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Clinical activity of anti-Gram-positive agents against methicillin-resistant *Staphylococcus aureus*

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Current concerns about multiresistance and a diminishing antibiotic pipeline are mainly addressed to Gram-negative bacteria. The greatest fear within the Gram-positive arena is vancomycin-resistant *Staphylococcus aureus*. Its epidemiology and clinical presentation give cause for concern, but so far its impact has been strictly limited. While this may change, the loss of glycopeptides as a treatment option may not, in fact, be all bad news.

Keywords: vancomycin-resistant staphylococci, linezolid, daptomycin

Introduction

Extreme, extensive and pan resistance are terms commonly used to describe the increasing problems of multiresistance in Gram-negative bacteria.[1,2] What exactly is the situation in Gram-positive organisms? Do these terms have any applicability? Certainly in the 1980s and 1990s methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) seemed to be among the main resistance issues for clinicians. Arguably though, the development of new agents has ameliorated the situation, although a glance at the number of old agents available and still reasonably active for many Gram-positive species does question how bad a situation we were ever in. Now, with the development of plasmid-mediated resistance to aminoglycosides, quinolones, cephalosporins and carbapenems, often linked on integrons and pathogenicity islands, Gram-negative resistance is again firmly on the agenda, exacerbated by the lack of a new drug pipeline. Within Gram-positive bacteria, clearly the biggest concern is vancomycin resistance. This takes various forms. Of most concern is vancomycin-resistant *S. aureus* (VRSA), which can arise following the transfer of the *vanA* gene encoding high-level glycopeptide resistance from *Enterococcus faecalis*.

VRSA

There are only 11 well-characterized VRSA isolates reported in the English literature, all of them MRSA, and 9 of these are from the USA,[3,4] with 7 of these coming from the state of Michigan. The first reported VRSA (USA1) was from Michigan (2002), with the second and third isolates being reported from Pennsylvania (2002) and New York (2003), respectively. The next five isolates were from Michigan (2005–7). Further isolates (2008) have been reported from India (Calcutta)[5] and Iran.[6] All 11 isolates had PCR-confirmed *vanA*. There have been several other reports of high-level vancomycin resistance in *S. aureus* from India, Iran and elsewhere, but none with *vanA* confirmed by PCR.[7,8] All of the prior USA strains have been accompanied by detailed clinical and infection control data, but there is little such information for the Indian and Iranian isolates, which were from surveys of several hundred clinical isolates. It is known that the Indian strain was isolated from a skin lesion of an outpatient and, unusually, was ciprofloxacin susceptible. The Iranian strain was isolated from a post-operative wound of a diabetic cardiac surgery patient. In common with all the USA strains, it seems as though there was no systemic spread of the organism in these two cases and none of the 11 patients was severely ill with the organism.

Where information was available, most infections were characterized by short-term carriage of the organism, good response to treatment and no spread to other patients, albeit in the face of strict infection control. Published data on susceptibility of the nine USA strains suggested all were susceptible to linezolid, although the MIC for one of the strains was on the breakpoint (4 mg/L).[9] Eight of the nine strains were susceptible to daptomycin, quinupristin/dalfopristin and rifampicin and two strains were resistant to tetracycline and trimethoprim/sulfamethoxazole.[9] In addition, we know that the Indian strain was gentamicin susceptible and co-trimoxazole and rifampicin resistant and the Iranian strain was susceptible to linezolid, tetracycline and rifampicin. The most serious clinical presentations seem to have been cases of necrotizing fasciitis and osteomyelitis. Otherwise, infections were more minor, of skin soft tissue, and in one (the New York strain) case, colonization of urine in a patient with a nephrostomy.

There are a lot of questions that need answers, such as will strains emerge globally, will they cross-infect other patients, will the *vanA* gene spread, and finally, why the relative abundance of strains from Michigan? It is indeed fortunate that

none of the strains was particularly virulent. Expression of resistance would seem to be associated with a high cost, but if not expressed, its biological cost may be minimal, so dissemination is a distinct possibility.[10] Also, resistance has so far evolved through at least three different mechanisms, potentially with involvement of coagulase-negative staphylococci. Emergence of USA1 involved conjugation and transposition of Tn1546 *vanA* operon to an MRSA plasmid with self-replicatory ability. USA2 had a plasmid with both staphylococcal and enterococcal sequences, while USA3–7 had enterococcal plasmids able to replicate in *S. aureus*. Typing data are available from just six USA strains. All were sequence type (ST) 5 (five USA100 and a single isolate of US800).[11]

If they were independent evolutionary occurrences, then why were so many of the isolates from Michigan? Michigan may have a peculiar propensity for producing these strains due to several factors, namely the high prevalence of an *E. faecalis* donor carrying a broad host range Inc18 plasmid; a relatively high proportion of patients carrying MRSA, often with co-existent diabetes or renal failure, which can 'enrich' for MRSA carriage; and high vancomycin use.[10] It is likely, however, that similar conditions occur elsewhere. More worryingly, an ascertainment bias may have occurred due to awareness and expertise. Current automated systems in widespread use are well able to detect known strains, so this may not be such an issue now.[12] Recent guidance on cessation of agar disc diffusion for glycopeptide susceptibility testing should also help to improve detection capabilities.[9]

It seems improbable that more strains of VRSA will not emerge and spread, but perhaps neither event will happen quickly. So far neither MRSA nor *S. aureus* seem to have discovered the correct ingredients for clonal spread of VRSA or horizontal gene transfer of *vanA*, despite vancomycin being in clinical use for more than 50 years with sustained high, if not increasing, use for the past 20 years.

Such a supposed doomsday scenario is greatly feared and VRSA is a classic 'alert' organism. But are vancomycin, or teicoplanin for that matter, really such good, indispensable drugs? Actually this is probably not the case.[13] Even in the few years after its introduction in 1955 vancomycin was deemed toxic, and from 1961 onwards, after the marketing of the first semisynthetic penicillins, it rapidly became a reserve drug. Obviously, with the worldwide surge in MRSA in the 1990s, vancomycin in a more purified form found extensive new uses, but this was still associated with significant nephrotoxicity, development of glycopeptide-intermediate *S. aureus* (GISA) and heterogeneous glycopeptide-intermediate *S. aureus* (hGISA) strains. In the last few years MIC creep or leap have resulted in many MRSA isolates having vancomycin MICs at or just below the breakpoint of 2 mg/L.[14]

Actually the situation is even worse than this. Although the breakpoint has recently been lowered from 4 to 2 mg/L,[9,15] the clinical and pharmacokinetic–pharmacodynamic (PK–PD) evidence is that the breakpoint should be 0.5 or 1 mg/L, thus classifying most MRSA [and methicillin-susceptible *S. aureus* (MSSA)] isolates as resistant in many published series.[14,16] The clinical evidence comes from at least six observational studies of serious MRSA infections, mainly bacteraemias, but also a significant number of pneumonia cases. These studies demonstrate a clinical breakpoint of 0.5 or 1 mg/L.[17] Studies that used Etest to determine the MIC had a clinical breakpoint of 1 mg/L and those that used reference method broth dilution had a lower breakpoint of 0.5 mg/L, perhaps because broth dilution methods, with a lower inoculum (10^4–10^5 cfu), are less likely to detect hGISA mutants than the higher inoculum of the Etest.[18] This conclusion can only be tentative until we get better clinical data, but it is backed up by the available PK–PD data suggesting that only 60% of patients with normal renal function and infected with a strain with a vancomycin MIC value of 1 mg/L would achieve the target AUC:MIC ratio of 400, even with high-dose vancomycin (potentially nephrotoxic).[19] The data are complicated, however, by a tendency for lower doses of vancomycin in the earlier studies, which were the ones to use reference antimicrobial susceptibility testing (AST) methods. Moreover, the PK–PD target of 400 seems to be a consensus based on just a couple of studies, one human and one animal, although it has to be said that the limited evidence could argue for even higher AUC:MIC ratios as a target if bactericidal activity is desired.[17,19] This may well be desirable, as vancomycin and teicoplanin are renowned for very slow cidal activity and, at least in immunosuppressed patients and for the treatment of bacteraemia and endocarditis, cidality is usually considered a desirable feature. Finally, and paradoxically, the most recent published clinical study in this area argues for a breakpoint of 1 mg/L but used reference broth dilution to establish MICs![20]

Other anti-MRSA drugs

In light of all this, and the well-established inferiority of vancomycin compared with β-lactams in the treatment of MSSA infection,[13,14] it is pertinent to ask if the loss of vancomycin and teicoplanin, whether from the march of VRSA or (more subtly, but more likely) from MIC creep or leap, is such a doomsday scenario? With the development of several exciting new agents in this field and the retained activity of older agents such as co-trimoxazole and tetracycline against most strains of MRSA, there do seem to be good alternatives. Admittedly there is little published clinical data to support the use of these older agents for the treatment of serious staphylococcal infection,[21,22] but following from a retrospective cohort study that showed co-trimoxazole had a safety and efficacy profile similar to that of vancomycin,[23] there is one ongoing trial comparing co-trimoxazole with vancomycin for MRSA bacteriaemia.[24] Tigecycline (currently the only available intravenous tetracycline derivative in the UK) is a potentially useful drug for certain types of MRSA infection, although its low blood levels probably preclude its use for primary bacteraemia.[25,26] More data are needed, however, particularly on the optimum dosing schedules.

Newer anti-MRSA drugs

Despite a lot of activity in anti-Gram-positive drug development over the past decade, only linezolid, daptomycin and, very recently, telavancin and ceftaroline have successfully negotiated the regulatory hurdles. Linezolid and daptomycin have been in widespread clinical use for several years, and some resistance mechanisms have been identified, although surveillance systems provide reassurance that they are not yet widespread.[27–32] Although telavancin is a glycopeptide, it is much more rapidly bactericidal than the older glycopeptides and

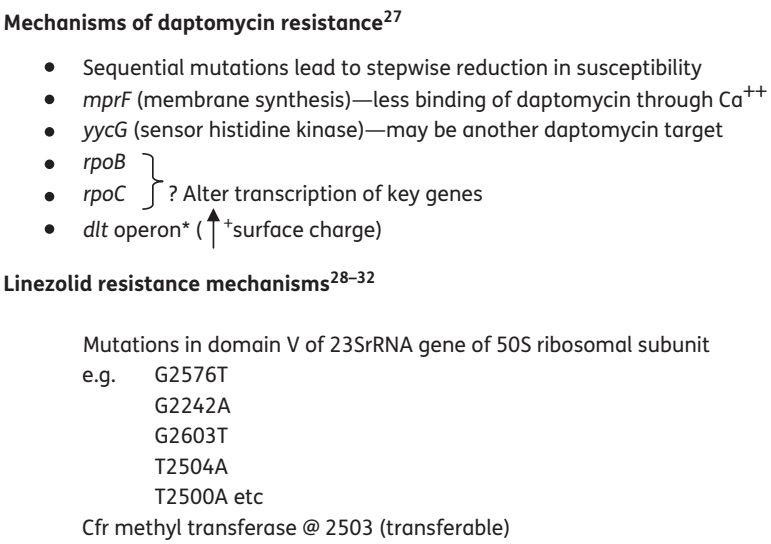

Figure 1. Described mechanisms of resistance to daptomycin and linezolid.

seems to have useful activity against VRSA, GISA and hGISA. Time will tell how quickly resistance develops.[33] Ceftaroline is a novel cephalosporin with broad-spectrum activity against Gram-positive pathogens, including MRSA. Its activity against MRSA is attributed to its ability to bind to penicillin-binding protein (PBP) 2a with high affinity and inhibit the biochemical activity of PBP2a more efficiently than other presently available β-lactams.[34]

Figure 1 lists the daptomycin and linezolid resistance mechanisms that have been described. For daptomycin, these are poorly understood, but can involve trapping of the drug in a thickened cell wall and loss of target binding affinity. There is some cross-resistance with glycopeptides due to this cell wall trapping, so it is important to check the daptomycin MIC if the strain being treated has had prior exposure to glycopeptides. Emergence of resistance during treatment is also of concern if there is a high inoculum infection or abscess with no possible drainage. There were a particularly alarming number of such cases in the daptomycin registration study of bacteraemia and endocarditis.[35] Subsequent cases have been described, although probably with less frequency than might have been anticipated following this original study.[36] Although the strains were technically resistant to daptomycin by breakpoint criteria, the drug usually retained its bactericidal activity. Doses higher than the original 6 mg/kg used in the above study may well reduce the emergence of resistance, and in surveillance studies, significant levels of daptomycin resistance are not recorded.

Linezolid resistance can be due to sequential mutations, like daptomycin resistance, but of most concern is potential transferable resistance through the *cfr* gene, which may be linked to pleuromutilin resistance.[37] Outbreaks of MRSA infection in intensive care units (ICUs) owing to high linezolid use and mediated by the *cfr* gene have been described, but they seem to have been controlled by a combination of reduced linezolid use and good infection control practices.[37] Of more concern perhaps is the carriage of this gene by coagulase-negative staphylococci with the potential for transfer to MRSA. Nevertheless, current surveillance systems continue to describe very little linezolid resistance. It remains to be seen whether newer oxazolidinones in development will have clinically significant improved activity against MRSA carrying the *cfr* gene.[32] Consecutive isolates of linezolid-resistant (VanB) *Enterococcus faecium* from one patient demonstrated the dynamic process of linezolid resistance due to G/T mutation at position 2576 in the genes coding for 23S rRNA. Here there was complete reversion of resistant alleles back to wild type (susceptible) in consecutive isolates.[31] Newer oxazolidinones (ranbezolid and radezolid) that can overcome the ribosomal binding issues of linezolid-resistant Gram-positive pathogens, particularly enterococci and pneumococci, are in development.[32]

Tigecycline, a glycylcycline derivative of tetracycline, is very broad spectrum, including most MRSA. It is a useful agent for skin and soft tissue infection (SSTI) and intra-abdominal infections where multiresistant bacteria are involved, and can be used as a second-line anti-MRSA agent in these situations. Resistance in MRSA has rarely been described thus far.[24,38,39]

Finally, topical and systemic antibiotics are often used to decolonize MRSA carriers. With the advent of high-level plasmid-mediated mupirocin resistance, this will become a bigger issue. Currently in Glasgow, 15% of MRSA bloodstream isolates are mupirocin resistant (G. Edwards, MRSA Reference Laboratory, Glasgow, personal communication). Trimethoprim is sometimes used for MRSA decolonization, but this can lead to high levels of resistance (Hunt AC, Edwards B, Girvan EK, Cosgrove B, Edwards GFS, Gould IM, manuscript in preparation). Similarly, fusidic acid and rifampicin are often used in this setting, but high levels of resistance mutations dictate they always be used as part of a combination.

Drugs in development

Dalbavancin[40] and oritavancin[41] have both failed FDA approval. Dalbavancin, a glycopeptide with a very prolonged half-life, has less than 5 years of patent left, so may not have further trials. Oritavancin is being restudied to include more MRSA patients. It looks to be the most active glycopeptide against strains containing *vanA*. Ceftobiprole, another cephalosporin with significant

activity against MRSA due to altered PBP2 affinity, is delayed in its regulatory approval because of issues of trial quality. Finally, iclaprim, a folate antagonist, did not achieve non-inferiority in an SSTI trial when compared with linezolid.[40]

Conclusions

In conclusion, the demise of vancomycin and teicoplanin is well heralded, but perhaps not quite accomplished yet, although surely it must be soon. However, this will not be the doomsday event that it once would have been, with existing and potential new drugs, both less toxic and potentially more efficacious, likely to replace them. Nevertheless, if MRSA is not controlled around the world, we will have to use these new drugs wisely or resistance is likely to become a clinical problem rather than just a curiosity.

Transparency declarations

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The author is on the speakers bureau or acting as a consultant for many companies producing novel therapies for MRSA.

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