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MINIREVIEW

Screening and Treatment of Infections Caused by Resistant Enterococci

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INTRODUCTION

The traditional therapy of serious enterococcal infections with penicillin and streptomycin was established in the 1950s based on the high success rate in treating what was previously a nearly uniformly fatal disease (21). Unfortunately, some enterococci have developed resistance to these agents. The necessary methods to screen for such bacteria, as well as current treatment recommendations, are discussed in this minireview.

MICROBIOLOGICAL SCREENING AND TREATMENT

Treatment of serious enterococcal infections usually requires a bactericidal combination of antibiotics which includes a cell wall-inhibitory agent to which the enterococcus is susceptible and an aminoglycoside to which the enterococcus does not exhibit high-level resistance. The American Heart Association-recommended aminoglycoside agents are either gentamicin, 1 mg/kg of body weight intravenously or intramuscularly every 8 h adjusted to obtain a peak level of approximately 3 μg/ml, or streptomycin, 7.5 mg/kg intramuscularly every 12 h adjusted to obtain a peak level of approximately 20 μg/ml (4). It is important to note that the dosage of gentamicin recommended is significantly lower than that used to treat gram-negative bacterial infections. Both experimental and clinical data on enterococcal endocarditis suggest that higher doses of gentamicin or streptomycin yield greater toxicity without improving clinical outcome (25, 42, 74, 75). However, some strains are synergistically killed by 5 μg of gentamicin per ml plus penicillin but not by 3 μg of gentamicin per ml, thus possibly justifying full gentamicin doses of 1.5 to 1.7 mg/kg every 8 h (12). Both penicillin G and ampicillin have been successful and are recommended as the cell wall-inhibitory agents of choice (4). In a patient with normal renal function, 20×10^6 to 30×10^6 U of penicillin G per day or 12 g of ampicillin per day should be administered intravenously either by continuous infusion or in six equal doses (4). Although ampicillin generally has the lower MIC, albeit usually by only one dilution (2, 3, 33, 38, 58, 70), penicillin G may be the preferred agent due to its narrow spectrum of activity, lower cost, and lower side-effect profile.

Vancomycin is recommended as the drug of choice only in cases of significant penicillin allergy or in treatment of ampicillin- and penicillin-resistant strains (4). Although vancomycin in combination with streptomycin or gentamicin has been demonstrated to be synergistic against the enterococcus in vitro and in animal models (28, 40, 72), the clinical experience using vancomycin in the treatment of serious enterococcal infections is much more limited (8, 19, 27, 44, 72) than the clinical experience with penicillin G or ampicillin (39, 44, 74). In fact, some of the patients reported as being successfully treated with vancomycin-containing regimens also received therapy with penicillin G or ampicillin, making it impossible to discern to what extent the vancomycin actually contributed to the outcome (8, 19, 27, 44, 72). Furthermore, vancomycin is more costly and generally has a higher MIC against the enterococcus than does penicillin or ampicillin (33), and when older formulations were used with aminoglycosides there was up to a 35% incidence of nephrotoxicity (16). Vancomycin should be administered at 30 mg/kg/day intravenously in two equal doses and adjusted as necessary to obtain a peak concentration of 30 to 45 μg/ml (4).

Ampicillin-resistant isolates are either β-lactamase producers or, more commonly, non-*Enterococcus faecalis* enterococcal species (usually *Enterococcus faecium*) (5, 7, 38, 43, 70, 73). Nitrocefin hydrolysis is the definitive test for β-lactamase production. Imipenem susceptibility testing may also serve as an aid in detecting β-lactamase producers, since such strains remain susceptible to imipenem while the most common non-*E. faecalis* species, *E. faecium*, is resistant (14, 34). However, caution must be used in interpreting the results of imipenem or β-lactamase inhibitor combinations (amoxicillin plus clavulanic acid or ampicillin plus sulbactam) to detect β-lactamase production since the results are inoculum dependent (31, 55). Vancomycin plus gentamicin is an alternative treatment for ampicillin-resistant strains, assuming that high-level gentamicin resistance is not also present. There is not enough clinical experience with β-lactamase-producing enterococci to make a recommendation on the optimal treatment of such infections. Although clinical data are lacking, ampicillin-sulbactam, teicoplanin, experimental *N*-alkyl vancomycin derivatives, daptomycin, and imipenem are possible alternatives to vancomycin as cell wall-active agents for β-lactamase-producing strains, while teicoplanin, daptomycin, and experimental *N*-alkyl vancomycin derivatives may also be useful alternatives for non-β-lactamase-producing ampicillin-resistant strains (26, 36, 41, 52, 60, 68, 71).

Pending clinical trials, the use of imipenem to treat serious enterococcal infections is not recommended when penicillin, ampicillin, or vancomycin can be used. Imipenem was found to be less effective in combination with streptomycin or gentamicin both in vitro and in experimental endocarditis than penicillin G combined with the aminoglycoside (30, 64). Additionally, experience with imipenem treatment of en-

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docarditis is limited, imipenem having been shown to be effective only in the treatment of staphylococcal endocarditis in intravenous drug abusers (11). Sulbactam possesses no activity against the enterococcus, and therefore its use is unlikely to provide added benefit over ampicillin alone in treating non-β-lactamase-producing isolates of *E. faecalis* and *E. faecium* (10). The ureidopenicillin antibiotics azlocillin, mezlocillin, and piperacillin have approximately the same activity against enterococci as penicillin and ampicillin, while ticarcillin and carbenicillin are considerably less active (20, 24, 33, 76). However, the ureidopenicillins are not active against ampicillin-resistant bacteria that produce penicillinase or against bacteria that possess a low-affinity penicillin-binding protein, such as *E. faecium*. If one of these agents is to be used either empirically or to treat polymicrobial infections when broader antimicrobial coverage is desired, either penicillin or ampicillin susceptibility may be used to guide the appropriateness of such therapy.

The decision as to which aminoglycoside susceptibilities to include in a screening battery is based on an understanding of the inactivation enzymes. The same bifunctional enzyme, 2''-phosphotransferase-6'-acetyltransferase, that mediates high-level gentamicin resistance also mediates tobramycin, netilmicin, amikacin, and kanamycin resistance (9). Some enterococci are susceptible to gentamicin, tobramycin, and netilmicin but resistant to kanamycin and amikacin because they produce 3'-phosphotransferase-III but not the aforementioned bifunctional enzyme (35). Such isolates are not synergistically killed by penicillin-amikacin combinations even though they may show high-level in vitro susceptibility to amikacin. It has been demonstrated by several investigators that an amikacin MIC of <2,000 μg/ml is not predictive of ampicillin-amikacin synergism (1, 13, 59, 62, 63). Kanamycin susceptibility, however, may be used to predict amikacin synergy. Streptomycin resistance is mediated either ribosomally or by a third enzyme, streptomycin adenyltransferase (13), neither of which causes high-level resistance to the other aminoglycosides. Therefore, aminoglycoside screening should include tests for high-level resistance to gentamicin and streptomycin. Kanamycin screening need be performed only in the event that a combination of amikacin plus a cell wall-active antibiotic is to be used instead of a combination of gentamicin plus a cell wall-active antibiotic. This may be required in the case of a polymicrobial infection in which both enterococci and gentamicin-resistant gram-negative organisms are involved.

The decision as to the concentration of aminoglycoside to use in screening is based on the level of aminoglycoside resistance at which combination therapy will no longer result in synergy. Studies have shown that a concentration of approximately 1,000 to 2,000 μg/ml in broth is adequate for predicting aminoglycoside synergy with cell wall-active antibiotics (46, 58, 67). The reader is referred to the recent review by Murray for recommendations on screening tests for high-level aminoglycoside resistance (49).

There are no synergistic antimicrobial combinations that have proven clinical efficacy against enterococci that possess high-level resistance to all aminoglycosides (29). For treatment of serious infections with these strains or with enterococci resistant to all cell wall-active antibiotics, alternative therapies must be considered. Ciprofloxacin administered by continuous intravenous infusion with or without azlocillin was effective in sterilizing heart valves in experimental endocarditis due to a β-lactamase-producing, highly gentamicin-resistant strain of *E. faecalis* in rats (15). With the exception of one other study using an animal model and azlocillin plus ciprofloxacin (56), there has been no definitive evidence to suggest that combining quinolones with other antimicrobial agents enhances antienterococcal activity (47, 51, 61, 65). Additionally, when enterococcal isolates from patients with infective endocarditis were used to create experimental endocarditis in rabbits, ciprofloxacin alone or combined with gentamicin was significantly less effective than procaine penicillin alone or procaine penicillin combined with gentamicin (17). The same study also demonstrated the combination of ciprofloxacin and penicillin to be no more effective in vitro than either antibiotic alone. Further clinical data are required before quinolone antibiotics can be recommended for use either alone or in combination to treat serious enterococcal infections.

Trimethoprim-sulfamethoxazole acts by inhibiting folate synthesis. Since the enterococcus can synthesize folates and incorporate exogenous folates, it has been felt to be resistant in vivo to the action of trimethoprim-sulfamethoxazole (22). This reasoning has been challenged recently (23), but until further in vivo data are available, the use of trimethoprim-sulfamethoxazole cannot be advocated (48). Since rifampin is bacteriostatic against the enterococcus and since resistance emerges rapidly when it is used alone, rifampin-containing regimens are unlikely to be useful in the treatment of serious enterococcal infections (45). Although daptomycin appears to be active in vitro, its activity in vivo is markedly reduced, probably due to its high degree of protein binding in serum (6). Synergistic bactericidal activity when daptomycin is combined with fosfomycin has been demonstrated (57). Further studies are needed to clarify the potential role of daptomycin in the treatment of enterococcal infections.

CLINICAL EXPERIENCE WITH MULTI-DRUG-RESISTANT ENTEROCOCCI

Kathpalia et al. reported a patient with endocarditis caused by an enterococcal isolate resistant to all aminoglycosides and possessing penicillin tolerance (32). Although ampicillin plus another unspecified antibiotic achieved sterile blood cultures, the patient died. Fernandez-Guerrero et al. reported a patient with *E. faecalis* endocarditis resistant to all aminoglycosides who developed acute cardiac failure after 4 weeks of antibiotic therapy (9 days of ampicillin plus gentamicin followed by an additional 19 days of ampicillin alone) (18). The patient underwent aortic valve replacement and an additional 2 weeks of ampicillin therapy. Cultures of the valve yielded *E. faecalis*. The patient remained well 14 months following discontinuation of therapy. Patterson et al. reported a case of possible endocarditis with a blood isolate of *E. faecalis* resistant to all aminoglycosides and possessing the ability to produce β-lactamase (54). The patient was treated successfully with a 6-week course of vancomycin alone. Lipman and Silva reported two cases of *E. faecalis* endocarditis with high-level gentamicin resistance (37). One patient was cured with ampicillin alone (MIC = 0.5 μg/ml), and the other was diagnosed postmortem by blood cultures and autopsy examination of the heart. Spiegel and Huycke reported a case of endocarditis with *E. faecalis* possessing high-level gentamicin resistance but lacking high-level streptomycin resistance (66). The patient was treated successfully with penicillin G and streptomycin, followed by vancomycin and streptomycin after a rash developed. Approximately 1 month after the discontinuation of antimicrobial therapy, the patient underwent mitral valve replacement for congestive heart failure. Blood cultures remained sterile, and histologic

examination of the mitral valve showed no evidence of endocarditis.

Although there have been reports of therapy for enterococcal endocarditis with penicillin or ampicillin alone, the overall success rate is low. Of 18 patients treated with penicillin alone by Geraci and Martin, 7 were cured and 11 failed despite the lack of use of high-dose penicillin in many of the patients (21). Beaty et al. reported one patient with enterococcal endocarditis in which the ampicillin MIC for the organism was 0.79 μg/ml (2). This patient was cured with ampicillin alone. Parker and Hoeprich reported one patient with enterococcal endocarditis cured with ampicillin alone (53). Based on these isolated case reports, if a serious enterococcal infection occurs with a strain possessing high-level resistance to both gentamicin and streptomycin, ampicillin alone in high dosages (at least 12 g daily in a patient with normal renal function) may be successful, especially if the MIC is low. If the patient has endocarditis, serious consideration should be given to early valve replacement. If treatment with other regimens is attempted based on the results of synergy studies in the microbiology laboratory, it should be done with the proviso that in vitro synergy may not necessarily translate to in vivo success in humans (69).

CONCLUSION

The number of reports of multiply antibiotic-resistant enterococci has increased over the past few years. Although a bactericidal combination of antibiotics appears to be needed for cure only in endocarditis and meningitis (50), serious consideration should be given to testing for cell wall-active antibiotic susceptibility and high-level aminoglycoside screening for other isolates as well. A knowledge of the prevalence of these resistant strains cultured from a hospital's patient population can be used to guide the selection of appropriate antimicrobial therapy. The combination of a cell wall-active antibiotic to which the organism is susceptible and an aminoglycoside to which the enterococcus does not possess high-level resistance remains the cornerstone of therapy when such a combination exists. Optimal antibiotic regimens for treatment of multiply resistant strains in serious enterococcal infections are yet to be determined.

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