

Safety and efficacy of glycopeptide antibiotics

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It would be difficult to envision the practice of infectious diseases over the past 20 years without the availability of the glycopeptide antibiotics. The two agents currently in clinical use, vancomycin and teicoplanin, have proven remarkably versatile in many common applications. Several attributes of these agents account for this favourable profile: (i) their broad spectrum of activity against Gram-positive bacteria, including strains resistant to many other antimicrobials; (ii) their favourable pharmacokinetic properties that allow the once- or twice-daily dosing regimens that have made out-of-hospital therapy possible; and (iii) their generally good safety profiles which, along with their structural dissimilarity to β -lactam and other antimicrobials, permits their use in many patients who are intolerant of other antibiotic regimens. It is not entirely surprising, therefore, that despite more than 40 years of clinical use and the interim appearance of bacterial strains resistant to this drug class, there remains continued interest in the development of newer members of the glycopeptide antibiotic class. This paper is intended to provide a global overview of the efficacy and safety of glycopeptide antibiotics currently in use, as background to understanding the need for and potential roles of new agents of this class.

Keywords: vancomycin, teicoplanin, oritavancin, dalbavancin, resistance

Background

Vancomycin was identified in 1956 as a result of intensive efforts to screen natural specimens for new antibiotics with activity against staphylococci, in which resistance to then-available agents had already been recognized as an emerging threat.¹ Vancomycin was approved by the US FDA in 1958. Although this drug was soon eclipsed by the introduction of the anti-staphylococcal β -lactams, the subsequent increase in annual usage of vancomycin coincided with the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) as an important clinical pathogen. The amount of injectable vancomycin used in the USA and five major European markets increased from less than 2000 kg annually in the early 1980s to over 13 000 kg in 1996.²

Vancomycin is a large molecule, consisting of a tricyclic heptapeptide core structure to which is attached a disaccharide unit consisting of the aminodeoxy sugar, vancosamine, and D-glucose.³ Hydrogen bond formation between the peptide core structure of vancomycin and terminal D-alanine-D-alanine residues of pentapeptide peptidoglycan precursors results in the inhibition of late steps in bacterial cell wall synthesis.⁴

The teicoplanin family of glycopeptides, discovered in 1978, differs from vancomycin in several ways. First, there are aromatic amino acids at positions 1 and 3, in contrast to the

aliphatic amino acids present in vancomycin, and these are joined in an ether linkage.⁵ The second difference is that instead of a vancosamine-containing disaccharide, teicoplanin contains a fatty acid moiety attached to glucosamine that is in turn attached to the core peptide structure.⁵ This fatty acyl side chain is believed to contribute to antimicrobial activity by providing a means of anchoring the molecule to the bacterial cell membrane.⁶

Modifications of a naturally occurring glycopeptide related to vancomycin, led to discovery of a series of compounds with enhanced activity against vancomycin-resistant enterococci.^{7,8} Oritavancin, possesses a *p*-chlorophenylbenzyl moiety attached to 4-epivancosamine, the sugar that replaces vancosamine in this glycopeptide.⁹ (An additional epivancosamine is attached to the core peptide of this parent compound.) This drug demonstrates activity against vancomycin-resistant enterococci (VRE), and a very long serum elimination half-life.^{7,8,10} The activity of this new compound against VRE could not be explained by any greater binding affinity, compared with vancomycin, to the modified D-alanine-D-lactate pentapeptide precursors that account for resistance to vancomycin in these enterococci. In contrast to vancomycin, oritavancin strongly dimerizes and is able to anchor into the bacterial cell membrane.⁹ The resulting cooperative interactions are believed to explain its enhanced activity. Other data indicate that the *p*-chlorophenylbenzyl-substituted

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disaccharide might inhibit cell wall synthesis at the level of transglycosylation, even in the absence of binding to the depsipeptide precursors.¹¹

Dalbavancin is another new compound derived semi-synthetically from a naturally occurring teicoplanin-like glycopeptide.^{4,12} This compound resembles teicoplanin in having ester-linked aromatic amino acids at positions 1 and 3. Dalbavancin differs from the latter by the presence of an acylaminoglucuronic acid instead of an acylglucosamine substituent, and by the presence of an additional (dimethyl aminopropylamine) aliphatic side chain attached to the core peptide.^{4,12} This compound is more potent than vancomycin or teicoplanin against staphylococci, but not more than teicoplanin against VRE, and has a prolonged elimination half-life.¹²

Telavancin is a semi-synthetic hydrophobic derivative of vancomycin.¹³ Like vancomycin, telavancin inhibits bacterial cell wall synthesis. However, the new lipoglycopeptide also affects cell membrane permeability and results in dissipation of the membrane potential.^{14,15} The multiple mechanisms of action of telavancin have been postulated to contribute to the rapid bactericidal activity observed against staphylococci.

Activity *in vitro*

Vancomycin and teicoplanin inhibit a broad range of Gram-positive bacteria, including staphylococci, streptococci and most enterococci. Recent large surveillance studies indicate that resistance to these agents is uncommon. Representative data for isolates collected in Europe and North America are shown in Table 1.

Most significant clinical isolates of VRE are *Enterococcus faecium*. Most of these are of the VanA type and thus are resistant to both vancomycin and teicoplanin.^{16,17} The VanB phenotype is more common among glycopeptide-resistant *Enterococcus faecalis*; these exhibit resistance to vancomycin,

but not teicoplanin, which is an inefficient inducer of the resistance mechanism. A small, but in some regions significant, proportion of coagulase-negative staphylococci exhibit resistance to teicoplanin, with MICs in the 16–32 mg/L range.¹⁸

The activity of oritavancin against staphylococci is comparable to that of vancomycin; approximately 90% of strains are inhibited at concentrations of 2 mg/L or less.¹⁹ This glycopeptide was more active (MICs, 1–2 mg/L) than vancomycin against three strains of vancomycin-intermediate *S. aureus*.²⁰ Based on comparisons of MIC₉₀ values, dalbavancin is 16- to 32-fold more potent than vancomycin against staphylococci and 8- to 16-fold more active against streptococci.²¹ The activity of telavancin *in vitro* against staphylococci is two- to eight-fold greater than that of vancomycin against *Staphylococcus* spp. based on comparison of MIC₉₀ values.^{15,22} Telavancin (MIC₉₀s, 0.016–0.125 mg/L) was also substantially more potent than vancomycin against streptococci and inhibited vancomycin-resistant enterococci, albeit at higher concentrations (MIC₉₀, 4 mg/L).²²

Clinical uses for serious infections

The glycopeptides have been widely employed in the treatment of infections due to MRSA.^{23,24} Hospital-associated strains of MRSA tend to be resistant to multiple antimicrobials, leaving the glycopeptides as one of the few classes with activity *in vitro* against these isolates. Recent surveys indicate that approximately 30% of *S. aureus* strains in Europe and 30–40% of those from the US are oxacillin-resistant.^{16,25} Even higher prevalence rates have been noted in the Asia–Western Pacific region.²⁵ Currently, about 50% of *S. aureus* causing nosocomial infections in US intensive care units are MRSA with similar rates for nosocomial *S. aureus* bacteraemia in the UK.

A worrisome recent trend has been the increasing recognition of MRSA infections acquired in the community.²⁶ These isolates appear to be distinct from those implicated in hospital-associated

Table 1. Susceptibility of common Gram-positive human pathogens, collected in Europe and North America, to vancomycin and teicoplanin

Organism	Number	Range of MIC ₉₀ values ^a (% resistant)		References
		vancomycin	teicoplanin	
<i>S. aureus</i>	> 13 000	1 (0)	1–2 (<0.1)	25
oxa ^b -susceptible	~ 5000	1–2 (0)	0.5–2 (0)	16, 18
oxa-resistant	> 3000	1–2 (0)	1–2 (0)	16, 18
Coagulase-negative staphylococci	> 5000	2–4 (0–0.5)	8 (0.8–6.5)	15, 18
oxa-susceptible	~ 1400	1 (0)	2 (0)	16
oxa-resistant	~ 750	2 (0.5)	4 (0.3)	16
Enterococci	> 4000	2–> 16 (3.2–12.4)	0.5–1 (2.2–9.1)	25
<i>E. faecalis</i>	875	4 (0.5)	0.5 (0.5)	18
<i>E. faecium</i>	~ 100	≥ 128 (24.1)	32 (20.4)	18
van ^c -resistant <i>E. faecalis</i>	~ 60		> 16 (21)	16
van-resistant <i>E. faecium</i>	~ 600		> 16 (63)	16
<i>Streptococcus pneumoniae</i>	> 1600	0.5–1 (0)	≤ 0.12 ^d	18, 25
β-Haemolytic streptococci	> 350	0.5 (0)	0.25 (0)	25
Viridans group streptococci	> 200	1 (0)	0.25 (0)	21

^amg/L.

^bOxacillin.

^cVancomycin.

^d631 strains only.

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infections. In the USA, the community-acquired MRSA are more likely to exhibit susceptibility to other antimicrobial classes and to contain the type IV staphylococcal cassette chromosome *mec* element.²⁷ Clonal spread of these organisms has been documented, and infections with onset in the community may be fulminating and deeply invasive.²⁸

Recent surveillance indicates that approximately three-quarters of coagulase-negative staphylococci are oxacillin-resistant.²⁵ Coagulase-negative staphylococci are now the most common bacteria causing nosocomial bloodstream infections.²⁹ Also, these organisms, in addition to *S. aureus*, are frequently implicated in wound infections and infections related to biomedical prosthetic devices. As a result, glycopeptides have been explored for peri-operative surgical prophylaxis in cardiothoracic and orthopaedic surgery.^{30–34} One study which compared vancomycin (1 g at induction of anaesthesia and again 12 h later) with cefazolin (three 1 g doses, beginning at induction and then at 8 h intervals) in >800 patients undergoing cardiac surgery illustrates the uncertainties affecting choice of empirical regimens.³⁵ In that study, there were no differences in surgical site infection rates, overall infection rates, mortality or post-operative hospital stays. However, while there was a non-significant trend toward more frequent surgical site infections due to MRSA and enterococci in patients receiving cefazolin, there was a statistically significant increase in frequency of infections due to methicillin-susceptible staphylococci in the patients who received vancomycin.³⁵

As a result of the increase in the proportion of staphylococcal infections caused by β -lactam-resistant isolates, vancomycin is used increasingly as empirical therapy when staphylococcal infection is suspected, for patients admitted from the community as well as for those with onset of infection in the hospital.

Because of its activity against MRSA and methicillin-resistant coagulase-negative staphylococci, vancomycin has become the core element of regimens to treat endocarditis of native or prosthetic valves due to these organisms. For prosthetic valve endocarditis, rifampicin and gentamicin are included in the treatment regimen when feasible.³⁶ Vancomycin is also used in patients intolerant of β -lactam antibiotics to treat endocarditis due to other Gram-positive organisms, including methicillin-susceptible staphylococci, viridans streptococci, and enterococci.³⁶ When bactericidal synergy can be predicted, an aminoglycoside is added for the treatment of enterococcal endocarditis.

In vitro, vancomycin is less rapidly bactericidal than are antistaphylococcal penicillins against strains of *S. aureus* susceptible to both classes.³⁷ When vancomycin is used to treat patients with MRSA endocarditis, fever and bacteraemia may persist for a median of 7 and 9 days, respectively,³⁸ which is longer than usually seen when β -lactam antibiotics are used to treat infective endocarditis due to methicillin-susceptible strains. These observations of a slow clinical response to vancomycin, taken together with reports of relapse after 4 week courses of therapy³⁷ and evidence that 2 week glycopeptide-aminoglycoside regimens may be inferior to antistaphylococcal penicillin/aminoglycoside combinations for right-sided endocarditis,³⁹ lead many clinicians to believe that endocarditis due to methicillin-susceptible *S. aureus* should be treated with an antistaphylococcal β -lactam, in preference to vancomycin, whenever possible.

The ability to dose vancomycin twice daily in patients with normal renal function, and once daily or less often in many with

reduced function, makes this drug relatively convenient to use, especially in outpatient antibiotic therapy. In the USA, where teicoplanin is not available, twice daily infusions of vancomycin, or less frequent administration in the substantial number of patients with some impairment of renal function, can be undertaken in the outpatient setting or in skilled nursing settings outside the hospital. Teicoplanin, usually administered once daily, can be infused more rapidly than vancomycin and can also be given intramuscularly, all of which would be desirable characteristics for outpatient management of infection.^{24,40}

Because the elimination half-life of vancomycin may reach 1 week in patients with advanced renal disease,¹ and because infections due to *S. aureus* or other Gram-positive pathogens are common in this population, this glycopeptide has proven to be a convenient and widely employed agent in this setting.⁴¹ A potential drawback of this usage is that VRE have emerged as a problem among dialysis patients, as have strains of *S. aureus* with reduced vancomycin susceptibility (SA-RVS).⁴¹ A recent case-control study confirmed prior MRSA and antecedent vancomycin exposure as risk factors for infection due to SA-RVS, but neither end-stage renal disease nor dialysis were independent risk factors.⁴²

Vancomycin, administered orally, has also been widely used for treatment of *Clostridium difficile*-associated diarrhoea.^{43,44} Because of cost and concerns about VRE, metronidazole is now commonly used as the primary treatment modality for this disorder; however, vancomycin remains an alternative.

Effectiveness in clinical use

Vancomycin has become a *de facto* standard comparison agent for recent clinical trials evaluating new antimicrobials with activity against Gram-positive pathogens. Therefore, examination of these results can be instructive.

A clinical trial was designed to compare linezolid with vancomycin in the treatment of infections due to MRSA.⁴⁵ This randomized, open-label, multicentre study enrolled more than 200 hospitalized patients in each arm; approximately one-half of these were proven to have MRSA infection. Seventy-three percent of patients in each group achieved clinical cure. The proportions of patients with successful microbiological outcomes were, likewise, equivalent: 59% of those treated with linezolid and 63% of those treated with vancomycin. Vancomycin was also the comparator agent in a study of linezolid for treatment of Gram-positive nosocomial pneumonia.⁴⁶ This was a randomized, double-blind, multi-national trial, with approximately 200 patients in each study arm. Aztreonam could be administered if needed because of concern about Gram-negative pathogens. Clinical and microbiological cure rates with vancomycin (68% and 72%, respectively, among evaluable patients) were equivalent to those observed with linezolid. In another study of hospital-acquired pneumonia, the clinical success rate among bacteriologically-evaluable patients with vancomycin (58%) was equivalent to that obtained with quinupristin/dalfopristin (56%).⁴⁷ This study allowed treatment with imipenem or tobramycin, if needed.

Studies evaluating teicoplanin for the treatment of severe staphylococcal infections reported inconsistent responses compared with flucloxacillin⁴⁸ or vancomycin,⁴⁹ while others reported results comparable to those seen with vancomycin.⁵⁰

In a study of right-sided *S. aureus* endocarditis in drug users, most of whom were also seropositive for the human immunodeficiency virus, a 2 week course of cloxacillin plus gentamicin (seven of eight patients cured) was more effective than a 28 day course of teicoplanin (two of six patients cured) at a dose of 7 mg/kg per day after decremental loading doses during the first week of therapy.⁵¹ Nevertheless, other studies have shown teicoplanin therapy to be comparable to vancomycin in Hickman catheter-associated infections⁵² and for Gram-positive infections in cancer patients.^{53–55} In one study, 635 neutropenic cancer patients with fever were treated empirically with ceftazidime plus amikacin and randomized to receive either teicoplanin 6 mg/kg once daily or vancomycin 1 g twice daily.⁵⁵ For those patients who were found to have bacteraemia due to a single Gram-positive organism, response rates were 92% and 87%, respectively.

Teicoplanin, typically combined with an aminoglycoside, has been used successfully in the treatment of endocarditis due to streptococci or enterococci.^{56–58} This glycopeptide, used alone, was successful in treatment of all 15 evaluable individuals with native valve endocarditis in another study.⁵⁹ A retrospective review of 115 cases from the European experience with teicoplanin therapy for infective endocarditis found most of the use in combination regimens.⁶⁰ For *S. aureus* infection, higher clinical success rates were noted for combination regimens than for monotherapy, both for the evaluable (18 of 21 versus 5 of 9, $P=0.15$) or the intent to treat populations (18 of 23 versus 5 of 12, $P=0.06$), although differences were not statistically significant. For streptococcal endocarditis, intent to treat efficacies were similar (~85%) for both monotherapy and combination therapy.

In studies of peri-operative prophylaxis, teicoplanin was found to be comparable to cefazolin or cefamandole for prosthetic joint implant surgery.^{61,62} Another study found more surgical site infections in vascular prosthetic surgery when teicoplanin was used (5.9%) than when cefazolin was employed (1.7%), but this difference was not statistically significant.⁶³ However, a study which randomized >3000 patients undergoing cardiac surgery to cefazolin (2 day course) or teicoplanin (15 mg/kg single dose) prophylaxis found a difference in favour of the cephalosporin.⁶⁴ There was a significantly greater number of deep sternotomy wound infections by 6 months after surgery in the group who underwent prophylaxis with the glycopeptide.

Taking advantage of the long elimination half-life of dalbavancin, a Phase 2 clinical trial was undertaken to compare this agent, given as one or two once-weekly doses, to standard-of-care regimens for treatment of skin and soft tissue infections.⁶⁵ In this study, only descriptive statistics were planned. The clinically-evaluable population was comprised of 51 patients (13 single-dose dalbavancin, 17 two-dose dalbavancin, 21 comparator). At the test-of-cure assessment, clinical success was documented in 94% of patients who received two doses of dalbavancin [1000 mg intravenously (iv), followed by 500 mg iv 1 week later], compared with 76% of those treated with comparators and 62% of those receiving a single 1100 mg iv dose of dalbavancin. Eradication of the pathogen (or presumed eradication) was also seen most commonly in the two-dose dalbavancin group (92% versus 71% and 58%, respectively). In this small study, dalbavancin was well-tolerated, and no serious adverse reactions to it were reported.⁶⁵

Safety in clinical use

Vancomycin was initially viewed as an antibiotic with considerable associated toxicity.¹ This may have been due in part to the relative impurity of early preparations, to the use of concurrent medications, or to other factors. At the present time, however, the wide use that vancomycin enjoys reflects its quite reasonable safety profile.

Infusion-related syndrome

Intravenous infusion of vancomycin may cause a dramatic histamine-release phenomenon, with flushing of the head and neck, and various parts of the upper body. This may be accompanied by pruritus, hypotension, tachycardia and chest tightness.⁶⁶ Cardiac arrest has been noted after rapid bolus injection of the drug.^{1,67} In one study, 11 of 12 healthy subjects experienced a histamine-release syndrome following administration of a 15 mg/kg dose of vancomycin infused over 60 min.⁶⁸ This was not seen with the same dose of teicoplanin infused over 30 min. *In vitro* studies using rat mast cells showed that histamine release upon vancomycin exposure was markedly enhanced in the presence of the muscle relaxants tubocurarine, vecuronium, pancuronium and succinylcholine (also known as suxamethonium), and the opiate, morphine.⁶⁹ Morphine was also shown to potentiate histamine release by vancomycin *in vivo* in rats; however, large doses of the former agent (10 mg/kg) were used in these experiments.⁶⁹ Case reports do suggest, however, that concomitant opiate administration may exacerbate infusion-related symptoms during vancomycin therapy.⁷⁰

Skin reactions

Rashes (other than infusion-related or due to thrombophlebitis) occur with vancomycin therapy but are infrequent; rash was not mentioned as an adverse effect encountered in two recent studies enrolling >300 patients.^{45,71} More severe reactions have been only rarely reported, including toxic epidermal necrolysis.⁷² Vancomycin administration has been associated with a cutaneous bullous disorder that on biopsy reveals linear IgA deposition along the dermal-epidermal junction.^{73–75} Recurrence after rechallenge with vancomycin has been observed.⁷⁵

Renal effects

Early clinical experience with vancomycin suggested a nephrotoxic potential for this glycopeptide.¹ Preparations of the drug used at the time were relatively impure, however, and many patients were critically ill and received other drugs with nephrotoxic potential. Rates of nephrotoxicity reported more recently among patients treated with vancomycin are lower, but vary widely. A meta-analysis of safety data for 544 patients from 11 studies reported that 10.7% of patients had evidence of nephrotoxicity, according to criteria established by individual investigators.⁷⁶ The author carefully points out that concurrent administration of other potentially nephrotoxic drugs was not precluded in these studies. Data from comparative clinical trials of vancomycin with teicoplanin revealed evidence of nephrotoxicity in 6.5% of 417 patients treated with the former antibiotic.⁷⁷ Nephrotoxicity, defined by a 20% or greater decrease in creatinine clearance from baseline, was noted in 17% of 726 oncology patients who received

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vancomycin and who were followed prospectively.⁷⁸ However, nephrotoxicity, that was described as asymptomatic and self-limited, occurred in only 8% of patients who did not receive other agents suspected to be nephrotoxic. In that study, a multivariable model showed that administration of known nephrotoxic agents and poor overall condition judged by APACHE score were significant risk factors for nephrotoxicity.

Although the risk of nephrotoxicity from vancomycin alone would appear to be low, several studies have reported particularly high rates (22–35%) of nephrotoxicity among patients receiving aminoglycoside therapy with vancomycin.^{79–81} Patients treated with this combination may not only be at increased risk of developing nephrotoxicity, but may also experience a greater rise in serum creatinine than those treated with an aminoglycoside alone.⁸⁰ Acute interstitial nephritis, sometimes accompanied by a rash, has been reported rarely in individuals treated with vancomycin.^{72,82,83}

Ototoxicity

Hearing loss, tinnitus, vertigo and dizziness have been associated with vancomycin therapy in a small minority of patients.⁸⁴ Many of these had received prior or concurrent treatment with aminoglycosides. In several reports, symptoms or abnormal audiograms resolved or improved upon discontinuation of therapy or with continued therapy at decreased dosage.⁸⁴ Elting *et al.*⁷⁸ followed prospectively 765 oncology patients who received vancomycin therapy for evidence of toxicity, which was assessed at least twice weekly by questioning the patients. A subset of asymptomatic patients (i.e. 15 patients who received concomitant ototoxic agents and 15 who did not) was selected randomly for audiometric testing. Three of the 30 asymptomatic patients who underwent audiometric testing had evidence of high frequency hearing loss (two were receiving other potentially ototoxic agents). By clinical evaluation, ototoxicity was observed in 12 of 423 patients who did not receive other potentially ototoxic agents (3%), but in 18 of 319 (6%) of patients who received one or more ototoxic drugs. This difference did not reach statistical significance. None of these patients with clinical evidence of ototoxicity underwent audiometric testing. Thus, symptoms of ototoxicity were observed in 4% of the entire evaluable group of 742 patients. Nephrotoxicity was found in only seven of the 30 patients in whom ototoxicity was observed. The authors indicated that the symptoms of ototoxicity elicited from the patients had resolved within a month of stopping vancomycin therapy.⁷⁸

Gendeh *et al.*⁸⁵ followed 16 patients for evidence of ototoxicity while receiving vancomycin therapy during continuous ambulatory peritoneal dialysis, during which serum levels are sustained over several days. Very ill patients and those with pre-existing sensorineural hearing loss or who received other potentially ototoxic drugs were excluded. Vancomycin was administered through the dialysate on day 0 and 6 of a 10 day observation period. Mean (\pm S.D.) serum vancomycin concentrations were 33.8 ± 13.8 mg/L and 11.1 ± 1.94 mg/L on days 1 and 5 of therapy, respectively. Patients were questioned for symptoms during therapy and pure-tone audiometry and caloric testing with electronystagmography were carried out before therapy and on days 6 and 10. They found no evidence of ototoxicity in any of the 16 patients, over 22 courses of vancomycin therapy.

Other toxicities

Phlebitis with vancomycin administration has been observed at rates ranging from 3% to >30%.^{78,79,86} In a compassionate use study of the new antimicrobial agent, linezolid, neutropenia was the reason for enrolment of 10 (6.6%) of the 151 patients enrolled in the study because of intolerance to vancomycin.⁸⁷ In contrast, 39 patients were enrolled in this study because of rash attributed to the glycopeptide. Neutropenia attributed to vancomycin is sometimes seen together with drug fever and can be associated with anti-neutrophil antibodies.^{88,89} In one patient who developed neutropenia after 6 weeks of therapy with vancomycin for osteomyelitis, therapy was completed with teicoplanin at a dose of 400 mg/day for 1 month without recurrence of this complication.⁹⁰ Thrombocytopenia during vancomycin therapy has also been reported.^{91,92} This is an infrequent adverse event. In one study recently completed, substantially low platelet counts (e.g. <75% of the lower limit of normal if the platelet count was normal at baseline) were seen in five of 231 patients receiving vancomycin for treatment of infections due to *Staphylococcus* species.⁹³ Thrombocytopenia attributable to vancomycin can be associated with anti-platelet antibodies.⁹⁴ In compliance with regulatory requirements for investigational antimicrobials, the effect of telavancin at doses of 7.5 and 15 mg/kg on cardiac repolarization was examined in healthy subjects.⁹⁵ In this randomized, double-blind trial, moxifloxacin was used as a positive control and telavancin vehicle was administered as placebo. Placebo-corrected mean change from baseline of QTc was 9.2 ms for moxifloxacin and 4.1 and 4.5 ms, respectively, for the two doses of telavancin. The authors observed that changes of this magnitude were within the range of recently approved agents, and concluded that telavancin should pose minimal risk of cardiac events.⁹⁵

Comparison of glycopeptides

A meta-analysis of 11 clinical trials comparing teicoplanin with vancomycin concluded that there were statistically fewer adverse events noted in patients treated with the former (13.9% versus 21.9%, $P=0.0003$).⁷⁶

Infusion-related syndrome due to histamine release is much less common with teicoplanin than with vancomycin.⁴⁰ In a cross-over study comparing vancomycin with teicoplanin, the histamine-release syndrome occurred in 11 of 12 volunteers during vancomycin infusion, but was not encountered during teicoplanin infusion.⁶⁸ Another study enrolled >3000 patients to compare teicoplanin in a single dose of 15 mg/kg with cefazolin administered for 2 days as prophylaxis for cardiac surgery.⁶⁴ Although histamine-release syndrome was not defined as a specific adverse event, symptoms possibly suggestive of this syndrome such as hypotension, rash or anaphylactic shock were rare. Such events were observed eight times among 1518 teicoplanin recipients and nine times among 1509 cefazolin recipients.

Comparison of exact rates of other toxicities between the two glycopeptides is complicated by the wide range of teicoplanin doses employed in treatment and by the concomitant use of other potentially toxic agents. The meta-analysis by Wood⁷⁶ concluded that nephrotoxicity was encountered statistically more often with vancomycin (10.7%) than with teicoplanin (4.8%), with those receiving aminoglycosides equally distributed

between the two groups. Ototoxicity with teicoplanin has been reported, but appears to be quite uncommon.^{60,77} Dalbavancin has been administered in escalating single dose levels or in multiple doses to healthy adults who subsequently underwent audiological assessment.⁹⁶ All individuals had normal baseline evaluations. In this study, no subjective or objective evidence of toxicity was found for the 39 individuals receiving study drug. As with vancomycin, neutropenia or thrombocytopenia has occasionally been reported during teicoplanin therapy.⁷⁷ Thrombocytopenia (and fever) has been observed more frequently when large doses of the drug have been employed.⁹⁷ Reversible thrombocytopenia with teicoplanin administration (400 mg/day) was reported in one patient undergoing therapy of acute myeloid leukaemia; during rechallenge with the drug 6 months later, after autologous bone marrow transplantation, the patient became refractory to platelet transfusions and developed mucosal bleeding which resolved with discontinuation of the drug and initiation of corticosteroids.⁹⁸

Limitations on glycopeptide use

The emergence of vancomycin-resistant strains of enterococci (VRE), where vancomycin use has been high, led to recommendations for severe restriction on the use of this agent in the absence of strong indications. The Hospital Infection Control Practices Advisory Committee recommendations advocate prudent use of vancomycin and discourage its use for certain situations such as routine surgical prophylaxis, most courses of empirical treatment for febrile neutropenic patients, and as primary (oral) therapy for antibiotic associated colitis.⁹⁹ In the individual patient, the effect of antecedent vancomycin exposure on acquisition of VRE is small.¹⁰⁰ Furthermore, because VRE are usually resistant to a number of other antimicrobials widely used in the hospital, exposure to several other drugs is associated with increased risk of VRE acquisition.¹⁰¹ Nevertheless, there is good evidence that ICUs that reduced the use of vancomycin, adjusted for changes in prevalence of MRSA, also experienced decreases in the prevalence of VRE.¹⁰²

The appearance of *S. aureus* with reduced susceptibility to glycopeptides has been a worrisome development and provides further impetus for efforts to minimize the inappropriate use of antibiotics of this class.⁴² Resulting guidelines further emphasize restriction on the use of vancomycin as well as prudent application of all antibiotics.¹⁰³ While reduction in the inappropriate use of these drugs is an important and potentially achievable goal, efforts to reduce the overall use of glycopeptides are limited by the high prevalence of MRSA in hospitals and the increasing prevalence of these organisms in the community. Indeed, in a US nationwide study of infections caused by *S. aureus* with reduced susceptibility to vancomycin, recent antecedent infection with MRSA and vancomycin use were independent risk factors for infection with these organisms.⁴²

Although extremely rare, strains of *S. aureus* that are fully resistant to vancomycin have appeared in the clinic. Since Noble *et al.*¹⁰⁴ reported in 1992 the transfer of vancomycin resistance genes from *E. faecalis* into *S. aureus*, the eventual occurrence of this phenomenon among clinical isolates was long anticipated. In 2002, two strains of *S. aureus* expressing the enterococcal *vanA* resistance determinant were reported from patients in

Michigan and Pennsylvania in the USA.^{105,106} A third isolate was identified in New York in 2004.¹⁰⁷ To date, there has not been evidence of dissemination of these organisms. A similar situation pertains in Europe, wherein extremely low prevalence rates of *S. aureus* isolates with reduced susceptibility to vancomycin have been observed.¹⁰⁸ Nevertheless, the occurrence of resistant isolates portends the eventual emergence of additional glycopeptide-resistant staphylococci.

Conclusions

The glycopeptides have proven remarkably useful antibiotics in clinical practice. Their spectrum of activity broadly addresses hospital-acquired as well as community-onset infections caused by Gram-positive bacteria. Activities of these agents against MRSA and methicillin-resistant coagulase-negative staphylococci have been especially important. These agents have provided important therapeutic alternatives to β -lactam antibiotics in patients allergic or otherwise intolerant of the latter. The pharmacokinetic and safety profiles of the available agents, vancomycin and teicoplanin, are such that they can be used effectively not only in the hospital, but also in the home or in specialized nursing environments. Nevertheless, while these glycopeptides may represent the best available option for many patients, neither agent can be viewed as an ideal drug for treatment of severe infections due to *S. aureus*. Newer agents with increased potency or enhanced bactericidal activity, or both, against staphylococci would be desirable. Use of glycopeptide antibiotics will, no doubt, continue to provide selective pressure favouring VRE, *S. aureus* with reduced susceptibility to glycopeptides, or fully glycopeptide-resistant *S. aureus*. While it is not certain that application of more potent or more effectively bactericidal glycopeptide antimicrobials would decrease the rate at which such organisms would emerge, this remains a plausible possibility that may be amenable to further experimental investigation.

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