American Journal of Transplantation 2013; 13: 59–67
Wiley Periodicals Inc.

doi: 10.1111/ajt.12099

Special Article

Vancomycin-Resistant *Enterococcus* Infections in Solid Organ Transplantation

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Key words: Antibiotic resistance, bacterial infection, *Enterococcus*, multidrug resistance, posttransplant infection

Abbreviations: BEAV, bile esculin azide agar; CLSI, Clinical and Laboratory Standards Institute; CNI, calcineurin inhibitor; LVAD, left ventricular assist device; MIC, minimum inhibitory concentration; mTOR, mammalian target of rapamycin; VRE, vancomycin-resistant *Enterococcus*.

Despite advances in surgical technique and immunosuppression, bacterial infections remain a significant source of morbidity in organ transplantation. Organ transplant recipients are at increased risk for acquisition of multidrug-resistant organisms due to critical illness, prolonged hospitalizations, extensive antimicrobial exposure and frequent device utilization. After staphylococci, *Enterococcus* species are the most common etiology of healthcare-associated infections in the United States (1). Although not traditionally considered virulent, enterococci are commonly implicated in catheter-associated bloodstream infections, catheter-associated urinary tract infections and surgical site infections. Of great concern is the incidence of vancomycin resistance among enterococci, particularly *E. faecium*. Infections with vancomycin-resistant *Enterococcus* (VRE) are associated with increased healthcare expenditures and significant mortality. Although antimicrobials exist with *in vitro* activity against these organisms, clinical outcomes are less than ideal and resistance to available agents is increasing (2,3).

Epidemiology and Risk Factors

Enterococcus is a commensal of the gastrointestinal tract and asymptomatic colonization often precedes infection (4). The first descriptions of vancomycin resistance among enterococci were in the mid to late 1980s subsequent to the introduction of third generation cephalosporins (5,6). Between 1989 and 1993, the Centers for Disease Control and Prevention reported a 20-fold increase in VRE in US hospitals (7). Prior exposure to antimicrobials, including vancomycin, cephalosporins, and agents with anti-anaerobic activity, is associated with both asymptomatic gastrointestinal carriage as well as invasive infections with VRE (8–12). Other cited risk factors include prolonged length of stay, indwelling devices, close proximity to another patient with VRE, especially in the setting of diarrhea, and placement in a contaminated room (13–15).

In the late 1980s, an increase in the isolation of *Enterococcus* species in abdominal organ transplant recipients was noted (16). In these early accounts, vancomycin susceptibility appeared to be universal. However, in the 1990s transplant centers observed increasing recovery of *E. faecium* and an associated increase in vancomycin resistance (17,18). Many studies evaluating the epidemiology of VRE in organ transplantation are limited to abdominal organ transplantation (e.g. liver and kidney transplantation) and are prior to the clinical introduction of quinupristin–dalfopristin and linezolid. In these initial reports, mortality rates associated with VRE infections were unacceptably high, ranging between 33–82% (3,18–23).

Between 1985 and 1993, 13% of liver transplant recipients at Mayo Clinic developed vancomycin-susceptible enterococcal bloodstream infections (16). In the setting of a selective bowel decontamination protocol at the same institution between 1995 and 1997, targeted surveillance identified VRE in 52 (11.7%) abdominal organ transplant recipients (23). The prevalence of gastrointestinal VRE colonization among liver and kidney transplant patients (pre- and posttransplantation) is reported to be between 3.4% and 55% with the highest rates among hospitalized liver transplant recipients in outbreak settings (23–28). Early outbreak investigations in transplant units confirm that colonized patients serve as reservoirs for horizontal transmission of VRE (22,23). Reported rates of VRE infections among colonized liver transplant patients range between 11.5–32% (23,26,27).

Most VRE infections present early posttransplantation in the setting of surgical complications and critical care. These include bloodstream infections, intra-abdominal

infections, urinary tract infections and surgical site infections (3,21). Mediastinitis and endocarditis are also reported (18,29–31).

Antimicrobial use and biliary complications (e.g. leaks and strictures), specifically those requiring re-exploration or percutaneous intervention, are common risk factors for development of VRE infections postliver transplantation (3,18–22,26). Hepatitis C infection, simultaneous kidney–pancreas transplantation, need for posttransplant renal replacement therapy, re-exploration and nephrostomy placement are associated with multidrug-resistant bacterial infections, including VRE, in kidney transplantation (32). Prior infections associated with left ventricular assist devices (LVAD) may be associated with posttransplantation invasive VRE infections including mediastinal infections and primary bloodstream infections (30). It is unclear, however, if this association is related to other factors including length of stay and antimicrobial exposures.

Diagnosis

Infection with VRE should be considered in a symptomatic patient growing Gram-positive cocci in pairs and chains with the aforementioned risk factors including prior infection or documented colonization with VRE. Isolation of VRE from an aseptically collected specimen from a normally sterile site is consistent with an infection. Specimens taken from longstanding drainage catheters may represent colonization rather than infection and their significance must be interpreted in conjunction with the patient's clinical status. Asymptomatic bacteriuria should not be routinely treated unless clinically indicated after kidney or pancreatic transplantation (III) (33). Endocarditis should be considered in patients with prolonged bacteremias or bloodstream infections without an obvious primary source in the setting of valvular abnormalities or cardiac devices (II-2).

Although great progress has been made in molecular diagnostics, most clinical laboratories rely on traditional culturing techniques in combination with automated systems to identify *Enterococcus* species and perform susceptibility testing. *E. faecalis* often demonstrates no hemolysis or rare β-hemolysis whereas *E. faecium* typically demonstrates α-hemolysis on sheep's blood agar. Enterococci produce a positive PYR test (a cherry red color produced after exposure to L-pyrrolidonyl-beta-naphthylamide [PYR] substrate with the addition of N, N methyl aminocynnamaldehyde). PYR testing may assist with early antimicrobial management. It should be noted that *Streptococcus pyogenes* is also PYR positive but is β-hemolytic.

Currently the Clinical and Laboratory Standards Institute (CLSI) recommends that enterococcal isolates with a minimum inhibitory concentration (MIC) to vancomycin of ≥32 μg/mL be reported as resistant. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) considers an MIC >4 μg/mL as vancomycin-resistant. In general, current automated susceptibility platforms are accurate at identifying high-level vancomycin resistance. Earlier generations of these systems, however, were not considered as sensitive at detecting low to intermediate levels of vancomycin resistance (34).

Glycopeptide (i.e. vancomycin and teicoplanin) resistance is primarily due to alterations in peptidoglycan precursors and is mediated by the presence of *van* gene clusters. To date, eight different genotypes have been described. VanA and VanB types are the most clinically relevant. The *van*C gene cluster is responsible for the intrinsic low level of vancomycin resistance found in *E. gallinarum* and *E. casseliflavus–E. flavescens* (35). The characteristics distinguishing these gene clusters were recently reviewed, but it should be noted that levels of phenotypic vancomycin resistance are variable (36).

Vancomycin resistance in *E. faecium* is commonly mediated by *van*A and is associated with high levels of resistance to both vancomycin and teicoplanin (37,38). *Van*B has been associated with outbreaks of VRE and demonstrates variable levels of vancomycin resistance (typically in the range of 16–64 μg/mL) and usually tests susceptible to teicoplanin (23,37). Both of these resistance determinants have been localized to transmissible elements and transfer of *van*A from *E. faecalis* is responsible for high-level vancomycin resistance in *Staphylococcus aureus* (VRSA; (39).

Despite little change in the handling of clinical specimens by microbiology laboratories, there have been several advances in rapid screening techniques for gastrointestinal carriage of VRE. Culture remains the gold standard for detection of VRE and is required for further susceptibility testing (40). Screening media for gastrointestinal colonization of VRE include Campylobacter medium containing supplemental vancomycin and bile esculin azide agar with supplemental vancomycin (BEAV). These media require additional testing to differentiate between *Enterococcus* species. Over the past several years, chromogenic agars have been studied and compared to BEAV. Most demonstrate high sensitivity and specificity and can differentiate between *E. faecalis* and *E. faecium* based on colony pigmentation (41–45). Real-time polymerase chain reaction (PCR) for *van*A and/or *van*B is both rapid and sensitive thus ideal for outbreak settings. Of note, due to acquisition of *van*B by anaerobic bacteria, the specificity of some of these PCR assays is not ideal and may require confirmatory testing (46). In institutions where a large percentage of *E. faecalis* is vancomycin susceptible, rapid differentiation between enterococcal species by peptide nucleic acid fluorescent *in situ* hybridization (PNA-FISH) may aid in early antimicrobial management (47).

Treatment

Enterococci are intrinsically resistant to traditional cephalosporins, anti-staphylococcal penicillins, and clindamycin and readily acquire mutations conferring resistance to other antimicrobial classes. A large percentage of *E.*

faecalis remain susceptible to ampicillin. In the setting of vancomycin resistance and retained susceptibility to ampicillin, ampicillin should be used (I). In the United States, the majority of *E. faecium*, however, are both ampicillin and vancomycin resistant with high-levels of aminoglycoside resistance. Although a handful of commercially available drugs demonstrate *in vitro* activity against VRE (Table 1), growing resistance threatens to compromise this limited armamentarium. With the exception of infective endocarditis, recommendations regarding antimicrobial duration remain undefined (48). Antibiotic choice and duration should be individualized based on source of infection, clinical severity and the potential for drug interactions and adverse events (III). Prolonged treatment courses of antimicrobials are seldom required.

Source control is paramount in the treatment of VRE. This includes removal of unnecessary catheters and devices as well as either percutaneous or open drainage of abscesses and debridement of wounds (II-2; Ref. 49). Prior to the advent of quinupristin-dalfopristin and linezolid, a variety of agents were used alone or in combination to treat serious VRE infections. Chloramphenicol is among these and many isolates continue to remain susceptible (37,50–52). With the availability of more specific therapy, clinical use of chloramphenicol is less common.

In 1999, the US Food and Drug Administration (FDA) approved the use of quinupristin-dalfopristin (Q/D) for the treatment of vancomycin-resistant *E. faecium*. Q/D is a combination of streptogramins which inhibits protein synthesis and demonstrates bacteriostatic activity against *E. faecium* with no appreciable activity against non-*E. faecium* enterococci. In prospective, noncomparative studies the overall treatment success rate was around 65–83% (53–55). Success varied by indication and lower response rates were reported in patients with intra-abdominal infections. Q/D is only available for parenteral administration and due to the risk of phlebitis, administration through a central venous catheter is recommended. Nausea and hyperbilirubinemia are common. However, debilitating arthralgias and myalgias can lead to premature discontinuation of therapy (54,55). Two reports describe an association between arthralgias and liver disease (56,57). A series of pediatric liver transplant recipients treated with Q/D did not support this finding (58). It should be noted that Q/D inhibits CYP450-3A4 and can potentially lead to calcineurin inhibitor toxicity. Levels of tacrolimus and cyclosporine should be monitored. Q/D resistance has been described (59). Clinical use of Q/D has substantially decreased with the introduction of better-tolerated agents.

Linezolid, an oxazolidinone, is bacteriostatic against both *E. faecium* and *E. faecalis* and is FDA-approved for the treatment of VRE infections. A moderate sized open-label noncomparative emergency use study reported clinical cure rates in 78% of patients with VRE; however, lower rates of clinical success were observed in patients with endocarditis (60). An evaluation of organ transplant recipients receiving linezolid described a modest improvement in overall survival of 62.4% with the highest attributable mortality rates in those patients requiring multiple surgeries and with polymicrobial infection (61).

Linezolid is available in both a parenteral and an oral formulation. The latter achieves appreciable levels in tissue and is an attractive option for patients with limited intravenous access and tolerating enteral nutrition. Adverse effects include myelosuppression (i.e. leukopenia and thrombocytopenia) that usually appears after two weeks of treatment. Peripheral neuropathy and optic neuropathy have been reported with extended use and may not be reversible with discontinuation of therapy (62–65). Caution should be used when administering linezolid to patients on serotonergic agents, including selective serotonin reuptake inhibitors, due to linezolid's potential to inhibit monoamine oxidase (66). Lactic acidosis is uncommon but has been reported with prolonged linezolid administration and serial serum chemistries monitoring for evidence of acidosis should accompany periodic complete blood counts while on therapy (III; Ref. 67). Linezolid resistance has been reported in organ transplant recipients both in the setting of protracted courses of linezolid as well as in the setting of cross-transmission (61,68–70).

Daptomycin, a lipopeptide, demonstrates rapid concentration-dependent bactericidal activity against most clinically relevant Gram-positive cocci including enterococci. Currently daptomycin is FDA-approved for the treatment of skin and skin structure infections, including those with vancomycin-susceptible *E. faecalis*, and for bloodstream infections. Despite not being a licensed indication, it has been used frequently in the treatment of VRE infections with some anecdotal success (71,72). Per CLSI, *E. faecalis* with a daptomycin MIC >4 μg/mL is resistant and *E. faecium* tends to have higher MICs than *E. faecalis*. Daptomycin is only available in a parenteral formulation. Although the dose of 6 mg/kg is recommended for bloodstream infections, higher doses have been used in severe infections (73,74). Myalgias and rhabdomyolysis are potential side effects with prolonged daptomycin use and serial monitoring of creatinine phosphokinase is recommended especially with higher doses and in the setting of renal failure or concomitant therapy with agents with similar side effect profiles (e.g. HMG CoA-reductase inhibitors; III). Although VRE pneumonia is unusual, due to inactivation by surfactant, daptomycin should not be used whenever a pulmonary source of infection is suspected. Like both Q/D and linezolid, resistance is described both in the setting of active treatment and possible antimicrobial pressure (75–77). Institutional daptomycin resistance rates of up to 15% have been reported in VRE isolates (76).

Tigecycline, a glycylcycline, is FDA-approved for the treatment of complicated skin and skin structure infections and abdominal infections with vancomycin-susceptible *E.*

Table 1: Agents with potential use in the treatment of infections with vancomycin-resistant *Enterococcus* (VRE) in the absence of susceptibility to ampicillin

Drug	Recommended adult dosing (with normal creatinine clearance)	Notable adverse events	Drug interactions in the transplant setting	Additional comments
Quinupristin-dalfopristin[1]	• 7.5 mg/kg IV every 8 hours through central venous catheter	• Infusion site reactions • Hyperbilirubinemia • Treatment limiting arthralgias and myalgias	Inhibits CYP3A4 and can increase levels of CNIs[2] and mTOR[3] inhibitors	• Bacteriostatic • No appreciable activity against *E. faecalis*
Linezolid[1]	• PO or IV dose 600 mg every 12 hours	• Myelosuppression usually after 2 weeks of therapy • Lactic acidosis • Peripheral and optic neuropathy • Sertonin syndrome	Risk of serotonin syndrome in the setting of concomitant use of serotonergic agents	• Bacteriostatic • Monitor weekly complete blood count (myelosuppression) • Monitor weekly anion gap (lactic acidosis) • Avoid use of serotonergic agents • Resistance has been reported and has been associated with prior exposure to linezolid
Daptomycin[4]	• Skin and soft tissue infections- 4 mg/kg IV every 24 hours • Bloodstream infections 6 mg/kg IV every 24 hours	• Myopathy • Acute eosinophilic pneumonia (101)	Use with caution with HMG-CoA reductase inhibitors due to similar adverse event profile	• Bactericidal • Cannot be used for primary pulmonary infections • Monitor weekly creatine phosphokinase • Higher doses have been used in the setting of severe infections
Tigecycline	• 100 mg IV once then 50 mg IV every 12 hours • Dose adjustment required in the setting of severe liver disease	• Nausea and gastrointestinal complaints		• Bacteriostatic • Not recommended for bloodstream infections or urinary tract infections • Avoid in pregnancy (category D) and children • Use of tigecycline has been associated with increased mortality with comparator agents (102)
Telavancin[4]	• 10 mg/kg IV every 24 hours	• Red Man Syndrome • QT prolongation • Nephrotoxicity • May interfere with coagulation tests (e.g. PT/INR, aPTT)	Use with caution with other potentially nephrotoxic agents	• Bacteriostatic against VanB expressing isolates • Avoid in pregnancy (Category C) • Safety and efficacy not established in children • Clincial data for treatment of infections with VRE are limited
Ceftaroline[4]	• 600 mg IV every 12 hours	• Similar to other cephalosporin agents		• Bactericidal • No appreciable activity against *E. faecium* • Safety and efficacy not established in children • Paucity of clinical data for the treatment of VRE

[1]FDA-approved for the treatment of infections with VRE.
[2]Calcineurin inhibitor (e.g. cyclosporine and tacrolimus).
[3]Mammalian target of rapamycin.
[4]Dose adjustment recommended for alterations in creatinine clearance.

faecalis and is bacteriostatic against susceptible enterococci (78,79). Due to rapid concentration of drug into tissue, serum concentrations may not be adequate to treat primary bloodstream infections and use in urinary tract infections is also controversial.

Telavancin is a long-acting lipoglycopeptide recently FDA-approved for complicated skin and skin structure infections including those with vancomycin-susceptible *E. faecalis* (80). Telavancin lacks appreciable activity against *van*A harboring strains of VRE although there is some evidence of bacteriostatic activity against *van*B expressing strains (81,82). Clinical data for the treatment of VRE infections are limited. Oritavancin is an investigational lipoglycopeptide with promising concentration-dependent *in vitro* bactericidal activity against a wide spectrum of Gram-positive bacteria, including enterococci expressing either *van*A or *van*B (83).

The novel cephalosporins, ceftobiprole and ceftaroline, demonstrate *in vitro* activity against other clinically relevant but traditionally cephalosporin-resistant Gram-positive organisms, notably MRSA (84). Both agents demonstrate activity against vancomycin-susceptible and -resistant *E. faecalis* but no appreciable *in vitro* activity against *E. faecium*. Ceftaroline recently received FDA approval for the treatment of complicated skin and skin structure infections and pneumonia.

Fluoroquinolones, nitrofurantoin and fosfomycin may be used to treat symptomatic VRE cystitis (III; Refs. 85-88).

Prevention and Infection Control Issues

In the United States, clinical isolation of VRE is uniformly associated with healthcare exposure. Epidemiologic surveys inclusive of organ transplant candidates and recipients cite antimicrobial exposure as a common risk factor for VRE. Unfortunately, antimicrobial use in organ transplantation is unavoidable. Broad-spectrum antimicrobials increase susceptibility for VRE acquisition by inadvertent suppression of normal gastrointestinal flora. Increases in stool concentration of VRE may increase the probability of environmental contamination and thus horizontal transmission.

Formal antimicrobial stewardship programs charged with promoting judicious and appropriate use of all antimicrobials are crucial in combating increased resistance (III). Long courses of antibiotics are rarely necessary and reevaluating continued administration of broad-spectrum agents or antimicrobials in general, is recommended (II-2; Refs. 9,11,89-91). Due to the prevalence of MRSA, empirical use of vancomycin may be inevitable in certain patient populations and in the appropriate clinical scenario. However, prolonged use in the absence of supportive culture data is discouraged (III).

Organ transplant patients are subject to general recommendations for the prevention of horizontal transmission of epidemiologically significant multidrug-resistant organisms (II-2; Ref. 92). The colonized patient remains the primary reservoir for VRE, but transmission is facilitated by healthcare workers and the soiled environment (93–95). When there is a high prevalence of VRE (i.e. colonization pressure), other risk factors for colonization may be less important (96).

Cleansing of patients with chlorhexidine may decrease the bioburden of VRE thus decreasing healthcare-associated VRE infections and horizontal transmission. However, chlorhexidine cleansing has been studied primarily in the ICU setting and its role in organ transplantation remains unclear but deserves further investigation (97). Removal of unnecessary catheters is encouraged (II-2).

Mandating routine active surveillance for VRE among organ transplant patients cannot be recommended (III; Ref. 98). A possible outbreak of VRE or a high prevalence of VRE, however, warrants implementation of active surveillance to identify asymptomatic colonization (II-2; Refs. 40,99) Isolation and contact precautions are recommended for all patients with a history of VRE colonization or infection during the index hospitalization as well as subsequent readmissions (II-3). This includes use of single rooms or cohorting as well as hand hygiene using either alcohol-based sanitizer or antiseptic soap before and after all patient contact (II-2). Gloves and gowns should be worn when entering the room and for all patient contact and discarded promptly when exiting the room (II-2). Dedicated equipment (e.g. stethoscopes, thermometers, sphygmomanometers) should be used for isolated patients and shared equipment requires disinfection prior to subsequent use (II-2). Monitoring for compliance with contact isolation precautions and hand hygiene with immediate feedback and continuing education is recommended (II-1).

Since asymptomatic colonization can persist for months to years, the optimal duration for maintaining contact precautions remains unclear. CDC recommendations for discontinuation of contact precautions suggest that in the absence of active antimicrobial agents, demonstration of at least three negative peri-rectal or stool specimens collected over several weeks may be sufficient (III; Ref. 99). In the setting of limited resources, including private rooms, and in the presence of other epidemiologically significant multidrug-resistant organisms, requiring such a labor-intensive process for historical colonization or infection with VRE may not be feasible. Policies for discontinuation of contact precautions are often institution-specific. It should be noted that rates of spontaneous decolonization in organ transplant recipients appear to be lower than that in the general population (23). Attempts at decolonization of high-risk patient are not recommended (III) and selective bowel decontamination may be a risk factor for VRE (100).

A history of VRE colonization or past infection is not a contraindication to organ transplantation (III). Despite the absence of specific recommendations for adjusting perioperative prophylaxis based on history of VRE colonization or infection, it may be something to consider (III).

Although not historically considered as virulent as other multidrug-resistant pathogens, VRE remains challenging not only because of its environmental resilience but its increasing resistance to available agents. A multidisciplinary approach that includes transplant program leadership is required to continue to educate and reinforce healthcare workers' understanding of the importance of complying with infection control practices as well as recommendations of antimicrobial stewardship programs. Administrative support for education, research, infection control and antimicrobial stewardship is crucial to continue to combat the rise and persistence of multidrug-resistant pathogens.

Acknowledgment

This manuscript was modified from a previous guideline written by Patricia Munoz published in the *American Journal of Transplantation* 2009; 9(Suppl 4): S50–S56, and endorsed by American Society of Transplantation/Canadian Society of Transplantation.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. Dr. Snydman is a past consultant for CSL Behrning, a current consultant for Genentech, Millenium and Microbiotix, receives grant support from Genentech, Pfizer, Merck, Cubist and Optimer, and is a member of the speakers bureau for Merck, Optimer and Cubist.

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