Managing *Enterococcus faecium* bloodstream infection: a Delphi document on clinical recommendations and research agenda

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Summary

Background Management of *E faecium* bloodstream infections (BSIs) remains debated, particularly the clinical impact of vancomycin resistance, the role of follow-up cultures, and optimal therapeutic regimens. This study aimed to reach expert consensus on these unresolved clinical domains and identify priorities for future research.

Methods We first conducted a systematic review and meta-analysis in January 20, 204 focusing on four predefined areas: mortality in *E faecium* BSIs compared with other BSIs, mortality in vancomycin-resistant enterococci (VRE)-BSIs compared with vancomycin-susceptible enterococci-BSIs, management of catheter-related *E faecium* BSIs, and 4) optimal antibiotic therapy for VRE-BSIs. These results informed a three-round Delphi process involving a panel of experts. An iterative approach was adopted: 16 initial questions developed from the systematic review (6-point Likert scale) were refined across rounds based on expert feedback. Consensus was defined as at least 80% agreement or disagreement.

Findings 13 statements were generated across three broader domains. Regarding clinical outcomes and diagnostics, experts agreed that mortality is heavily influenced by comorbidities; thus, therapeutic assessment should rely on clinical trends and inflammatory markers, with follow-up blood cultures used to confirm eradication. Catheter-related BSI should be managed with device removal and short-course (<7 days) antibiotics in selected uncomplicated cases. For therapeutic management, teicoplanin is preferred for vanB VRE-BSI. For vanA VRE-BSI, both linezolid and high-dose daptomycin (>9 mg/kg per day) are effective, reserving daptomycin-based combinations for challenging cases (deep-seated infections and/or high Minimum Inhibitory Concentrations). Finally, future trials evaluating the impact of antimicrobial therapy should use Desirability-of-Outcome-Ranking analysis; the in-vitro potential of oritavancin justifies targeted randomized trials to define its clinical efficacy in VRE-BSI.

Interpretation This paper delineates current evidence and expert consensus on management of *E faecium* BSI while identifying crucial knowledge gaps to guide future clinical research.

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Introduction

Enterococci are a leading cause of healthcare-associated infections, with a steady increase in their prevalence over the last decade.[1,2] *E faecium* has become an increasingly pathogen of interest in recent years due to its higher levels of antimicrobial resistance and high mortality rates.[3–6] However, bloodstream infections (BSIs) usually occurs in patients affected by several underlying conditions and/or in critically ill patients, as a result of selective antimicrobial pressure due to previous antibiotic treatments.[6–9] Despite the clinical burden, several clinical domains remain poorly defined, specifically: 1) clinical outcomes and attributable mortality, as it remains an open question whether the higher risk of poor outcome in *E faecium* BSIs is due to the pathogen itself or host fragility; 2) diagnostic and follow-up strategies, including the role of inflammatory markers and blood culture clearance; 3) management of catheter-related infections, where the optimal duration of antibiotic treatment beyond device removal is currently unclear[10–12]; 4) optimal antimicrobial therapy, particularly for Vancomycin-Resistant Enterococci (VRE)-BSI. Regarding this last domain, although only linezolid is approved, daptomycin is considered a key agent, though its efficacy appears dose-dependent and results from combination strategies remain heterogeneous.[1,13–15] Furthermore, the role of newer agents like oritavancin remains to be established in the context of bacteraemia.[16,17] Current literature on these topics is characterised by significant heterogeneity, a lack of randomised controlled trials, and a predominance of observational studies often confounded by host factors, which limit the availability of high-quality evidence to guide clinical practice. To bridge these gaps, we conducted a study with a three-fold objective: to synthesise existing evidence through a systematic review and meta-analysis; to generate expert consensus statements across the predefined clinical domains; and

Research in context

Evidence before this study

We conducted a systematic review and meta-analysis of English-language studies published between January 2014 and January 2024 across PubMed-MEDLINE, EMBASE, and Scopus. The existing evidence revealed a fragmented landscape, predominantly composed of observational studies with a moderate risk of bias and a notable absence of randomised controlled trials.

Added value of this study

This study provides a formal expert consensus and a prioritized research agenda for *E faecium* bloodstream infection (BSI), using a three-round Delphi methodology involving 25 international experts. 13 statements were provided covering different areas. For clinical management, because mortality in *E faecium* BSI could be heavily driven by host comorbidities, follow-up blood cultures might have a supportive role, particularly in the management of device-related infections or non-responding cases. For catheter-related BSI, a strong consensus was reached for device removal and the possibility of short-course (<7 days) antibiotic therapy in selected uncomplicated cases. Considering targeted therapy for vanA VRE-BSI, both linezolid and high-dose daptomycin (>9 mg/kg per day) were deemed effective, with a preference for daptomycin-based combinations in challenging scenarios (e.g., deep-seated infections). Teicoplanin was identified as the preferred option for vanB VRE-BSI.

Implications of all the available evidence

Our findings bridge the gap between current low-quality evidence and the urgent need for standardized clinical practice. Apart from practical recommendations, a research agenda was implemented. Desirability-Of-Outcome-Ranking analysis could be adopted for future studies to better account for the interplay between survival, microbiological eradication, and adverse events. Finally, the panellists advocated the need of future trials on oritavancin for the treatment of VRE BSI.

to propose a research agenda based on identified evidence gaps. The Delphi methodology was selected to resolve the aforementioned uncertainties by providing a structured synthesis of expert opinion where a solid and definitive consensus in the literature is currently lacking. This approach aims to provide practical guidance for the management of *E faecium* BSI while identifying priorities for future clinical research.

Methods

Study design and selection of experts

We employed a three-round Delphi method to reach a consensus on a list of statements in *E faecium* BSI management. The invitation to participate in the Delphi was sent to an interdisciplinary panel, with a high-degree of expertise in *E faecium* infection management. Panellists were identified based on their clinical experience on this topic, relevant peer-reviewed publications on *E faecium* infection management, and participation as members in national and international scientific societies and study groups, with a focus on diversity in gender and geographic area. A total of 28 experts were invited to participate, of these, 25 experts (from 8 different countries) agreed to participate and completed all three rounds. The panel was composed of infectious diseases specialists (21), clinical pharmacologists (3) and an intensive care clinician (1). All participants operate in Tertiary Care University Hospitals or Clinical Research Institutes located in high-income countries. These institutions are characterised by high-volume clinical activities (typically >500 beds) and serve as referral centres for complex infections. The panel included executive members and chairs from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the ESGBIES (ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis), the SEIMC (Spanish Society of Infectious Diseases and Clinical Microbiology), and the GESITRA-IC (Study Group of Infections in Transplant Recipients). On average, the experts possessed over 15 years of clinical experience, with more than 80% holding senior academic positions as Full Professors or Directors of Infectious Disease Units. Their collective expertise is evidenced by an extensive publication record on *E faecium* management and antimicrobial stewardship in high-impact peer-reviewed journals. The Delphi process was structured following the Delphi studies in social and health sciences recommendations for an interdisciplinary standardised reporting (DELPHISTAR methodology, Supplementary Appendix).[18]

Development of Delphi questions

A systematic review and a meta-analysis was carried out from January 2024, encompassing randomised controlled trials or prospective/retrospective observational studies published in English in the last 10 years in PubMed-MEDLINE, EMBASE and Scopus databases. To ensure the robustness of the findings, the systematic review prioritised studies reporting adjusted outcomes (e.g., through multivariable analysis or propensity score matching) to minimise the impact of confounding factors. The study was registered in the PROSPERO database, number CRD42024505969, and was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)

guidelines.[19] Detailed inclusion and exclusion criteria, the risk-of-bias assessment methodology, and the PRISMA flow diagram describing the study selection process are provided in the Supplementary Appendix. The search was focused on the last 10 years to ensure that the evidence base reflected current epidemiological trends in antimicrobial resistance and contemporary management strategies for *E faecium* BSI. The systematic review was based on 4 different PICO/PECO questions, and evidence gathered from this research was made available to the panellists during the first round of the Delphi process. Briefly, the following areas were investigated: mortality in patients with *E faecium* BSI compared to other BSIs; mortality in patients with VRE BSI compared to Vancomycin-Susceptible Enterococci (VSE) BSI; management of *E faecium* catheter-related BSI; and optimal antibiotic treatment for VRE BSI. For PECO 1 only one study was retrieved, whereas none of the screened studies were included for PICO 3. Thus, only for PECO 2 and PICO 4 a meta-analysis was performed. Participants were provided with the complete systematic review report, including the study selection process, evidence tables, and risk-of-bias assessments. According with the systematic review, 16 different questions were created and submitted in the first round of the Delphi questionnaire. These initial items were developed by the research team to cover the clinical domains defined by the PICO/PECO frameworks. While some questions were directly based on the retrieved evidence, others were specifically designed to address the knowledge gaps and clinical uncertainties identified during the literature search. The objective of the research team was to summarise the evidence base and knowledge gaps on the management of *E faecium* BSIs, highlighting critical aspects to be addressed by future studies. Given the scarcity of high-quality evidence in certain areas, the systematic review served as a foundational substrate for a dynamic Delphi process. Panellists were encouraged not only to rate the initial items but also to provide qualitative feedback. This allowed the experts to refine the scope and highlight clinically relevant themes which, although inherently linked to the PICO domains, were not sufficiently addressed in the existing literature.

Data collection

The three rounds of the Delphi process were conducted anonymously with the first round from March to April 2025, the second round in May 2025, and the third round in June 2025. None of the research team participating in the questions' development participated as experts in the Delphi process. The Delphi survey was electronically administered, using the REDCap electronic data capture tool hosted by University of Bologna.[20] Participants were asked to answer the first 16 questions using a 6-point Likert scale: strongly disagree, disagree, somewhat disagree, somewhat agree, agree, strongly agree. In addition, under each question, panellists were encouraged to make comments using an open-text box. Consensus was defined a priori in the study protocol as agreement among at least 80% of respondents, corresponding to at least 20 of the 25 experts. As a way to assign a strength of recommendation and to make it easier to determine a consensus, the 6-point scales of the responses were divided into 4 different categories, as outlined below: Strong Disagreement: strongly disagree (1) + disagree (2); Moderate Disagreement: disagree (2) + somewhat disagree (3); Moderate Agreement: somewhat agree (4) + agree (5); Strong agreement: agree (5) + strongly agree (6). Any item with a consensus of 80% or more in the first round was excluded from the questionnaire administered in the second round. The results of the first round and all the comments received were combined and given to the participants during the second and third round. This approach allowed each expert to re-evaluate their initial response in light of the other panellists'–anonymous-responses and comments. Based on expert comments, questions were re-phrased in the second and third round. Final statements for the questions that obtained consensus were generated, along with the percentage of agreement/disagreement, the round of consensus, and a recommendation strength (moderate or strong). Questions administered during the three rounds and related results are summarised in Table 1.

Data analysis

Simple descriptive statistics -absolute and relative frequencies–were used to analyse the results obtained from the three rounds. Calculations were performed using SPSS 21.00 IBM statistical software. The meta-analysis was performed using MedCalc for Windows (MedCalc statistical software, version 19.6.1, MedCalc Software Ltd, Ostend, Belgium).

Ethics

The approval of an Institutional Review Board was not required as this Delphi study did not involve research and data on human subjects or animals. The study was based completely on the feedback provided by the experts. Participants were asked for their willingness and authorisation to participate and to process the data provided for the purpose of scientific research.

Results

All 25 experts participated in the three rounds. The panels mainly represent the opinion of infectious diseases physicians and researchers from Europe, with the majority from Spain (n = 9), Italy (n = 7), Germany (n = 3) and Switzerland (n = 1). The rest were from Australia (n = 2), Unites States (n = 1), Israel (n = 1) and Singapore (n = 1). In total, there were 7 females and 18

	Question round 1	Round 1				Question round 2	Round 2				Question round 3	Round 3			
		SD (%)	MD (%)	MA (%)	SA (%)		SD (%)	MD (%)	MA (%)	SA (%)		SD (%)	MD (%)	MA (%)	SA (%)
1	Among patients with a bloodstream infection (BSI), *E. faecium* BSI is associated with a higher mortality risk compared to BSIs due to other bacteria.	24	44	56	32	In patients with bloodstream infection, those from whom *E. faecium* is isolated are frequently more complex than patients with BSI due to other pathogens. This can result in higher associated mortality rates.	8	12	64	80		.	.	.	.
2	In a clinical setting, mortality is the most accurate endpoint to evaluate the management of *E. faecium* BSIs.	24	52	48	32	In clinical practice, mortality should be the most accurate endpoint to evaluate the management of *E. faecium* BSIs.	16	36	60	32	In clinical practice, considering that mortality in patients with *E. faecium* BSI may be affected by multiple underlying comorbidities, the assessment of optimal therapeutic management should also rely on the trend of clinical parameters and inflammatory markers, as well as follow-up blood cultures to confirm microbiological eradication.	0	4	84	68
3	In a clinical setting, microbiological eradication is the most accurate endpoint to evaluate the management of *E. faecium* BSIs.	16	40	56	28	In clinical practice, pending evidence that persistent *E. faecium* BSIs are associated with increased mortality, microbiological eradication should not be systematically pursued.	24	44	44	32					
4	For research purposes, mortality is the most accurate endpoint to evaluate the management of *E. faecium* BSIs.	16	40	48	36	In a clinical trial focused on the impact of therapy in patients with *E. faecium* BSI, a composite outcome including at least survival and microbiological eradication should be used following DOOR analysis methodology.	12	12	72	80		.	.	.	.
5	For research purposes, microbiological eradication is the most accurate endpoint to evaluate the management of *E. faecium* BSIs.	12	40	52	32										
6	In a clinical setting, among patients with *E. faecium* BSIs, follow-up blood cultures (FUBC) are mandatory for the optimal management (for both device-related and primary/secondary BSIs).	12	17	54	54	In clinical practice, among patients with *E. faecium* BSI, execution of FUBC could be considered in patients with device-related BSI and in those without clinical improvement.	0	0	72	84		.	.	.	.
7	For research purposes, among patients with *E. faecium* BSIs, FUBC are mandatory for the optimal management (for both device-related and primary/secondary BSIs).	4	4	68	72	Studies assessing the yielding and the impact on outcome of FUBC in patients with *E. faecium* BSI (for both device-related and primary/secondary BSIs) are needed to establish cost/benefit of such procedure.	4	4	76	84		.	.	.	.
8	Among patients with *E. faecium* BSI, VRE-BSI is associated with a higher mortality risk than VSE-BSI.	12	20	64	60	Further studies properly addressing confounders related to patients underlying conditions are needed to definitively establish the increased risk of mortality among patients with VRE-BSI compared to VSE-BSI.	0	0	56	92		.	.	.	.
9	In patients with *E. faecium* CR-BSI, the optimal management consists in early catheter removal without antibiotic therapy.	44	52	32	12	In patients with *E. faecium* CR-BSI, catheter removal and antibiotic therapy are considered the cornerstone of therapeutic management. However, there could be low-risk cases where antibiotic treatment is not necessary or very short (<7) treatment duration could be appropriate.	0	16	68	72	In patients with *E. faecium* CR-BSI, catheter removal and antibiotic therapy are considered the cornerstone of therapeutic management. However, there could be low-risk cases where a very short (<7) antibiotic treatment duration could be appropriate.	0	0	64	84
10	In patients with *E. faecium* CR-BSI, catheter removal is the cornerstone of therapeutic management, whereas appropriate antibiotic therapy could be reserved to specific populations (nowadays still not identified)	28	28	40	28										

(Table 1 continues on next page)

	Question round 1	Round 1				Question round 2	Round 2				Question round 3	Round 3			
		SD (%)	MD (%)	MA (%)	SA (%)		SD (%)	MD (%)	MA (%)	SA (%)		SD (%)	MD (%)	MA (%)	SA (%)
(Continued from previous page)															
11	Among patients with VRE-BSI, both daptomycin and linezolid are effective treatment options.	20	20	72	40	Among patients with VanA VRE-BSI, the current approved options, daptomycin (administered at high-dose) and linezolid are both effective. Teicoplanin could be the preferred choice for VanB VRE-BSI. Oritavancin is a promising agent according to in vitro and early clinical data, however as it is not currently approved for bacteremia, future ad hoc studies are needed to broadly implement its use in the management of *E. faecium* BSI.	4	8	76	84		.	.	.	.
12	Among patients with VRE-BSI, high-dose daptomycin (>9 mg/kg) is more effective than standard-dose daptomycin.	4	4	72	80		.	.	.	.		.	.	.	.
13	Among patients with VRE-BSI, daptomycin-based combination therapy is more effective than daptomycin monotherapy.	8	24	74	44	Among patients with VanA VRE BSI, daptomycin based combination treatment could be administered in selected cases according with clinical severity, deep/not removable infection sites, both high daptomycin MIC (i.e. >2 µg/mL) and linezolid MIC (i.e. >2 µg/mL).	4	8	80	84		.	.	.	.
14	Among patients with VRE-BSI, daptomycin-based combination therapy should be reserved only for strains with high daptomycin MIC (i.e. >2 µg/mL) and linezolid MIC (i.e. >2 µg/mL) in which a first-line agent is not available.	16	32	60	28										
15	Among patients with VRE-BSI, high-dose daptomycin therapy is the best treatment option if daptomycin MIC (Minimum Inhibitory Concentration) is $\leq$ 2 µg/mL and linezolid MIC is $\leq$ 2 µg/mL.	8	24	60	36	Among patients with VanA VRE-BSI, high-dose daptomycin therapy is the best treatment option if daptomycin MIC (Minimum Inhibitory Concentration) is $\leq$ 2 µg/mL and linezolid MIC is $\leq$ 2 µg/mL.	4	8	84	72		.	.	.	.
16	Among patients with VRE-BSI, linezolid is the best treatment option if daptomycin MIC is 4 µg/mL and linezolid MIC is 2 µg/mL.	0	24	76	36	Among patients with VanA VRE-BSI, linezolid is the best treatment option if daptomycin MIC is 4 µg/mL and linezolid MIC is 2 µg/mL.	0	8	88	60		.	.	.	.
17						Among patients with VanB VRE-BSI, teicoplanin is the best choice if MIC $\leq$2 µg/mL, linezolid MIC is 2 µg/mL and daptomycin MIC is 2 µg/mL.	4	4	84	56		.	.	.	.
18						Among patients with VRE-BSI, a randomized clinical trial evaluating the safety and efficacy of oritavancin compared to current approved agents is needed.	0	12	36	80		.	.	.	.

Abbreviations: VRE vancomycin-resistant Enterococcus, VSE vancomycin-suscpeptible Enterococcus, CR-BSI catheter related bloodstream infection, MIC minimum inhibitory concentration, DOOR desiderability of outcome ranking.

Table 1: **List of questions and results of the three rounds of the Delphi study (SD = Strong Disagreement; MD = Moderate Disagreement; MA = Moderate Agreement; SA = Strong Agreement).**

males. Consensus was achieved for only 1 of the 16 (6.3%) items after the first round, for 11 out of 14 (78.6%) questions of the second round, and for 3 of 3 (100%) remaining in the third round, resulting in 18 final items with 100% consensus reached. A total of 13 final statements were conceived and reported with a

strength of recommendation. The structural alignment between the initial PECO/PICO questions, the findings of the systematic review, and the subsequent development of the Delphi statements is summarised in Table 2.

Mortality risk and outcome assessment in patients with *E faecium* BSI

The topic was addressed through 7 questions rephrased during the three rounds (questions #1-7, Table 1), leading to 5 statements.

Statement 1: "E faecium BSI frequently occurs in more complex patients compared to patients with other BSI, resulting in higher mortality rates" [Strong agreement].

Statement 2: "In clinical practice, since mortality in patients with E faecium BSI may be affected by multiple underlying comorbidities, the trend of clinical parameters and inflammatory markers, as well as follow-up blood cultures (FUBC) to confirm microbiological eradication, could be considered as indicators of treatment response" [Moderate agreement].

Statement 3: "The performance of FUBC should be mainly considered in patients with device-related BSI and in those without clinical improvement" [Strong agreement].

Statement 4: "In a clinical trial aimed at assessing the impact of therapy in patients with E faecium BSI, a composite outcome including at least survival and microbiological eradication should be used following DOOR analysis methodology" [Strong agreement].

Statement 5: "Studies assessing the yield of FUBC and their impact on outcome in patients with E faecium BSI are needed to establish cost/benefit of such procedure" [Strong agreement].

Issues concerning the morbidity and mortality associated with *E faecium* BSI, considering the frequent concomitant underlying conditions in patients developing this infectious complication, were addressed in question #1. A single study reporting adjusted data for mortality associated with *E faecium* BSI compared to other pathogens was identified.[21] Adjusted Odd Ratios (aOR) for 7-day mortality, 30-day mortality and in-hospital mortality for *E faecium* were 0.82 (0.71–0.96, $p = 0.01$), 1.79 (1.58–2.04, $p < 0.001$) and 1.74 (1.54–1.96, $p < 0.001$), respectively. Considering in-hospital and 30-day mortality, *E faecium* BSIs showed the highest mortality risk compared to other bacteria. The majority of panellist agreed with an increased mortality risk among patients with *E faecium* BSI, but some concerns about attributable mortality and all-cause mortality were raised. Questions #2 and #3 focused on the most accurate endpoint in clinical practice to evaluate the management of *E faecium* BSI. For the majority of panellists, mortality—especially short term (i.e. 7-14 days) or attributable—remains the most important variable to define the optimal management of *E faecium* BSI. However, following the first question, it remains unclear whether mortality is always directly caused by *E faecium* BSI or whether it is a marker of poor underlying health leading to death.[22] For this reason, the evolution of clinical and biochemical parameters was considered helpful in the management of VRE BSI—apart from FUBC (see below). Questions #4 and #5 focused on the most accurate endpoint for research purposes to evaluate the management of

Area/topic	Evidence from systematic review	Panel rationale & Delphi evolution	Final statement (Consensus Strength)
1. Mortality & Outcome Assessment	Evidence is scarce: only one study provided adjusted data for *E. faecium* mortality compared to other pathogens.	Given the limited literature, the panel emphasized that *E. faecium* BSI is often a marker of poor underlying conditions and/or complexity. Experts proposed the DOOR methodology for future trials.	**Statements 1, 4** (Strong Agreement)
2. Role of Follow-up Blood Cultures	Retrospective data suggest survival benefits, but the association between persistent bacteremia and mortality is inconsistent in *E. faecium*.	Experts expressed a nuanced position: FUBC should not be routine for everyone but prioritized for high-risk cases to optimize resources.	**Statements 2, 3, 5** (Strong to Moderate)
3. Vancomycin Resistance Impact	Meta-analysis showed an increased risk of mortality, but with high heterogeneity and predominantly retrospective data.	The panel considered the evidence quality too low for a definitive causal link. They called for better-adjusted prospective studies to address confounding factors.	**Statement 6** (Strong Agreement)
4. Catheter-Related BSI (CR-BSI)	No studies directly addressed treatment duration specifically for *E. faecium* CR-BSI. Guidelines lack species-specific granularity.	Based on the perceived lower pathogenicity of *E. faecium*, experts suggested that short-course therapy (<7 days) might be safe after source control in selected cases.	**Statement 7** (Strong Agreement)
5. Daptomycin Dosing & Combinations	Meta-analysis confirmed that high-dose daptomycin (>9 mg/kg) significantly reduces mortality.	Direct evidence supports high-dose daptomycin. Combination therapy was proposed for severe cases or high MICs, despite the lack of direct comparative trials.	**Statements 8, 9, 10, 11** (Strong to Moderate)
6. VanB Strains & Teicoplanin	SR was not primarily focused on this drug. Limited retrieved data showed conflicting results vs. linezolid.	This topic was explicitly added following experts' requests in Round 1 to address clinical needs in settings where *vanB* is prevalent.	**Statements 8, 12** (Strong Agreement)
7. Novel Agents (Oritavancin)	SR was not primarily focused on this drug. No large cohorts identified; evidence limited to in vitro data and case reports.	Despite the lack of primary focus in the SR, the panel identified a major evidence gap and a strong clinical interest, calling for a dedicated RCT.	**Statements 8, 13** (Strong Agreement)

Table 2: **Structural alignment between PICO questions, Systematic Review (SR) findings, and Delphi Consensus Statements.**

E faecium BSI. During the first round, some panellists suggested to follow Desirability Of Outcome Ranking (DOOR) analysis methodology for addressing the impact of antimicrobial therapy in patients with *E faecium* BSI.[23] This methodology may allow to take into account not only mortality, but also improvement of symptoms and rates of adverse events. Questions #6 and #7 focused on the role of FUBC in the management of any type of *E faecium* BSI (primary, secondary, device-related) in clinical practice and for research purposes. A recent retrospective study reported that the execution of FUBC is a protective intervention for 30-day mortality in cases of any *E faecium* BSI.[6] A prospective multicentre study highlighted the importance of FUBC, as microbiological failure was independently associated with in-hospital mortality (OR 2.4, 95% CI 1.34–4.31, p = 0.003).[24] A study focusing on enterococcal BSI showed that persistent bacteraemia is an independent risk factor for 30-day mortality.[25] However, half of included patients had an *Enterococcus faecalis* BSI. Another retrospective study reported that FUBC were associated with reduced mortality in any type of *E faecium* BSI, especially in the subgroup of patients with device-related BSI.[6] The role of FUBC remains controversial due to the inconsistent association between persistent *E faecium* BSI and mortality[6,26] as well as the relatively low rate of persistent BSI among patients with *E faecium* infections.[25] Given the lack of prospective well-designed studies exploring the role of FUBCs in improving outcomes, the panel expressed a nuanced position. While some panellist disagreed with the routinely execution of FUBC in all patients, a strong consensus was reached on prioritising FUBC for high-risk scenarios, such as device-related infections or patients lacking clinical improvement. Furthermore, the panellists highlighted that the current evidence is too indirect to mandate a universal standard of care, leading to a strong recommendation for future prospective studies to specifically assess the cost-benefit ratio of this procedure.

Relationship between mortality rates and vancomycin-resistance

The topic was addressed through one question (question #8, Table 1), generating one statement.

Statement 6: "Further studies properly addressing confounders related to patients underlying conditions are needed to definitively establish the increased risk of mortality among patients with VRE-BSI compared to VSE-BSI" [Strong agreement].

The question #8 "Among patients with E faecium BSI, VRE-BSI is associated with a higher mortality risk than VSE-BSI" did not reach the predetermined consensus threshold, and following panellist comments was then rephrased in the second round, reaching the consensus of strong agreement (92%). The systematic review identified six studies addressing this topic, for an overall number of 7490 patients with *E faecium* BSI (725 VRE BSI vs. 6765 VSE BSI).[27–32] Only one study was prospective,[27] other included studies were retrospective and observational, with significant variability in the methods used to adjust for confounders. Patients with VRE BSI showed an increased risk for mortality (OR 1.63, 95% 1.12–2.37). However, the interpretation of this pooled estimate was limited by a high degree of heterogeneity (I^2 = 66.38%, p = 0.011) and the inherent difficulty in distinguishing attributable mortality from host-related factors and comorbidities. The funnel plot and Egger's test (p = 0.12) did not show evidence of publication bias. A formal quality assessment of the included studies revealed an overall moderate risk of bias, primarily due to inconsistent adjustment for clinical severity. Conversely, in a cohort of over 1000 enterococcal isolates, *E faecium* was an independent risk factor for in-hospital mortality and prolonged hospital stay compared to *E. faecalis*, and vancomycin resistance did not further increase the risk for unfavourable outcomes.[32] During the first round, more than half of the panellists agreed with the association between VRE and mortality, considering also the limited therapeutic options, as well as delays in the administration of active empirical antibiotic therapy in VRE-BSI. However, reflecting the low-to-moderate quality of available evidence, the majority of panellists advocated for the need of future studies able to properly address patient-related confounders, leading to the formulation of Statement 6.

Management of *E faecium* catheter-related BSI

The topic was addressed through two questions (questions #9 and #10, Table 1), generating one final statement.

Statement 7: "In patients with E faecium catheter-related BSI, catheter removal and antibiotic therapy are considered the cornerstone of therapeutic management. Furthermore, there could be individual cases where a short (<7) antibiotic treatment duration could be appropriate" [Strong agreement].

Unfortunately, none of the retrieved studies in our systematic review addressed this specific topic directly. Therefore, this statement represents a consensus based on expert opinion and extrapolation from indirect evidence. Guidelines recommend device removal along with targeted antibiotic therapy in enterococcal catheter-related BIS, without distinction between species.[33] However, *E faecium* is generally considered as a microorganism with a low level of pathogenicity,[34] probably justifying a different approach compared to *E faecalis*. Few indirect data supporting this management are available.[35,36] Among cancer patients with mixed enterococcal catheter-related BIS (50% *E faecium*), early (<3 days) catheter removal was associated with a better overall outcome.[37] In another study of 61 enterococcal catheter-related BISs, higher rates of

favourable outcome were observed in patients managed with catheter removal, regardless of appropriateness of antibiotic therapy.[11] Similarly, in a cohort of 151 patients with *E faecium* catheter-related BIS,[6] device removal was found to associated with lower mortality (HR 0.229, 95% CI 0.117–0.451, p < 0.001) regardless of appropriate antibiotic treatment, suggesting that antimicrobial treatment may have a marginal role in this specific setting. Finally, a multicentre cohort study demonstrated that a 7-day treatment strategy vs. a 15-day treatment regime in uncomplicated *E faecium* BSI is not associated with worse outcome.[38] A randomised trial focused on this topic is ongoing.[39] Despite the lack of a standardised definition, previously published studies define uncomplicated E faecium BSI as an episode with low-risk sources or adequate source control achieved within the first 72 h, in the absence of septic emboli or endovascular complications such as endocarditis or thrombophlebitis.[38,39] During the first round it was discussed whether antibiotic therapy could be reserved only to specific populations, but the panellists emphasised that current evidence is insufficient to establish the role of antibiotic treatment. Nonetheless, there was high agreement regarding the possibility of reducing treatment durations to less than 7 days in selected uncomplicated cases. Efforts are required to identify groups of patients who could benefit from shorter antibiotic therapy.

Optimal antibiotic treatment for VRE BSI

The topic was addressed through eight questions (questions #11 to #18, Table 1), generating 6 statements.

Statement 8: "Among patients with *VanA* VRE-BSI, the current approved options, daptomycin (administered at >9 mg/kg per day) and linezolid are both effective. Teicoplanin could be the preferred choice for *VanB* VRE-BSI. Oritavancin could be a promising agent according to in vitro and early clinical data" [Strong agreement].

Statement 9: "Among patients with *VanA* VRE BSI, daptomycin based combination treatment could be considered in selected cases according with clinical severity, deep or not removable infection sites, or high daptomycin (i.e. >2 μg/mL) and linezolid (i.e. >2 μg/mL) Minimum Inhibitory Concentrations (MICs)" [Strong agreement].

Statement 10: "The best treatment option for *VanA* VRE-BSI with daptomycin MIC ≤2 μg/mL and linezolid MIC is ≤ 2 μg/mL is high-dose daptomycin" [Moderate agreement].

Statement 11: "The best treatment option for *VanA* VRE-BSI with daptomycin MIC ≥ 4 μg/mL and linezolid MIC of ≤2 μg/mL is linezolid" [Moderate agreement].

Statement 12: "The best treatment option for *VanB* VRE-BSI with teicoplanin MIC ≤2 μg/mL, daptomycin MIC ≥ 2 μg/mL and linezolid MIC ≥ 2 μg/mL is teicoplanin" [Strong agreement].

Statement 13: "A randomised clinical trial evaluating the safety and efficacy of oritavancin compared to current approved agent for the treatment of VRE-BSI is needed" [Strong agreement].

Only question #12: "Among patients with VRE-BSI, high-dose daptomycin (>9 mg/kg) is more effective than standard-dose daptomycin" reached a strong agreement during the first round (80%). The systematic review identified six studies addressing this topic, encompassing 2116 patients with VRE-BSI.[15,40–44] High-dose daptomycin was defined as the administration of daptomycin daily dose >9 mg/kg, 10 mg/kg, and 11 mg/kg in three, two, and one study, respectively. Overall, the administration of high-dose daptomycin was associated with significant lower risk of mortality compared to standard doses (OR 0.67; 95% CI 0.52–0.86; I^2 = 61.7%). Three observational studies (N = 999 patients) provided data for assessing mortality in patients receiving daptomycin combination therapy vs. monotherapy.[14,43,44] In two studies daptomycin was used in association with beta-lactams, whereas fosfomycin was administered for combination therapy in the other. Overall, a lower risk of mortality was found in patients treated with daptomycin combination therapy compared to monotherapy (OR 0.56; 95% CI 0.36–0.89; I^2 = 33.8%). The panellists raised concerns about the indication of combination regimens solely based on MIC values, as this should also consider site of infection (especially for deep seated or not removable infection site) and clinical severity. In addition, no studies specifically focused on type of combination treatment, thus it was not possible to give recommendations about one regimen over another. A total of six studies (N = 2993 patients) provided data for assessing mortality rate in patients with VRE-BSI treated with daptomycin vs. linezolid. Two studies each evaluated mortality rate at 14-[40,45] and 30-days,[46,47] whereas one study each assessed in-hospital[48] and 90-day mortality.[49] No significant difference in mortality emerged between daptomycin and linezolid (OR 1.08; 95% CI 0.85–1.38). No substantial degree of heterogeneity was identified (I^2 = 46.9%; p = 0.09), and no evidence of publication bias was reported. In addition, two studies (N = 2350 patients) provided data for microbiological failure.[46,47] Overall, linezolid was associated with a significantly higher risk of microbiological failure compared to daptomycin (OR 1.18; 95% CI 1.06–1.31; I^2 = 0.0%). The MIC values used in the clinical scenarios (i.e. daptomycin MIC = 4 μg/mL) were intentionally selected to represent clinical grey zones. Regarding daptomycin, although EUCAST does not currently provide a formal breakpoint for *Enterococcus* spp., cumulative clinical evidence and PK/PD studies suggest that a MIC of 4 μg/mL is associated with a significantly higher risk of therapeutic failure and the emergence of resistance.[50,51]

In case of a *VanA* VRE-BSI with daptomycin MIC = 4 μg/mL and linezolid MIC = 2 μg/mL, the majority of panellists preferred to avoid the use of daptomycin. Previous studies showed that daptomycin MICs of 3–4 μg/mL are an independent risk factor for microbiological failure (OR: 4.7 [1.37–16.12]; p = 0.014).[50] However, only half of included patients received a dose of daptomycin >8 mg/kg. Similar results were reported in a large multicentre registry[51] and among hematologic patients.[52] Some panellist commented that combination therapy may have a role in such scenarios, as highlighted in previous studies in which combination therapy was associated with better outcomes.[14,43,44] Although the systematic review was not primarily focused on this specific drug, few studies evaluated the impact of teicoplanin for the treatment of *VanB* VRE-BSI on mortality or microbiological failure. The inclusion of a dedicated question on this topic was prompted by the experts' feedback during the first round. A retrospective study found that definitive linezolid therapy for *VanB* VRE-BSI was associated with lower mortality rates compared to teicoplanin.[29] However, teicoplanin was administered at 6–12 mg/kg q12 h for 3 doses and then with maintenance doses of 400–800 mg daily. In a cohort of cancer patients, teicoplanin monotherapy was associated with lower 30-day mortality and lower rates of ICU admission compared to other regimens.[53] To avoid treatment failure and emergence of further resistances, a dose of 12 mg/kg per day along with therapeutic drug management is usually provided in clinical practice for *VanB* VRE-BSI.[54,55] However, optimal dosing and management of teicoplanin was not explored in this survey. There were no published studies including large cohort of patients with VRE-BSI treated with oritavancin. However, a strong rationale exists based on in vitro studies.[56,57] Real-life experiences mainly consist in treatment of bone and joint infections with high rates of positive clinical outcomes.[58,59] For bacteraemia, oritavacin was mainly employed for *Staphylococcus aureus* with similar results.[60,61] Finally, in a case report oritavancin was administered as target therapy for VRE prosthetic endocarditis, with clinical success after surgical valve replacement.[62] Despite the scarcity of robust clinical evidence identified in our systematic review, this topic was explicitly raised by the participants during the first Delphi round as a priority for future research. Giving this promising biological activity, and following the panelists' specific request, the expert group agreed with the strong need for a randomised clinical trial evaluating safety and efficacy of oritavancin for the management of VRE-BSI, especially for those species with high daptomycin and linezolid MICs. This recommendation reflects the high level of consensus reached by the panel, aiming to bridge the gap between current preclinical rationale and the lack of high-quality interventional data.

Discussion

This Delphi survey among international experts yielded several statements with moderate or strong agreement. As *E faecium* BSIs usually occur in patients with multiple comorbidities or severely impaired clinical status, the interpretation of therapeutic outcomes remains inherently challenging. A major methodological hurdle is the extreme difficulty in establishing the attributable mortality in such a fragile population. In clinical practice and retrospective research, disentangling the specific contribution of the infection to the patient's death from the impact of severe underlying diseases is really challenging. Consequently, the assessment of optimal therapeutic management should be dynamic and focus on the trend of clinical parameters and inflammatory markers. FUBCs are suggested as potentially useful to confirm microbiological eradication, especially in those with device-related BSI and/or without clinical improvement. For this reason, in future studies evaluating the impact of antimicrobial therapy in patients with *E faecium* BSI, a composite outcome including at least survival and microbiological eradication should be used following DOOR analysis methodology. This methodology could reduce biases linked to underlying conditions. Considering statements regarding practical advice, there was moderate agreement that *E faecium* catheter-related BIS can be managed with catheter removal and a short (<7 days) antibiotic treatment, especially for low-risk cases. However, given the lack of direct comparative trials, this recommendation should be framed as hypothesis-generating rather than a definitive standard of care. For *VanB* VRE-BSI, there was strong agreement on teicoplanin as the preferred treatment, although adequate dosing has not been properly defined. For *VanA* VRE-BSI, both high-dose daptomycin (>9 mg/kg per day) and linezolid both high-dose daptomycin (>9 mg/kg per day) and linezolid were considered effective strategies; however, the preference for daptomycin-based combinations in challenging scenarios (e.g., high MICs or deep-seated infections) remains largely supported by observational evidence and expert clinical judgment rather than high-quality prospective data. The systematic review conducted alongside this Delphi process highlighted several critical evidence gaps that limit current clinical decision-making. The most prominent deficit is the near-total absence of randomised controlled trials specifically targeting *E faecium*. Most current recommendations, including those regarding the management of catheter-related BIS and the use of newer lipoglycopeptides like oritavancin, rely heavily on expert consensus and the extrapolation of indirect data. To transition from expert-opinion-based guidance to evidence-based recommendations, future research must prioritise methodological standardisation. Prospective studies should focus on high-risk populations and use standardised endpoints to mitigate the

confounding effect of comorbidities. Specifically, the strong call from this panel for an RCT evaluating oritavancin reflects the need to validate in vitro potency with robust clinical safety and efficacy data in the setting of VRE-BSI. Although the Delphi process is a reliable method frequently used for assessing degrees of consensus on different areas where scientific evidence is weak, it has several limitations. First, the domains analysed and the final set of questions were conceived by a research team working in Italy, potentially introducing bias in the selection of the issues to be addressed. However, the option of writing comments during the three rounds allowed for the modification of questions in subsequent rounds, and in some cases, for the introduction of new topics not initially administered. Comments were analysed by two independent reviewers (M.R. and M.G.). In addition, the panel was composed of experts from different countries and different areas of expertise. Moreover, all the procedures were conducted using anonymous surveys, and there was no face-to-face meeting at the end of the three rounds. However, the statements of this Delphi study were circulated among the panellists to obtain their approval. Finally, we acknowledge that, although we aimed for broad geographic diversity during the recruitment phase, the final panel was predominantly composed of experts from Western Europe. This may limit the generalisability of some statements to low-resource settings or regions with different clinical traditions, and future efforts should aim to include a more globally diverse group of participants. Of note, the consensus statements do not always represent a direct transposition of the meta-analysis results. Instead, they reflect the experts' critical appraisal of the evidence, accounting for the risk of bias and the clinical relevance of the retrieved data. This explains why some recommendations, despite being informed by the systematic review, incorporate nuanced clinical perspectives on monitoring and management that extend beyond the primary study outcomes. To conclude, this Delphi process highlights the paucity of robust data in the optimal management of *E faecium* BSI. While we provide practical advice for clinical management, these statements should be interpreted as expert-led guidance for areas of significant clinical uncertainty. Several moderate and strong agreement consensus statements, including practical advice for clinical management of VRE-BSI, catheter-related infections, and optimal antibiotic treatment based on susceptibility test have been formulated. In addition, recommendations regarding methodology and focus on future studies have been made.

Contributors

Study Design and Methodology, writing, data analysis: M.R. Data Collection and Investigation (Delphi Panelists): M.B.; P.C.; L.E.; N.F., D.H., C.G.; B.G.G.; L.E.L.C.; W.V.K.; I.L.; P.M.; A.O.; M.P.; M.P.P.; F.P.; J.M.P.; S.R.; A.R.; A.S.; K.A.T.; A.A.U; M.V.; D.Y.; Y.M.; P.V. Systematic review design and methodology: Mi.Ga. Study Design and Methodology, Data Verification, Review & Editing: Ma.Gi. Writing—Review & Editing: All authors. All authors read and approved the final version of the manuscript.

Data sharing statement

The data analysed and supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of interests

M.B. reports grants from Biomerieux to his institution; consulting fees from MSD, Gilead, Pfizer, and Advanzpharma; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer, Advanzpharma, Gilead, Mundipharma, Tillots, and Infectopharm outside the submitted work. L.E.L.C. reports consulting fees from Angelini as a scientific advisor; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Angelini, ViiV, Gilead, and Correvio outside the submitted work. D.H. reports receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Lake Constance Symposium on infectious diseases, Pfizer, and the German Society for internal medicine outside the submitted work. F.P. reports consulting fees from Advanz Pharma, Gilead, MSD, Mundipharma, Pfizer, Shionogi, and Viatris; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Advanz Pharma, Angelini, Gilead, InfectoPharm, MSD, Mundipharma, Pfizer, Thermo-Fisher, and Viatris outside the submitted work. Mi.Ga. reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Angelini, Advanz Pharma, and Viatris outside the submitted work. Ma.Gi. reports consulting fees from Pfizer; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer, MSD, Shionogi, and Menarini outside the submitted work. I.L.A. reports support for attending meetings and/or travel from Gilead, Merck, Mundipharma, Menarini, and Shionogi (payment only for expenses related to travel and accommodation for educational events) outside the submitted work. M.R. reports receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Shionogi, Pfizer, and Viatris; and support for attending meetings and/or travel from Pfizer outside the submitted work. A.S. reports grants from Pfizer; consulting fees from Pfizer, MSD, Angelini, Shionogi, Gilead, and Menarini; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer, MSD, Angelini, Shionogi, Gilead, and Menarini; and support for attending meetings and/or travel from Pfizer outside the submitted work. A.U. reports that his institution received in-kind support (trial consumables) from Integra Lifesciences for a project outside the current work. P.V. reports consulting fees from Pfizer; and participation on a Data Safety Monitoring Board or Advisory Board for Pfizer, MSD, Gilead, Viatris, Menarini, and Advanz outside the submitted work. D.Y. reports that her institution received funding for a collaborative retrospective study from Pfizer, and funding for an investigator-initiated clinical study from Shionogi outside the submitted work. S.R. reports receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Med Update GmbH, streamedup! GmbH, Deutsches Beratungszentrum für Hygiene, Deutscher Apotheker-Verlag, Forum für medizinische Fortbildung, and Meet The Experts Academy; and holding a leadership or fiduciary role as an elected member of the Steering Committee and Vice chairman of the 'Deutsche Gesellschaft für Infektiologie (DGI)' outside the submitted work. M.P.P., M.V., M.Y., N.F.H., P.G.C., P.M., W.V.K., J.M.P., K.T., L.E., M.O.P., A.O., A.R., B.G.G., and C.G. declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.103925.

References

1 Cairns KA, Udy AA, Peel TN, Abbott IJ, Dooley MJ, Peleg AY. Therapeutics for vancomycin-resistant enterococcal bloodstream infections. *Clin Microbiol Rev*. 2023;36:e00059-22. https://doi.org/10.1128/cmr.00059-22.

2 Hornuss D, Göpel S, Walker SV, et al. Epidemiological trends and susceptibility patterns of bloodstream infections caused by Enterococcus spp. in six German university hospitals: a prospectively evaluated multicentre cohort study from 2016 to 2020 of the R-Net study group. *Infection*. 2024;52:1995–2004. https://doi.org/10.1007/s15010-024-02249-2.

3 Gök ŞM, Türk Dağı H, Kara F, Arslan U, Fındık D. [Investigation of Antibiotic Resistance and Virulence Factors of Enterococcus faecium and Enterococcus faecalis Strains Isolated from Clinical Samples]. *Mikrobiyol Bul*. 2020;54:26–39. https://doi.org/10.5578/mb.68810.

4 Top J, Willems R, Blok H, et al. Ecological replacement of Enterococcus faecalis by multiresistant clonal complex 17 Enterococcus faecium. *Clin Microbiol Infect*. 2007;13:316–319. https://doi.org/10.1111/j.1469-0691.2006.01631.x.

5 Prematunge C, MacDougall C, Johnstone J, et al. VRE and VSE bacteremia outcomes in the era of effective VRE therapy: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2016;37:26–35. https://doi.org/10.1017/ice.2015.228.

6 Rinaldi M, Rancan I, Malerba F, et al. Enterococcus faecium bacteraemia: a multicentre observational study focused on risk factors for clinical and microbiological outcomes. *J Antimicrob Chemother*. 2025;80:2247–2256. dkaf197. https://doi.org/10.1093/jac/dkaf197

7 Serapide F, Serraino R, Spadafora L, et al. Clinical characteristics, therapy and outcome of bloodstream infections caused by vancomycin-resistant enterococci: a multicentre clinical experience. *J Antimicrob Chemother*. 2025;80:1241–1247. https://doi.org/10.1093/jac/dkaf055.

8 Gudiol C, Ayats J, Camoez M, et al. Increase in bloodstream infection due to vancomycin-susceptible Enterococcus faecium in cancer patients: risk factors, molecular epidemiology and outcomes. *PLoS One*. 2013;8:e74734. https://doi.org/10.1371/journal.pone.0074734.

9 Scharloo F, Cogliati Dezza F, López-Hernández I, et al. Clinical characteristics, predisposing factors and outcomes for Enterococcus faecalis versus Enterococcus faecium bloodstream infections: a prospective multicentre cohort study. *Eur J Clin Microbiol Infect Dis*. 2024;43:2011–2022. https://doi.org/10.1007/s10096-024-04917-5.

10 Rosselli Del Turco E, Pasquini Z, Scolz K, et al. Treatment duration for central line-associated infection caused by Enterococcus spp.: a retrospective evaluation of a multicenter cohort. *Eur J Clin Microbiol Infect Dis*. 2022;41:1203–1206. https://doi.org/10.1007/s10096-022-04481-w.

11 Sandoe JAT, Witherden IR, Au-Yeung H-KC, Kite P, Kerr KG, Wilcox MH. Enterococcal intravascular catheter-related bloodstream infection: management and outcome of 61 consecutive cases. *J Antimicrob Chemother*. 2002;50:577–582. https://doi.org/10.1093/jac/dkf182.

12 Marschall J, Piccirillo ML, Fraser VJ, Doherty JA, Warren DK. Catheter removal versus retention in the management of catheter-associated enterococcal bloodstream infections. *Can J Infect Dis Med Microbiol*. 2013;24:e83–e87. https://doi.org/10.1155/2013/678503.

13 Shi C, Jin W, Xie Y, et al. Efficacy and safety of daptomycin versus linezolid treatment in patients with vancomycin-resistant enterococcal bacteraemia: an updated systematic review and meta-analysis. *J Glob Antimicrob Resist*. 2020;21:235–245. https://doi.org/10.1016/j.jgar.2019.10.008.

14 Tseng T-C, Chuang Y-C, Yang J-L, et al. The combination of daptomycin with fosfomycin is more effective than daptomycin alone in reducing mortality of vancomycin-resistant enterococcal bloodstream infections: a retrospective, comparative cohort study. *Infect Dis Ther*. 2023;12:589–606. https://doi.org/10.1007/s40121-022-00754-1.

15 Britt NS, Potter EM, Patel N, Steed ME. Comparative effectiveness and safety of standard-medium-and high-dose daptomycin strategies for the treatment of vancomycin-resistant enterococcal bacteremia among veterans affairs patients. *Clin Infect Dis*. 2017;64:605–613. https://doi.org/10.1093/cid/ciw815.

16 Carvalhaes CG, Sader HS, Streit JM, Castanheira M, Mendes RE. Activity of oritavancin against gram-positive pathogens causing bloodstream infections in the United States over 10 years: focus on drug-resistant enterococcal subsets (2010-2019). *Antimicrob Agents Chemother*. 2022;66:e0166721. https://doi.org/10.1128/AAC.01667-21.

17 Echeverria-Esnal D, Sorli L, Navarrete-Rouco ME, et al. Ampicillin-resistant and vancomycin-susceptible Enterococcus faecium bacteremia: a clinical narrative review. *Expert Rev Anti Infect Ther*. 2023;21:759–775. https://doi.org/10.1080/14787210.2023.2223977.

18 Niederberger M, Schifano J, Deckert S, et al. Delphi studies in social and health sciences—Recommendations for an interdisciplinary standardized reporting (DELPHISTAR). Results of a Delphi study. *PLoS One*. 2024;19:e0304651. https://doi.org/10.1371/journal.pone.0304651.

19 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097. https://doi.org/10.1371/journal.pmed.1000097.

20 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inf*. 2009;42:377–381. https://doi.org/10.1016/j.jbi.2008.08.010.

21 Choi MH, Kim D, Kim J, Song YG, Jeong SH. Shift in risk factors for mortality by period of the bloodstream infection timeline. *J Microbiol Immunol Infect*. 2024;57:97–106. https://doi.org/10.1016/j.jmii.2023.11.008.

22 Rohde AM, Walker S, Behnke Met al, DZIF R-NET Study Group. Vancomycin-resistant Enterococcus faecium: admission prevalence, sequence types and risk factors-a cross-sectional study in seven German university hospitals from 2014 to 2018. *Clin Microbiol Infect*. 2023;29:515–522. https://doi.org/10.1016/j.cmi.2022.11.025.

23 Ong SWX, Petersiel N, Loewenthal MR, Daneman N, Tong SYC, Davis JS. Unlocking the DOOR-how to design, apply, analyse, and interpret desirability of outcome ranking endpoints in infectious diseases clinical trials. *Clin Microbiol Infect*. 2023;29:1024–1030. https://doi.org/10.1016/j.cmi.2023.05.003.

24 Contreras GA, Munita JM, Simar S, et al. Contemporary clinical and molecular epidemiology of vancomycin-resistant enterococcal bacteremia: a prospective multicenter cohort study (VENOUS I). *Open Forum Infect Dis*. 2022;9:ofab616. https://doi.org/10.1093/ofid/ofab616.

25 Bussini L, Rosselli Del Turco E, Pasquini Z, et al. Risk factors for persistent enterococcal bacteraemia: a multicentre retrospective study. *J Glob Antimicrob Resist*. 2022;29:386–389. https://doi.org/10.1016/j.jgar.2022.05.003.

26 Rogers R, Rice LB. State-of-the-art review: persistent enterococcal bacteremia. *Clin Infect Dis*. 2024;78:e1–e11. https://doi.org/10.1093/cid/ciad612.

27 Rao C, Dhawan B, Vishnubhatla S, Kapil A, Das B, Sood S. Clinical and molecular epidemiology of vancomycin-resistant Enterococcus faecium bacteremia from an Indian tertiary hospital. *Eur J Clin Microbiol Infect Dis*. 2021;40:303–314. https://doi.org/10.1007/s10096-020-04030-3.

28 Bager P, Kähler J, Andersson M, et al. Comparison of morbidity and mortality after bloodstream infection with vancomycin-resistant versus -susceptible Enterococcus faecium: a nationwide cohort study in Denmark, 2010–2019. *Emerg Microbes Infect*. 2024;13:2309969. https://doi.org/10.1080/22221751.2024.2309969.

29 Cheah ALY, Spelman T, Liew D, et al. Enterococcal bacteraemia: factors influencing mortality, length of stay and costs of hospitalization. *Clin Microbiol Infect*. 2013;19:E181–E189. https://doi.org/10.1111/1469-0691.12132.

30 Huh K, Chung DR, Ha YEet al, Korean Antimicrobial Resistance Surveillance Network KARS-Net investigators. Impact of vancomycin resistance in Enterococcus faecium bloodstream infection on mortality: a retrospective analysis of nationwide surveillance data. *Int J Infect Dis*. 2023;134:8–14. https://doi.org/10.1016/j.ijid.2023.04.411.

31 Dubler S, Lenz M, Zimmermann S, et al. Does vancomycin resistance increase mortality in Enterococcus faecium bacteraemia after orthotopic liver transplantation? A retrospective study. *Antimicrob Resist Infect Control*. 2020;9:22. https://doi.org/10.1186/s13756-020-0683-3.

32 Kramer TS, Remschmidt C, Werner S, et al. The importance of adjusting for enterococcus species when assessing the burden of vancomycin resistance: a cohort study including over 1000 cases

of enterococcal bloodstream infections. *Antimicrob Resist Infect Control*. 2018;7:133. https://doi.org/10.1186/s13756-018-0419-9.
33 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;49:1–45. https://doi.org/10.1086/599376.
34 Willems RJ, van Schaik W. Transition of Enterococcus faecium from commensal organism to nosocomial pathogen. *Future Microbiol*. 2009;4:1125–1135. https://doi.org/10.2217/fmb.09.82.
35 Tsiatis AC, Manes B, Calder C, Billheimer D, Wilkerson KS, Frangoul H. Incidence and clinical complications of vancomycin-resistant enterococcus in pediatric stem cell transplant patients. *Bone Marrow Transplant*. 2004;33:937–941. https://doi.org/10.1038/sj.bmt.1704462.
36 Fitzgibbons LN, Puls DL, Mackay K, Forrest GN. Management of gram-positive coccal bacteremia and hemodialysis. *Am J Kidney Dis*. 2011;57:624–640. https://doi.org/10.1053/j.ajkd.2010.12.013.
37 Awadh H, Chaftari A-M, Khalil M, et al. Management of enterococcal central line-associated bloodstream infections in patients with cancer. *BMC Infect Dis*. 2021;21:643. https://doi.org/10.1186/s12879-021-06328-9.
38 Bahrs C, Rieg S, Hennigs Aet al, German Clinical Study Group in Infectious Diseases DESTINi. Short-course versus long-course antibiotic treatment for uncomplicated vancomycin-resistant enterococcal bacteraemia: a retrospective multicentre cohort study. *Clin Microbiol Infect*. 2023;29:200–207. https://doi.org/10.1016/j.cmi.2022.08.023.
39 Maldonado N, Rosso-Fernández CM, Portillo-Calderón I, et al. Randomised, open-label, non-inferiority clinical trial on the efficacy and safety of a 7-day vs 14-day course of antibiotic treatment for uncomplicated enterococcal bacteraemia: the INTENSE trial protocol. *BMJ Open*. 2023;13:e075699. https://doi.org/10.1136/bmjopen-2023-075699.
40 Chuang Y-C, Lin H-Y, Chen P-Y, Lin C-Y, Wang J-T, Chang S-C. Daptomycin versus linezolid for the treatment of vancomycin-resistant enterococcal bacteraemia: implications of daptomycin dose. *Clin Microbiol Infect*. 2016;22:890.e1–890.e7. https://doi.org/10.1016/j.cmi.2016.07.018.
41 Chuang Y-C, Lin H-Y, Chen P-Y, et al. Effect of daptomycin dose on the outcome of vancomycin-resistant, daptomycin-susceptible Enterococcus faecium bacteremia. *Clin Infect Dis*. 2017;64:1026–1034. https://doi.org/10.1093/cid/cix024.
42 Chuang Y-C, Lin H-Y, Chen P-Y, et al. Survival of patients with vancomycin-resistant Enterococcus faecium bacteremia treated with conventional or high doses of daptomycin or linezolid is associated with the rate of bacterial clearance. *Crit Care Med*. 2018;46:1634–1642. https://doi.org/10.1097/CCM.0000000000003264.
43 Chuang Y-C, Wang J-T, Yang J-L, et al. The combination of daptomycin with β-lactam antibiotics is more effective than daptomycin alone for vancomycin-resistant Enterococcus faecium bloodstream infection. *J Infect Public Health*. 2022;15:1396–1402. https://doi.org/10.1016/j.jiph.2022.10.017.
44 Chuang Y-C, Tseng T-C, Wang J-T, et al. Influence of daptomycin dose and fosfomycin susceptibility on outcome of vancomycin-resistant Enterococcus faecium bloodstream infections treated with daptomycin and fosfomycin combination. *J Antimicrob Chemother*. 2022;77:1436–1443. https://doi.org/10.1093/jac/dkac023.
45 Ye J-J, Shie S-S, Cheng C-W, et al. Clinical characteristics and treatment outcomes of vancomycin-resistant Enterococcus faecium bacteremia. *J Microbiol Immunol Infect*. 2018;51:705–716. https://doi.org/10.1016/j.jmii.2017.08.025.
46 Britt NS, Potter EM, Patel N, Steed ME. Comparison of the effectiveness and safety of linezolid and daptomycin in vancomycin-resistant enterococcal bloodstream infection: a national cohort study of veterans affairs patients. *Clin Infect Dis*. 2015;61:871–878. https://doi.org/10.1093/cid/civ444.
47 Britt NS, Potter EM, Patel N, Steed ME. Effect of continuous and sequential therapy among veterans receiving daptomycin or linezolid for vancomycin-resistant Enterococcus faecium bacteremia. *Antimicrob Agents Chemother*. 2017;61:e02216-16. https://doi.org/10.1128/AAC.02216-16.
48 Hayakawa K, Martin ET, Gudur UM, et al. Impact of different antimicrobial therapies on clinical and fiscal outcomes of patients with bacteremia due to vancomycin-resistant enterococci. *Antimicrob Agents Chemother*. 2014;58:3968–3975. https://doi.org/10.1128/AAC.02943-14.
49 Suleyman G, Mahan M, Zervos MJ. Comparison of daptomycin and linezolid in the treatment of vancomycin-resistant Enterococcus faecium in the absence of endocarditis. *Infect Dis Clin Pract*. 2017;25:151–154. https://doi.org/10.1097/IPC.0000000000000482.
50 Shukla BS, Shelburne S, Reyes K, et al. Influence of minimum inhibitory concentration in clinical outcomes of Enterococcus faecium bacteremia treated with daptomycin: is it time to change the breakpoint? *Clin Infect Dis*. 2016;62:1514–1520. https://doi.org/10.1093/cid/ciw173.
51 Moise PA, Sakoulas G, McKinnell JA, et al. Clinical outcomes of daptomycin for vancomycin-resistant enterococcus bacteremia. *Clin Ther*. 2015;37:1443–1453.e2. https://doi.org/10.1016/j.clinthera.2015.04.008.
52 Chong PP, van Duin D, Bangdiwala A, et al. Vancomycin-resistant enterococcal bloodstream infections in hematopoietic stem cell transplant recipients and patients with hematologic malignancies: impact of daptomycin MICs of 3 to 4 mg/L. *Clin Ther*. 2016;38:2468–2476. https://doi.org/10.1016/j.clinthera.2016.09.011.
53 Xie O, Slavin MA, Teh BW, Bajel A, Douglas AP, Worth LJ. Epidemiology, treatment and outcomes of bloodstream infection due to vancomycin-resistant enterococci in cancer patients in a *VanB* endemic setting. *BMC Infect Dis*. 2020;20:228. https://doi.org/10.1186/s12879-020-04952-5.
54 Holmes NE, Ballard SA, Lam MMC, et al. Genomic analysis of teicoplanin resistance emerging during treatment of *VanB* vancomycin-resistant Enterococcus faecium infections in solid organ transplant recipients including donor-derived cases. *J Antimicrob Chemother*. 2013;68:2134–2139. https://doi.org/10.1093/jac/dkt130.
55 Gatti M, Rinaldi M, Giannella M, Viale P, Pea F. Usefulness of a TDM-guided approach for optimizing teicoplanin exposure in the treatment of secondary bloodstream infections caused by glycopeptide-susceptible Enterococcus faecium. *Microorganisms*. 2025;13:162. https://doi.org/10.3390/microorganisms13010162.
56 McKay GA, Beaulieu S, Arhin FF, et al. Time-kill kinetics of oritavancin and comparator agents against Staphylococcus aureus, Enterococcus faecalis and Enterococcus faecium. *J Antimicrob Chemother*. 2009;63:1191–1199. https://doi.org/10.1093/jac/dkp126.
57 Smith JR, Yim J, Raut A, Rybak MJ. Oritavancin combinations with β-Lactams against multidrug-resistant Staphylococcus aureus and vancomycin-resistant enterococci. *Antimicrob Agents Chemother*. 2016;60:2352–2358. https://doi.org/10.1128/AAC.03006-15.
58 Van Hise NW, Chundi V, Didwania V, et al. Treatment of acute osteomyelitis with once-weekly oritavancin: a two-year, multicenter, retrospective study. *Drugs Real World Outcomes*. 2020;7:41–45. https://doi.org/10.1007/s40801-020-00195-7.
59 Dahesh S, Wong B, Nizet V, Sakoulas G, Tran TT, Aitken SL. Treatment of multidrug-resistant vancomycin-resistant Enterococcus faecium hardware-associated vertebral osteomyelitis with oritavancin plus ampicillin. *Antimicrob Agents Chemother*. 2019;63:e02622-18. https://doi.org/10.1128/aac.02622-18.
60 Stewart CL, Turner MS, Frens JJ, Snider CB, Smith JR. Real-world experience with oritavancin therapy in invasive gram-positive infections. *Infect Dis Ther*. 2017;6:277–289. https://doi.org/10.1007/s40121-017-0156-z.
61 Ahiskali A, Rhodes H. Oritavancin for the treatment of complicated gram-positive infection in persons who inject drugs. *BMC Pharmacol Toxicol*. 2020;21:73. https://doi.org/10.1186/s40360-020-00452-z.
62 Johnson JA, Feeney ER, Kubiak DW, Corey GR. Prolonged use of oritavancin for vancomycin-resistant Enterococcus faecium prosthetic valve endocarditis. *Open Forum Infect Dis*. 2015;2:ofv156. https://doi.org/10.1093/ofid/ofv156.