Outcome of Immediate Versus Early Antibiotics in Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis

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Study objective: Debate exists about the mortality benefit of administering antibiotics within either 1 or 3 hours of sepsis onset. We performed this meta-analysis to analyze the effect of immediate (0 to 1 hour after onset) versus early (1 to 3 hours after onset) antibiotics on mortality in patients with severe sepsis or septic shock.

Methods: This review was consistent with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Searched databases included PubMed, EMBASE, Web of Science, and Cochrane Library, as well as gray literature. Included studies were conducted with consecutive adults with severe sepsis or septic shock who received antibiotics within each period and provided mortality data. Data were extracted by 2 independent reviewers and pooled with random effects. Two authors independently assessed quality of evidence across all studies with Cochrane's Grading of Recommendations Assessment, Development and Evaluation methodology and risk of bias within each study, using the Newcastle-Ottawa Scale.

Results: Thirteen studies were included: 5 prospective longitudinal and 8 retrospective cohort ones. Three studies (23%) had a high risk of bias (Newcastle-Ottawa Scale). Overall, quality of evidence across all studies (Grading of Recommendations Assessment, Development and Evaluation) was low. Pooling of data (33,863 subjects) showed no difference in mortality between patients receiving antibiotics in immediate versus early periods (odds ratio 1.09; 95% confidence interval 0.98 to 1.21). Analysis of severe sepsis studies (8,595 subjects) found higher mortality in immediate versus early periods (odds ratio 1.29; 95% confidence interval 1.09 to 1.53).

Conclusion: We found no difference in mortality between immediate and early antibiotics across all patients. Although the quality of evidence across studies was low, these findings do not support a mortality benefit for immediate compared with early antibiotics across all patients with sepsis. [Ann Emerg Med. 2020;76:427-441.]

Please see page 428 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

In 2017, 48.9 million sepsis cases and 11 million sepsis deaths were estimated to have occurred worldwide, accounting for nearly 20% of all global deaths.[1] Sepsis remains the most common diagnosis related to mortality in hospitalized patients, contributing to one third to half of all inpatient deaths.[2,3] Early antibiotics have been described as an important component in decreasing mortality from sepsis.[4-6] The original landmark study cited by experts and guidelines describing improved outcome with earlier antibiotics comprised inpatients who had extreme delays in antibiotic administration of 6 to 12 hours after onset of sepsis-related hypotension.[4,5,7-9] More recent studies describing a worse outcome in patients with a longer time to initiation of antibiotics showed that a delay of more than 3 to 12 hours after sepsis onset or recognition is associated with increased mortality.[10-12]

Debate exists about whether outcome differs in patients receiving antibiotics within an earlier time frame, especially within 1 hour versus 3 hours of sepsis onset or patient arrival at the hospital. This divergence of opinion is manifested in differing recommendations for antibiotic administration in sepsis between the Surviving Sepsis Campaign, who recommend antibiotics within 1 hour of sepsis onset or recognition, and multiple specialty societies

Editor's Capsule Summary

What is already known on this topic

Despite a lack of evidence, recent recommendations suggest a requirement of a 1-hour interval from arrival for antibiotic administration in patients with sepsis.

What question this study addressed

This meta-analysis of 13 studies with greater than 33,000 patients assessed the effect of immediate (<1 hour) versus early (1 to 3 hours) administration of antibiotics on mortality in patients with sepsis.

What this study adds to our knowledge

Immediate administration of antibiotics showed no effect on mortality compared with early administration.

How this is relevant to clinical practice

Early in the treatment of sepsis, timing of antibiotic administration within the first 3 hours has no measurable benefit for outcome.

plus the Centers for Medicare & Medicaid Services, who recommend antibiotics within 3 hours of sepsis recognition.[4-6,10-17]

IMPORTANCE

Experts have argued that the previous Surviving Sepsis Campaign mandate to administer antibiotics within 1 hour of patient arrival potentially leads to overdiagnosis, overtreatment, excess cost, excess resource use, increased drug resistance, and increased rates of *Clostridium difficile* infection.[15,18,19] Knowledge of the differential outcomes of patients given antibiotics in the 0- to 1-hour versus 1- to 3-hour period will allow clinicians to make more informed decisions regarding the urgency to administer antibiotics in patients with suspected sepsis.

Goals of This Investigation

The purpose of this systematic review was to compare mortality rates in patients with severe sepsis and septic shock who received immediate antibiotics versus early antibiotics (0 to 1 versus >1 to 3 hours).

MATERIALS AND METHODS

Study Design

We performed this systematic review and meta-analysis consistent with the Preferred Reporting Items for Systematic Reviews and Meta-analyses methodology (Table E1, available online at http://www.annemergmed.com). The protocol was registered with PROSPERO (CRD42020154674). Our study was performed to analyze the association of immediate (0 to 1 hour after onset) versus early (>1 to 3 hours after onset) antibiotic administration on mortality rates of patients with severe sepsis and septic shock.

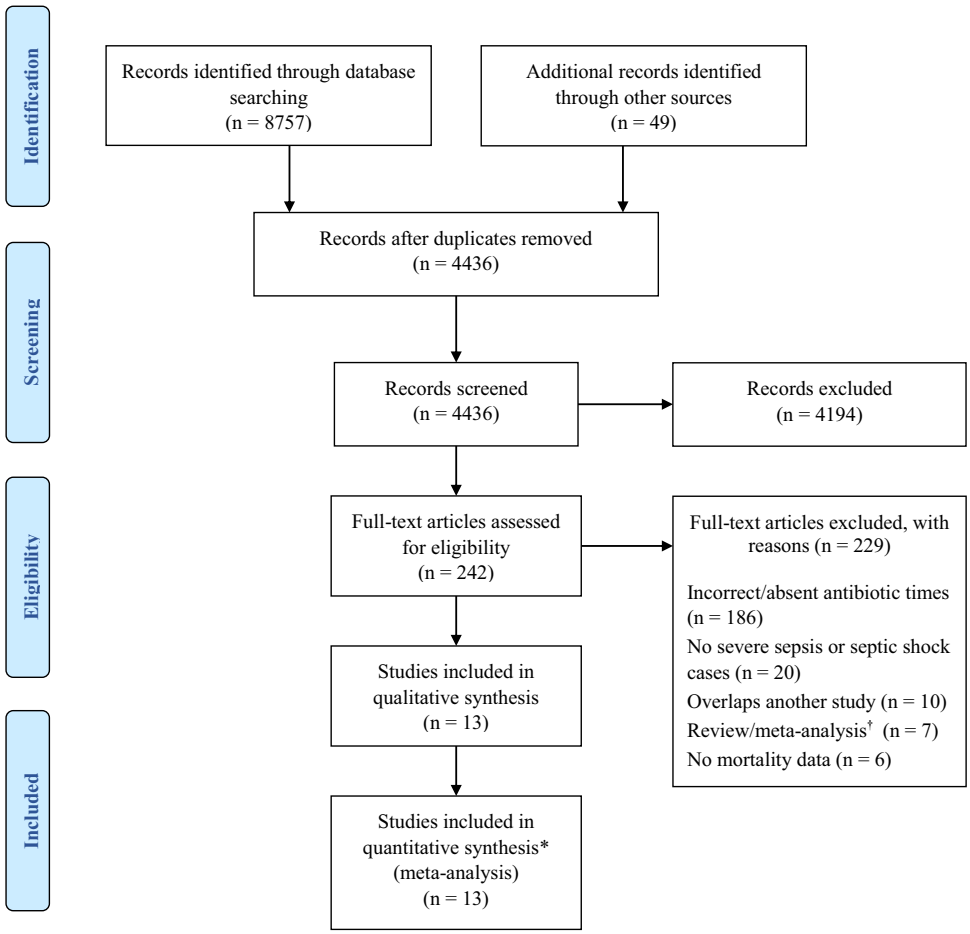
We performed a comprehensive literature search of MEDLINE's PubMed, EMBASE, Cumulative Index of Nursing and Allied Health Plus, Wiley's Cochrane Library, and Web of Science (version 5.34) between November 22 and December 5, 2019. A targeted gray literature search was performed with OpenGrey, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (Table E2, available online at http://www.annemergmed.com). Before the search was performed, the search protocol was augmented and assessed with PRESS guidelines by an experienced librarian.[20]

Two study authors (M.B., S.G.R.) independently reviewed each title and abstract from the literature search to select potential articles.

For patient, population, and problem, inclusion criteria were adults (≥18 years) with severe sepsis or septic shock described in English-language publications or in unpublished literature after December 31, 2000. This date was chosen to coincide with development of the first iteration of Sepsis-2 international definitions for severe sepsis and septic shock.[21] To be included, studies required consecutive patients with these diagnoses. All prospective, retrospective, observational, cross-sectional, cohort, case-control studies, and cases series were considered for inclusion. For intervention, inclusion criteria were antibiotics within 0 to 3 hours of arrival or diagnosis of severe sepsis or septic shock. For comparison, the inclusion criterion was patients who received antibiotics within 0 to 1 versus greater than 1 to 3 hours. For outcome, inclusion criteria were mortality rates for each subset supplied, with mortality defined as either during index hospitalization or within 30 days of the index admission.

Exclusion criteria included the following: absence of total number of patients for either the 0 to 1-hour or 1- to 3-hour groups, absence of mortality data for either antibiotic period, duplicate studies or studies using the same patient database during the same period, and population comprising patients aged 17 years or younger.

The full text and references of each article or abstract that passed this initial screening of either reviewer were analyzed to further identify missed articles. Full text from each selected article obtained during the initial screening and from references within were read by each reviewer and



* includes six previously published studies where authors provided collected but unpublished data and 43 studies identified through references within articles.
† includes one letter to the editor

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram.

selected according to predetermined inclusion or exclusion criteria. At the full-text screening stage, 2 authors (M.R., S.G.R.) independently reviewed each article for final article inclusion and group consensus was used to resolve conflicts. Authors of articles that appeared to collect but not publish data within our inclusion criteria were contacted by e-mail on 2 occasions. Interrater reliability agreement for final study selection by each initial reviewer during full-text review was assessed with Cohen's κ.

Data Collection and Processing

For included studies, 2 reviewers independently analyzed each study to extract information, directly placing information into an Excel spreadsheet. Extracted data from each article included a description of the study population (emergency department [ED] and inpatient), study details (author, median or mean age, sex, publication year, population country, and design), and specific endpoint data (number receiving immediate versus early antibiotics, any risk adjustment between periods, any other indicator of severity between periods [number with severe sepsis or septic shock], and mortality). Group consensus was used to resolve any conflicts regarding data extracted.

The quality of evidence across studies and risk of bias for individual studies was independently assessed by 2 study authors. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess quality of evidence across studies as high, moderate, low, or very low.[22] The risk of bias was assessed for individual studies with the Newcastle-Ottawa Scale for observational studies. With that scale, studies received up to 9 points based on study subjects, study comparability, and outcome of interest assessment. A Newcastle-Ottawa Scale score of 0 to 5 indicates a high risk of bias; 6 to 9, a low risk.[23,24] For GRADE and Newcastle-Ottawa Scale

assessments, any disagreement between the 2 independent reviewers was settled by a third reviewer.

Publication bias was evaluated with funnel plot inspection and Egger's test, with $P<.10$ considered evidence of bias.[25] The trim-and-fill approach was planned to estimate any effect size accounting for publication bias.

Primary Data Analysis

The summary effects of immediate versus early antibiotics on mortality was determined with a random-effects model using the Mantel-Haenszel approach. Odds ratios with 95% confidence intervals (CIs) were calculated. Results were displayed graphically with forest plots. Subset analysis was performed for studies with ED patients, septic shock patients, severe sepsis patients, US studies, and low risk of bias. Observed heterogeneity for summary and subgroup analyses was measured with the I^2 statistic. I^2 less than 40% was considered low, 30% to 60% moderate, 50% to 90% substantial, and 75% to 100% considerable.[26] Univariate random-effects meta-regression was performed to investigate the potential influence of individual study variables on heterogeneity among studies (patient age, sex, location [ED versus inpatient], country [United States versus non–United States], study type [prospective versus retrospective], study setting [single versus multiple hospitals], mortality timing [inhospital versus 28 day], and risk of bias [high versus low]). Meta-regression was not performed if variables were not documented in the 0- to 3-hour cohorts for at least 10 studies.[26]

Data synthesis and statistical analyses were performed with MedCalc Statistical Software (version 18.11; MedCalc Software bvba, Ostend, Belgium), RevMan Review Manager (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), Meta-essentials (Erasmus Research Institute of Management, Rotterdam, The Netherlands),[27] and Comprehensive Meta-analysis (version 3; Englewood, NJ).

RESULTS

The initial database searches resulted in 8,806 publications of potential relevance, with 2,167 identified through MEDLINE/PubMed, 3,806 through EMBASE, 1,912 through Web of Science, 537 through the Cumulative Index of Nursing and Allied Health, 246 through Wiley's Cochrane Library, 89 through gray literature, and 49 through reference examination. After initial screening and full-text review, 13 studies were included in the final review: 5 that were prospective observational studies and 8 that were retrospective cohort studies, with a combined 33,863 total subjects (Figure 1).[10,12,28-38] Interrater reliability for 2-reviewer selection of final included articles after full-text review was perfect ($\kappa=1$; 95% CI 1 to 1).

Six of 13 included studies were conducted in the United States, with 8 occurring across multiple hospitals and 5 composed of single hospitals. Studied populations included 249 hospitals and 10 ambulance services. Nine studies included only patients within EDs, 2 contained a mixture of ED and inpatient populations (ED+inpatient, ED+ICU+inpatient), 1 contained only ICU patients, and 1 contained a mixture of out-of-hospital and ED patients, although out-of-hospital patients within this study were excluded because they received antibiotics before ED arrival (Table 1). Time zero for onset of sepsis was defined as ED or triage arrival in 9 studies, onset of organ dysfunction in 2 studies, onset of hypotension or lactate level greater than or equal to 4 mmol/L in 1 study, and 1 study that included both ED patients (onset time defined as triage arrival) and inpatients with onset of organ dysfunction as time zero. Mortality was defined as occurring with the hospital for the index visit in 9 studies and within 28 days of admission in 4 studies.

The Newcastle-Ottawa Scale score for individual studies ranged from 4 to 8, with 10 studies rated as having a low risk of bias and 3 studies having a high risk of bias (Table E3 [available online at http://www.annemergmed.com], Figure 2). Based on GRADE, the overall quality of evidence across all studies was initially low and could not be decreased or increased according to features of the meta-analysis (Table E4, available online at http://www.annemergmed.com).

Pooling of data (N=33,863 subjects) showed no difference in mortality between patients receiving antibiotics in the 0- to 1-hour versus the greater than 1- to 3-hour periods (crude odds ratio 1.09; 95% CI 0.98 to 1.21) (Figure 3). Subgroup analysis of data is provided (Table 2, Figures 4 to 8).

Heterogeneity was low to moderate across all studies ($I^2=42\%$) and subsets of ED studies and subjects ($I^2=31.7\%$), septic shock studies and subjects ($I^2=0\%$), severe sepsis studies and subjects ($I^2=0\%$), and studies from the United States ($I^2=50\%$) (Table 2, Figure 9). Univariate meta-regression showed no statistically significant effect on heterogeneity for any studied variable (Table E5, available online at http://www.annemergmed.com). Age and sex were excluded from meta-regression because only one study contained this information for the subset of patients who received antibiotics between 0 and 3 hours after ED triage or sepsis onset.[36] Egger regression revealed no publication bias (intercept –0.74; 95% CI –2.27 to 0.8; $P=.32$) across all studies. Trim-and-fill analysis revealed no missing studies.

Table 1. Summary of included studies.

Author, Year Published Region, State, Country	Study Group	Design	Setting (ED vs IP vs ICU)	Median Age and IQR (Mean Age ± SD)†	Men, %‡	Definition of Onset, Time Zero	Mortality Defined	Median Time to Antibiotics, All Cases, Entire Study (Minutes)	Mortality: Subjects Received Antibiotics 0–1 Hours From Onset (%)	Mortality: Subjects Received Antibiotics 1–3 Hours From Onset (%)	Risk Adjustment or Alternate Severity Comparison, 0–1 Hour vs 1–3 Hours
Alam,[28] 2018* Netherlands	10 ambulance services, 34 hospitals; PHANTASi Trial Investigators: Prehospital Antibiotics Against Sepsis trial; ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium	Prospective Controlled Open Label	ED (out-of-hospital excluded)	(72.5±14.1)	57	ED arrival	Hospital	70	31/281 (11)	16/230 (7)	0–1 h (8.5% septic shock) vs 1–3 h (3.9% septic shock), *P*=.052
Bloos,[29] 2014 Germany	44 hospitals MEDUSA: Medical Education for Sepsis Source Control and Antibiotics	Prospective observational	ICU	69 58–77	62.7	Time of first organ dysfunction	28 days	126	65/186 (34.9)	86/249 (34.5)	None
Castano,[30] 2019* Columbia	3 hospitals	Prospective observational	ED	(63±17)	53.1	ED triage	Hospital	Not specified	15/57 (26.3)	33/183 (18)	0–1 h (35% septic shock), 1– 3 h (23% septic shock), *P*=.12
de Groot,[31] 2015 Netherlands	3 hospitals	Prospective observational	ED	(62±17)	55.7	ED registration	28 days	Not specified	46/330 (13.9)	47/336 (14)	0–1 h (36% PIRO score >14), 1–3 h (26% PIRO score >14), *P*=.02
Drumheller,[32] 2016 Philadelphia, PA	1 hospital	Retrospective cohort	ED	(59.5±16.3)	56.7	ED triage	Hospital	120	16/90 (17.8)	46/180 (25.6)	100% septic shock. No risk adjustment for 0–1 h vs 1–3 h
Ferrer,[10] 2014 Europe, South America, United States	144 hospitals; Surviving Sepsis Campaign database	Retrospective cross sectional	ED, IP, ICU	Not provided	Not provided	ED triage time, IP/ICU, onset organ dysfunction	Hospital		1,512/4,728 (32)	2,155/7,615 (28.3)	0–1 h (69.6% septic shock) vs 1–3 h (62.1% septic shock), *P*<.001

Table 1. Continued.

Author, Year Published Region, State, Country	Study Group	Design	Setting (ED vs IP vs ICU)	Median Age and IQR (Mean Age ± SD)†	Men, %‡	Definition of Onset, Time Zero	Mortality Defined	Median Time to Antibiotics, All Cases, Entire Study (Minutes)	Mortality: Subjects Received Antibiotics 0–1 Hours From Onset (%)	Mortality: Subjects Received Antibiotics 1–3 Hours From Onset (%)	Risk Adjustment or Alternate Severity Comparison, 0–1 Hour vs 1–3 Hours
Filbin,[33] 2020* Boston, MA	1 hospital	Retrospective cohort	ED	Not provided	59.2	Onset hypoperfusion (systolic BP <90 mm Hg or lactate ≥4 mmol/L) at triage or in ED	Hospital	48 (patients with explicit symptoms) 96 (those with vague symptom)	32/149 (21.5)	59/243 (24.3)	100% septic shock. Time to antibiotics not associated with mortality (adjusted OR 1.01, 95% CI 0.94–1.08)
Hwang,[34] 2019 Seoul, Korea	1 hospital	Retrospective cohort	ED	66 5–73	57.6	ED triage	28 days	132	20/178 (11.2)	159/1,067 (14.9)	100% septic shock. No risk adjustment for periods
Leisman,[35] 2019* New York (state)	9 hospitals, Northwell Sepsis Database	Retrospective cohort	ED, IP	74 62–85	51.3	Time of infection+2 SIRS criteria met+organ dysfunction	Hospital	48.3% antibiotics within 1 h (80.8% within 3 h)	1,046/5,399 (19.4)	699/3,641 (19.2)	% septic shock not specified for 0–1 and 0– 3 h
Peltan,[36] 2019* Utah	4 hospitals	Retrospective cohort	ED	(60.9±19.3)	48.1	ED arrival§	Hospital	166	139/599 (23.2)	1,082/5,559 (19.5)	0–1 h (45.1% septic shock), 1–3 h (30% septic shock), $P<.001$
Puskarich,[37] 2011 Time zero=ED triage Charlotte, NC; Boston MA; Camden, NJ	3 hospitals	Prospective, randomized, nonblinded	ED	62 50–73	53.6	ED triage	Hospital	114	11/65 (16.9)	35/158 (22.2)	100% septic shock cases. Adjusted OR for mortality at 0–1 h 1.81 vs 0.66 at 1–2 h, 1.07 at 2–3 h
Puskarich,[37] 2011 Time zero=septic shock onset				62 50-73	53.6	Onset of 2 SIRS criteria+SBP <90 mm Hg after fluids at 20 mL/kg or lactate level ≥4 mmol/L returned			26/101 (25.7)	13/63 (20.6)	Patients with antibiotics before shock onset excluded from this subset

Ryoo,[38] 2015 Seoul, South Korea	1 hospital	Retrospective cohort	ED	(63±13)	61	ED triage	28 days	91.5	29/150 (19.3)	40/199 (20.1)	100% septic shock cases. No risk adjustment between 0–1 h and 1–3 h
Whiles,[12] 2017* Kansas City, KS	1 hospital	Retrospective cohort	ED	(58.9±17.5)	53.5	ED arrival	Hospital	177	55/450 (12.2)	142/1,541 (9.2)	100% severe sepsis cases. Charlson comorbidity index (0–1 h [2.08] vs 1–3 h [2.6]) P=.91
Overall[‖¶]	5 single hospital 8 multihospital	5 prospective 8 retrospective	12 ED 3 IP (2 mixed)		51.9	—	9-hospital mortality, 4 with 28-day mortality	—	3,017/12,662 (23.8)	4,599/21,201 (21.7)	—

IP, Inpatient; *IQR*, interquartile range; *BP*, blood pressure; *OR*, odds ratio; *SBP*, systolic blood pressure.

*Data obtained directly from authors.

†Median age in years and interquartile range. With the exception of Peltan et al,[36] the listed median and average ages were descriptors of the entire population within a study and not cohorts who received antibiotics from 0 and 3 hours.

‡With the exception of Peltan et al,[36] the listed sex was a descriptor of the entire population within a study and not cohorts who received antibiotics from 0 and 3 hours.

§The only study that used Sepsis-3 consensus definitions. Sepsis: organ dysfunction (caused by infection) with an increase in the Sequential [Sepsis-related] Organ Failure Assessment score of 2 points or more above the patient's baseline, using only data before hospital admission. Septic shock: vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) despite adequate volume resuscitation.[21,37,40]

‖Total calculations using ED triage time as time zero in the study by Puskarich et al.[37]

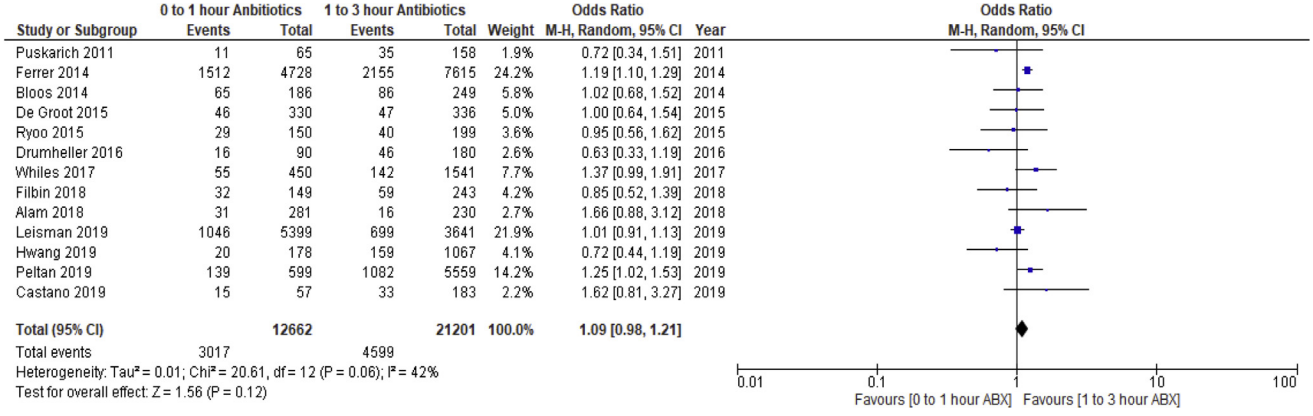
¶Overall, of 13 included studies, 5 provided no risk adjustment nor compared percentage with septic shock between groups, 3 had significantly more septic shock cases in the 0- to 1-hour group, 3 had no difference in percentage of cases with septic shock in the 0- to 1-hour group (versus 1- to 3-hour group), 1 had similar Charlson comorbidity indices and similar progression to septic shock at 0 to 1 versus 1 to 3 hours, and 1 had patients with higher PIRO scores in the 0- to 1-hour group.

Figure 2. Summary Newcastle-Ottawa Scale for all studies.

LIMITATIONS

The majority of included studies in this meta-analysis (8) were retrospective. For these studies, data extracted from charts may have been incomplete or incorrect, with documented times estimated or timed after they were performed. It is also possible that retrospectively collected data used to adjust for risk or severity were incomplete or incorrect.

Only 2 studies provided an adjusted odds ratio for the periods studied, 1 with no mortality difference between immediate versus early periods and 1 with a higher mortality for immediate compared with early antibiotics.[33,37] In a similar manner, lack of an adjustment (standardization) for nonantibiotic treatments between groups might mask a difference in outcomes between immediate versus early periods. The amount and timing of fluids, type of antibiotics, timing and appropriateness of vasopressors, and other treatments may have differed between groups. It is possible that higher mortality in the immediate group is related to these differences and not to antibiotic timing. In a similar manner, these unmeasured and unadjusted variables may be responsible for a lack of



* Odds ratios to the right (> 1) favor higher mortality with immediate antibiotics (0 to 1 hour); to the left (< 1) favor higher mortality with early (1 to 3 hour) antibiotics.
ABX - antibiotics

Figure 3. Forest diagram of odds ratios comparing mortality with immediate versus early antibiotics (all studies).

Table 2. Odds ratios for group and subsets.

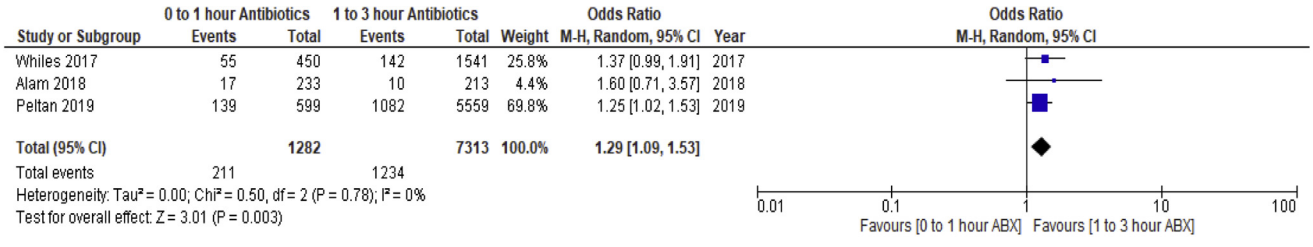
Studies (Cases)*	No. of Studies	No. of Subjects	OR† (95% CI)	Heterogeneity I^2 Statistic
All studies (A)‡	13	33,863	1.09 (0.98–1.21)	0.418
All studies (B)‡	13	33,804	1.10 (1–1.23)	0.382
ED cases	12	28,650	1.06 (0.95–1.18)	0.317
US studies	6	18,074	1.06 (0.88–1.26)	0.5
Severe sepsis cases§	3	8,595	1.29 (1.09–1.53)	0
Septic shock, triage onset (A)‡	7	2,712	0.8 (0.64–1.01)	0
Septic shock, shock onset (B)‡	7	2,653	0.84 (0.68–1.07)	0
All studies, risk of bias low	10	20,419	1.06 (.91–1.24)	0.43

*This column delineated between studies and cases because cases comprised only a subset of patients within individual studies.
†Odds ratio for mortality with immediate antibiotics (0 to 1 hour) compared with early antibiotics (1 to 3 hours).
‡Puskarich et al[37] defined time zero for septic shock as ED triage time (A) and as onset hypotension or lactate level greater than or equal to 4 (B) while providing time data for both instances.
§All 3 severe sepsis studies had a low risk of bias.

mortality benefit in the subset with septic shock. Only a prospective study controlling for each of these factors and randomization of antibiotic timing to immediate versus early periods would definitively show a benefit of antibiotics within either specified period. Such a study would be problematic because immediate antibiotics would need to be withheld in a subset of patients with proven severe sepsis or septic shock. This type of study also would be size prohibitive, requiring enrollment of greater than 12,500 subjects who had sepsis recognized within 1 hour of onset to have 80% power to detect the observed mortality difference between immediate versus early antibiotics (α=.05), assuming half were randomized to 0- to 1-hour antibiotics and half were randomized to wait until greater than 1 to 3 hours before antibiotics were given.

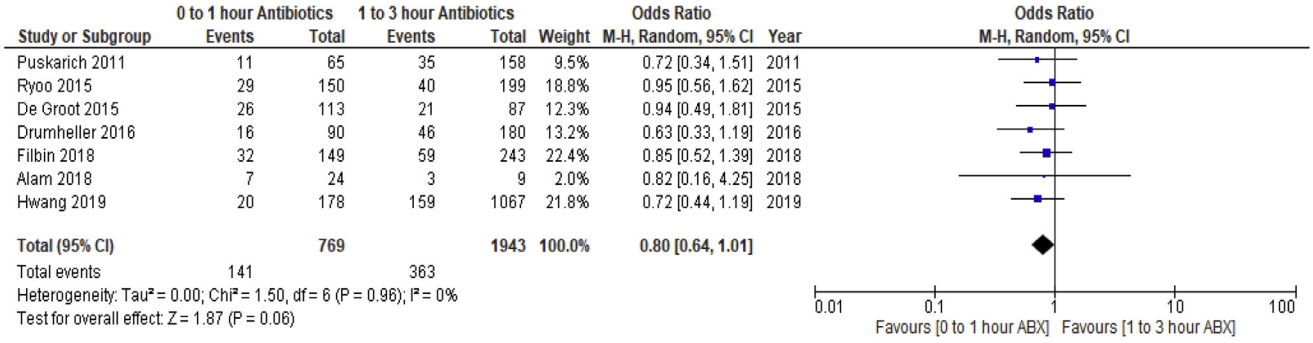
Puskarich et al[37] used 2 different definitions for time zero: ED triage time and onset shock (onset hypotension or lactate level $\geq$4 mmol/L). Data were provided for both intervals: ED triage to antibiotics and onset shock to antibiotic administration (Table 2). Because time from ED triage to antibiotic administration was the most conservative time, was used by 10 studies within this review, and reflected previously published Surviving Sepsis Campaign recommendations, we chose to include this time zero definition for ED patients from the study by Puskarich et al[37] in our main calculations.[4]

Although statistical heterogeneity across studies was low to moderate, there were multiple differences between studies, including patient location (ED versus inpatient ward versus ICU), category of sepsis (only septic shock, only severe sepsis, or combined), sepsis definitions (Sepsis-2 definitions, Sepsis-3 definitions, and Predisposition, Infection/Injury Type, Response and Organ Dysfunction [PIRO] score), timing of mortality (hospital versus 28 days), and definition of time zero (ED arrival, time of organ dysfunction, and onset of hypoperfusion). For studies with combined septic shock and severe sepsis cases, the percent with septic shock ranged from 8.5% to 69.6% septic shock in the immediate period and 3.9% to 62.1% in the early period. Median time to antibiotic administration across all



* Odds ratios to the right (> 1) favor higher mortality with immediate antibiotics (0 to 1 hour); to the left (< 1) favor higher mortality with early (1 to 3 hour) antibiotics.
ABX - antibiotics

Figure 4. Forest diagram of odds ratios comparing mortality with immediate versus early antibiotics (severe sepsis).



* Odds ratios to the right (> 1) favor higher mortality with immediate antibiotics (0 to 1 hour); to the left (< 1) favor higher mortality with early (1 to 3 hour) antibiotics.
ABX - antibiotics

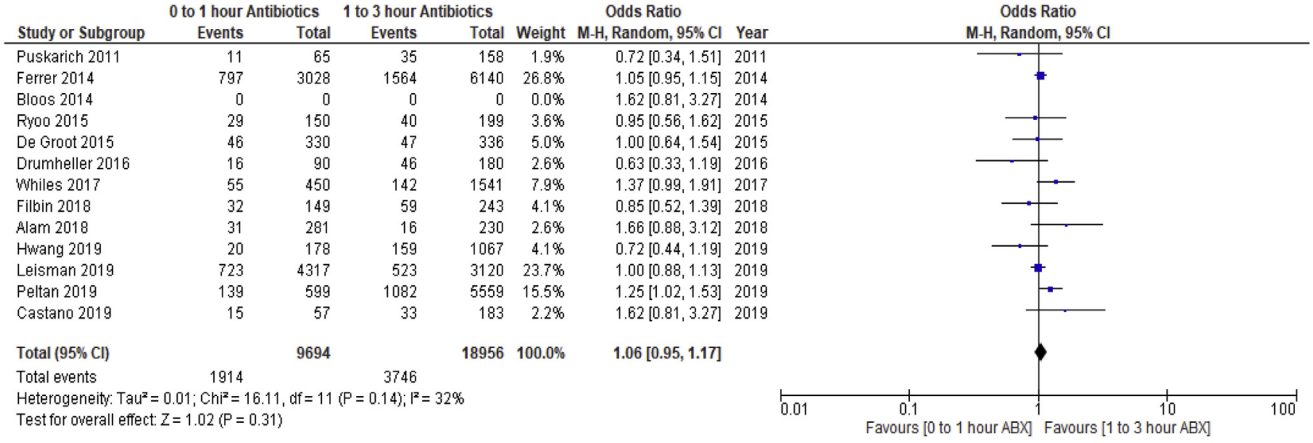
Figure 5. Forest diagram of odds ratios comparing mortality with immediate versus early antibiotics (septic shock).

studies ranged from 48 to 177 minutes. These findings reflect potential important differences between studies not identified by statistical measures of heterogeneity.

We included a single study that used PIRO scores greater than or equal to 8 to categorize severe sepsis and septic shock cases.[31] Like the Sepsis-2 and Sepsis-3 consensus definitions, the PIRO score uses organ dysfunction to categorize patients.[21,39,40] Multiple studies have shown that a score greater than or equal to 8 is 100% specific for severe sepsis and septic shock.[41-44] Howell et al[41] found that PIRO was accurate at predicting sepsis severity and mortality. McDonald et al[43] found that all patients with PIRO scores in the 8 to 14 and greater than 14 groups had severe sepsis or septic shock. Quinten et al[44] found that all ED patients with septic shock had a PIRO score of 12.5 or higher (mean 16), and severe sepsis patients had a PIRO score of greater than or equal to 6 (mean 8). The study by de Groot et al[31] included subjects who had PIRO scores of 8 to 14 and greater than 14 categories; thus, all of these cases likely had severe sepsis or septic shock. Because there is an overlap of severe sepsis and septic shock with these cutoffs, we chose to categorize the entire cohort in the study by de Groot et al[31] as combined severe sepsis and septic shock and not the subcategories of severe sepsis and septic shock.

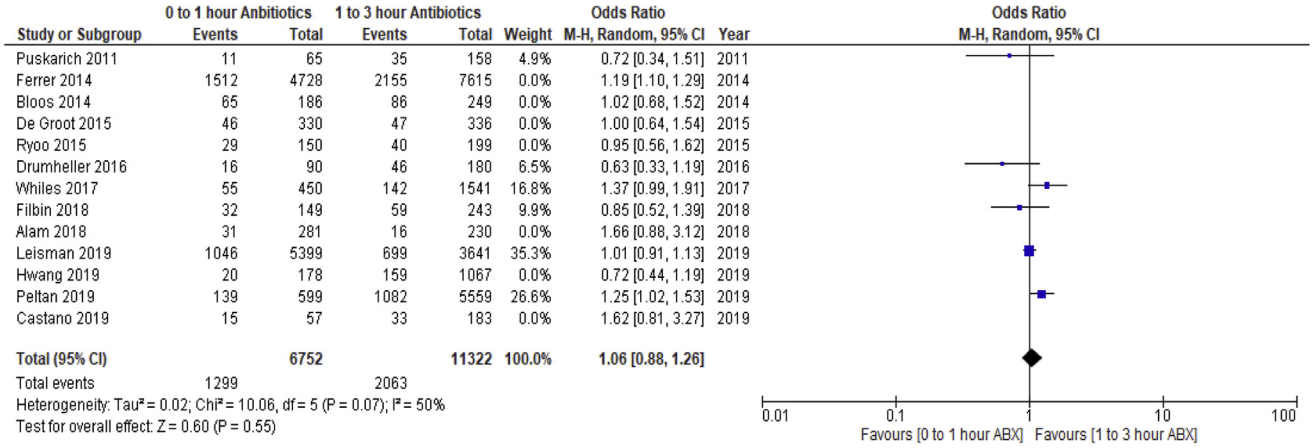
The GRADE quality of evidence was low in this meta-analysis, indicating that the true effect might be different from the estimated effect. The majority of Cochrane systematic reviews and World Health Organization guidelines, as well as many online medical resources of medical interventions, are based on low or very low quality of evidence.[45-47]

Before performing this study, we chose a cutoff of greater than or equal to 6 to indicate a low risk of individual



* Odds ratios to the right (> 1) favor higher mortality with immediate antibiotics (0 to 1 hour); to the left (< 1) favor higher mortality with early (1 to 3 hour) antibiotics.
ABX – antibiotics; ED – Emergency Department

Figure 6. Forest diagram of odds ratios comparing mortality with immediate versus early antibiotics (ED studies).



* Odds ratios to the right (> 1) favor higher mortality with immediate antibiotics (0 to 1 hour); to the left (< 1) favor higher mortality with early (1 to 3 hour) antibiotics.
ABX – antibiotics; US – United States

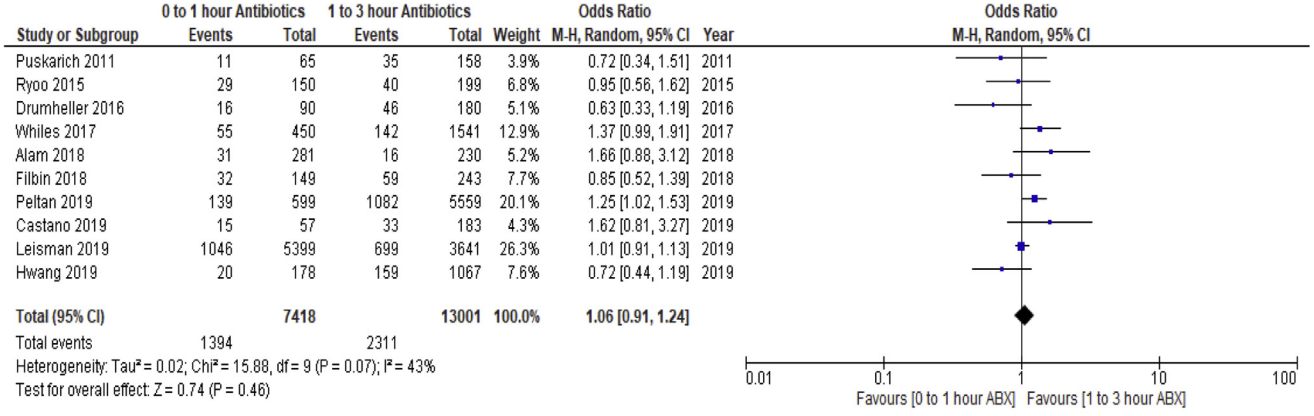
Figure 7. Forest diagram of odds ratios comparing mortality with immediate versus early antibiotics (US studies).

study bias, using the Newcastle-Ottawa Scale. Others have used cutoffs of greater than or equal to 5, greater than or equal to 6, and greater than or equal to 7 to define a low risk of bias.[24,25,48,49] If we had used a cutoff of greater than or equal to 7 to define low risk of bias, the majority of included studies would have had a moderate or high risk of bias. This would have decreased the overall GRADE quality of evidence for the study from low to very low.

DISCUSSION

Our study found no difference in mortality among severe sepsis and septic shock patients receiving antibiotics within the immediate or early groups. We found higher mortality among the subgroup with severe sepsis in the immediate groups compared with the early group.[12,28,36] Subgroup analysis of severe sepsis cases contained data from only 3 studies (N=8,595 cases), with 84% of subjects enrolled in a single study, potentially skewing this finding toward the results of a single study.[36] Overall, there was no difference in mortality between periods for septic shock patients, ED patients, and patients enrolled in US studies. These data do not support an overall mortality benefit for immediate versus early antibiotics across all patients with severe sepsis and septic shock.

In 2015, Sterling et al[50] published a meta-analysis that assessed the timing of antibiotics in sepsis, primarily concentrating on administration less than 3 hours versus more than 3 hours from onset, concluding there was "no significant mortality benefit of administering antibiotics



* Odds ratios to the right (> 1) favor higher mortality with immediate antibiotics (0 to 1 hour); to the left (< 1) favor higher mortality with early (1 to 3 hour) antibiotics. ABX – antibiotics; US – United States

Figure 8. Forest diagram of odds ratios comparing mortality with immediate versus early antibiotics (studies with a low risk of bias).

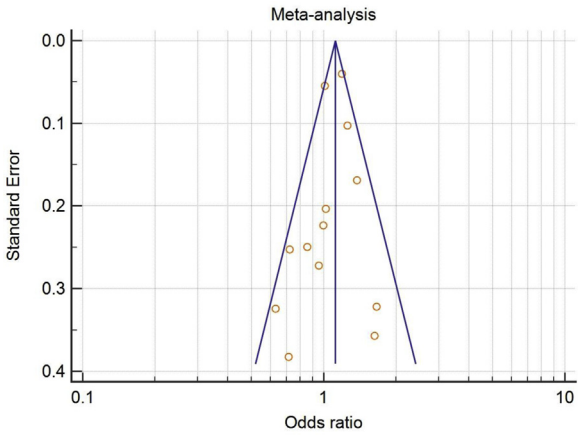


Figure 9. Funnel plot for publication bias.

within three hours of ED triage or within one hour of shock recognition." Subset analysis of their published data showed that mortality did not differ between patients who received antibiotics within 1 hour (36.6%) and 1 to 3 hours (36.8%) of ED triage.[50] That meta-analysis included only 4 studies that compared periods less than 3 hours.[7,10,38,51] Our study had nearly 8 times as many patients in the 0- to 3-hour period (33,863 versus 4469), excluded duplicate databases, and included 8 studies published after 2014, with 1 study published in 2014 that was not included in this original meta-analysis.[12,28,30-36] Johnston et al[52] and Xantus et al[53] performed meta-analyses comparing antibiotics administered less than or equal to 1 hour to greater than 1 hour after ED arrival in sepsis, concluding there was "equivocal evidence of survival benefit" and that antibiotics "seemed" to reduce mortality if given less than or equal to 1 hour after ED presentation. However, these meta-analyses included studies with simple sepsis, included studies that did not analyze antibiotics given less than or equal to 1 hour after ED arrival, and grouped patients who received antibiotics greater than 1 hour to more than 6 hours from ED arrival into the same cohort when making comparisons with those receiving antibiotics less than or equal to 1 hour after ED arrival.[52,53] Thus, neither meta-analysis compared antibiotics between the time frames we analyzed (0 to 1 versus 1 to 3 hours).

The Surviving Sepsis Campaign guidelines currently recommend administration of intravenous antibiotics within 1 hour of recognition for both severe sepsis and septic shock.[6] These guidelines cite 2 studies that concluded each hour delay in the administration of antibiotics is associated with a "measurable" increase in mortality.[7,10,54] Neither study compared outcome in patients who received antibiotics within 0 to 1 hour or 1 to 3 hours of sepsis onset. The first landmark study, by Kumar et al,[7] primarily compared mortality in patients who received antibiotics within less than 1 hour versus greater than 1 to 12 hours after the onset of persistent hypotension (unresponsive to >2 L of fluid) or recurrent hypotension (reoccurrence of hypotension within 1 hour of a >2-L fluid bolus).[54] In this study, each hour of delayed antibiotics after patients developed persistent or recurrent hypotension was associated with a 7.6% higher mortality rate.[7] The median time to antibiotic administration in this study was 6 hours (average >13.5 hours), with the majority of patients receiving antibiotics well after the current 1- and 3-hour recommendations and 25% receiving antibiotics 15 or more hours after persistent or recurrent hypotension developed.[7] A second study cited to justify immediate antibiotic administration found that patients who received antibiotics in the first hour had a higher crude mortality rate (32%) than those who received antibiotics between 1 and 3 hours after presentation (28.1% to 28.6%).[5,10] Although the crude mortality rate was higher for patients receiving antibiotics within 1 hour of ED arrival, the authors found a slightly lower adjusted mortality rate for those receiving antibiotics within 1 hour of sepsis onset.[10] A more recent study with nearly 50,000 patients concluded that delayed antibiotics increased mortality by 4% for each hour of delay after presentation. The authors did not directly publish data to determine exact crude or adjusted mortality rate for each of the first 3 hours after sepsis onset. However, the majority of increased mortality (14% increase per hour) occurred in patients treated with antibiotics between 3 and 12 hours after presentation.[11] Thus, previous recommendations for early antibiotics primarily have been based on data showing increased mortality in patients receiving delayed antibiotics (more than 3 hours after onset).

Differences in outcome were likely influenced by patient factors not addressed in individual studies within this meta-analysis. Previous studies have compared patients with classic and vague symptoms of severe sepsis and septic shock and found that those with classic symptoms are treated earlier and more aggressively.[55,56] Filbin et al[55] concluded that presenting features appear to influence sepsis recognition, influence antibiotic timing, represent variability in disease pathophysiology, and affect mortality. Seymour et al[57] found that there are at least 4 separate sepsis phenotypes with different host-response patterns, inflammatory mediator levels, and clinical outcomes. It is possible that each phenotype also responds differently, depending on the timing of antibiotics or other treatments. These studies support the concept that immediate and early populations differ clinically. A prospective study adjusting for presenting features and patient subtypes in addition to other features affecting mortality is required to determine

whether outcome truly differs between patients receiving antibiotics within immediate versus early periods.

It is possible that there are unexplored biological factors related to the resuscitation of patients with sepsis that cause harm when antibiotics are administered and that could explain a worse outcome for the immediate antibiotic population in our meta-analysis. With bacterial meningitis, it has been postulated that the inflammatory cascade from dying bacteria leads to some of the harm associated with this disease.[58] For this reason, steroid administration before antibiotic administration may improve mortality, neurologic outcome, and hearing loss in a subset of patients.[59,60] In a similar manner, it possible that a certain degree of hemodynamic resuscitation or a nuanced sequence of treatments is required before an antibiotic-induced release of inflammatory mediators to improve outcome in a subset of patients with sepsis.

Independent of outcome for patients with sepsis, knowledge of the relative benefit of antibiotics between immediate and early periods has important implications for patients with suspected sepsis eventually determined not to be sepsis. Researchers have noted that implementation of Centers for Medicare & Medicaid Services core measures (SEP-1) has led to an increase in antibiotic administration without a decrease in mortality, presumably because of overtreatment of patients without sepsis.[61] Others have found that implementing Surviving Sepsis Campaign guidelines has led to increased use of antibiotics and a corresponding increase in the rate of *C difficile* infections.[62] It is possible that allowance for a longer time frame for antibiotic administration in sepsis would lead to decreased antibiotic administration in patients without sepsis and a decrease in antibiotic-related adverse outcomes.

In summary, our study did not find a difference in mortality between patients receiving immediate compared with early antibiotics across all patients with septic shock and severe sepsis. For the subgroup of patients with severe sepsis, mortality was higher in those receiving immediate antibiotics. Lack of risk adjustment, differences between studies (eg, percentage with septic shock), and overall Cochrane GRADE low quality of evidence limit the ability to definitively conclude that mortality is higher with immediate antibiotics. However, our findings do not support an advantage of immediate compared with early antibiotics for all patients with sepsis.

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