

New Antimicrobials for Glycopeptide-Resistant Infections

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Therapy for infections due to glycopeptide-resistant organisms presents real challenges for the clinician. An important first approach to infections due to glycopeptide-resistant organisms is to remove any foreign bodies (e.g. intravenous, peritoneal, urinary catheters, etc.) and drain or debride any collections of infected fluid or tissue present. Generally, the most serious infections due to glycopeptide-resistant enterococci (GRE) occur in severely ill and often immunocompromised patients. However, enterococcal urinary tract infections may occur in any patient, regardless of the state of debility or immunocompetence. Most isolates of GRE remain susceptible to nitrofurantoin, which has been successfully used to treat urinary tract infections caused by GRE (26). In GRE strains which remain susceptible to penicillin and ampicillin, these agents can be utilized. Unfortunately, most GRE isolates in the United States are resistant to ampicillin and penicillin. Additionally, most GRE in the United States exhibit high levels of aminoglycoside resistance. Therefore, the use of combination therapy for a bactericidal effect is not possible, which is a particular problem in cases of endocarditis caused by GRE.

Combinations of vancomycin plus ampicillin sometimes exhibit in vitro synergism against GRE (22). The mechanism by which this synergy occurs probably relates to the fact that subinhibitory concentrations of vancomycin induce the synthesis of modified cell wall precursors ending in D-alanyl-D-lactate; the bacteria, in response, utilize an alternative penicillin-binding protein for cross-linking these cell wall precursors. Because it appears that this penicillin binding protein is more susceptible to penicillin and ampicillin than is penicillin binding protein 5, which normally performs this function in enterococci and is intrinsically resistant to penicillin, the combination might be synergistic (26). Unfortunately, this phenomenon is inconsistent at best. In animal models, colonies resistant to synergism occur with relatively high frequency during therapy (4). In one study, the addition of gentamicin to the β -lactam-vancomycin combination prevented the emergence of mutant strains in animals, provided that the strain was not highly resistant to the aminoglycoside (5). The combination of ampicillin and imipenem appeared effective in an experimental model of endocarditis in rabbits performed in our laboratory (3). High dose continuous infusion ampicillin/sulbactam plus gentamicin has been reported to be effective therapy for persistent bacteremia due to glycopeptide-resistant, ampicillin-resistant *E. faecium* (25).

Teicoplanin has been used to treat selected infections caused by vanB GRE but emergence of resistance has complicated therapy. If such therapy is to be optimally effective, a second antimicrobial exhibiting in vitro susceptibility, preferably an aminoglycoside, should be used (26).

Selected strains of GRE may be susceptible to tetracyclines, chloramphenicol, rifampin, ciprofloxacin, ofloxacin, and/or novobiocin, and there have been anecdotal reports of successes with these agents when used alone or in combination (12). All of these agents are only bacteriostatic and are not particularly useful in treating serious enterococcal infections such as endocarditis or meningitis. Chloramphenicol has only been partially effective in the treatment

of GRE infections in humans (21, 29). In an experimental model of endocarditis in rats, a 5-day course of treatment with ciprofloxacin/rifampin/gentamicin was effective, although selection of rifampin-resistant mutants occurred in all animals (38). Novobiocin and bacitracin have been used in attempts to suppress fecal carriage of GRE, with less than impressive results (27, 30).

Strains of glycopeptide-intermediate *S. aureus* may be susceptible to rifampin, fusidic acid, aminoglycosides (gentamicin, streptomycin, arbekacin), tetracyclines, trimethoprim-sulfamethoxazole, chloramphenicol, novobiocin or nitrofurantoin. Anecdotal successful therapy of glycopeptide-intermediate *S. aureus* with arbekacin/ampicillin/sulbactam (6), rifampin/trimethoprim-sulfamethoxazole (35), and vancomycin/gentamicin/rifampin (35), have been reported.

Linezolid is an investigational oxazolidinone antimicrobial agent which acts by inhibiting protein synthesis in a unique fashion, suggesting that it may be a promising alternative to currently available agents (32). Activity against GRE and glycopeptide-intermediate *S. aureus* has been reported (10, 19, 24, 36, 39). In vitro studies performed in our laboratory demonstrated that all isolates of GRE were inhibited by $\leq 1 \mu\text{g/ml}$ of linezolid and all isolates of MRSA were inhibited by $\leq 2 \mu\text{g/ml}$ of linezolid. Strains of glycopeptide-intermediate *S. aureus* are also reportedly inhibited by $\leq 1 \mu\text{g/ml}$ of linezolid. Unfortunately linezolid is bacteriostatic.

A limited number of linezolid experimental animal studies have been published to date. Linezolid was active in MRSA, *S. epidermidis*, and GRE murine systemic infection models (13). In *S. aureus* and *E. faecalis* murine soft tissue infection models, linezolid exhibited acceptable curative activity (13). In monomicrobial *S. aureus* murine infections, linezolid exhibited indifferent or additive activity when combined with other antibiotics active against gram positive bacteria (13). Excellent oral bioavailability makes linezolid an attractive candidate for the treatment of infections such as endocarditis and osteomyelitis for which extended courses of treatment are typically required for cure. In this regard, we are investigating the activity of linezolid in a rat methicillin-resistant and methicillin-sensitive *S. aureus* osteomyelitis model. Fortunately, it appears from previous studies that in vitro selection of resistant mutants does not readily occur (28, 39). Phase III human studies with linezolid, including skin and soft tissue infection and community acquired pneumonia studies, are in progress.

Quinupristin-dalfopristin (Synercid) is, like other streptogramin antibiotics, a synergistic combination of streptogramin A (dalfopristin) and streptogramin B (quinupristin). Quinupristin and dalfopristin are water-soluble derivatives of the streptogramins pristinamycin IA (factor B) and IIA (factor A), respectively, produced by *Streptomyces pristinaespiralis*. They are given parenterally in the same ratio as they are produced by the actinomycete. The two drugs are structurally unrelated, bind to distinct sites of the 50S ribosomal subunit, and cooperate to inhibit protein synthesis. Synergy displayed by antibiotics containing a streptogramin A and a streptogramin B results in bactericidal activity, whereas the individual components are only bacteriostatic. Quinupristin-dalfopristin is active against most gram positive bacteria. At 1 mg/ml, quinupristin-dalfopristin inhibits 90% of *S. aureus* and CNS, including strains that are resistant to methicillin. Strains of glycopeptide-intermediate *S. aureus* are also reportedly inhibited by $\leq 1 \mu\text{g/ml}$ of quinupristin-dalfopristin. Quinupristin-dalfopristin is active against *E. faecium* (2, 11), including strains resistant to ampicillin, gentamicin, and vancomycin, but not against *E. faecalis*, probably because strains of this species are resistant to dalfopristin.

In one clinical study, 15 patients were treated with quinupristin/dalfopristin for GRE infection, including bacteremia (4), urinary tract infection (4), intraabdominal infection (5), otitis (1), and

meningitis (1) (9). Three patients had clinical and bacteriologic cures. Relapses occurred in five patients with recovery of GRE from infected sites in post-treatment cultures. Ten patients died of severe underlying disease; GRE was believed to contribute directly to the death of only one patient. In another study the clinical and bacteriological outcomes of 20 patients with GRE bacteremia treated with quinupristin/dalfopristin were compared, with a historical cohort of 42 patients with GRE bacteremia treated with other agents (23). There were five cases of recurrent GRE bacteremia in the quinupristin/dalfopristin-treated cohort and 21 in the controls; persistence of GRE at the primary site was found in six and 18 of the available patients with follow-up cultures in these two cohorts. In-hospital mortality was high in both groups: 65% in the quinupristin/dalfopristin group and 52% in the control group; however, GRE-associated mortality was significantly lower in the quinupristin/dalfopristin group (five and 17 respectively; $P = 0.05$). Emergence of resistance to quinupristin/dalfopristin during therapy for *E. faecium* bacteremia has been noted (7). Phase III human studies with quinupristin/dalfopristin including skin and soft tissue infection, nosocomial pneumonia and community acquired pneumonia studies have been performed.

Unfortunately, there are reports of resistance to quinupristin/dalfopristin among isolates of *E. faecium* and staphylococci. Resistance has been reported not only in France, where it is probably related to long-standing use of streptogramins in humans, but also in countries where these antibiotics have never been used for human beings. Virginiamycin displays complete cross-resistance with quinupristin-dalfopristin, and its use as an additive in animal feeds might have led to the selection of resistance to streptogramins in animal strains and to their subsequent spread to human commensals. A recent study has shown that most strains of *E. faecium* isolated from the feces of turkeys fed with virginiamycin were resistant to streptogramins (37).

LY333328 is an investigational N-alkyl semisynthetic derivative of the naturally occurring glycopeptide LY264826 (8). Activity against GRE and MRSA has been reported (1, 14, 16, 17, 20, 34). In our laboratory, all isolates of GRE were inhibited by 2 ug/ml of LY333328, and 8 ug/ml of LY333328 was bactericidal against all isolates tested (31). All isolates of MRSA were inhibited by 1 ug/ml of LY333328, and 4 ug/ml of LY333328 was bactericidal against all methicillin-resistant *S. aureus* isolates tested (31). LY333328 has been shown to be active in a GRE rabbit experimental endocarditis model (33).

The everninomycin derivative ziracin is the first of a new class of oligosaccharide antibiotics and is active against gram positive bacteria. MIC₉₀ values of ziracin against MRSA, glycopeptide-intermediate *S. aureus*, and GRE are 1, 0.5, and 0.5 ug/ml, respectively.

Other investigational agents with in vitro activity against glycopeptide-resistant organisms include ramoplanin, daptomycin, ketolides (e.g. HMR 3647 and ABT-773), trinemis, new broad-spectrum cephalosporins (e.g. TOC-39) and some of the new fluoroquinolones (15, 18).

In conclusion, despite the emergence of glycopeptide-resistant organisms over the past several years, impressive strides are being taken in the development of new antimicrobial agents.

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