Systematic Review/Meta-analysis

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Transitioning to oral therapy compared to IV in *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis

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Background and Objective: *Staphylococcus aureus* bloodstream infections pose a significant threat to public health and necessitate substantial healthcare resources. The optimal antimicrobial therapy for these infections remains a subject of debate. This systematic review and meta-analysis evaluated the efficacy and safety of early transition to oral antimicrobial therapy compared with continued intravenous (IV) therapy in patients with MRSA and MSSA bloodstream infections.

Method: A PRISMA-guided systematic review and meta-analysis compared the early transition from intravenous to oral antibiotics with continued intravenous therapy in patients with *S. aureus* infections, utilizing relevant studies from the PubMed, Embase, Scopus, and Web of Science databases from August 2003 to June 2024.

Results: This meta-analysis of 11 studies (N = 54–220, primarily male, age: mid-30s to early 70s) revealed a 71.6% higher risk of all-cause mortality for patients transitioned to early oral therapy than for those who continued IV therapy (RR: 1.716; 95% CI: 1.039–2.836; $P = 0.035$; $I^2 = 44\%$). Treatment failure, rehospitalization rates, adverse events, and hospital stay lengths did not differ significantly between groups.

Conclusion: Early oral antimicrobial therapy for *S. aureus* bloodstream infections significantly reduces mortality compared to prolonged intravenous treatment, without increasing the incidence of adverse events or the risk of rehospitalization, suggesting its safety and efficacy as an alternative therapeutic approach; however, further randomized controlled trials are necessary to corroborate these findings.

Keywords: bloodstream infections, early oral therapy, hospital stay, intravenous therapy, mortality, Staphylococcus aureus

Introduction

The persistent threat of *Staphylococcus aureus* infections has intensified, characterized by two distinct epidemiological trends: an increase in healthcare-associated infections, particularly in cardiovascular and prosthetic device contexts, and a widespread community outbreak of skin and soft tissue infections attributed to virulent, β-lactam-resistant strains[1]. *S. aureus*, first identified in Scotland in 1880[2], is a common commensal organism and pathogen that causes various clinical infections, including skin, respiratory tract, joint, cardiovascular, and bloodstream infections[3]. As a global pathogen, *S. aureus* contributes significantly to morbidity and mortality worldwide and is primarily transmitted through direct skin contact with infected or colonized individuals[3]. Its ability to produce various virulence factors enables it to evade the human immune system, causing infections particularly bloodstream infections, which are challenging to treat. Methicillin-resistant *Staphylococcus aureus* (MRSA), identified in the early 1960s due to the acquisition of the mecA gene on the staphylococcal cassette chromosome mec (SCCmec), presents a significant clinical problem[1]. Seven distinct SCCmec types (I–VII) have been identified, and molecular epidemiological techniques have revealed the evolution and global spread of MRSA clones since the 1960s[4]. Initially, MRSA was predominantly hospital-associated (HA-MRSA), but from the late 1990s, community-associated MRSA (CA-MRSA) clones emerged, typically carrying SCCmec type IV, V, or VII, and often producing the Panton-Valentine leukocidin (PVL) toxin[5]. The distinction between HA-MRSA and CA-MRSA has become increasingly blurred,and CA-MRSA is now endemic in many hospitals in the US[6].Healthcare-associated methicillin-resistant *S. aureus* (HA-MRSA) poses a significant threat to patient safety, leading to increased mortality, morbidity, and prolonged

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hospital stays, thereby straining healthcare resources worldwide[7]. In comparison, methicillin-sensitive *S. aureus* (MSSA) demonstrates a relatively more favorable outcome[8]. According to the European Antimicrobial Resistance Surveillance System (EARSS), the prevalence of HA-MRSA in European acute care and long-term facilities varies significantly[9,10]. Furthermore, pan-European studies suggest that MRSA affects a substantial number of patients annually, resulting in a significant cost burden on the healthcare systems[4]. The average cost per MRSA-positive patient was estimated to be cost-effective[11]. A significant knowledge gap exists regarding the optimal timing of transitioning from intravenous (IV) to oral therapy in *S. aureus* bacteremia (SAB), particularly between MRSA and MSSA infections. Factors such as clinical stability, complications, and bacterial resistance profiles contribute to this uncertainty. Current guidelines recommend prolonged IV therapy for MRSA (4–6 weeks); however, studies suggest that early switching to oral antibiotics may be feasible for uncomplicated SAB cases. Despite the existing research, a clear consensus remains elusive[12]. The optimal timing for transitioning from intravenous to oral antibiotics remains uncertain, as current research has not yielded conclusive, randomized controlled trial-based evidence to guide specific recommendations on treatment duration (e.g., 3, 5, or 14 days).

Conventional treatment for *S. aureus* infections typically involves prolonged intravenous (IV) antibiotic therapy, which can lead to extended hospital stays, increased risk of catheter-related complications, and higher healthcare costs[3]. Over the past two decades, two significant trends have emerged: an increase in healthcare-associated infections, particularly infective endocarditis and prosthetic device infections, and an epidemic of community-associated skin and soft tissue infections caused by strains with specific virulence factors and resistance to β-lactam antibiotics[1]. Various antibiotics are used to treat these infections, including penicillins, sulphonamides and tetracycline's, depending on the site and severity of the infection[4]. However, antibiotic resistance in *S. aureus*, particularly in MRSA, poses a significant challenge. MRSA strains, first identified in the 1960s, are typically treated with vancomycin or daptomycin, with linezolid and clindamycin as alternative options[4,5]. Intravenous (IV) and oral antibiotic have unique benefits and drawbacks. IV antibiotics are frequently used for severe, life-threatening infections, patients intolerant to oral antibiotics, and immunocompromised individuals[13]. *S. aureus* infections necessitating intravenous antibiotics include bacteremia, complex SSTIs, severe pneumonia, epidural abscess, prosthetic valve endocarditis, necrotizing fasciitis, toxic shock syndrome, and staphylococcal scalded skin syndrome[4]. Mild infections, including uncomplicated SSTIs, pneumonia, impetigo, mastitis, and conjunctivitis, can be treated with oral antibiotics such as amoxicillin, doxycycline, and trimethoprim-sulfamethoxazole[4]. Effective antibiotic therapy is required to reach therapeutic concentrations at the infection site. IV antibiotics, with 100% bioavailability, are more effective for severe infections but pose a higher risk of adverse drug events and catheter-associated complications, including thrombophlebitis and infections[9,10,13,14]. IV antibiotics are also more expensive than oral alternatives. Early transition from IV to oral antibiotics can reduce costs, complications, and hospital stays[14]. The shift from IV to oral antibiotic therapy is a crucial component of antimicrobial stewardship, aimed at optimizing patient outcomes while reducing healthcare expenses and complications[14]. Despite the apparent benefits, the decision and timing of transitioning from IV to oral antibiotics require careful consideration of multiple factors unique to each patient. Additionally, studies have shown that using oral antibiotics instead of IV antibiotics can be cost-effective without compromising clinical outcomes[7]. It is important to differentiate between uncomplicated and complicated bacteremia. Complicated bacteremia is characterized by persistent bacteremia lasting more than 4 days, absence of negative follow-up blood cultures within 4 days, absence of fever resolution within three days after starting effective therapy, evidence of infection spread to other sites, presence of intracardiac prostheses, or a diagnosis of endocarditis[15]. Recent investigations and clinical practices have examined the feasibility and efficacy of an early transition from intravenous to oral antibiotics in the management of SAB. This approach presents potential advantages, including a reduced risk of complications associated with prolonged intravenous therapy, enhanced patient comfort, and decreased healthcare expenditure. However, contradictory evidence exists regarding the optimal timing for this transition, selection of appropriate antimicrobial agents, and patient populations that would derive the greatest benefit from this strategy[15]. This systematic review and meta-analysis aimed to address this gap by evaluating the efficacy and safety of early oral therapy compared to continued intravenous therapy for SAB. By elucidating the role of early oral therapy in managing these infections, the findings will contribute to optimizing treatment strategies for SAB and mitigating the healthcare burdens associated with prolonged intravenous therapy.

Methodology

Protocol development

A rigorous protocol was devised for this systematic review and meta-analysis by AH, adhering to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[16]. Additionally, the Cochrane Handbook and Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were consulted to ensure methodological rigor in the evaluation of randomized controlled trials (RCTs) and observational studies.

Search strategy

A comprehensive search strategy was developed by S.M.S.A and A.R., utilizing both free-text terms and Medical Subject Headings (MeSH) terms to ensure a robust and structured approach. The search included terms such as "*Staphylococcus aureus*," "antibiotics," "intravenous," "oral administration," "bacteremia," and "bloodstream infections." These terms were combined using Boolean operators (AND, OR) to optimize the search results, using relevant studies from PubMed, Embase, Scopus, and Web of Science databases up to June 2024.This systematic review included studies that were published between August 2003 and January 2024. Supplementary sources, including references and citations, have also been explored. The search was confined to English-language studies, with no restrictions on study type, date, or location.

Eligibility criteria and screening

Studies were selected based on the following Criteria: Observational studies and randomized controlled trials (RCTs) that focused on populations infected with *S. aureus*, including both MRSA and MSSA strains; studies involving antibiotic

treatment; studies that compared the effectiveness and safety of early transition from intravenous to oral antibiotics against a control group that continued to receive intravenous antibiotics exclusively.

Conference papers, reviews, editorials, case reports, case series, and animal research are among the studies that were not included. Studies reporting infections with pathogens other than *S. aureus* were also excluded.

Two authors, O.S and M.A.S, conducted a stepwise screening process, initially evaluating titles, then abstracts, and finally the full texts. Any discrepancies were resolved by the third author, M.S.M. A PRISMA flowchart was employed to enhance transparency and provide a visual representation of the study selection process, highlighting the rationale for excluding specific studies as shown in Figure 1.

Data extraction and statistical analysis

Data extraction was performed independently by two authors, M.A.S. and A.H., who gathered information on authorship, study year, study design, demographics (age, sex, sample size), comorbidities (diabetes, hypertension, coronary heart disease, etc.), and outcome data (all-cause mortality, failed treatment, rehospitalization, length of stay, and adverse events). Disagreements were resolved through mutual consensus.

Statistical analysis was conducted by M.S.M using the Comprehensive Meta-Analysis V3 software. Separate forest plots were generated for dichotomous outcomes, pooled risk ratios (RR) and 95% confidence intervals (CI) for all-cause mortality, failed treatment, rehospitalization, and adverse events. For continuous outcomes that are length of stay standardized mean differences (SMD) with 95% confidence intervals (CI) were employed to generate forest plots. Heterogeneity was considered substantial when I^2 was >50%, necessitating a leave-one-out analysis (Supplementary Figure 1, available at: http://links.lww.com/MS9/A645; Figure 2, available at: http://links.lww.com/MS9/A646; and Figure 3, available at: http://links.lww.com/MS9/A647).

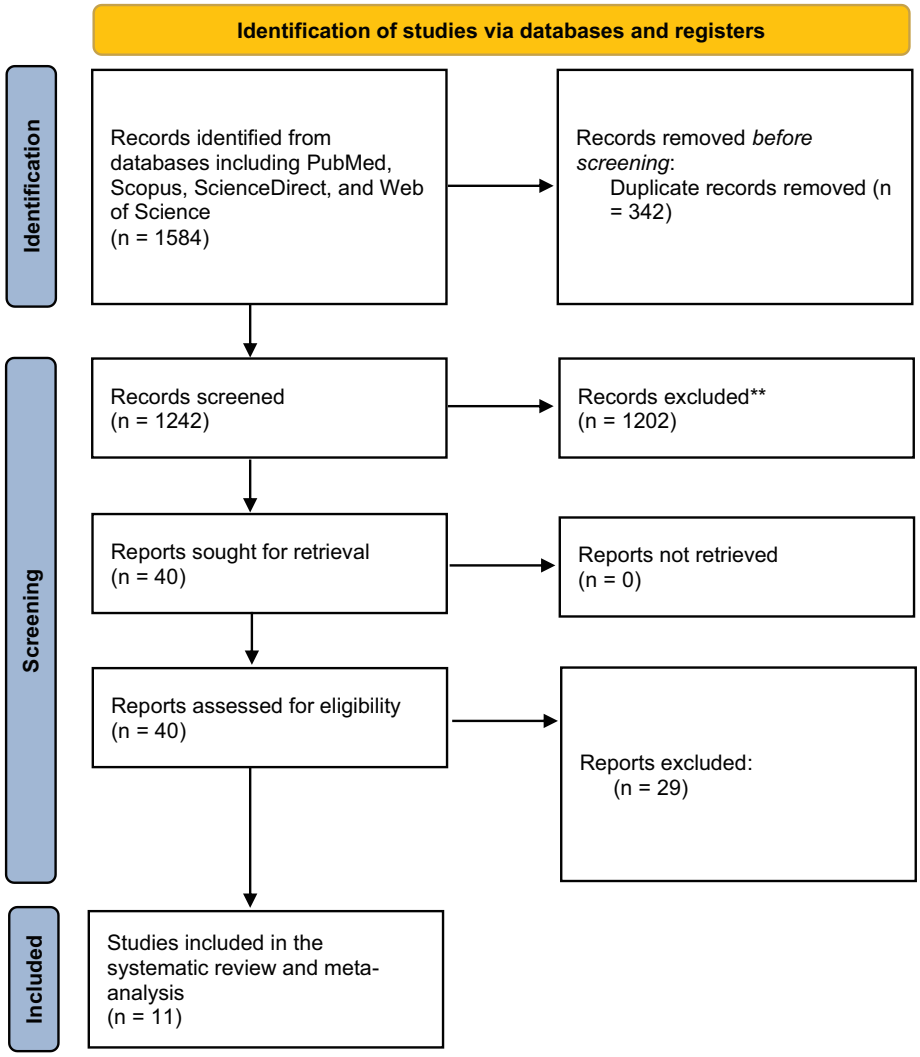


Figure 1. PRISMA flow chart showing number of included studies.

Quality assessment

Two authors, H.M.C and W.L.H, carefully evaluated the risk of bias in included RCTs and observational studies. The Cochrane Collaboration Tool for Assessing Risk of Bias and the Newcastle-Ottawa Scale were employed for RCTs and observational studies, respectively as shown in Supplementary Table 1 (available at: http://links.lww.com/MS9/A648). RCTs were graded based on selection bias, detection bias, reporting bias, and attrition bias, and were classified as low risk, high risk, or uncertain risk. Observational studies were evaluated for biases in selection, comparability, and outcomes. Studies with a total score of 7 or greater than 7 out of 9 were considered to have low risk bias.

To address potential publication bias, a funnel plot was employed, and the Eggers regression intercept was used to evaluate the studies. This comprehensive approach ensured a meticulous evaluation of study quality and potential biases, yielding trustworthy and unbiased results.

Results

Study selection

An extensive search across databases, such as PubMed, Scopus, ScienceDirect, and Web of Science, identified 1584 papers. After removing duplicates and excluding records that did not meet our inclusion criteria, we focused on comparing early oral versus IV treatments for *S. aureus* bloodstream infections, 1242 papers remained for further screening. Among these, 40 papers underwent a detailed eligibility assessment, with exclusions based on irrelevant outcomes or insufficient details. Ultimately, 11 studies were deemed suitable for inclusion in this systematic review (Fig. 1).

Baseline characteristics

The baseline characteristics of the 11 included studies encompassed observational, prospective cohort, retrospective cohort studies, and one randomized controlled trial, conducted across diverse geographic locations including the Netherlands, USA, Spain, New Zealand, France, South Korea, Germany, and Japan. These studies primarily investigated populations with *S. aureus* bloodstream infections, such as osteomyelitis, endocarditis, and cellulitis. The median participant age ranged widely from the mid-30s to the early 70s, with predominantly male population cohorts ,comprising of varying sample sizes ranging from 54 to 220. Among the 11 studies, we observed varying durations of transitioning from intravenous (IV) to oral therapy. The shortest reported period was 3 days, as reported in the study by Diego-Yagüe *et al*[17] and Parodi *et al*[18], where the switch occurred after 3–5 days. 14 days was the highest number of days, observed in the studies by Kouijzer *et al*[12] and Petithomme *et al*[19]. Other studies had an average switch time of 5–7 days, including those by Willekens *et al*, Bupha-Intr O *et al*[20], Daver *et al*[21], Mun *et al*[15], Kaasch *et al*[22], and Tanaka *et al*[23]. Common comorbidities include diabetes, chronic kidney disease, HIV infection, hepatitis C, and hypertension. Studies have compared the efficacy and safety of shifting to early oral versus continuing IV treatments for *S. aureus* bloodstream infections. The baseline characteristics of studies are summarized in Table 1.

Primary outcome: all-cause mortality

In a meta-analysis of nine studies, the risk ratio for all-cause mortality comparing patients who shifted to early oral versus those continuing with IV treatments was 1.716 (95% CI: 1.039 to 2.836; $P = 0.035$; $I^2 = 44\%$). This indicates a 71.6% higher risk of mortality in the IV continuation group than in the early oral shift group, with statistically significant findings suggesting that this difference is unlikely to be due to chance. Moderate heterogeneity ($I^2 = 44\%$) indicated variability in study designs, populations, and methodologies, highlighting the potential benefits of shifting to early oral therapy in managing *S. aureus* bloodstream infections (Fig. 2).

Failed treatment

Across the four studies, the risk ratio for treatment failure comparing patients who shifted to early oral versus those continuing with IV therapies was 1.859 (95% CI: 0.841–4.107; $P = 0.125$; $I^2 = 54\%$). Although there was a trend toward higher treatment failure rates in the IV continuation group than in the early oral shift group, this difference was not statistically significant ($P = 0.125$). Moderate heterogeneity ($I^2 = 54\%$) among the studies underscored the variability in the study designs or patient populations (Fig. 3). A leave-one-out sensitivity analysis was conducted to assess the robustness of these findings, as depicted in the supplementary forest plot.

Rehospitalization

In the analysis of eight studies, the risk ratio for rehospitalization comparing patients who shifted to early oral versus those continuing with IV therapies was 1.098 (95% CI: 0.664–1.815; $P = 0.715$; $I^2 = 67\%$). The results indicated no statistically significant difference in rehospitalization rates between the early oral shift and IV continuation groups ($P = 0.715$) (Fig. 4). Substantial heterogeneity ($I^2 = 67\%$) among the studies reflects differences in study designs or patient characteristics, supported by the leave-one-out sensitivity analysis shown in the supplementary materials.

Length of hospital stay

Across the five studies, the standardized difference in the mean length of hospital stay between patients who shifted to early oral versus those who continued IV therapies was 1.939 (95% CI: 1.076 to 2.802; $P = 0.0001$; $I^2 = 95\%$). This indicated a statistically significant difference in hospital stay duration, favoring the early oral shift group ($P = 0.0001$) (Fig. 5). High heterogeneity ($I^2 = 95\%$) suggested substantial variability in study methodologies or patient populations, with a leave-one-out sensitivity analysis provided in the supplementary file.

Adverse events

Across the three studies, the risk ratio for adverse events comparing patients who shifted to early oral versus those continuing with IV therapies was 0.986 (95% CI: 0.678–1.432; $P = 0.939$; $I^2 = 44\%$). This indicated no statistically significant difference in the occurrence of adverse events between the early oral shift and IV continuation groups ($P = 0.939$). Moderate heterogeneity ($I^2 = 44\%$) among the studies suggests variability in study designs or patient populations, as shown in the supplementary forest plot (Fig. 6).

Table 1

Baseline characteristics of included studies

Study	Year	Study design	Country	Population	Age (years)		Sample size (N)		Comorbidities		Type of infection	
					IV	Oral	IV	Oral	IV	Oral	IV	Oral
Kouijzer *et al* [12]	2021	OS	Netherland	Bacteremia without endovascular infection	58.9	61.4	27	44	-	-	VO (14) NO (7) Arthritis (12)	VO (9) NO (16) Arthritis (11)
Wildenthal *et al* [45]	2022	OS	USA	Bacteremia	35 (30–42)	37 (32–44)	62	36	Hep C (77)	Hep C (77)	SA (25) VO(18)	SA (20) VO (16)
Willekens *et al* [27]	2019	PS	Spain	Bloodstream Infections	63 (49–76)	61 (45–69)	68	30	HIV (3)	HIV (0)	-	-
Bupha-Intr *et al* [20]	2020	OS	New Zealand	Bacteremia	67 (38–91)	63 (18–93)	15	58	-	-	-	-
Petithomme-Nanrocki *et al* [19]	2023	RC	France	Bone and joint infections	70 (58.0–75.5)	66 (60–77)	24	24	DM (7) CKD (15)	DM (11) CKD (10)	DFI (3)	DFI (3)
Diego-Yague *et al* [17]	2023	OS	Spain	Bacteremia	68 (58–81)	68 (52–80)	82	73	HTN (72) DM (38) CKD (28)	HTN (47) DM (25) CKD (17)	-	-
Daver *et al* [21]	2007	RC	USA	Osteomyelitis	>50(16) <50(20)	>50(16) <50(24)	26	28	DM(6)	DM(10)	-	-
Mun *et al* [15]	2022	OS	South Korea	Bacteremia	55.0 ± 19.8	53.7 ± 13.2	44	16	DM (15) CKD (13)	DM (5) CKD (1)	CA (4)	CA (2)
Kaasch *et al* [22]	2024	RCT	Spain, Germany, France, Netherland	Bloodstream Infections	62.6 ± 17.6	64.4 ± 16.8	77	71	DM (15) CKD (13)	NR	-	-
Tanaka *et al* [23]	2016	RC	Japan	Bacteremia	65 (16)	64 (19)	40	19	-	-	LRI (13) BI (20) UTI (3)	LRI (7) BI (7) UTI (2)
Parodi *et al* [18]	2003	RC	USA	Bacteremia	67.9 ± 12.6		171		-	-	Skin infection (31) UTI (28) Bacteremia (8)	

UTI, urinary tract infection; RCT, randomized control trial; RC, retrospective cohort; OS, observational study; PS, prospective study; VO, vertebral osteomyelitis; NO, nonvertebral osteomyelitis; LRI, lower respiratory infection; DFI, diabetic foot infection; BI, bone infection; DM, diabetes mellitus; CKD, chronic kidney disease; CA, community acquired; HTN, hypertension; SA, septic arthritis.

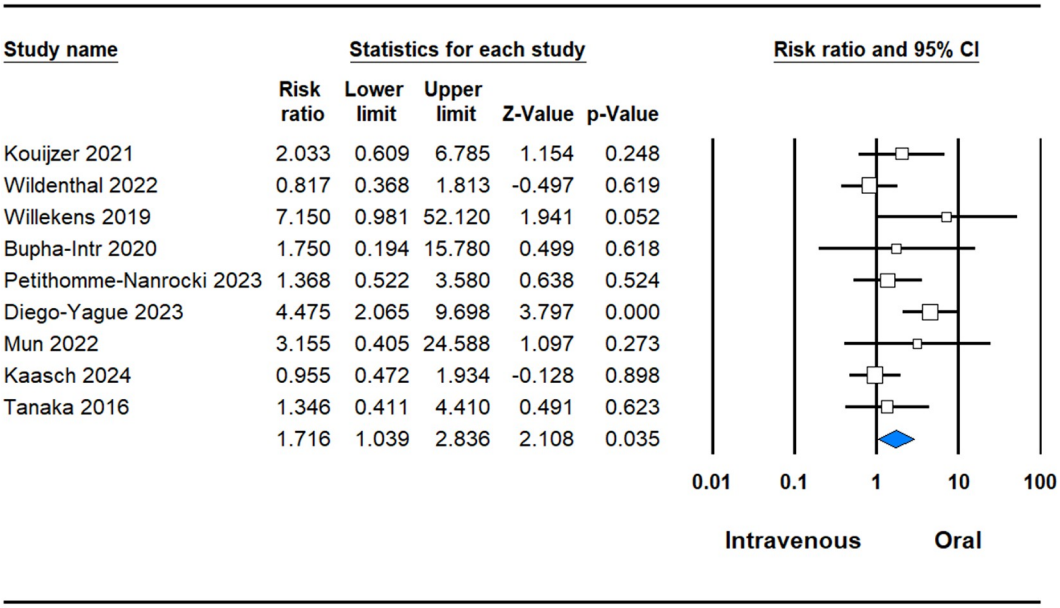


Figure 2. Forest plot demonstrating all-cause mortality outcome between intravenous and oral antibiotics group.

Publication bias

Publication bias was assessed using a funnel plot constructed for the primary outcome, revealing a slight asymmetry suggestive of potential publication bias. Further evaluation using the Egger test yielded an intercept value of 1.194 and a *P* value of 0.185, indicating no statistically significant publication bias ($P = 0.185$). The findings suggest some degree of asymmetry in publication related to the primary outcome, although not statistically significant based on the Egger test results (Fig. 7). These results underscore the importance of cautious interpretation of findings related to mortality outcomes in patients with *S. aureus* bloodstream infections who shift to early oral versus continued IV treatments.

Discussion

S. aureus bloodstream infections pose a significant threat to public health, necessitating substantial healthcare resources for effective treatment[24,25]. The selection of appropriate antimicrobial treatment for patients with *S. aureus* bloodstream infections has been a subject of debate among medical professionals. This comprehensive review and statistical analysis aims to evaluate the efficacy and safety of transitioning to oral antibiotics in low-

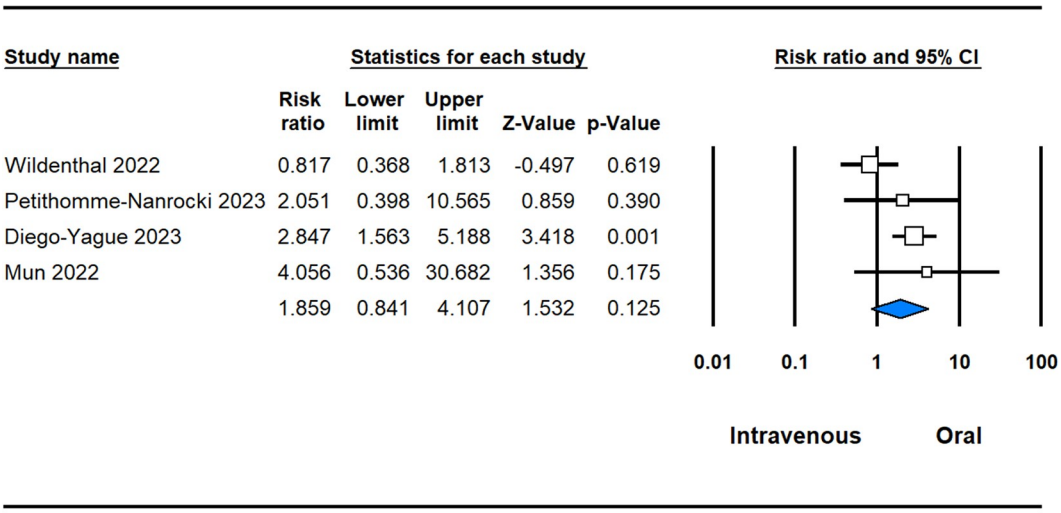
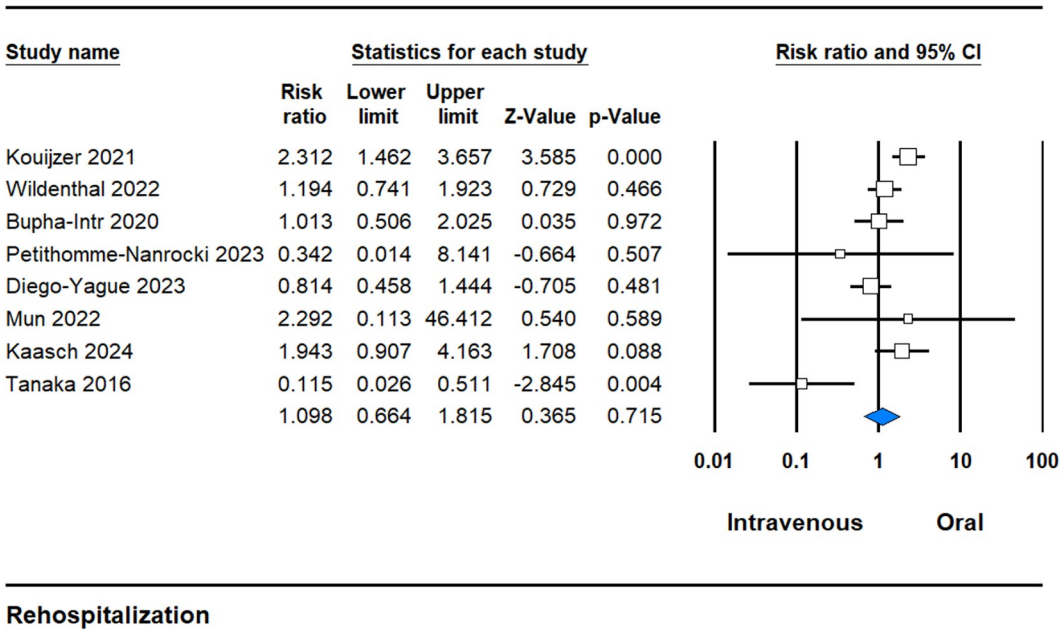


Figure 3. Forest plot demonstrating failed treatment outcome between intravenous and oral antibiotics group.

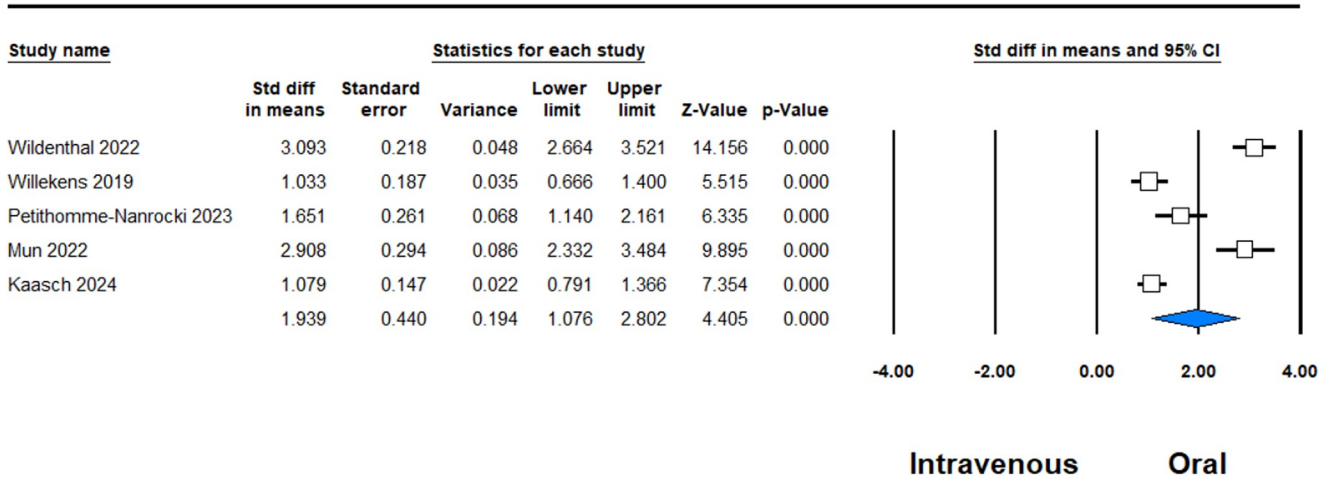


Rehospitalization

Figure 4. Forest plot demonstrating rehospitalization outcome between intravenous and oral antibiotics group.

risk cases, as opposed to the conventional method of intravenous antibiotic administration. By aggregating and analyzing data from various research studies, including observational and randomized controlled trials, this meta-analysis endeavors to determine whether early oral therapy can yield comparable clinical outcomes while potentially reducing hospital stays and minimizing the risks associated with prolonged intravenous treatment. Our meta-analysis aimed to assess whether transitioning to oral antibiotics earlier is more effective than transitioning later when treating SAB and joint space infections. The focus of our study was on determining effect for this switch, rather than examining the susceptibility of bacteria to particular antibiotics. This study not only addresses current gaps in the literature but also serves as a key resource for guiding clinical decision-making and shaping future research directions in the management of *S. aureus* bloodstream infections.

Our meta-analysis of 11 studies, including observational, cohort, and randomized controlled trials, assessed *S. aureus* bloodstream infections across multiple countries. The predominantly male study population, aged between the fourth and eighth decades, had comorbidities such as diabetes mellitus,



Length of hospital stay

Figure 5. Forest plot demonstrating length of hospital stay outcome between intravenous and oral antibiotics group.

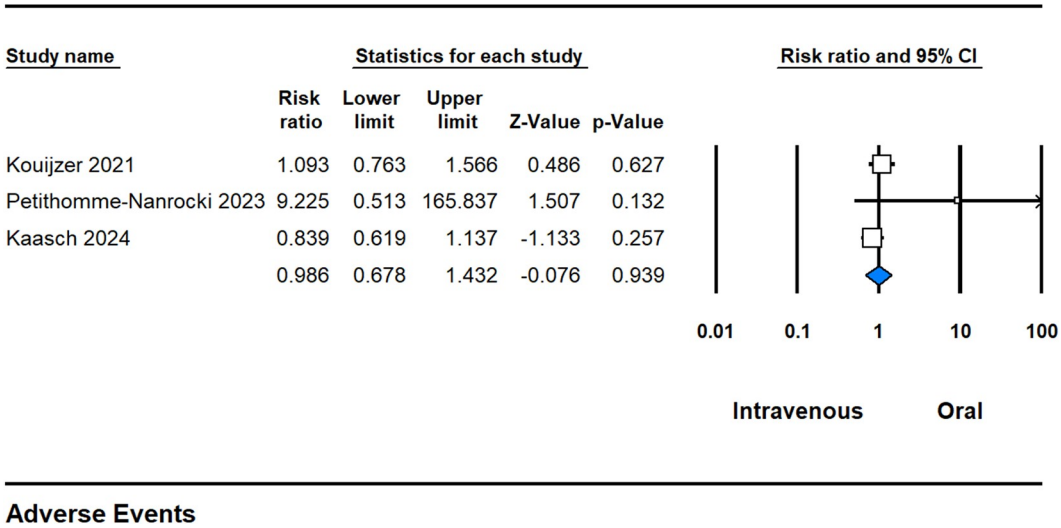


Figure 6. Forest plot demonstrating adverse events outcome between intravenous and oral antibiotics group.

chronic kidney disease, HIV, hepatitis C, and hypertension. The analysis indicated a higher mortality risk for patients continuing intravenous (IV) treatment compared to those switching to early oral therapy, with moderate study heterogeneity. Although the IV group showed a trend toward higher treatment failure, it was not statistically significant. Rehospitalization rates did not significantly differ between groups, despite considerable variability. Early oral therapy significantly reduced hospital stay duration, despite high heterogeneity. Adverse event rates were similar between the two treatment methods. Funnel plot analysis suggested publication bias; however, the Egger test did not statistically confirm this.

Recent investigations have primarily utilized oral beta-lactams[20,26], albeit some have also explored oral antibiotics with high bioavailability, such as linezolid, quinolones, and TMP/SMX[27-29]. Oral beta-lactams generally exhibit lower bioavailability and tolerable doses compared to their intravenous counterparts, which makes it more difficult to attain effective

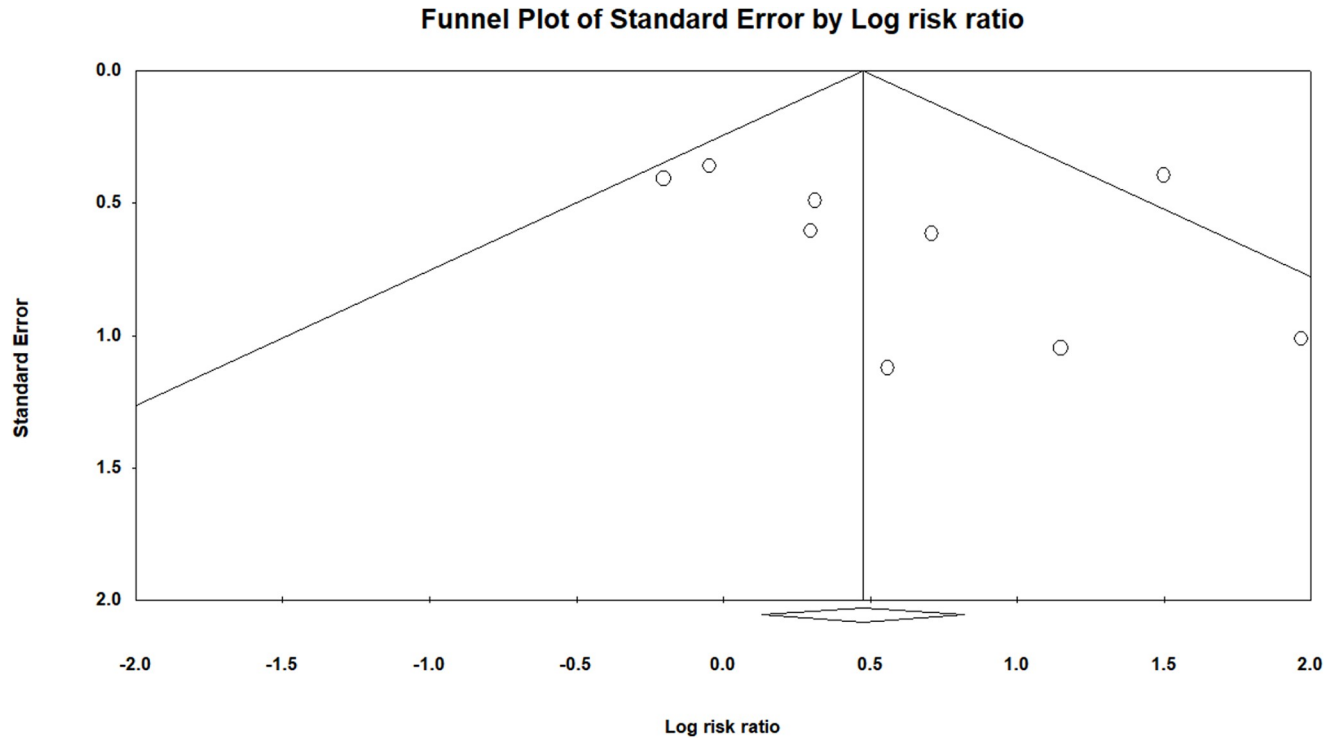


Figure 7. Funnel plot demonstrating publication bias of included studies for all-cause mortality outcome.

tissue concentrations[30,31]. Nevertheless, studies concentrating on oral beta-lactams have demonstrated encouraging results for oral step-down therapy. This might be because only patients with MSSA bacteremia were treated with oral beta-lactams. Prior to transitioning to oral step-down therapy, patients typically received intravenous beta-lactams, which are more bactericidal than vancomycin, potentially compensating for the limitations of oral beta-lactams in oral step-down therapy.

Patients who have primary healthcare-associated SAB are frequently observed in clinical settings. Moving these patients from intravenous antibiotics to oral step-down therapy can provide significant advantages for both the patients and the healthcare system. In terms of economics, OT is generally less costly than prolonged IV therapy, as it reduces expenses connected with hospital stays, IV equipment, and nursing care necessary for IV administration[1,32,33]. Moreover, OT can free up hospital beds and healthcare resources, allowing for a more efficient use of medical facilities. This transition also minimizes the risk of complications associated with long-term IV use, such as infections from IV lines, thereby enhancing patient safety and comfort. By simplifying the treatment process and reducing the duration of hospital stays, OT can contribute to a more sustainable and effective healthcare system[1,32,33].

A recent study has shown that switching to oral antibiotics early in patients with community-acquired pneumonia did not lead to worse results, but instead was associated with shorter hospital stays and fewer days on antibiotics. Despite these advantages, early switching is not done frequently. Even in hospitals with high rates of switching, fewer than 15% of low-risk patients are switched early. This suggests that a much larger number of patients could be transitioned to oral therapy without compromising their outcomes[34-36]. A meta-analysis conducted by McMullan *et al* evaluated the feasibility of replacing intravenous antibiotics with oral antibiotics for treating bacterial infections in children. The study indicated that making this transition in pediatric patients is not only secure but also beneficial. It can result in shorter hospital stays, decreased healthcare expenses, and fewer problems linked with extended IV therapy[37]. The sole extensive RCT concerning this topic indicated that subjects who switched to oral antibiotics experienced lower mortality rates and shorter hospital stays[22]. Nevertheless, the study discovered a higher incidence of unfavorable events and serious adverse events in the oral switch group compared to the intravenous group, though this distinction was not statistically significant[22].

As per the current guidelines, it is typically recommended to administer intravenous antimicrobial therapy for at least 14 days for low-risk *S. aureus* bloodstream infections[38,39]. The recently updated UK guidelines for MRSA bacteremia also consider oral co-trimoxazole as a viable step-down therapy option. Starting oral antimicrobial therapy early in the treatment course could potentially reduce hospital stays and decrease complications associated with intravenous administration[40]. However, it is essential to achieve adequate serum concentrations with oral medications for successful treatment of *S. aureus* bloodstream infections. Furthermore, managing patients earlier as outpatients could lead to challenges such as reduced adherence to prescribed treatment regimens and delayed detection of complications. In recent years, numerous vaccines have been created to enhance the immune system's defense against infectious agents, including bacteria and viruses[41]. While vaccines targeting bacterial pathogens such as *S. aureus* are still in development, animal studies have yielded encouraging outcomes[42]. Concurrently, environmental changes and the improper use of antibiotics have contributed to the emergence of antibiotic-resistant bacterial strains. This has led to the proliferation of over 200 infectious diseases, encompassing staphylococcal and zoonotic infections[43,44].

This study has several limitations that warrant attention. First, many studies in the analysis were observational, introducing inherent biases; thus, more RCTs are needed to strengthen the evidence base. Second, the lack of long-term follow-up studies limits insights into sustained treatment outcomes. Third, the absence of standardized protocols across studies necessitates uniform methodologies for consistent and comparable findings. The studies included both MRSA and MSSA infections, as well as complicated and uncomplicated SAB cases, but lacked sufficient data for meaningful subgroup analysis. Future research should prioritize optimal timing for transitioning from intravenous to oral antibiotics owing to the current lack of guidelines. Addressing these limitations is crucial for advancing our understanding and improving clinical practices in this area.

This meta-analysis has several strengths that are essential for advancing our understanding of the topic. The first extensive meta-analysis on this issue, fills a significant gap in the literature. Integrating data from various study designs, including observational studies and RCTs, provides compelling evidence on the effectiveness and implications of switching from intravenous to oral antibiotics. It reveals critical insights into outcomes such as mortality, hospital stay duration, and adverse events, establishing a solid platform for future research. To Address a previously underexplored research question, this meta-analysis offers valuable insights into the efficacy of transitioning to oral antibiotics in infectious disease management. These findings are crucial for guiding clinical practice and shaping future research initiatives in healthcare management.

Conclusion

This meta-analysis addresses a critical knowledge gap by examining the effect of transitioning from intravenous to oral antibiotics in SAB and joint space infections. Our systematic review demonstrated that early transition to oral antimicrobial therapy for *S. aureus* bloodstream infections can significantly reduce mortality rates and hospital stays compared to continued IV therapy, without increasing adverse events or rehospitalization. The analysis of 11 studies, including observational, cohort studies, and a randomized controlled trial, elucidated the benefits of early oral therapy in improving patient outcomes and reducing healthcare resource utilization. The integration of various study designs enhances the robustness of the conclusions. Despite the high heterogeneity and study design limitations, the findings support early oral therapy as an effective alternative to prolonged IV treatment, emphasizing the need for well-designed trials to validate these results and guide clinical practice. Our findings contribute to the development of improved management strategies in infectious disease treatment, addressing both the clinical and healthcare resource implications.

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Consent

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Authors' contributions

A.R. and A.H. did conceptualization and supervision. A.H., M.A.S., O.S., W.L.H., M.A.S., and H.M.C. did writing process. A.G.P., S.M.S.A., and T.K.F.A. performed data extraction and editing. M.S.M. performed statistical analysis.

Conflicts of interest disclosure

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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Data available within the article. The authors confirm that the data supporting the findings of this study are available within the article.

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