

Macrolides

Bacteriostatic 50S ribosomal inhibitors with strong atypical cover, defined clinically by their QT and CYP3A4 liabilities.

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

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Quick revision

One Liner: Macrolides bind the 50S subunit and stop peptidyltransferase extending the peptide chain - bacteriostatic at usual doses, strong on atypicals, and defined in practice by QT prolongation and CYP3A4 interactions.

1. Three main agents: erythromycin, clarithromycin and azithromycin. [1]
2. Mechanism: bind the bacterial 50S ribosomal subunit and prevent peptidyltransferase adding amino acids to the growing peptide chain. [1]
3. Bacteriostatic at usual doses; bactericidal activity at elevated doses is inconsistent and should not be relied on. [1]
4. Cover the atypical pneumonias: *Mycoplasma pneumoniae*, *Legionella* and *Chlamydia pneumoniae*. [1]
5. All three prolong the QT and QTc intervals - erythromycin carries the highest risk and azithromycin the lowest. [1]
6. CYP3A4: clarithromycin is a strong inhibitor and erythromycin a moderate one, while azithromycin does not inhibit it at all. [5]
7. Gastrointestinal upset happens because macrolides are motilin agonists. [1]
8. Resistance is chiefly post-transcriptional methylation of bacterial 23S ribosomal RNA. [1]

Overview

1. Macrolides are a class of drugs used to manage and treat a wide range of bacterial infections. Three primary antimicrobials make up the class in practice: erythromycin, clarithromycin and azithromycin. [1]
2. They work at the ribosome rather than the cell wall, binding the bacterial 50S subunit and halting protein synthesis. Their broad activity follows from the fact that bacterial ribosomes are highly conserved across species, which is also why the class reaches organisms - the atypicals - that have no cell wall for a beta-lactam to target. [1]
3. Clinically the class is defined as much by its liabilities as by its spectrum. Every macrolide prolongs the QT interval, clarithromycin is a strong CYP3A4 inhibitor and erythromycin a moderate one, and the whole class causes gastrointestinal upset through motilin agonism. Choosing between the three is usually a question of which of those liabilities matters most for a given patient. [1][5]

Classification and drug examples

Intro: A small class best learned as three agents. QT risk falls as you move from erythromycin to azithromycin, but the CYP3A4 liability does not follow that order - it peaks in the middle, with clarithromycin.

Name: Macrolides

Note: Three primary antimicrobials, differing mainly in interaction profile, QT risk and the balance between typical and atypical cover.

1. Name: Erythromycin

1. Route: Oral, topical, ophthalmic

1. Note: Highest QT risk of the three, and a moderate CYP3A4 inhibitor. [1][5]

2. Name: Clarithromycin

2. Route: Oral

2. Note: Spectrum similar to erythromycin with additional activity against some staphylococcal and streptococcal species; a strong CYP3A4 inhibitor, and so the highest interaction liability of the three. [1][5][6]

3. Name: Azithromycin

3. Route: Oral and injectable

3. Note: Better activity than erythromycin against respiratory gram-negatives such as *Haemophilus influenzae* and *Moraxella catarrhalis*, less against streptococci; lowest QT risk and no CYP3A4 inhibition. [1][8] [1]

Mechanism of action

Summary: Macrolides bind the bacterial 50S ribosomal subunit and prevent peptidyltransferase from adding amino acids to the growing peptide chain, halting protein synthesis.

Target: Bacterial 50S ribosomal subunit

Cidal Static: bacteriostatic (bactericidal at elevated doses)

Kill Kinetics: time-dependent

1. Step: 1

1. Title: The drug binds the 50S subunit

1. Detail: Macrolides bind the bacterial 50S ribosomal subunit, the large half of the bacterial ribosome. [1]

2. Step: 2

2. Title: Peptide chain elongation stops

2. Detail: Binding prevents peptidyltransferase from adding further amino acids to the growing peptide chain. [1]

3. Step: 3

3. Title: Protein synthesis ceases

3. Detail: Without elongation the organism cannot make the proteins it needs, and growth halts. [1]

4. Step: 4

4. Title: The effect is usually static, not cidal

4. Detail: At usual doses this arrests growth rather than killing. The class can become bactericidal at elevated doses, but that effect is inconsistent, so macrolides should not be relied on as bactericidal agents in practice. [1]

5. Step: 5

5. Title: Conserved ribosomes explain the breadth

5. Detail: Broad-spectrum activity follows from how highly conserved bacterial ribosomes are across species. [1]

Spectrum of activity

Intro: Macrolide cover is concentrated on atypical organisms and selected gram-positives. Gram-negative activity is limited across the class, though azithromycin reaches respiratory gram-negatives such as *Haemophilus influenzae* and *Moraxella catarrhalis* better than erythromycin does. A macrolide is still not general gram-negative cover.

Subclass Id: macrolides

1. Streptococci

2. Some staphylococcal species (clarithromycin)

1. *Haemophilus influenzae* and *Moraxella catarrhalis* (azithromycin)

2. Limited activity against most other common gram-negative pathogens

1. *Mycoplasma pneumoniae*

2. *Legionella*

3. *Chlamydia pneumoniae*

1. Most commonly encountered gram-negative pathogens

2. Organisms carrying 23S rRNA methylation [1][7]

Major clinical uses

1. Drug: Azithromycin

1. Organism: *Mycoplasma pneumoniae*, *Legionella*, *Chlamydia pneumoniae*

1. Indication: Atypical pneumonia

1. Line: first-line

1. Note: The class is effective against the atypical pneumonias specifically. [1]

2. Drug: Clarithromycin

2. Organism: *Helicobacter pylori*

2. Indication: *H. pylori* eradication as part of standard triple therapy

2. Line: alternative

2. Note: Clarithromycin triple therapy is reserved for patients with no previous macrolide exposure who live where clarithromycin resistance among *H. pylori* isolates is known to be low. Where resistance is not known to be low, or a macrolide has been used before, bismuth quadruple therapy or concomitant therapy is preferred, and rising resistance has made susceptibility-guided selection increasingly important. [1][4]

3. Drug: Erythromycin

3. Organism: Susceptible respiratory pathogens

3. Indication: Pneumonia, sinusitis, pharyngitis and tonsillitis

3. Line: alternative

3. Note: Common indications across the class. [1]

4. Drug: Azithromycin

4. Organism: *Chlamydia trachomatis*

4. Indication: Uncomplicated chlamydial infection

4. Line: alternative

4. Note: CDC recommends doxycycline for seven days as the first-line regimen, with single-dose azithromycin listed as an alternative. Azithromycin is no longer recommended for gonorrhoea, where ceftriaxone alone is now the recommended treatment. Azithromycin is also used for chest and ear infections, Lyme disease, pneumonia and sinusitis. [9][10][2]

5. Drug: Clarithromycin

5. Organism: Susceptible paediatric pathogens

5. Indication: Uncomplicated skin infection and otitis media in paediatric patients

5. Line: alternative

5. Note: A recognised paediatric use of the class; clarithromycin is also used for cellulitis, chest and ear infections and stomach ulcers. [1][3]

6. Drug: Azithromycin

6. Organism: Not organism-directed

6. Indication: Non-cystic-fibrosis bronchiectasis and COPD exacerbations

6. Line: adjunct

6. Note: Used for anti-inflammatory effect; improves spirometry and quality of life in bronchiectasis. [1]

Pharmacokinetics

1. Drug: Erythromycin

1. Route: Oral, topical, ophthalmic

1. Absorption: Oral, with topical and ophthalmic formulations available

1. Csf Penetration: See prescribing reference

1. Metabolism: Moderate CYP3A4 inhibitor

1. Elimination: See prescribing reference

1. Half Life: See prescribing reference

1. Dose Adjust: See prescribing reference [5]

2. Drug: Clarithromycin

2. Route: Oral

2. Absorption: Oral tablets, extended-release and suspension
2. Csf Penetration: See prescribing reference
2. Metabolism: Strong CYP3A4 inhibitor - the highest interaction liability of the three
2. Elimination: See prescribing reference
2. Half Life: See prescribing reference
2. Dose Adjust: See prescribing reference [5][6]
3. Drug: Azithromycin
3. Route: Oral and IV
3. Absorption: Oral tablets, suspension and injectable powder
3. Csf Penetration: See prescribing reference
3. Metabolism: Does not participate in CYP3A4 interactions
3. Elimination: See prescribing reference
3. Half Life: See prescribing reference
3. Dose Adjust: See prescribing reference [1]
1. The metabolic column is the practical reason to prefer one macrolide over another: an interaction that is disqualifying for erythromycin may be irrelevant for azithromycin. [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

Effect: Gastrointestinal upset

Detail: Nausea, vomiting, abdominal pain and diarrhoea. Macrolides are motilin agonists, which directly increases gastrointestinal upset, and they also disrupt commensal gut flora. [1]

1. Effect: QT and QTc prolongation

1. Detail: All macrolides prolong these intervals, raising the risk of Torsades de Pointes and ventricular arrhythmias. Erythromycin carries the highest risk and azithromycin the lowest.

1. Action: Assess QT risk and concurrent QT-prolonging drugs before prescribing. [1]

2. Effect: Sensorineural hearing loss

2. Detail: Reported as either reversible or irreversible.

2. Action: Seek assessment if hearing changes develop during therapy. [1]

3. Effect: Severe cutaneous reactions

3. Detail: Stevens-Johnson syndrome and toxic epidermal necrolysis are reported.

3. Action: Stop the drug and seek urgent specialist assessment. [1]

4. Effect: Hepatotoxicity in pregnancy

4. Detail: Reported in pregnant women.

4. Action: Requires careful consideration before use in pregnancy. [1]

1. Drug: Erythromycin

1. Effect: Carries the greatest QT liability in the class and inhibits CYP3A4 moderately. [1][5]

2. Drug: Macrolides in newborns

2. Effect: Increased risk of pyloric stenosis. [1]

Contraindications, precautions and interactions

Prolonged QT interval or congenital long QT syndrome type 2. [1]

1. Concurrent Class Ia or Class III antiarrhythmic therapy, where macrolides should be avoided. [1]

2. Pregnancy, particularly with erythromycin, which requires careful consideration. [1]

3. Local resistance patterns, which prescribers should evaluate given resistance concerns across the class. [1]

1. With: CYP3A4 substrates - carbamazepine, ciclosporin, terfenadine, astemizole, theophylline

1. Effect: Clarithromycin is a strong inhibitor of CYP3A4 and erythromycin a moderate one, so both raise substrate exposure; azithromycin does not inhibit the enzyme and does not participate in these interactions. [5][6]
2. With: Other QT-prolonging drugs
2. Effect: Additive QT prolongation raises the risk of Torsades de Pointes and ventricular arrhythmia. [1]

Resistance mechanisms

1. Mechanism: 23S rRNA methylation
 1. Detail: Post-transcriptional methylation of bacterial 23S ribosomal RNA is the primary route, arising through plasmid-mediated or chromosomal mechanisms.
 - MLS-B phenotype
 1. Countermeasure: Susceptibility-directed therapy; a different mechanistic class where methylation is present. [1]
 2. Mechanism: Cross-resistance across three classes
 2. Detail: Genetic mutations can confer simultaneous resistance to macrolides, lincosamides and streptogramins, with transposable elements spreading the resistance genes.
 - Macrolide-lincosamide-streptogramin resistance
 2. Countermeasure: Do not assume a lincosamide is a safe substitute when macrolide resistance is present. [1]
- Stewardship Note: Because one resistance determinant can remove three classes at once, macrolide resistance is a broader loss than it first appears; local resistance patterns should be checked before prescribing.

Comparison tables

Title: The three macrolides compared

Caption: The two gradients that drive agent choice: CYP3A4 interaction and QT risk. Local susceptibility data governs actual therapy.

1. Key: drug
 1. Label: Drug
 1. Is Row Header: true
2. Key: cyp
 2. Label: CYP3A4 interaction
3. Key: qt
 3. Label: QT risk
4. Key: spectrum
 4. Label: Spectrum emphasis
5. Key: forms
 5. Label: Formulations
1. Drug: Erythromycin
 1. Cyp: Moderate inhibitor
 1. Qt: Highest
 1. Spectrum: Baseline class spectrum
 1. Forms: Oral, topical, ophthalmic [1][5]
2. Drug: Clarithromycin
 2. Cyp: Strong inhibitor
 2. Qt: Intermediate
 2. Spectrum: Like erythromycin plus some staph and strep species
 2. Forms: Oral, extended-release, suspension [1][5][6]
3. Drug: Azithromycin
 3. Cyp: Does not inhibit CYP3A4
 3. Qt: Lowest

- 3. Spectrum: Better respiratory gram-negative reach, less streptococcal potency, strong atypical cover
- 3. Forms: Oral, suspension, injectable [1][8]

High-yield exam pearls

- 1. Pearl: Macrolide GI upset is a pharmacological action, not just intolerance.
- 1. Why: Macrolides are motilin agonists, which is why erythromycin in particular drives cramping and diarrhoea - and why it gets used as a prokinetic. [1]
- 2. Pearl: Clarithromycin, not erythromycin, is the strong CYP3A4 inhibitor of the class.
- 2. Why: The FDA lists clarithromycin among its strong CYP3A index inhibitors and erythromycin among the moderate ones, while azithromycin does not inhibit CYP3A4 at all. Ranking erythromycin highest is a common revision error. [5][6]
- 3. Pearl: The QT risk gradient runs the same way: erythromycin highest, azithromycin lowest.
- 3. Why: All three prolong QT and QTc, raising the risk of Torsades de Pointes and ventricular arrhythmias. [1]
- 4. Pearl: Macrolides are the classic atypical-pneumonia cover.
- 4. Why: They are effective against *Mycoplasma pneumoniae*, *Legionella* and *Chlamydia pneumoniae* - organisms with no cell wall for a beta-lactam to attack. [1]
- 5. Pearl: One mutation can knock out three classes at once.
- 5. Why: Methylation of 23S rRNA confers simultaneous resistance to macrolides, lincosamides and streptogramins - the MLS-B phenotype. [1]
- 6. Pearl: Azithromycin gained gram-negative reach over erythromycin; what it gave up was streptococcal potency.
- 6. Why: It is an erythromycin derivative with enhanced activity against gram-negative organisms, *Haemophilus influenzae* and *Moraxella catarrhalis* among them, and less activity against streptococci and enterococci. Activity against staphylococci is comparable. [8][7]

Common exam traps

- 1. Trap: "Macrolides are bactericidal."
- 1. Correction: They are bacteriostatic at usual doses, though they can become bactericidal at elevated doses. [1]
- 2. Trap: "Azithromycin is just a longer-acting erythromycin."
- 2. Correction: Their profiles differ in the ways that matter: azithromycin reaches gram-negative organisms erythromycin struggles with, is less active against streptococci, carries the lowest QT risk of the three, and does not inhibit CYP3A4. [8][5]
- 3. Trap: "A macrolide is a safe default in someone on antiarrhythmics."
- 3. Correction: Patients with a prolonged QT interval, congenital long QT syndrome type 2, or taking Class Ia or Class III antiarrhythmics should avoid macrolides. [1]
- 4. Trap: "Macrolide resistance only affects macrolides."
- 4. Correction: Methylation of 23S rRNA can confer resistance to macrolides, lincosamides and streptogramins simultaneously, and transposable elements spread those genes. [1]

Self-test questions

- 1. Question: Where in the bacterial cell do macrolides act, and what step do they interrupt?
- 1. They inhibit DNA gyrase, so supercoiling of the chromosome fails
- 2. They bind the 30S subunit, causing the genetic code to be misread
- 3. They bind the 50S subunit and stop peptidyltransferase adding further amino acids to the growing chain
- 4. They bind penicillin-binding proteins and halt peptidoglycan cross-linking
- 1. Explanation: The target is the large half of the bacterial ribosome. Once a macrolide occupies it, peptidyltransferase can no longer extend the nascent peptide, translation stalls, and the organism cannot build the proteins it needs.

Because ribosomes are so highly conserved between species, this single target gives the class its breadth. [1]

2. Question: Which statement best describes whether macrolides kill or merely arrest bacteria?

1. They are dependably bactericidal at every clinically used exposure
2. They arrest growth at usual doses; killing may appear at elevated doses but is inconsistent enough that it should not be relied on
3. They are static against gram-positives and cidal against atypical organisms
4. They kill only under anaerobic conditions, where the ribosome is more exposed

2. Explanation: Ordinary exposure halts multiplication rather than killing the organism. Higher exposure can tip the effect towards killing, but that behaviour is unreliable, so in practice the class is treated as growth-arresting rather than lethal. [1]

3. Question: Which statement about QT effects across the three macrolides is correct?

1. Only erythromycin lengthens the QT interval; clarithromycin and azithromycin are free of the effect
2. Every member lengthens QT and QTc, with erythromycin at the top of the risk gradient and azithromycin at the bottom
3. Azithromycin carries the greatest risk of the three because of its longer duration of action
4. QT effects appear only when a macrolide is combined with an antiarrhythmic drug

3. Explanation: All three lengthen both intervals, so none of them is a QT-neutral option. What differs is degree: the risk runs highest with erythromycin and lowest with azithromycin. The consequence that matters is Torsades de Pointes and other ventricular arrhythmias. [1]

4. Question: A student describes azithromycin as simply a longer-acting erythromycin. Which set of differences shows that this is wrong?

1. Azithromycin is the strongest CYP3A4 inhibitor of the three and carries the highest QT risk
 2. The two are pharmacologically identical and differ only in the formulations available
 3. Azithromycin is the more potent of the two against common gram-positive organisms and is equally interaction-prone
 4. Azithromycin reaches respiratory gram-negatives such as *Haemophilus influenzae* and *Moraxella catarrhalis* better than erythromycin, is less active against streptococci, sits lowest of the three for QT risk, and does not inhibit CYP3A4
4. Explanation: The two agents differ in exactly the respects an exam tests. Azithromycin was derived from erythromycin with improved gram-negative reach, gives up some streptococcal potency, and sits at the bottom of the class QT gradient. Interactions do not follow the same order: clarithromycin is the strong CYP3A4 inhibitor, erythromycin a moderate one, and azithromycin does not inhibit the enzyme at all. [8][5]

5. Question: Macrolides are the classic cover for atypical pneumonia. Which organisms does that describe, and why does a beta-lactam fail against them?

1. *Pseudomonas aeruginosa* and *Acinetobacter*, because they hyperproduce beta-lactamase
2. *Staphylococcus aureus* and *Enterococcus*, because they express altered penicillin-binding proteins
3. *Mycoplasma pneumoniae*, *Legionella* and *Chlamydia pneumoniae*, because none of them builds the cell wall a beta-lactam needs as a target
4. *Escherichia coli* and *Klebsiella*, because their porin channels exclude beta-lactams

5. Explanation: Acting at the ribosome rather than the cell envelope is what lets this class reach the atypical pneumonia pathogens. A cell-wall agent has nothing to attack in organisms that lack a wall, which is precisely the gap a macrolide fills. [1]

6. Question: Post-transcriptional methylation of bacterial 23S ribosomal RNA has which consequence for antimicrobial choice?

1. It removes macrolide activity alone, leaving lincosamides a reliable substitute
2. It abolishes activity of macrolides, lincosamides and streptogramins simultaneously
3. It increases macrolide binding affinity and improves killing
4. It confers beta-lactam resistance through altered penicillin-binding proteins

6. Explanation: Methylating the ribosomal RNA alters a site that three separate classes depend on, producing the MLS-B phenotype. One determinant therefore costs three treatment options at once, and transposable elements spread the responsible genes - so switching to a lincosamide is not the safe fallback it looks like. The change can arise by plasmid-mediated or chromosomal routes. [1]

7. Question: Which patient background argues most strongly against selecting a macrolide?

1. Congenital long QT syndrome type 2, or current treatment with a Class Ia or Class III antiarrhythmic
2. Well-controlled type 2 diabetes mellitus
3. A past episode of iron-deficiency anaemia
4. Mild seasonal allergic rhinitis

7. Explanation: An already prolonged QT interval or the congenital type 2 long QT phenotype is an absolute bar, and antiarrhythmic therapy in the Class Ia or Class III groups is a situation in which the class should be avoided. Stacking a QT-prolonging antibiotic onto either raises the arrhythmia risk further. The other three backgrounds carry no comparable class-specific concern. [1]

8. Question: What accounts for the cramping and diarrhoea that macrolides, and erythromycin especially, produce?

1. Direct mucosal irritation from an acidic oral formulation
2. Osmotic retention of water within the small bowel lumen
3. Agonist action at the motilin receptor, a direct pharmacological effect on gut motility
4. Inhibition of the gastric proton pump

8. Explanation: Gastrointestinal upset here is a pharmacological action rather than mere intolerance: these drugs stimulate motilin receptors, which is also why erythromycin finds a separate use as a prokinetic agent. Loss of commensal gut flora, which any antibiotic causes, adds to the nausea, vomiting, abdominal pain and diarrhoea. [1]

Frequently asked questions

1. Question: Why do macrolides cause so much stomach upset?

1. Answer: Because they are motilin agonists. That is a direct pharmacological action on gut motility, on top of the disruption of commensal gut flora that any antibiotic causes. [1]

2. Question: Which macrolide is safest for someone on multiple other medicines?

2. Answer: Azithromycin does not inhibit CYP3A4 and carries the lowest QT risk of the three, which makes it the interaction-sparing choice. Clarithromycin is a strong CYP3A4 inhibitor and erythromycin a moderate one, so both warrant an interaction check. [5]

3. Question: Why are macrolides used for atypical pneumonia?

3. Answer: They act on the ribosome rather than the cell wall, so they reach *Mycoplasma pneumoniae*, *Legionella* and *Chlamydia pneumoniae* - organisms a beta-lactam cannot touch. [1]

4. Question: Are macrolides bactericidal or bacteriostatic?

4. Answer: Bacteriostatic at usual doses, though they can become bactericidal at elevated doses. [1]

5. Question: Why does macrolide resistance also affect clindamycin?

5. Answer: Methylation of 23S ribosomal RNA alters a binding site shared by macrolides, lincosamides and streptogramins, so a single genetic change can confer resistance to all three classes. [1]

References

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