

Introduction

The glycopeptides are a class of agents composed of amino acid residues and attached sugars. Glycopeptides were first used in the 1950s but were not widely used until the emergence of multi-resistant staphylococci in the 1980s. Glycopeptides are active against Gram-positive bacteria but Gram-negative bacteria are intrinsically resistant. The clinically available glycopeptides differ in potency and pharmacokinetics. Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various *van* gene complexes. These genes have rarely been found in *Staphylococcus aureus*. Changes in cell wall structure in *S.aureus* also result in vancomycin resistance, which is most commonly heterogeneous (formerly referred to as VISA/hVISA isolates). Low-level resistance to teicoplanin is also seen in some coagulase-negative staphylococci, especially in *Staphylococcus haemolyticus*.

EUCAST has defined clinical breakpoints for the parenteral use of the glycopeptides vancomycin and teicoplanin, which are available throughout Europe. Unlike vancomycin, no oral formulation of teicoplanin is available. Since vancomycin and teicoplanin are active against the same microorganisms, the same species or species groups have received breakpoints for both glycopeptides.

Vancomycin is mainly used to treat severe or complicated infections caused by multi-resistant microorganisms among *Staphylococcus* spp., *Enterococcus* spp. and *Streptococcus* spp. (including *Streptococcus pneumoniae*). In clinical practice, vancomycin is effective in the therapy of skin and soft tissue infection, pneumonia, urinary infection, endocarditis, prosthetic device associated infection, blood stream infections, and other systemic infections.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	1000 x 2 iv 125 x 4 oral	1000 x 2 iv or 500 x 4 iv 125 x 4 oral	500 x 3 iv or 1000 x 2 iv 125 x 4 oral	500 x 4 iv 125 x 4 oral	500 x 4 iv or 1000 x 2 iv 125 x 4 oral	20 mg/kg x 2 iv 125 x 4 oral
Maximum dose schedule (mg)	1500 x 2 iv 1000 x 4 oral	1000 x 2 iv or 500 x 4 iv 125 x 4 oral	500 x 3 iv or 1000 x 2 iv 125 x 4 oral	500 x 4 iv 125 x 4 oral	500 x 4 iv or 1000 x 2 iv 125 x 4 oral	20 mg/kg x 2 iv 125 x 4 oral
Available formulations ¹	iv, oral	iv, oral	iv, oral	iv, oral	iv, oral	iv, oral

¹Vancomycin is used orally in the treatment of *Clostridium difficile* associated diarrhoea.

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
<i>Streptococcus anginosus</i>	0	0	0	0	0	0	11	4	52	86	18	0	0	0	0	0	0	0	0	1
<i>Streptococcus bovis</i>	0	0	0	0	0	0	0	108	181	12	1	0	0	0	0	0	0	0	0	1
<i>Streptococcus constellatus</i>	0	0	0	0	0	0	2	1	31	57	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus equinus</i>	0	0	0	0	0	0	0	4	2	0	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus gordonii</i>	0	0	0	0	0	0	0	0	8	1	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus</i> group C	0	0	0	0	0	0	0	2	3	1	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus</i> group G	0	0	0	0	0	0	4	218	148	4	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus intermedius</i>	0	0	0	0	0	0	0	3	32	30	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus milleri</i>	0	0	0	0	0	0	1	4	50	53	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus mitis</i>	0	0	0	0	0	0	1	42	418	55	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus mutans</i>	0	0	0	0	0	0	0	4	13	16	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus oralis</i>	0	0	0	0	0	0	0	0	47	51	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus parasanguis</i>	0	0	0	0	0	0	0	4	6	1	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus pneumoniae</i>	0	0	0	0	4	93	384	20079	29574	800	115	4	0	0	0	0	0	0	0	1
<i>Streptococcus pyogenes</i>	0	0	0	0	0	3	36	3419	7221	49	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus salivarius</i>	0	0	0	0	0	0	1	6	58	29	1	0	0	0	0	0	0	0	0	1
<i>Streptococcus sanguis</i>	0	0	0	0	0	0	1	6	113	25	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus uberis</i>	0	0	0	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0	1
<i>Streptococcus viridans</i> group	0	0	0	0	0	0	14	142	893	357	6	0	0	0	0	0	0	0	0	1

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

3. Breakpoints prior to harmonisation (mg/L) S_≤/R_>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI ¹
General breakpoints							
		4/16	4/8	4/16	4/8	4/4	
Species related breakpoints							
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.	4/4	4/16			4/8	4/4	4/16 ²
<i>Streptococcus</i> spp.	4/4	4/16				2/2	1/-
<i>Streptococcus pneumoniae</i>	4/4	4/16			2/4	2/2	1/-
<i>Enterococcus</i> spp.	4/4	4/16			4/8	4/4	4/16
<i>Haemophilus</i> spp.							
<i>Moraxella</i> spp.							
Corynebacteria						4/4	
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes Gram-positive							
Anaerobes Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							
<i>Bacillus anthracis</i>							0.5/-

¹CLSI breakpoints converted to EUCAST terminology.

²The CLSI *S. aureus* breakpoints were reduced to 2/8 mg/L in 2006.

4. Pharmacokinetics

Dosage	1000 mg x 1 or 15 mg/kg x 1			
Cmax (mg/L)	20-50			
Cmin (mg/L)	5 -15			
Total body clearance (L/h/kg)	0.58			
T ½ (h), mean (range)	4-8			
AUC24h (mg.h/L)	520			
Fraction unbound (%)	10-55			
Volume of distribution (L/kg)	0.3			
Comments	<ul style="list-style-type: none">• A number of different dosing strategies for intravenous administration exist for vancomycin from single daily doses to continuous infusion.• The drug is not absorbed from the intestines, is not metabolised to a significant degree, and is excreted through glomerular filtration• Two values are given where references differ. Cells are left empty when data are not readily available.			
References	<ul style="list-style-type: none">• James et al. Antimicrob Agents Chemother 1996; 40: 696• Wysoki et al. Antimicrob Agents Chemother 2001; 45: 2460• Van Bambeke et al. Drugs 2004; 64: 913• Greenwood. Antibiotic & Chemotherapy 2003; 8th Edn: 303			

5. Pharmacodynamics

	<i>S. aureus</i>			
AUC/MIC for bacteriostasis	-			
fAUC/MIC for 2 log reduction	130-270			
fAUC/MIC from clinical data	-			
Comments	<ul style="list-style-type: none"> • In pre-clinical pharmacodynamic models AUC has been related to antibacterial effect. Cmax has also been related to effect. • A free drug AUC/MIC of 138-263 has been associated with a 2 log kill of <i>S. aureus</i> in animal models and an fAUC of 130 with a 2 log kill in in vitro models. Inoculum has a major impact on the magnitude of the fAUC/MIC. fAUC/MICs for static effects and 1 log kills are lower than those for 2 log kills but are not clearly established. • A total drug AUC/MIC ratio of >350 has been associated with higher rates of clinical success and bacterial eradication than lower AUC/MIC values in the therapy of 50-60 patients with staphylococcal pneumonia. In a further study of 102 patients with MRSA, healthcare associated pneumonia AUC could not be related to in-hospital mortality. • Two values are given where references differ. Cells are left empty when data are not readily available. 			
References	<ul style="list-style-type: none"> • Ebert S et al 1987. Abstract of the 27th ICAAC. 1987; Abstract 439: p173. • Craig WA, Andes DR. Abstract of the 46th ICAAC 2006; Abstract A-644: p16. • MacGowan AP et al. Abstract of 18th ECCMID 2008; p1242 (www.blackwellpublishing.com/eccmid18/abstract.asp?id=69142). • Knudsen JD et al. Antimicrob Agents Chemother 2000; 44: 1247-1254. • Moise PA et al. Am J Health Syst Pharm 2000; 57, Suppl 2: S4-9. • Jeffries MN et al. Chest 2006; 130: 947-953. 			

6. Monte Carlo simulations and Pk/Pd breakpoints

Insufficient data.

7. Clinical data

Recently performed randomised controlled trials comparing vancomycin with developmental agents to treat Gram-positive infection indicated clinical effectiveness of vancomycin against susceptible pathogens in infections including complicated skin and soft tissue infection, diabetic foot infections, hospital acquired pneumonia, right sided endocarditis and blood stream infection. Clinical experience indicates that vancomycin is adequate therapy for susceptible Gram-positive infections related to infections of prosthetic implantable devices (heart valves, IV lines, prosthetic joints etc), intra-abdominal infection, pleural infection, bone and joint infection, UTI and other body sites. A number of clinical studies have been performed relating vancomycin MIC to clinical outcome. Most studies have been retrospective and conducted in single centres and are mainly of MRSA blood stream infection. High vancomycin MICs could be related to clinical outcomes and MIC breakpoints for poor responses of ≥ 2 mg/L or ≥ 1.5 mg/L are suggested by more than one case series. However, not all case series have been able to relate increased vancomycin MIC to poor outcome (Table 1). In addition, a number of clinical studies have been performed to assess the clinical significance hVISA/VISA phenotype. Again, many of these studies are single centre retrospective case series. However, the hVISA/VISA phenotype appears to be associated with impaired clinical responses to vancomycin (Table 2).

Therefore, based primarily on clinical evidence, those strains of *S. aureus* with vancomycin MIC values of 2 mg/L which are on the border of the wild type MIC distribution including those with hVISA phenotype are likely to have impaired clinical responses to vancomycin. It is unclear if increased doses of vancomycin will improve clinical outcomes (Hidayat et al, 2006) hence the R breakpoint was reduced from >8 to >2 mg/L to avoid reporting VISA isolates as intermediate. High doses of vancomycin are clearly associated with an increased risk of nephrotoxicity (Lodise et al, 2008; Ingram et al, 2008; Lodise et al, 2009) and perhaps also ototoxicity (Forouzesh et al, 2009).

Although MSSA have the same MIC distribution as MRSA to vancomycin there is ample clinical evidence that MSSA infections respond more poorly to vancomycin than to β -lactams (Kim et al, 2008, reviewed MacGowan, 2008).

Table 1: Clinical studies relating vancomycin MIC to outcome in staphylococcal Infection

Reference	Clinical Study Design	Number of patients and MICs for pathogens	Findings
Fridkin et al 2003	Multicentre case control study.	n=21 vancomycin MIC ≥ 4 mg/L. n=41 vancomycin MIC ≤ 2 mg/L. MRSA infection, mainly BSI, respiratory and cSSTI.	Mortality 63% (12/19) if MIC ≥ 4 mg/L. Mortality 12% (5/42) if MIC ≤ 2 mg/L, Odds Ratio 12.7, 95% CI 3.4-48.
Sakoulas et al 2004	Patients previously enrolled in Phase III, IV prospective studies. Most patients were recruited due to unsatisfactory response to conventional therapy.	n=9 vancomycin MIC ≤ 0.5 mg/L. n=21 vancomycin MIC 1-2 mg/L. MRSA BSI.	Vancomycin success 55.6% if MIC ≤ 0.5 mg/L. Vancomycin success 9.5% if MIC 1-2 mg/L.

Charles et al 2004	Single centre prospective study.	n=5 vancomycin MIC 2-4 mg/L, median 2 mg/L hVISA phenotype. n=48 vancomycin MIC 0.5-2 mg/L, median 1 mg/L. MRSA BSI.	Patients infected with hVISA phenotype had longer duration of bacteraemia (mean 39±32d versus 6.0±9d, p=0.02) and time to becoming afebrile (mean 35±26d versus 3±3d p<0.001).
Hidayat et al 2006	Single centre prospective study.	n=51 vancomycin MIC ≥2 mg/L. n=41 vancomycin MIC <2 mg/L. MRSA respiratory and BSI.	End of treatment response 62% (24/39) if with MIC ≥2 mg/L versus 85% (34/40) if MIC <2mg/L (p<0.02). Higher infection mortality if MIC ≥2 mg/L 24% (11/52) versus 10% (4/44) if MIC <2 mg/L, p=0.16; but high MIC independent predictor of poor treatment response in a multi-variate analysis.
Soriano et al 2008	Retrospective single centre study.	n=38 vancomycin MIC 1 mg/L. n=90 vancomycin MIC 1.5 mg/L. n=40 vancomycin MIC 2mg/L. MRSA BSI.	In multi-variate analysis, infection with MRSA with vancomycin MIC 2 mg/L (Odds Ratio 6.39, 95% CI 1.68-24.3) predicted mortality.
Hsu et al 2008	Prospective observational single case study.	n=92 mainly respiratory infection and BSI with MRSA. Vancomycin MICs determined by four methods.	Multi-variate analysis of Etest MICs indicated MIC (Odds Ratio 5.6, 95% CI 1.5-20.9, p=0.011) was an independent predictor of response. Etest MIC of ≥1.5 mg/L appeared to identify non-response.
Lodise et al 2008	Retrospective cohort single centre study.	n=9 vancomycin MIC ≤0.75 mg/L. n=17 vancomycin MIC 1.0 mg/L. n=57 vancomycin MIC 1.5 mg/L. n=9 vancomycin MIC 2.0 mg/L.	Clinical failure was defined by a composite end point of 30 day mortality, MRSA in blood cultures after 10 days vancomycin, or recurrent MRSA bacteraemia in 60 days. MIC ≥1.5 mg/L when compared with MIC <1.5 mg/L was associated with higher rates of failure (Odds Ratio 2.6, 95% CI 1.3-5.4), p<0.05) and increased length of stay.

Price et al 2009	Retrospective single centre cohort study	n=45, MIC range 0.75-2mg/L.	MIC <1.5 mg/L associated with a higher risk of death at 3 months compared to MIC ≥ 1.5 mg/L (Odds Ratio 12, 95% CI 1.73-83.2, p=0.001).
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Table 2: Clinical Studies on hVISA, VISA phenotype and outcome

Reference	Clinical Trial Design	Findings
Charles et al 2004	Single centre retrospective study of MRSA bacteraemia (n=53)	Patients with hVISA phenotype more likely to have high bacterial load infections (undrained collections, infected prosthetic material, i.e. persistent bacteraemia and fever >7 days) and initially low vancomycin serum concentrations
Neoh et al 2007	Single centre retrospective study of MRSA bacteraemia (n=20)	Vancomycin population analysis was related to clinical response in terms of days until afebrile and days until CRP ≤30% maximum value.
Maor et al 2009	Single centre retrospective study of MRSA bacteraemia (n=250)	hVISA phenotype associated with longer period of bacteraemia, and greater prevalence of complications such as endocarditis or osteomyelitis.

- Fridkin SK et al. Clin Infect Dis 2003; 36: 429-39.
- Sakoulas G et al. J Clin Microbiol 2004; 42: 2398-2402.
- Charles PG et al. Clin Infect Dis 2004; 38: 448-451.
- Hidayat LK et al. Arch Intern Med 2006; 166: 2138-2144.
- Soriano A et al. Clin Infect Dis 2008; 46: 193-200.
- Hsu D et al. Int J Antimicrob Agents 2008; 32: 378-385.
- Lodise TP et al. Antimicrob Agents Chemother 2008; 52: 3315-3320.
- Price J et al. Clin Infect Dis 2009; 48: 997-998.
- Neoh HM et al. Annals of Clin Microbiol and Antimicroblals 2007; 6: 13-20.
- Maor Y et al. J Infect Dis 2009; 199: 619-24.
- Lodise et al. Antimicrob Agents Chemother 2008; 52:1330-1336.
- Ingram PR et al. J Antimicrob Chemother 2008; 62: 168-171.
- Lodise et al. Clin Infect Dis 2009; 49: 507-14.
- Forouzesh A et al. Antimicrob Agents Chemother 2009; 53: 483-486.
- Kim S-H et al. Antimicrob Agents Chemother 2008; 52: 192-7.
- MacGowan AP. J Antimicrob Chemother 2008; 62, Suppl 2: 105-14.

8. Clinical breakpoints

Non-species-related breakpoints	Most pre-clinical and clinical data are relevant only to <i>S.aureus</i> and MRSA in particular (see sections 5 and 7). On this basis no non-species-related breakpoints are set.
Species-related breakpoints	<p>Breakpoints were based on Pk data, microbiological data and clinical experience.</p> <p>For <i>Staphylococcus</i> spp. the breakpoints are 2/2 mg/L. These breakpoints avoid reporting “GISA/VISA” isolates intermediate, as serious infections with “GISA/VISA” isolates are not treatable with increased doses of vancomycin.</p> <p>For <i>Enterococcus</i> spp, the breakpoints are 4/4 mg/L. These breakpoints avoid dividing the wild type MIC distribution and isolates with <i>vanA</i> or <i>vanB</i> will be reported resistant.</p> <p>For streptococci, including <i>Streptococcus pneumoniae</i>, and Gram-positive anaerobes breakpoints were set at 2/2 mg/L as strains with MIC values above 2 mg/L are rare or not yet reported.</p>
Species without breakpoints	Enterobacteriaceae, <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Neisseria</i> spp. and Gram-negative anaerobes are considered poor targets for vancomycin therapy and for that reason did not receive breakpoints.
Clinical qualifications	It is unclear if high dose vancomycin is sufficient to overcome <i>S.aureus</i> strains with MICs 2-4mg/L, however, high dose therapy is associated with an increased risk of nephrotoxicity and perhaps ototoxicity. MSSA infections respond more poorly to vancomycin than to β -lactam agents.
Dosage	Breakpoints apply to an intravenous dose of 1000 mg x 2, 500 mg x 4 or 2g/day by continuous infusion.
Additional comment	Glycopeptide breakpoints have been revised in the light of concerns regarding reporting of VISA isolates as susceptible, the absence of evidence for successful treatment of infections caused by enterococci appearing intermediate with previous breakpoints, and the few pharmacodynamic data now available.

9. Vancomycin - EUCAST clinical MIC breakpoints

These can be found at <http://www.eucast.org>

10. Exceptions noted for individual national committees

None