Title Page

Intended category: systematic review

Title: Oral switch vs continued intravenous antibiotic therapy in patients with bacteraemia and sepsis: a systematic review and meta-analysis

Qinyuan Li[1,†], Qi Zhou[2,3,4,†], Jiangbo Fan[5], Siyuan Huang[5], Yaolong Chen[2,3,6,7,8], Fujian Song[7,8,9], Zhou Fu[1], Enmei Liu[1], Daolin Tang[10], Ling Zeng[5*], Zhengxiu Luo[1*]

[1)]Department of Respiratory Medicine Children's Hospital of Chongqing Medical University, National Clinical Research Centre for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Child Rare Diseases in Infection and Immunity, China International Science and Technology Cooperation base of Child development and Critical Disorders, Key Laboratory of Children's Vital Organ Development and Diseases of Chongqing Health Commission, Chongqing, China

[2)]Evidence-Based Medicine Centre, School of Basic Medical Sciences, Lanzhou University, Lanzhou, China

[3)]Lanzhou University, an Affiliate of the Cochrane China Network, Lanzhou, China

[4)]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

[5)]Department of Trauma Medical Centre, Daping Hospital, State Key Laboratory of Trauma and Chemical Poisoning, Burns and Combined Injury, Army Medical University, Chongqing, China

[6)]Research Unit of Evidence-Based Evaluation and Guidelines, Chinese Academy of Medical

Sciences (2021RU017), School of Basic Medical Sciences, Lanzhou University, Lanzhou, China

[7)]National Clinical Research Centre for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Child Infection and Immunity, China International Science and Technology Cooperation base of Child development and Critical Disorders, Chongqing, China

[8)]Chevidence Lab Child & Adolescent Health, Department of Paediatric Research Institute, Children's Hospital of Chongqing Medical University, Chongqing, China

[9)]Norwich Medical School, Faculty of Medicine and Health Science, University of East Anglia, Norwich, NR4 7TJ, UK

[10)]Department of Surgery, UT Southwestern Medical Centre, Dallas, Texas, USA

Correspondence to: Zhengxiu Luo, MD; Postal address: Department of Respiratory Medicine Children's Hospital of Chongqing Medical University, No.136 Zhongshan 2nd Road, Yuzhong District, Chongqing 400010, China; Email address: luozhengxiu816@hospital.cqmu.edu.cn; Tel: +86-23-68370122; Fax: +86-23-63624479; Ling Zeng, MD, PhD, Postal address: Department of Trauma Medical Centre, Daping Hospital, State Key Laboratory of Trauma and Chemical Poisoning, Burns and Combined Injury, Army Medical University, Chongqing, China; Email address: zengling_1025@tmmu.edu.cn; Tel: +86-23-68757512; Fax: +86-23-63654675

† Contributed equally； * Corresponding author

Total word count of the manuscript: 3135

Abstract: 295

Tables: 2, **Figures**: 3

References: 54

ABSTRACT

Background: Bacteraemia and sepsis have traditionally required continued intravenous (IV) antibiotics.

Objectives: To evaluate if early transition to oral antibiotics is noninferior to continued IV antibiotic therapy in treating patients with bacteraemia and sepsis.

Data sources: MEDLINE, Embase, Web of Science, the Cochrane library, and Wanfang databases from inception to July 13, 2024, along with clinical trial registries and Google.com.

Study eligibility criteria: Randomised controlled trials (RCTs) and cohort studies.

Participants: Patients with bacteraemia and sepsis.

Interventions: Early transition to oral antibiotics versus continued IV antibiotics. Early oral switch was defined as 5-9 days for uncomplicated *Staphylococcus aureus* bacteraemia, <4 weeks for complicated *Staphylococcus aureus* bacteraemia, 3-7 days for uncomplicated *Streptococcus* bacteraemia, and 3-5 days for uncomplicated *Enterobacterales* bacteraemia.

Assessment of risk of bias: Cochrane risk of bias tool and Newcastle-Ottawa Scale.

Methods of data synthesis: Random-effects models were used to pool the data. The primary outcome was treatment failure. The non-inferiority margin for treatment failure was 10%. The GRADE approach was used to rate the certainty of the evidence.

Results: In total, 38 studies (6 RCTs, 10 adjusted cohorts, and 22 unadjusted cohorts) involving 11,566 patients were included. A primary analysis of 6 RCTs and 10 adjusted cohorts comprised 7,102 patients. High-certainty evidence from six RCTs showed that early transition to oral antibiotics was noninferior to continued IV therapy for treatment failure (n=529; OR 0.89; 95% CI: 0.54 to 1.48). Low-certainty evidence from five adjusted cohorts

also found no significant difference in treatment failure between the two groups (n=929; OR 0.60; 95% CI: 0.29 to 1.72). Moderate-certainty evidence showed that oral switch therapy significantly reduced hospital stay (n=2,041; mean difference: -5.19 days; 95% CI: -8.16 to -2.22).

Conclusions: Early transition to oral antibiotics was noninferior to continued IV antibiotic treatment for bacteraemia and sepsis.

Introduction

Bacteraemia, a severe infection characterized by bacteria in the bloodstream, can rapidly progress to sepsis, organ failure, and death if not treated promptly [1]. It imposes a significant burden on global healthcare systems [2-4]. The conventional treatment approach involves intravenous (IV) antibiotics throughout the entire course [5], which necessitates prolonged hospitalization or outpatient treatment, thereby increasing costs and the risk of catheter-related infections. In contrast, oral antibiotics provide a shorter hospital stay, reduced expenses, and an improved quality of life [5,6].

Given these considerations, a critical question arises: Can patients with bacteraemia and sepsis safely transition from IV to oral antibiotics early in the treatment course? This issue is recognized as pivotal by clinicians, patients, researchers, and policymakers, necessitating urgent resolution [7,8]. Early studies suggested caution due to perceived lower effectiveness of oral antibiotics [9,10]. Recent studies, however, suggest that early transition from IV to oral antibiotics may be as effective as continued IV therapy, with additional safety and cost benefits [11,12]. Despite this, inconsistent research evidence and patient dissatisfaction concerns have led to reluctance among physicians to adopt this approach [13]. Consequently, few clinical guidelines currently recommend early transition, underscoring the need for a systematic review and meta-analysis.

This systematic review and meta-analysis aimed to comprehensively evaluate whether transitioning from IV to oral antibiotics in patients with bacteraemia and sepsis is as effective as continued IV therapy. We also investigated patient subgroups, appropriate transition timing, and the best choices of oral antibiotics, thereby providing a foundation for future clinical guidelines and decision-making.

Methods

Our systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook [14] and were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement [15]. The review protocol was prospectively registered with PROSPERO, CRD42024534251.

Search Strategy and Selection Criteria

We searched MEDLINE (via PubMed), Embase, Web of Science, the Cochrane Library, and the Wanfang Data databases for eligible studies from the inception of database to July 13, 2024, without language restrictions. Detailed search strategies are provided in Supplementary Table S1. We also searched ClinicalTrials.gov and the WHO International Clinical Trial Registry Platform, and Google.com. Handsearching through the reference lists of included publications and previous meta-analysis was also performed.

We included randomized controlled trial (RCTs) and cohort studies comparing IV switch to oral antibiotic therapy versus continued IV antibiotic therapy for patients with bacteraemia and/or sepsis. Studies were excluded if they focused on comparing the efficacy of different drug regimens rather than evaluating the non-inferiority of an IV-to-oral switch, even if one group received an IV-to-oral regimen and another received IV therapy alone (e.g., IV-to-oral linezolid versus IV vancomycin). We also excluded studies involving patients with occult bacteraemia or sepsis not meeting Sepsis-3 criteria [16], those that did not separately report outcomes for bacteraemia or were published only as conference abstracts, and those that did not adhere to the defined "early" IV-to-oral switch timing. In line with published definitions, we defined early switch timing as follows: 5-9 days for uncomplicated *Staphylococcus aureus*

bacteraemia [11,17], <4 weeks for complicated *Staphylococcus aureus* bacteraemia [18], 3-7 days for uncomplicated *Streptococcus* bacteraemia [19,20], and 3-5 days for uncomplicated *Enterobacterales* bacteraemia [12]. Study selection was conducted independently and in duplicate by two groups of investigators (group 1 was Q.L. and J.F.; group 2 was Q.Z. and S.H.). Any discrepancies were resolved through consensus discussions or, if necessary, by consulting a third investigator (Z.L.).

Data Extraction and Quality Assessment

Two groups of researchers collected data separately. The data was checked by a third investigator (Z.L.) before inclusion in the analysis. We used a predesigned spreadsheet to collect information such as study type; sample size; participant details; complication and pathogen of bacteraemia; route, duration, type, and dose of antibiotics; length of follow-up; and outcomes. The primary outcome was treatment failure. Secondary outcomes included all-cause mortality, relapse, readmission, length of hospital stay, adverse events, and antimicrobial cost. Outcomes are defined in Supplementary Table S2. If an RCT provided various datasets, including Intention-to-treat (ITT), modified ITT (mITT), and Per-protocol (PP), we prioritized the use of mITT, followed by ITT, and then PP datasets [21]. For cohort studies, if possible, we used results adjusted for baseline characteristics. If outcome data were reported at multiple follow-up points, we used data from the longest follow-up. For missing data or issues with reporting format, we contacted the authors for clarification. We assessed the risk of bias of the included RCTs and cohort studies using the Cochrane Risk of Bias tool and the Newcastle Ottawa Scale (NOS), separately [14,22]. The assessments of risk of biases were performed by two independent reviewers, and disagreements in these assessments were resolved by a third investigator (Y.C.).

Statistical Analysis

Results for dichotomous outcomes were presented as odds ratios (ORs) and 95% confidence intervals (CIs). To facilitate interpretation of non-inferiority margins, risk differences (RDs) were also presented for dichotomous outcomes in RCTs. Continuous variables were presented as mean differences (MDs) with 95% CIs. Based on published literature, the non-inferiority margin for the primary outcome of treatment failure is defined as 10% [11,12]. Heterogeneity was assessed using the I^2 statistic, with a value above 50% indicating substantial statistical heterogeneity [23]. To reduce the impact of confounding factors, our primary analysis integrated data exclusively from RCTs and cohorts that were properly adjusted for confounders (termed adjusted cohorts) employing the inverse variance method within a random-effect model. Cohorts with insufficient adjustments were categorized as unadjusted (termed unadjusted cohorts) and utilized solely for sensitivity analysis. Adequate adjustments encompassed patient age, gender, comorbidities, and disease severity.

Subgroup analyses were conducted on type of bacteraemia (complicated *vs.* uncomplicated), pathogen type (*Staphylococcus aureus vs. Streptococcus vs. Enterobacterales*), and oral antibiotic bioavailability (high *vs.* low). Further details of the definition of the subgroups can be found in Supplementary Table S2. Publication bias was assessed using funnel plots and Egger's tests [24]. The threshold for significance for *p* values was 0.05. We performed data analyses with STATA15.0 (StataCorp, College Station, Texas, USA). We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to rate the certainty of evidence as 'high', 'moderate', 'low', or 'very low' for all outcomes [25].

Results

We initially retrieved 30,026 articles and conducted full-text screening on 84 studies. We excluded 46 studies (see Supplementary Table S3) and included 38 studies in this study (**Figure 1**). Of the included studies, there were 6 RCTs [11,12,26-29], 10 adjusted cohort studies [17,20, 30-37], and 22 unadjusted cohort studies (the reference list for unadjusted cohort studies is available in Supplementary Table S4). The total number of patients was 7,102 in the RCTs and adjusted cohort studies, and 4,464 in the unadjusted cohort studies.

Of patients in RCTs [11,12,26-29] and adjusted cohorts [17,20, 30-37] for the primary analysis, the average age was 65.1 (SD: 17.9) years, 53.1% were male, 89.7% were immunocompetent, 87.2% had uncomplicated bacteraemia, 12.8% had complicated bacteraemia, and 0.6% had sepsis. Further basic characteristics of each RCTs and adjusted cohorts are shown in **Table 1** and in Supplementary Table S5 for unadjusted cohorts.

All included RCTs [11,12,26-29] had appropriate randomization and were free from selective outcome reporting and other biases. However, two RCTs [27,29] had a high risk of bias related to blinding of patients, researchers, and outcome assessors, and one RCT [27] had a high risk of bias concerning the completeness of outcome data. No risk of bias was identified in ten adjusted cohorts [17,20, 30-37]. Detailed results of the risk of bias assessment for the included studies are shown in Supplementary Table S6-S7. The summary of the GRADE assessment regarding the certainty of evidence for both primary and secondary outcomes is provided in Supplementary Table S8.

Six RCTs [11,12,26-29] with 529 patients reported on treatment failure. Treatment failure rates were 13.3% (34/256) in the oral switch group and 14.3% (39/273) in the IV group.

Overall, the treatment failure rate in the oral switch group was non-inferior to that in the IV group (OR = 0.89; 95% CI: 0.54 to 1.48; I^2 = 0.0%; **Figure 2**; RD = -0.01; 95% CI: -0.06 to 0.04; I^2 = 0.0%; Supplementary Figure S1; high certainty of evidence). Five adjusted cohorts [20,30,35-37] with 929 patients reported on treatment failure. The pooled results of the adjusted cohorts showed no significant difference in treatment failure between the oral switch group and the IV group (OR = 0.60; 95% CI: 0.29 to 1.72; I^2 = 72.1%; **Figure 2**; low certainty of evidence).

We performed a subgroup analysis on treatment failure. Results showed that, in uncomplicated bacteraemia patients, the treatment failure rate for oral switch therapy was not significantly different from IV antimicrobial therapy (n = 1290 patients; OR = 0.66; 95% CI: 0.41 to 1.09; I^2 = 47.1%; **Table 2**). This finding was consistent across infections by *Staphylococcus aureus* (n = 535 patients; OR = 0.63; 95% CI: 0.23 to 1.69; I^2 = 71.2%), *Streptococcus species* (n = 396 patients; OR = 1.04; 95% CI: 0.33 to 3.28; I^2 = 77.8%), and *Enterobacterales* (n = 508 patients; OR = 0.59; 95% CI: 0.32 to 1.08; I^2 = 8.1%)(**Table 2**).

Seven studies (three RCTs [11,12,26] and four adjusted cohorts [20,30,31,34], with 1,688 patients) reported 90-day mortality rates: 9.0% (74/819) in the oral switch group and 13.7% (119/869) in the IV group. Meta-analysis demonstrated no significant difference between the groups (OR = 0.70; 95% CI: 0.35 to 1.42; I^2 = 64.0%; **Figure 3**; moderate certainty of evidence). Seven studies (one RCT [11] and six adjusted cohorts [20,30-34], with 5,918 patients) reported 30-day mortality rates: 7.3% (142/1950) in the oral switch group and 6.6% (263/3968) in the IV group. Pooled analysis indicated no significant difference (OR = 0.77; 95% CI: 0.50 to 1.20; I^2 = 49.5%; **Figure 3**; low certainty of evidence). Three studies (one RCT [11] and two adjusted cohorts [17,32], with 3,240 patients) reported 14-day

mortality rates: 2.2% (14/635) in the oral switch group and 2.5% (66/2605) in the IV group. Combined results showed no significant difference (OR = 0.93; 95% CI: 0.26 to 3.26; I^2 = 28.2%; **Figure 3**; very low certainty of evidence).

Seven studies (three RCTs [11,12,29] and four adjusted cohorts [17,20,30,33]), involving 2,487 patients, reported relapse rates. The pooled analysis revealed no statistically significant difference in relapse rates between the oral switch and IV groups (OR = 0.99; 95% CI: 0.57 to 1.72; I^2 = 0.0%; Supplementary Figure S2; moderate certainty of evidence)

Five studies (two RCTs [11,12] and three adjusted cohorts [20,30,32]), comprising 3,556 patients, reported readmission rates. The meta-analysis found no significant difference in readmission rates between the oral switch and IV groups. (OR = 1.16; 95% CI: 0.77 to 1.73; I^2 = 0.0%; Supplementary Figure S3; moderate certainty of evidence).

Five studies (three RCTs [11,12,26] and two adjusted cohorts [17,33]) with 2,041 patients reported length of hospital stay. Overall, the oral switch group had a significantly shorter hospital stay than the IV group (MD = -5.19 days; 95% CI: -8.16 to -2.22 days; I^2 = 94.1%; Supplementary Figure S4; moderate certainty of evidence).

Five RCTs [11,12,26,27,29] involving 604 patients reported any adverse events and serious adverse events. Meta-analysis revealed no significant differences in the rates of any adverse events (OR = 1.05; 95% CI: 0.74 to 1.50; I^2 = 0.0%; Supplementary Figure S5; moderate certainty of evidence) or serious adverse events (OR = 1.36; 95% CI: 0.88 to 2.09; I^2 = 0.0%; Supplementary Figure S5; moderate certainty of evidence) between the oral switch and IV groups. Three studies (two RCTs [11,29] and one adjusted cohort [32]) with 3,210 patients reported IV-related complications. The oral switch group experienced fewer IV-related complications than the IV group (OR = 0.40; 95% CI: 0.21 to 0.76; I^2 = 0.0%; Supplementary

Figure S5; moderate certainty of evidence).

Regarding total healthcare costs, one RCT found that switching 24 patients to oral ciprofloxacin saved $77,946 compared to IV treatment [26]. Another RCT reported an average savings of $1,291 per patient [29]. A cohort study also showed significantly lower healthcare costs in the oral ciprofloxacin group (mean dollars (SD): 74 (52.81) *vs.* 305.59 (304.70); $P < 0.001$) [38]. Additionally, studies reported significantly lower antibiotic costs in the oral group, with median savings ranging from $10.9 to $43.38 compared to IV treatment (all $P < 0.001$) [33,39,40].

Sensitivity analysis indicated that in unadjusted cohort studies, the treatment failure rate, 30-day mortality, relapse rate, readmission rate, length of hospital stay and IV-associated complications were lower in the oral switch group compared to the IV group, while other outcomes showed no significant differences between the two groups (Supplementary Figure S6). In addition, we performed sensitivity analyses with RCT datasets and found no significant difference in treatment failure rates between oral switch and continued IV therapy, irrespective of whether data were aggregated from ITT, mITT or PP (Supplementary Figure S7). No evidence of publication bias was found (Egger's $P = 0.960$, Supplementary Figure S8).

Discussion

Our systematic review and meta-analysis included 38 studies, with a primary analysis focusing on results from 6 RCTs and 10 adjusted cohorts. The findings revealed that, compared to continued IV treatment, early transition from IV to oral antibiotics in patients with bacteraemia resulted in similar rates of treatment failure, all-cause mortality, relapse, and readmission. Additionally, the oral switch significantly reduced IV-associated

complications, hospital stays, and healthcare costs.

Early systematic reviews reached conclusions similar to ours [41,42], but did not include the latest high-quality RCTs and lacked quantitative analysis. A recent meta-analysis that pooled only RCT results [43] also reached a similar conclusion to ours, but it included some studies that were not appropriately selected. For instance, it included RCTs comparing the efficacy of two drugs rather than evaluating the non-inferiority of an IV-to-oral switch [44-47]. Another recent meta-analysis found that in patients with Gram-negative bacteraemia, the treatment failure rate in the oral switch group was significantly lower than in the IV group, which contradicts our findings and those of other systematic reviews [48]. This discrepancy arose from the systematic review authors' combination of unadjusted cohort data with adjusted cohort and RCT results, causing baseline imbalances between oral switch and IV groups and leading to biased outcomes. Moreover, this review only included a total of 17 RCTs and cohort studies [48], leaving out many important studies.

To optimize the selection of patients for early oral antibiotic transition, we performed subgroup analyses. Distinguishing between uncomplicated and complicated bacteraemia is challenging due to complex diagnostic criteria, which may not capture all clinical scenarios [42]. Complications such as epidural abscesses and infectious endocarditis often present with atypical early symptoms, leading to missed diagnoses [42]. Our subgroup analysis revealed that the oral switch was non-inferior to IV therapy for uncomplicated bacteraemia. However, the limited data for complicated bacteraemia make it unclear whether the oral switch strategy is equally effective, necessitating further research, particularly high-quality RCTs. Additionally, research on sepsis is scarce, necessitating future RCTs to evaluate the efficacy and timing of IV-to-oral transitions in sepsis patients. To mitigate patient heterogeneity, it is advisable for

283 future research to consistently use the latest international diagnostic criteria for sepsis.

284 We conducted subgroup analyses based on pathogens. Our findings suggested that early
285 oral switch therapy was comparable to IV treatment in patients infected with
286 *Enterobacterales*, *Staphylococcus aureus*, and *Streptococcus*. This aligned with a meta-analysis
287 on *Staphylococcus aureus* bacteraemia [49]. Currently, most studies focus on uncomplicated
288 *Enterobacterales* and *Staphylococcus aureus* bacteraemia, with less research on *Streptococcus*
289 and other pathogens. More studies are needed to assess the effectiveness of IV-to-oral switch
290 in these infections. Additionally, it is important to note that the timing of the IV-to-oral switch
291 varies depending on the pathogen involved. Based on the results from existing studies, we
292 have outlined the recommended timing for an early IV-to-oral switch for different pathogens.
293 In published research, the timing for initiating an early IV-to-oral switch has been set at a
294 minimum of 3 days or longer. However, ongoing studies are currently investigating the
295 efficacy and safety of switching to oral therapy within 72 hours from the time of index blood
296 culture collection [50]. We anticipate future research to provide additional evidence
297 supporting earlier oral treatment. It is crucial to emphasize that the timing of the IV-to-oral
298 antibiotic switch should not be confined to a fixed time range but should be individualized on
299 the basis of the patient's clinical response, adherence to oral treatment, and other pertinent
300 factors.

301 We also explored the efficacy of transitioning to oral antibiotics with different
302 bioavailability. Physicians often prefer high-bioavailability oral antibiotics for transitioning
303 due to their superior absorption and higher blood concentrations [51]. However, our results
304 showed that the IV-to-oral switch had similar efficacy to IV treatment regardless of the
305 bioavailability of the oral antibiotics used. Pharmacological studies confirmed that the

306 success of oral therapy depended on the antibiotic concentration-time curve within the
307 therapeutic window, rather than bioavailability per se [5]. Increasing the dose of
308 low-bioavailability antibiotics, like β-lactams, can achieve similar efficacy to
309 high-bioavailability drugs and IV administration [5,52,53]. However, given the small sample
310 sizes in some subgroups, caution is advised, and more research is needed to explore the
311 applicability of different bioavailability antibiotics in IV-to-oral therapy.
312 Our study has limitations. First, due to the limited number of RCTs, we included adjusted
313 cohort studies in our primary analysis, which reduced the certainty of evidence despite
314 consistent results. Second, the scarcity of RCTs in regions such as China hampers the
315 generalizability of our findings. This research gap can be attributed to multiple factors:
316 insufficient physician knowledge, as evidenced by 60% of surveyed clinicians being unaware
317 of IV-to-oral transitioning; perceived challenges, including the perception of IV therapy as
318 superior and patient preferences for IV treatment; and limited drug availability, with certain
319 antimicrobials lacking oral formulations [51]. We hope that disseminating research findings
320 will enhance global acceptance of IV-to-oral antibiotic treatments, accelerating the
321 development of oral formulations and creating more opportunities for high-quality research
322 in this field. Third, heterogeneity in pathogens and antibiotic types may affect the reliability of
323 combined results, although subgroup analyses suggest minimal impact. Lastly, factors like sex,
324 infection source, severity, comorbidities, and immune status, which can influence the
325 IV-to-oral transition's efficacy [54], were not analysed due to a lack of data. Future
326 high-quality RCTs are needed to validate the effectiveness and safety of the IV-to-oral strategy
327 across different subgroups.
328

Conclusion

Our findings suggest that in immunocompetent adult patients with uncomplicated bacteraemia, transitioning from IV to oral antibiotic therapy is as effective as continued IV treatment. This approach provides benefits such as reduced IV-associated complications, shorter hospital stays and lower treatment costs. However, in patients with complicated bacteraemia and sepsis, the efficacy and safety of IV-to-oral antibiotic therapy remain uncertain and warrant further investigation. These conclusions support the consideration of IV-to-oral antibiotic transition strategies in clinical practice. Future high-quality RCTs are needed to identify the optimal patient populations, timing, and types of oral antibiotics for transitioning from IV therapy.

Author Contributions

QL, QZ, LZ, and ZL were responsible for the conceptualization and study design. QL, QZ, JF, SH, YC, and ZL conducted the literature searches, study selection, data extraction, and risk of bias assessments. QL, QZ, YC, FS, ZF, EL, DT, LZ, and ZL handled the analysis and interpretation of the data. QL, QZ, LZ, and ZL drafted the paper. All authors contributed to reviewing and revising the manuscript and have approved the final version for publication.

Data sharing

All relevant data are disclosed in the manuscript and the supplementary materials.

Transparency declaration

The authors declare that they have no conflicts of interest. This systematic review was supported by the Outstanding Paediatric Elite Training Program of the National Clinical

Research Centre of Children's Hospital of Chongqing Medical University, the Project of Young and Middle Medical Distinguished Team in Chongqing, China (Grant No. 020291), the National Natural Science Foundation of China (Grant No. 82222038), the Outstanding Young Talents of National Defence Biotechnology (Grant No. 01-SWKJYCJJ06), and the Military Clinical Key Specialty Construction Project. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The authors thank all the people who participated in the primary studies and the research teams who did them.

References

1. Kern WV, Rieg S. Burden of bacterial bloodstream infection-a brief update on epidemiology and significance of multidrug-resistant pathogens. Clin Microbiol Infect 2020;26:151-7. https://doi.org/10.1016/j.cmi.2019.10.031.
2. Bai AD, Lo CKL, Komorowski AS, Suresh M, Guo K, Garg A, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. Clin Microbiol Infect 2022;28:1076-84. https://doi.org/10.1016/j.cmi.2022.03.015.
3. Buetti N, Atkinson A, Marschall J, Kronenberg A; Swiss Centre for Antibiotic Resistance (ANRESIS). Incidence of bloodstream infections: a nationwide surveillance of acute care hospitals in Switzerland 2008-2014. BMJ Open 2017;7:e013665. https://doi.org/10.1136/bmjopen-2016-013665.
4. Kadri SS, Rhee C, Strich JR, Morales MK, Hohmann S, Menchaca J, et al. Estimating Ten-Year Trends in Septic Shock Incidence and Mortality in United States Academic Medical Centers Using Clinical Data. Chest 2017;151:278-85. https://doi.org/10.1016/j.chest.2016.07.010.
5. Landersdorfer CB, Gwee A, Nation RL. Clinical pharmacological considerations in an early intravenous to oral antibiotic switch: are barriers real or simply perceived?. Clin Microbiol Infect 2023;29:1120-5. https://doi.org/10.1016/j.cmi.2023.04.009.
6. Eii MN, Walpole S, Aldridge C. Sustainable practice: Prescribing oral over intravenous medications. BMJ 2023;383:e075297. https://doi.org/10.1136/bmj-2023-075297.
7. Alhammadi A, Alshawaf R, Chavda S, Ramondino S, Schuster M. Infectious Diseases: What You May Have Missed in 2023. Ann Intern Med 2024;177:S37-46. https://doi.org/10.7326/M24-0679.

8. Doernberg SB, Lodise TP, Thaden JT, Munita JM, Cosgrove SE, Arias CA, et al. Gram-Positive Bacterial Infections: Research Priorities, Accomplishments, and Future Directions of the Antibacterial Resistance Leadership Group. Clin Infect Dis 2017;64:S24-9. https://doi.org/10.1093/cid/ciw828.
9. MORGAN WL, BLAND EF. Bacterial endocarditis in the antibiotic era. Circulation 1959;19:753-65. https://doi.org/10.1161/01.cir.19.5.753.
10. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. N Engl J Med 1970;282:198-206. https://doi.org/10.1056/NEJM197001222820406.
11. Kaasch AJ, López-Cortés LE, Rodríguez-Baño J, Cisneros JM, Dolores Navarro M, Fätkenheuer G, et al. Efficacy and safety of an early oral switch in low-risk Staphylococcus aureus bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial. Lancet Infect Dis 2024;24:523-34. https://doi.org/10.1016/S1473-3099(23)00756-9.
12. Omrani AS, Abujarir SH, Ben Abid F, Shaar SH, Yilmaz M, Shaukat A, et al. Switch to oral antibiotics in Gram-negative bacteraemia: a randomized, open-label, clinical trial. Clin Microbiol Infect 2024;30(4):492-8. https://doi.org/10.1016/j.cmi.2023.10.014.
13. Broom J, Broom A, Adams K, Plage S. What prevents the intravenous to oral antibiotic switch? A qualitative study of hospital doctors' accounts of what influences their clinical practice. J Antimicrob Chemother 2016;71:2295-9. https://doi.org/10.1093/jac/dkw129.
14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane handbook for systematic reviews of interventions. Version 6.4; vol 2023. Cochrane.

https://training.cochrane.org/handbook/PDF/v6.4.

15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.
16. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-810. https://doi.org/10.1001/jama.2016.0287
17. Willekens R, Puig-Asensio M, Ruiz-Camps I, Larrosa MN, González-López JJ, Rodrí guez-Pardo D, et al. Early Oral Switch to Linezolid for Low-risk Patients With Staphylococcus aureus Bloodstream Infections: A Propensity-matched Cohort Study. Clin Infect Dis 2019;69:381-7. https://doi.org/10.1093/cid/ciy916.
18. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:e18-e55. https://doi.org/10.1093/cid/ciq146.
19. Waked R, Craig WY, Mercuro NJ, Wungwattana M, Wood E, Rokas KE. Uncomplicated Streptococcal Bacteremia: The Era of Oral Antibiotic Step-down Therapy?. Int J Antimicrob Agents 2023;61:106736. https://doi.org/10.1016/j.ijantimicag.2023.106736.
20. Yetmar ZA, Chesdachai S, Lahr BD, Challener DW, Arensman Hannan KN, Epps K, et al. Comparison of Oral and Intravenous Definitive Antibiotic Therapy for Beta-Hemolytic Streptococcus Species Bloodstream Infections from Soft Tissue Sources: a Propensity Score-Matched Analysis. Antimicrob Agents Chemother 2023;67:e0012023.

https://doi.org/10.1128/aac.00120-23.

21. Li Q, Zhou Q, Florez ID, Mathew JL, Shang L, Zhang G, et al. Short-Course vs Long-Course Antibiotic Therapy for Children With Nonsevere Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. JAMA Pediatr 2022;176:1199-1207. https://doi.org/10.1001/jamapediatrics.2022.4123.
22. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60. https://doi.org/10.1136/bmj.327.7414.557.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34. https://doi.org/10.1136/bmj.315.7109.629.
25. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6. https://doi.org/10.1136/bmj.39489.470347.AD.
26. Amodio-Groton M, Madu A, Madu CN, Briceland LL, Seligman M, McMaster P, et al. Sequential parenteral and oral ciprofloxacin regimen versus parenteral therapy for bacteremia: a pharmacoeconomic analysis. Ann Pharmacother 1996;30:596-602. https://doi.org/10.1177/106002809603000605.
27. Gangji D, Jacobs F, de Jonckheer J, Coppens L, Serruys E, Hanotte F, et al. Randomized study of intravenous versus sequential intravenous/oral regimen of ciprofloxacin in the treatment of gram-negative septicemia. Am J Med 1989;87:S206-8.

https://doi.org/10.1016/0002-9343(89)90060-0.

28. Monmaturapoj T, Montakantikul P, Mootsikapun P, Tragulpiankit P. A prospective, randomized, double dummy, placebo-controlled trial of oral cefditoren pivoxil 400mg once daily as switch therapy after intravenous ceftriaxone in the treatment of acute pyelonephritis. Int J Infect Dis 2012;16:e843-9. https://doi.org/10.1016/j.ijid.2012.07.009.
29. Paladino JA, Sperry HE, Backes JM, Gelber JA, Serrianne DJ, Cumbo TJ, et al. Clinical and economic evaluation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. Am J Med 1991;91:462-70. https://doi.org/10.1016/0002-9343(91)90181-v.
30. Diego-Yagüe I, Mora-Vargas A, Vázquez-Comendador JM, et al. Sequential oral antibiotic in uncomplicated Staphylococcus aureus bacteraemia: a propensity-matched cohort analysis. Clin Microbiol Infect 2023;29:744-50. https://doi.org/10.1016/j.cmi.2023.02.001.
31. Itoh N, Hadano Y, Saito S, Myokai M, Nakamura Y, Kurai H. Intravenous to oral switch therapy in cancer patients with catheter-related bloodstream infection due to methicillin-sensitive Staphylococcus aureus: A single-center retrospective observational study. PLoS One 2018;13:e0207413. https://doi.org/10.1371/journal.pone.0207413.
32. Lee CC, Chen PL, Hsieh CC, Yang CY, Lin CH, Ko WC. Is Early Oral Antimicrobial Switch Useful for Less Critically Ill Adults with Community-Onset Bacteraemia in Emergency Departments?. Antibiotics (Basel) 2020;9:807. https://doi.org/10.3390/antibiotics9110807.
33. Tamma PD, Conley AT, Cosgrove SE, Harris AD, Lautenbach E, Amoah J, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients

476 Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med 2019;179:316-23.
477 https://doi.org/10.1001/jamainternmed.2018.6226.
478 34. Tingsgård S, Bastrup Israelsen S, Jørgensen HL, Østergaard C, Benfield T. Early Switch
479 From Intravenous to Oral Antibiotics for Patients With Uncomplicated Gram-Negative
480 Bacteremia. JAMA Netw Open 2024;7:e2352314.
481 https://doi.org/10.1001/jamanetworkopen.2023.52314
482 35. Tossey JC, El Boghdadly Z, Reed EE, Dela-Pena J, Coe K, Williams SN, et al. Oral
483 fluoroquinolones for definitive treatment of gram-negative bacteremia in cancer patients.
484 Support Care Cancer 2021;29:5057-5064.
485 https://doi.org/10.1007/s00520-021-06063-6
486 36. Waked R, Craig WY, Mercuro NJ, Wungwattana M, Wood E, Rokas KE. Uncomplicated
487 Streptococcal Bacteremia: The Era of Oral Antibiotic Step-down Therapy?. Int J
488 Antimicrob Agents 2023;61:106736. https://doi.org/10.1016/j.ijantimicag.2023.106736
489 37. Wildenthal JA, Atkinson A, Lewis S, Sayood S, Nolan NS, Cabrera NL, et al. Outcomes of
490 Partial Oral Antibiotic Treatment for Complicated Staphylococcus aureus Bacteremia in
491 People Who Inject Drugs. Clin Infect Dis 2023;76:487-96.
492 https://doi.org/10.1093/cid/ciac714.
493 38. Cooke J, Cairns CJ, Tillotson GS, Conner S, Lewin SK, Nicholls J, et al. Comparative clinical,
494 microbiologic, and economic audit of the use of oral ciprofloxacin and parenteral
495 antimicrobials. Ann Pharmacother 1993;27:785-9.
496 https://doi.org/10.1177/106002809302700621
497 39. Nguyen N, Jayachandran A, Mui M, Olson K. Clinical Impact of Oral Step-Down Therapy for
498 Gram-Negative Bacteremia: A Retrospective Study. HCA Healthc J Med 2023;4:119-24.

https://doi.org/10.36518/2689-0216.1399

40. Gasparetto J, Tuon FF, Dos Santos Oliveira D, Zequinao T, Pipolo GR, Ribeiro GV, et al. Intravenous-to-oral antibiotic switch therapy: a cross-sectional study in critical care units. BMC Infect Dis 2019;19:650. https://doi.org/10.1186/s12879-019-4280-0
41. McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, et al. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. Lancet Infect Dis 2016;16:e139-52. https://doi.org/10.1016/S1473-3099(16)30024-X.
42. Dagher M, Fowler VG Jr, Wright PW, Staub MB. A Narrative Review of Early Oral Stepdown Therapy for the Treatment of Uncomplicated Staphylococcus aureus Bacteremia: Yay or Nay?. Open Forum Infect Dis 2020;7:ofaa151. https://doi.org/10.1093/ofid/ofaa151.
43. Wald-Dickler N, Holtom PD, Phillips MC, Centor RM, Lee RA, Baden R, et al. Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review. Am J Med 2022;135:369-379.e1.
44. Jantausch BA, Deville J, Adler S, et al. Linezolid for the treatment of children with bacteremia or nosocomial pneumonia caused by resistant gram-positive bacterial pathogens. Pediatr Infect Dis J. 2003;22(9 Suppl):S164-S171. doi:10.1097/01.inf.0000086956.45566.55
45. Kaplan SL, Deville JG, Yogev R, et al. Linezolid versus vancomycin for treatment of resistant Gram-positive infections in children. Pediatr Infect Dis J. 2003;22(8):677-686. doi:10.1097/01.inf.0000078160.29072.42
46. Wilcox MH, Tack KJ, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study.

Clin Infect Dis. 2009;48(2):203-212. doi:10.1086/595686

47. Deville JG, Adler S, Azimi PH, et al. Linezolid versus vancomycin in the treatment of known or suspected resistant gram-positive infections in neonates. Pediatr Infect Dis J. 2003;22(9 Suppl):S158-S163. doi:10.1097/01.inf.0000086955.93702.c7

48. Mohammed C, Choi H, Altaf S, Saja J, Ezike LA, Wang J, et al. Continued Intravenous Versus First Week Transition to Oral Antibiotic Therapy in Bloodstream Infections: A Systematic Review and Meta-Analysis. Cureus 16: e65298. https://doi.org/10.7759/cureus.65298.

49. Mourad A, Nwafo N, Skalla L, Holland TL, Jenkins TC. Oral versus intravenous antibiotic therapy for Staphylococcus aureus bacteremia or endocarditis: a systematic review and meta-analysis of randomized controlled trials. Clin Infect Dis 2024 Sep 18:ciae476. https://doi.org/10.1093/cid/ciae476

50. Lee IR, Tong SYC, Davis JS, Paterson DL, Syed-Omar SF, Peck KR, et al. Early oral stepdown antibiotic therapy versus continuing intravenous therapy for uncomplicated Gram-negative bacteraemia (the INVEST trial): study protocol for a multicentre, randomised controlled, open-label, phase III, non-inferiority trial. Trials 2022;23:572. https://doi.org/10.1186/s13063-022-06495-3

51. Zhang H, Pan J, Hu Z, Pan J, Zhang H. Physicians' understanding of antibiotic intravenous-to-oral switching-a qualitative study in Suzhou, China. BMC Health Serv Res 2024;24:686. https://doi.org/10.1186/s12913-024-11064-2.

52. Kutob LF, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections. Int J Antimicrob Agents 2016;48:498-503. https://doi.org/10.1016/j.ijantimicag.2016.07.013.

53. Mercuro NJ, Stogsdill P, Wungwattana M. Retrospective analysis comparing oral stepdown therapy for enterobacteriaceae bloodstream infections: fluoroquinolones versus β-lactams. Int J Antimicrob Agents 2018;51:687-92. https://doi.org/10.1016/j.ijantimicag.2017.12.007.

54. Westgeest AC, Lambregts MMC, Ruffin F, Korn RE, Webster ME, Kair JL, et al. Female Sex and Mortality in Patients with Staphylococcus aureus Bacteremia: A Systematic Review and Meta-analysis. JAMA Netw Open 2024;7:e240473. https://doi.org/10.1001/jamanetworkopen.2024.0473

554

555 **Figure Legends**

556 **Figure 1. Study Flow Diagram**

557 RCTs: randomised controlled trials

558

559 **Figure 2. Results for the Outcome of Treatment Failure**

560

561 **Figure 3. Results for the Outcome of All-Cause Mortality**

Table 1. Characteristics of RCTs and adjusted cohort studies

Study ID	Country	Sample size	Study design	Male, No. (%)	Age, year, mean (SD)	Type of disease	Source of infection	Pathogen	Antibiotic type			Duration (days) *				Definition of early IV-oral switch (days)
									IV-Oral		IV	IV-Oral			IV	
									IV	Oral		IV	Oral	Total		
Amodio-Groton et al, 1996 [26]&	USA	50	RCT	20 (40.0)	62.1 (NR)	UB	Urinary tract, respiratory tract, skin and soft tissue, biliary tract, or unknown	Mainly *Enterobacterales*	The choice of antimicrobial agents was determined by the treating physicians.	Ciprofloxacin	The choice of antimicrobial agents was determined by the treating physicians.	3	NR	NR	NR	3
Gangji et al, 1989 [27]&	Belgium	65	RCT	35 (53.8)	66.0 (NR)	UB	Urinary tract, biliary tract, gastrointestinal tract, respiratory tract, venous catheter, or unknown	Mainly *Enterobacterales*	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin	3	NR	Range: 10-14	Range: 10-14	3
Kaasch et al, 2024 [11]#	Germany, France, Netherlands, and Spain	213	RCT	147 (69.0)	63.5 (17.5)	UB	Venous catheter, skin and soft tissue, urinary tract, respiratory tract, cholecystitis, or unknown	*Staphylococcus aureus* (including 8% MRSA)	Antimicrobials were selected by the study physician according to susceptibility results and suspected allergy or intolerance.	MSSA: co-trimoxazole, clindamycin；MRSA: co-trimoxazole, linezolid	MSSA: flucloxacillin (cloxacillin), cefazolin, vancomycin；MRSA: vancomycin, daptomycin	6 (6-7)	8 (7-9)	14 (14-15)	14 (14-15)	5-7
Monmaturapoj et al, 2012 [28]&	Thailand	17	RCT	NR	45.2 (19.7)	UB	Urinary tract	Mainly *Escherichia coli*	Ceftriaxone	Cefditoren	Ceftriaxone	3	7	10	10	3
Omrani et al, 2024 [12]^	Bahrain, Kuwait, Qatar, and Türkiye	174	RCT	85 (48.9)	56.6 (16.7)	UB	Urinary tract, intra-abdominal, biliary tract, respiratory tract, skin and soft tissue, venous catheter, or unknown	*Enterobacterales* (including 16.3% ESBL-producers)	Beta-lactam/Beta-lactamase inhibitor combination, carbapenem, and cephalosporin	Beta-lactam/ Beta-lactamase inhibitor combination, cephalosporin, fluoroquinolone, and trimethoprim/ sulfamethoxazole	Beta-lactam/Beta-lactamase inhibitor combination, carbapenem, and cephalosporin	Range: 3-5	NR	14 (11-16)	11 (8-14)	3-5

Paladino et al, 1991 [29][&]	USA	105	RCT	NR	65.0 (NR)	UB	Skin and soft tissue, respiratory tract, urinary tract, bone and joint	*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacterales*	The choice of antimicrobial agents was determined by the treating physicians.	Ciprofloxacin	The choice of antimicrobial agents was determined by the treating physicians.	3	≥5	≥8	≥8	3
Diego-Yagüe et al, 2023 [30]	Spain	154	ACS	108 (70.1)	67.3 (18.3)	UB	Venous catheter, skin and soft tissue, respiratory tract, or unknown	*Staphylococcus aureus* (including 18.7% MRSA)	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	7 (4-11)	9 (7-14)	16 (14-21)	16 (14-21)	NR
Itoh et al, 2018 [31]	Japan	60	ACS	35 (58.3)	60.4 (16.0)	CB	Postoperative wound, respiratory tract, skin and soft tissue, endocarditis, thromboembolism, liver abscess	*Staphylococcus aureus*	Mainly cefazolin and meropenem	Mainly cefalexin, amoxicillin/Clavulanate, levofloxacin	Mainly cefazolin and meropenem	17.5 (13-24)	NR	32.5 (26-52.3)	16.5 (13-30.5)	NR
Lee et al, 2020 [32]	Taiwan, China	2892	ACS	141 (48.8)	68.9 (17.1)	UB, CB, sepsis	Urinary tract, skin and soft tissue, intra-abdominal, respiratory tract, biliary tract, liver abscess	Mainly *Enterococcus Coli*, *Klebsielu species*, *Streptococcus species*, *Staphylococcus aureus*	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	0.9 (0.3-2.0)	NR	13 (10.5-14.3)	13 (10-16)	NR
Tamma et al, 2019 [33]	USA	1478	ACS	768 (52.0)	58.7 (15.6)	UB	Respiratory tract, skin and soft tissue, urinary tract, biliary tract, gastrointestinal tract, venous catheter	*Enterobacterales*	The choice of antimicrobial agents was determined by the treating physicians.	Maily ciprofloxacin hydrochloride, levofloxacin, trimethoprim-sulfamethoxazole	The choice of antimicrobial agents was determined by the treating physicians.	3 (2-4)	NR	14 (11-16)	14 (11-16)	≤5
Tingsgård et al, 2024 [34]	Denmark	914	ACS	512 (56)	73.6 (14.8)	UB	Urinary tract, gastrointestinal tract, respiratory tract, or unknown	Mainly *Enterobacterales*	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	4	NR	Range: 7-14	Range: 7-14	4

Tossey et al, 2019 [35]	USA	211	ACS	115 (54.5)	62.3 (10.3)	UB	Venous catheter, urinary tract, intra-abdominal, respiratory tract, abdominal abscess, oral mucositis, other	Mainly *Enterobacterales*	Ciprofloxacin, cefepime, and ertapenem	Ciprofloxacinas and levofloxacin	Ciprofloxacin, cefepime, and ertapenem	Range : 3-5	NR	Median (IQR) 14 (13-16)	Median (IQR) 15 (14-17)	3-5
Waked et al, 2023 [36]	USA	264	ACS	165 (62.5)	64.4 (17.2)	UB	Skin and soft tissue, respiratory tract, gastrointestinal tract, dental, urinary tract, venous catheter, or unknown	*Streptococcus spp*	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	≤5	NR	Median (IQR) 13 (10-14)	Median (IQR) 14 (13-14)	3-5
Wildenthal et al, 2022 [37]	USA	238	ACS	126 (52.9)	36.1 (8.2)	CB	Infective endocarditis, epidural abscess, septic arthritis	*Staphylococcus aureus* (including 41.6% MRSA)	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	18 (7-32)	21 (9-33)	NR	42 (42-42)	NR
Willekens et al, 2019 [17]	Spain	135	ACS	89 (65.9)	61.1 (21.3)	UB, sepsis	Venous catheter, skin and soft tissue, respiratory tract, genitourinary tract or unknown	*Staphylococcus aureus* (including 12.6% MRSA)	MSSA: cloxacillin, cefazolin, β-lactam/β-lactamase inhibitor combinations; MRSA: daptomycin, vancomycin, linezolid	Linezolid	MSSA: cloxacillin, cefazolin, β-lactam/β-lactamase inhibitor combinations; MRSA: daptomycin, vancomycin, linezolid	7 (6-8)	NR	15 (14-16)	15 (14-19)	3-9
Yetmar et al, 2023 [20]	USA	132	ACS	89 (67.5)	73.5 (15.1)	UB	Skin and soft tissue	*Beta-Haemolytic Streptococcus species*	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	The choice of antimicrobial agents was determined by the treating physicians.	4.5 (4-5.8)	10 (8-12)	15 (12-16)	16 (15-17)	≤7

ACS: adjusted cohort studies; CB: complicated bacteraemia; ESBL: extended-spectrum beta-lactamase; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*; NR: not report; RCT: randomized controlled trial; UB: uncomplicated bacteraemia. *The data results are presented in the form of median and interquartile range. [#]:The study provided ITT and PP datasets; we utilized ITT data for our primary analysis. [^]:The study provided ITT and mITT datasets; we utilized mITT data for our primary analysis. [&]: The study provided ITT data; thus, we used ITT data for our primary analysis

Table 2. Subgroup Analyses of the Outcome of Treatment Failure

Variables		No. of studies	Sample size	Relative risk		
				Odds ratio* (95% CI)	I^2	*P* value
Complication of bacteraemia	Uncomplicated bacteraemia	10	1290	0.66 (0.41 to 1.09)	47.1	0.105
	Complicated bacteraemia	1	168	1.02 (0.34 to 3.05)	NA	0.968
Pathogen	*Staphylococcus aureus*	3	535	0.63 (0.23 to 1.69)	71.2	0.358
	Streptococcus species	2	396	1.04 (0.33 to 3.28)	77.8	0.946
	Enterobacterales	5	508	0.59 (0.32 to 1.08)	8.1	0.088
Oral antibiotic bioavailability	High bioavailability	5	558	0.63 (0.28 to 1.43)	28.9	0.271
	Low bioavailability	1	17	0.54 (0.02 to 15.30)	NA	0.717
	High and low bioavailability	5	883	0.73 (0.39 to 1.38)	66.1	0.337

*: OR<1 favours oral switch; NA: Not applicable