

Tetracyclines

Broad-spectrum bacteriostatic 30S inhibitors, defined clinically by photosensitivity, cation chelation, and their contraindication in pregnancy and young children.

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

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Quick revision

One Liner: Tetracyclines bind the 30S subunit and block aminoacyl-tRNA from reaching the mRNA-ribosome complex - broad-spectrum, bacteriostatic, chelated by cations, and off-limits in pregnancy and under-8s.

1. Mechanism: inhibit the bacterial 30S ribosomal subunit, preventing aminoacyl-tRNA binding to the mRNA-ribosome complex. [1]
2. Bacteriostatic: they stop growth rather than killing the organism. [1]
3. Broad-spectrum, covering gram-positive and gram-negative bacteria, spirochetes, chlamydia and rickettsia. [2]
4. Contraindicated in pregnancy and in children under 8 because of permanent tooth staining and impaired bone growth. [1]
5. Absorption is severely impaired by aluminium, calcium, iron and magnesium through chelation - so dairy and antacids matter. [1]
6. Photosensitivity is a class effect, presenting as red rashes or blistering. [1]
7. Minocycline ranks within the ten most common causes of drug-induced liver injury in the United States. [2]
8. Three resistance mechanisms: ribosomal protection proteins, efflux pumps, and drug modification. [1]

Overview

1. Tetracyclines are protein synthesis inhibitor antibiotics and are considered broad-spectrum. The class is used to manage and treat a wide range of bacterial infections, and its members include tetracycline, doxycycline, minocycline and tigecycline. [1]
2. Coverage extends across gram-positive and gram-negative bacteria as well as spirochetes, chlamydia and rickettsia - an unusually wide reach for an old class, achieved by binding bacterial ribosomes and inhibiting protein synthesis. [2]
3. Much of what makes tetracyclines distinctive is not antibacterial at all. They chelate multivalent cations, which governs how they must be taken; they cause photosensitivity and deposit in developing teeth and bone, which governs who may take them; and several agents have useful anti-inflammatory and immunomodulatory effects that extend their use well beyond infection. [1][3]

Classification and drug examples

Intro: Grouped by origin and generation: naturally occurring agents, semi-synthetic derivatives, the single glycylicycline, and a newer group developed against resistant organisms.

1. Name: Naturally occurring tetracyclines
 1. Note: The original members of the class.
 1. Name: Tetracycline
 1. Route: Oral
 1. Note: The parent compound of the class. [1]
 2. Name: Oxytetracycline
 2. Route: Oral
 2. Note: A naturally occurring member of the class. [1]
 3. Name: Chlortetracycline

3. Route: Topical

3. Note: A naturally occurring member of the class. [1]

4. Name: Demeclocycline

4. Route: Oral

4. Note: A naturally occurring member of the class. [1] [1]

2. Name: Semi-synthetic tetracyclines

2. Note: Chemically modified derivatives; these are the agents most used in current practice.

1. Name: Doxycycline

1. Route: Oral

1. Note: Used for urinary, sexually transmitted, chest and gum infections, acne and rosacea, and malaria prophylaxis. [3]

2. Name: Minocycline

2. Route: Oral

2. Note: Carries the highest liver-injury risk in the class. [2]

3. Name: Lymecycline

3. Route: Oral

3. Note: A semi-synthetic member of the class. [1]

4. Name: Methacycline

4. Route: Oral

4. Note: A semi-synthetic member of the class. [1]

5. Name: Rolitetracycline

5. Route: Parenteral

5. Note: A semi-synthetic member of the class. [1] [1]

3. Name: Glycylcycline

3. Note: A subclass containing a single agent.

Name: Tigecycline

Route: IV

Note: The one glycylcycline subclass agent. [1] [1]

4. Name: Newer tetracyclines

4. Note: A more recent group developed to extend the class.

1. Name: Omadacycline

1. Route: Oral/IV

1. Note: One of the newer tetracyclines. [1]

2. Name: Eravacycline

2. Route: IV

2. Note: One of the newer tetracyclines. [1]

3. Name: Sarecycline

3. Route: Oral

3. Note: One of the newer tetracyclines. [1] [1]

Mechanism of action

Summary: Tetracyclines inhibit the bacterial 30S ribosomal subunit, preventing aminoacyl-tRNA from binding the mRNA-ribosome complex, which halts protein synthesis and stops bacterial replication.

Target: Bacterial 30S ribosomal subunit

Cidal Static: bacteriostatic

Kill Kinetics: time-dependent

1. Step: 1

1. Title: The drug binds the 30S subunit

1. Detail: Tetracyclines inhibit the bacterial 30S ribosomal subunit - the small half of the bacterial ribosome. [1]

2. Step: 2

2. Title: Aminoacyl-tRNA cannot dock

2. Detail: Binding prevents aminoacyl-tRNA from attaching to the mRNA-ribosome complex, so the next amino acid never arrives. [1]

3. Step: 3

3. Title: Protein synthesis halts

3. Detail: Translation stops and bacterial replication is prevented. [1]

4. Step: 4

4. Title: Growth stops, but the organism is not killed

4. Detail: Unlike bactericidal drugs, tetracyclines simply stop growth, leaving clearance to host immunity. [1]

Spectrum of activity

Intro: Genuinely broad, and unusually inclusive of organisms that live inside host cells or lack a conventional cell wall.

Subclass Id: class-wide

1. Gram-positive bacteria

2. Some MRSA strains

1. Gram-negative bacteria

2. Vibrio

1. Mycoplasma

2. Chlamydia

3. Rickettsia

4. Borrelia

5. Mycobacterium marinum

Organisms carrying ribosomal protection proteins or tetracycline efflux pumps [1][2]

Major clinical uses

1. Drug: Doxycycline

1. Organism: Chlamydia trachomatis and other susceptible organisms

1. Indication: Sexually transmitted infections, including chlamydia

1. Line: first-line

1. Note: Also used for urinary, chest and gum infections. [3][1]

2. Drug: Doxycycline

2. Organism: Borrelia

2. Indication: Lyme disease

2. Line: first-line

2. Note: Borrelia is within the class's documented spectrum. [1]

3. Drug: Doxycycline

3. Organism: Plasmodium species

3. Indication: Malaria prophylaxis for travellers

3. Line: first-line

3. Note: A non-antibacterial-infection use of the drug. [3]

4. Drug: Tetracycline

4. Organism: Rickettsia

4. Indication: Rickettsial infection

4. Line: first-line

4. Note: Rickettsial and atypical infections are a core class indication. [1]
5. Drug: Doxycycline
5. Organism: Not organism-directed
5. Indication: Acne and rosacea
5. Line: adjunct
5. Note: Uses anti-inflammatory and immunomodulatory effects rather than antibacterial killing alone. [3][1]
6. Drug: Minocycline
6. Organism: Susceptible organisms
6. Indication: Infections within the class spectrum, and non-antibiotic uses including rheumatoid arthritis
6. Line: alternative
6. Note: Weigh against its liver-injury risk, the highest in the class. [1][2]

Pharmacokinetics

1. Drug: Doxycycline
1. Route: Oral
1. Absorption: Severely impaired by aluminium, calcium, iron and magnesium
1. Csf Penetration: See prescribing reference
1. Metabolism: See prescribing reference
1. Elimination: See prescribing reference
1. Half Life: See prescribing reference
1. Dose Adjust: See prescribing reference [1]
2. Drug: Minocycline
2. Route: Oral
2. Absorption: Subject to the same cation chelation
2. Csf Penetration: See prescribing reference
2. Metabolism: See prescribing reference
2. Elimination: See prescribing reference
2. Half Life: See prescribing reference
2. Dose Adjust: See prescribing reference [1]
3. Drug: Tetracycline
3. Route: Oral
3. Absorption: Subject to the same cation chelation
3. Csf Penetration: See prescribing reference
3. Metabolism: See prescribing reference
3. Elimination: Primarily renal, unlike doxycycline, whose renal excretion falls from about 40% to as little as 1 to 5% over 72 hours in severe impairment with compensatory faecal elimination and an unchanged half-life
3. Half Life: See prescribing reference
3. Dose Adjust: Renal failure requires dose reduction for tetracycline; the doxycycline label states no such adjustment is needed [1][4][5]
1. Cation chelation is the defining pharmacokinetic feature of the class and the reason administration timing relative to dairy, antacids and iron matters clinically. [1]
2. High-dose intravenous tetracycline historically caused a distinctive acute fatty liver disease; this is largely of historical interest now that parenteral use has been discontinued. [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: Gastrointestinal distress
 1. Detail: Nausea, vomiting and abdominal discomfort. [1]
2. Effect: Photosensitivity
 2. Detail: Red rashes or blistering on sun-exposed skin; mitigated by sun avoidance and protective clothing. [1]
1. Effect: Permanent tooth discolouration and impaired bone growth
 1. Detail: Yellow-brown staining of developing teeth, with impaired bone growth, in children.
 1. Action: Avoid in children under 8 and in pregnancy. [1]
2. Effect: Hepatotoxicity
 2. Detail: Reported across the class, with substantial variation between agents.
 2. Action: Assess urgently if jaundice or unexplained malaise develops. [1]
3. Effect: Intracranial hypertension
 3. Detail: A recognised serious adverse effect of the class.
 3. Action: Seek assessment for persistent headache or visual change. [1]
4. Effect: Oesophageal ulceration and stricture
 4. Detail: A recognised serious adverse effect, relevant to how the drug is swallowed.
 4. Action: Seek assessment for painful or difficult swallowing. [1]
5. Effect: Clostridioides difficile infection
 5. Detail: A recognised serious complication of therapy.
 5. Action: Seek urgent assessment for severe or persistent diarrhoea. [1]
1. Drug: Minocycline
 1. Effect: Highest liver-injury risk in the class, ranking within the ten most common causes of drug-induced liver injury in the United States, typically with prolonged latency and autoimmune features. [2]
2. Drug: Doxycycline
 2. Effect: Liver injury typically shows a shorter latency, from 1 to 60 days, with variable enzyme elevation patterns. [2]
3. Drug: Minocycline
 3. Effect: Central nervous system effects - lightheadedness, dizziness and vertigo - are reported with minocycline and set it apart from the rest of the class. Patients affected are cautioned against driving or operating hazardous machinery. The symptoms may settle during continued therapy and usually resolve rapidly once the drug is stopped. [6]

Contraindications, precautions and interactions

1. Pregnancy, because of the risk of maternal hepatotoxicity and fetal tooth discolouration. [1]
2. Children under 8 years, because of permanent tooth staining. [1]
 1. Renal impairment, where the rule is agent-specific rather than class-wide. Tetracycline itself accumulates: its label warns that higher serum levels may lead to azotaemia, hyperphosphataemia and acidosis, and directs dose reduction. Minocycline's label caps the total daily dose at 200 mg and advises creatinine and BUN monitoring. Doxycycline is the exception - its label states that usual recommended doses do not lead to excessive accumulation in renal impairment, and that the antianabolic BUN rise seen with other tetracyclines does not occur with it. [4][6][5]
2. Sun exposure during therapy, given class-wide photosensitivity. [1]
 1. With: Multivalent cations - aluminium, calcium, iron, magnesium
 1. Effect: Chelation severely impairs absorption; dairy products and antacids containing these elements interfere in the same way. [1]
 2. With: Oral contraceptives
 2. Effect: Tetracyclines may reduce effectiveness, and barrier protection is recommended. [1]

Resistance mechanisms

1. Mechanism: Ribosomal protection proteins

1. Detail: These allow the ribosome to keep functioning despite high drug concentrations.

1. Countermeasure: Susceptibility-directed therapy; newer tetracyclines were developed partly against resistant organisms. [1]

2. Mechanism: Efflux pumps

2. Detail: Transmembrane transporters actively remove the drug from the bacterial cell.

2. Countermeasure: Susceptibility-directed therapy. [1]

3. Mechanism: Tetracycline modification

3. Detail: A less studied mechanism that alters the drug's structure.

3. Countermeasure: Susceptibility-directed therapy. [1]

Stewardship Note: Resistance genes are typically encoded on plasmids or transposons, which makes them readily transferable between bacteria and is why tetracycline resistance spreads quickly once established.

Comparison tables

Title: Tetracycline subclasses at a glance

Caption: Origin and representative agents. Local susceptibility data governs actual therapy.

1. Key: group

1. Label: Group

1. Is Row Header: true

2. Key: examples

2. Label: Examples

3. Key: feature

3. Label: Distinguishing feature

1. Group: Naturally occurring

1. Examples: Tetracycline, chlortetracycline, oxytetracycline, demeclocycline

1. Feature: The original agents of the class [1]

2. Group: Semi-synthetic

2. Examples: Doxycycline, minocycline, lymecycline, methacycline, rolitetracycline

2. Feature: Chemically modified; the mainstays of current practice [1]

3. Group: Glycylcycline

3. Examples: Tigecycline

3. Feature: A subclass with a single agent [1]

4. Group: Newer tetracyclines

4. Examples: Eravacycline, sarecycline, omadacycline

4. Feature: Recent additions extending the class [1]

High-yield exam pearls

1. Pearl: Tetracyclines are chelated by multivalent cations.

1. Why: Aluminium, calcium, iron and magnesium bind the drug and severely impair absorption, which is why dairy products and antacids interfere with therapy. [1]

2. Pearl: Under 8 years old and pregnancy are the two hard age-related contraindications.

2. Why: Permanent yellow-brown tooth discolouration and impaired bone growth in children; maternal hepatotoxicity and fetal tooth discolouration in pregnancy. [1]

3. Pearl: Breastfeeding is different from pregnancy here.

3. Why: Tetracyclines are considered safe in breastfeeding because calcium chelation in milk limits infant exposure - the same chemistry that causes the absorption problem becomes protective. [1]
4. Pearl: Minocycline is the tetracycline to associate with liver injury.
4. Why: It carries the highest risk in the class and ranks within the ten most common causes of drug-induced liver injury in the US, typically with prolonged latency and autoimmune features. [2]
5. Pearl: Tigecycline is the glycylcycline.
5. Why: It is the single agent in that subclass, sitting apart from the natural and semi-synthetic tetracyclines. [1]
6. Pearl: Tetracyclines retain activity against some MRSA and VRE strains.
6. Why: Unusual for a bacteriostatic protein-synthesis inhibitor, and part of why the class persists despite its age. [1]

Common exam traps

1. Trap: "Tetracyclines are bactericidal because they are broad-spectrum."
1. Correction: Breadth and killing effect are unrelated. Tetracyclines are bacteriostatic - they simply stop growth rather than killing the organism. [1]
2. Trap: "If a tetracycline is unsafe in pregnancy it must be unsafe in breastfeeding."
2. Correction: The opposite applies here: calcium chelation in breast milk limits infant exposure, so tetracyclines are considered safe during breastfeeding. [1]
3. Trap: "Taking a tetracycline with milk just slows absorption a little."
3. Correction: Absorption is severely impaired by chelation with multivalent cations, and antacids containing aluminium, calcium or magnesium interfere the same way. [1]
4. Trap: "Tetracycline resistance is one mechanism."
4. Correction: Three are documented: ribosomal protection proteins, efflux pumps and drug modification, with genes typically carried on plasmids or transposons. [1]

Self-test questions

1. Question: How do tetracyclines interrupt bacterial protein synthesis?
1. They bind the 50S subunit and prevent peptide bond formation
2. They cause the ribosome to misread the genetic code
3. They act at the 30S subunit so that aminoacyl-tRNA cannot attach to the mRNA-ribosome complex
4. They cleave bacterial mRNA before translation can begin
1. Explanation: Inhibition happens at the small ribosomal subunit. With the charged tRNA unable to dock at the mRNA-ribosome complex, the growing chain never receives its next amino acid, translation stalls, and the organism cannot replicate. [1]
2. Question: A student argues that tetracyclines must be bactericidal because they are broad-spectrum. Which response is correct?
1. Spectrum and killing effect are independent properties: this class reaches gram-positives, gram-negatives, spirochetes, chlamydia and rickettsia yet only arrests growth
2. Correct - any agent covering both gram-positive and gram-negative organisms is bactericidal by definition
3. Incorrect, because tetracyclines are in fact narrow-spectrum agents
4. Correct, because every inhibitor acting at the 30S subunit is bactericidal
2. Explanation: How wide a drug's coverage runs says nothing about whether it kills. These agents reach an impressively wide range of organisms, spirochetes, chlamydia and rickettsia among them, and still only hold multiplication in check, so the host's own defences finish the job. [1][2]
3. Question: Why do dairy products and an aluminium-containing antacid matter during tetracycline therapy?
1. They raise gastric pH enough to destroy the drug chemically
2. They accelerate hepatic metabolism of the drug
3. They induce efflux pumps in gut flora

4. They supply multivalent cations that chelate the drug and severely impair its absorption
3. Explanation: Aluminium, calcium, iron and magnesium bind these molecules directly. The complex that forms is poorly taken up, and the loss of absorption is severe rather than marginal, which is why the interval between the drug and milk, antacids or iron preparations is a real clinical variable rather than a footnote. [1]
4. Question: Why are tetracyclines contraindicated in pregnancy and in children under 8 years of age?
 1. They inhibit fetal folate synthesis
 2. They deposit in developing teeth and bone, producing permanent yellow-brown discolouration and impaired bone growth, with maternal liver toxicity a further concern in pregnancy
 3. They cross the placenta and cause fetal renal failure
 4. Absorption in young children is too unpredictable to be relied upon
4. Explanation: Deposition into mineralising tissue is the problem. A child exposed before roughly 8 years old can be left with permanently stained teeth and slowed skeletal growth, and pregnancy adds two further recorded risks: hepatotoxicity in the mother and discolouration of the fetus's teeth. [1]
5. Question: Given that tetracyclines are contraindicated in pregnancy, what is the position during breastfeeding?
 1. Equally contraindicated, since anything unsafe in pregnancy is unsafe in lactation
 2. Contraindicated for the first six months of lactation only
 3. Considered safe, because calcium in milk chelates the drug and limits how much reaches the infant
 4. Considered safe, because the drug is not excreted into breast milk at all
5. Explanation: This is the counter-intuitive one. The same chelation chemistry that ruins absorption when the drug meets dairy turns protective during lactation - calcium in the milk ties the drug up, infant exposure stays low, and the class is regarded as acceptable here even though pregnancy rules it out. [1]
6. Question: Which tetracycline is most strongly associated with drug-induced liver injury?
 1. Minocycline
 2. Doxycycline
 3. Oxytetracycline
 4. Demeclocycline
6. Explanation: Minocycline carries the greatest hepatic risk of the class and sits among the ten commonest causes of drug-induced liver injury recorded in the United States, characteristically after a long latent period and with autoimmune features. Doxycycline can also injure the liver, but its latency is shorter, roughly one to sixty days, and its enzyme patterns are variable. [2]
7. Question: Which set correctly describes the documented mechanisms of tetracycline resistance?
 1. Beta-lactamase hydrolysis alone
 2. Altered penicillin-binding proteins together with porin loss
 3. Methylation of 23S rRNA at the target site only
 4. Ribosomal protection proteins, efflux pumps, and modification of the drug itself
7. Explanation: Three routes are recognised rather than one. Protection proteins keep the ribosome translating despite high drug concentrations, transmembrane transporters pump the drug back out of the cell, and a less studied modification pathway alters the molecule. The genes responsible usually sit on plasmids or transposons, so they pass between bacteria easily and resistance spreads quickly once established. [1]
8. Question: Where does tigecycline sit within the classification of the tetracyclines?
 1. Among the naturally occurring tetracyclines
 2. As the sole member of the glycylcycline subclass
 3. Among the semi-synthetic tetracyclines, alongside doxycycline and minocycline
 4. Among the newer tetracyclines, alongside eravacycline and sarecycline
8. Explanation: The class is grouped by origin and generation: the original natural agents, the semi-synthetic derivatives that dominate current practice, a recent group that includes omadacycline, eravacycline and sarecycline, and the glycylcyclines - a subclass whose only occupant is tigecycline. [1]

Frequently asked questions

1. Question: Why can tetracyclines not be taken with milk or antacids?
1. Answer: They chelate multivalent cations. Aluminium, calcium, iron and magnesium bind the drug and severely impair its absorption, and dairy products and antacids containing those elements interfere in the same way. [1]
2. Question: Why are tetracyclines avoided in young children and pregnancy?
2. Answer: They deposit in developing teeth and bone, causing permanent yellow-brown tooth discolouration and impaired bone growth. In pregnancy there is also a risk of maternal hepatotoxicity and fetal tooth discolouration. [1]
3. Question: Are tetracyclines safe while breastfeeding?
3. Answer: They are considered safe during breastfeeding, because calcium chelation in milk limits how much reaches the infant - the same chemistry that causes the absorption problem works in the infant's favour here. [1]
4. Question: Which tetracycline is most associated with liver injury?
4. Answer: Minocycline. It carries the highest risk in the class and ranks within the ten most common causes of drug-induced liver injury in the United States, typically with prolonged latency and autoimmune features. [2]
5. Question: Why are tetracyclines used for acne and rosacea?
5. Answer: Alongside their antibacterial action they have anti-inflammatory and immunomodulatory effects, which is what makes them useful in inflammatory skin conditions and in some non-infectious indications. [1][3]

References

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