



New Agents Against Nosocomial Gram-Positive Pathogens

David Livermore

Antibiotic Resistance Monitoring & Reference Laboratory
Health Protection Agency, UK

The 1980s and 1990s saw accumulation of multi-resistant gram-positive cocci in many hospitals worldwide - notably methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE). The 1990s also saw the first reports of vancomycin-intermediate MRSA and many more of teicoplanin-resistant *S. aureus*. More recently there have been 2 reports of vancomycin-resistant *S. aureus*, these having acquired *VanA* from *Enterococci*. The answer to these resistance problems partly lies in better infection control but, whilst several countries (e.g. the Netherlands, Denmark, Sweden and Norway) have kept MRSA rates impressively low by such measures, there few examples (except perhaps Denmark in the 1960s) when established MRSA rates have been reduced dramatically. So, development of new therapies against gram-positive pathogens remains critical. Those newly launched include linezolid and quinupristin/dalfopristin; those in advanced development include daptomycin, oritavancin, tigecycline, and ramoplanin. Others, less advanced, include cephalosporins that bind to PBP-2' of MRSA.

Linezolid Linezolid binds the 50S ribosomal sub-unit, preventing formation of a functional initiation complex for protein synthesis. It has near-universal activity vs. gram-positive bacteria at 1-4 mg/L but gram-negative bacteria are resistant owing to endogenous efflux. Full activity is retained vs. MRSA and VRE. Excellent bioavailability allows oral administration, permitting early discharge of some patients. Linezolid is as effective as established therapies in skin and soft tissue infections and community-acquired and nosocomial pneumonias. Toxicity is limited but prolonged use (>2 weeks) may cause haematological effects, principally thrombocytopenia. Resistance is difficult to select *in vitro* but can be obtained by stepwise passage; it may also be selected *in vivo* in prolonged therapy, if the drug is under-dosed, or the infection is sequestered. Most reports of emergent resistance concern enterococci, but two relate to *S. aureus*; one describes nosocomial spread of linezolid-resistant VRE.² The mechanism entails mutation of Domain V of the 23S rRNA, with a G2576U substitution. The difficulty of selecting resistance is because multiple gene copies (4-7 according to the species) must be altered. Experimental oxazolidinones show small improvements in MIC ranges over linezolid; none is in advanced development.

Streptogramins Quinupristin/dalfopristin comprises two unrelated components that act synergistically to block peptide elongation. Activity at 0.5-2 mg/L is near universal vs. *Staphylococci*, *Streptococci* and *Enterococcus faecium*; *E. faecalis* is resistant (MICs 16-32 mg/L) owing to efflux. Administration is parenteral and, to minimise local venous disturbance, should be via a central line. Even then, the compound has 10% rates of arthralgia and myalgia. Clinical trials showed equivalence to vancomycin in skin and soft tissue infections, and an extensive compassionate-use programme gave impressive results, notably in bone and joint infections due to MRSA.³ Unlike linezolid, quinupristin/dalfopristin is bactericidal, though this activity is lost (without any rise in MIC) vs. strains with constitutive expression of *erm*, a transposon-mediated gene determining an rRNA methylase that

modifies the 23S rRNA to block binding of B streptogramins (e.g. quinupristin), macrolides and lincosamides. Frank resistance arises if the streptogramin A component (dalfopristin) is inactivated by plasmid-mediated acetyltransferases, or removed by acquired efflux determinants. These mechanisms are rare in human isolates.

Daptomycin Daptomycin, a lipopeptide, was investigated by Eli Lilly in the late 1980s, using a bds regimen, but was discarded owing to causing muscle weakness. It has since been reformulated by Cubist as once daily, without recurrence of this side effect. It is likely to be licensed during the next year. MICs for gram-positive bacteria are 0.12-2 mg/L, but vary with the divalent cation content. Daptomycin causes cytoplasmic membrane disorganisation and depolarisation, preventing membrane transport and energy generation. The molecule is too large to enter gram-negative bacteria. Equivalence to vancomycin was found in a trial against skin and soft tissue infections but - for unclear reasons - daptomycin proved inferior to ceftriaxone in some (but not other) countries in a trial for community-acquired pneumonia. Bacteraemia and endocarditis trials are in progress and will provide rigorous assessment. Resistance is difficult to select *in vitro* but was selected *in vivo* in experimental *S. aureus* endocarditis.⁴

Oritavancin Oritavancin (LY333328), a glycopeptide with a biphenyl side chain, was another Lilly discovery, now licensed to InterMune, and in phase III development for skin and soft tissue infections. Unlike other glycopeptides, oritavancin retains activity vs. enterococci with VanA and B. This may be owing to the formation of dimers that bind to D-Ala-D-Lac or to a secondary mode of action; most probably inhibition of fatty acid synthesis by the side chain but possibly inhibition of peptidoglycan transglycosylase activity. Whatever its precise nature, this second target can be lost by mutation and VRE -unlike their vancomycin-susceptible counterparts- yield oritavancin-resistant mutants. Perhaps also owing to its second target, oritavancin is rapidly bactericidal and is active vs. *Streptococci*, including pneumococci at concentrations (c. 0.06 mg/L) 16-32 fold below its MICs for other gram-positive cocci. It has a serum half-life of 144h, contingent on protein binding. This may facilitate early discharge, or home i.v. therapy, but would create serious problems if any toxic side effect was to be identified. Another developmental glycopeptide, dalbavancin, has similar pharmacokinetics to oritavancin, but does not share its activity vs. VRE.

Tigecycline Tigecycline (GAR-936 Wyeth) is a glycylcycline, related to tetracycline. Unlike the agents so far discussed it has broad-spectrum activity, encompassing *Enterobacteriaceae*, *Bacteroides* and *Acinetobacter* spp. (but not *Pseudomonas* spp.), as well as gram-positive cocci. It remains active vs. isolates with efflux-mediated (e.g. *tetA-E* and *tetK*) determinants, also those with *tetM*, which modifies the ribosome so as to block binding of other tetracyclines. MICs for *Staphylococci*, *Streptococci* and *Enterococci*, including MRSA and VRE, are 0.06 to 0.5 mg/L and resemble those of minocycline vs. susceptible isolates. As with any tetracycline, activity is bacteriostatic. Phase III trials are in progress in intra-abdominal sepsis and community acquired pneumonia. Emergent resistance has not been recorded in gram-positive pathogens, but has been associated with mutation of *tetB* efflux in *E. coli*. Although adoption of tetracyclines in severe infections would require a major shift in perceptions of the drug class for many clinicians, it should be noted that minocycline was widely and successfully used in infections caused by MRSA with *tetK* efflux (which minocycline escapes) in Japan.

Ramoplanin Owing to systemic toxicity ramoplanin is suitable for topical use only, and is being developed for clearance of VRE colonisation of the gut, on the rationale that this colonisation may presage invasion and infection. It might reasonably also be investigated as an alternative to mupirocin as for nasal clearance of MRSA.

Anti-PBP-2 cephalosporins Gonzalez *et al.*⁵ showed mortality of 47% among patients treated with vancomycin for bacteraemic pneumonia caused by methicillin-susceptible *S. aureus* (MSSA), compared with 0% for cloxacillin. No nearly developed anti-gram-positive agent shows such a differential over vancomycin; so a great

potential is seen for any β -lactam that is tailored to bind PBP-2 and thereby can inhibit MRSA. Anti-PBP-2 activity has repeatedly been found since BRL-44154 -an oxyimino-penicillin- was investigated by Beecham in the 1980s. Unfortunately, none of these agents has yet proved suitable for development. Analogues still under investigation include the cephalosporins RWJ 54428, (Microcide/Johnson & Johnson), BAL5788 and 9141 (Basilea) and BMS-247243 (Bristol). These have MICs of ≤ 4 mg/L for MRSA - values no more than 4-fold above those for MSSA, even under conditions where induction of PBP-2' is likely.⁶ It remains to be seen whether these drugs are pharmacologically and commercially suitable for development.

Summar. Several agents directed vs. VRE and MRSA have been launched recently and clinicians no longer face the dearth of treatment option that confronted them when VRE first began to spread. Linezolid and quinupristin/dalfopristin are as active as vancomycin in infections caused by susceptible strains and linezolid, at least may be more active in some settings; moreover, the facility for oral administration may allow for earlier discharge. Thus, the situation vs. multi-resistant gram-positive isolates is improving, whereas that vs. multi-resistant gram-negative is deteriorating, with no new antipseudomonal agents, in particular.

Reference

1. Rosdahl VT, Knudsen AM. The decline of methicillin resistance among Danish *Staphylococcus aureus* strains. *Infect Control Hosp Epidemiol.* 1991;12:83-8.
2. Herrero IA, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin-resistant *Enterococcus faecium*. *N Engl J Med.* 2002;346:867-9.
3. Drew RH, Perfect JR, Srinath L, et al. Treatment of methicillin-resistant *Staphylococcus aureus* infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. For the Synercid Emergency-Use Study Group. *J Antimicrob Chemother.* 2000;46:775-84.
4. Kaatz GW, Seo SM, Reddy VN, et al. Daptomycin compared with teicoplanin and vancomycin for therapy of experimental *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother.* 1990;34:2081-5.
5. Gonzalez C, Rubio M, Romero-Vivas J, et al. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis.* 1999;29:1171-7.
6. Abbanat D, Macielag M, Bush K. Novel antibacterial agents for the treatment of serious gram-positive infections. *Expert Opin Investig Drugs.* 2003;12:379-99.