Antibiotic treatment duration for patients with bloodstream infection: a systematic review and meta-analysis

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Research

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Abstract

Objectives: The optimal duration of therapy for primary bloodstream infection (BSI) and BSI secondary to major organ system infections has been poorly defined. A systematic review and meta-analysis was performed to evaluate the impact of short (≤10 days)and long course(>10 days) of antibiotic treatment on clinical outcomes in patients with BSI.

Methods: We searched the PubMed, Cochrane, and Embase databases for randomized controlled trials(RCTs) and cohort studies from inception to the 1st of October 2020. We included studies involving patients with BSI. All authors reported our primary outcome of all-cause mortality and clearly comparing short versus long course of antibiotic treatment with clinically relevant secondary outcomes(source control and relapse). Results were expressed as odds ratio (OR) with accompanying 95% confidence interval (CI).

Results: Six studies including 3593 patients were included. The primary outcome of this meta-analysis showed that there was no statistically significant difference in the all-cause mortality between two groups (OR=1.10; 95% CI, 0.82 to 1.48; P=0.52; Chi^2=7.57; I^2=34%) . Secondary outcomes demonstrated that there was no statistically significant difference in the source control(OR=0.82; 95% CI, 0.61 to 1.10; P=0.18; Chi^2=2.68; I^2=25%)and relapse(OR=1.20; 95%CI,0.71 to 2.01; P=0.49; Chi^2=0.26; I^2=0%) between two groups.

Conclusions: Short course of antibiotic treatment is not associated with either an increased risk of mortality or an increased odds of relapse compared with longer antibiotic treatment course for BSI. Furthermore, short course of antibiotic therapy is non-inferior to long course in terms of source control. Further large-scale RCTs are still required to confirm these results.

1. Introduction

Bloodstream infection (BSI) is defined by positive blood cultures in a patient with systemic signs of infection and may be either secondary to a documented source or primary-that is, without identified origin[1]. Timely administration of the appropriate antibiotic treatment remains the cornerstone for favorable clinical outcome in patients with BSI[2–4]. However, the optimal duration of therapy for primary BSI and BSI secondary to major organ system infections has been poorly defined[5]. Sufficient duration of antimicrobial therapy is required to prevent clinical failure and relapse. However, the risk of a longer antibiotic course may lead to Clostridium difficile infection, development of microbial resistance, potential need for central line access, venous thrombosis, line infection and bacteremia and increased cost[6].

A multicenter observational study of patients who have BSI in Canadian intensive care units(ICUs) suggests that most patients are treated with 2-week courses of antimicrobials, but with substantial practice heterogeneity among individual patients and with no clear relationship between duration of treatment and survival[7]. The current Infectious Diseases Society of America(IDSA) guidelines suggest that the duration of treatment for intravascular catheter related BSI should be between 7 and 14 days [8], but there is no consensus on the optimal duration of the antimicrobial therapy for non-catheter related BSI. The lack of data on the appropriate treatment duration for this subset of patient leads to uncertainty, usually resolved by prolonged treatment durations.

Since the optimal duration of the antibiotic treatment for patients with BSI remains unknown, we conducted a meta-analysis which extracted results from published studies to evaluate the impact of short and long course of antibiotic treatment on clinical outcomes in patients with BSI.

2. Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].Ethical approval was not necessary for this study because it was a review of the published literature.

2.1. Search strategy

We searched the PubMed, Cochrane, and Embase databases for studies from inception to the 1st of October 2020 using the following search terms: bloodstream infection, bacteremia, duration of treatment, antibiotic treatment duration, optimal duration, antibacterial treatment, antibiotics, antibacterial agents, short course, long course, sepsis. The search was slightly adjusted according to the requirements of the different databases. The authors' personal files and reference lists of relevant review articles were also reviewed. The flow chart of the search strategies is summarized in Fig. 1.

2.2. Types of outcome measures

The primary outcome was all-cause mortality, all-cause mortality included hospital mortality, 28-day mortality,30-day mortality and 90-day mortality. Secondary outcomes were source control and relapse. Weighted means were calculated based on the number of patients in each study.

2.3. Study selection

The inclusion criteria were as follows: (1) RCTs as well as prospective and retrospective cohort studies;(2) patients with BSI;(3) all authors reported our primary outcome of all-cause mortality;(4)clearly comparing short(≤ 10 days) versus long course(> 10 days) of antibiotic treatment with clinically relevant secondary outcomes. We excluded studies that did not define the duration of treatment based on the 10-day limit and studies without clear comparisons of the outcomes. In addition, we excluded review articles and studies about pediatric.

2.4. Quality assessment

Two reviewers (YL and JY) independently performed quality assessment. The quality of studies was assessed using the Newcastle-Ottawa Scale(NOS) for cohort studies[10]. NOS allocates a maximum of 9 points according to the quality of the selection, comparability, and outcomes of the cohort study populations. Study quality was defined as poor (0–3), fair (4–6) or good (7–9). The quality of the included cohort studies is presented in Table 1.

Table 1
Quality of the included cohort studies(The Newcastle-Ottawa Scale)

	Selection				Comparability	Outcome			
Study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total Score
Havey 2013	★	★	★	★	★	★	★	★	8
Nelson 2017	★	★	★	★	★★	★	★	★	9
Chotiprasit	★	★	★	★	★★	★	★	★	9
Sakul 2018	★	★	★	★	★	★	★	★	8
Giannella	★	★	★	★	★★	★	★	★	9
2018									
Sousa									
2019									
Lee 2019									

2.5. Statistical analysis

Statistical analyses were performed using Review Manager Version 5.3(RevMan, The Cochrane Collaboration, Oxford, United Kingdom). Odds ratio (OR) with 95% confidence intervals (CI) was calculated for dichotomous variables. A random-effects model was used to pool studies with significant heterogeneity, as determined by the chi-squared test ($P < 0.10$) and inconsistency index ($I^2 \geq 50\%$)[11]. A P-value < 0.05 was set as the threshold of statistical significance.

3. Result

3.1. Study characteristics

The search strategy identified 1269 studies, and the data were from six cohort studies comprising 3593 patients (Table 2)[12–17]. The characteristics of the included studies are shown in Table 2. A total of six eligible studies were published between 2013 and 2019. Among these studies, two studies were conducted in USA, one study was conducted in Spain, one study was conducted in Colombia, one study was conducted in Canada and one study was conducted in China/Taiwan. Four of these studies were single-center studies and two were multicenter studies. The definitions of short and long course of antibiotic treatment in studies included in the meta-analysis are outlined in Table 3.

Table 2
The basic characteristics of studies included in meta-analysis

Author	Year	Country	Study period	All-cause mortality	Study design	No. of patients		
						Total	Short course	Long course
Havey [12]	2013	Canada	Mar.2010-Mar.2011	Hospital	Single center, retrospective cohort study	72	19	53
Nelson [13]	2017	USA	Jan.2010-Dec.2013	90-day	Multicenter, retrospective cohort study	101	57	44
Chotiprasitsakul [14]	2018	USA	2008–2014	30-day	Multicenter,	770	385	385
Giannella [15]	2018	Colombia	Jan.2013-Dec.2016	28-day	retrospective cohort study	856	426	430
Sousa[16]	2019	Spain		30-day	Single center,	395	163	232
Lee[17]	2019	China/ Taiwan	Oct.2015-Oct.2016	30-day	retrospective cohort study	1089	726	363
			Jan.2007-dec.2014		Single center, prospective cohort study			
					Single center, retrospective cohort study			

Table 3
Definitions of short and long course of antibiotic treatment in studies included in the meta-analysis

Study	Short course	Long course
Havey 2013	≤ 10 days	> 10 days
Nelson 2017	7–10 days	> 10 days
Chotiprasitsakul 2018	6–10 day	11–16 days
Giannella 2018	≤ 10 days	> 10 days
Sousa 2019	7–10 days	> 10 days
Lee 2019	5–10 days	11–16 days

3.2. Primary outcome

A total of six studies including 3593 patients were included, and the all-cause mortality was about 5.5% (93/1836 in the short-course group and 105/1757 in the long-course group). There was no statistically significant difference in the all-cause mortality between two groups (OR = 1.10; 95% CI, 0.82 to 1.48; P = 0.52; Chi^2 = 7.57; I^2 = 34%) (Fig. 2). A funnel plot was used to assess the publication bias(Fig. 3).

3.3. Secondary outcomes

3.3.1. Source control.

Three of included studies were analyzed to assess the source control. There was no statistically significant difference in the source control between two groups (OR = 0.82; 95% CI, 0.61 to 1.10; P = 0.18; Chi^2 = 2.68; I^2 = 25%) (Fig. 4).

3.3.2. Relapse.

Three of included studies were analyzed to assess the relapse. Relapse included recurrence within 3 months, restarting antibiotics for the same infection and relapse of bacteremia. There was no statistically significant difference in the relapse between two groups (OR = 1.20; 95% CI,0.71 to 2.01; P = 0.49; Chi^2 = 0.26; I^2 = 0%) (Fig. 5).

4. Discussion

The optimal duration of treatment for BSI has not been established. Prescribing practices vary widely, and durations of therapy can range from fewer than 7 days to greater than 14 days. The catheter-related BSI guidelines suggest a 7- to 14-day course of therapy for Gram-negative bacteremia[18]. However, these recommendations are largely consensus based and have poor evidence. A national survey of Canadian ID and critical care specialists identified significant

practice variation in the recommended duration of antibiotic treatment for BSI. The most commonly recommended treatment duration for BSI was 14 days, but more than one-half of clinicians recommended shorter treatment durations (usually 7 days or 10 days)[19].

This systematic review and meta-analysis of six studies including 3593 patients compared short(≤ 10 days) and long course(> 10 days) of antibiotic treatment on clinical outcomes in patients with BSI. We found that the all-cause mortality was about 5.5% and we did not identify an increased all-cause mortality among patients treated with shorter durations compared with those treated with longer durations. In addition, we found short course of antibiotic therapy to be non-inferior to long course in terms of source control and relapse. The extensive use of antibiotics worldwide is closely related

to the increasing issues of antimicrobial resistance and antibiotic-associated infections [20, 21]. Long-course antibiotic treatment, as used for BSI, plays a critical role in this context. Among patients with suspected bloodstream infections, broad-spectrum antibiotics must be initiated empirically because early adequate empiric treatment is associated with improved survival [22, 23]. Due to the rising prevalence of resistant organisms, the tailoring or de-escalation of these empiric regimens is not possible even

when blood culture and susceptibility results become available. Patients must then remain on broad-spectrum agents for their full treatment course[24].Therefore, decreasing the duration of antibiotic treatment to the bare minimum required to treat infections is a reasonable approach to reduce the prevalence of resistance[25]. Of course, It is important to evaluate the efficacy of short-course antimicrobial therapy to avoid treatment failure and recurrence.

Shorter courses of antibiotics may reduce drug related adverse events, duration of hospitalization, emergence of antibacterial resistance and superinfections, including fungal and Clostridium difficile infection[26]. When judging of duration of antibiotic treatment, there is this second time point at 5–7 days. The decision of escalation/de-escalation/no change or dose adjustments should be taken after 2–3 days when microbiological specimens became available[27]. The effectiveness of therapy should be assessed after one week of treatment on clinical and microbiological resolution of the infection. This will include defervescence and resolution of organ failures and shock, negative subsequent cultures, the absence of endocarditis or metastatic sites of infection and no implanted prosthesis which are all required to define an uncomplicated infection [28]. Problems with source control and/or superinfections at the source will also uncover around that time point. If those are resolved and the pathogen or the source is not specifically requiring extended treatments antibiotic therapy can be safely stopped.

Up to 30–50% of antimicrobial use in most hospitals is inappropriate, with the most common culprit being an excessive duration of therapy[29]. Shorter durations of therapy have been explored for a number of infectious diseases and have been shown to be equally efficacious compared with longer courses of therapy. Appropriate use of antibiotics includes a variety of strategies, such as generating hospital antibiograms, encouraging the use of narrow spectrum antibiotics when feasible, and facilitating the transition from IV to oral antibiotic therapy reducing the need for central line placement[6]. Reducing treatment length in BSI could induce earlier discharge from the hospital, decreased risk of hospital-acquired infections, decreased risk of severe adverse events, and an increased quality of life. Additionally, from a national and international perspective, decreasing the consumption of antibiotics will play an important role in preventing resistance development and secure future antimicrobial treatment[30].

Our meta-analysis has several limitations. First, the number of included studies is small. Further randomized clinical studies should be conducted in order to confirm the results. Second, many of the secondary outcomes such as source control or relapse were not included in all of the studies examined in this meta-analysis. Third, there was still substantial heterogeneity among the included studies. Very heterogeneous populations were included in both prospective and retrospective studies. In addition, definitions of short and long course of antibiotic treatment were widely different among included studies which supposed a limitation to interpret results. Therefore, our findings should be interpreted with caution.

5. Conclusion

Short course of antibiotic treatment is not associated with either an increased risk of mortality or an increased odds of relapse compared with longer antibiotic treatment course for BSI. Furthermore, short course of antibiotic therapy is non-inferior to long course in terms of source control. Further large-scale RCTs are still required to determine the effectiveness and appropriate duration of antibiotic therapy of BSI.

Key Messages

- Short course(≤10 days) of antibiotic treatment is not associated with either an increased risk of mortality or an increased odds of relapse compared with longer antibiotic treatment course for BSI.
- Short course of antibiotic therapy is non-inferior to long course in terms of source control.
- Further large-scale RCTs are still required to determine the effectiveness and appropriate duration of antibiotic therapy of BSI.

Abbreviations

BSI: Bloodstream infection; IDSA: Infectious Diseases Society of America; RCTs: Randomized controlled trials; ICUs: Intensive care units; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NOS: Newcastle-Ottawa Scale; OR: Odds ratio; CI: Confidence interval

Declarations

Acknowledgements

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Availability of supporting data

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YL searched the scientific literature and drafted the manuscript. JY contributed to conception, design and data interpretation. JG helped to collect the data and performed statistical analyses. DZ contributed to conception, design, data interpretation, manuscript revision for critical intellectual content and supervision of the study. All authors read and approved the manuscript.

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

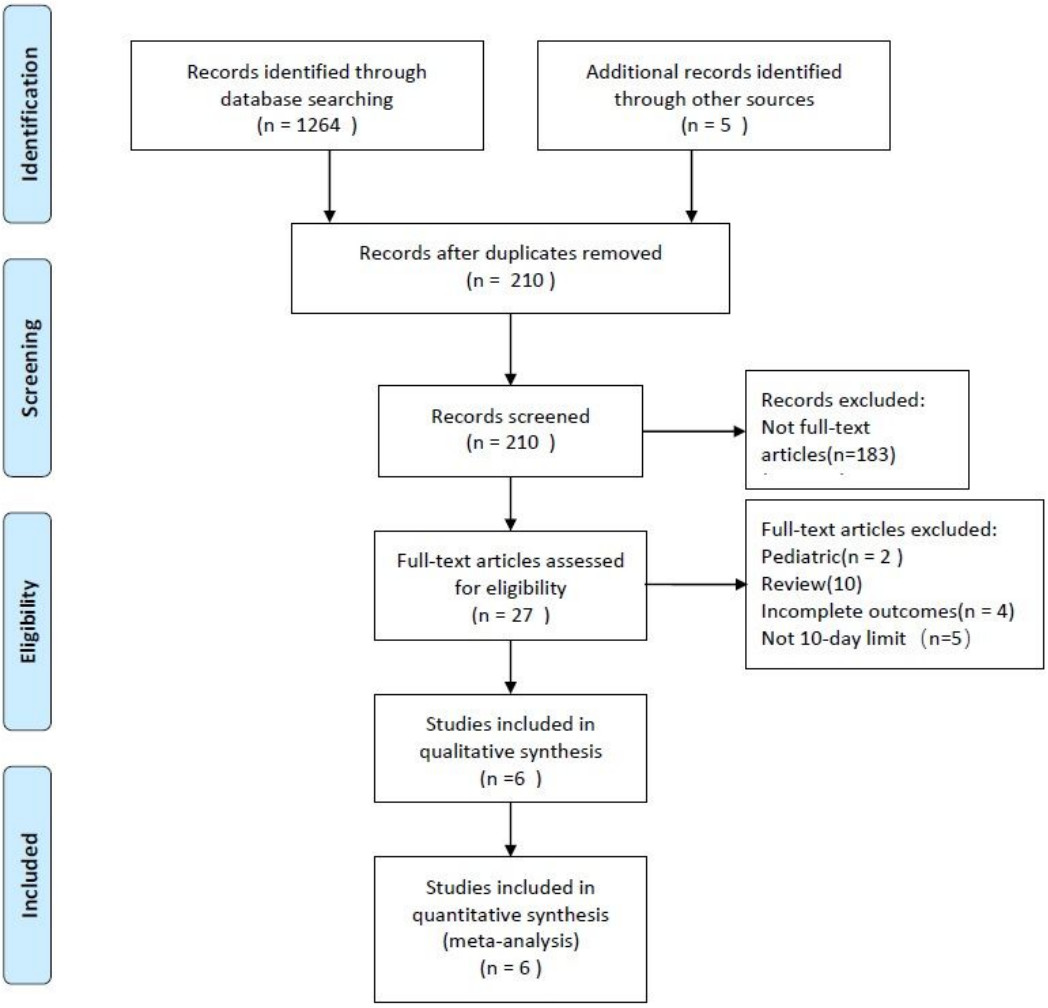

Figure 1

Flow chart of literature selection.

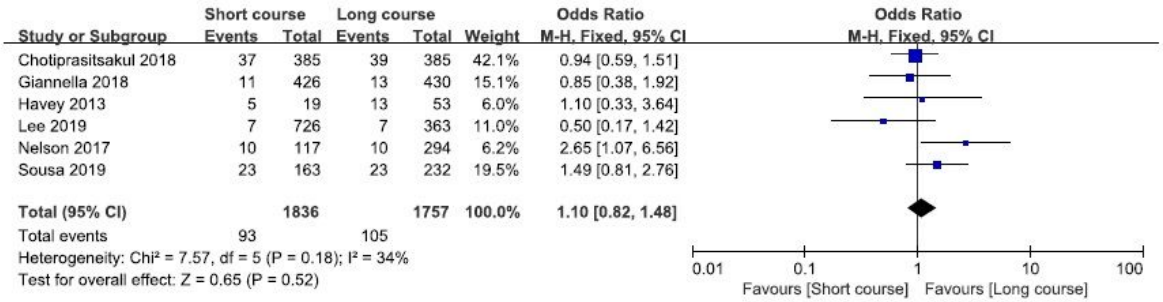

Figure 2

Forest plot for all-cause mortality.

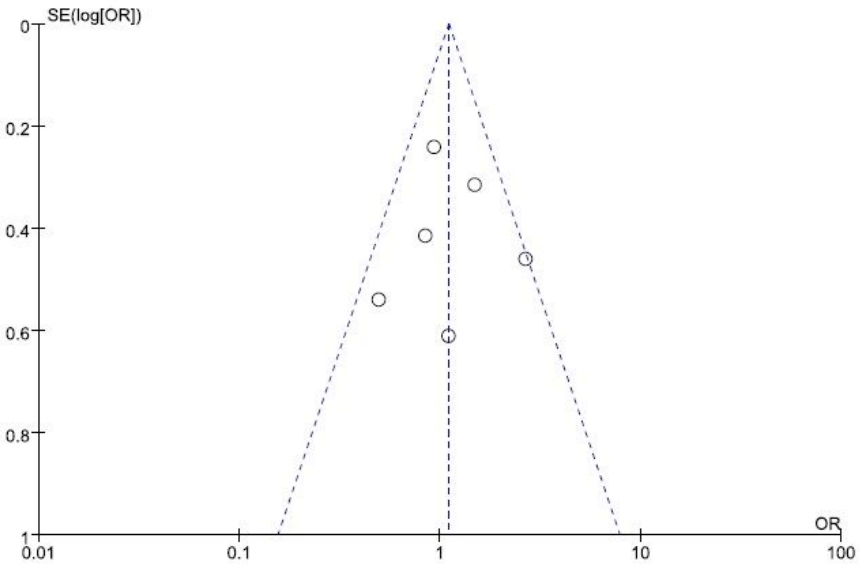

Figure 3

Funnel plot for all-cause mortality.

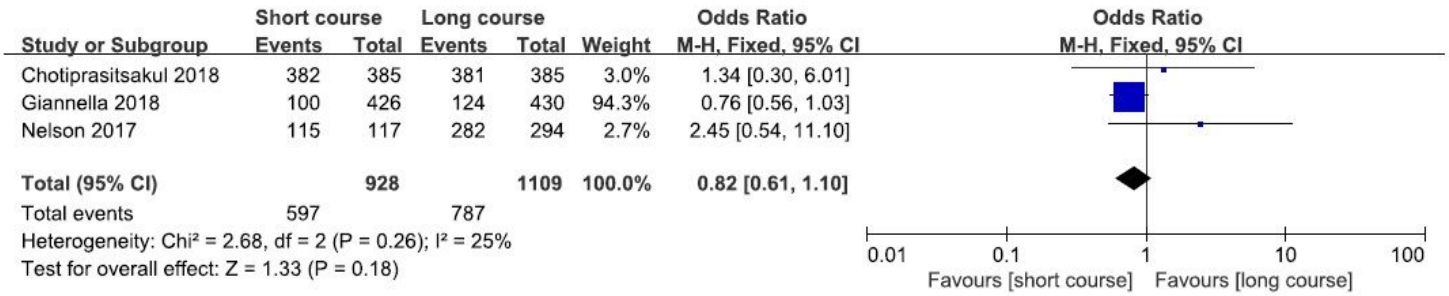

Figure 4

Forest plot for source control.

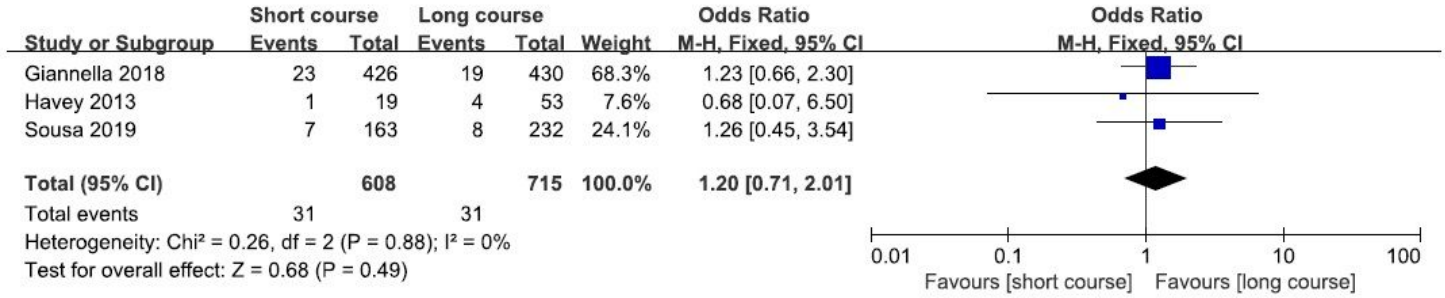

Figure 5

Forest plot for relapse.