Title: Clinical Considerations in the Approach to Vancomycin-Resistant *Enterococci*: A Narrative Review

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1. Are healthcare-associated vancomycin-resistant enterococci (VRE) infections an unresolved problem?
2. How is VRE treated?
3. Be better prepared when you see VRE in healthcare settings.
4. VRE: Understanding infections in hospitalized patients.

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ABSTRACT.

Vancomycin-Resistant *Enterococci* (VRE) increasingly colonize and infect assorted patient populations throughout the world, maintaining a continual reservoir of opportunistic pathogens with varying antibiotic resistance. Here we present the current general epidemiology and classification of these pathogens within the scope of healthcare-associated infections (HAIs). Risk factors for colonization and conditions for subsequent infection are reviewed, along with infection characteristics. Current infection control protocols and their effectiveness, selected evidence-based medical therapies, and ongoing research into alternative therapies are summarized.

Key Words: Vancomycin-resistant enterococci, *Enterococcus faecalis, Enterococcus faecium*, vancomycin resistance, healthcare-associated infection, nosocomial infection (Source: MeSH-NLM).

INTRODUCTION.

First identified in the UK and France during the 1980s, *Enterococci* possessing vancomycin-resistance (VRE) colonizes patients in the United States at increasing rates.[1,2] Infections stemming from VRE colonization account for approximately 30% of all healthcare-associated *Enterococci* infections in the United States.[3] During the late 2000s, VRE-related hospitalizations doubled in the United States alone.[1] Worldwide reported VRE surveillance data varies widely by continent and country. Reports from Africa are diverse, with the published prevalence of VRE among human isolates varying from 2.5% to 44.3%.[4] 2016 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) reported that between 25% and 50% of surveillance isolates of *E. faecium* from Ireland, Eastern and Southern Europe were positive for VRE.[5] While a U.S. Centers for Disease Control (CDC) report in 2019 showed decreasing cases over the last several years from 84,800 confirmed VRE infections in hospitalized patients in 2012 to 54,500 cases in 2017; the prevalence of vancomycin resistance is still alarmingly high at 30% of all healthcare-associated infections.[6] Variable surveillance data from Asia and Australasia suggest a low prevalence of VRE compared to Europe and the U.S., for instance, a 5-year study in Singapore found a prevalence of vancomycin resistance in isolates at 0.4-0.7%, but these rates appear to be increasing.[7] The variable yet increasing prevalence of vancomycin resistance should be of concern to physicians, scientists, and patients worldwide.

Colonization rate increases may be attributed to *Enterococci*'s natural habitat and genetic structure. One of many bacterial species composing normal human enteric microbiota, *Enterococci* gaining vancomycin-resistance are perfectly positioned for enhanced opportunistic pathogenicity. *Enterococci* already possess intrinsic resistance to many antibacterial agents, including β-lactams and aminoglycosides.[8–10] Existence with other commensal bacteria provides ample opportunities for acquiring vancomycin-resistance via transposition of resistance-containing plasmids.[11–13] Nine different phenotypes – VanA, VanB, VanC, VanD, VanE, VanG, VanL, VanM and VanN – named for the *vancomycin-resistance gene* (*van*) expressed currently describe degrees of vancomycin-resistance and pathogenicity within *Enterococci*.[11,14,15] For example, *E. faecium* most frequently expresses the *van*A gene and thus is most frequently associated with the VanA phenotype which identifies the highest vancomycin-resistance and, consequently, the highest pathogenicity.[10,14] The VanB phenotype identifies expression of the *van*B gene and an intermediate level of vancomycin-resistance that, while less pathogenic, still commonly appears in surveillance cultures of patient populations.[10,15–17] VanC phenotype *Enterococci* express the *van*C gene and possess much lower vancomycin-resistance.[10,15] VRE are thus a family of variably-resistant opportunistic pathogens, with *E. faecium* and *E. faecalis* being the most commonly identified.[8–10,18] Increasing VRE prevalence intensifies the need to quickly identify patients at risk for colonization and infection in order to treat colonized and infected patients with the potential for lowering overall rates of colonization. The aim of this review is to present the general epidemiology and medical management of healthcare-associated VRE infections. In order to clarify the variable at risk patient populations, we reviewed important factors for colonization and recently reported conditions for subsequent infection, followed by a review of infection control protocols, which are of heightened importance in health care settings. Further, recent updates to the pharmacological interventions and alternative therapies, including rebiosis, are discussed and compared.

METHODS

A narrative review of English language literature from 1994 to August 2019 was utilized to assess the historic development of vancomycin-resistance within the *Enterococcus* family. This timeline was revisited prior to publication and updated to include the time frame to March 2022. Scale for Assessment of Narrative Review Articles (SANRA) was used to guide appropriate research methods.[19] The primary research method was an online search, conducted in September of 2019, of Google scholar and PubMed. Search terms included: vancomycin resistance OR vre OR “vancomycin-resistant” OR multidrug resistant OR mdro OR infec* AND enterococc* OR “E. faecalis” OR “E. faecium” OR “enterococcus faecalis” OR “enterococcus faecium” OR microbiome OR microbiota. Meta-analyses and systematic reviews were given a narrower time frame, namely the past 10 years, when compared to case reports or series and other literature reviews or position papers. This allowed for more recent data on current treatment practices and protocols while allowing a broader scope for assessing the historic development and response to vancomycin-resistant *Enterococci*. The competencies of evidence-based medicine were utilized when developing inclusion/exclusion criteria.[20] These competencies include recognition of a problem, retrieving and critically appraising the literature, and integration of information found. Papers dealing specifically with human models were preferred; however, some animal model studies were included due to lack of data with human models.

Inclusion required:

1. Title or abstract inclusion of at least 2 of the search term(s) OR
2. Significant (2+ pages) discussion of at least 2 of the search terms within the body of the paper OR
3. Position papers whose content would apply to at least 2 of the search terms, even if not specifically stated

Exclusion required:

1. Any paper published more than 25 years ago at time of search (1994 or earlier)
2. Any meta-analysis or systematic review published more than 10 years ago at time of search (2009 or earlier)
3. Any paper that contained only 1 search term and failed to meet the inclusion criteria outlined above
4. Any paper that included 1 or more search terms but whose primary focus was either another form of drug resistance or another species of bacteria (e.g. methicillin-resistant *Staphylococcus aureus*)

RESULTS AND DISCUSSION.

COLONIZATION AND INFECTION

Colonization, or the incorporation of a microorganism into a host, occurs through the interaction of the host with a reservoir of that microorganism. Studies by Hamel *et al*. in 2010 and Kaki *et al*. in 2014 identified VRE colonized patients and contaminated surfaces within hospitals or care centers as possible VRE reservoirs.[21,22] *Enterococci* inhabit every human colon, but colonization with VRE rarely occurs among healthy populations.[23] Further, in a recent large study (n=674 including controls) of healthcare personnel and their rates of colonization with multi-drug resistant organisms (MDROs), Decker *et al*. found that there were not any healthcare workers or control subjects positive for VRE colonization, including those in contact with MDRO+ patients.[24] A meta-analysis of 37 studies found that 10% of patients in Intensive Care Units (ICU) are already colonized with VRE at admission and an additional 10% were colonized during their ICU stay.[23,25] A meta-analysis of dialysis patients, who are typically immunocompromised, in the United States found that more than 6% are colonized with VRE.[26]

VRE colonization risk is multifactorial. Recent high dose antibiotic use, especially vancomycin, is the most frequently identified risk factor in multiple studies.[13,22,26] Surgical, oncological, and dialysis patients demonstrate increased risk, especially when recovery requires ICU services.[3,10,23,25–28] Patients sharing a room with a VRE colonized patient have a 1 in 3 chance of themselves becoming colonized during hospitalization.[21,22,29] Acquired immunodeficiency, from HIV infection or medically-induced immunosuppression, may also increase VRE colonization risk.[18,27,28,30–32]

Immunocompromised patients requiring recurrent medical interventions within a hospital or long-term care center thus comprise both the highest risk group for colonization and the potentially largest VRE reservoir.[3,33] Patients in these circumstances are prime for a VRE-mediated infection when a critical lapse in immune function occurs. For example, Brennen *et al*. found only 1% of colonized patients in a nursing facility develop VRE infections.[34] Yet Zaas *et al*. reported that 13% of colonized oncology patients develop VRE infections.[35] In a 2008 study, Zirakzadeh *et al*. found that hematopoietic stem cell transplant (HSCT) patients colonized with VRE have a significantly higher 100-day mortality rate (45%) compared to non-colonized patient controls (25%) and are more prone to develop VRE bacteremia (27%) than non-colonized patients (0%).[30] Colonized dialysis patients demonstrate significantly higher VRE infection risk compared to non-colonized patients, especially when recently hospitalized.[26] A 2013 meta-analysis by Ziakas *et al*. found that among ICU patients, VRE infection rates among those colonized can be anywhere from 0%-45% yet the infection rate for non-colonized patients consistently stayed below 2%.[23] As recently as 2018, Freedberg *et al*. found that VRE colonization was associated with a 19% increased risk for death (P<.01) and a 22% increased risk of infection (P<.01).[25] Infection rate discrepancies point to a predisposition among VRE-colonized patients for acquiring a VRE infection after a major medical procedure.

VRE infections generally correlate with either the location or method of medical intervention **(Figure 1)**. VRE infections may localize around surgical incisions with limited spread to adjacent tissues.[27] VRE meningitis, while rare, may complicate cranial surgical procedures in colonized patients.[9,18,36] VRE urinary tract infections (UTIs) commonly afflict colonized patients with indwelling catheters.[27] Peritoneal dialysis in patients colonized with VRE may result in VRE peritonitis.[9,26,37] Up to 10% of patients undergoing HSCT or

solid organ transplant that develop VRE bacteremia may experience VRE infective endocarditis.[9,18,31] These patients may also be more likely to progress to septic shock.[30,32]

All VRE infections cause significant increases in morbidity and mortality when compared to similar infections with vancomycin-sensitive *Enterococci* (VSE).[10,25,26,30] Mortality rates for surgical patients with VRE bacteremia may be as high as 67%, nearly double the rate for matched control patients.[30,33] VRE infections among leukemia patients may result in mortality rates as high as 73%.[18] Mortality rates among VRE-infected allogeneic HSCT recipients with VRE infections vary between 45% and 80% depending on the infection.[30]

INFECTION CONTROL PROTOCOLS

Alarmingly high mortality rates underscore the extensive research and discussion surrounding VRE infection control protocols. The CDC published recommendations for identifying and preventing VRE colonization in the mid-1990s.[27,28] Recommendations included: active patient surveillance using perianal swabs, culture on selective media, using gloves and gowns for universal contact precautions (CP), and isolating VRE-colonized patients during treatment.[27,28] These recommendations became the standard in hospital-based VRE infection control protocols, as well as for other multidrug resistant organisms (MDROs). Numerous studies since the CDC's guidelines were published have evaluated the effectiveness and limitations of these infection control measures, as discussed below.

Active surveillance of high-risk patients, typically those hospitalized in the intensive care unit or receiving i.v. antibiotic therapy, has been a mainstay of infection control; however, limitations primarily involve the time required to culture the surveillance swabs. Cultures take 48 to 72 hours to grow, during which time yet undetected VRE may colonize additional patients.[17,38] in 2017, Holzknecht *et al*. demonstrated that PCR assay for the *van*A and/or *van*B genes may significantly reduce the time required to identify VRE-colonized patients (8 hours for PCR assay compared to 48-72 hours for culture). Very recent PCR assay development has led to a vastly reduced time frame of 2 hours to identify VRE, though costs and availability issues remain.[39] This built on the work of Paule *et al*., which showed in 2003 that PCR of the *van*A gene demonstrates a high specificity (99.7%) and sensitivity (87.1%) for identifying VRE (compared to about 60% sensitivity for swab and culture).[16,17,38,40] Decreased detection time may lead to earlier implementation of universal CP and isolation, thus preventing further VRE exposure in unprotected patients and healthcare workers.

Studies evaluating universal CP in VRE infection control protocols contain positive but non-specific findings. Research by Calfee *et al*. in 2003 confirmed the work done earlier by Montecalvo *et al*. in 1999, reporting a 50% decrease in the incidence of VRE colonization following CP implementation.[27,38,41] Research by Slaughter *et al*. in 1996 affirmed the use of universal CP; however, they could find no additional reduction in VRE colonization when using gloves and gowns compared to gloves alone.[42] More recent studies by Harris *et al*. in 2013 and Morgan *et al*. in 2015 argue for continued use of universal CP for MDROs, including VRE, while acknowledging that the clinical research supporting such practice is still lacking.[43–45] Recent research by Eichel *et al*. found that CP did not alter the transmission rates of VRE nor the rate of VRE bacteremia while hand and environment hygiene were maintained.[46]

VRE patient isolation protocols focus on maintaining standard of care. Montecalvo *et al*. and Calfee *et al*. both reported isolation as a component of successful VRE colonization reduction; however, the degree of benefit that isolation alone provided remains unquantified.[27,38,41] Unlike gloves or surveillance cultures, which

cause little to no harm to patients, isolation protocols may actually cause harm to patients. In 2003, Stelfox *et al*. reported that isolated patients experience two adverse events during treatment compared to one for non-isolated patients.[47] The charts of isolated patients contained fewer vital sign records, fewer physician progress notes, and elevated complaint and dissatisfaction levels at discharge.[47] While evidence supports isolation as a component of VRE infection control protocols, concerted efforts must ensure these patients receive the same standard of care during treatment as compared to their non-isolated counterparts.

The CDC continually updates practice guidelines for VRE and other MDROs, advocating for effective use of infection control measures in a multi-disciplinary approach that emphasizes prevention as well as treatment.[48] Prevention methods include sterilization of medical equipment, using anti-bacterial washes on patients, and hand hygiene.[48] In 2019, Messler *et al*. reported that octenidine-based body washing reduced VRE colonization by 65% in a German surgical ICU population.[40] This infection control technique, alongside established recommendations, may more effectively combat rising VRE colonization rates.

MEDICAL MANAGEMENT

Despite the best efforts of healthcare teams and continual refinement of infection control protocols, VRE infections continually plague susceptible patients. Proper culture and resistance profiling of patient isolates is essential to ensure patients receive the most appropriate course of treatment. Few effective antibacterial agents remain to treat vancomycin-resistant enterococcal infections. **Table 1** summarizes commonly sited medical therapies that are now or have been indicated for VRE infections, including their class and mechanism of action. Currently, the only antibiotic approved by the U.S. Food and Drug Administration (FDA) for medical management of VRE-mediated infections is linezolid, an oxazolidinone. While only bacteriostatic to VRE, linezolid has been successfully used as a monotherapy in several VRE infective endocarditis cases.[13,31] VRE-mediated UTIs and central nervous system (CNS) infections also respond well to linezolid monotherapy.[13,36] Daptomycin, a cyclic lipopeptide, has bactericidal action against VRE in certain disease states and may be used for both VRE-mediated UTIs and infective endocarditis.[8,13,32] A recent comparison study revealed that linezolid was associated with significantly lower rate of clinical failure as compared to the standard dose of daptomycin.[49] The same study found that higher doses of daptomycin may overcome some of the clinical failures. A recent study by Kelly *et al*. found that a majority of patients receiving daptomycin for VRE infections had no side effects at a dose of 8-12mg/kg/day.[50] Further, a cost analysis found that these therapies are similar, with linezolid being slightly more cost-effective in the United States.[51] Other medications once indicated for VRE infections, such as chloramphenicol and quinupristin/dalfopristin, have fallen into disuse due to low bacteriostatic/bactericidal activity or side effects requiring cessation of medical therapy.[13,30]

Current VRE antimicrobial therapy relies heavily on two primary agents: linezolid and daptomycin, both of which have a regular incidence of notable adverse events in patients. Linezolid can lead to central nervous system and gastrointestinal symptoms in up to 9.8% of patients, including headache, nausea, vomiting, and diarrhea.[52] Daptomycin is reported to be associated with myopathies at higher doses, neuropathy, and acute eosinophilic pneumonia, though this is thought to be rare.[53,54] Additionally, both linezolid and daptomycin use can lead to anemia, thrombocytopenia and renal insufficiency in patients.[55] The prevalence of these adverse events underscores the importance of antibiotic development against VRE.

The World Health Organization (WHO), CDC and other national and international organizations continually urge pharmaceutical and academic entities to develop novel regimens.[6,56] VRE resistance to linezolid, though currently a rare occurrence, only accentuates the need for new approaches to VRE infection management.[8,13] A new oxazolidinone, tedizolid, may be efficacious against linezolid resistant VRE strains, though it is not currently approved by the FDA for that indication.[13,32] Recent investigations into the use of oritavancin, a lipoglycopeptide, and omadacycline, a tetracycline, are showing marked efficacy against VRE in small studies, though more coordinated clinical studies are required.[57–59] *In vitro* studies exploring combinations of daptomycin and ceftaroline, a fifth-generation cephalosporin, showed promise against VRE infections; however, Chuang *et al*. in 2017 found no significant difference in mortality between patients receiving the combination therapy compared to daptomycin monotherapy.[8,13,56]

High mortality rates underscore the need for effective antibiotics against VRE.[27] Two studies examining VRE bacteremia in transplant patients reported mortality rates of 80% and 100% despite treatment with linezolid, daptomycin, and quinupristin/dalfopristin.[13,30] While VRE infection may not have been the sole cause of death in all instances, reported mortality rates would not have been this high without VRE infection.[27,30,32] Further research must focus on finding alternative antimicrobial therapies or combination therapies that provide more significant efficacy against VRE infections.

POTENTIAL THERAPIES

New research into alternative treatment options is producing promising results. Our current understanding of the human microbiome and its synergistic effects on health has led to new, targeted treatment modalities affecting a number of physiological processes, including metabolism and the immune response.[60,61] Colonic dysbiosis, or the disruption of normal enteric microbiota favoring opportunistic infections, is a proven component of disease pathogenesis in *Clostridioides difficile*infections, irritable bowel syndrome, and Crohn's disease.[60,61] Currently, research examining the links between colonic dysbiosis and VRE colonization are underway by multiple groups.[60–64] This research may lead to new treatment paradigms that can reduce VRE colonization rates, morbidity, and mortality associated with VRE infections.

Clinical application of current research offers two different therapeutic approaches: primary rebiosis and secondary rebiosis. Primary rebiosis consists of integrating probiotic species, or components of these species, within the human microbiome to restore normal immune function and prevent seeding by opportunistic pathogens such as VRE.[61–63] Secondary rebiosis consists of integrating a donor microbiome *en totum* to a dysbiotic individual, most commonly accomplished via Fecal Microbiota Transplant (FMT).[60,64] This procedure isolates and purifies a healthy donor sample for direct implantation into a dysbiotic colon.[60,61]

Primary rebiosis shows encouraging results in both animal models and preliminary clinical trials. A 2018 study by Wasilewska *et al*. of *Streptococcus* and *Lactobacillus* in mouse models confirm earlier reports that probiotic regimens have a two-fold benefit in combating enteric-related infections: modulating colonic immune responses to favor healthy gut microbiota and enhancing immune response against opportunistic pathogens within intestinal lymphoid tissues.[65] Research by Li *et al*. of *Lactobacillus* extracellular vesicles in worm models suggests that components of this probiotic species alone may be effective in treating VRE colonization.[63] Kim *et al*. studied *Blautia producta* in mouse models suggesting that administration in a newly colonized host may restore natural resistance to VRE colonization after antibiotic administration.[66] A 2019

retrospective analysis by Borgmann *et al*. of probiotic therapy conducted in Ingolstadt, Germany suggests that adding the probiotics *Saccharomyces boulardii* and *Escherichia coli* Nissle to traditional antibiotic regimens reduces VRE transmission in stroke and trauma patients without any adverse side effects.[62] Following implementation of probiotic regimens, VRE colonization rates dropped from 78 patients per year to 51 per year, an overall 35% reduction.[62] These studies highlight the potential impact of primary rebiosis as an emerging VRE therapy that may improve the efficacy of existing antimicrobial regimens.

Secondary rebiosis, via FMT, may be effective in reducing VRE colonization where other methods have proven ineffective. First employed in refractory *Clostridium difficile* infections in 2013, FMT has shown surprising efficacy.[60,61] Research utilizing mouse model FMT treatments for VRE colonization reduced overall VRE load, though the effect was transient.[64] In 2018, Davido *et al*. performed the largest human trial to date utilizing FMT as a treatment to decolonize VRE, resulting in 7 of 8 initial study patients remaining VRE free 3 months post FMT.[64] Ongoing trials will assess whether these limited but encouraging results will hold up in larger clinical studies.[67] FMT has been shown to be relatively safe with the most common side-effects being mild and self-limiting increases in flatulence, changes in bowel regularity, and abdominal bloating and tenderness.[68] Identification and screening of healthy donor material play a large role in mitigating the risks associated with the procedure.[68] Directly replacing a patient's colonized colonic microbiome with a healthy, VRE-free microbiome may provide the means to greatly reduce the functional reservoir of VRE and prevent continued colonization.

CONCLUSION.

In the years since physicians identified vancomycin-resistant *Enterococci*, our understanding of this family of multidrug-resistant, opportunistic pathogens has grown exponentially. While this body of evidence has grown, we are still looking for the most appropriate measures to limit the spread of antibiotic resistant infections. Clinical cases and meta-analyses have provided clues into the reservoirs of VRE and the patient populations most at risk from VRE colonization. Incredibly high rates of morbidity and mortality have prompted the development of VRE infection control protocols that have been implemented, studied, and critiqued for their relative effectiveness. Further, the development of cost-effective rapid diagnostic testing may limit the spread of unidentified VRE infections in healthcare settings. Current medical therapies for VRE infections are unfortunately limited and resistance to linezolid has been reported but is not widespread as of yet, adding credence to the cries of the WHO, CDC, and others for new antimicrobial therapies. Ongoing research into the human microbiome has provided two potentially promising alternative therapy choices, primary and secondary rebiosis. Though both are still in development, the potential benefits of replacing a defective microbiome with a healthy and balanced population of normal non-pathogenic microbes highlights how increased understanding of our own being may provide the key to discovering how to control and contain vancomycin-resistant *Enterococci* without the risk of additional antimicrobial resistance. The evidence we have reviewed here suggests the necessity of a multifactorial approach to VRE: combining surveillance of at-risk populations, infection control measures, rapid diagnostics, and safe therapies.

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FIGURES AND TABLES.

Figure 1. Common Locations of Medical Procedures with Resulting VRE-Mediated Infections.
Note the localized nature of the resulting infections, with two major exceptions: Solid organ transplant and hematopoietic stem cell transplant (HSCT). Patients undergoing these major medical interventions are more likely to suffer from systemic VRE-mediated infections such as: bacteremia, infective endocarditis (IE), sepsis and possible progression and worsening to septic shock. This may be due to the highly vascular nature of both solid organs and bone marrow which facilitate systemic spread of VRE in susceptible patients.

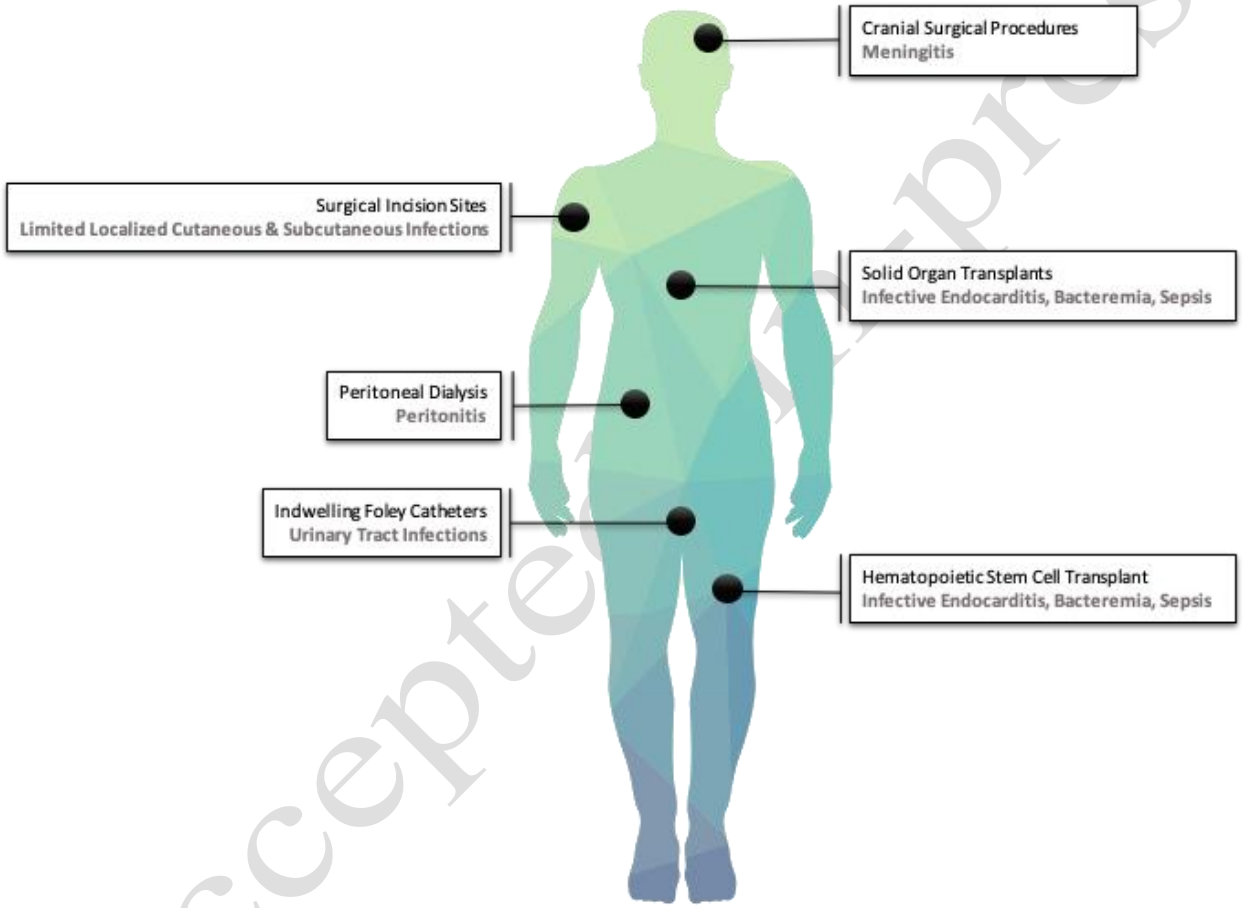

Table 1: Medical Therapies Indicated for VRE Infections.

Medication	Class	Mechanism	Reported VRE Efficacy	Monotherapy or Combination
Linezolid	Oxazolidinone	Protein synthesis inhibitor – Binds the 23S subunit of ribosomal 50S unit	*IE, UTI, Meningitis, Peritonitis, Bacteremia	Monotherapy
Daptomycin	Lipopeptide (cyclic)	Cell membrane depolarizer – Inhibits membrane functionality, decreasing DNA, RNA, and protein synthesis	IE, UTI	Monotherapy or in combination with Ceftaroline
Tedizolid	Oxazolidinone	Protein synthesis inhibitor – Binds the ribosomal 50S unit	Bacteremia, IE	Monotherapy
Tigecycline	Glycylcycline	Protein synthesis inhibitor – Binds the ribosomal 30S unit	UTI, Meningitis	Monotherapy
Quinupristin/ Dalfopristin	Streptogramin	Protein synthesis inhibitor – Binds the ribosomal 50S unit	Bacteremia, Meningitis, IE	Combination
Chloramphenicol	Amphenicol	Protein synthesis inhibitor – Binds the ribosomal 50S unit	Bacteremia, Meningitis	Monotherapy

*IE = infective endocarditis, UTI = urinary tract infection