

Appropriate use of **metronidazole**

How does metronidazole work?

Metronidazole is a core antibiotic for the treatment of anaerobic infections. Its mechanism of action is not entirely clear, but it is thought that the active metabolite interferes with DNA synthesis.¹

Metronidazole is active against most anaerobic protozoa including *Giardia lamblia*, *Trichomonas vaginalis*, *Entamoeba histolytica* and *Blastocystis hominis*. Gram-negative anaerobic bacteria, such as those belonging to the *Bacteroides fragilis* group and Gram-positive anaerobic bacteria such as *Peptostreptococcus* and *Clostridium* species, are also usually sensitive to metronidazole.²

Despite extensive use worldwide, acquired resistance to metronidazole among anaerobic bacteria is rare.³

However, *Propionibacterium propionica* and approximately 70 – 75% of *Actinomyces* species are resistant to metronidazole.

Anaerobic infections are usually treated empirically, without susceptibility testing. Studies carried out in New Zealand have shown that anaerobic bacteria are still mostly susceptible to metronidazole and it remains a good empirical choice for suspected anaerobic infections.^{4,5}

Which infections should metronidazole be used for?

Indications for the use of metronidazole include; bacterial vaginosis, trichomoniasis, pelvic inflammatory disease (PID), giardiasis and *Clostridium difficile* infection. Metronidazole is an alternative to amoxicillin for the treatment of some oral infections. Table 1 lists first and second-line indications for metronidazole.

Table 1: First and second line indications for metronidazole

Infection	First-line	Second-line
Bacterial vaginosis	Metronidazole	–
Trichomoniasis	Metronidazole	–
Pelvic inflammatory disease	Metronidazole + ceftriaxone + doxycycline	Azithromycin (instead of doxycycline)
Giardiasis	Metronidazole or ornidazole	–
<i>Clostridium difficile</i>	Metronidazole	Vancomycin (hospital treatment)
Tooth abscess	Metronidazole or amoxicillin	–
Bites	Amoxicillin clavulanate	Metronidazole + doxycycline or co-trimoxazole
Diabetic foot infection	Amoxicillin clavulanate	Cefaclor or metronidazole + co-trimoxazole
<i>H. pylori</i>	Amoxicillin + clarithromycin + omeprazole	Metronidazole + clarithromycin + omeprazole

NB. Use of amoxicillin clavulanate and metronidazole together is unnecessary

 For further information see “Antibiotic choices for common infections”, available from: www.bpac.org.nz

First line indications for metronidazole

Bacterial vaginosis

-  Metronidazole 400 mg, twice daily, for seven days OR a single dose of metronidazole 2 g (5 x 400 mg tablets)

Bacterial vaginosis results from the replacement of normal vaginal flora by anaerobic bacteria such as *Gardnerella*, *Bacteroides* and *Mobilunculus* species. A seven day course of metronidazole is now favoured as it is more effective than the single dose regimen for resolving symptoms, although compliance may be an issue. One study found that symptoms had resolved in 62% of women three to four weeks after the single-dose course and in 82% after the seven day course.⁶ The seven day course is more appropriate for pregnant women because single dose regimens may result in higher serum concentrations, which can reach the foetal circulation.⁷ The seven day course of metronidazole is also recommended in women who are breast feeding to reduce the concentration in the breast milk. Treating the male sexual partner of a woman with bacterial vaginosis is unnecessary because there is no evidence that it reduces the risk of relapse.⁷

Ornidazole has similar antimicrobial activities to metronidazole and is an effective alternative in the treatment of bacterial vaginosis. It is administered as a single dose of 1.5 g or 500 mg, twice daily, for five days. Unlike metronidazole, ornidazole does not interact with alcohol (Page 42), but it does potentiate the effect of warfarin.⁸

Trichomoniasis

-  Metronidazole 400 mg, twice daily, for seven days or a single dose of metronidazole 2 g (5 x 400 mg tablets)

Trichomoniasis is a sexually transmitted infection caused by *Trichomonas vaginalis*. Metronidazole is active against this pathogen. The seven day treatment course is preferable. Single high dose metronidazole may improve compliance but it is associated with a higher rate of treatment failure and an increased risk of adverse effects, such as nausea, vomiting and a metallic taste. One review found that the cure rate in women treated with a single dose of metronidazole 2 g was 88% compared to 92% in women treated with the metronidazole for five to seven days.⁹

Sexual partners of a person with confirmed trichomoniasis should also be treated, even if asymptomatic. Culture is not required in males as it is seldom positive, even if infection is present.

Ornidazole is an effective alternative to metronidazole (see above).

Pelvic inflammatory disease

-  Ceftriaxone 250 mg IM, plus doxycycline 100 mg, twice daily and metronidazole 400 mg, twice daily, for two weeks

Sexually transmitted pathogens are frequently the initiating cause of pelvic inflammatory disease (PID), however, PID should be treated as a polymicrobial infection. Two studies found that 35% and 50% of women with gonococcal PID had a polymicrobial infection.¹⁰ Treatment should include cover for the most likely pathogens, *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and anaerobes. For this reason, the recommended treatment is ceftriaxone plus doxycycline and metronidazole. Metronidazole is included in this regimen to improve coverage for anaerobic bacteria, however, United Kingdom guidelines suggest that anaerobic bacteria are of relatively greater importance in women with severe PID so metronidazole may be stopped in women with mild or moderate PID who cannot tolerate it.¹¹

Giardiasis

-  Metronidazole 2 g, once daily, for three days or ornidazole 1.5 g, once daily, for one to two days

Giardiasis is caused by infection with the parasite *Giardia lamblia* (also known as *Giardia intestinalis*). Metronidazole or ornidazole are the recommended first-line antibiotics for giardia. The single daily dose, shorter course regimen (three days) is recommended as it improves compliance, and is as effective as longer courses.¹² If treatment fails, after excluding re-infection from asymptomatic contacts, metronidazole 400 mg three times daily for seven days can be used. Isolates of *Giardia lamblia* have been found with reduced susceptibility to metronidazole.²

Clostridium difficile infection

-  Metronidazole 400 mg, three times per day, for ten to fourteen days

C. difficile is an anaerobic Gram-positive organism that causes diarrhoea, which in some cases can be severe. *C. difficile* infection most commonly occurs after use of broad-spectrum antibiotics, but can also be associated with the use of cytotoxic medicines, e.g. methotrexate. The normal bowel flora is altered, causing overgrowth of *C. difficile* and the production of toxins.²

A new highly pathogenic strain has caused severe outbreaks of disease in the United States and United Kingdom. This has not yet been observed in New Zealand, but a surveillance system has been set up as an early warning system.

If *C. difficile* infection occurs, where possible, discontinue the antibiotics for the original indication, or use a narrower spectrum antibiotic. This may lead to resolution of symptoms. Antidiarrhoeals, e.g. loperamide, should be avoided because they slow the clearance of the *C. difficile* toxin and worsen colitis.

Metronidazole and vancomycin (hospital treatment) are effective in the treatment of *C. difficile* colitis. Metronidazole is first-line treatment for mild to moderate *C. difficile* infection.¹³ A 10 – 14 day course is recommended because, although 70% of patients respond to metronidazole in five days, 91% respond with a 14 day course.⁷ Metronidazole can be given by intravenous infusion if oral treatment is inappropriate.¹⁴ Vancomycin is reserved for severe *C. difficile* infection, for those who do not tolerate or respond to metronidazole and for cases that recur more than twice.¹⁵

Dental infection or abscess

✔ Metronidazole 400 mg, three times daily, for five days (or amoxicillin)

While acute symptoms of dental infection or abscess can be managed in general practice, most people should be referred to a dentist, in case further dental treatment such as root canal treatment or extraction is required. When signs of severe infection are present or the patient is systemically unwell, it is appropriate to prescribe metronidazole or amoxicillin.¹⁶ There is no clear guidance about which antibiotic is preferable first. It is also possible to use metronidazole and amoxicillin together for severe dental infections.¹⁷

Second line indications for metronidazole

Bites – human and animal

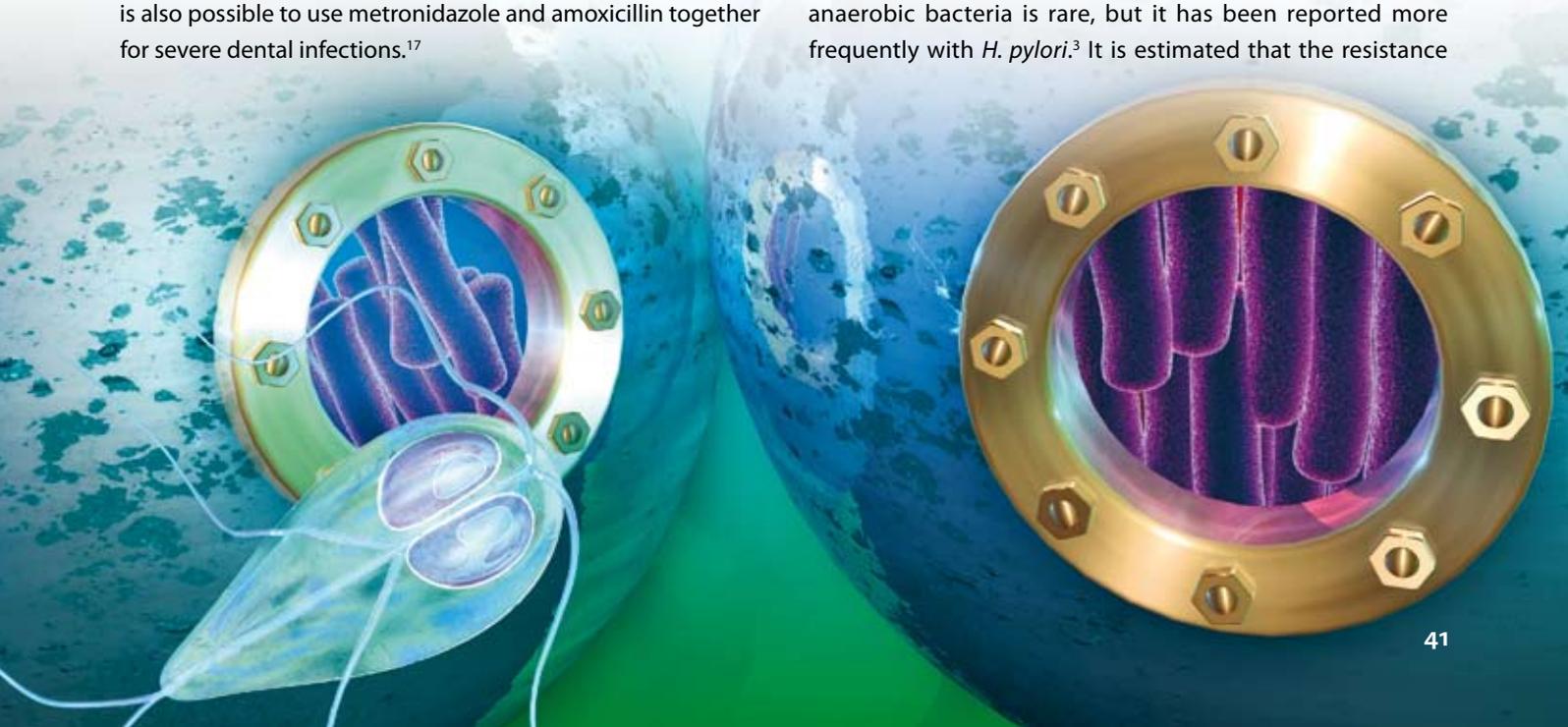
Metronidazole 200 mg to 400 mg, three times daily, plus doxycycline or cotrimoxazole is an alternative to amoxicillin clavulanate for the prophylaxis or treatment of human or animal bites in people who are allergic to penicillin. Most infections caused by bites are polymicrobial, with studies finding an average of three to four different species of bacteria per wound culture, including one anaerobe, from cat and dog bites and an average of five species of bacteria, including up to three anaerobes, for human bites.¹⁸ Metronidazole is included in the regimen to cover beta-lactamase producing anaerobes. It is recommended that patients using the metronidazole plus doxycycline or cotrimoxazole regimen are reviewed after 24 and 48 hours because these antibiotics cover most but not all of the likely pathogens from a human or animal bite.⁷

Diabetic foot infection

Metronidazole 400 mg, three times daily in combination with cotrimoxazole is an alternative to amoxicillin clavulanate for the treatment of foot infection in a patient with diabetes who is allergic to penicillin. Cefaclor is also an alternative treatment. Diabetic foot infections are most likely to be polymicrobial. A wound swab is usually not necessary, but may be considered if the infection is not resolving.

H. pylori eradication

Metronidazole is an alternative to amoxicillin in triple therapy for the eradication of *H. pylori* for patients allergic to penicillin. Triple therapy consists of a seven day course of omeprazole 20 mg, clarithromycin 250 mg and amoxicillin 1 g (or metronidazole 400 mg) all taken twice daily. Metronidazole resistance in anaerobic bacteria is rare, but it has been reported more frequently with *H. pylori*.³ It is estimated that the resistance



rate of *H. pylori* to metronidazole is 27%, however, there is considerable variation depending on location.¹⁹ Failure rates of up to 20% have been reported for triple therapy including metronidazole.²⁰

NICE guidelines suggest avoiding the use of clarithromycin or metronidazole if they have been used in the last year for any other infection because monotherapy with these antibiotics often leads to resistance.²¹

Issues associated with metronidazole

People taking metronidazole should avoid alcohol

Some people may experience adverse effects when alcohol is consumed while being treated with metronidazole. The existence of this interaction has been disputed, however, it is appropriate to advise people taking metronidazole to avoid alcohol (including products containing alcohol) during the course of treatment and for 48 hours afterwards.²²

The mechanism of the interaction between alcohol and metronidazole is not well understood but it is thought that it is due to an accumulation of acetaldehyde (such as occurs in a disulfiram reaction) and the inhibition of other enzymes related to alcohol metabolism. This causes adverse symptoms such as nausea, vomiting, flushing, headache and palpitations.

Metronidazole potentiates the effect of warfarin

Elevated INR and bleeding events have been reported with concurrent use of warfarin and metronidazole (and ornidazole). It is suggested that metronidazole inhibits the metabolism of S-warfarin, the more potent isomer of warfarin, resulting in increased serum levels of warfarin, potentially increasing its anticoagulant effects. INR should be monitored when warfarin and metronidazole are used together and the dose of warfarin adjusted if required.²² N.B. Depending on the clinical circumstances, INR monitoring may be increased for patients taking warfarin who are unwell enough to require antibiotics, regardless of the type of antibiotic used.

ACKNOWLEDGMENT: Thank you to **Dr Rosemary Ikram**, Clinical Microbiologist, Christchurch for expert guidance in developing this article.

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