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Therapeutic and preventative options for the management of vancomycin-resistant enterococcal infections

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Enterococci are naturally resistant to a wide range of antimicrobial agents. In addition, some enterococci, known as vancomycin-resistant enterococci (VRE) have become resistant to glycopeptide antibiotics. The therapeutic options for VRE infections are therefore very limited. New antimicrobials have been developed that are active against VRE, such as linezolid and quinupristin/dalfopristin. Others, e.g. tigecycline, daptomycin and oritavancin, are in the later stages of development. However, resistance has already been detected to some of these agents. Some success has been enjoyed through the application of older antibiotics against VRE. The lack of therapeutic options has led to the consideration of measures to prevent infection with VRE. In addition to standard infection control procedures such as isolation and hand washing, decolonization of the gastrointestinal tract has been investigated as a method for the prevention of VRE infection in vulnerable patient groups. Several decolonization regimens have been investigated. These include the use of ramoplanin, a new glycolipodepsipeptide antibiotic that has features that particularly suit it for decolonization. Ramoplanin is not absorbed from the gastrointestinal tract, has potent bactericidal activity against Gram-positive organisms and limited side effects. These features and current clinical evidence suggest that ramoplanin may have a role in future gastrointestinal decolonization regimens.

Introduction

Enterococci are intrinsically resistant to many antimicrobial agents, including cephalosporins, penicillinase-resistant penicillins, co-trimoxazole and clindamycin. Low-level intrinsic resistance to aminoglycosides occurs in most strains, and when compared with most streptococci, enterococci are also relatively resistant to penicillins. Vancomycin-resistant enterococci (VRE) have acquired resistance to vancomycin and other glycopeptides; most VRE have also acquired high-level resistance to aminoglycosides and have chromosomally mediated intrinsic resistance to penicillins.[1–3] Thus, therapeutic options for serious VRE infections are limited.[2,4] Several new antimicrobial agents have been developed; however, resistance has already been reported to these new agents. A parallel approach to the development of new therapeutic agents for VRE infections is the implementation of measures to decrease or contain the reservoir of VRE. Infection control efforts focusing on isolation precautions and education about the methods of transmission of VRE have been shown to be helpful in containing the spread of the organism. Antibiotic restrictions and guidelines help to decrease the selective pressure that allows VRE to flourish in the gastrointestinal tract, but they are difficult to implement, especially in a very ill population in which empirical antibiotic use is common. Recently, there has been much interest in the use of oral non-absorbable antimicrobial agents to eliminate VRE from the gastrointestinal tract of colonized patients to reduce the risk of serious VRE infections and prevent its further spread.

Enterococcal infections

Enterococci are normally found in the gastrointestinal tract and the female genitourinary tract. They are of relatively low virulence, but may cause urinary tract infections, intra-abdominal abscesses, bacteraemia and endocarditis. Meningitis and osteoarticular infections are less commonly attributed to enterococci. The bacteria can be spread by direct or indirect contact within a particular institution. Enterococci can also be spread between hospitals by healthcare professionals who

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work at more than one institution or by patients who were previously infected at another institution. Continuous control measures in hospitals are important in preventing the development of multidrug-resistant strains of enterococci. These control measures should be ongoing and multidisciplinary, involving hospital epidemiologists, pharmacy and therapeutics committee members, infection control committee members and the staff.

Treatment of VRE infections

Following identification of VRE infections, the first step in treatment is drainage of abscesses, debridement of wounds and removal of foreign bodies that may serve as a nidus for infection. Bacteraemia has been treated successfully without the use of antimicrobial agents and with only removal of an indwelling intravenous catheter.[5–7] Similarly, removal of an indwelling bladder catheter may be all that is required to clear VRE from the urinary tract.[5] Failure to clear the bacterium with catheter removal alone will mandate initiation of antimicrobial therapy.

Antimicrobial agents

There are several therapeutic options for VRE urinary tract infections that are not useful for other visceral infections or bacteraemias. Lower urinary tract infections due to VRE can be treated with fosfomycin or nitrofurantoin, agents that achieve adequate levels in the urine, but not in the blood. Fosfomycin has good *in vitro* activity against VRE[8,9] and has been shown to be effective in a small number of patients with VRE urinary tract infections.[10] Similarly, nitrofurantoin appears to have excellent *in vitro* activity against VRE[11] and has been shown to be effective in a few patients with urinary tract infections.[5] Fluoroquinolones can also be used for simple urinary tract infections due to isolates that are susceptible *in vitro*.

There are fewer therapeutic options for serious deep-seated visceral infections and bacteraemias. Anecdotal reports have noted the effectiveness of doxycycline.[12,13] Fluoroquinolones are generally not useful for systemic infections unless combined with other antibiotics.[2,4] Chloramphenicol has been used for the treatment of VRE bacteraemia and other serious infections.[6,14–16] The overall efficacy appears to vary between 57% and 61%; unfortunately, these reports are of a small number of patients and are retrospective. In the largest series reported, no effect on overall mortality could be attributed to chloramphenicol treatment of VRE bacteraemia, probably reflecting the serious underlying illnesses in these patients.[6] Teicoplanin, a glycopeptide that is widely used in Europe but not available in the USA, is effective against VRE that express the VanB phenotype, rather than the VanA phenotype. However, even in those strains expressing VanB phenotype, the development of resistance to teicoplanin has been noted.[17,18]

Newer therapeutic options

The introduction of quinupristin/dalfopristin and linezolid has greatly increased the therapeutic options for the treatment of serious VRE infections. Quinupristin/dalfopristin, a combination of a streptogramin A (dalfopristin) and a streptogramin B (quinupristin), has proved effective for therapy of VRE infections due to *Enterococcus faecium*, but *Enterococcus faecalis* are intrinsically resistant.[19,20] Quinupristin/dalfopristin is bacteriostatic and not bactericidal. Resistance of *E. faecium* to quinupristin/dalfopristin has been reported in animals fed a related streptogramin, virginiamycin,[21] and resistance has been noted during therapy with quinupristin/dalfopristin.[22,23] Successful treatment of VRE endocarditis with quinupristin/dalfopristin alone or in combination with other agents, such as rifampicin, has been noted in a few cases,[24,25] but failures have also been described.[26,27]

Quinupristin/dalfopristin is available only as an intravenous formulation, should be administered through a central intravenous catheter to avoid phlebitis, and can cause painful arthralgias and myalgias. In several recent series, each comprising 32–56 patients, myalgias and arthralgias were noted in 36–50% of patients, and frequently led to discontinuation of the drug.[28–30] Two of these reports noted an association of this side effect with liver disease,[28,29] although another series in children with liver transplants did not find this.[31]

Linezolid, an oxazolidinone agent, has become the drug of choice for many types of VRE infection. Unlike quinupristin/dalfopristin, linezolid is active against both *E. faecium* and *E. faecalis*;[32] however, like quinupristin/dalfopristin, linezolid is only bacteriostatic against enterococci. Linezolid is approved in some countries for serious VRE infections, including bacteraemias, urinary tract infections, and skin and soft tissue infections.[33,34] Linezolid has been reported to cure VRE endocarditis and other serious intravascular infections.[27,35]

A major advantage of linezolid is the availability of both parenteral and oral formulations; the oral formulation is almost 100% bioavailable. The most serious side effect noted with linezolid therapy is bone marrow suppression; thrombocytopenia is especially common,[36,37] noted in as many as 32% of patients in one report.[37] This side effect severely limits long-term suppressive therapy with this agent and is of concern in patients who have a haematological malignancy or who have received a haematopoietic stem cell transplant. Although rare, resistance has been noted to arise during therapy with linezolid.[38–40]

Future therapeutic options

Several new agents are under investigation for the treatment of VRE infections. Daptomycin, a lipopeptide antimicrobial agent, is bactericidal for VRE. Phase II trials indicate efficacy for skin and soft tissue infections and bacteraemias due to VRE,[41,42] and a Phase III trial comparing daptomycin with linezolid for the treatment of VRE bacteraemia is ongoing. Oritavancin (LY333328), a new semisynthetic glycopeptide, has demonstrated *in vitro* activity against VRE.[43–45] This agent is currently under study in clinical trials for the treatment of bacteraemia and skin and soft tissue infections. Glycylcyclines are yet a third class of antimicrobial agent under investigation for the treatment of VRE. Tigecycline (GAR-936) is a derivative of minocycline that has activity against VRE *in vitro* and in animal models of infection and is currently undergoing clinical trials.[46,47]

Preventative measures: gastrointestinal decolonization with antimicrobial agents

Given the sparse armamentarium available for treating serious VRE infections and the reports of resistance to newer agents, new approaches to the prevention of infection are needed. Decolonization of the gastrointestinal tract, the primary reservoir for VRE, could prove to be useful.

Principles of decolonization

The attributes of the ideal agent for VRE decolonization include: (i) not used for treatment of VRE infections; (ii) low potential for development of resistance; (iii) unlikely to lead to cross resistance with other agents used for treating VRE; (iv) narrow spectrum of activity; (v) bactericidal; (vi) taken orally and not systemically absorbed; and (vii) well tolerated.

The basic tenets for use of any preventative agent—target only those patients at high risk of infection and administer the decolonizing agent only during the highest risk period—should be followed for any attempt at decolonization. Most VRE-colonized patients will not develop symptomatic infection. Therefore, decolonization efforts should not aim to eradicate VRE from all carriers, but should be focused on those groups that have an increased risk of serious VRE infection. One such group includes patients who have a haematological malignancy or who have received a haematopoietic stem cell transplant.[48–51] Additionally, patients in the intensive care unit, liver transplant recipients and haemodialysis patients are also at increased risk of serious VRE infections.[15,52–57]

For certain of these groups, the period of highest risk is well defined. This is especially true for those with haematological malignancies and recipients of haematopoietic stem cell transplants. In these patients, the period of highest risk is when they are neutropenic; mucositis and the presence of *Clostridium difficile* colitis also appear to contribute to the risk for development of VRE bacteraemia in this group.[48,49,58,59] For liver transplant recipients, most VRE infections have been reported in the first 60 days post-transplantation.[15,55] For other patients in the intensive care unit and those on haemodialysis, the period of risk is either not as well defined or extends indefinitely. Thus, the latter two groups are not ideal candidates for decolonization efforts.

Decolonization regimens

Various different oral antimicrobial regimens have been tried for VRE decolonization; these include bacitracin, gentamicin, tetracycline, doxycycline, novobiocin, rifampicin and ramoplanin.[60–66] Single agents as well as combinations of several of these agents have been used. Those trials that used only non-absorbable agents have a greater potential to define an appropriate decolonization regimen; adding doxycycline or rifampicin to non-absorbable agents may well obviate the use of these agents for later treatment of VRE infections.

Several studies have been reported using bacitracin for decolonization. Two early, uncontrolled trials showed that the combination of bacitracin with doxycycline appeared to be effective in decolonization of VRE from the gastrointestinal tract.[60,62] Three subsequent studies showed that bacitracin was ineffective.[64–66] One observational cohort study in a haemodialysis unit used bacitracin solution, 75 000 U four times daily, and doxycycline capsules 100 mg daily, for 14 days.[66] At the end of 14 days, all 15 treated patients had cleared VRE from their stool compared with only eight (33%) of 24 control patients who had received no treatment. However, at 30 day follow-up only 40% of treated patients and 37.5% of untreated patients were VRE free. Another observational cohort study in cancer patients used 25 000 U bacitracin with 80 mg oral gentamicin, both given three times daily for a median of 14 days.[64] Of note is the fact that 38% of the 45 patients could not tolerate the regimen and dropped out of the study by day 3. Only five of the remaining 28 patients, compared with one of 28 matched controls, showed eradication of VRE from the stool at 3 month follow-up. More importantly, VRE bacteraemias occurred in six patients in each group. The only randomized, placebo-controlled, blinded study compared treatment with 50 000 U zinc bacitracin capsules with placebo capsules, given to six patients in each group four times daily for 10 days.[65] At 3 weeks, VRE was eradicated from stool in only two patients in each group.

Novobiocin has been tried for VRE decolonization in a small number of oncology patients, some of whom were also bacteraemic.[61] Tetracycline, doxycycline or rifampicin was added to the non-absorbable agent; in only one of eight patients was VRE cleared from stool, and novobiocin was poorly tolerated.

It should be mentioned that persistence of VRE in the gastrointestinal tract for long periods appears to be the rule.[51,67–70] Sampling methods (stool versus rectal swabs), times that samples are obtained after decolonization regimens were used and use of enrichment broth before plating the sample vary among these studies and can have substantial effects on the yield of VRE.[71,72]

Ramoplanin

The most promising agent for gastrointestinal tract decolonization of VRE is ramoplanin, the first of a new class of antibiotics called glycolipodepsipeptides. Ramoplanin inhibits cell wall synthesis independently of the D-Ala–D-Ala site that is targeted by glycopeptides.[73] The drug interferes with cell wall biosynthesis by inhibition of *N*-acetylglucosaminyl transferase-catalysed conversion of lipid intermediate I to lipid intermediate II. Cross-resistance between glycopeptides and ramoplanin is unlikely and has not been noted in clinical isolates to date.[74,75] Although there is one *in vitro* study suggesting that ramoplanin could induce vancomycin resistance in *E. faecalis*,[76] another study did not verify this.[77] Ramoplanin is potent and rapidly bactericidal against Gram-positive bacteria only, including all strains of *E. faecium* and *E. faecalis*, *Staphylococcus aureus*, coagulase-negative staphylococci and *Clostridium* spp., including *C. difficile*.[74,75,78] The drug is not absorbed when taken orally, and thus achieves high faecal concentrations and has minimal side effects.

In a placebo-controlled, blinded study of two different dosages, 400 mg and 100 mg, ramoplanin taken twice daily significantly decreased VRE colonization at the end of 7 days of therapy ($P < 0.001$) (Figure 1).[63] Both dosages were effective when compared with placebo, but the 400 mg dosage suppressed VRE colonization below the limits of detection in a greater percentage of patients and for a longer period. However, by 3 weeks after the drug was stopped, there was no difference in colonization rates in any of the three groups: ~75% of all patients were colonized with VRE. Further analysis showed that recolonization in those receiving ramoplanin 400 mg was as likely to be with a new strain as with the original strain,[79] suggesting that many patients had their original VRE eradicated only to be recolonized after treatment was stopped. More patients treated with placebo or ramoplanin 100 mg were recolonized with the original strain and not with a new strain. Decolonization was more likely to persist in those patients who did not receive subsequent antibiotics active against anaerobes. By day 21 after treatment had finished, 14 of 34 (41%) patients who became recolonized with VRE had received anti-anaerobic antibiotics, but none of five who remained VRE negative had received such antibiotics (relative risk 0.16, $P = 0.02$).[79]

Adverse events were similar for all treatment groups, indicating that ramoplanin was safe and well tolerated. An important issue not addressed by this Phase II study is confirmation of the relationship between VRE colonization and subsequent infection. Assuming these are linked, then use of this agent throughout the highest risk period in neutropenic patients, for example, could potentially prevent serious VRE infections. This concept is currently under study in a Phase III, multicentre, randomized, blinded, placebo-controlled trial in patients who have a haematological malignancy or are undergoing haematopoietic stem cell transplant and who are neutropenic.

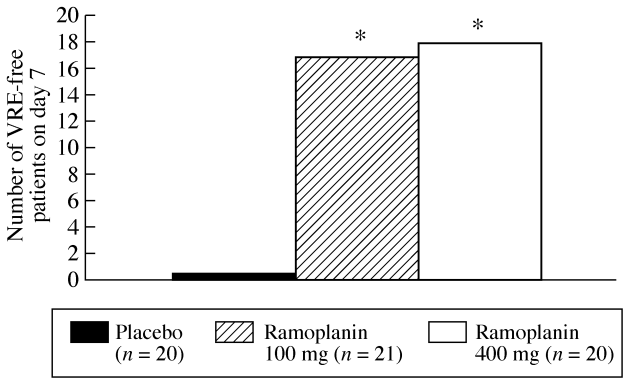

Figure 1. Ramoplanin is highly effective in suppressing gastrointestinal VRE levels below the limit of detection (*$P < 0.001$ compared with placebo).[63]

Other preventative measures

Infection control

Although it is possible that antimicrobial decolonization of the gastrointestinal tract could decrease environmental contamination and thus help to reduce the nosocomial spread of VRE, this concept has not been studied. Until this is shown to be true, isolation precautions recommended by the US Hospital Infection Control Practices Advisory Committee (HICPAC) should be used for VRE-colonized patients.[80] Several studies have shown that the use of isolation precautions does lead to decreased transmission of VRE within a unit.[56,81,82] Precautions include the use of a private room for colonized patients and dedicated equipment to be kept in the room for that patient's care. Clean, non-sterile gloves and disposable gowns should be worn by those entering the room. Wearing gloves has been shown to prevent acquisition of VRE on healthcare workers' hands.[83] The requirement for gowns remains controversial – they are costly, take additional time and can be uncomfortably warm.[82,84] However, gowns have been shown to be helpful in an outbreak situation and probably do increase healthcare workers' cognizance of their personal role in the transmission of VRE.[56] Careful attention to hand cleansing, even though gloves are worn, cannot be overemphasized. Transient carriage of enterococci on the hands of healthcare workers has been documented,[83] and

VRE purposely inoculated on to hands persist for as long as 60 min.[85]

The recommendations for such strict precautions have been generated, in part, by the important role played by the environment in the transmission of VRE[56,86,87] and the recognition that patients remain persistently colonized for extremely long periods.[67–70] Environmental contamination by VRE is common; the highest concentrations of organisms occur on bed rails, over-the-bed tables, bed linen, urinals and bedpans. Persistence of viable enterococci on environmental surfaces for days to weeks has been noted in several studies.[88,89] Contamination of the environment increases when colonized patients have diarrhoea[59] and when the amount of VRE in the stool increases because of the selective pressure of antibiotics.[90–92] Patients with diarrhoea are also more likely to have VRE isolated from the skin of the groin and even the arms.[93]

Antibiotic restrictions

It has now been shown that colonization of the gastrointestinal tract persists for months to years.[51,67–70] Studies in both experimental animals and colonized patients have shown that the quantity of VRE found in stool increases several-fold when antibiotics with anti-anaerobic activity are administered.[90,91] Cyclic changes in the concentration of VRE in the stool are correlated with the use of antibiotics that decrease the quantities of anaerobes in the stool. Thus, there are times when no VRE are detectable in stool, only to be followed by large increases in VRE concentrations when broad-spectrum antibiotics are again administered.

The HICPAC guidelines strongly recommend decreasing the use of vancomycin for prophylaxis and empirical therapy as a measure to decrease VRE colonization.[80] In the USA, the increase in vancomycin resistance can be linked partly to the tremendous increase in vancomycin use during the past 20 years.[1] However, as discussed above, many studies have found a stronger correlation with the use of extended-spectrum cephalosporins and antimicrobial agents with activity against anaerobes.[90] Thus, not only restriction of vancomycin, but also diligent prescribing of other broad-spectrum and anti-anaerobic antimicrobials is important to decrease colonization with VRE. However, in certain settings, such as oncology and haematopoietic stem cell transplant units, broad-spectrum antimicrobial agents are an essential component of empirical treatment of febrile patients who are neutropenic. In such units, gastrointestinal decolonization measures might be especially useful.

Conclusions

Resistance to antimicrobial agents by VRE means that there is continued demand for development of new therapeutic agents and the implementation of measures to decrease or contain the reservoir of VRE. Decolonization of the gastrointestinal tract, the primary reservoir of VRE, could prove to be a useful new approach to the prevention of infection. Ramoplanin, the first of a new class of antibiotics called glycolipodepsipeptides, is the most promising agent for gastrointestinal tract decolonization. Isolation precautions should continue to be used and attention paid to diligent prescribing of vancomycin and other broad-spectrum and anti-anaerobic antimicrobials.

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