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ORIGINAL ARTICLE

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Short-course versus long-course antibiotic treatment in patients with uncomplicated gram-negative bacteremia: A systematic review and meta-analysis

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Abstract

What is known and objective: Gram-negative bacteremia remains a major health problem around the world. The optimal duration of antibiotic treatment has been poorly defined, and there are significant differences of opinion between clinicians. We conducted this systematic review and meta-analysis to compare the clinical outcomes of short-course and long-course treatments in patients with uncomplicated gram-negative bacteremia.

Methods: We searched public databases (PubMed, EMBASE and Cochrane Library) to identify eligible studies. The primary outcomes were all-cause mortality and the incidence of recurrent bacteremia through day 30. We used the Cochrane risk of bias assessment tool to evaluate the risk of bias for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for non-RCTs.

Results and discussion: Six studies involving 2689 patients were included in the systematic review and meta-analysis. No significant difference was found between short-course and long-course antibiotic treatments in 30-day mortality (risk ratio [RR] 0.85; 95% confidence interval [CI] 0.65-1.13; $P = .26$), 30-day recurrent bacteremia (RR 1.07; 95% CI 0.68-1.67; $P = .78$), 90-day mortality (RR 0.84; 95% CI 0.57-1.24; $P = .38$), 90-day recurrent bacteremia (RR 0.98; 95% CI 0.50-1.89; $P = .94$), adverse events (RR 1.14; 95% CI 0.89-1.45; $P = .30$), *Clostridium difficile* infection (RR 0.86; 95% CI 0.40-1.86; $P = .71$) or resistance development (RR 1.19; 95% CI 0.66-2.14; $P = .57$).

What is new and conclusion: Short-course was non-inferior to long-course antibiotic treatments for patients with uncomplicated gram-negative bacteremia. Considering the drug-related side effects and cost-effectiveness, a shorter duration of antibiotic treatment may be preferable for this particular population. However, additional high-quality RCTs are needed to further assess whether a shorter course

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of antibiotic treatment is of greater benefit for patients with uncomplicated gram-negative bacteremia.

KEYWORDS
antibiotic treatment, duration, gram-negative bacteremia, meta-analysis., systematic review, uncomplicated

1 | WHAT IS KNOWN AND OBJECTIVE

Although great progress has been made in medical science in the past few decades, bloodstream infections (BSI), particularly those due to gram-negative bacilli (GNB), remain a major health problem worldwide and are associated with high morbidity and mortality.[1] More than 30% of hospital-acquired infections and approximately 45% of community-acquired infections are due to GNB, and gram-negative bacteremia increases the length of hospital stays and medical burdens.[2,3]

For patients with gram-negative bacteremia, the optimal duration of antibiotic treatment has been poorly defined and there is a significant difference of opinion between clinicians. In the absence of strong evidence on this issue, the duration of antibiotic treatment for patients with gram-negative bacteremia ranges from 7 to 14 days, which are based to some extent on clinical practice guidelines for catheter-related infections and expert opinion.[4] Timely and adequate antibiotic treatment may improve the prognosis of patients with BSI[5]; however, prolonged exposure to antibiotics may increase the incidence of adverse drug events, such as multidrug-resistant organisms and *Clostridium difficile* infections (CDI).[6,7] Reducing the treatment duration is one way to reduce antibiotic consumption, which has become a major public health priority.[8]

There are several systematic reviews and meta-analyses comparing the efficacy of short-course vs long-course antibiotic treatment for bacteremia, and no significant differences in terms of clinical outcomes have been identified.[9,10] However, no reviews have focused on uncomplicated gram-negative bacteremia. A retrospective cohort study conducted by Nelson et al concluded that long-course antibiotic treatment may be superior to short-course.[11] Two recently completed non-inferiority randomized controlled trials (RCTs) indicated that an antibiotic course of 7 days was non-inferior to a 14-day course in patients with uncomplicated gram-negative bacteremia.[12,13] In order to examine the therapeutic equivalence between short-course and long-course antibiotic treatment for uncomplicated gram-negative bacteremia, we conducted this systematic review and meta-analysis.

2 | METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) guidelines to perform the meta-analysis.[14]

2.1 | Selection of studies

We reviewed PubMed, EMBASE and the Cochrane Central Register of Controlled Trials Library database on 6 June 2020. The following keywords were included in our search strategy: 'duration', 'short-course', 'long-course', 'prolonged' AND 'uncomplicated' AND 'bacteremia' OR 'bacteraemia' OR 'bloodstream infection'. We did not impose any language restrictions. To find additional citations, the reference lists of the included studies and recent review articles were manually reviewed as necessary.

Studies were selected if they met the following criteria: (a) population: patients, whether adults or children, were diagnosed with uncomplicated gram-negative bacteremia; (b) intervention: patients received antibiotic treatment; (c) comparison intervention: short-course vs long-course antibiotic treatment (as defined by the study authors); and (d) outcome: at least one of the following clinical outcomes were available (30-day mortality, 90-day mortality, recurrent bacteremia, adverse events, CDI and resistance development). The exclusion criteria were as follows: (a) uncomplicated gram-negative bacteremia was not specified; (b) data regarding clinical outcomes were unavailable; and (c) animal studies. Two authors (X. L. and C. L.) independently assessed the selected studies for final analysis, and any discrepancies were resolved through consultation with a third author (F. Z.).

2.2 | Data extraction and quality assessment

The following information was extracted using a standard form by two authors (X. L. and C. L.) and reviewed by a third (Z. M.): first author, year of publication, study design, sample size, male percentage, median age of each group, duration of short-course and long-course treatment, main causative pathogen, main source of bacteremia and clinical outcomes, including 30-day mortality, 90-day mortality, recurrent bacteremia, adverse events, CDI and resistance development.

For RCTs, the Cochrane risk of bias assessment tool was used to evaluate the risk of bias. Items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. For non-RCTs, the risk of bias was assessed using the Newcastle-Ottawa Scale (NOS), which included selection, comparability and outcome.[15,16]

2.3 | Data synthesis and analysis

The primary outcomes were the incidence of all-cause mortality and recurrent bacteremia within 30 days. The secondary outcomes included the incidence of all-cause mortality and recurrent bacteremia through day 90, CDI, resistance development and adverse events.

Clinical outcomes between the two groups were reported as risk ratios (RRs) and 95% confidence intervals (CIs). Statistical heterogeneity among the trials included in the meta-analysis was assessed and quantified using the I^2 statistic and chi-squared test, which estimates the percentage of total variation across studies due to heterogeneity rather than chance. When $I^2 < 50\%$ and $P > .10$ were considered to have no significant heterogeneity, we used the fixed-effect mode. Otherwise, the random-effects model was used as appropriate.[17,18] We performed Egger's test to assess publication bias.[19] To further ascertain which factors may have influenced clinical outcomes among the included studies, sensitivity and subgroup analyses were conducted within the particular groups: RCTs vs non-RCTs, special bacteremia vs non-special bacteremia and adults vs children.

If the two-sided P value was <.05, the results were considered statistically significant. Except for Egger's test, which was conducted using STATA (version 14.0, Stata Corporation, College Station, TX), all other statistical analyses were performed using Review Manager (version 5.3, The Cochrane Collaboration, Oxford, UK).

3 | RESULTS

3.1 | Selection and characteristics of the studies

A total of 247 potentially relevant studies were identified by our search strategy, of which 124 duplicate publications were excluded. According to the inclusion and exclusion criteria, we excluded 112 studies by evaluating the titles and abstracts. After reading the full texts of the remaining eleven studies, only six studies containing a total of 2689 patients were included in the systematic review and meta-analysis.[12,13,20-23] Two studies were excluded due to the unavailability of data.[11,24] Three studies were excluded because patients were not clearly defined as having uncomplicated gram-negative bacteremia[25-27] (Figure 1).

The characteristics of the included studies are presented in Table 1 (RCT: 2; prospective: 1; retrospective: 3). The definition of short course and long course varied among the included studies, but ranged from 6 to 11 days for the short course and more than 10 days for the long course. The main causative pathogen was *Escherichia coli*, and the main source of bacteremia was the urinary tract. Five studies involved adults,[12,13,21-23] while one involved children.[20] Four studies included patients diagnosed with uncomplicated gram-negative bacteremia,[12,13,20,23] whereas two studies only included patients with Enterobacteriaceae bacteremia[21] or *Pseudomonas aeruginosa* in the bloodstream.[22]

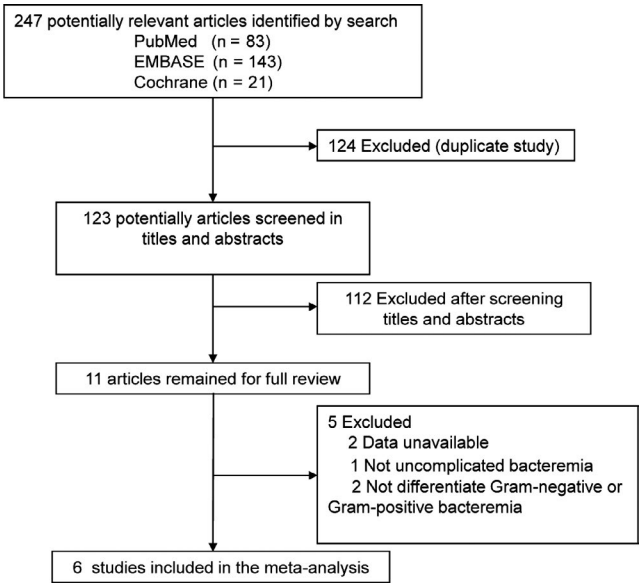

FIGURE 1 Flow diagram for the identification of eligible studies

3.2 | Study quality and publication bias

Because blinding was not performed in one RCT study, we assessed performance bias and detection bias as unclear, while the other items were assessed as having low bias (Appendix S1). For non-RCTs, which were assessed by NOS, two scored 7 points, one 8 points and one 9 points (Appendix S2). Egger's test indicated that publication bias may exist ($P = .010$; Appendix S3).

3.3 | Primary outcomes

All studies reported 28- or 30-day all-cause mortality. There was no significant difference between the short-course and long-course groups (7.3% vs 6.3%, respectively). The pooled RR of 30-day all-cause mortality was 0.85 (95% CI 0.65.1.13; $P = .26$; Figure 2A). No heterogeneity was detected among the studies ($I^2 = 0\%$). Four studies reported the occurrence of recurrent bacteremia through day 30,[13,20-22] and the pooled RR of 1.07 (95% CI 0.68.1.67; $P = .78$; Figure 3) indicated no significant difference between the two groups (4.2% vs 5.1%, respectively). No significant heterogeneity was detected among the studies ($I^2 = 23\%$).

We conducted subgroup analyses divided by study type, and neither the RCT subgroup nor the non-RCT subgroup showed statistically significant differences in 30-day all-cause mortality between short-course and long-course antibiotic treatments. The pooled RR was 0.83 (95% CI 0.44-1.55; $P = .56$) and 0.86 (95% CI 0.63-1.17; $P = .34$), respectively (Figure 2A). Subgroup analyses according to the type of bacteremia showed no statistically significant differences (specific bacteremia subgroup: RR 0.96; 95% CI 0.65.1.43; $P = .85$; non-specific bacteremia subgroup: RR 0.77; 95% CI 0.52-1.13; $P = .18$; Figure 2B). When we excluded the study on children,[20] we also did not find a statistically significant

TABLE 1 Characteristics of included studies

Study	Study type	Population	Definition of uncomplicated GNB	Number (male) Short-course Long-course	Median age (IQR) Short-course Long-course	Definition of short-/long-course Short-course Long-course	Main pathogen (%) Short-course Long-course	Main source of bacteremia (%) Short-course Long-course
von Dach et al[13]	RCT	Uncomplicated GNB	Without complicated infections (eg, abscess, endocarditis)	169 (62) 165 (71)	78 (69-86) 80 (67-85)	7 d 14 d	*Escherichia coli* (73%) *E coli* (75%)	Urinary tract (63%) Urinary tract (71%)
Yahav et al[12]	RCT	Uncomplicated GNB	Without other sources of infection, uncontrolled focus of infection, polymicrobial growth, specific pathogens (Brucella, Salmonella)	306 (150) 298 (135)	71 (61.8-81) 71 (61-80)	7 d 14 d	*E coli* (60.8%) *E coli* (65.1%)	Urinary tract (69.3%) Urinary tract (66.8%)
Sousa et al[23]	Prospective	Uncomplicated GNB	Without deep-seated infections such as not-drained intra-abdominal or pelvic abscesses	163 (78) 232 (137)	74 (26-94) 70 (18-105)	7-10 d >10 d	*E coli* (60%) *E coli* (53%)	Urinary tract (56%) Urinary tract (48%)
Fabre et al[22]	Retrospective	*P aeruginosa* BSI	Without osteoarticular infections, endocarditis/endovascular infections or central nervous system infections	72 (48) 179 (111)	61 (50-79) 66 (52-76)	7-11 d >11 d	*P aeruginosa* (100%) *P aeruginosa* (100%)	Urinary tract (30.4%) Urinary tract (30.3%)
Chotiprasitsakul et al[21]	Retrospective	Uncomplicated Enterobacteriaceae Bacteremia	Without polymicrobial bacteremia	385 (194) 385 (211)	60 (49-69) 60 (49-70)	6-10 d 11-16 d	*E coli* (46%) *E coli* (47.8%)	Urinary tract (34.8%) Urinary tract (37.4%)
Park et al[20]	Retrospective	Uncomplicated GNB	Without infective endocarditis, suppurative thrombophlebitis, CNS infection, osteomyelitis or deep-seated undrained abscesses	170 (NA) 170 (NA)	2.5 (0.6-11) 2 (0.5-8)	7-10 d >10 d	*Klebsiella* spp. (31.8%) *Klebsiella* spp. (28.2%)	Central line (63.5%) Central line (61.1%)

Abbreviations: CNS, central nervous system; GNB, gram-negative bacteremia; NA, not available; IQR, interquartile range; *P aeruginosa* BSI, *Pseudomonas aeruginosa* bloodstream infections; RCT, randomized controlled trial.

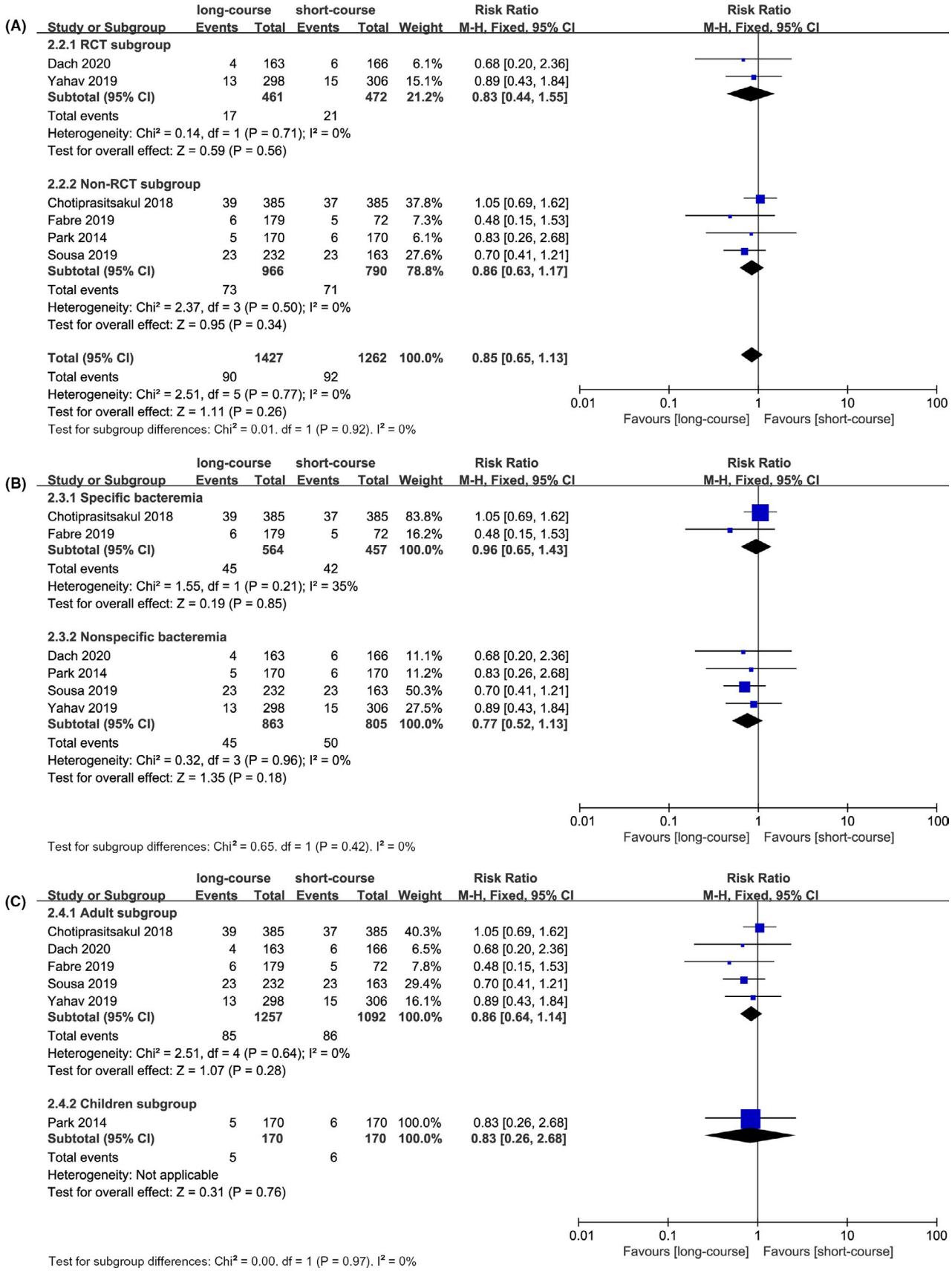

FIGURE 2 Forest plot of comparison: long course vs short course. A, Subgroup analyses for 30-d mortality divided by study type (RCTs vs non-RCTs); (B) subgroup analyses for 30-d mortality divided by infecting organisms (specific bacteremia vs non-specific bacteremia); and (C) subgroup analyses for 30-d mortality divided patient's age (adult group vs children group). RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

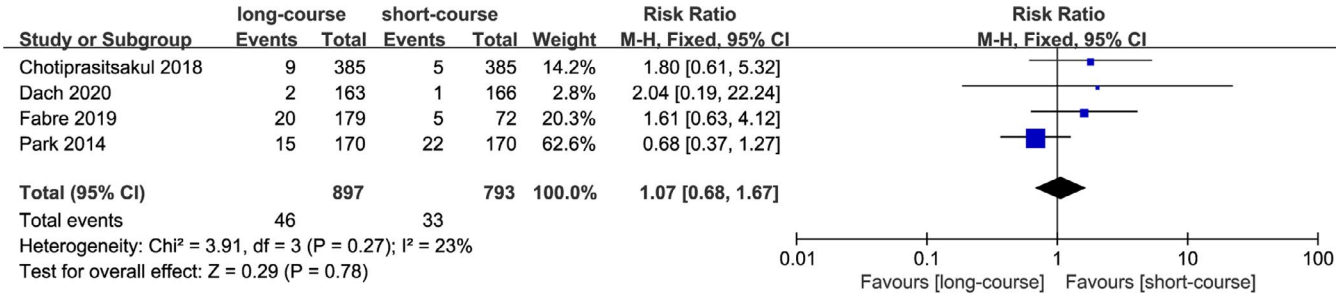

FIGURE 3 Forest plot of 30-d recurrent bacteremia [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Summary of secondary outcomes analyses

Outcome	No. of trials	No. of patients	Risk ratio (95% CI)	*P* value	Heterogeneity I^2, %	Heterogeneity *P* value for I^2
90-d all-cause mortality	2[12][13]	921	0.84 (0.57-1.24)	0.38	0	0.47
90-d recurrent bacteremia	3[12][13][23]	1316	0.98 (0.50-1.89)	0.94	0	0.77
Adverse events	2[12][13]	933	1.14 (0.89-1.45)	0.30	0	0.62
Clostridium difficile infection	4[12][13][20][21]	2043	0.86 (0.40-1.86)	0.71	0	0.61
Resistance development	2[12][21]	1374	1.19 (0.66-2.14)	0.57	59	0.12

difference between short-course and long-course antibiotic treatments (RR 0.86; 95% CI 0.64.1.14; P = .28; Figure 2C). No heterogeneity between studies was detected for the RCT subgroup, non-RCT subgroup, non-specific bacteremia subgroup or adult subgroup. The specific bacteremia subgroup showed mild heterogeneity (I^2 = 35%).

3.4 | Secondary outcomes

Only two RCTs reported 90-day all-cause mortality and adverse events.[12,13] No statistically significant difference was found in either 90-day all-cause mortality or adverse events, and the pooled RR was 0.84 (95% CI 0.57-1.24; P = .38; I^2 = 0%; Appendix S4a) and 1.14 (95% CI 0.89-1.45; P = .30; I^2 = 0%; Appendix S4b), respectively. The main adverse event in the study by Dach et al was CDI,[13] while Yahav et al reported diarrhoea as the main adverse event.[12] The data of 90-day recurrent bacteremia in three studies involving 1316 patients were available.[12,13,23] The results failed to show that long-term treatment could reduce 90-day recurrent bacteremia compared with short-course treatment (RR 0.98; 95% CI 0.50-1.89; P = .94; I^2 = 0%; Appendix S4c). Four studies[12,13,20,21] involving 2043 patients reported CDI and two studies[12,21] involving 1374 patients reported resistance development. These results indicated that the duration of antibiotic treatment was not associated with CDI (RR 0.86; 95% CI 0.40-1.86; P = .71; I^2 = 0%; Appendix S4d) or resistance development (RR 1.19; 95% CI 0.66-2.14; P = .57; I^2 = 59%; Appendix S4e). Detailed results of the secondary analysis are presented in Table 2.

4 | DISCUSSION

This systematic review and meta-analysis identified studies comparing short-course and long-course antibiotic treatment in patients with uncomplicated gram-negative bacteremia. In terms of clinical outcomes, including 30-day mortality, 90-day mortality, recurrent bacteremia, adverse events, CDI and resistance development, no significant difference was detected between the two groups.

Although we only included a specific population of uncomplicated gram-negative bacteremia, there were differences in pathogenic bacteria, infection site and infection severity among the studies, leading to differences in antibiotic treatment regimens and duration of antibiotic treatment. As a result, the definitions of short course and long course varied among the included studies. One problem was that patients who were classified in the short-course group in one study could be classified into the long-course group in another. However, the main demographics, clinical outcomes and antibiotics prescribed were comparable between the short-course and the long-course groups in each study.

There has been continuous debate regarding the optimal duration of antibiotic treatment for BSI. Prolonged antibiotic treatment

duration can increase adverse events and antibiotic resistance,[6,7,28] while inadequate antibiotic treatment may be associated with poor clinical prognosis.[5,29-31] A meta-analysis conducted by Havey et al, including 24 RCTs, concluded that, in terms of a clinical cure, microbiologic cure and survival among most patients with BSI, shorter-duration therapy may be as effective as longer-duration therapy.[9] Another meta-analysis conducted by Tansarli et al focusing on patients with bacteremia due to Enterobacteriaceae drew a similar conclusion that there was no significant difference in clinical outcomes between the short-course and long-course antibiotic treatment groups.[10] Compared with complicated BSI, such as BSI complicated by osteoarticular infections, central nervous system infections and endocarditis, uncomplicated BSI may require a shorter duration of antibiotic treatment and have a better prognosis. Moreover, for patients with uncomplicated gram-negative bacteremia, shortening the antibiotic treatment duration may be more feasible and safer than for complicated gram-negative bacteremia.

Among the included studies, the 30-day all-cause mortality rate ranged from 3.5% to 14.1% and from 2.5% to 10.1% in the short-course and long-course groups, respectively. Different inclusion and exclusion criteria among the studies may account for these differences. The highest overall mortality rate was found in a study conducted by Sousa et al, which included patients with immunosuppression. Moreover, a higher rate of inadequate empirical antibiotic treatment, an independent risk factor for mortality,[25] existed in that study. In contrast, in an RCT conducted by Dach et al, the 30-day all-cause mortality rate was 3.6% and 2.5% in the short-course and long-course groups, respectively.[13] Patients with hemodynamic instability, immunosuppression and complicated infections, which were associated with poor prognosis, were excluded.

Adverse events, recurrent bacteremia, CDI, and resistance development must be taken into consideration when planning to adjust the duration of antibiotic treatment. In our study, no significant difference was detected, which indicates that the safety and efficacy of short-course and long-course antibiotic treatment were comparable. Only two RCTs had available data on distal complications and suppurative complications, and both studies found no significant difference between the short-course and long-course groups.[12,13]

Although our study suggested that short course was non-inferior to long-course antibiotic treatment, the results should be interpreted with caution. Our study has several limitations. First, non-RCTs were included in our meta-analysis, meaning the data were prone to confounding factors. Second, inclusion and exclusion criteria were significantly different among the studies. Four studies included patients with mixed GNB infection, while one study only included patients with *P aeruginosa* infection and another study only included patients with Enterobacteriaceae infection. Moreover, one study of children was also included in our meta-analysis. However, no significant heterogeneity was detected in any of the analyses. Third, due to the limited data, we did not perform further analysis of medical costs and length of hospital stay. There is an underlying assumption that the antibiotics used were equally appropriate across studies. Finally, our study focused on uncomplicated gram-negative bacteremia; consequently, the findings cannot be generalized to other types of bacteremia, so additional high-quality studies are required.

5 | WHAT IS NEW AND CONCLUSIONS

This systematic review and meta-analysis found that short-course antibiotic treatment was not inferior to long-course antibiotic treatment for patients with uncomplicated gram-negative bacteremia. Considering the drug-related side effects and cost-effectiveness, a shorter duration of antibiotic treatment may be preferable for this particular population. However, additional high-quality RCTs are needed to compare efficacy, resistance development, cost-effectiveness, and safety between short- and long-course treatments, and to further assess whether a shorter course of treatment is of greater benefit to patients with uncomplicated gram-negative bacteremia.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interests.

AUTHORS' CONTRIBUTIONS

Xiaoming Li: conceptualization; data curation; formal analysis; methodology; writing – original draft. **Chao Liu:** conceptualization; data curation; investigation; and formal analysis. **Zhi Mao:** data curation; investigation; and project administration. **Qinglin Li:** formal analysis and software. **Shuang Qi:** methodology and software. **Feihu Zhou:** funding acquisition; supervision; validation; writing – review and editing.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article (and its Supporting Information Appendix files).

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REFERENCES

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect*. 2013;19(6):501-509.
2. Diekema DJ, Beekmann SE, Chapin KC, Morel KA, Munson E, Doern GV. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. *J Clin Microbiol*. 2003;41(8):3655-3660.
3. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. *N Engl J Med*. 2010;362(19):1804-1813.
4. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(1):1-45.
5. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*. 2000;118(1):146-155.
6. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med*. 2004;10(12 Suppl):S122-S129.

7. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med*. 2017;177(9):1308-1315.
8. Wintenberger C, Guery B, Bonnet E, et al. Proposal for shorter antibiotic therapies. *Med Mal Infect*. 2017;47(2):92-141.
9. Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. *Crit Care*. 2011;15(6):R267.
10. Tansarli GS, Andreatos N, Pliakos EE, Mylonakis E. A systematic review and meta-analysis of antibiotic treatment duration for bacteremia due to Enterobacteriaceae. *Antimicrob Agents Chemother*. 2019;63(5):e02495-18.
11. Nelson AN, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Optimal duration of antimicrobial therapy for uncomplicated gram-negative bloodstream infections. *Infection*. 2017;45(5):613-620.
12. Yahav D, Franceschini E, Koppel F, et al. Seven versus 14 days of antibiotic therapy for uncomplicated gram-negative bacteremia: a noninferiority randomized controlled trial. *Clin Infect Dis*. 2019;69(7):1091-1098.
13. von Dach E, Albrich WC, Brunel AS, et al. Effect of C-reactive protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated gram-negative bacteremia: a randomized clinical trial. *JAMA*. 2020;323(21):2160-2169.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
15. Wells G.The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Paper presented at: Symposium on Systematic Reviews: Beyond the Basics 2000.
16. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-605.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
20. Park SH, Milstone AM, Diener-West M, Nussenblatt V, Cosgrove SE, Tamma PD. Short versus prolonged courses of antibiotic therapy for children with uncomplicated gram-negative bacteraemia. *J Antimicrob Chemother*. 2014;69(3):779-785.
21. Chotiprasitsakul D, Han JH, Cosgrove SE, et al. Comparing the outcomes of adults with Enterobacteriaceae bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort. *Clin Infect Dis*. 2018;66(2):172-177.
22. Fabre V, Amoah J, Cosgrove SE, Tamma PD. Antibiotic therapy for *Pseudomonas aeruginosa* bloodstream infections: how long is long enough? *Clin Infect Dis*. 2019;69(11):2011-2014.
23. Sousa A, Perez-Rodriguez MT, Suarez M, et al. Short- versus long-course therapy in gram-negative bacilli bloodstream infections. *Eur J Clin Microbiol Infect Dis*. 2019;38(5):851-857.
24. Erickson RM, Tritle BJ, Spivak ES, Timbrook TT. Impact of an antimicrobial stewardship bundle for uncomplicated gram-negative bacteremia. *Open Forum Infect Dis*. 2019;6(12):ofz490.
25. Giannella M, Pascale R, Toschi A, et al. Treatment duration for *Escherichia coli* bloodstream infection and outcomes: retrospective single-centre study. *Clin Microbiol Infect*. 2018;24(10):1077-1083.
26. Hojat LS, Bessesen MT, Huang M, et al. Effectiveness of shorter versus longer durations of therapy for common inpatient infections associated with bacteremia: a multicenter, propensity-weighted cohort study. *Clin Infect Dis*. 2019;https://doi.org/10.1093/cid/ciz1197
27. Lee CC, Hsieh CC, Yang CY, et al. Short versus long duration antimicrobial treatment for community-onset bacteraemia: a propensity score matching study. *Int J Antimicrob Agents*. 2019;54(2):176-183.
28. Canton R, Morosini MI. Emergence and spread of antibiotic resistance following exposure to antibiotics. *FEMS Microbiol Rev*. 2011;35(5):977-991.
29. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-acquired pneumonia study group. *Intensive Care Med*. 1996;22(5):387-394.
30. Chong YP, Moon SM, Bang KM, et al. Treatment duration for uncomplicated *Staphylococcus aureus* bacteremia to prevent relapse: analysis of a prospective observational cohort study. *Antimicrob Agents Chemother*. 2013;57(3):1150-1156.
31. Chen HC, Lin WL, Lin CC, et al. Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections. *J Antimicrob Chemother*. 2013;68(4):947-953.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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