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REVIEW ARTICLE

Immediate versus latent antibiotic administration for septic shock or severe sepsis in emergency department - a systematic review

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ABSTRACT

Background: Sepsis is a time-dependent, host response to infection that is linked to an unacceptable high death rate, making it a medical emergency and potentially fatal illness. Therefore, during the first hour of sepsis diagnosis, doctors treating suspected or confirmed cases must start treating patients with broad-spectrum antibiotics. In order to examine research on the effect of early (1-3 hours) versus immediate (0-1 hours) antibiotic administration on mortality in septic shock or severe sepsis patients, we conducted this systematic review.

Method: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this review. Grey literature and databases including Web of Science, PubMed, EMBASE, and the Cochrane Library were searched. We considered studies that included mortality data from consecutive adult patients with septic shock or severe sepsis who were treated with antibiotics within each time frame. All writers extracted the data.

Result: Following screening, eight papers were included in the final evaluation. Seven trials were carried out in the emergency department (ED), and one research was done in the intensive care unit and ED. The ED triage in three studies, ED arrival in three studies, period of organ failure in one research, and ED registration in one study were all considered the zero time for sepsis start. Ferrer et al. and Alan et al. carried out the two largest investigations, involving 34 and 144 hospitals, respectively. Seven studies classified mortality as occurring in the hospital during the index visit, while one research defined it as occurring within 28 days following admission.

Conclusion: The study found that patients with septic shock or severe sepsis who received their first antibiotic later had higher in-hospital mortality.

Keywords: Sepsis, septic shock, early antibiotic administration.

Introduction

One of the biggest problems emergency physicians face is treating septic patients. It is true that sepsis is a potentially fatal organ failure brought on by an abnormal host reaction to an infection. A subtype of sepsis called "septic shock" is characterized by anomalies in the circulatory, cellular, and metabolic systems that lead to a higher death rate [1].

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Early goal-directed treatment, which emphasizes the early administration of antibiotics and the early optimization of hemodynamic perfusion and oxygen supply, is one of the most widely used recommendations for controlling sepsis [2].

The question of whether treating patients with antibiotics sooner - that is, within 1 hour as opposed to 3 hours - after the beginning of sepsis or the patient's admission to the hospital has generated debate. The Surviving Sepsis Campaign recommends antibiotics be administered within 1 hour of the onset or recognition of sepsis, while multiple specialty societies and the Centers for Medicare & Medicaid Services recommend antibiotics be administered within 3 hours of the recognition of sepsis. These recommendations show a divergence of opinion [3].

The former Surviving Sepsis Campaign policy, according to experts, requiring the administration of antibiotics within 1 hour of a patient's arrival may have contributed to overdiagnosis, overtreatment, excessive expense, overuse of resources, increased drug resistance, and higher incidence of *Clostridium difficile* infection [4]. This systematic review aimed to examine fatality rates between patients who received early (1-3 hours) versus immediate (0-1 hour) antibiotic administration for septic shock and severe sepsis.

Method

Study design

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, we conducted this systematic review. Between 2010 and 2022, we conducted a thorough literature search of Web of Science, PubMed, EMBASE, and the Cochrane Library. In order to choose suitable papers, each author separately examined each title and abstract from the literature search.

Inclusion criteria

Adults with septic shock or severe sepsis who had an English-language description met the inclusion criteria. Antibiotics within 0-3 hours of arrival or a diagnosis of severe sepsis or septic shock were inclusion criteria for the intervention. In contrast, patients who got antibiotics within 0-1 hour as opposed to more than 1-3 hours met the inclusion criteria. Mortality rates were the inclusion criterion for the outcome.

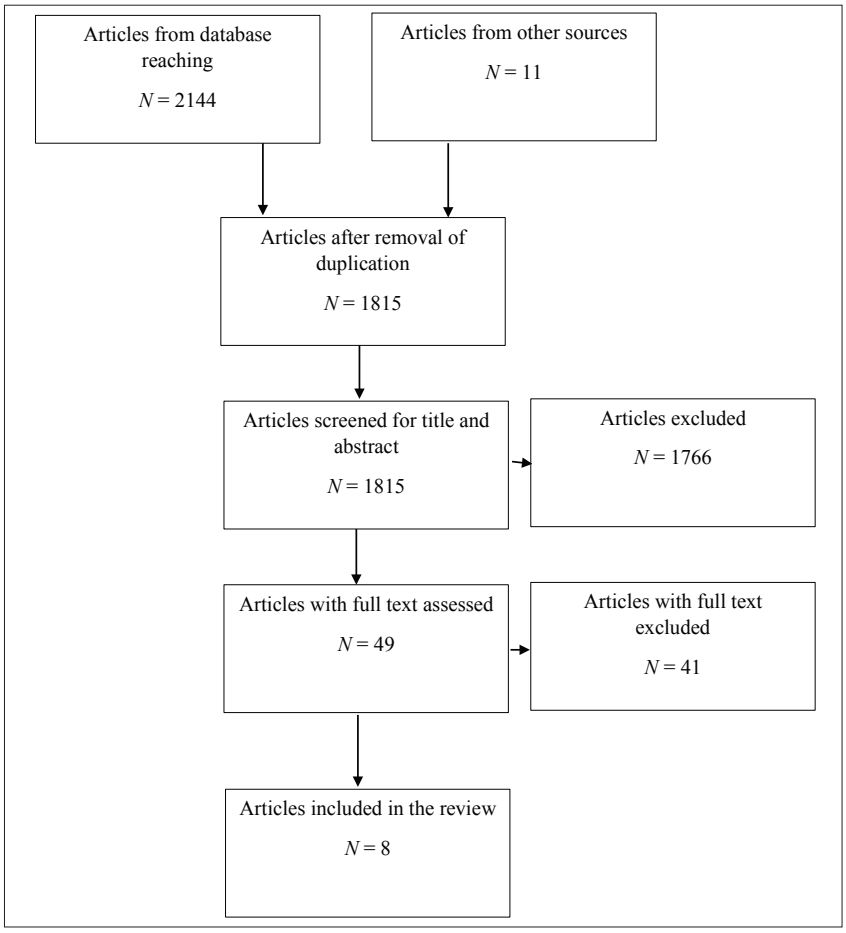

Figure 1. *Consort chart of selected studies.*

Exclusion criteria

The population of patients who were 17 years of age or younger, the absence of death statistics, and the absence of the total number of patients were among the exclusion criteria.

Data processing

All authors independently examined each included study to extract data, which was then entered into Google sheet and Google documents (with access to all authors) to avoid duplicating or missing information. The study population, study specifics (author, population country, publication year, and design), and specific endpoint data (number receiving immediate versus early antibiotics, any risk adjustment between periods, any other indicator of severity between periods, and mortality) were among the data that were extracted from each article. In order to settle disputes over the retrieved data, the group consensus method was applied.

Table 1. *Method and conclusion of included reviews.*

Citation	Method	conclusion
Alam et al. [5]	Twelve regional ambulance services that cover 34 secondary and tertiary care institutions in the Netherlands participated in a randomized controlled open-label experiment. The effects of early antibiotic therapy in the ambulance and standard care were examined in this research. Block-randomization with blocks of size 4 was used to randomly assign eligible patients (1:1) to either normal treatment (fluid resuscitation and supplemental oxygen) or the intervention of intravenous ceftriaxone 2,000 mg in addition to usual care. Each region's randomization was stratified. All-cause mortality at 28 days was the main result, and intention to treat was used for analysis.	Antibiotics were given to the intervention group for a median of 26 minutes. After ED arrival, the median antibiotic time for the standard care group was 70 minutes. On day 28, the intervention group had lost 8% of its patients, while the group with usual care had lost 8% as well. Within 28 days, 10% of patients in the usual care group and 7% of patients in the group of intervention were readmitted to the hospital.
Peltan et al. [6]	This retrospective cohort research comprised adult patients in ED with clinical sepsis who were not trauma survivors. Authors assessed the relationship between antibiotic administration time and mortality.	Clinically significant increases in long-term sepsis mortality are linked to delays in antibiotics administration in the ED.
Leisman et al. [7]	The study was conducted in nine hospitals retrospectively. All hospitalized patients meeting the criteria for acute organ failure, two or more systemic inflammatory response syndrome criteria, and concomitant infection are considered to be in sepsis or septic shock. While physically in the ED, EDPS satisfied the inclusion requirements. Once out of the ED, HPS satisfied the requirements.	The clinical presentation, comorbidities, and source of admission were HPS and EDPS diverged. A considerable amount of the variations in mortality might be explained by the fact that these individuals got first resuscitation much less quickly than other patients.
de Groot et al. [8]	Three EDs are the sites of this prospective multicenter trial. Based on the predisposition, infection, response, and organ failure score, patients were divided into three groups according to the severity of their illnesses: low, middle, and high. The trial was open to consecutive hospitalized ED patients receiving intravenous antibiotic treatment for a suspected illness. The number of days that the patient survived outside the hospital on day 28 regarded as the main outcome measure.	A shorter duration before starting antibiotics was not observed to be linked to better relevant clinical outcomes in ED patients with moderate to severe sepsis who were treated with antibiotics within 6 hours of ED arrival.
Drumheller et al. [11]	In this ED-based retrospective observational cohort research, 411 adult patients with septic shock or severe sepsis were included. The medical record provided information on in-hospital outcomes, microbiological cultures, and ED factors.	ED patients who are receiving early, resuscitation care yet nevertheless have severe sepsis or septic shock.
Castaño et al. [9]	A prospective cohort research conducted in three hospitals to examine length of stay and hospital fatality rates based on various antibiotic prescription categories.	There was no correlation seen between duration of stay or death and improper antibiotic prescribing or delayed treatment initiation.
Ferrer et al. [10]	Analysis done in retrospect on a sizable dataset that was gathered in advance for the sepsis patients.	The study demonstrates that patients with septic shock and severe sepsis with delayed delivery of the initial antibiotic were linked to higher in-hospital mortality. Furthermore, the chance of death increased linearly with every hour that the introduction of antibiotics was delayed.
Whiles et al. [12]	Retrospective cohort at ED patients with septic shock or severe sepsis who are at least 18 years old and who get antibiotics within a day.	This study highlights the significance of early, administration of antibiotic in severe sepsis patients who are admitted through the ED.

Table 2. *Characteristics of included studies.*

Citation	Setting	Number of hospitals included	Antibiotics median time (minutes)	0-1 hour antibiotic recipient mortality	1-3 hours antibiotic recipient mortality
Alam et al. [5]	ED	34	70	11%	7%
Peltan et al. [6]	ED	4	166	23.2	19.5
Leisman et al. [7]	ED	9	60 minutes in 48% of participants and 180 minutes in 80% of them	19.4	19.2
de Groot et al. [8]	ED	3	Not recorded	13.9	14
Drumheller et al. [11]	ED	1	Not recorded	17.8	25.6
Castaño et al. [9]	ED	3	Not recorded	26.3	18
Ferrer et al. [10]	ED and ICU	144	Not recorded	32	28.3
Whiles et al. [12]	ED	1	177	12.2	9.2

Result

2,411 articles were found by the first database searches, and 11 of those were found through reference inspection (Figure 1). Eight studies were included in the final evaluation after screening and full-text review (Table 1) that describe the method and conclusion of the included studies. seven studies were conducted in the emergency department (ED) while one study conducted in intensive care unit (ICU) and ED. The zero time for sepsis onset was defined as ED triage in three studies, ED arrival in three studies, time of organ dysfunction in one study and ED registration in one study. The largest two studies were conducted by Ferrer et al. [10] and Alam et al. including 144 and 34 hospitals respectively. Mortality was defined in seven studies as happening in the hospital during the index visit and in one research as happening within 28 days after admission.

The highest antibiotic administration median time was observed in Whiles et al. [12] (177 minutes) while the lowest was observed in Leisman et al. [7] (60 minutes) 0-1 hour antibiotic recipient mortality ranged from 11% to32%, while 1-3 hours antibiotic recipient mortality ranged from 7% to28.3% (Table 2).

Alam et al. [5] study found that within 28 days, 10% of patients in the usual care group and 7% of patients in the group of intervention were readmitted to the hospital. In Peltan et al. study [6] clinically significant increases in long-term sepsis mortality are linked to delays in antibiotics administration in the ED. According to Leisman et al. [7] study the clinical presentation, comorbidities, and source of admission were hospital-presenting sepsis (HPS) and EDPS diverged. In de Groot et al. [8], shorter duration before starting antibiotics was not observed to be linked to better relevant clinical outcomes in ED patients, also Castaño et al. [9] found that There was no correlation seen between duration of stay or death and improper antibiotic prescribing or delayed treatment initiation. while in Ferrer et al. [10] patients with septic shock and severe sepsis with delayed delivery of the initial antibiotic were linked to higher in-hospital mortality.

Discussion

In the immediate or early groups, there was no difference in mortality between individuals with septic shock and severe sepsis who were getting antibiotics, according to our research. When comparing the immediate groups to the early group, we discovered that the group with severe sepsis had a greater fatality rate [5,12].

A meta-analysis that evaluated the administration of antibiotics in sepsis in 2015 came to the conclusion that there was “no significant mortality benefit of administering antibiotics,” with the majority of the investigation focused on the time between onset and 3 hours. Within an hour of shock detection or 3 hours after ED triage. A subset study of their published data revealed no difference in mortality between patients who were triaged to the ED within an hour and those who were triaged between 1 and 3 hours. Only four studies that compared durations shorter than 3 hours were included in that meta-analysis [13].

In metaanalyses comparing antibiotics given less than or equal to 1 hour to those given more than 1 hour after ED arrival in sepsis, Johnston et al. [14] and Xantus et al. [15], found “equivocal evidence of survival benefit” and that antibiotics “seemed” to reduce mortality if given less than or equal to 1 hour after ED presentation. When comparing patients who received antibiotics more than 1 hour to more than 6 hours after ED arrival to those who received antibiotics less than or equal to 1 hour after ED arrival, these meta-analyses, however, included studies with simple sepsis and studies that did not analyze antibiotics given less than or equal to 1 hour after ED arrival [14,15].

According to the current guidelines of the Surviving Sepsis Campaign, intravenous antibiotics should be administered within 1 hour of the diagnosis of septic

shock or severe sepsis [16]. These recommendations mention two studies that found there is a "measurable" increase in mortality for every hour that antibiotics are delayed [10,16-18]. In the study, conducted by Kumar et al. [7], the primary comparison of mortality was made between patients who received antibiotics within 1 hour and those who received them between 1 and 12 hours after the onset of recurrent hypotension or persistent hypotension. According to his study, there was a 7.6% increase in mortality for every hour that patients in this trial were not given antibiotics after developing persistent or recurrent hypotension [19]. The majority of patients in this research received antibiotics far after the current 1- and 3-hour guidelines, and 25% received medicines 15 hours or more after persistent or recurrent hypotension emerged. The median time to antibiotic treatment in this study was 6 hours [19].

Patients who got antibiotics within the first hour of presentation had a greater crude mortality rate than those who received medicines between 1 and 3 hours after presentation, according to a second research that was used to support the prompt administration of antibiotics [20].

Conclusion

According to the study, in-hospital mortality was greater among patients with septic shock and severe sepsis who had their first antibiotic administered later. Moreover, for every hour that passed after antibiotics were introduced, the risk of dying rose linearly.

List of Abbreviations

ED	Emergency department
HPS	Hospital-presenting sepsis
ICU	Intensive care unit

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent to participate

Not applicable.

Ethical approval

Not applicable.

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