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THERAPEUTIC OPTIONS FOR VANCOMYCIN RESISTANT ENTEROCOCCAL INFECTIONS

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ABSTRACT

Vancomycin-resistant *Enterococcus* (VRE) is an increasing problem throughout the world. Nosocomial infections caused by VRE are associated with high morbidity and mortality. The most common VRE infections are urinary tract infections, bacteremia, and wound infections. They have also been implicated in serious infections such as endocarditis and meningitis. Vancomycin resistance has reduced the therapeutic options in management of enterococcal infections. Currently, linezolid is the only drug approved by Food and Drug Administration (FDA) for treatment of various VRE infections. Quinupristin/dalfopristin, tedizolid, beta lactam-aminoglycoside combination, dual beta lactam combination, daptomycin, daptomycin-beta lactam combination, tigecycline, doxycycline, chloramphenicol, teicoplanin, new glycopeptides such as dalbavancin and oritavancin, and nitrofurantoin have also shown promising results and can be recommended as alternative drugs for treatment of infections caused by VRE. However, further studies are required to assess their clinical impact, especially in the treatment of serious infections.

KEYWORDS: Vancomycin-Resistant *Enterococcus*, Therapeutic Options, Linezolid, Quinupristin/Dalfopristin.

INTRODUCTION

Infections associated with vancomycin-resistant *Enterococcus* (VRE) strains have become increasingly common in the recent years.[1]

Vancomycin has been very useful drug for long in treatment of serious enterococcal infections but the resistance of these bacterial pathogens to vancomycin has significantly complicated the management of the patients as vancomycin resistance reduces the therapeutic options for serious enterococcal infections.[2] The purpose of this review is to find the antimicrobials that may be the possible options for treatment of vancomycin resistant enterococcal infection.

MATERIALS AND METHODS

A search of the literature was made using Medline database, Google database and online journals. The search was limited to publications in the English language. The search terms 'Enterococci', 'Vancomycin resistant Enterococci', 'Treatment of vancomycin resistant enterococci or VRE' were used. Additional information was obtained from standard book and the websites of Medscape and agencies such as Centers for Disease Control and Prevention (CDC).

RESULTS

The following were the findings of literature search

1. Enterococci: General features

Enterococci are Gram positive cocci which often occur in pairs (diplococci) or short chains and inhabit the intestinal tract, oral cavity and genitourinary tract of humans and animals as the commensal flora.[3,4]

These bacteria are relatively hardy organisms and have the ability to grow at both 10 and 45°C, at pH 9.6, and in 6.5% NaCl and survive at 60°C for 30 min and can hydrolyze esculin in the presence of 40% bile.[5]

More than 50 species of *Enterococcus* have been described in the literature.[6] While most species are commensal organisms, some species are opportunistic human pathogens. *E. faecalis* and *E. faecium* have become particularly important etiological agents of nosocomial infections, including urinary tract infections, endocarditis, bacteremia, neonatal infections, central nervous system (CNS) infections, and abdominal and pelvic infections.[7] Infections with *Enterococcus* species

are associated with a significant burden of illness, and previous studies of patients with enterococcal bloodstream infections have demonstrated mortality rates up to 43%.[8]

Enterococci exhibit an intrinsic and acquired resistance to antibiotics.[9] They are intrinsically resistant to penicillinase-susceptible penicillin (low level), penicillinase-resistant penicillins, cephalosporins, nalidixic acid, aztreonam, macrolides, and low levels of clindamycin and aminoglycosides.[9] Since they use already-formed folic acid, they bypass the inhibition of folate synthesis, resulting in resistance to trimethoprim-sulfamethoxazole.[9]

Enterococci also show acquired resistance, which includes resistance to penicillin by beta-lactamases, chloramphenicol, tetracyclines, rifampin, fluoroquinolones, aminoglycosides (high levels), and vancomycin.[9] The genes that encode intrinsic or acquired vancomycin resistance result in a peptide to which vancomycin cannot bind; therefore, cell-wall synthesis is still possible.[9]

Of all the enterococcal species, *E. faecalis* is the most common cause of infections whereas *E. faecium* has been found to be intrinsically more resistant to antibiotics than *E. faecalis.*[10]

2. Vancomycin-resistant *Enterococcus (*VRE): Epidemiology

Therapeutic difficulty with enterococcal infection was recognized as early as 1950s when enterococcal endocarditis did not respond well to penicillin alone.[11] Later, the problem was largely overcome by adding aminoglycoside to penicillin or to other cell wall synthesis inhibitor vancomycin.[12] However, after about 30 years of successful use of vancomycin, its resistance was first reported in late 1980s from Europe.[13] It was later postulated that VRE in Europe arose first in livestock owing to the association of the emergence of VRE with the use of avoparcin, a glycopeptide antibiotic used as a growth promoter, a finding that led to the ban of this practice in 1997.[14] Subsequently, US and other parts of the world started to experience the rapid spread of VRE in hospitals.[10]

In the recent years, VRE has been described as a leading cause of nosocomial infections and results in higher morbidity and mortality rates than vancomycin-susceptible enterococci.[15] The most common infections caused by VRE are urinary tract infections (UTIs), bacteremia, and wound infections.[16] Endocarditis and meningitis are the two serious infections caused by them.[17]

Vancomycin resistance is most often seen among *E. faecium* with 95% of isolates also demonstrating multidrug resistance to vancomycin, aminoglycosides, and penicillins.[18] *E. faecium* is often responsible for recalcitrant infections in severely ill patients.[19]

Six distinct vancomycin resistance phenotypes (VanA, VanB, VanC, VanD, VanE, and VanG) have been described and distinguished based upon gene content, glycopeptide minimum inhibitory concentrations (MICs), and inducibility and transferability properties.[20] The vanA and vanB phenotypes have the highest prevalence and clinical importance and uniformly confer high-level vancomycin resistance (MIC > 64 mg/ mL).[21]

Interestingly, VRE has also been reported to transfer vancomycin resistance genes to methicillin-resistant *Staphylococcus aureus* (MRSA) converting them to a vancomycin-resistant *Staphylococcus aureus* (VRSA).[22] Although exact modes of nosocomial transmission of VRE are difficult to prove, molecular, microbiological and epidemiological evidence have suggested that transmission can occur through direct contact with colonized of infected patients or through indirect contact via the hands of health care workers or via contaminated patient care equipment or environmental surfaces.[23]

Use of specific classes of antimicrobial agents has been suggested to promote the spread of VRE.[9] Extended-spectrum cephalosporins and drugs with potent activity against anaerobic bacteria are believed to promote infection and colonization with VRE and may exert different effects on the initial establishment and persistence of high-density colonization.[9]

CDC has listed the various groups of people who are at increased risk becoming infected with VRE.[24]

- People who have been previously treated with the antibiotic vancomycin or other antibiotics for long periods of time.
- People who are hospitalized, particularly when they receive antibiotic treatment for long periods of time.
- People with weakened immune systems such as patients in intensive care units, or in cancer or transplant wards.
- People who have undergone surgical procedures such as abdominal or chest surgery.
- People with medical devices that stay in for some time such as urinary catheters or central intravenous (IV) catheters.
- People who are colonized with VRE.

VRE has been distributed throughout the world. Their rate of isolation is highest in North America.[10] According to the National Healthcare Safety Network (NHSN), from 2009 to 2010, 35.5% of enterococcal clinical strains were resistant to vancomycin and were the second most common cause of nosocomial infections in the US.[25] In Canada, according to CANWARD, 6% of enterococci were resistant to vancomycin from 2007 to 2011.[26] In Europe, VRE is much less prevalent, but is on the rise. Only 4% prevalence of VRE was reported by European Antimicrobial Resistance Surveillance System

(EARSS) in Europe, however, the prevalence varied from country to country.[10] VRE has been reported from Africa, Australia, and South America as well.[27- 29] In Asia also, they have been reported from various countries such as Korea, Taiwan, China, India as well as Nepal.[30-32]

3. Antimicrobial options for treatment of infections caused by VRE

To treat the infections caused by VRE, careful review of in-vitro susceptibility data is required. Empiric therapy should be guided by local patterns of drug resistance.

Though linezolid is the only antimicrobial agent approved by the Food and Drug Administration (FDA) in the current situation for the treatment of various infections caused by VRE, some alternatives are also considered in clinical practice.[10]

I. Oxazolidinones

These drugs act on 50S subunit of bacterial ribosomes and inhibit protein synthesis. Two members of oxazolidinones have gained clinical importance for treatment of VRE infections.

a. Linezolid

Linezolid is a synthetic compound.[33] It is the first representative of oxazolidinones getting FDA approval for VRE infections.[34] It exhibits a broad Gram-positive spectrum but has bacteriostatic activity against vancomycin-resistant or susceptible enterococci.[21] The drug is available in parenteral and oral formulations, which is particularly useful for transitioning admitted patients to outpatient treatment.[34] It has been indicated in children and adults with hospital-acquired pneumonia, ventilator-associated pneumonia (VAP), complicated and uncomplicated skin and skin-structure infections (SSSIs), and Gram-positive bacteremia in patients without renal failure.[17] Since the drug has excellent central nervous system penetrating power, it is often considered a first-line therapy for enterococcal meningitis.[33] Although resistance to this drug by enterococci was thought to be rare, reports on their resistance have begun to appear.[35]

b. Tedizolid

It is a next generation oxazolidinone approved recently by FDA for acute bacterial skin and skin-structure infections, including those caused by *Enterococcus faecalis* but not *E. faecium*.[36] The drug is currently undergoing clinical trials for the treatment of bacteremia and pneumonia.[10] It exhibits broad-spectrum activity against the majority of Gram-positive organisms, including VRE.[36] It is a good option for the treatment of VRE, surpassing linezolid for several reasons.[36] In vitro, tedizolid exhibit several-fold lower minimum inhibitory concentrations (MIC) against VRE than linezolid, indicating its higher potency than linezolid.[37] Moreover, it appears to have activity against linezolid- and daptomycin-resistant enterococci, displaying MIC values on average 4- to 8-fold lower compared to linezolid.[38]

II. Quinupristin-Dalfopristin

Quinupristin/Dalfopristin (Q/D) is a parenteral combination of streptogramin type A (70% dalfopristin) and type B (30% quinupristin).[10]

The two drugs are protein synthesis inhibitors and act in a synergistic manner. Dalfopristin initially binds to the 50S bacterial ribosomal unit and induces a permanent conformational change that accelerates quinupristin ribosomal binding. Protein synthesis is impaired via both the interruption of peptide chain elongation and the inhibition of formed peptide extrusion.[21]

The combination has bactericidal activity against various Gram-positive bacteria but it is only bacteriostatic against VRE *faecium*, and lacks activity against *E. faecalis* due to efflux pumps.[10] Previously, the combination was approved for the treatment of all VRE infections, but this indication was removed due to a failure to show a clinical benefit.[10] The drug has been clinically effective in approximately three-quarters of vancomycin-resistant *E. faecium* infections.[39] To improve the drug's activity or spectrum of activity, various studies have assessed antibiotic combinations including quinupristin-dalfopristin.[34] The addition of ampicillin to quinupristin-dalfopristin provides antimicrobial activity against *E. faecalis*, although the combination was not synergistic against *E. faecium*.[34] Doxycycline augmented the inhibitory activity of quinupristin-dalfopristin against a number of *E. faecium* isolates, but this inhibitory synergy was not uniform.[34] Since venous phlebitis has been found as an important adverse effect of treatment with quinupristin-dalfopristin, it is recommended that the drug be infused through a centrally placed venous catheter.[34]

III. Beta-lactams and aminoglycoside synergy

Beta lactams are cell wall synthesis inhibitors whereas aminoglycosides inhibit protein synthesis in bacteria. Ampicillin monotherapy can be used for any ampicillin-susceptible VRE infection that does not require bactericidal activity.[10] However, when bactericidal activity is required such as for the treatment of infective endocarditis, a synergistic combination of a beta lactam with an aminoglycoside (gentamicin or streptomycin) is recommended.[10]

IV. Dual beta lactam combination

For the first time in 1995, a combination of two beta lactams (amoxicillin and cefotaxime) was reported to have a synergistic effect when tested in vitro against *E. faecalis*.[40] This effective synergism was explained by the different affinity of these two antibiotics for the penicillin-binding proteins (PBPs) of *E. faecalis*.[41] A subsequent clinical study also noted that the combination of two beta lactams (ceftriaxone and ampicillin) had similar efficacy against *E. faecalis* in infective endocarditis compared to standard therapy (ampicillin plus an aminoglycoside).[42] However, the combination may not be effective for *E. faecium* strains that exhibit high levels of ampicillin resistance. Infectious Diseases

Society of America (IDSA) guidelines on adult infective endocarditis recommend double beta 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.[43]

V. Daptomycin: Daptomycin is a novel cyclic lipopeptide compound and has a broad Gram-positive spectrum and rapid bactericidal activity.[21] The drug is currently approved for complicated skin–skin structure infection and *S. aureus* bacteremia, including right-sided endocarditis.[21] It acts by attaching to the exterior of the bacterial cytoplasmic membrane with membrane penetration of a lipophilic tail and disruption of the transmembrane potential due to ion efflux, an effect that is both concentration- and calcium ion–dependent and leads to nonlytic bacterial cell death.[21] In vitro studies have revealed that the drug has nearly uniform activity against vancomycin resistant *E. faecium* as well as *E. faecalis* strains.[21] The drug has been clinically proven as an option for VRE treatment but reports of resistance have emerged with its use.[44]

VI. Daptomycin and beta lactam Combinations

Literature have reported a potential role of combination of daptomycin plus beta lactams for the treatment of recalcitrant enterococcal infections.[41] The mechanism of the combination has been described as "see-saw" effect in which strains that develop increased minimum inhibitory concentrations to daptomycin become more susceptible to certain β-lactams. The beta lactams that have shown the best results are ampicillin, ceftaroline, and ertapenem.[41]

VII. Tigecycline: Tigecycline is a bacteriostatic agent belonging to the class of glycylcycline antibiotic, a group closely related to the tetracyclines.[21] It is the first approved member of the class and synthetically modified agent to achieve an enhanced spectrum of activity against Methicillin resistant Staphylococcus aureus, other multidrug resistant Gram positive species, and many Gram-negative bacilli.[45] Although it is not approved to treat VRE infections, in vitro and animal data and published case reports support the use of tigecycline against VRE.[33]

VIII. Doxycycline

Doxycyclin**e** is an older tetracycline. It binds reversibly to the 30S ribosomal subunit, possibly to the 50S ribosomal subunit as well, thereby blocking the binding of aminoacyl-tRNA to the mRNA-ribosome complex and inhibits protein synthesis.[46] Studies have revealed approximately 60% and 31% susceptibility rates of vancomycin-resistant *E. faecium* and *E. faecalis*, respectively.[47,48] Due to the improved intrinsic activity against VRE and less-frequent dosing, it is considered a viable option for the treatment of VRE urinary tract infections, particularly in the outpatient setting.[47] However their use is questionable for serious infections, such as VRE bacteremia since these agents possess only bacteriostatic activity.[47]

IX. Chloramphenicol: Chloramphenicol is a broad-spectrum bacteriostatic antibiotic acting on 50S ribosomal subunit of bacteria and inhibits protein synthesis.[49] Studies have reported their effectiveness in treating VRE infections, primarily urinary tract infections.[47,50]

X. Glycopeptides: Glycopeptides inhibit cell wall synthesis in Gram-positive bacteria by interacting with peptidoglycan D-Ala-D-Ala peptide stem termini of the pentapeptide side chains of the peptidoglycan precursors.[51] In the situation of enterococcal resistance to vancomycin which is an important member of glycopeptide antibiotic, the other members of glycopeptides which have been found to be effective against VRE are.

a. Teicoplanin: This is a semisynthetic glycopeptide antibiotic.[33] Studies have indicated that it is effective against most VRE strains that express the VanB phenotype and those expressing the VanC phenotype but it is rarely active against the VanA phenotype.[52,53]

b. Two new members Dalbavancin and Oritavancin got FDA approval in 2014 for the treatment of acute bacterial skin and skin structure infections by *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant *S aureus* [MSSA, MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group.[54] These drugs have shown good in-vitro bactericidal activity against VRE and are gaining clinical importance.[21]

XI. Nitrofurantoin

Nitrofurantoin is synthetic antimicrobial approved by the FDA in 1953 for treatment of uncomplicated lower urinary tract infection.[55] It is effective against most Gram-positive and Gram-negative organisms. It is taken up by bacterial intracellular nitroreductases to produce the active form of the drug via reduction of the nitro group.[55] The active form of the drug then binds to bacterial ribosomes and inhibit bacterial enzymes involved in the synthesis of DNA, RNA, cell wall protein synthesis, and other metabolic enzymes.[55] Lower urinary tract infections due to VRE can be treated with nitrofurantoin that achieves adequate level in urine but not in blood.[53]

CONCLUSION

Linezolid is the only drug approved by FDA in the present context for the treatment of various VRE infections. However, few alternative drugs can also considered in clinical practice. Future studies are required to assess their clinical effectiveness especially in the treatment of serious infections.

CONFLICT OF INTEREST: None.

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