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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (K CLAEYS AND A VEGA, SECTION EDITORS)

Novel Strategies for the Management of Vancomycin-Resistant Enterococcal Infections

German A. Contreras[1,2] · Jose M. Munita[3,4] · Cesar A. Arias[1,2,4,5,6,7,8]

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Abstract

Purpose of Review Vancomycin-resistant enterococci (VRE) are important nosocomial pathogens that commonly affect critically ill patients. VRE have a remarkable genetic plasticity allowing them to acquire genes associated with antimicrobial resistance. Therefore, the treatment of deep-seated infections due to VRE has become a challenge for the clinician. The purpose of this review is to assess the current and future strategies for the management of recalcitrant deep-seated VRE infections and efforts for infection control in the hospital setting.

Recent Findings Preventing colonization and decolonization of multidrug-resistant bacteria are becoming the most promising novel strategies to control and eradicate VRE from the hospital environment. Fecal microbiota transplantation (FMT) has shown remarkable results on treating colonization and infection due to *Clostridiodes difficille* and VRE, as well as to recover the integrity of the gut microbiota under antibiotic pressure. Initial reports have shown the efficacy of FMT on reestablishing patient microbiota diversity in the gut and reducing the dominance of VRE in the gastrointestinal tract. In addition, the use of bacteriophages may be a promising strategy in eradicating VRE from the gut of patients. Until these strategies become widely available in the hospital setting, the implementation of infection control measures and stewardship programs are paramount for the control of this pathogen and each program should provide recommendations for the proper use of antibiotics and develop strategies that help to detect populations at risk of VRE colonization, prevent and control nosocomial transmission of VRE, and develop educational programs for all healthcare workers addressing the epidemiology of VRE and the potential impact of these pathogens on the cost and outcomes of patients. In terms of antibiotic strategies, daptomycin has become the standard of care for the management of deep-seated infections due to VRE. However, recent evidence indicates that the efficacy of this antibiotic is limited, and higher (10–12 mg/kg) doses and/or combination with β-lactams is needed for therapeutic success. Clinical data to support the best use of daptomycin against VRE are urgently needed.

Summary This review provides an overview of recent developments regarding the prevention, treatment, control, and eradication of VRE in the hospital setting. We aim to provide an update of the most recent therapeutic strategies to treat deep-seated infections due to VRE.

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✉ Cesar A. Arias
caa22@cantab.net; cesar.arias@uth.tmc.edu

Jose M. Munita
Jose.M.Munita@uth.tmc.edu

[1] Division of Infectious Diseases and Center for Antimicrobial Resistance and Microbial Genomics (CARMiG), UTHealth McGovern Medical School, Houston, TX, USA

[2] Department of Internal Medicine, UTHealth McGovern Medical School, Houston, TX, USA

[3] Millennium Initiative for Collaborative Research on Bacterial Resistance (MICROB-R), Santiago, Chile

[4] Genomics and Resistant Microbes Group, Facultad de Medicina Clinica Alemana, Universidad del Desarrollo, Santiago, Chile

[5] Department of Microbiology and Molecular Genetics, UTHealth McGovern Medical School, Houston, TX, USA

[6] Center for Infectious Diseases, UTHealth School of Public Health, Houston, TX, USA

[7] Molecular Genetics and Antimicrobial Resistance Unit—International Center for Microbial Genomics, Universidad El Bosque, Bogotá, Colombia

[8] University of Texas Health Science Center, 6431 Fannin St. MSB 2.112, Houston, TX 77030, USA

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Introduction

Vancomycin-resistant enterococci (VRE) are important nosocomial pathogens that commonly affect critically ill patients who have received multiple courses of antibiotics and have been hospitalized for prolonged periods. These organisms are particularly important as causative agents of infective endocarditis (IE), catheter-related bloodstream infections (BSIs), urinary tract infections (UTIs), and bacteremia of unknown source. The majority of VRE are *Enterococcus faecium*, an emergent opportunistic pathogen characterized by its remarkable ability to acquire antibiotic-resistant determinants and adapt to the hospital environment. In general, enterococci can be found in the gastrointestinal tract of most mammals and have evolved to become first-rate nosocomial pathogens due to their remarkable genetic plasticity, which facilitates adaptation and their establishment and dissemination across hospital settings. The ability of enterococci to colonize the gastrointestinal (GI) tract of hospitalized humans for long periods is a crucial factor that influences the development and transmission of drug resistance, becoming a continuous threat in the hospital setting and posing major therapeutic challenges. Here, we review current and future strategies for the management of recalcitrant deep-seated VRE infections.

Therapeutic Strategies for the Management of Vancomycin-Resistant Enterococci

The development of VRE infections usually occur after establishment of colonization of the GI tract with subsequent translocation to the bloodstream of adjacent tissues (i.e., intra-abdominal infections). In this process, colonization of indwelling devices is another major source of deep-seated VRE infections. Thus, successful management of VRE infections requires addressing three important components of the colonization–infection dynamics, which are as follows: (a) preventing colonization, (b) development of infection and avoiding in-hospital transmission, and (c) appropriate treatment of deep-seated VRE infections.

Preventing Colonization

The first and foremost step to drive a persistent source of infection in any microorganism is the establishment of a persistent reservoir. The gut microbiota of healthy individuals is characterized by a wide bacterial diversity (mainly composed of *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*, among others). The composition of this microbiota is highly influenced by geographical location, infections, diet, and antibiotic treatment [1]. Enterococci are part of the gut microbiota but only in a small portion (ca < 1%) in healthy individuals. However, the proportion of enterococci in the gut can markedly change under the influence of antibiotic therapy, particularly associated with the use of antimicrobials that have anti-anaerobic activity. Several studies—both in animals and humans—have shown that antibiotic use promotes and maintains a high density of enterococci (including VRE) in the gut, facilitating the transmission of these microorganisms [2, 3]. Indeed, persistent VRE colonization has been shown to be a major risk factor for invasive infections, especially among vulnerable populations [4, 5].

Given the clinical importance of the GI tract as source for infection, colonization, and the dynamics of VRE infections, GI decolonization has been proposed as a potential tool to curtail infections and transmission of these pathogens. Several modalities of decolonization have been used and include (a) selective GI decontamination, (b) use of probiotics, and (c) fecal microbiota transplantation (FMT). Of these three methods, the latter appears to be the most promising strategy. Indeed, the most robust evidence of FMT to decrease colonization and infections has been among patients with *Clostridiodes difficile* infections, resulting in an increase of microbiota diversity, decrease in the number and diversity of antimicrobial-resistant genes in the environment (including vancomycin-resistant genes), and recovery of the intestinal barrier [6–8].

For enterococci, a study by Stripling et al. showed that FMT given via nasogastric tube in a patient with a history of heart–kidney transplant and recurrent *C. difficile* and VRE infections (with VRE fecal dominance) was able to reestablish microbiota diversity in the gut and reduce the dominance of VRE in the patient's colon. Furthermore, this strategy was able to prevent *C. difficile* and VRE infections one year after the procedure [9]. Similarly, Dubberke et al. showed that among 30 patients who received one or two doses of microbiota-based drug via enema from a healthy volunteer, 19 cleared VRE at 7 days post-treatment and 8 cleared VRE by 6 months of follow-up; clearance of colonization was unsuccessful in three subjects. Of note, patients who had repetitive positive stool cultures on re-testing after initial administration of the FMT had a history of receiving antimicrobials after the procedure [10]. Currently, there are two ongoing clinical trials aimed to evaluate whether fecal microbiota transplantation is safe and effective to eradicate intestinal colonization of VRE and carbapenem-resistant *Enterobacteriaceae*. Thus, FMT seems like a promising tool to decrease VRE colonization in vulnerable patients.

Another novel strategy that has emerged during the last years is the use of bacteriophages for the eradication of antibiotic-resistant strains. A number of groups have reported the isolation of phages from sewage, compost, and water channel with in vitro capacity to eradicate VRE strains [11–14]. Haddad et al. isolated five different types of phages from the stool samples of 9 hematopoietic cell transplant recipients that had the capacity to eradicate VRE strains in vitro and in vivo. Moreover, it appears that the efficacy of VRE eradication was increased when a number of phages were combined [15]. More recently, using an *Enterococcus faecalis* mouse peritonitis model, Gelman et al. showed that the mix of two lytic bacteriophages was associated with a lower mortality as compared to antibiotic therapy (ampicillin). Furthermore, the reduction in mortality was striking when phage therapy was associated to antibiotic therapy [16].

Hospital Transmission and Infection Control

Hospital-acquired infections are common complications in the hospital setting, and, independent of the type of the infection, these complications are associated with high morbidity and mortality, with an estimated cost ranging from US$ 28 to 45 billion. In the specific case of VRE, Putcher et al. showed that the median overall cost of a VRE infection was significantly higher than that of VSE infection (€57,675 vs. €38,344; $p = 0.030$). The most striking difference between these two groups in terms of cost was the use of medications for each infection (€6030 vs. €2801 for VRE vs VSE, respectively; $p = 0.008$), availability of nursing staff (€8956 vs. €4621 for VRE and VSE, respectively; $p = 0.032$), medical products (€3312 vs. €1838, respectively; $p = 0.020$), and use of assistant medical technicians (€3766 vs. €2474, respectively; $p = 0.023$) [17].

In order to gain important insights into the dynamics of colonization and infection by VRE, researchers have developed mathematical models to characterize the main actors in this process. Among the most important variables included in these models are the following: (a) natural history and duration of colonization and infection, (b) transmission routes and their implications on the spread of pathogens (medical staff and environment), and (c) behaviors and geography (Fig. 1). The value of this conceptual framework has relied on the possibility of evaluating the magnitude of several interventions on the outcome of VRE infections and drive resources to areas where such intervention will produce the best benefit [18]. For instance, Frakking et al. showed that the use of standard infection control guidelines was not sufficient to control a VRE outbreak that affected a hospital for two years in the Netherlands [19]. In fact, the control of this outbreak was only possible when each one of the three above-mentioned components was studied in detail, permitting the investigators to apply more extended infection control measures than those described in current guidelines (Table 1). Antibiotic stewardship is an important component for the control of VRE in the hospital setting, and multiple studies have strongly demonstrated that antimicrobial exposure is an important risk factor for VRE increased colonization and/or infection. Therefore, each institution should provide information and directions for antibiotic use and when such prescription should be discouraged. Indeed, it is particularly important to have proper control of antimicrobials with activity against anaerobes, like clindamycin and metronidazole, as well as cephalosporins. For instance, Ozorowski et al. showed that after introducing an antibiotic policy characterized by monitoring and recommending antimicrobials for specific infections in their hospital formulary, they were able to reduce antibiotic consumption by 30% and decreased the rate of VRE infections to zero in their hospital [20].

Strategies for the Treatment of Deep-Seated VRE Infections

E. faecalis and *E. faecium* are the most common species associated with nosocomial infections. In general, *E. faecium* are the species that more often exhibit multidrug resistance, including to ampicillin and vancomycin, and high-level resistance to aminoglycosides, linezolid, and daptomycin. Thus, *E. faecium* often cause recalcitrant infections with some deemed untreatable in severely ill patients [21].

There is no optimal therapy for the treatment of vancomycin and ampicillin-resistant *E. faecium* infections. In fact, only linezolid is currently approved by the Food and Drug administration (FDA) for the treatment of VRE infections, but concerns regarding its bacteriostatic activity and recent data suggesting it maybe suboptimal to manage VRE bacteremia (see subsequent texts) have markedly decreased linezolid use against VRE [22]. Daptomycin, a cyclic lipopeptide with in vitro bactericidal activity against VRE, has become the cornerstone for the management of severe infections caused by these organisms, despite lacking an FDA approval for this indication.

Several small retrospective studies have attempted to compare the outcomes of patients with VRE bacteremia treated with linezolid or daptomycin, and at least three meta-analyses have pooled these results [23–25]. Although results from some of those retrospective efforts suggested better outcomes with linezolid; detailed analyses of the data made evident most of the studies had an obvious imbalance among groups. Indeed, patients receiving daptomycin were frequently more severely ill, with higher rates of hematopoietic stem-cell transplants, neutropenia, or shock. More recently, larger studies using propensity analyses have contributed to further clarify the issue. The largest retrospective cohort study attempting to compare the efficacy of linezolid vs daptomycin in the treatment of VRE bacteremia included 644 patients. In this study, patients were treated with daptomycin (average

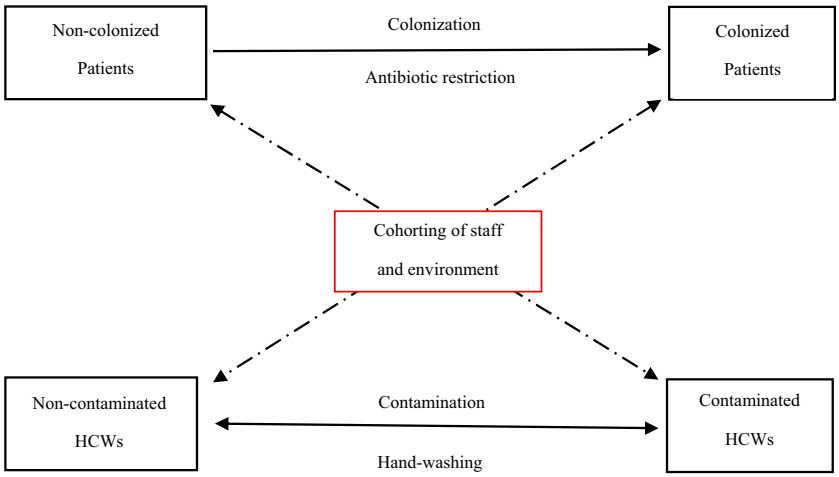

Fig. 1 Flow of transmission between patient–health care worker and environment

dose 5.93 mg/kg [IQR 5.33–6.10 mg/kg]) or linezolid (600 mg twice daily). The clinical outcomes derived from this cohort study suggested that treatment with daptomycin was associated with a significant decrease in 7- and 30-day mortality, less microbiologic failure, and shorter duration of bacteremia when compared to linezolid [26]. In a subsequent study by the same group, patients who were started on linezolid and then switched to daptomycin had lower mortality than those remaining on linezolid (RR 1.29; 95% CI, 1.03 to 1.63; $p = 0.021$), further suggesting a potential benefit of daptomycin [27]. Moreover, this difference in mortality was mainly driven by patients with infective endocarditis (RR 1.20; 95% CI, 1.02 to 1.41; $p = 0.024$), suggesting the benefit of daptomycin is particularly important in deep-seated VRE infections [27].

After the publication of these retrospective studies, daptomycin has become a first-line drug for severe VRE infections. However, the use of daptomycin is hampered by uncertainties in the appropriate dose for VRE infections and major issues in susceptibility testing, including the poor reproducibility of the MIC test methods and the recent change in susceptibility breakpoints [28]. Indeed, the current CLSI breakpoint has included a category of "susceptible dose-dependent," which includes isolates with MICs > 1 and ≤ 4 μg/ml, although the data supporting this recommendation are not robust [29]. When MICs are tested under stringent conditions, clinical data have suggested that treatment of strains with MICs close to 4 μg/ml (which was the former cut-off for susceptibility) was associated with poorer efficacy in terms of microbiological eradication [30].

In vitro data using a simulated endocardial vegetation model has shown that daptomycin doses of < 10 mg/kg resulted in lack of efficacy against strains of *E. faecium*. Moreover, an *E. faecium* strain exposed to 6 and 8 mg/kg, but not 12 mg/kg, developed reduced susceptibility to daptomycin with a change in MIC from 0.5 to 16 mg/ml [31]. Only doses of 10 and 12 mg/kg resulted in sustained reduction in colony counts at 96 h and less likelihood of developing of resistance [31, 32]. These data are supported by some limited clinical studies indicating patients treated with high doses of daptomycin (≥ 9 mg/kg) have better outcomes than those treated with lower doses [33]. Indeed, Britt and colleagues stratified the outcomes of 911 patients with VRE bacteremia treated with daptomycin by the daptomycin daily dose (6, 8, or ≥ 10 mg/kg) and reported subjects receiving high dose (i.e., ≥ 10 mg/kg) had improved survival and higher rates of microbiological clearance (34). Similarly, Chuang et al. analyzed 112 patients with VRE bacteremia receiving daptomycin and reported lower rates of 14-day overall mortality in those receiving doses ≥ 9 mg/kg as compared to those prescribed lower daily doses (35). Thus, the available evidence suggests that, when using daptomycin monotherapy, doses of 10–12 mg/kg should be used in deep-seated infections.

Daptomycin and β-Lactam Combinations

A series of reports (mostly small case series) and in vitro data have shown that the combination of daptomycin plus β-lactams (e.g., ampicillin, ceftaroline, and ertapenem) has a potential role for the management of recalcitrant enterococcal infections [34–40]. A recent retrospective cohort study found that patients receiving high-dose of daptomycin (defined as ≥ 9 mg/kg) plus a β-lactam exhibited a better survival than those receiving low-dose daptomycin, low-dose daptomycin plus β-lactam, or high-dose of daptomycin [41]. It appears that the mechanistic basis for this effect is related to the "see-saw" effect in which strains that develop increased MICs to daptomycin become more susceptible to certain β-lactams. Although the choice of the best β-lactam is unclear, the best results seem to be associated with the use of ampicillin, ceftaroline, and ertapenem. In fact, in a simulated endocardial vegetation (SEV) model, Kebriaei et al. were able to show that the daptomycin MIC was reduced by 64, 8, and 4 fold when daptomycin was used in combination with ceftaroline,

Table 1 Recommended strategies for infection control of vancomycin-resistant enterococci[a]

Situation	Strategy
No history of VRE outbreak	-At least quarterly hospital-wide screening for VRE of patients admitted for at least four days
	-Screening of patients who had been admitted from other institutions
Identification of single VRE-positive patient	-Contact isolation precautions and electronic labelling of VRE-positive patients (and contacts)
	-Screening of contact patients, e.g., by four to five separate cultures, last one at least seven days after (possible) exposure
	-Inform patient and contact
Suspected outbreak	-Type VRE strains (in own hospital or reference center)
	-Categorize patients: VRE-positive, contact/possible VRE-positive, VRE-negative
	-Cohort isolation
	-Actions to increase awareness of standard hygiene measures and improve compliance
	-(Audits of) Adherence to cleaning protocol
Defined outbreak	-Ward closure for new admissions
	-Facilitate (large-volume) screening possibilities in laboratory, e.g., by polymerase chain reaction, pooling of patients
	-Optimize information and communication technology support
	-Inform hospital personnel (management, medical staff, nursing personnel, members of communication, safety, housekeeping, and logistic departments) and mobilize for cooperation
	-Inform patients, surrounding hospitals, public health agency, and the public
	-Give feedback on achievements during the outbreak
	-Increased surveillance, choose at least one strategy: -intensified screening of high-risk wards, -intensified screening of patients admitted for at least four days, -intensified hospital-wide screening of all patients
	-Initiation of outbreak management team
	-Screen all patients on hospital ward of VRE-positive patient, screen high-risk wards
	-Risk of transmission to multiple persons or wards: hospital-wide screening for VRE of patients admitted for at least four days
	-Notification to public health agency and/or healthcare inspectorate
	-Environmental cultures
	-Disinfection of rooms of VRE-positive patients with hydrogen peroxide vapor
	-Disinfection of wards where VRE transmission occurs, e.g., with hydrogen peroxide vapor
	-Evaluate sanitary conditions and cleaning of patient rooms and other vehicles of possible transmission
	-Develop antibiotic policy
Ongoing transmission on ward, despite measures	-More than contact isolation precautions alone, e.g., strict precautions, for increased awareness
	-Contact precautions and electronic labelling in all (VRE-positive and VRE-negative) patients on specific ward
	-Introduction of VRE quarantine ward
	-Precautions specific for patient group of a particular ward
After recent control of VRE outbreak	-Outbreak in one ward: periodical (e.g., monthly) ward screening for VRE of patients admitted for at least four days
	-Outbreak in multiple wards: intensified periodical (e.g., monthly) hospital-wide screening for VRE of patients admitted for at least four days. Gradually decline frequency

[a] Adapted from Frakking et al. [19] with permission from Elsevier

ampicillin, and ertapenem, respectively. Moreover, the use of the combination of DAP and β-lactams seems to also work when lower doses of DAP are used [41].

Dual β-Lactam Combinations

The initial description of the effectiveness of this combination was performed in 1995 when Mainardi et al. showed that amoxicillin and cefotaxime had a synergistic effect when tested in vitro against *E. faecalis* [42]. This synergism was explained by the different affinity of these two antibiotics for the penicillin-binding proteins (PBPs) of *E. faecalis*. A subsequent observational clinical study from Spain showed that the combination of ceftriaxone and ampicillin had similar efficacy against *E. faecalis* in infective endocarditis compared to standard therapy (ampicillin plus an aminoglycoside). Indeed, although no significant differences in mortality were observed between groups, the β-lactam and aminoglycoside combination was associated with a significant increase in renal toxicity [43, 44]. Of note, this combination does not seem to be effective for *E. faecium* strains that exhibit high levels of ampicillin resistance. Based on these data, the Infectious Diseases Society of America (IDSA) guidelines on adult infective endocarditis recommend double β-lactam therapy as one of the first-line treatment options for endocarditis involving a native or prosthetic valve or other prosthetic material caused by *E. faecalis* strains susceptible to penicillin and gentamicin [45].

Recommended Management

The available evidence suggests that daptomycin should be used as front-line therapy against vancomycin-resistant *E. faecium* causing severe infections. Due to the lack of reliable measurement on MIC, daptomycin should be used in high doses (10–12 mg/kg), regardless of the MIC level within the susceptibility range ($\leq$ 4 μg/ml). Nonetheless, in severe disease affecting critically ill patients and those with severe compromise of the immune system (e.g., neutropenia), combination with β-lactams (i.e., ampicillin) should be considered as definitive therapy. Robust clinical data to support these recommendations are still weak and urgently needed.

Conclusions

Screening, isolation, and decolonization are the main strategies that reduce the spread of VRE and decrease the subsequent risk of infection. Decolonization by FMT seems the most promising, although the clinical evidence for VRE is still lacking and ongoing clinical trials would shed some light on the use of this strategy. The generation of clinical data for the use of daptomycin in the treatment of VRE infections is of paramount importance. Novel genomic tools for susceptibility testing may help in determining whose patients will benefit from combination therapies vs monotherapy.

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Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Greenhalgh K, Meyer KM, Aagaard KM, Wilmes P. The human gut microbiome in health: establishment and resilience of microbiota over a lifetime. Environ Microbiol. 2016;18:2103–16.
2. Donskey CJ, Chowdhry TK, Hecker MT, Hoyen CK, Hanrahan JA, Hujer AM, et al. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. N Engl J Med. 2000;343:1925–32.
3. Paterson DL, Muto CA, Ndirangu M, Linden PK, Potoski BA, Capitano B, et al. Acquisition of rectal colonization by vancomycin-resistant Enterococcus among intensive care unit patients treated with piperacillin-tazobactam versus those receiving cefepime-containing antibiotic regimens. Antimicrob Agents Chemother. 2008;52:465–9.
4. Ubeda C, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, et al. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest. 2010;120:4332–41.
5. Zhang X, Top J, de Been M, Bierschenk D, Rogers M, Leendertse M, et al. Identification of a genetic determinant in clinical Enterococcus faecium strains that contributes to intestinal colonization during antibiotic treatment. J Infect Dis. 2013;207:1780–6.
6. Battipaglia G, Malard F, Rubio MT, Ruggeri A, Mamez AC, Brissot E, et al. Fecal microbiota transplantation before or after allogeneic hematopoietic transplantation in patients with hematological malignancies carrying multidrug-resistance bacteria. Haematologica. 2019. https://doi.org/10.3324/haematol.2018.198549.
7. Seekatz AM, Aas J, Gessert CE, Rubin TA, Saman DM, Bakken JS, et al. Recovery of the gut microbiome following fecal microbiota transplantation. MBio. 2014;5:e00893–14.
8. Hui W, Li T, Liu W, Zhou C, Gao F. Fecal microbiota transplantation for treatment of recurrent C. difficile infection: an updated randomized controlled trial meta-analysis. PLoS One. 2019;14:e0210016.
9. Stripling J, Kumar R, Baddley JW, Nellore A, Dixon P, Howard D, et al. Loss of vancomycin-resistant Enterococcus fecal dominance in an organ transplant patient with Clostridium difficile colitis after fecal microbiota transplant. Open Forum Infect Dis. 2015;2:ofv078.

10. Dubberke ER, Mullane KM, Gerding DN, Lee CH, Louie TJ, Guthertz H, et al. Clearance of vancomycin-resistant enterococcus concomitant with administration of a microbiota-based drug targeted at recurrent Clostridium difficile infection. Open Forum Infect Dis. 2016;3:ofw133.
11. Biswas B, Adhya S, Washart P, Paul B, Trostel AN, Powell B, et al. Bacteriophage therapy rescues mice bacteremic from a clinical isolate of vancomycin-resistant Enterococcus faecium. Infect Immun. 2002;70:204–10.
12. Rahmat Ullah S, Andleeb S, Raza T, Jamal M, Mehmood K. Effectiveness of a lytic phage SRG1 against vancomycin-resistant Enterococcus faecalis in compost and soil. Biomed Res Int. 2017;2017:9351017.
13. Otawa K, Hirakata Y, Kaku M, Nakai Y. Bacteriophage control of vancomycin-resistant enterococci in cattle compost. J Appl Microbiol. 2012;113:499–507.
14. Uchiyama J, Rashel M, Maeda Y, Takemura I, Sugihara S, Akechi K, et al. Isolation and characterization of a novel Enterococcus faecalis bacteriophage phiEF24C as a therapeutic candidate. FEMS Microbiol Lett. 2008;278:200–6.
15. Haddad LE, Mark Stibich M, Chemaly RF. The successful recovery of bacteriophages with activity against vancomycin-resistant enterococci (VRE) from stool samples of hematopoietic cell transplant (HCT) recipients. Open Forum Infect Dis. 2017;4(Suppl 1):S288.
16. Gelman D, Beyth S, Lerer V, Adler K, Poradosu-Cohen R, Coppenhagen-Glazer S, et al. Combined bacteriophages and antibiotics as an efficient therapy against VRE Enterococcus faecalis in a mouse model. Res Microbiol. 2018;169:531–9.
17. Puchter L, Chaberny IF, Schwab F, Vonberg RP, Bange FC, Ebadi E. Economic burden of nosocomial infections caused by vancomycin-resistant enterococci. Antimicrob Resist Infect Control. 2018;7:1.
18. Grundmann H, Hellriegel B. Mathematical modelling: a tool for hospital infection control. Lancet Infect Dis. 2006;6:39–45.
19. Frakking FNJ, Bril WS, Sinnige JC, Klooster JEV, de Jong BAW, van Hannen EJ, et al. Recommendations for the successful control of a large outbreak of vancomycin-resistant Enterococcus faecium in a non-endemic hospital setting. J Hosp Infect. 2018;100:e216–25.
20. Ozorowski T, Kawalec M, Zaleska M, Konopka L, Hryniewicz W. The effect of an antibiotic policy on the control of vancomycin-resistant enterococci outbreak and on the resistance patterns of bacteria isolated from the blood of patients in a hematology unit. Pol Arch Med Wewn. 2009;119:712–8.
21. Papanicolaou GA, Ustun C, Young JH, Chen M, Kim S, Ahn KW, et al. Bloodstream infection (BSI) due to Vancomycin-Resistant Enterococcus (VRE) is associated with increased mortality after hematopoietic cell transplantation for acute leukemia and myelodysplastic syndrome: a multicenter, retrospective cohort study. Clin Infect Dis. 2019. https://doi.org/10.1093/cid/ciz031.
22. Munita JM, Murray BE, Arias CA. Daptomycin for the treatment of bacteraemia due to vancomycin-resistant enterococci. Int J Antimicrob Agents. 2014;44:387–95.
23. Whang DW, Miller LG, Partain NM, McKinnell JA. Systematic review and meta-analysis of linezolid and daptomycin for treatment of vancomycin-resistant enterococcal bloodstream infections. Antimicrob Agents Chemother. 2013 Oct;57(10):5013–8. https://doi.org/10.1128/AAC.00714-13.
24. Balli EP, Venetis CA, Miyakis S. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia. Antimicrob Agents Chemother. 2014;58(2):734–9. https://doi.org/10.1128/AAC.01289-13.
25. Chuang YC, Wang JT, Lin HY, Chang SC. Daptomycin versus linezolid for treatment of vancomycin-resistant enterococcal bacteremia: systematic review and meta-analysis. BMC Infect Dis. 2014;14:687. https://doi.org/10.1186/s12879-014-0687-9.
26. 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;61:871–8.
27. Britt NS, Potter EM, Patel N, Steed ME. 2017. Effect of continuous and sequential therapy among veterans receiving daptomycin or linezolid for vancomycin-resistant Enterococcus faecium bacteremia. Antimicrob Agents Chemother 61.
28. Campeau SA, Schuetz AN, Kohner P, Arias CA, Hemarajata P, Bard JD, Humphries RM. 2018. Variability of daptomycin MIC values for Enterococcus faecium when measured by reference broth microdilution and gradient diffusion tests. Antimicrob Agents Chemother 62.
29. Avery LM, Kuti JL, Weisser M, Egli A, Rybak MJ, Zasowski EJ, et al. Pharmacodynamic analysis of daptomycin-treated enterococcal bacteremia: it is time to change the breakpoint. Clin Infect Dis. 2018;68:1650–7. https://doi.org/10.1093/cid/ciy749.
30. Shukla BS, Shelburne S, Reyes K, Kamboj M, Lewis JD, Rincon SL, 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;62:1514–20.
31. Akins RL, Rybak MJ. Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptide intermediate-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus faecium, and methicillin-resistant Staphylococcus aureus isolates in an in vitro pharmacodynamic model with simulated endocardial vegetations. Antimicrob Agents Chemother. 2001;45:454–9.
32. Hall AD, Steed ME, Arias CA, Murray BE, Rybak MJ. Evaluation of standard- and high-dose daptomycin versus linezolid against vancomycin-resistant Enterococcus isolates in an in vitro pharmacokinetic/pharmacodynamic model with simulated endocardial vegetations. Antimicrob Agents Chemother. 2012;56:3174–80.
33. Foolad F, Taylor BD, Shelburne SA, Arias CA, Aitken SL. Association of daptomycin dosing regimen and mortality in patients with VRE bacteraemia: a review. J Antimicrob Chemother. 2018;73:2277–83.
34. Dhand A, Bayer AS, Pogliano J, Yang SJ, Bolaris M, Nizet V, et al. Use of antistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant Staphylococcus aureus: role of enhanced daptomycin binding. Clin Infect Dis. 2011;53:158–63.
35. Sakoulas G, Bayer AS, Pogliano J, Tsuji BT, Yang SJ, Mishra NN, et al. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant Enterococcus faecium. Antimicrob Agents Chemother. 2012;56:838–44.
36. Sakoulas G, Rose W, Nonejuie P, Olson J, Pogliano J, Humphries R, et al. Ceftaroline restores daptomycin activity against daptomycin-nonsusceptible vancomycin-resistant Enterococcus faecium. Antimicrob Agents Chemother. 2014;58:1494–500.
37. Hall Snyder A, Werth BJ, Barber KE, Sakoulas G, Rybak MJ. Evaluation of the novel combination of daptomycin plus ceftriaxone against vancomycin-resistant enterococci in an in vitro pharmacokinetic/pharmacodynamic simulated endocardial vegetation model. J Antimicrob Chemother. 2014;69:2148–54.
38. Smith JR, Barber KE, Raut A, Rybak MJ. Beta-lactams enhance daptomycin activity against vancomycin-resistant Enterococcus faecalis and Enterococcus faecium in in vitro pharmacokinetic/pharmacodynamic models. Antimicrob Agents Chemother. 2015;59:2842–8.
39. Smith JR, Barber KE, Raut A, Aboutaleb M, Sakoulas G, Rybak MJ. Beta-lactam combinations with daptomycin provide synergy

against vancomycin-resistant Enterococcus faecalis and Enterococcus faecium. J Antimicrob Chemother. 2015;70:1738–43.

40. Pericas JM, Garcia-de-la-Maria C, Brunet M, Armero Y, Garcia-Gonzalez J, Casals G, et al. Early in vitro development of daptomycin non-susceptibility in high-level aminoglycoside-resistant Enterococcus faecalis predicts the efficacy of the combination of high-dose daptomycin plus ampicillin in an in vivo model of experimental endocarditis. J Antimicrob Chemother. 2017;72:1714–22.
41. Kebriaei R, Rice SA, Singh KV, Stamper KC, Dinh AQ, Rios R, Diaz L, Murray BE, Munita JM, Tran TT, Arias CA, Rybak MJ. 2018. Influence of inoculum effect on the efficacy of Daptomycin monotherapy and in combination with beta-lactams against Daptomycin-susceptible Enterococcus faecium harboring LiaSR substitutions. Antimicrob Agents Chemother 62.
42. Mainardi JL, Gutmann L, Acar JF, Goldstein FW. Synergistic effect of amoxicillin and cefotaxime against *Enterococcus faecalis*. Antimicrob Agents Chemother. 1995;39:1984–7.
43. Brandt CM, Rouse MS, Laue NW, Stratton CW, Wilson WR, Steckelberg JM. Effective treatment of multidrug-resistant enterococcal experimental endocarditis with combinations of cell wall-active agents. J Infect Dis. 1996;173:909–13.
44. Fernandez-Hidalgo N, Almirante B, Gavalda J, Gurgui M, Pena C, de Alarcon A, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis. Clin Infect Dis. 2013;56:1261–8.
45. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435–86.