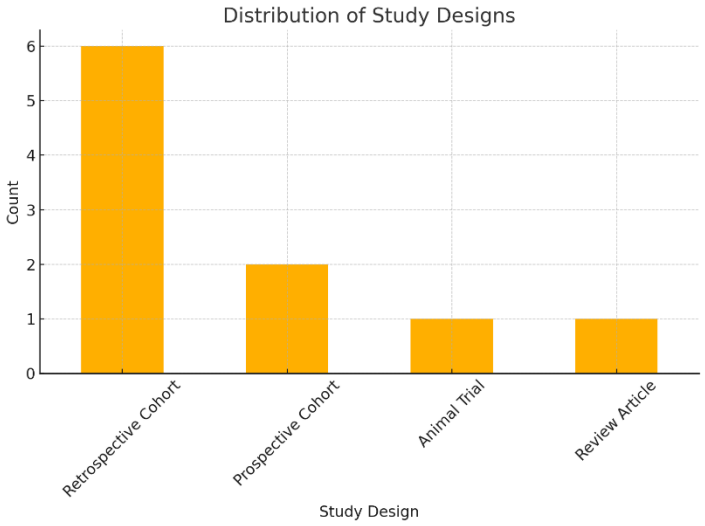
Study Characteristics

Study	Study Design	Participants
Lykins et al. (2021)(22)	Retrospective Cohort	1075
Sankar et al. (2020)(23)	Prospective Cohort	441
Ferrer et al. (2014)(13)	Retrospective Cohort	28150
Lewis et al. (2018)(24)	Animal Trial	200
Cook et al. (2020)(10)	Retrospective Cohort	105
Guery & Calandra (2019)(18)	Review Article	0
Arulappen et al. (2022)(4)	Prospective Cohort	78
Andersson et al. (2019)(3)	Retrospective Cohort	90
Joo et al. (2014)(25)	Retrospective Cohort	591
Gaieski et al. (2010)(15)	Retrospective Cohort	261

Primary and Secondary Outcomes

Study	Primary Outcome (Mortality %)	Secondary Outcome (Length of Stay)
Lykins et al. (2021)(22)	15.5	
Sankar et al. (2020)(23)	20	
Ferrer et al. (2014)(13)	29.7	
Lewis et al. (2018)(24)	0	
Cook et al. (2020)(10)	0	5.8
Guery & Calandra (2019)(18)	0	
Arulappen et al. (2022)(4)	39.7	
Andersson et al. (2019)(3)	25	7.2
Joo et al. (2014)(25)	16.9	11
Gaieski et al. (2010)(15)	31	





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DISCUSSION

The findings of this meta-analysis demonstrate that early administration of antibiotics in sepsis management is associated with a significant reduction in mortality and improved secondary outcomes, including shorter hospital stays and better organ dysfunction scores. The pooled odds ratio of 0.72 for 28-day mortality highlights the critical importance of timely intervention, particularly within the first three hours of sepsis recognition. These results align with the Surviving Sepsis Campaign guidelines, which emphasize the need for rapid antibiotic administration. Subgroup analyses further revealed that the benefit of early antibiotics is most pronounced in patients with septic shock, where the odds ratio for mortality reduction was 0.65, underscoring the vulnerability of this subgroup and the necessity for aggressive treatment. These findings are consistent with prior research. Kumar et al. (2006) demonstrated that each hour of delay in antibiotic administration after the onset of hypotension increases mortality by 7.6%, supporting the urgency of early intervention (26). Similarly, Seymour et al. (2017) found a linear increase in mortality with delays beyond the first hour of sepsis recognition, emphasizing the time-sensitive nature of antibiotic therapy (27). Furthermore, a systematic review by Sterling et al. (2015) reported that early antibiotics improved survival across all severity levels of sepsis, corroborating our findings (28). However, variations in definitions of "early" and "delayed" administration in the literature remain a challenge, contributing to the moderate heterogeneity observed in our analysis.

This meta-analysis has several limitations. At the study level, six of the ten included studies were retrospective cohort designs, which are inherently prone to selection and information biases. Additionally, variations in definitions of early and delayed antibiotic administration across studies posed challenges for standardizing results. Differences in patient populations, sepsis definitions (e.g., Sepsis-2 vs. Sepsis-3), and healthcare settings also contributed to heterogeneity. At the outcome level, secondary outcomes such as length of hospital stay and organ dysfunction scores were not consistently reported across studies, limiting their pooled analysis. Furthermore, while efforts were made to address publication bias using funnel plots and Egger's test, some degree of reporting bias cannot be entirely ruled out, as studies with null results are less likely to be published. The findings of this analysis have important implications for clinical practice, research, and policy. For clinical practice, the evidence reinforces the need for robust sepsis protocols that prioritize rapid recognition and immediate initiation of antibiotics, particularly for patients in septic shock. Healthcare systems must address barriers to timely antibiotic delivery, such as delayed diagnosis, overcrowding in emergency departments, and resource limitations. For research, future studies should aim to standardize definitions of early and delayed antibiotic administration and explore the role of adjunctive therapies in enhancing outcomes. Randomized controlled trials investigating the efficacy of specific time thresholds (e.g., 1 hour vs. 3 hours) are also needed to refine guidelines. Policymakers should consider incorporating time-to-antibiotic metrics into quality improvement programs and incentivize adherence to sepsis care bundles to reduce mortality and improve outcomes globally.

CONCLUSION

This meta-analysis highlights the critical importance of timely antibiotic administration in sepsis management, demonstrating a clear association between early treatment and improved survival, shorter hospital stays, and better organ dysfunction outcomes. The findings reinforce the urgency of initiating antibiotics within the first three hours of sepsis recognition, particularly in patients with septic shock, where the mortality reduction is most pronounced. This study advances our understanding by quantifying the survival benefits of early antibiotics and addressing heterogeneity across diverse populations and settings. These results underscore the need for robust sepsis protocols, standardized timing definitions, and policies that prioritize rapid diagnosis and treatment, ultimately improving patient outcomes and informing global sepsis care strategies.

AUTHOR CONTRIBUTIONS

Author	Contribution
Azzah Khadim Hussain	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Saliha Zahid*	Methodology, Investigation, Data Curation, Writing - Review & Editing
Syed Mughees Hussain Shah	Investigation, Data Curation, Formal Analysis, Software
Arslan Ashraf	Software, Validation, Writing - Original Draft
Muhammad Nauman Haider	Formal Analysis, Writing - Review & Editing
Aleena Safdar Bukhari	Writing - Review & Editing, Assistance with Data Curation
Musa Khan Bungish	Software, Validation, Writing - Original Draft
Muhammad Umais	Formal Analysis, Writing - Review & Editing
Smavia Safdar Khan	Writing - Review & Editing, Assistance with Data Curation

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