

Cephalosporins

Beta-lactam antibiotics grouped into five generations, with gram-negative coverage broadly widening from the first generation onward.

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

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Quick revision

One Liner: Cephalosporins are bactericidal beta-lactams sorted into five generations; as a rough rule gram-negative cover widens from the first generation onward, with ceftazidime and cefepime reaching *Pseudomonas* and only the fifth generation touching MRSA.

1. Five generations, defined by spectrum against gram-positive and gram-negative bacteria and by when they were discovered. [1]
2. First generation (cefazolin, cephalexin) covers most gram-positive cocci with minimal gram-negative activity; cefazolin is the preferred agent for surgical prophylaxis. [1]
3. Ceftazidime and cefepime carry *Pseudomonas aeruginosa* activity; ceftaroline does not. [1]
4. Only the fifth generation - ceftaroline and ceftobiprole - covers MRSA. [1]
5. Ceftriaxone, cefotaxime, ceftazidime and cefepime penetrate the blood-brain barrier and are therefore options in meningitis. [1]
6. Mechanism is identical to the penicillins: the beta-lactam ring binds penicillin-binding proteins and blocks cell-wall synthesis. [1][2]
7. Penicillin cross-reactivity is highest with first- and second-generation agents; third-generation and beyond show minimal cross-reactivity. [1]

Overview

1. Cephalosporins are beta-lactam antimicrobials used against infections caused by both gram-positive and gram-negative bacteria. They are categorised into five generations based on their spectrum of coverage and on when they were discovered. [1]
2. Across those generations the class treats skin and soft-tissue infections, pneumonia, meningitis and a range of other infections. The generation framework is worth learning properly, because it is the fastest way to predict which organisms a given cephalosporin is likely to reach. [1]
3. Newer agents continue to extend the class. Cefiderocol is a siderophore cephalosporin that exploits bacterial iron transporters to reach the periplasm, and it retains stability against beta-lactamases including some carbapenemases. [1]

Classification and drug examples

Intro: Five generations, distinguished by spectrum. The pattern to hold onto: gram-positive cover is strongest early, gram-negative cover broadens later, antipseudomonal activity is limited to specific agents, and MRSA cover arrives only at the end.

1. Name: First generation

1. Note: Covers most gram-positive cocci such as staphylococci and streptococci, with some gram-negative activity against *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae*.

1. Name: Cefazolin

1. Route: IV/IM

1. Note: Preferred agent for surgical prophylaxis. [1]

2. Name: Cephalexin

Cefalexin

2. Route: Oral

2. Note: Oral agent used for infections including urinary tract infections, pneumonia and other chest infections. [3]

3. Name: Cefadroxil

3. Route: Oral

3. Note: Oral first-generation agent. [1]

4. Name: Cephadrine

4. Route: Oral

4. Note: First-generation agent. [1] [1]

2. Name: Second generation

2. Note: Enhanced gram-negative coverage including *Haemophilus influenzae*, *Moraxella catarrhalis* and *Bacteroides* species. The cephamycins form a subgroup within this generation.

1. Name: Cefuroxime

1. Route: Oral/IV

1. Note: Standard second-generation agent used in respiratory infections. [1]

2. Name: Cefprozil

2. Route: Oral

2. Note: Standard second-generation agent. [1]

3. Name: Cefoxitin

3. Route: IV

3. Note: Cephamycin subgroup. [1]

4. Name: Cefotetan

4. Route: IV

4. Note: Cephamycin subgroup; one of the two cephalosporins most likely to cause drug-induced immune haemolytic anaemia. [1]

5. Name: Cefmetazole

5. Route: IV

5. Note: Cephamycin subgroup. [1] [1]

3. Name: Third generation

3. Note: Extended gram-negative spectrum. Ceftazidime is the member with *Pseudomonas aeruginosa* coverage; ceftriaxone and cefotaxime are the agents used where blood-brain barrier penetration is needed.

1. Name: Ceftriaxone

1. Route: IV/IM

1. Note: Penetrates the blood-brain barrier; used in meningitis. Contraindicated in neonates with hyperbilirubinaemia. [1]

2. Name: Cefotaxime

2. Route: IV

2. Note: Penetrates the blood-brain barrier; used in meningitis. [1]

3. Name: Ceftazidime

3. Route: IV

3. Note: The third-generation agent with *Pseudomonas aeruginosa* coverage. [1]

4. Name: Cefdinir

4. Route: Oral

4. Note: Oral third-generation agent. [1]

5. Name: Cefpodoxime

5. Route: Oral

5. Note: Oral third-generation agent. [1]

6. Name: Cefixime

6. Route: Oral

6. Note: Oral third-generation agent. [1]

7. Name: Cefoperazone

7. Route: IV

7. Note: Third-generation agent; associated with disulfiram-like reactions. [1] [1]

4. Name: Fourth generation

4. Note: Broad-spectrum cover across gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa* and beta-lactamase producers, with blood-brain barrier penetration.

Name: Cefepime

Route: IV

Note: Neurotoxicity - seizures and encephalopathy - is reported in overdose and in unadjusted renal impairment. [1] [1]

5. Name: Fifth generation

5. Note: The generation that reaches methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*.

1. Name: Ceftaroline

1. Route: IV

1. Note: Covers MRSA but does not cover *Pseudomonas aeruginosa*. [1]

2. Name: Ceftobiprole

2. Route: IV

2. Note: Fifth-generation agent with MRSA activity. [1] [1]

Mechanism of action

Summary: Cephalosporins are bactericidal beta-lactams: the beta-lactam ring binds penicillin-binding proteins and inhibits their normal activity, preventing cell-wall synthesis and killing the organism.

Target: Penicillin-binding proteins (bacterial transpeptidases)

Cidal Static: bactericidal

Kill Kinetics: time-dependent

1. Step: 1

1. Title: The beta-lactam ring engages its target

1. Detail: The drug binds penicillin-binding proteins and inhibits their normal activity. [1]

2. Step: 2

2. Title: Cell-wall synthesis is blocked

2. Detail: With the transpeptidases inactivated, peptidoglycan cross-linking cannot be completed and the wall cannot be finished. [1][2]

3. Step: 3

3. Title: The organism dies

3. Detail: Loss of a competent cell wall leads to loss of viability and lysis - the class is bactericidal rather than merely growth-arresting. [1][2]

4. Step: 4

4. Title: Some agents get in by a different door

4. Detail: Cefiderocol is recognised by bacterial iron transporters, which carries it efficiently into the periplasm where it binds penicillin-binding proteins strongly. [1]

Spectrum of activity

Intro: Learn the class as a shifting spectrum rather than a widening one. Gram-positive activity is strongest early,

gram-negative reach grows later, and specific agents rather than whole generations carry antipseudomonal and anti-MRSA activity.

1. Subclass Id: first-generation

Most gram-positive cocci: staphylococci, streptococci

1. *Escherichia coli*

2. *Proteus mirabilis*

3. *Klebsiella pneumoniae*

1. MRSA

2. *Pseudomonas aeruginosa* [1]

2. Subclass Id: second-generation

Gram-positive cocci

1. *Haemophilus influenzae*

2. *Moraxella catarrhalis*

Bacteroides species (cephamycins)

1. MRSA

2. *Pseudomonas aeruginosa* [1]

3. Subclass Id: third-generation

Reduced relative to the first generation

1. Extended gram-negative spectrum

2. *Pseudomonas aeruginosa* (ceftazidime only)

MRSA [1]

4. Subclass Id: fourth-generation

Gram-positive organisms

Broad gram-negative cover including *Pseudomonas aeruginosa* and beta-lactamase producers

MRSA [1]

5. Subclass Id: fifth-generation

1. MRSA

2. Penicillin-resistant *Streptococcus pneumoniae*

Gram-negative cover

Pseudomonas aeruginosa (ceftaroline) [1]

Major clinical uses

1. Drug: Cefazolin

1. Organism: Gram-positive skin flora

1. Indication: Surgical prophylaxis

1. Line: preferred

1. Note: The first-generation agent named as preferred for this indication. [1]

2. Drug: Cephalexin

2. Organism: Susceptible gram-positive and gram-negative organisms

2. Indication: Urinary tract infection, pneumonia and other chest infections

2. Line: first-line

2. Note: Oral first-generation option. [3]

3. Drug: Cefuroxime

3. Organism: *Haemophilus influenzae*, *Moraxella catarrhalis*

3. Indication: Respiratory infections

3. Line: first-line

3. Note: Standard second-generation agent. [1]

- 4. Drug: Ceftriaxone
- 4. Organism: Susceptible meningeal pathogens
- 4. Indication: Meningitis
- 4. Line: first-line
- 4. Note: One of the agents that effectively penetrates the blood-brain barrier. [1]
- 5. Drug: Ceftazidime
- 5. Organism: Pseudomonas aeruginosa
- 5. Indication: Serious infection where Pseudomonas is a concern
- 5. Line: targeted
- 5. Note: The third-generation agent carrying antipseudomonal activity. [1]
- 6. Drug: Ceftaroline
- 6. Organism: MRSA, penicillin-resistant Streptococcus pneumoniae
- 6. Indication: Infection caused by resistant gram-positive organisms
- 6. Line: targeted
- 6. Note: Does not cover Pseudomonas aeruginosa. [1]

Pharmacokinetics

- 1. Drug: Cefazolin
- 1. Route: IV/IM
- 1. Absorption: Not orally administered
- 1. Csf Penetration: Poor
- 1. Metabolism: Limited
- 1. Elimination: Renal
- 1. Half Life: Short
- 1. Dose Adjust: Renal impairment [1]
- 2. Drug: Cephalexin
- 2. Route: Oral
- 2. Absorption: Orally absorbed
- 2. Csf Penetration: Poor
- 2. Metabolism: Limited
- 2. Elimination: Renal
- 2. Half Life: Short
- 2. Dose Adjust: Renal impairment [3]
- 3. Drug: Ceftriaxone
- 3. Route: IV/IM
- 3. Absorption: Not orally administered
- 3. Csf Penetration: Effective
- 3. Metabolism: Limited
- 3. Elimination: Renal and biliary
- 3. Half Life: Long enough for once-daily use
- 3. Dose Adjust: See prescribing reference [1]
- 4. Drug: Cefepime
- 4. Route: IV
- 4. Absorption: Not orally administered
- 4. Csf Penetration: Effective
- 4. Metabolism: Limited
- 4. Elimination: Renal

4. Half Life: Short

4. Dose Adjust: Renal impairment - neurotoxicity risk if unadjusted [1]

1. Ceftriaxone, cefotaxime, ceftazidime and cefepime are the members that effectively penetrate the blood-brain barrier, which is what makes them usable in meningitis. [1]

2. 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: Hypersensitivity reactions

1. Detail: Rash, hives and swelling; reported more commonly with first- and second-generation agents. [1]

2. Effect: Gastrointestinal upset

2. Detail: Diarrhoea and related gastrointestinal symptoms. [3]

1. Effect: Pseudomembranous colitis

1. Detail: Reported commonly with third-generation agents.

1. Action: Seek urgent medical assessment for severe or persistent diarrhoea. [1]

2. Effect: Drug-induced immune haemolytic anaemia

2. Detail: Cefotetan and ceftriaxone are the two cephalosporins most likely to cause it.

2. Action: Requires prompt recognition and specialist management. [1]

3. Effect: Cefepime neurotoxicity

3. Detail: Seizures and encephalopathy, particularly in overdose or unadjusted renal impairment.

3. Action: Adjust dose for renal function and review promptly if neurological features appear. [1]

4. Effect: Hypoprothrombinaemia from vitamin K deficiency

4. Detail: Not a class-wide effect. It is tied to the cephalosporins carrying an N-methylthiotetrazole side chain - cefotetan, cefamandole, cefmetazole, cefoperazone and moxalactam - whose structure interferes with vitamin K metabolism and so with synthesis of clotting factors.

4. Action: Prothrombin time or INR is monitored where one of those agents is used, particularly alongside warfarin. [1]

1. Drug: Cefamandole, cefoperazone, moxalactam

1. Effect: The cephalosporins most commonly associated with disulfiram-like reactions. [1]

2. Drug: Cefotetan and ceftriaxone

2. Effect: The two agents most likely to cause drug-induced immune haemolytic anaemia. [1]

Contraindications, precautions and interactions

1. Allergy to cephalosporins, or anaphylaxis to penicillin or other beta-lactams. [1]

2. Ceftriaxone in neonates with hyperbilirubinaemia, and in infants under 28 days old expected to receive calcium-containing products, because of precipitation risk. [1]

1. Renal impairment, where dose adjustment is required - cefepime neurotoxicity is the clearest consequence of getting this wrong. [1]

2. A reported but unverified penicillin allergy. Cross-reactivity is driven by R-group similarity and is minimal from the third generation onward, and fewer than 1% of patients carrying a penicillin allergy label are truly allergic on evaluation. [1][4]

1. With: Alcohol

1. Effect: Disulfiram-like reactions are reported with cefamandole, cefoperazone and moxalactam. [1]

2. With: Calcium-containing intravenous products

2. Effect: Precipitation risk with ceftriaxone in neonates and young infants. [1]

Resistance mechanisms

1. Mechanism: Modified penicillin-binding protein

1. Detail: Bacteria acquire a gene encoding an altered penicillin-binding protein, which stops the cephalosporin's beta-lactam ring from inactivating it. This is the MRSA mechanism.

MRSA

1. Countermeasure: Fifth-generation agents (ceftaroline, ceftobiprole) are the cephalosporins that reach MRSA. [1]

2. Mechanism: Beta-lactamase production

2. Detail: The enzyme cleaves the beta-lactam ring so the drug can no longer attach to penicillin-binding proteins.

Extended-spectrum beta-lactamase producers

2. Countermeasure: Agents with greater beta-lactamase stability, guided by susceptibility testing. [1][2]

3. Mechanism: Reduced penetration and efflux

3. Detail: Beta-lactam resistance also arises from decreased penetration to the target site and from efflux pumping.

3. Countermeasure: Selection guided by susceptibility testing; cefiderocol's iron-transporter route is one way around a permeability barrier. [2][1]

Stewardship Note: Because the mechanisms differ, an organism resistant to one cephalosporin is not automatically resistant to all of them. Therapy is directed by local susceptibility data.

Comparison tables

Title: The five generations compared

Caption: Representative agents and the distinguishing feature of each generation. Spectrum statements are general; local susceptibility data governs actual therapy.

1. Key: generation

1. Label: Generation

1. Is Row Header: true

2. Key: examples

2. Label: Examples

3. Key: feature

3. Label: Distinguishing feature

4. Key: pseudomonas

4. Label: Pseudomonas

5. Key: mrsa

5. Label: MRSA

1. Generation: First

1. Examples: Cefazolin, cephalexin, cefadroxil, cephadrine

1. Feature: Most gram-positive cocci; limited gram-negative

1. Pseudomonas: No

1. Mrsa: No [1]

2. Generation: Second

2. Examples: Cefuroxime, cefprozil; cephamycins cefoxitin, cefotetan, cefmetazole

2. Feature: Adds H. influenzae, M. catarrhalis, Bacteroides

2. Pseudomonas: No

2. Mrsa: No [1]

3. Generation: Third

3. Examples: Ceftriaxone, cefotaxime, ceftazidime, cefdinir, cefpodoxime, cefixime

3. Feature: Extended gram-negative; CNS penetration (ceftriaxone, cefotaxime)

3. Pseudomonas: Ceftazidime only

3. Mrsa: No [1]
4. Generation: Fourth
4. Examples: Cefepime
4. Feature: Broad gram-positive and gram-negative, beta-lactamase producers, CNS penetration
4. Pseudomonas: Yes
4. Mrsa: No [1]
5. Generation: Fifth
5. Examples: Ceftaroline, ceftobiprole
5. Feature: Reaches MRSA and penicillin-resistant *S. pneumoniae*
5. Pseudomonas: No (ceftaroline)
5. Mrsa: Yes [1]

High-yield exam pearls

1. Pearl: Cefazolin is the go-to first-generation agent for surgical prophylaxis.
1. Why: It covers the gram-positive skin flora that cause most surgical site infections and is the preferred agent named for this indication. [1]
2. Pearl: Ceftazidime is the third-generation cephalosporin with antipseudomonal activity.
2. Why: Third-generation agents broadly extend gram-negative reach, but *Pseudomonas aeruginosa* coverage within that generation is specifically ceftazidime's. [1]
3. Pearl: MRSA cover arrives only at the fifth generation.
3. Why: Ceftaroline and ceftobiprole bind the modified penicillin-binding protein that makes MRSA resistant to earlier beta-lactams. [1]
4. Pearl: The cephamycins - cefoxitin, cefotetan, cefmetazole - sit inside the second generation and add *Bacteroides* cover.
4. Why: Second-generation coverage extends to *Haemophilus influenzae*, *Moraxella catarrhalis* and *Bacteroides* species. [1]
5. Pearl: Ceftriaxone is contraindicated in neonates with hyperbilirubinaemia, and in infants under 28 days expected to receive calcium-containing products.
5. Why: Ceftriaxone-calcium precipitation is the reason, and this is a classic exam contraindication. [1]
6. Pearl: Cefepime causes neurotoxicity - seizures and encephalopathy - in overdose or unadjusted renal impairment.
6. Why: It is the cephalosporin most associated with this effect, which is why renal dose adjustment matters. [1]

Common exam traps

1. Trap: "Each generation simply covers more than the one before it."
1. Correction: Gram-negative cover broadly widens, but gram-positive activity is strongest in the first generation and MRSA cover appears only in the fifth. It is a shift in spectrum, not a straight expansion. [1]
2. Trap: "All third-generation cephalosporins cover *Pseudomonas*."
2. Correction: Within the third generation, ceftazidime is the agent with *Pseudomonas aeruginosa* coverage - not the generation as a whole. [1]
3. Trap: "Any penicillin allergy rules out every cephalosporin."
3. Correction: Cross-reactivity is driven by R-group similarity and is more common with first- and second-generation agents; third-generation and beyond show minimal cross-reactivity. A reported penicillin allergy also deserves evaluation, since under 1% of labelled patients are truly allergic. [1][4]
4. Trap: "Fifth-generation means broadest of all."
4. Correction: Ceftaroline adds MRSA and penicillin-resistant pneumococcal cover but does not cover *Pseudomonas aeruginosa*. [1]

Self-test questions

1. Question: On what basis are cephalosporins divided into their five generations?

1. Route of administration and duration of action
2. Spectrum of coverage against gram-positive and gram-negative organisms, together with when each agent was discovered
3. Degree of renal versus biliary elimination
4. Chemical modification of the beta-lactam ring itself

1. Explanation: The generation label is a shorthand for two things at once: which organisms an agent reaches across the gram-positive and gram-negative divide, and the historical order in which the drugs appeared. It is not a statement about how a drug is given or cleared. [1]

2. Question: Which cephalosporin is named as the preferred agent for surgical prophylaxis, and why?

1. Ceftriaxone, because its long half-life allows once-daily administration
2. Cefepime, because of its broad gram-negative reach
3. Ceftazidime, because it reaches methicillin-resistant staphylococci
4. Cefazolin, because it covers the gram-positive skin flora responsible for most surgical site infections

2. Explanation: The organisms that seed most post-operative wound infections are gram-positive skin residents, and the first-generation agent cefazolin is the one specifically preferred to cover them before surgery. Broader later-generation agents are not the answer here. [1]

3. Question: A candidate writes that 'third-generation cephalosporins cover *Pseudomonas aeruginosa*.' What is the correct refinement?

1. Only ceftazidime carries that activity within the third generation
2. Only ceftriaxone carries that activity within the third generation
3. The whole generation covers it, but only when a beta-lactamase inhibitor is added
4. No third-generation agent has any gram-negative activity

3. Explanation: Antipseudomonal reach is a property of a single member rather than the whole tier. Ceftazidime is the third-generation drug that covers this organism; its stablemates such as ceftriaxone and cefotaxime extend gram-negative range but do not. Cefepime in the fourth generation also reaches *Pseudomonas*. [1]

4. Question: Which statement about ceftaroline is correct?

1. It is the broadest cephalosporin, covering every organism the earlier generations reach
2. It has no activity against gram-positive organisms
3. It covers MRSA and penicillin-resistant pneumococci but has no *Pseudomonas aeruginosa* activity
4. It belongs to the fourth generation and is used mainly for meningitis

4. Explanation: Being newest does not mean widest. This fifth-generation agent adds two things the earlier tiers lack - methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae* - while leaving *Pseudomonas aeruginosa* uncovered, which is a listed gap for it. [1]

5. Question: Seizures and encephalopathy in a patient with unadjusted renal impairment should raise suspicion of which cephalosporin?

1. Cefazolin
2. Cefoxitin
3. Cephalexin
4. Cefepime

5. Explanation: Neurotoxic effects of this pattern are the signature problem of the fourth-generation agent cefepime, and they surface in overdose or when the dose has not been scaled to reduced renal clearance. That link is precisely why renal function governs how this drug is used. [1]

6. Question: Why is ceftriaxone contraindicated in neonates with hyperbilirubinaemia and in infants under 28 days old expected to receive calcium-containing products?

1. Because ceftriaxone and calcium can precipitate together
2. Because ceftriaxone is not absorbed in neonates
3. Because ceftriaxone induces neonatal seizures through calcium depletion
4. Because calcium blocks ceftriaxone binding to penicillin-binding proteins
6. Explanation: The problem is a physical one: the drug and calcium can come out of solution together, and that precipitation risk is why this agent is barred in jaundiced newborns and in very young infants who are due calcium-containing intravenous products. It is a frequently examined contraindication. [1]
7. Question: Which group of cephalosporins is described as penetrating the blood-brain barrier effectively, making them usable in meningitis?
 1. Cefazolin and cephalexin
 2. Cefoxitin, cefotetan and cefmetazole
 3. Ceftriaxone, cefotaxime, ceftazidime and cefepime
 4. Ceftaroline and ceftobiprole
7. Explanation: Four members of the class cross into the central nervous system well enough to be treatment options for meningeal infection, and they span the third and fourth generations. The first-generation agents penetrate the cerebrospinal fluid poorly, so they are not alternatives here. [1]
8. Question: How does cephalosporin cross-reactivity in a patient labelled penicillin-allergic vary across the generations?
 1. Cross-reactivity is uniform across all five generations
 2. It is greatest with first- and second-generation agents and minimal from the third generation onward
 3. It is absent in the early generations and appears only in the fifth
 4. It rises steadily with each successive generation
8. Explanation: Shared R-group chemistry, not the beta-lactam ring alone, drives the overlap, so the risk clusters in the earlier agents and falls away in the later ones. A separate point worth remembering is that the allergy label itself is often wrong, since fewer than one percent of labelled patients prove truly allergic on assessment. Anaphylaxis to a beta-lactam nonetheless remains an absolute bar. [1][4]

Frequently asked questions

1. Question: What do the cephalosporin generations actually mean?
 1. Answer: They group the drugs by their spectrum of coverage against gram-positive and gram-negative bacteria, and by the order in which they were discovered. They are a learning and prescribing shorthand for what a given agent is likely to reach. [1]
2. Question: Which cephalosporins work against *Pseudomonas aeruginosa*?
 2. Answer: Ceftazidime in the third generation and cefepime in the fourth. Ceftaroline, despite being fifth generation, does not cover *Pseudomonas*. [1]
3. Question: Which cephalosporins are used in meningitis?
 3. Answer: Ceftriaxone, cefotaxime, ceftazidime and cefepime all penetrate the blood-brain barrier effectively, which is what makes them treatment options for meningitis. [1]
4. Question: Can someone with a penicillin allergy receive a cephalosporin?
 4. Answer: It depends on the reaction and the agent. Anaphylaxis to a beta-lactam is a contraindication. Otherwise cross-reactivity tracks R-group similarity - higher with first- and second-generation agents, minimal from the third generation onward - and a reported penicillin allergy is itself worth evaluating, since under 1% of labelled patients are truly allergic. [1][4]
5. Question: Why is cefazolin used for surgical prophylaxis?
 5. Answer: It covers the gram-positive cocci responsible for most surgical site infections, and it is the first-generation agent specifically preferred for this purpose. [1]

References

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