# Effect of Immediate Administration of Antibiotics in Patients With Sepsis in Tertiary Care: A Systematic Review and Meta-analysis

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## ABSTRACT

**Purpose:** The goal of this review was to synthesize existing evidence regarding outcomes (mortality) for patients who present to the emergency department, are administered antibiotics immediately (within 1 hour) or later (>1 hour), and are diagnosed with sepsis.

**Methods:** A search of PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and CINAHL, using the MeSH descriptors "sepsis," "systemic inflammatory response syndrome," "mortality," "emergency," and "antibiotics," was performed to identify studies reporting time to antibiotic administration and mortality outcome in patients with sepsis. The included studies (published in English between 1990 and 2016) listed patient mortality based on time to antibiotic administration. Studies were evaluated for methodologic quality, and data were extracted by using a data extraction form tailored to this study. From an initial pool of 582 potentially relevant studies, 11 studies met our inclusion criteria, 10 of which had quantitative data for meta-analysis. Three different models (a random effects model, a bias-adjusted quality-effects [synthetic bias] model, and an inverse variance heterogeneity model) were used to perform the meta-analysis.

**Findings:** The pooled results suggest a significant 33% reduction in mortality odds for immediate (within 1 hour) compared with later (>1 hour) antibiotic administration (OR, 0.67 [95% CI, 0.59–0.75]) in patients with sepsis.

**Implications:** Immediate antibiotic administration (<1 hour) seemed to reduce patient mortality. There was some minor negative asymmetry suggesting that the evidence may be biased toward the direction of effect. Nevertheless, this study provides strong evidence for early, comprehensive, sepsis management in the emergency department. (*Clin Ther*. 2017;39:190–202) 

**Key words:** antibiotics, emergency services, medication appropriateness, mortality, sepsis, systemic inflammatory response syndrome.

## INTRODUCTION

It is estimated that 18 million cases of sepsis occur per year worldwide. More than 17,000 of those episodes are in Australia and that number is projected to grow at a rate of 1.5% per year.[1] Sepsis has a high mortality rate and results in significant morbidity.[2]

Sepsis arises when the body's immune response to infection causes a widespread inflammatory response. Often described under the umbrella term "sepsis," there is an acknowledged continuum now evaluated

*Accepted for publication December 2, 2016.*
http://dx.doi.org/10.1016/j.clinthera.2016.12.003
0149-2918/$ - see front matter

by using a sequential (sepsis-related) organ failure assessment[3] and sometimes evaluated with the use of a staging score.[4] Each form of sepsis is progressively more severe, with a higher mortality rate. Septic shock (with acute organ dysfunction) has a mortality rate up to 46%.[5] Sepsis is a time-sensitive illness in which rapid, relatively uncomplicated treatment (including the administration of antibiotics) can translate into lives saved.[6]

International consensus guidelines recommend initiating broad-spectrum antibiotic coverage immediately (within the first hour) once a diagnosis of severe sepsis and septic shock is considered.[7] This recommendation is largely based on 1 large retrospective study by Kumar et al[8] and expert consensus. Kumar et al estimated that mortality rates increase by 7.6% with every 1-hour delay in starting antimicrobial therapy in the first 6 hours after hypotension onset. Furthermore, it was shown that effective antimicrobial administration within the first hour of documented hypotension in septic shock was associated with increased survival to hospital discharge.

A Cochrane review of "early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults" did not locate any randomized controlled trials.[9] They were therefore unable to make any specific recommendations other than the need exists for large prospective, double-blind, randomized controlled trials examining the efficacy of immediate (within 1 hour) versus later broad-spectrum antibiotics in adult patients with severe sepsis.[9] In the interim, research derived from other (less rigorous) study types incorporating broader (additional) sepsis diagnoses may be useful to guide practice in the emergency setting.[10]

The aim of the present systematic review and meta-analysis was to study and assess the current evidence regarding patients who present to the emergency department (ED) and are diagnosed with a sepsis illness (ie, systemic inflammatory syndrome, sepsis, severe sepsis, sepsis with septic shock, sepsis with organ dysfunction) in terms of in-hospital mortality outcomes for those who are administered antibiotics immediately (within 1 hour) or later (>1 hour).

## MATERIALS AND METHODS

### Identification of Studies

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[11] Ethical review is not required for a review study. EMBASE, MEDLINE, CINAHL, and the Cochrane Central Register of Controlled Trials were searched. All terms were mapped to the appropriate MeSH/EMTREE/CINAHL headings and "exploded." Search terms used included "sepsis," "systemic inflammatory response syndrome," "mortality," "emergency," and "antibiotic agent." Additional search strategies (ie, PubMed, Google, reference lists of articles, forward and backward reference chaining) were used to identify additional articles for potential inclusion.[12,13]

### Study Selection

Studies were included if they were published in the English language between 1990 and 2016; the Surviving Sepsis Campaign was formulated in 1990, and guidelines of early, goal-directed therapy (which included early use of antibiotics) were produced at that time. All original research studies that included the term sepsis, were associated with EDs as a setting for antibiotic administration, and described outcomes that include mortality pertaining to early (<1 hour) versus late (>1 hour) administration of broad-spectrum antibiotics were included.[11,13] Studies were excluded if they were qualitative in nature, did not include an assessment of early versus late antibiotic administration, and did not include some measure of mortality as an outcome.[14]

### Data Extraction and Quality Assessment

Two authors (Drs. Clark and Johnston) independently undertook the initial screening for article inclusion using the Rayyan platform to facilitate study selection.[15] Clarification of inclusion was resolved by discussion with other authors. The article selection process is displayed in Figure 1. Data extracted from each study included author, year and country of publication, sample size, study design, main outcomes measured, and results (Tables I and II).

The quality of articles that met inclusion criteria were independently reviewed and assessed by 2 authors (Dr. Johnston and Ms. Sharman) with clarification resolved by a third author (Julia Crilly). Included studies were assessed by careful reading of the articles for their methodologic quality according to National Health and Medical Research Council guidelines[16] and a generic scale created by the authors (Table III). The latter includes 17 questions (with