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ORIGINAL ARTICLE

In vitro Superiority of Teicoplanin Over Vancomycin in Clinical Isolates of *Enterococcus* species

Hidemasa Akazawa [1], Shinnosuke Fukushima [1, 2], Koji Iio [3], Hideharu Hagiya [1]

[1] *Department of Infectious Diseases, Okayama University Hospital, Okayama, Japan*
[2] *Department of Bacteriology, Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[3] *Microbiology Division, Clinical Laboratory, Okayama University Hospital, Okayama, Japan*

SUMMARY

Background: **Enterococci are clinically important pathogens exhibiting intrinsic and acquired resistance to multiple antimicrobial classes. Vancomycin (VCM) and teicoplanin (TEIC) are glycopeptide antibiotics used in cases of β-lactam intolerance or resistance, yet TEIC is less frequently recommended in the guidelines despite its favorable safety profile. This study aimed to compare the *in vitro* activity of VCM and TEIC against clinical *Enterococcus* isolates by analyzing minimum inhibitory concentration (MIC) distributions.**

Methods: **Between July 2024 and March 2025, 552 *Enterococcus* isolates were collected at Okayama University Hospital. MICs were determined using the microdilution method.**

Results: **Among the 551 isolates, 370 (67%) were *E. faecalis*, 117 (21%) were *E. faecium*, 31 (6%) were *E. avium*, 21 (4%) were *E. casseliflavus*, and 12 (2%) were *E. gallinarum*. Cumulative MIC distributions revealed notably lower MICs for TEIC compared to VCM in *Enterococcus faecalis*, *Enterococcus casseliflavus*, and *Enterococcus gallinarum*, while *Enterococcus faecium* and *Enterococcus avium* showed comparatively equivalent MIC profiles. Particularly, the MIC_{50} and MIC_{90} values for VCM in *E. faecalis* (1 and 2 μg/mL, respectively) were substantially higher than those for TEIC (0.125 and 0.25 μg/mL), which remained considerably below the established antimicrobial susceptibility breakpoint. The MIC_{50} and MIC_{90} values of VCM against *E. faecium* were both 1 μg/mL, whereas those of TEIC were 0.5 μg/mL and 1 μg/mL, respectively.**

Conclusions: **These findings suggest TEIC may provide a therapeutic advantage in the management of selected enterococcal infections. Further clinical investigations to validate its role in treatment strategies for enterococcal infections are warranted.**

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Correspondence:
Hideharu Hagiya, MD, PhD
Department of Infectious Diseases
Okayama University Hospital 2-5-1 Shikata-cho
Kitaku, Okayama, 700-8558
Japan
Phone: +81 86-235-7342
Fax: +81-86-235-7345
Email: hagiya@okayama-u.ac.jp

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INTRODUCTION

Enterococcus species represent clinically significant pathogens that frequently cause common infectious diseases, such as urinary tract infections, cholecystitis, cholangitis, and bacteremia [1]. Mortality rates of enterococcal bloodstream infections are consistently high, ranging from 14.3% to 32.3% [2], necessitating optimized antimicrobial management. Enterococci exhibit intrinsic resistance to an array of antimicrobials, such as

cephalosporins, aminoglycosides, trimethoprim-sulfamethoxazole, and macrolides. In addition, they can acquire resistance to fluoroquinolones and tetracyclines as well [3], complicating the therapeutic management of patients.

Glycopeptides, including vancomycin (VCM) and teicoplanin (TEIC), are the preferred therapeutic options for patients with β-lactam intolerance or infections caused by penicillin-resistant isolates [4]. Clinical guidelines recommend VCM over TEIC for enterococcal infections due to the more robust evidence supporting better VCM efficacy. However, VCM frequently induces adverse effects, particularly nephrotoxicity [5], whereas TEIC is associated with a more favorable safety profile. In fact, TEIC is broadly used in European and Asia-Pacific medical situations, primarily owing to its extended pharmacokinetic half-life, which facilitates once-daily dosing regimens [6].

Recent literature increasingly supports the clinical efficacy of TEIC compared to VCM for enterococcal bloodstream infections, including infective endocarditis [7-9]. However, microbiological evidence demonstrating the *in vitro* superiority of TEIC remains incompletely elucidated. We aimed to evaluate the potential superiority of TEIC over VCM by analyzing their respective *in vitro* minimum inhibitory concentration (MIC) profiles.

MATERIALS AND METHODS

From July 2024 to March 2025, we collected microbiological data on *Enterococcus* species from the clinical microbiology laboratory of Okayama University Hospital, Japan. The need for informed consent was waived because the data were fully anonymized without any clinical information. The MICs of VCM and TEIC were determined by the microdilution method using Dry Plate Eiken (Eiken Chemical Co., Ltd, Tokyo, Japan) with the following MIC points: ≤ 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, and 16 μg/mL. We followed the manufacturer's instructions for the preparation of the bacterial suspension and MIC measurements. Data were stratified by species level and expressed in cumulative MIC distribution curves, with MIC_{50} and MIC_{90} values representing the antimicrobial concentrations that inhibited growth of 50% and 90% of the tested isolates, respectively. Based on the MIC data, we generated cumulative MIC distribution curves for each representative *Enterococcus* species.

RESULTS

Of the total 551 Enterococcus isolates, *E. faecalis* accounted for the majority at 67% (n = 370), followed by *E. faecium* at 21% (n = 117), *E. avium* at 6% (n = 31), *E. casseliflavus* at 4% (n = 21), and *E. gallinarum* at 2% (n = 12). For *E. faecalis*, which constituted the predominant isolates (n = 370; 67.0%), VCM MICs ranged from 0.5 to 2 μg/mL in a majority (99.2%) of isolates (1.4% at 0.5 μg/mL, 80.5% at 1 μg/mL, and 17.3% at 2 μg/mL), whereas TEIC MICs were ≤ 0.25 μg/mL in 99.1% of the isolates (1.9% at ≤ 0.06 μg/mL, 69.7% at 0.125 μg/mL, and 26.5% at 0.25 μg/mL) (Figure 1A). The MIC_{50} and MIC_{90} values for VCM in *E. faecalis* were 1 and 2 μg/mL, respectively, whereas those for TEIC were 0.125 and 0.25 μg/mL, which are substantially below the established susceptibility breakpoint. In contrast, among 117 (21.2%) *E. faecium* isolates, the VCM MIC distributed from 0.25 μg/mL, with 95.7% of the isolates demonstrating MICs ≤ 1 μg/mL (4.3% at 0.25 μg/mL, 28.2% at 0.5 μg/mL, and 63.2% at 1 μg/mL) (Figure 1B). The MIC_{50} and MIC_{90} for VCM in *E. faecium* were both 1 μg/mL. The TEIC MIC distribution for *E. faecium* exhibited higher values compared to *E. faecalis*, ranging from 0.25 to 1 μg/mL (26.5% at 0.25 μg/mL, 56.4% at 0.5 μg/mL, and 12.8% at 1 μg/mL), yielding MIC_{50} and MIC_{90} values of 0.5 and 1 μg/mL, respectively.

Cumulative MIC distribution curves of other *Enterococcus* species (31 *E. avium*, 21 *E. casseliflavus*, and 12 *E. gallinarum*) are presented in Figure 2. All *E. avium* isolates had MICs ≤ 0.5 μg/mL for both VCM and TEIC, demonstrating minimal MIC differentials; MIC_{50} and MIC_{90} were both 0.5 μg/mL for VCM, and 0.25 μg/mL and 0.5 μg/mL for TEIC. In contrast, *E. casseliflavus* and *E. gallinarum* showed larger differences in the MIC distribution patterns, resembling those observed in *E. faecalis*. MIC_{50} and MIC_{90} for VCM against *E. casseliflavus* (both 4 μg/mL) were significantly greater than those of TEIC (both 0.5 μg/mL). Similarly, MIC_{50} and MIC_{90} for VCM against *E. casseliflavus* (4 μg/mL and 8 μg/mL, respectively) were also considerably higher than those of TEIC (both 0.5 μg/mL).

DISCUSSION

MIC values for TEIC were considerably lower in *E. faecalis*, as well as *E. casseliflavus* and *E. gallinarum*. Less pronounced but still comparatively lower MIC values were also observed in *E. faecium* and *E. avium*. The clinical significance of these differentials within the susceptible range necessitates further clinical investigation. Nevertheless, our findings suggest a therapeutic advantage of TEIC in the treatment of patients with severe or refractory enterococcal infections.

When considering its clinical application, species-stratified considerations may be warranted. Regarding *E. faecalis*, a growing body of evidence has accumulated. Clinical efficacy of TEIC monotherapy for the treatment of *E. faecalis* infective endocarditis was suggested in retrospective single-facility data [7]. Also, TEIC treatment showed comparable lower in-hospital mortality, reduced duration of hospitalization, and equivalent relapse and one-year mortality outcomes compared to ampicillin plus ceftriaxone combination regimen among

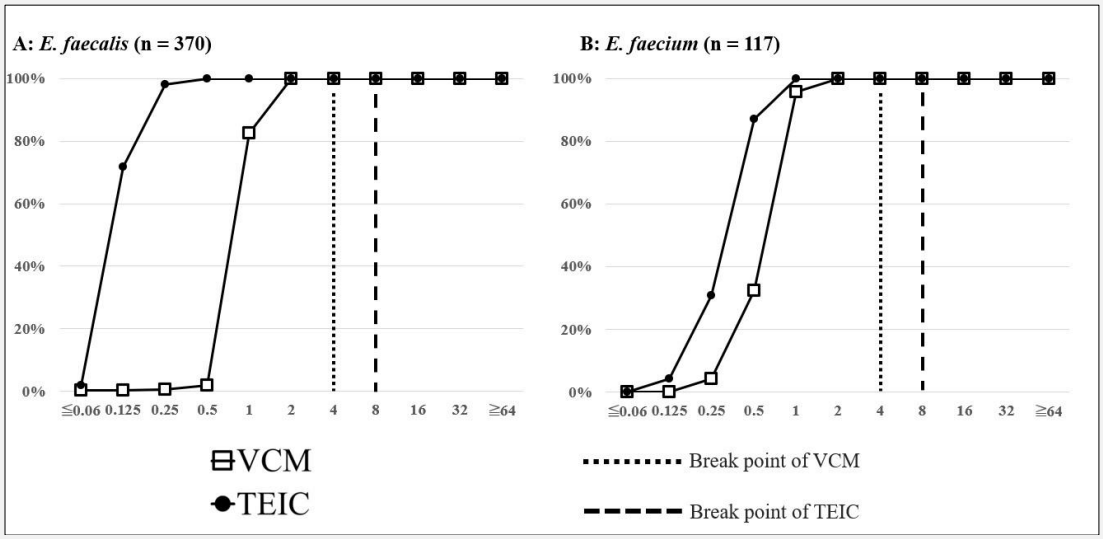

Figure 1. Cumulative MIC distribution curves for *Enterococcus faecalis* and *Enterococcus faecium*.

MIC minimum inhibitory concentration. Breakpoints were based on the guidelines of the Clinical and Laboratory Standards Institute (CLSI, M100, 35th edition). The fine dashed line indicates the vancomycin breakpoint, and the coarse dashed line indicates the teicoplanin breakpoint.

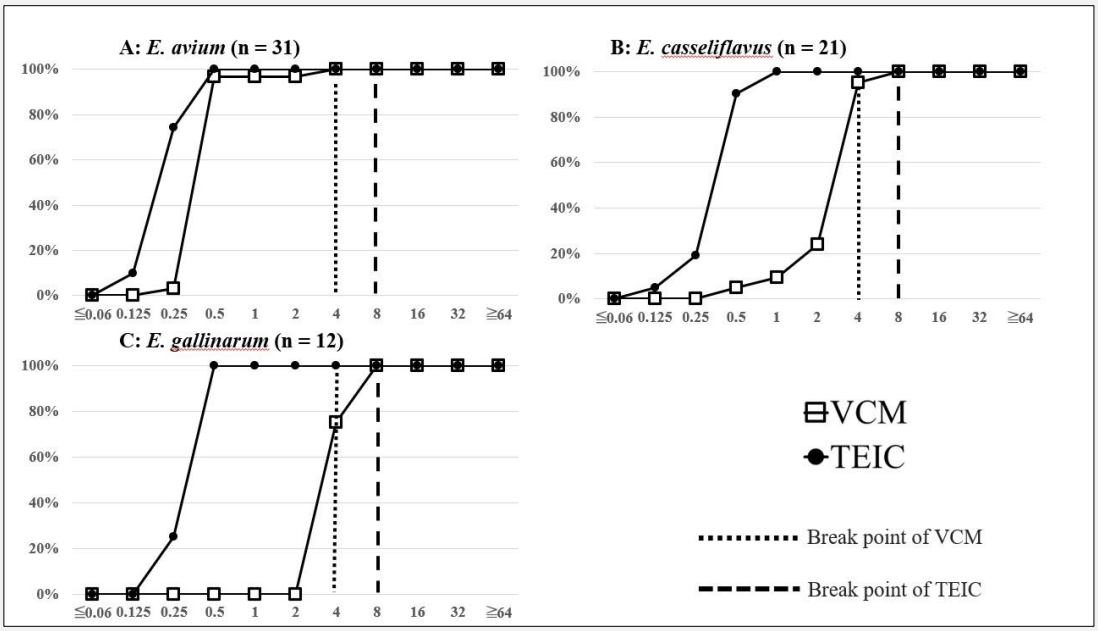

Figure 2. Cumulative MIC distribution curves for other *Enterococcus* species.

MIC minimum inhibitory concentration. Breakpoints were based on the guidelines of the Clinical and Laboratory Standards Institute (CLSI, M100, 35th edition). The fine dashed line indicates the vancomycin breakpoint, and the coarse dashed line indicates the teicoplanin breakpoint.

patients with *E. faecalis* infective endocarditis [10]. Comparative data for *E. faecium* infections, although less abundant, have been reported in the literature. A propensity score-adjusted comparative study demonstrated that TEIC exhibited non-inferiority to VCM in the treatment of *E. faecium* bacteremia, with the additional benefit of fewer incidences of acute kidney injury [11]. A posthoc analysis of nationwide Korean surveillance revealed no significant differences in 7-day and 30-day in-hospital mortality rates between patients treated with VCM and TEIC [8]. Our *in vitro* findings corroborate these clinical observations, potentially supporting expanded clinical applications of TEIC in future therapeutic protocols.

A comprehensive delineation of the differential antimicrobial activities between VCM and TEIC needs to be discussed. Glycopeptide antimicrobials are taxonomically classified into VCM and lipoglycopeptides, the latter encompassing TEIC, telavancin, dalbavancin, and oritavancin. Distinguished from other antimicrobial classes, these compounds operate as substrate binders rather than active-site enzyme inhibitors, functioning by obstructing the cross-linkage formation in bacterial cell-wall peptidoglycan layers through specific binding to the D-alanyl-D-alanine terminus of the lipid II monomeric structure. Despite the ubiquitous expression of lipid II substrate across most bacterial species, the inherent physicochemical attributes of glycopeptide molecular architectures significantly impede their translocation through the outer membrane of Gram-negative bacterial species, consequently preventing interaction with the lipid II molecular target. Thus, these agents exhibit exclusive efficacy against Gram-positive organisms.

The differential molecular architecture and distinct antimicrobial mechanisms of action likely elucidate the observed lower MIC for TEIC compared to VCM. VCM interacts with the lipid II layer through the formation of back-to-back dimers (vancosamine-vancosamine [V-V]), or noncovalent self-association of molecules [12], which demonstrate superior *in vitro* antimicrobial activity compared to monomeric vancomycin. VCM additionally antagonizes peptidoglycan remodeling processes. TEIC possesses a distinctive hydrophobic substituent that substantially differentiates its physicochemical properties from those of VCM. While TEIC, analogously to VCM, exerts its antimicrobial activity via binding to the D-alanyl-D-alanine moiety and sequestration of the lipid II substrate, thereby inhibiting bacterial peptidoglycan biosynthesis [13], its structural characteristics negatively impact the dimerization phenomenon critical for enhanced target affinity in glycopeptides. In compensation, the lipophilic moiety of TEIC interacts with the phospholipid bilayer of the bacterial cytoplasmic membrane, facilitating localization, or membrane anchoring, in proximity to the lipid II substrate, thus augmenting antimicrobial efficacy through this alternative molecular interaction [14].

Limitation

The limitations of this investigation are as follows. First, due to the limited number of isolates examined and the single-facility nature of the study, the generalizability of our findings requires further validation across multiple centers. Also, we did not exclude duplicates or more isolates from a single patient, which may have resulted in collection bias. Second, the potential influence of *van* genes on the study outcomes was not evaluated at the molecular level. Production of *van* genes facilitates the synthesis of alternative aminoacidic residues in the peptidoglycan structure, modifying the original D-alanyl-D-alanine terminus to alternative configurations such as D-alanyl-D-lactate or D-alanyl-D-serine. Third, in the absence of complementary clinical data, our findings necessitate corroboration through prospective clinical investigations prior to therapeutic practice. Fourth, no remarkable MIC gaps between VCM and TEIC were observed in *E. faecium*, which is becoming increasingly prevalent as *E. faecalis* and associated with greater clinical significance [15]. Thus, the clinical superiority of TEIC for *E. faecium* infections needs to be evaluated with particular vigilance and careful consideration.

CONCLUSION

We have demonstrated substantially lower MIC values for TEIC compared to VCM against clinical isolates of *Enterococcus* species. TEIC potentially represents a more efficacious antimicrobial agent against enterococcal infections; however, further acquisition of clinical evidence is warranted to validate these preliminary observations.

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This study did not involve any experiments on human participants or animals conducted by the authors.

Data Availability:
The data in detail are available from the corresponding author upon reasonable request.

Declaration of Generative AI in Scientific Writing:
None to declare.

Declaration of Interest:
The authors declare that they have no conflicts of interest.

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