

Daptomycin

A calcium-dependent cyclic lipopeptide that depolarizes gram-positive membranes for rapid cidal killing - inactivated by pulmonary surfactant, so never used for pneumonia.

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

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Quick revision

One Liner: Daptomycin inserts into the gram-positive cell membrane in a calcium-dependent way, depolarizes it through potassium efflux, and kills rapidly without lysis - but pulmonary surfactant inactivates it, so it is never an option for pneumonia.

1. Mechanism: calcium-dependent insertion of the lipopeptide tail into the bacterial cell membrane, causing depolarization through potassium efflux. [1]
2. Rapidly bactericidal with concentration-dependent killing, and the cell dies without lysing. [1]
3. Spectrum is gram-positive only, including MRSA and vancomycin-resistant enterococci (VRE). [1]
4. Pulmonary surfactant binds and inactivates daptomycin, so it must never be used to treat pneumonia. [1]
5. Approved uses are complicated skin and skin structure infections and Staphylococcus aureus bloodstream infection, including right-sided infective endocarditis. [3]
6. Creatine phosphokinase (CPK) elevation and myopathy are the characteristic toxicity - monitor CPK at least weekly and consider suspending statins during therapy. [3][1]
7. Eosinophilic pneumonia is a recognised serious adverse reaction to daptomycin. [3][1]
8. Daptomycin can falsely elevate prothrombin time and INR with certain recombinant thromboplastin reagents - a laboratory artefact, not true coagulopathy. [3]

Overview

1. Daptomycin is a cyclic lipopeptide antibiotic, the first of its class, derived from *Streptomyces roseosporus*. It occupies a specific niche: rapid bactericidal therapy for resistant gram-positive infection, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), when the infection is anywhere except the lung. [1]
2. Its mechanism is unusual among antibacterials. Rather than attacking the cell wall or the ribosome, daptomycin binds calcium and inserts its lipophilic tail directly into the gram-positive cell membrane, causing depolarization through potassium efflux. Loss of membrane potential arrests DNA, RNA and protein synthesis and the cell dies rapidly - without lysing. [1]
3. Two facts dominate its clinical profile. First, pulmonary surfactant binds and inactivates the drug, so daptomycin is never used for pneumonia - the classic examination trap. Second, its characteristic toxicity is muscular: creatine phosphokinase elevation and myopathy, which is why CPK monitoring at least weekly, and consideration of suspending statins, are built into any daptomycin course. [1][3]

Classification and drug examples

Intro: Daptomycin is currently the only cyclic lipopeptide in clinical use, so the class and the drug are learned as one.

Name: Cyclic lipopeptide

Note: A 13-amino-acid cyclic peptide with a lipophilic decanoyl tail; the tail is what inserts into the bacterial membrane once calcium is bound.

Name: Daptomycin

Cubicin

Route: IV

Note: Approved for complicated skin and skin structure infections and for *S. aureus* bloodstream infection, including right-sided infective endocarditis. [3] [1]

Mechanism of action

Summary: Calcium-bound daptomycin inserts its lipophilic tail into the gram-positive cell membrane, aggregates, and depolarizes the membrane through potassium efflux; the loss of membrane potential halts DNA, RNA and protein synthesis and the bacterium dies rapidly without lysis.

Target: Bacterial cytoplasmic membrane of gram-positive organisms

Cidal Static: bactericidal

Kill Kinetics: concentration-dependent

1. Step: 1

1. Title: Calcium binding turns the drug into a membrane-seeking cation

1. Detail: Daptomycin complexes with calcium, and the calcium-bound molecule behaves like a cationic peptide attracted to the bacterial cytoplasmic membrane. [1]

2. Step: 2

2. Title: The lipophilic tail inserts into the membrane

2. Detail: The decanoyl tail anchors the drug in the gram-positive cell membrane - insertion that is strictly calcium-dependent. [1]

3. Step: 3

3. Title: Drug molecules aggregate within the membrane

3. Detail: Inserted daptomycin oligomerizes, disrupting the membrane's integrity and creating channels that leak ions. [1]

4. Step: 4

4. Title: Potassium efflux depolarizes the membrane

4. Detail: Potassium leaks out of the cell, membrane potential collapses, and DNA, RNA and protein synthesis all arrest. [1]

5. Step: 5

5. Title: Rapid cell death without lysis

5. Detail: The organism dies quickly - killing is concentration-dependent - but the cell is not lysed, so intracellular contents are not spilled. [1]

Spectrum of activity

Intro: Gram-positive organisms only. The large lipopeptide cannot cross the gram-negative outer membrane, and pulmonary surfactant inactivates it in the airspaces, so the anatomical gap (lung) matters as much as the microbiological one (gram-negatives).

Subclass Id: cyclic-lipopeptide

1. *Staphylococcus aureus*, including MRSA

2. *Streptococcus pyogenes* and other beta-haemolytic streptococci

3. *Enterococcus faecalis* (vancomycin-susceptible strains)

4. *Enterococcus faecium*, including vancomycin-resistant enterococci (VRE)

1. All gram-negative organisms

2. Pneumonia of any cause - pulmonary surfactant inactivates the drug [1][3]

Major clinical uses

1. Drug: Daptomycin

1. Organism: Susceptible gram-positive organisms, including MRSA
1. Indication: Complicated skin and skin structure infections
1. Line: targeted
1. Note: One of the two approved indications; used where resistant gram-positive organisms are proven or strongly suspected. [3]
2. Drug: Daptomycin
2. Organism: Staphylococcus aureus, including MRSA
2. Indication: Bloodstream infection (bacteremia), including right-sided infective endocarditis
2. Line: targeted
2. Note: Right-sided endocarditis with septic pulmonary emboli remains an approved use - the surfactant problem applies to airspace pneumonia, not bloodstream-seeded disease. [3][1]
3. Drug: Daptomycin
3. Organism: Vancomycin-resistant enterococci (VRE)
3. Indication: Resistant gram-positive infection where first-line agents cannot be used
3. Line: reserve
3. Note: Activity against VRE is a key reason the drug is held in reserve rather than used routinely. [1]
4. Drug: Daptomycin
4. Organism: Any organism
4. Indication: Pneumonia - NOT an indication
4. Line: avoid
4. Note: Surfactant in the alveoli neutralises the drug, so pneumonia is not a treatable indication however susceptible the organism appears on testing. [1]

Pharmacokinetics

Drug: Daptomycin

Route: IV

Absorption: Not orally absorbed; given by intravenous infusion or injection

Csf Penetration: Poor

Metabolism: Minimal hepatic metabolism; not a cytochrome P450 substrate or inhibitor

Elimination: Renal, primarily as unchanged drug

Half Life: See prescribing reference

Dose Adjust: Renal impairment requires interval adjustment; consult a prescribing reference [1][3]

1. Daptomycin is highly protein-bound and eliminated by the kidney largely unchanged, so renal function drives both exposure and toxicity risk - CPK monitoring is intensified when creatinine clearance is reduced. [1][3]
2. Killing is concentration-dependent, which supports once-daily administration and makes peak exposure, not time above a threshold, the pharmacodynamic driver. [1]
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: Creatine phosphokinase (CPK) elevation
1. Detail: The characteristic laboratory abnormality of the class, ranging from asymptomatic elevation to symptomatic myopathy. CPK is checked at baseline and at least weekly during therapy. [3][1]
2. Effect: Gastrointestinal upset and injection site reactions
2. Detail: Diarrhoea, nausea and vomiting are among the more frequently reported adverse reactions in trials. [3]
1. Effect: Myopathy and rhabdomyolysis
1. Detail: Muscle pain or weakness with marked CPK elevation; risk rises in renal impairment and with concomitant

statin therapy.

1. Action: Monitor CPK at least weekly (more often if at risk), consider suspending statins during therapy, and discontinue daptomycin for signs of myopathy with significant CPK rise. [3][1]
2. Effect: Eosinophilic pneumonia
2. Detail: Fever, dyspnoea, hypoxia and pulmonary infiltrates with eosinophilia, typically developing after two or more weeks of therapy.
2. Action: Stop daptomycin promptly; systemic corticosteroids are used in reported cases. [3][1]
3. Effect: Peripheral neuropathy
3. Detail: Paraesthesiae and neuropathy have been reported during therapy.
3. Action: Assess new neurological symptoms and reconsider the agent. [3]
4. Effect: Clostridioides difficile-associated diarrhoea
4. Detail: Reported with nearly all systemic antibacterial agents, daptomycin included.
4. Action: Evaluate significant diarrhoea during or after therapy. [3]
1. Drug: Daptomycin
1. Effect: Falsely elevated prothrombin time and INR with certain recombinant thromboplastin laboratory reagents - an assay interference, not a true coagulopathy. Repeat testing near the drug trough or with an alternative reagent clarifies the picture. [3]
2. Drug: Daptomycin
2. Effect: Clinically apparent liver injury is rare; serum aminotransferase elevations occur in a small proportion of treated patients and CPK elevation from muscle is the far more common laboratory signal. [2]

Contraindications, precautions and interactions

Known hypersensitivity to daptomycin. [3]

1. Renal impairment - reduced clearance raises drug exposure and myopathy risk, and requires interval adjustment with closer CPK monitoring. [3][1]
2. Pneumonia is not a caution but an ineffectiveness problem: surfactant inactivation makes daptomycin the wrong drug for any pneumonia, however susceptible the organism. [1]
1. With: HMG-CoA reductase inhibitors (statins)
1. Effect: Additive myopathy risk; consider temporarily suspending statins during daptomycin therapy. [3]
2. With: Certain recombinant thromboplastin PT/INR assays
2. Effect: Falsely elevated results - a laboratory interaction rather than a pharmacological one, but a real source of clinical error. [3]

Resistance mechanisms

1. Mechanism: Cell membrane remodelling
1. Detail: Mutations such as those in mprF alter membrane charge and phospholipid composition, repelling the calcium-bound cationic drug and reducing its insertion into the membrane.
1. Daptomycin-non-susceptible Staphylococcus aureus
2. Daptomycin-non-susceptible enterococci
1. Countermeasure: Repeat susceptibility testing on persistent isolates and switch or combine agents under specialist guidance. [1]
2. Mechanism: Emergence of non-susceptibility during therapy
2. Detail: Reduced susceptibility has been reported to emerge on treatment, particularly in deep-seated or high-inoculum infection with persistently positive cultures.
- S. aureus bacteremia failing to clear
2. Countermeasure: Recheck cultures and susceptibilities when bacteremia persists rather than assuming continued activity. [1][3]

Stewardship Note: Daptomycin is a reserve gram-positive agent: keeping it effective against MRSA and VRE means using it for proven resistant infection outside the lung, not as a convenience alternative to first-line therapy.

Comparison tables

Title: Where daptomycin works and where it cannot

Caption: The site of infection, not the organism, decides whether daptomycin is usable. Local susceptibility data and a prescribing reference govern actual therapy.

1. Key: site

1. Label: Infection site

1. Is Row Header: true

2. Key: suitable

2. Label: Daptomycin suitable?

3. Key: why

3. Label: Why

1. Site: Complicated skin and skin structure infection

1. Suitable: Yes - approved indication

1. Why: Gram-positive spectrum including MRSA; no surfactant in the way. [3]

2. Site: S. aureus bacteremia

2. Suitable: Yes - approved indication

2. Why: Rapid concentration-dependent cidal killing in the bloodstream. [3]

3. Site: Right-sided infective endocarditis

3. Suitable: Yes - approved indication

3. Why: Bloodstream-seeded valve infection; septic pulmonary emboli are not airspace pneumonia. [3][1]

4. Site: Pneumonia (any organism)

4. Suitable: No - never

4. Why: Pulmonary surfactant binds and inactivates daptomycin in the alveoli. [1]

High-yield exam pearls

1. Pearl: Calcium is part of the mechanism.

1. Why: Daptomycin needs calcium to insert its lipophilic tail into the gram-positive cell membrane; the calcium-bound drug behaves like a cationic peptide attracted to the bacterial membrane. [1]

2. Pearl: It kills without lysing the cell.

2. Why: Membrane depolarization through potassium efflux shuts down DNA, RNA and protein synthesis and the bacterium dies intact - one reason the inflammatory burden of lysis is avoided. [1]

3. Pearl: Surfactant inactivation is the single most examined fact about daptomycin.

3. Why: Pulmonary surfactant binds and inactivates the drug in the alveoli, which is why daptomycin failed in pneumonia trials and is never used for pneumonia despite covering the usual gram-positive culprits. [1]

4. Pearl: Bacteremia yes, pneumonia no.

4. Why: Daptomycin is approved for S. aureus bloodstream infection including right-sided infective endocarditis - septic pulmonary emboli from a right-sided valve arrive via the bloodstream, which is distinct from airspace pneumonia where surfactant defeats the drug. [3][1]

5. Pearl: Think of daptomycin when vancomycin cannot be used.

5. Why: Its gram-positive spectrum including MRSA and VRE makes it a key alternative for resistant gram-positive infection outside the lung. [1]

6. Pearl: CPK monitoring is written into the prescription.

6. Why: Myopathy with CPK elevation is the characteristic toxicity; CPK is checked at baseline and at least weekly, more often in renal impairment or with concomitant statins, and statin suspension should be considered during therapy.

[3]

Common exam traps

1. Trap: "Daptomycin covers MRSA, so it is a good choice for MRSA pneumonia."
 1. Correction: Pulmonary surfactant binds and inactivates daptomycin, so it is ineffective in pneumonia regardless of in-vitro susceptibility. Vancomycin or linezolid are the agents used for MRSA pneumonia. [1]
 2. Trap: "Daptomycin cannot be used when the chest is involved at all."
 2. Correction: Right-sided infective endocarditis with septic pulmonary emboli is an approved use - the infection is bloodstream-seeded, not airspace pneumonia. The prohibition is specifically on treating pneumonia. [3][1]
 3. Trap: "A rising INR on daptomycin means the patient is coagulopathic."
 3. Correction: Daptomycin can falsely elevate PT/INR with certain recombinant thromboplastin laboratory reagents. Draw the sample at trough drug levels or use a different assay before treating a coagulopathy that may not exist. [3]
 4. Trap: "Daptomycin works like vancomycin on the cell wall."
 4. Correction: It does not inhibit cell wall synthesis. It is a cyclic lipopeptide that inserts into the cell membrane and depolarizes it - a different target, which is why it retains activity against some vancomycin-resistant organisms. [1]
 5. Trap: "Muscle aches on daptomycin are trivial."
 5. Correction: Myopathy with CPK elevation is the class-defining toxicity. CPK is monitored at least weekly, and the drug is discontinued for signs of myopathy with significant CPK rise. [3]

Self-test questions

1. Question: Which description of the daptomycin mechanism is correct?
 1. It binds the D-alanyl-D-alanine terminus of peptidoglycan precursors and blocks cross-linking
 2. Bound to calcium, it inserts its lipophilic tail into the gram-positive cell membrane and depolarizes it through potassium efflux
 3. It binds the 50S ribosomal subunit and prevents formation of the initiation complex
 4. It disrupts lipopolysaccharide in the outer membrane by displacing divalent cations
 1. Explanation: Calcium is part of the mechanism rather than an incidental cofactor: complexed with calcium the molecule behaves like a cationic peptide drawn to the bacterial membrane, where its decanoyl tail anchors and the inserted molecules oligomerize. Potassium then leaks out, membrane potential collapses, and synthesis of DNA, RNA and protein arrests. Killing is rapid and concentration-dependent, and notably the cell dies intact rather than bursting. [1]
 2. Question: An isolate of MRSA from a patient with pneumonia tests susceptible to daptomycin. Why is daptomycin still the wrong choice?
 1. Daptomycin cannot achieve adequate concentrations in blood to reach the lung
 2. Airway pathogens rapidly develop efflux-mediated resistance during therapy
 3. Susceptibility testing overestimates daptomycin activity against all staphylococci
 4. Pulmonary surfactant binds the drug and inactivates it in the alveoli
 2. Explanation: The organism is susceptible in the laboratory but the drug never gets to act in the airspaces, because surfactant lining the alveoli sequesters and neutralises it. That is why trials in pneumonia failed and why the prohibition holds irrespective of what the susceptibility report says. Vancomycin or linezolid are the agents turned to for MRSA pneumonia. [1]
 3. Question: If surfactant inactivates daptomycin in the lung, why does right-sided infective endocarditis with septic pulmonary emboli remain an approved use?
 1. Because the infection is seeded through the bloodstream, where the drug is active, rather than being an airspace pneumonia
 2. Because septic emboli generate so much inflammation that surfactant production ceases
 3. Because the higher exposure achieved in endocarditis overwhelms surfactant binding

4. Because the emboli are treated surgically and the antibiotic is only adjunctive

3. Explanation: The distinction is anatomical. A right-sided valve infection lives in the circulation and the drug reaches embolic lesions the same way, so surfactant never stands between drug and organism. Airspace infection is the specific setting the drug cannot treat, and generalising the prohibition to any chest involvement is a common error.

[3][1]

4. Question: Which laboratory parameter defines the characteristic toxicity monitoring of daptomycin therapy?

1. Serum potassium
2. Serum bilirubin
3. Creatine phosphokinase
4. Serum magnesium

4. Explanation: Muscle injury is the signature adverse effect, spanning silent enzyme elevation through to painful or weak muscles with markedly raised creatine phosphokinase. The enzyme is checked before treatment and at least weekly during it, more often where renal clearance is reduced or a statin is being taken concurrently, since both raise the risk. Temporarily suspending a statin during a course is a recognised consideration, and the antibiotic is withdrawn when myopathic symptoms accompany a significant enzyme rise. [3][1]

5. Question: A patient receiving daptomycin has an unexpectedly prolonged prothrombin time and raised INR. What is the most likely explanation?

1. Depletion of vitamin K-dependent clotting factors caused by the drug
2. Interference with certain recombinant thromboplastin reagents, producing a falsely elevated result
3. Disseminated intravascular coagulation triggered by bacterial lysis
4. Displacement of warfarin from plasma protein binding sites

5. Explanation: This is an artefact of the assay, not evidence of a bleeding tendency. Repeating the sample near the drug trough, or running it with a different reagent, resolves the discrepancy and avoids treating a coagulopathy that does not exist. Notably, the drug does not lyse the organisms it kills, so a lysis-driven coagulation cascade is not the explanation either. [3][1]

6. Question: Which organisms fall within the daptomycin spectrum?

1. Gram-positive and gram-negative aerobes, but not anaerobes
2. Gram-negative organisms only, including *Pseudomonas aeruginosa*
3. Atypical intracellular pathogens together with staphylococci
4. Gram-positive organisms only, including MRSA and vancomycin-resistant enterococci

6. Explanation: Activity stops at the gram-positive boundary - the bulky lipopeptide cannot get past a gram-negative outer membrane - so any gram-negative cover has to come from a separate agent. Within gram-positives it reaches *Staphylococcus aureus* including methicillin-resistant strains, beta-haemolytic streptococci and enterococci including vancomycin-resistant *Enterococcus faecium*, which is what makes it a valuable alternative when vancomycin is unusable outside the lung. [1][3]

7. Question: How do bacteria become non-susceptible to daptomycin?

1. By acquiring an enzyme that cleaves the cyclic peptide ring
2. By producing an altered penicillin-binding protein with low drug affinity
3. By remodelling the cell membrane, through changes such as *mprF* mutations, so the calcium-bound cationic drug is repelled
4. By methylating the ribosomal target site

7. Explanation: Since the target is the membrane itself, resistance means changing the membrane. Altered charge and phospholipid composition repel the calcium-bound drug and reduce how much of it inserts. Reduced susceptibility has been reported to appear during treatment, particularly in deep-seated or high-inoculum infection where cultures stay positive, so persistent bacteraemia is a reason to repeat cultures and susceptibility testing rather than assume the drug is still working. [1][3]

Frequently asked questions

1. Question: Why does daptomycin not work for pneumonia?

1. Answer: Pulmonary surfactant in the alveoli binds and inactivates daptomycin, so it cannot achieve effective activity in the airspaces even when the organism is fully susceptible in vitro. Vancomycin or linezolid are used for MRSA pneumonia instead. [1]

2. Question: If surfactant inactivates it, how can daptomycin treat right-sided endocarditis with lung emboli?

2. Answer: Right-sided endocarditis is a bloodstream infection seeded onto a heart valve, and the drug reaches septic pulmonary emboli through the circulation. That is different from airspace pneumonia, where the drug must act within surfactant-lined alveoli. [3][1]

3. Question: Why is calcium mentioned in daptomycin's mechanism?

3. Answer: Daptomycin must complex with calcium before it can insert its lipophilic tail into the gram-positive cell membrane. The calcium-bound drug acts like a cationic peptide drawn to the bacterial membrane, where aggregation and potassium efflux then depolarize and kill the cell. [1]

4. Question: What monitoring does a daptomycin course require?

4. Answer: Creatine phosphokinase at baseline and at least weekly, more frequently in renal impairment or with concomitant statins, alongside review for new muscle pain or weakness. Suspending statins during therapy should be considered, and the drug is stopped for myopathy with significant CPK elevation. [3]

5. Question: Does daptomycin really interfere with INR results?

5. Answer: Yes - with certain recombinant thromboplastin reagents it can falsely elevate prothrombin time and INR. It is an assay artefact, not a bleeding tendency; repeating the test near the drug trough or with a different reagent resolves the discrepancy. [3]

6. Question: Does daptomycin cover gram-negative organisms?

6. Answer: No. Its activity is confined to gram-positive bacteria - including MRSA and vancomycin-resistant enterococci - and gram-negative cover must come from another agent entirely. [1]

References

[1] Daptomycin (StatPearls). StatPearls Publishing / NCBI Bookshelf 2024. <https://www.ncbi.nlm.nih.gov/books/NBK470407/>

[2] Daptomycin (LiverTox). LiverTox, NIDDK / NCBI Bookshelf 2020. <https://www.ncbi.nlm.nih.gov/books/NBK547852/>

[3] CUBICIN RF (daptomycin) injection - FDA prescribing information (DailyMed). DailyMed, U.S. National Library of Medicine 2025. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0b1a8885-2198-4a0e-8105-0c76c1cba6c2>

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