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Anti-infective treatment in intensive care: the role of glycopeptides

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Abstract. Antibiotics are used in 80% of patients in the ICU, encouraging nosocomial infections with resistant organisms. If the antibiotic susceptibilities of the pathogen are known, a narrow-spectrum antibiotic is preferable to preserve the patient's resistance to colonization. However, treatment is often empirical and broad-spectrum combinations are commonly used. Gram-positive bacteraemia is associated with invasive monitoring or intravascular catheters. If the device cannot be removed easily, the glycopeptides are the only agents likely to be active against most strains of the commonest pathogen, the coagulase-negative staphylococcus. Long-stay patients are susceptible to infection with enterococci and methicillin-resistant *Staphylococcus aureus*, which are often resistant to all the usual agents other than glycopeptides. Vancomycin is long established, but is nephrotoxic, requires serum monitoring, must be administered as an infusion and can cause red man syndrome. Teicoplanin can be given as a single daily bolus without similar side-effects or monitoring. In deep-seated staphylococcal infection, the usual dose of teicoplanin is adequate if given in combination with other agents, but it may need to be doubled if used as monotherapy. Monitoring of the levels in the serum is helpful to ensure an adequate dose in patients with renal failure or in drug abusers, but is not needed to prevent toxicity.

Key words: Intensive care – Glycopeptides – Vancomycin – Teicoplanin

Patients in the ICU are at great risk of infection. The defences of the host are compromised by the need for invasive monitoring and intravenous fluids, tracheal intubation and urinary catheterization, in addition to the underlying illness and the activation of complement associated with haemofiltration or extracorporeal circulation. The pressure of work and high numbers of staff can result in cross-infection, particularly with patients who have been burned or undergone multiple trauma.

Over 80% of patients receive antibiotics (which are usually broad spectrum) and they rapidly lose their resistance to colonization with nosocomial pathogens. The widespread use of broad-spectrum cephalosporins in critically ill patients does not prevent the proliferation of enterococci and coagulase-negative staphylococci. Daschner [1] found that, with the exception of *Klebsiella* spp., the bacterial flora of the ICU need not have more antibiotic resistance than that of the general wards, but use of broad-spectrum antibiotics mirrored the incidence of resistance to methicillin and gentamicin in staphylococci. In a randomized trial of selective decontamination versus none in a general ICU, significantly more patients in the trial developed gut colonization with enterococci, regardless of the group, compared with historical controls (Table 1) [2]. The transmission of gut flora between patients was thought to be responsible for the similarity between the groups. However, this was not reflected in an increase in enterococcal infections.

If the organism is known to be susceptible, a narrow-spectrum agent is preferable. Unfortunately, immediate empirical treatment is usually necessary and agents are required that are likely to be active even against local multiply resistant organisms. Glycopeptides are commonly chosen because of their reliable activity against nosocomial Gram-positive pathogens.

In vitro activity

Coagulase-negative staphylococci are resistant to cephalosporins and methicillin in 35–65% of cases [3]. The range of concentrations of teicoplanin needed to inhibit 90% of the strains of coagulase-negative staphylococci is wide, partly because of variations between various media and conditions. For methicillin-sensitive strains of *Staphylococcus epidermidis*, the minimum con-

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Table 1. Rectal enterococcal colonization in patients receiving selective decontamination, concurrent controls not receiving additional antibiotics and historical controls [2]

Day of ICU stay	Total number of patients and proportion colonized with rectal enterococci					
	Historical controls		Concurrent controls		Selective decontamination	
	n	%	*n*	%	*n*	%
1	84	58	92	59	91	58
2	84	58	92	62	91	61
5	33	30	36	70	39	80
8	21	41	21	38	16	53
11	14	25	15	100	8	100

centration producing inhibition of 90% of strains (MIC_{90}) is 0.25–4 mg/l of teicoplanin, similar to vancomycin (1–2 mg/l), but for methicillin-resistant strains, the activity is less consistent (MIC_{90} 0.25–64 mg/l versus 0.3–3.1 mg/l) [4–7]. Some coagulase-negative staphylococci are resistant to teicoplanin, for example *S. haemolyticus* (MIC_{90} 1–64 mg/l), but these strains are sensitive to vancomycin (MIC_{90} 1–4 mg/l) [4, 8]. Reduced susceptibility of these organisms to vancomycin has been reported. In one series of eight patients with invasive infection, the MIC was 10 mg/l in four cases and in one case it was 20 mg/l [9]. Schwalbe [10] reported a reduction in the susceptibility of *S. haemolyticus* to vancomycin during the treatment of peritonitis. This strain was already resistant to teicoplanin. Both vancomycin and teicoplanin tend to have poor bactericidal activity against *S. haemolyticus*, as judged by timekill curves [11].

Streptococci are susceptible to both glycopeptides with MICs of 1 mg/l or less, teicoplanin having the slightly greater activity [12]. The MIC_{90} of enterococci is usually 0.02–3 mg/l for teicoplanin compared with 3–8 mg/l for vancomycin [12]. For 90% of 140 rectal isolates from patients in the ICU, teicoplanin was inhibitory at 0.25 mg/l and vancomycin at 4 mg/l, but ampicillin was inhibitory only at 32 mg/l [2]. Of 60 blood culture isolates of enterococci, the MIC_{90} of teicoplanin was 0.16 mg/l and of vancomycin 1.87 ng/l [13]. Some enterococci, especially *Enterococcus faecium*, are resistant to either or both glycopeptides. Resistance to both glycopeptides is associated with the production of a cytoplasmic membrane protein of molecular weight 39 kD [14] and in some strains resistance has been shown to be plasmid mediated [15]. There are three distinct resistance phenotypes of *Enterococcus faecium*. VanA strains have an inducible high-level resistance to all glycopeptides, while VanB strains have an inducible resistance to vancomycin but not teicoplanin. VanC strains have a constitutive resistance to vancomycin but not teicoplanin. We have reported from our own hospital a neutropenic patient with bacteraemia due to *E. faecium*, which was sensitive to teicoplanin (2 mg/l) but resistant to vancomycin (>64 mg/l) [16].

Most strains of methicillin-resistant *S. aureus* are inhibited by 3 mg/l of teicoplanin or vancomycin [12]. The rarity of resistance to glycopeptides is in contrast to the increasing isolation of ciprofloxacin-resistant strains. In a survey of 106 strains of methicillin-resistant *S. aureus* from 21 countries, all were sensitive to teicoplanin and vancomycin [17].

Pharmacokinetics

Correct dosing with antibiotics presents particular challenges in the critically ill patient. The concentrations achieved in the serum and the rate of elimination are affected by rapid changes in cardiac output, renal function, hepatic function and serum proteins [18]. The large number of drugs administered increases the chances of adverse drug reactions and interactions. For teicoplanin, administration of a loading dose of 6 mg/kg every 12 h i.v. for three doses is usually recommended to achieve steady-state levels rapidly. Alternatively, in the critically ill, the steady state can be achieved after a single dose of 18 mg/kg infused over a 30-min period [19]. The 24-h trough level is then 13 mg/l, a concentration reached only after a fourth 12-hourly dose of 6 mg/kg. Unlike vancomycin, it can be given as a bolus dose and the long half-life permits once-daily dosing. Although teicoplanin can be administered intramuscularly, this would not be a method of choice as blood flow and absorption would be erratic in the presence of cardiac failure. Vancomycin must be given intravenously and the short half-life requires twice-daily dosing if renal function is normal. An infusion over 0.5–1 h is needed to prevent the red man syndrome.

Acute renal failure is common following trauma, major sepsis or surgery and it greatly prolongs the half-life of both glycopeptides. The dose may be decreased and the dosing interval maintained, or the same dose given with a longer dosing interval. The latter is preferred for antibiotics such as aminoglycosides, in which a high trough level is associated with toxicity. However, teicoplanin has a high therapeutic index and either adjustment is acceptable. The dosing interval may be increased to 2 days for a creatinine clearance of 40–60 ml/min and to 3 days for severe renal impairment [20, 21]. It is important to give the same loading dose regardless of renal function, to ensure that the levels in the serum are therapeutic. In patients requiring haemodialysis, a loading dose of 800 mg followed by 400 mg once a week is associated with a trough level of 5.7 mg/l or more [22]. After loading doses of 800, 400 and 400 mg, a once-weekly dose of 400 mg is associated with trough levels of 15–25 mg/l [23]. Serum monitoring can be useful to ensure an adequate concentration of the drug, but it is not required to prevent toxicity.

The normal half-life of vancomycin is 6 h, but in renal failure it can reach 240 h. The normal recommendations are to extend the dosing interval to 72–240 h if the creatinine clearance is between 10 and 50 ml/min and to 240 h for a creatinine clearance of <10 ml/min [19]. Dose adjustments must be made on the results of serum assays [24]. In 37 critically ill patients in whom the dose was determined by a nomogram [25], many developed high serum concentrations, with a mean trough of

23 mg/l. The volume of distribution and clearance varied greatly between patients [24].

The dose of glycopeptides need not be adjusted in hepatic failure, although high doses of teicoplanin have been associated with transient liver dysfunction.

Intravascular catheters and prostheses

The incidence of bacteraemia associated with intravascular devices depends on the definition used, the method of culture, the site and the time since insertion. Superficial signs of infection are unreliable and blood cultures should be obtained both via the catheter and from a distant site. The site of insertion should be swabbed. In most cases, removal of the catheter and semiquantitative culture is preferable. However, Hickman lines and prostheses are much more difficult to remove and attempts will need to be made to eradicate infection.

The usual pathogens are the coagulase-negative staphylococci, making them one of the most common Gram-positive isolates from the blood in the ICU. A possible pathogenic mechanism of *S. epidermidis* is its production of an extracellular slime which interferes with the antimicrobial activity of teicoplanin and vancomycin [3]. A four-fold increase in the MIC is observed on the addition of slime extract to a broth culture. Infections with slime-producing strains have been shown by several investigators to be more difficult to cure than those with slime-negative strains.

O'Connell [26] reported the results of treating 25 patients with bacteraemia related to right atrial catheters. Coagulase-negative staphylococci were responsible in each case. Five patients, who were changed from vancomycin after allergic responses, were cured, as were 12 of 20 given teicoplanin from the start. *S. haemolyticus* was responsible for three of the eight failures. Four patients who were changed to vancomycin were later cured. A double-blind comparison of teicoplanin and vancomycin conducted by Gilbert et al. [27] involved nine patients with staphylococcal bacteraemia related to catheters, all of whom were cured.

An unpublished blinded trial in the USA [28] compared teicoplanin (6 mg/kg/day) and vancomycin (15 mg/kg/day) in the treatment of vascular access-associated bacteraemia. Of 242 patients, only 124 patients were thought assessable, but the clinical success rate was 44 (73%) of 60 for teicoplanin, and 44 (69%) of 64 for vancomycin. The eradication rates for *S. aureus* were 77 and 79% (24/31 versus 23/29), and for coagulase-negative staphylococci 90 and 89% (26/29 versus 31/35), respectively.

Prophylactic administration of antibiotics does not seem to prevent infection related to the use of catheters. Aseptic technique in the insertion and management of lines is of far greater importance. McKee et al. [29] administered vancomycin or no agent in a randomized trial of patients with insertion of intravenous nutrition lines. Clinical catheter-related sepsis occurred in 10 of 29 patients given no prophylaxis and in 7 of 24 patients given vancomycin; *S. epidermidis* was the most common pathogen. Teicoplanin, 400 mg, given before the insertion of Hickman catheters did not significantly reduce soft tissue infections related to the use of the catheters compared to no agent (14/43 versus 20/45) [30]. Two weeks later, episodes of bacteraemia during periods of neutropenia were reduced, but the relationship to prophylaxis was not certain (7/40 versus 16/40, $\chi^2 = 3.9$, $p < 0.05$).

Other staphylococcal infections

Patients with deep-seated sepsis caused by *S. aureus* can present considerable therapeutic problems. Glycopeptides would be used if the patient was allergic to penicillin or the organism was methicillin resistant. Small open studies reported high rates of failure when low doses (3 mg/kg/day) of teicoplanin were used [31, 32]. However, at a dose of 6 mg/kg/day, the efficacy of teicoplanin appears to be similar to that of vancomycin for most indications (Table 2) [33].

In the treatment of staphylococcal endocarditis, teicoplanin should be combined with other agents or given at a higher dose. Using teicoplanin monotherapy at a dose of 6 mg/kg/day, Gilbert et al. [27] reported 6 of 8 patients failed treatment compared with 1 of 4 patients given vancomycin (Table 2). In an unpublished open study, 6 of 10 treatments failed when the serum trough levels fell below 20 mg/l, whereas only 1 of 11 failed with trough levels over 20 mg/l [33]. However, in combination with other agents (e.g. aminoglycosides) doses of 6 mg/kg/day appear to be satisfactory [46]. There have also been failures associated with the use of vancomycin. One review reported failure in 5 of 12 patients [47] and, of 13 drug abusers with staphylococcal endocarditis, 5 failed despite combination therapy in 3 cases [48]. Six of 42 patients with staphylococcal endocarditis given vancomycin with or without rifampicin were not cured or died [49].

Between 8 and 26% of nosocomial pneumonias may be caused by *S. aureus* and are associated with a high mortality [50, 51]. The glycopeptides can be used as alternatives to isoxazolyl penicillins or in those cases caused by methicillin-resistant strains. Amaducci et al. [52] reported 20 cases of nosocomial pneumonia in which *S. aureus* was isolated from bronchoscopy specimens. Patients were given a low dose (3 mg/kg) of teicoplanin once a day for a mean of 8 days. Of 18 evaluable cases, *S. aureus* was eliminated in 16 and the overall cure rate was 78%. Teicoplanin was effective in open studies of infection of the lower respiratory tract, 113 of 135 being cured in the Lewis trial [46], but controlled trials in pneumonia are lacking.

Although many trials include some patients with infections due to methicillin-resistant *S. aureus*, few report these separately. In a small randomized trial of patients with septicaemia or osteomyelitis, 7 of 12 given teicoplanin were cured, 4 improved and 1 failed treatment, while 6 of 9 patients given vancomycin were cured, and 3 improved [34]. Drabu et al. [53] reported cure in 75% of 26 patients who had ventilator-associated respiratory infections, wound infections or urinary infections. Additional antibiotics were used in 10 cases and most courses were between 3 and 12 days in length.

Table 2. Published comparative trials of teicoplanin (T) versus vancomycin (V) in severe Gram-positive sepsis

Reference	Indication	Dose (loading)	Duration (days)	Total no. of patients	Cure/ improve	Fail	Odds ratio (95% CI)
Van Laethem et al. [34]	MRSA infections	T: 400 mg 24 h	10–80	11	10	1	–
		V: 1 g 12 h	10–48	9	9	0	
Smith et al. [35]	Hickman catheter infections	T: 200–400 mg 24 h (400 mg × 1–2 12 h) + pip/gent	Mean 8	32	21	9	1.1 (0.3–3.3)
		V: 1 g 12 h + pip/gent	Mean 7	28	20	8	
Neville et al. [36]	Various	T: 200–400 mg 24 h (400 mg × 1)	4–30	18	13	4	0.7 (0.2–2.9)
		V: 1 g 12 h	1–19	19	13	6	
Gilbert et al. [27]	Bacteraemia	T: 6 mg/kg 24 h (6 mg/kg × 3 12 h)	NK	14	13	1	0.8 (0.05–15)
		V: 15 mg/kg 12 h	NK	12	11	1	
	Endocarditis	T: as above	NK	8	3	5	8 (0.6–110)
		V: as above	NK	6	5	1	
Gerard et al. [37]	Staphylococcal infections	T: 200 mg 24 h (400 mg × 3 24 h)	NK	21	13	5	1.8 (0.4–9.0)
		V: 1 g 12 h	NK	19	14	3	
Van der Auwera et al. [38]	Various (immune compromised)	T: 200 mg 24 h (400 mg × 3 24 h)	4–17	16	12	4	0.96 (0.2–3.8)
		V: 1 g 12 h	9–35	35	26	9	0.96 (0.3–3.4)
		T: 400 mg 24 h (400 mg × 38 h)	4–17	20	15	5	
Del Favero [39]	Febrile neutropenia	T: 6 mg/kg 24 h (6 mg/kg × 3 12 h) + ceftazidime + amikacin	NK	152	123	29	0.74 (0.4–1.3)
		V: 15 mg/kg 12 h + ceftazidime + amikacin	NK	149	113	36	
Cony-Makhoul et al. [40]	Febrile neutropenia	T: 6 mg/kg 24 h (6 mg/kg × 3 12 h) + ceftazidime	NK	35	21	14	0.8 (0.3–2.2)
		V: 15 mg/kg 12 h + ceftazidime	NK	24	13	11	
Choi et al. [41]	Febrile neutropenia	T: 400 mg 24 h (400 mg/kg × 3 12 h) + ceftazidime/ aztreonam	7–12	22	17	7	1.1 (0.3–4.4)
		V: 500 mg 8 h + ceftazidime/ aztreonam	7–12	20	14	6	
Charbonneau et al. [42]	Various	T: 6 mg/kg 24 h (6 mg/kg × 3 12 h) + netilmicin	5–31	24	16	4	1.4 (0.3–6.3)
		V: 8 mg/kg 8 h + netilmicin	3–42	32	20	4	
Kureishi et al. [43]	Febrile neutropenia	T: 6 mg/kg 24 h (6 mg/kg × 3 12 h) + piperacillin + tobramycin	22	25	23	0	
		V: 15 mg/kg 12 h + piperacillin + tobramycin	16	25	21	1	
Hedstrom et al. [44]	Gram-positive infections	T: 400 mg 24 h (400 mg × 3)	7–22	31	27	4	1.9 (0.2–19)
		V: 1 g 12 h		17	13	1	
Neville et al. [45]	Gram-positive infections	T: 200–400 mg 24 h (400 mg × 1)	5–14	17	13	4	0.7 (0.2–2.9)
		V: 1 g 12 h		19	13	6	

MRSA, Methicillin-resistant *Staphylococcus aureus*
NK, Not known pip/gent = piperacillin plus gentamicin

Enterococcal infections

Part of the normal gut flora, enterococci can produce opportunistic infections in the critically ill patient, and their isolation is becoming more frequent. In a longitudinal study of urinary infection, enterococci were isolated in 4% of specimens in 1971, but 12.6% in 1990 [54]. Bacteraemia and endocarditis are often treated with benzylpenicillin and gentamicin. However, the glycopeptides must be used for the increasing proportion of organisms resistant to β-lactams.

Vancomycin has been recommended as the second-line treatment of serious enterococcal disease [55]. If there is no high-level resistance to aminoglycosides, combination with gentamicin is synergistic. However, there could be up to a 35% incidence of nephrotoxicity [56]. For strains resistant to gentamicin, high doses of ampicillin or penicillin alone have been used, but with little success; for example only 7 of 18 patients with endocarditis were cured in one series [57].

Teicoplanin is effective in enterococcal infections. In the multicentre European open trial of teicoplanin, the eradication rate for enterococcal infections was 98% (47 of 48 cases) [46]. In unpublished USA trials, the eradication rate for enterococci was 91% (41 of 45) [58]. Of these 19 were soft-tissue infections, 19 were bone and joint, 6 were septicaemia and 1 was endocarditis. In unpublished comparative trials, 6 of 6 patients with enterococcal bacteraemia were cured by teicoplanin versus 6 of 8 cured by vancomycin. However, adequate comparative information is lacking.

Adverse effects

In most respects, the incidence of adverse effects of vancomycin and teicoplanin are similar. However, several trials have suggested that nephrotoxicity in association with aminoglycosides is less during treatment with teicoplanin than with vancomycin [35, 59]. A double-blind trial in febrile neutropenic patients showed significantly fewer patients developing nephrotoxicity with teicoplanin rather than vancomycin (0/25 versus 6/25, $p = 0.02$, Fisher's test) [43]. Unlike vancomycin, monitoring of the levels of teicoplanin in the serum is not necessary for the avoidance of toxicity. The red man syndrome, a common adverse effect of the administration of vancomycin, can be troublesome in the critically ill patient. It is exceedingly rare with teicoplanin [35]. Ototoxicity is rare, but can occur with both glycopeptides. It was detected by serial audiograms in 1 of 298 patients given teicoplanin and in 1 of 43 given vancomycin in unpublished studies in the USA. The latter patient had been given aminoglycosides.

Conclusions

The glycopeptides are increasingly widely used in ICUs because of the high numbers of patients experiencing Gram-positive bacteraemia. Enterococci and staphylococci, especially coagulase-negative strains, are often resistant to other agents. Both glycopeptides should be available because some bacterial strains may be resistant to only one and some patients may have adverse reactions to only one. However, teicoplanin has the advantage of rapid bolus injection, once-daily dosage, reduced nephrotoxicity and the lack of red man syndrome. More comparative trials of the two agents in the critically ill patient are needed to assess their efficacy.

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