Fourteen years ago, two near-simultaneous reports documented the emergence of enterococci with high-level resistance to vancomycin and teicoplanin.1,2 These reports featured a cluster of isolates from a single hospital in London and isolates from two patients in France, but over the next decade, glycopeptide-resistant enterococci (GRE) were isolated from many countries worldwide, and are now a major problem, particularly in North America. The recent report of the isolation of a fully glycopeptide-resistant *Staphylococcus aureus* (GRSA; vancomycin MIC > 128 mg/L; teicoplanin MIC 32 mg/L),3 in Michigan, USA, therefore begs the question: ‘Will history repeat itself?’ Are we just looking at an interesting isolate from a single patient, or is it the forerunner of a potentially major crisis in health care? Obviously, only time will tell; however, the future need not necessarily bring doom and gloom. The Michigan GRSA harboured the *vanA* gene, which, in conjunction with several linked genes, encodes high-level glycopeptide resistance. These genes are the most common determinants of acquired glycopeptide resistance in enterococci. At the time of writing, the most likely explanation for the emergence of this GRSA is the acquisition of this gene complex from a GRE strain that was also present at the site of infection (a chronic foot ulcer).3 Transfer of vancomycin resistance from GRE to *S. aureus* was demonstrated in vitro some 10 years previously,4 since when there has been no evidence of such transfer occurring in nature, prior to the recent report. Thus, the likelihood of other strains of GRSA emerging would appear to be fairly low, at least on the basis of our experience to date. The extreme infrequency of natural transmission of glycopeptide resistance from enterococci to staphylococci suggests that most enterococcal plasmids or transposons encoding glycopeptide resistance may not transfer efficiently to, or be readily maintained in, *S. aureus*. However, theoretical routes whereby this could occur have been identified,5 and identical genes encoding resistance to other antibiotic classes, such as aminoglycosides, are prevalent in both genera, suggesting that intergeneric transfer does occur in nature.6

Even if high-level GRSA were to become widespread in hospitals, the occurrence of such organisms would not necessarily equate with the widespread occurrence of ‘untreatable’ infections, as some have suggested. The clinical impact of the potential loss of efficacy of glycopeptides, which are a mainstay of anti-staphylococcal therapy, should not be understated, but by the same token, it should not be overstated. The Michigan GRSA, while resistant to glycopeptides and all β-lactams (by virtue of its methicillin resistance), remained susceptible to trimethoprim/sulfamethoxazole (which was successfully used to treat the patient), tetracycline, minocycline, chloramphenicol, quinupristin/dalfopristin and linezolid.3 However, should high-level glycopeptide resistance emerge in more multi-resistant MRSA, such as the recently described EMRSA-17 strain from the UK,7 treatment options would be more limited. Moreover, it should be cautioned that resistance to quinupristin/dalfopristin and linezolid, although rare, can arise in MRSA.8,9 It is therefore reassuring that a number of antimicrobial agents with anti-staphylococcal activity, including daptomycin (a lipopeptide)10 and tigecycline (a glycylcycline, formerly known as GAR-936),11 are in the late stages of clinical development, while other agents including new cephalosporins with anti-MRSA activity are in earlier stages of development.12 For these reasons, the Michigan report, although alarming, should not generate the same degree of consternation as it might have done had it appeared more than five years ago.

If, on the other hand, the clinical impact of GRSA should turn out to be more acute and wide-ranging, what steps might be taken to contain their spread? Obviously, infection control

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measures will be central. Indeed, the level of concern over the spread of GRSA, the emergence of which has been postulated with associated trepidation for several years, may provide a stronger incentive for healthcare staff to comply more rigorously with infection control procedures, than that generated by current resistant pathogens, such as MRSA and GRE, whose spread we all too often fail to control. Clearly, prompt recognition of GRSA in the clinical laboratory is a prerequisite for the prompt initiation of relevant infection control procedures. The recent GRSA isolate was reported as having been initially detected by ‘commercial MIC testing’ (the precise method not being stated). Although the ability of disc testing to detect such resistance has not yet been reported, the fact that the vancomycin MIC for this vanA-containing isolate was >128 mg/L suggests that 5 µg vancomycin discs may prove suitable, based on widespread experience of detecting high-level vancomycin resistance in enterococci. The same experience suggests that the lower level of resistance to teicoplanin exhibited by this strain of GRSA (MIC 32 mg/L) would not be reliably detected by disc diffusion. Furthermore, should future GRSA arise through acquisition of other glycopeptide resistance determinants (e.g. vanB, vanD), which typically confer lower levels of resistance to vancomycin (with susceptibility to teicoplanin retained), disc testing might again be unreliable. At present, it seems reasonable to recommend that clinical laboratories encountering suspected isolates of GRSA supplement their disc testing by undertaking MIC determinations (e.g. Etest). Any putative GRSA should be submitted to a reference laboratory for independent confirmation and, if appropriate, for detailed genotypic analysis.

The first outbreak of GRE affected patients on a renal unit, and renal patients have featured in many subsequent reports, not only of GRE but also of the GRSA, as well as MRSA isolates with intermediate resistance to glycopeptides (see below). This patient population therefore appears to be at high risk of acquiring glycopeptide-resistant organisms. In this regard it is of interest that in a recent double-blind trial involving patients with end-stage renal disease who were receiving haemodialysis, a conjugate vaccine comprising S. aureus type 5 and 8 capsular polysaccharides conjugated to non-toxic recombinant Pseudomonas aeruginosa exotoxin A, conferred partial immunity against S. aureus bacteraemia for ~40 weeks. Thus, the emergence of GRSA may provide an additional spur for further vaccine-related research. It is said that prevention is better than cure, and this would hold even more strongly if, in the worst-case scenario, the cure (i.e. antibiotic treatment) was no longer available.

Five years ago, the first report of a strain of MRSA showing intermediate resistance to vancomycin and teicoplanin appeared in this Journal. This was followed by an explosion of Editorials, Leading articles and Commentaries, many citing leading investigators in microbiology or infectious diseases proffering such warnings as ‘The finding increases the possibility that levels of resistance will eventually develop which could make infections untreatable with currently available drugs’. However, as of June 2002, only eight patients with glycopeptide-intermediate S. aureus (GISA) have been confirmed in the USA, while only one case has been seen in England. Whether GRSA will only appear sporadically as seen with GISA, or will follow the same epidemiological trend as GRE to become a widespread problem, is hard to predict. However, awareness of the one recent isolate found in the clinical setting should alert microbiologists, epidemiologists and physicians to be on their guard. Prompt recognition of future GRSA isolates, together with a rapid response by infection control staff, may contain this potential problem.

References

Leading article


