

Appropriate use of tetracyclines



What are tetracyclines and how do they work?

Tetracyclines are broad spectrum antibiotics which are active against a number of microbes including; chlamydiae, mycoplasmas, rickettsiae, mycobacteria, spirochetes, many aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria and some protozoa.¹

Tetracyclines were first discovered in the 1950s (first generation), and newer agents were introduced in the late 1960s with a longer half-life (second generation). Recently third generation agents have been developed, such as tigecycline which is used intravenously for difficult to treat infections in the hospital setting.

There are two second generation tetracycline antibiotics available on the Pharmaceutical Schedule in New Zealand – doxycycline (fully subsidised) and minocycline (partially subsidised). Other tetracyclines include lymecycline (not subsidised) and demeclocycline (only available under Section 29).²

Tetracyclines are taken up into bacterial cells by an active transport process. Once within the cell they bind reversibly to ribosomes and inhibit protein synthesis, and therefore impair cell growth.¹

Which infections should tetracyclines be used for?

Tetracyclines are used to treat a variety of infections including chest, urethral, pelvic and skin infections. They are often used in combination with other antibiotics.

First-line indications for tetracyclines

Community acquired pneumonia – suspected atypical infection



Amoxicillin 500 mg – 1000 mg, three times daily, for seven days **plus** erythromycin 400 mg, four times daily (or 800 mg, twice daily), for seven days **or** roxithromycin 150 mg, twice daily (or 300 mg once daily), for seven days **or** doxycycline 100 mg, twice daily, for the first day, then 100 mg, once daily, for six days.


Table 1: Common first-line indications for tetracyclines

Infection	First-line treatment
Suspected atypical pneumonia (adult)	Amoxicillin 500 mg – 1000 mg, three times daily, for seven days plus erythromycin, roxithromycin or doxycycline .
Pelvic inflammatory disease	Ceftriaxone 250 mg IM stat and Doxycycline 100 mg, twice daily, for two weeks and Metronidazole 400 mg, twice daily, for two weeks
Epididymo-orchitis (if STI pathogens suspected, usually males < 35 years)	Ceftriaxone 250 mg, IM stat and Doxycycline 100 mg, twice daily, for at least two weeks
Acne (moderate severity)	Doxycycline 100 mg, daily (or alternate days), for four to six months
Rosacea (moderate severity)	Doxycycline 50 mg, daily, for six to twelve weeks.
Specific infections including Q fever, Lyme disease and anthrax exposure .	These infections occur rarely in New Zealand. Consider in people who have recently travelled from an endemic area and in those who have handled animals such as sheep and goats or been bitten by ticks.


 For further information see “Antibiotic choices for common infections”, bpac^{nz} (Apr, 2011).

Amoxicillin is the first-line treatment for community-acquired pneumonia. Erythromycin, roxithromycin or doxycycline should be added to the treatment regimen for suspected atypical infections, or if the patient has not improved within 24 – 48 hours. This is to cover atypical respiratory pathogens including *C. pneumoniae*, *M. pneumoniae*, *C. psittaci*, and *Legionella pneumophila*.

Due to the high rate of tetracycline resistance among *S. pneumoniae* and *Haemophilus influenzae*, doxycycline is not used first-line as monotherapy for community acquired pneumonia unless the patient is allergic to penicillin (erythromycin or roxithromycin are also alternatives to amoxicillin).³

 For further information see: “The management of community-acquired pneumonia”, BPJ 45 (Aug, 2012)

Pelvic inflammatory disease


 Ceftriaxone 250 mg IM stat, **plus** doxycycline 100 mg twice daily, for two weeks, **plus** metronidazole 400 mg twice daily, for two weeks

Pelvic inflammatory disease is a polymicrobial infection, which, if left untreated, can result in serious consequences such as ectopic pregnancy and infertility. Testing should be carried out for chlamydia, gonorrhoea and trichomonas and consider a pregnancy test, full blood count and CRP. A broad-spectrum treatment regimen is indicated to cover *Neisseria gonorrhoea*, *Chlamydia trachomatis* and anaerobes.

Azithromycin 1 g stat, repeated in seven days (i.e. two doses in total) may be used instead of doxycycline in this treatment regimen, if chlamydia is present and compliance is an issue.⁴

N.B. Ceftriaxone is subsidised if prescribed for the treatment of confirmed ciprofloxacin-resistant gonorrhoea, and the prescription or MPSO is endorsed accordingly


Epididymo-orchitis

 Ceftriaxone 250 mg IM stat **plus** doxycycline 100 mg, twice daily, for at least two weeks

Epididymo-orchitis is an inflammation of the epididymis and/or testis. It is usually due to infection, most commonly from a urine tract or sexually transmitted infection. Doxycycline is included in the antibiotic regimen when sexually transmitted pathogens are suspected. Most guidelines recommend this regimen in males aged less than 35 years.⁵ Tests for *Chlamydia trachomatis* and *Neisseria gonorrhoea* should also be requested.

If urinary tract pathogens are suspected (e.g. in males aged over 35 years), an appropriate treatment regimen is amoxicillin + clavulanic acid 500/125 mg, three times daily, for two to three weeks or ciprofloxacin 500 mg, twice daily, for 10 – 14 days.⁵

Acne vulgaris – moderate severity


 Doxycycline 100 mg, daily, for four to six months

Oral antibiotics may be trialled in people aged over 12 years with moderate acne and when acne has not improved with topical treatment alone. Tetracycline antibiotics such as doxycycline are usually the first-line choice. They inhibit the growth of *Propionibacterium acnes* and also have a direct anti-inflammatory effect.


It is recommended that doxycycline is used in combination with a topical retinoid or benzoyl peroxide. It can be prescribed for four to six months and tapered, e.g. used alternate days, and discontinued once acne improves.

Minocycline (partly subsidised) may be considered second-line, but it is associated with rare adverse effects such as blue-gray pigmentation of the skin, hepatic dysfunction and, in very rare cases, systemic lupus erythematosus (Page 20).² If minocycline is used for longer than six months, liver function tests should be requested every three months.

Tetracyclines should not be used with oral retinoids, e.g. isotretinoin, as this may increase the risk of idiopathic intracranial hypertension (Page 20).²

 For further information see: “How to treat acne”, BPJ 20 (Apr, 2009)

Rosacea – moderate severity

 Doxycycline 50 mg, once or twice daily, for six to 12 weeks

N.B. Doxycycline 50 mg tablets are subject to a part-charge

Rosacea is a chronic facial rash, which most commonly affects people with fair skin, aged 30 – 60 years. It may be transient, recurrent or persistent, and may be aggravated by facial creams or oils, topical steroids and by alcohol.⁶

For mild cases of rosacea, metronidazole cream or gel is first-line treatment, used intermittently or long-term. For more severe cases, topical metronidazole may be used in combination with oral antibiotics.⁶ Azelaic acid cream or lotion is an alternative to topical metronidazole.⁶

Tetracycline antibiotics reduce inflammation, papules, pustules and eye symptoms of rosacea, therefore doxycycline is the first-line oral antibiotic choice. The dose and duration of treatment is dependent on the severity of the symptoms. Repeat courses are often required as antibiotics suppress the symptoms, rather than cure them.⁶ Low dose, oral isotretinoin is an alternative to doxycycline if it is ineffective or not tolerated.⁶ N.B. Oral isotretinoin and doxycycline should not be used concurrently (Page 21).²




Second-line indications for tetracyclines

Tetracyclines may be used as a second-line alternative in the treatment of many infections (Table 2). However, emergence of bacterial resistance and the development of other antibacterials have limited their use in recent years.

Malaria prophylaxis

Doxycycline is commonly prescribed to travellers for malaria prophylaxis, depending on susceptibility in the region(s) visited. Doxycycline 100 mg daily (2 mg/kg per day in children

aged over 12 years, weighing less than 50 kg) should be commenced two days before entering and continued until four weeks after leaving the malarial area.

 WHO publishes annually updated information on malaria, its geographical distribution and recommended preventive measures: www.who.int/malaria/travellers/en



 For further information see: "Providing medical advice to travellers", BPJ 41 (Dec, 2011)

Table 2: Common second-line indications for tetracyclines

	First Line treatment	Second line treatment
Chlamydia	Azithromycin 1 g stat	Doxycycline 100 mg, twice daily, for seven days
Acute non-specific urethritis	Azithromycin 1 g stat If purulent discharge, treat as for gonorrhoea, i.e. ceftriaxone 250 mg IM stat and azithromycin 1g stat	Doxycycline 100 mg, twice daily, for seven days
Acute exacerbation of chronic bronchitis or COPD	Amoxicillin 500 mg, three times daily, for five days	Doxycycline 100 mg, twice daily, for five days
Acute sinusitis (only if antibiotic indicated)	Amoxicillin 500 mg, three times daily, for seven days	Doxycycline , co-trimoxazole or cefaclor
Bites and clenched fist infections	Amoxicillin clavulanate 500/125 mg, three times daily, for five to ten days	Metronidazole plus either doxycycline or co-trimoxazole

 For further information see:

"Antibiotic choices for common infections", bpac^{nz} (Apr, 2011).

"Treatment of sexually transmitted and other genital infections", BPJ 20 (Apr, 2009).

Prescribing notes for tetracyclines

Advice to patients taking doxycycline

- Take with a full glass of water and avoid lying down for at least one hour to reduce risk of oesophageal irritation
- Take with food to reduce gastrointestinal adverse effects
- Avoid sun exposure, wear protective clothing and use sunscreen due to the risk of photosensitivity
- Do not take antacids, iron, calcium or zinc supplements within two hours of taking doxycycline as they may decrease effectiveness

Adverse effects associated with tetracyclines

Tetracyclines are generally safe and their most common adverse effects relate to gastrointestinal symptoms.

Gastrointestinal adverse effects are common, especially with high doses, and are mostly attributed to irritation of the mucosa. They include nausea, vomiting and diarrhoea. Oesophageal ulceration has been reported, particularly after a dose is taken with insufficient water or at bedtime.¹

Photosensitivity may occur, depending on the tetracycline dose and degree of sun exposure. Symptoms include exaggerated sunburn and itching within minutes to hours of sun exposure. In most cases, symptoms resolve within days (provided no further sun exposure occurs). In severe cases, vesicles and bullae may develop, resulting in hyperpigmentation of the skin, which may take weeks to months to resolve. Studies have demonstrated phototoxic reaction rates of 3%, 20% and 42%, for doses of 100, 150 and 200 mg of doxycycline respectively.⁷ The use of broad-spectrum sunscreen (UV-A + UV-B) can minimise or prevent the potential effects of a phototoxic reaction.

Autoimmune adverse effects are very rarely associated with minocycline, such as systemic lupus erythematosus, autoimmune hepatitis, serum sickness and vasculitis, with or without the development of antinuclear antibodies or other autoantibodies. Symptoms may be expressed as fever, malaise, loss of appetite, rash, arthralgia or myalgia. Most cases occur in young females being treated for acne (i.e. long-term use).¹ Minocycline is also very rarely associated with blue-grey pigmentation of the skin, which may be irreversible.

Idiopathic intracranial hypertension with headache, dizziness, visual disturbances and papilloedema has been reported in people using tetracyclines long-term. Symptoms can develop from within two weeks to one year or more of starting a tetracycline.¹

Renal and hepatic impairment

Both doxycycline and minocycline can be used with caution in people with renal impairment, however, high doses should be avoided.² All tetracyclines should be avoided or used with caution in patients with hepatic impairment.²

Avoid tetracyclines in children

Tetracyclines are contraindicated in children aged under 12 years, as they are associated with impaired bone growth and permanent discoloration of teeth and enamel hypoplasia.² This is because tetracyclines bind to calcium molecules and are deposited in calcifying areas in bone, nails and teeth.¹

Avoid tetracyclines during pregnancy and breast feeding

Tetracyclines are contraindicated in women who are pregnant or breast feeding.²


Doxycycline and minocycline are classified as pregnancy category D.* Effects on skeletal development of the embryo during the first-trimester have been documented in animal studies. Administration during the second or third trimester may cause discoloration of the child's teeth.² Large parenteral doses of tetracyclines have been associated with acute fatty necrosis of the liver in pregnant women, especially those with pyelonephritis.^{2,8}

Chelation with calcium in breast milk is likely to reduce the adverse effects (i.e. tooth discoloration) of tetracyclines in an infant who is breast feeding, however, they still should not be used in women who are breast feeding.²

* **Category D:** Drugs that have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Common medicine interactions with tetracyclines²

Interacts with:	Notes:
Isotretinoin	Avoid: Increases risk of intracranial hypertension
Acitretin	Avoid: Increases risk of intracranial hypertension
Antacids containing aluminum or magnesium	Adjust: reduces efficacy of tetracyclines; separate antacid and tetracycline doses by two to three hours (or use an H ₂ -receptor antagonist)
Calcium	Adjust: reduces efficacy of tetracyclines; separate calcium and tetracycline doses by two to three hours
Iron	Adjust: reduces absorption of tetracyclines and may reduce absorption of iron; give iron three hours before or two to three hours after tetracycline
Zinc (oral)	Adjust: reduces absorption of tetracyclines; give zinc three hours before or two to three hours after tetracycline
Quinapril	Adjust: reduces absorption of tetracyclines (effect may be less with doxycycline); separate quinapril and tetracycline doses by two to three hours
Carbamazepine	Adjust: reduced serum levels of doxycycline in patients using carbamazepine long-term; consider doubling dose of doxycycline
Phenytoin	Adjust: reduced serum levels of doxycycline in patients using phenytoin long-term; consider doubling dose of doxycycline
Warfarin	Monitor: may increase effect of warfarin, monitor coagulation within three days of commencing tetracycline

 For further information see New Zealand Formulary. Available from: www.nzf.org.nz

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References

1. Sweetman S, editor. The complete drug reference. London: Pharmaceutical Press, 2011.
2. New Zealand Formulary (NZF). NZF v4. NZF, 2012. Available from: www.nzf.org.nz (Accessed Oct, 2012).
3. Grayson M. Kucers' the use of antibiotics. 6th ed. Credo; 2010. Available from: www.medicinescomplete.com (Accessed Sep, 2012).
4. New Zealand Sexual Health Society (NZSHS). Pelvic inflammatory disease (PID). Treatment guidelines. NZSHS, 2012. Available from: www.nzshs.org (Accessed Sep, 2012).
5. New Zealand Sexual Health Society (NZSHS). Epidymo-orchitis. Treatment guidelines. NZSHS, 2009. Available from: www.nzshs.org (Accessed Sep, 2012).
6. DermNet NZ. Rosacea. New Zealand Dermatological Society Inc, 2012. Available from: www.dermnetnz.org (Accessed Sep, 2012).
7. Drucker AM, Rosen CF. Drug-Induced Photosensitivity: Culprit Drugs, Management and Prevention. *Drug Saf* 2011;34(10):821-37.
8. Mylan New Zealand Ltd. Doxine. Medicine datasheet. 2012. Available from: www.medsafe.govt.nz (Accessed Sep, 2012).