

Glycopeptides

Non-beta-lactam cell-wall inhibitors that bind the D-alanyl-D-alanine terminus, active against gram-positive organisms including MRSA.

Online guide: <https://www.medguideglobal.com/pharmacology/antibiotics/glycopeptides>

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Quick revision

One Liner: Glycopeptides bind D-alanyl-D-alanine rather than a penicillin-binding protein, which is why they work on gram-positive organisms including MRSA and why beta-lactamases are irrelevant to them.

1. Vancomycin binds D-alanyl-D-alanine, inhibiting glucosyltransferase (peptidoglycan synthase) and blocking synthesis and cross-linking of peptidoglycan. [2]
2. Active exclusively against gram-positive organisms: streptococci, enterococci and staphylococci including MRSA and MSSA. [2]
3. Oral vancomycin has bioavailability under 10%, so it treats colonic infection only; intravenous vancomycin does not treat *C. difficile* because it penetrates the colon poorly. [2]
4. Vancomycin flushing syndrome is an infusion-rate reaction, not an allergy - flushing, pruritus and erythematous rash on face, neck and upper torso 4 to 10 minutes after starting. [2]
5. Nephrotoxicity risk rises with trough levels above 15 mg/L, concurrent nephrotoxic drugs and existing renal impairment. [2]
6. Three lipoglycopeptides are available in the United States: dalbavancin, oritavancin and telavancin. [3]
7. Vancomycin-resistant enterococci are the resistance concern that defines stewardship for this class. [2]

Overview

1. The glycopeptides are cell-wall synthesis inhibitors that work without a beta-lactam ring. Vancomycin, the defining member, is a tricyclic glycopeptide used for severe gram-positive bacterial infection and is bactericidal against susceptible organisms. [2]
2. Because the class binds the peptidoglycan building block itself rather than an enzyme, none of the beta-lactamase machinery that defeats penicillins and cephalosporins applies here. That independence is exactly what makes glycopeptides useful against methicillin-resistant *Staphylococcus aureus*. [2]
3. The class has since been extended. Glycopeptide antibiotics are semisynthetic macromolecules structurally related to vancomycin with activity against several gram-positive organisms including MRSA, and three lipoglycopeptides - dalbavancin, oritavancin and telavancin - are available for use in the United States. [3]

Classification and drug examples

Intro: Split by generation of development rather than by spectrum: the original glycopeptides, and the semisynthetic lipoglycopeptides derived from them.

1. Name: Glycopeptides

1. Note: The original members of the class, used for severe gram-positive infection.

1. Name: Vancomycin

1. Route: IV and oral

1. Note: Tricyclic glycopeptide; route determines indication because oral bioavailability is under 10%. [2]

2. Name: Teicoplanin

2. Route: IV/IM

2. Note: A natural glycopeptide alongside vancomycin, structurally related to it. [3] [2][3]

2. Name: Lipoglycopeptides

2. Note: Semisynthetic macromolecules structurally related to vancomycin, with activity against gram-positive organisms including MRSA.

1. Name: Dalbavancin

1. Route: IV

1. Note: Semisynthetic lipoglycopeptide available for use in the United States. [3]

2. Name: Oritavancin

2. Route: IV

2. Note: The second of the three US lipoglycopeptides. [3]

3. Name: Telavancin

3. Route: IV

3. Note: The third US lipoglycopeptide in this group. [3] [3]

Mechanism of action

Summary: Vancomycin binds the D-alanyl-D-alanine terminus of the peptidoglycan precursor, so the precursor can no longer be processed. The bound drug blocks the transglycosylase and transpeptidase steps, preventing both polymerisation and cross-linking of peptidoglycan and weakening the wall until the organism dies.

Target: The D-alanyl-D-alanine terminus of the peptidoglycan precursor

Cidal Static: bactericidal

Kill Kinetics: time-dependent

1. Step: 1

1. Title: The drug binds the building block, not the builder

1. Detail: Vancomycin binds D-alanyl-D-alanine - the peptide terminus of the peptidoglycan precursor - rather than an enzyme. [2]

2. Step: 2

2. Title: Peptidoglycan synthase is blocked

2. Detail: That binding inhibits glucosyltransferase, also called peptidoglycan synthase. [2]

3. Step: 3

3. Title: Synthesis and cross-linking both stop

3. Detail: The organism can neither extend nor cross-link its peptidoglycan polymers. [2]

4. Step: 4

4. Title: The wall weakens and the cell dies

4. Detail: Loss of a competent cell wall leads to bacterial death - the class is bactericidal. [2]

5. Step: 5

5. Title: Size limits the reach

5. Detail: Activity is exclusive to gram-positive organisms; the class does not act on gram-negatives. [2]

Spectrum of activity

Intro: Gram-positive only, and that is the whole story. The clinically important variable is not which organism but which route reaches it.

1. Subclass Id: natural-glycopeptides

1. Streptococci

2. Enterococci

3. Staphylococci including MRSA and MSSA

Clostridioides difficile - by the oral route only

1. All gram-negative organisms

2. Vancomycin-resistant enterococci [2]

2. Subclass Id: lipoglycopeptides

Several gram-positive organisms including MRSA

All gram-negative organisms [3]

Major clinical uses

1. Drug: Vancomycin (oral)

1. Organism: Clostridioides difficile

1. Indication: C. difficile-associated diarrhoea; pseudomembranous colitis

1. Line: first-line

1. Note: Oral route is required - intravenous vancomycin penetrates the colon poorly. [2]

2. Drug: Vancomycin (intravenous)

2. Organism: Staphylococci including MRSA

2. Indication: Staphylococcal bacteraemia, and skin, soft tissue, bone and respiratory infection

2. Line: first-line

2. Note: An FDA-approved indication for systemic therapy. [2]

3. Drug: Vancomycin (intravenous)

3. Organism: Diphtheroid, enterococcal, staphylococcal or streptococcal organisms

3. Indication: Endocarditis

3. Line: first-line

3. Note: An FDA-approved indication. [2]

4. Drug: Vancomycin (oral)

4. Organism: Staphylococci

4. Indication: Staphylococcal enterocolitis

4. Line: first-line

4. Note: An intestinal indication treated by the oral route. [2]

5. Drug: Vancomycin (intravenous)

5. Organism: Susceptible gram-positive organisms

5. Indication: Meningitis, osteomyelitis, prosthetic joint infection, surgical prophylaxis

5. Line: off-label

5. Note: Recognised off-label uses alongside community-acquired pneumonia. [2]

6. Drug: Teicoplanin

6. Organism: Gram-positive organisms including MRSA

6. Indication: Gram-positive infection where a glycopeptide is appropriate

6. Line: alternative

6. Note: A natural glycopeptide structurally related to vancomycin. [3]

Pharmacokinetics

1. Drug: Vancomycin (intravenous)

1. Route: IV

1. Absorption: Standard systemic delivery with rapid peak concentrations

1. Csf Penetration: Used off-label in meningitis

1. Metabolism: Limited

1. Elimination: Renal

1. Half Life: See prescribing reference

1. Dose Adjust: Renal impairment, with concentration monitoring guided by area under the curve in serious MRSA infection [2][1]

2. Drug: Vancomycin (oral)

- 2. Route: Oral
- 2. Absorption: Bioavailability under 10%
- 2. Csf Penetration: Not applicable
- 2. Metabolism: Minimal systemic exposure
- 2. Elimination: Faecal
- 2. Half Life: Not clinically relevant by this route
- 2. Dose Adjust: No renal adjustment needed [2]
- 1. Concentration monitoring is recommended in severe infection, critical illness, renal impairment, obesity, advanced age, or where response is inadequate. For serious MRSA infection, consensus guidance targets an area-under-the-curve to minimum inhibitory concentration ratio of 400 to 600 and has replaced trough-only monitoring; trough-guided monitoring, with a target range typically 10 to 20 micrograms per millilitre, remains reasonable for less invasive non-MRSA infection. Oral vancomycin typically requires no serum concentration monitoring. [2][1]
- 2. Renal function should be tested before, during and after therapy, especially in patients over 65. Serial auditory testing may minimise ototoxicity risk, and leukocyte counts are monitored periodically during prolonged therapy. [2]
- 3. This page gives no dose regimens by design. Doses depend on indication, organism, renal function, age and weight, and belong in a prescribing reference used by the treating clinician.

Adverse effects

- 1. Effect: Vancomycin flushing syndrome
 - 1. Detail: Flushing, pruritus and an erythematous rash on the face, neck and upper torso, beginning 4 to 10 minutes after an infusion starts; reported incidence ranges from 3.7 to 47%. [2]
- 2. Effect: Gastrointestinal effects and dysgeusia
 - 2. Detail: Abdominal pain, nausea and distorted taste are reported with oral therapy. [2]
- 3. Effect: Phlebitis
 - 3. Detail: A recognised consequence of intravenous administration. [2]
- 1. Effect: Nephrotoxicity
 - 1. Detail: Risk is elevated with high trough levels above 15 mg/L, concurrent nephrotoxic agents, and pre-existing renal impairment.
 - 1. Action: Monitor renal function before, during and after therapy. [2]
- 2. Effect: Ototoxicity
 - 2. Detail: Transient or permanent hearing loss, tinnitus or vertigo, more common with excessive doses or concurrent ototoxic medicines.
 - 2. Action: Serial auditory testing may minimise the risk. [2]
- 3. Effect: Severe cutaneous reactions
 - 3. Detail: DRESS syndrome and Stevens-Johnson syndrome are reported, though less commonly.
 - 3. Action: Stop the drug and seek urgent specialist assessment. [2]
- 4. Effect: Neutropenia and drug fever
 - 4. Detail: Less common intravenous adverse effects.
 - 4. Action: Monitor leukocyte counts during prolonged therapy. [2]

Drug: Glycopeptides as a class

Effect: Transient serum enzyme elevations occur during therapy, but the class has not been convincingly linked to clinically apparent acute liver injury, and no acute liver failure, chronic hepatitis or vanishing bile duct syndrome has been reported. [3]

Contraindications, precautions and interactions

- 1. Renal impairment, where nephrotoxicity risk is elevated and dose adjustment plus monitoring are required - this applies to intravenous therapy, not to oral. [2]

2. Age over 65, where renal function testing before, during and after therapy is specifically emphasised. [2]
3. Prolonged or inappropriate therapy, which drives vancomycin-resistant enterococci and makes stewardship and adherence counselling part of prescribing. [2]
1. With: Other nephrotoxic agents
 1. Effect: Concurrent use raises the risk of vancomycin nephrotoxicity. [2]
 2. With: Other ototoxic medicines
 2. Effect: Concurrent use raises the risk of hearing loss, tinnitus or vertigo. [2]

Resistance mechanisms

1. Mechanism: Vancomycin-resistant enterococci
 1. Detail: Prolonged or inappropriate treatment with vancomycin can lead to bacterial resistance, of which vancomycin-resistant enterococci are the emerging concern for this class.
 - VRE
 1. Countermeasure: Antimicrobial stewardship and patient adherence counselling to prevent multidrug-resistant infection. [2]
 2. Mechanism: Beta-lactamase is not a mechanism here
 2. Detail: Because glycopeptides bind D-alanyl-D-alanine rather than a penicillin-binding protein, beta-lactamase production confers no resistance to them. This is the structural reason the class works against MRSA.
 2. Countermeasure: None needed - this is why the class exists in the MRSA setting. [2]
 3. Mechanism: Reduced glycopeptide susceptibility in *S. aureus*
 3. Detail: Sporadic hVISA, VISA and VRSA infections may not respond to glycopeptide antibiotics, so susceptibility cannot be assumed even in staphylococci.
 1. hVISA
 2. VISA
 3. VRSA
 3. Countermeasure: Monitor vancomycin trough levels and adjust dosing; escalate to an alternative agent where the organism does not respond. [4]
- Stewardship Note: Resistance in this class is driven by how much the drug is used, which makes stewardship the primary countermeasure rather than an afterthought.

Comparison tables

Title: Vancomycin: route decides the indication

Caption: The single most exam-relevant contrast in this class. Local guidance and susceptibility data govern actual therapy.

1. Key: route
 1. Label: Route
 1. Is Row Header: true
 2. Key: bioavailability
 2. Label: Systemic exposure
 3. Key: treats
 3. Label: Treats
 4. Key: monitoring
 4. Label: Serum monitoring
 5. Key: renal
 5. Label: Renal dose adjustment
 1. Route: Oral
 1. Bioavailability: Bioavailability under 10%

1. Treats: Colonic infection: C. difficile, staphylococcal enterocolitis
1. Monitoring: Typically none
1. Renal: Not needed [2]
2. Route: Intravenous
2. Bioavailability: Full systemic delivery, rapid peak
2. Treats: Bacteraemia, endocarditis, skin, bone and respiratory infection
2. Monitoring: Trough levels, target typically 10-20 g/mL
2. Renal: Required [2]

High-yield exam pearls

1. Pearl: Glycopeptides bind the substrate, not the enzyme.
1. Why: Vancomycin binds D-alanyl-D-alanine, the peptide terminus itself, rather than a penicillin-binding protein - which is why beta-lactamase production does nothing to it. [2]
2. Pearl: Intravenous vancomycin is the drug of choice for most MRSA infections in hospitalised patients.
2. Why: MRSA resistance comes from the mecA gene, which generates transpeptidase PBP2a and lowers the organism's affinity for beta-lactams - a change vancomycin's mechanism simply bypasses. [4]
3. Pearl: Route decides the indication: oral for the colon, intravenous for everywhere else.
3. Why: Oral bioavailability under 10% means oral vancomycin stays in the gut, and intravenous vancomycin penetrates the colon poorly, so it is ineffective against C. difficile. [2]
4. Pearl: Vancomycin flushing syndrome is about infusion rate, not immunology.
4. Why: It appears 4 to 10 minutes after an infusion starts and is managed by slowing the infusion - treating it as a drug allergy wrongly removes a needed antibiotic. [2]
5. Pearl: Oral vancomycin needs no serum level monitoring.
5. Why: Poor oral bioavailability means minimal systemic absorption, which also removes the need for renal dose adjustment in oral therapy. [2]
6. Pearl: Glycopeptides are gram-positive only.
6. Why: The drug is too large to cross the gram-negative outer membrane, so the class covers streptococci, enterococci and staphylococci and nothing gram-negative. [2]

Common exam traps

1. Trap: "Intravenous vancomycin treats C. difficile."
1. Correction: It does not. Intravenous vancomycin penetrates the colon poorly; oral administration is required for intestinal infection. [2]
2. Trap: "Vancomycin flushing syndrome means the patient is allergic to vancomycin."
2. Correction: It is an infusion reaction related to rate of administration, with flushing, pruritus and rash on the face, neck and upper torso - distinct from IgE-mediated allergy. [2]
3. Trap: "Beta-lactamase makes organisms resistant to vancomycin too."
3. Correction: Vancomycin has no beta-lactam ring and binds D-alanyl-D-alanine rather than a penicillin-binding protein, so beta-lactamase production is irrelevant to it. [2]
4. Trap: "All glycopeptides are just vancomycin with a different name."
4. Correction: The lipoglycopeptides - dalbavancin, oritavancin and telavancin - are semisynthetic macromolecules structurally related to vancomycin, designed with different properties, and are counted as their own group. [3]

Self-test questions

1. Question: Vancomycin's molecular target differs from that of the beta-lactams. What does it bind?
1. Penicillin-binding proteins, the transpeptidases that cross-link peptidoglycan

2. The D-alanyl-D-alanine end of the peptidoglycan precursor

3. The 50S ribosomal subunit

4. Bacterial DNA gyrase

1. Explanation: The drug latches onto the peptide terminus of the wall precursor itself rather than onto an enzyme. With D-alanyl-D-alanine occupied, glucosyltransferase - peptidoglycan synthase - is inhibited, so neither elongation nor cross-linking of the polymer can proceed and the organism dies. [2]

2. Question: Why does methicillin resistance in *Staphylococcus aureus* fail to confer resistance to vancomycin?

1. The *mecA* gene product PBP2a lowers affinity for beta-lactams, and vancomycin does not act on a penicillin-binding protein at all

2. Vancomycin inhibits transcription of *mecA* directly

3. Methicillin-resistant strains have no peptidoglycan cell wall

4. Vancomycin is a beta-lactam whose modified ring PBP2a cannot recognise

2. Explanation: Methicillin resistance rests on *mecA*, which generates the transpeptidase PBP2a and reduces the organism's affinity for beta-lactams. A glycopeptide never touches that enzyme, so the change is simply beside the point, and intravenous vancomycin remains the agent of choice for most methicillin-resistant infection in hospitalised patients. [4]

3. Question: Which statement about the route of vancomycin therapy is correct?

1. Intravenous therapy is required for *Clostridioides difficile* because swallowed drug is destroyed by gastric acid

2. Either route treats colonic infection equally well

3. Oral therapy is required for intestinal infection because intravenous vancomycin penetrates the colon poorly

4. Oral therapy achieves full systemic concentrations and can replace intravenous therapy in bacteraemia

3. Explanation: Under a tenth of a swallowed dose is absorbed, so oral drug stays in the gut where colonic infection sits. Delivered into a vein, the same molecule reaches the bloodstream but barely reaches the colon, which is why that route fails against *C. difficile*. [2]

4. Question: About five minutes into a vancomycin infusion a patient develops flushing, itching and an erythematous rash over the face, neck and upper torso. What does this represent?

1. An IgE-mediated anaphylactic reaction requiring permanent avoidance of the drug

2. DRESS syndrome

3. The earliest sign of vancomycin nephrotoxicity

4. Vancomycin flushing syndrome, a reaction to infusion rate rather than a true allergy

4. Explanation: Onset four to ten minutes after an infusion begins, with that face, neck and upper-torso distribution, is the classic picture, and the speed of administration is what provokes it. Recording it as a drug allergy wrongly removes an antibiotic the patient may need. DRESS and Stevens-Johnson syndrome are separate and less common cutaneous events reported with this drug. [2]

5. Question: Which factor increases the risk of vancomycin nephrotoxicity?

1. Oral administration for *Clostridioides difficile* infection

2. Patient age under 30

3. Concurrent use of a beta-lactam antibiotic

4. Trough concentrations above 15 mg/L

5. Explanation: Three things push renal risk upward: troughs running above 15 mg/L, other nephrotoxic agents given alongside, and kidney impairment that was already present. Renal function is accordingly checked before, during and after a course, with particular emphasis beyond the age of 65. Oral therapy sits outside this concern because so little of the drug is absorbed. [2]

6. Question: Which three lipoglycopeptides are available for use in the United States?

1. Vancomycin, teicoplanin and daptomycin

2. Teicoplanin, telavancin and linezolid

3. Dalbavancin, oritavancin and telavancin

4. Dalbavancin, vancomycin and tigecycline

6. Explanation: These three are semisynthetic macromolecules built around the vancomycin structure, and they hold activity against gram-positive organisms including MRSA. Treating them as vancomycin under other names misses the point that they were engineered with deliberately different properties. [3]

7. Question: What drives the emergence of vancomycin-resistant enterococci?

1. Prolonged or inappropriate treatment with vancomycin

2. Beta-lactamase production by enterococci

3. Concurrent administration of an aminoglycoside

4. Oral rather than intravenous administration

7. Explanation: Excessive and unnecessarily long exposure is what selects these organisms out, so the countermeasure is stewardship and adherence counselling rather than any pharmacological trick. Enzymatic destruction is not the issue: a beta-lactamase does nothing to a drug that carries no beta-lactam ring and binds D-alanyl-D-alanine instead. [2]

8. Question: Which statement about staphylococcal susceptibility to glycopeptides is correct?

1. Every *Staphylococcus aureus* isolate remains fully susceptible to vancomycin

2. Sporadic hVISA, VISA and VRSA infections may fail to respond to glycopeptide therapy

3. Reduced susceptibility is confined to coagulase-negative staphylococci

4. Glycopeptide resistance in staphylococci arises through porin loss

8. Explanation: Susceptibility cannot be assumed even within *S. aureus*. Isolates with hetero-intermediate, intermediate or frank resistance appear sporadically and may not respond, which is why trough levels are followed and an alternative agent is considered when an organism fails to improve. [4]

Frequently asked questions

1. Question: Why does vancomycin work against MRSA when penicillins do not?

1. Answer: Methicillin resistance is an altered penicillin-binding protein, and vancomycin does not target a penicillin-binding protein at all. It binds D-alanyl-D-alanine, the peptidoglycan precursor itself, so the change that defeats beta-lactams is irrelevant to it. [2]

2. Question: Why is oral vancomycin used for *C. difficile* but intravenous vancomycin is not?

2. Answer: Oral vancomycin has bioavailability under 10%, so it stays in the gut where the infection is. Intravenous vancomycin penetrates the colon poorly, which makes it ineffective for intestinal infection. [2]

3. Question: What is vancomycin flushing syndrome?

3. Answer: An infusion reaction causing flushing, pruritus and an erythematous rash on the face, neck and upper torso, typically starting 4 to 10 minutes after an infusion begins. Reported incidence ranges widely, from 3.7 to 47%. [2]

4. Question: When do vancomycin levels need monitoring?

4. Answer: Serum trough concentrations are recommended in severe infection, critical illness, renal impairment, obesity, advanced age, or where the response is inadequate, with a target range typically 10 to 20 micrograms per millilitre. Oral therapy typically needs no serum monitoring. [2]

5. Question: What are the lipoglycopeptides?

5. Answer: Semisynthetic macromolecules structurally related to vancomycin with activity against gram-positive organisms including MRSA. Three are available in the United States: dalbavancin, oritavancin and telavancin. [3]

References

[1] Therapeutic monitoring of vancomycin for serious MRSA infections - revised consensus guideline. PubMed Central, U.S. National Library of Medicine . <https://pmc.ncbi.nlm.nih.gov/articles/PMC8034673/>

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