

Appropriate use of

AMOXICILLIN CLAVULANATE

Why should amoxicillin clavulanate be reserved for only certain conditions?

Amoxicillin clavulanate is a broad spectrum antibiotic which is used frequently in New Zealand general practice. While amoxicillin clavulanate and other broad spectrum antibiotics (quinolones and cephalosporins) are effective, they are best avoided when other more narrow-spectrum antibiotics could be used because they increase the risk of *Clostridium difficile*, MRSA and other resistant infections.¹ Amoxicillin clavulanate has been associated with cholestatic jaundice (see opposite).² It is also commonly associated with antibiotic related diarrhoea and vaginal and oral thrush.

The use of amoxicillin clavulanate is declining in New Zealand, however, the volume of prescriptions for this medicine is still high. Between April 2008 and March 2009, the average number of amoxicillin clavulanate dispensings per General Practitioner in New Zealand was 170. In the same period in 2009/2010, this average decreased to 153.

Cholestatic jaundice with amoxicillin clavulanate

Hepatitis and cholestatic jaundice have been reported with the use of amoxicillin clavulanate. It appears that this adverse effect can occur during treatment or up to six weeks after treatment cessation. Increasing age, prolonged treatment and male gender are risk factors. Cholestatic jaundice occurs in approximately 1 in 6000 patients. Acute liver toxicity occurs in people taking amoxicillin clavulanate at six times the rate of people taking amoxicillin. As a result of this adverse effect, the United Kingdom Committee on Safety of Medicines (CSM) recommended that amoxicillin clavulanate only be used for bacterial infections that are thought to be caused by amoxicillin-resistant strains and treatment length should be suitable for the indication and not usually exceed 14 days.^{2,3}

Table 1: First and second line indications for amoxicillin clavulanate

	First-line	Second-line
Bites (mammalian – including human)	✓	
Diabetic foot infections	✓	
Periorbital/facial cellulitis	✓	
Acute pyelonephritis	<i>Ciprofloxacin</i>	✓
Sinusitis	<i>Amoxicillin</i>	✓
Pneumonia	<i>Amoxicillin</i>	✓

Preliminary data from 2010/2011 suggest that the rate of decrease is slowing, with an average of 147 dispensings for amoxicillin clavulanate per General Practitioner (data calculated from NZHIS Pharmaceutical Warehouse).

Amoxicillin clavulanate is best reserved for the few indications where it is necessary so that it remains an effective antibiotic when needed and the adverse effects associated with the use of broad spectrum antibiotics are avoided.

When is use of amoxicillin clavulanate appropriate?

First-line indications for amoxicillin clavulanate

Amoxicillin clavulanate has only a few indications where it is recommended as a first line antibiotic, e.g. mammalian bites (including human), diabetic foot infection and periorbital cellulitis. These infections require this broad spectrum antibiotic to cover the large range of potential causative organisms.

Mammalian bite treatment or prophylaxis

Amoxicillin clavulanate is appropriate for mammalian bites because it is active against the organisms most commonly isolated: e.g. alpha- and beta haemolytic streptococci, *Staphylococcus aureus*, *Staphylococcus epidermis*, *Corynebacterium species* and *Eikenella corrodens* in human bites and *Pasteurella*, streptococci, staphylococci, *Moraxella*, *Neisseria* and anaerobes in other mammalian bites.¹

All infected bites should be treated with antibiotics. Prophylactic treatment with antibiotics is appropriate for human and cat bites (even if they do not appear to be infected) and any bites that occur to the hand, foot, face, tendon or ligament, or in immunocompromised people. Consider referral to secondary care for any bites that involve the bones or joints.¹

N.B.: Injuries that occur to the fist as a result of contact with teeth are essentially treated the same as for bites.

Diabetic foot infections

Diabetic foot infections may involve staphylococci, streptococci or facultative anaerobes such as *Bacteroides species*. Early infection is usually due to *S. aureus* and/or streptococci. Later infection may be polymicrobial with a mixture of gram-positive cocci, gram-negative bacilli and anaerobes. To cover these organisms, a broad spectrum antibiotic such as amoxicillin clavulanate is appropriate as a first-line option.¹

Radiological assessment may be required to determine whether the infection involves the bones of the feet (i.e. whether there is osteomyelitis). Intravenous antibiotics will be required if this is the case.

Facial and periorbital cellulitis

Amoxicillin clavulanate is appropriate for facial and periorbital cellulitis because it covers a broader range of organisms than flucloxacillin. In the past, facial cellulitis, arising from infection in the buccal mucosa, was often a result of *H. influenzae* infection, however, this is less common now because of the *H. influenzae* type B (Hib) immunisation programme.¹

In all but very mild cases of facial cellulitis and especially periorbital cellulitis, referral to secondary care is advised.⁵

Second-line indications

There are a few indications where amoxicillin clavulanate is a suitable second-line alternative to cover persistent infection, when anaerobes are suspected (e.g. in some cases of sinusitis or when treating post viral/influenza pneumonia) or as an alternative to ciprofloxacin for acute pyelonephritis.

Acute pyelonephritis – second-line alternative to ciprofloxacin

Amoxicillin clavulanate is appropriate for second-line use in acute pyelonephritis because it has good kidney penetration and covers the broad range of pathogens that may cause acute pyelonephritis.¹ Using a broad spectrum antibiotic such as amoxicillin clavulanate reduces the

risk of treatment failure and the potential for serious complications.

It is only appropriate to manage a patient with pyelonephritis as an outpatient if they have mild symptoms, e.g. low fever and no nausea or vomiting. Patients should be referred to secondary care for intravenous antibiotics if they are systemically unwell or vomiting.

Sinusitis – after failure of first-line antibiotics

Most cases of sinusitis are viral or resolve spontaneously (80% resolve spontaneously without antibiotics in 14 days).¹ Patients can be advised that it is common for symptoms of sinusitis to continue for approximately two weeks.⁶ Antibiotics should only be considered if symptoms have been present for five to seven days in conjunction with fever or unilateral maxillary sinus tenderness, severe headache or worsening symptoms after initial improvement.

While acute sinusitis rarely involves anaerobes, they are more likely to be the cause of chronic infections.¹ If first-line antibiotics have been tried and were ineffective, check compliance and then consider second-line options such as amoxicillin clavulanate.⁷ Amoxicillin clavulanate is

appropriate as a second-line choice for persistent sinusitis because it has good activity against anaerobes and also *H. influenzae*, *Streptococcus pneumoniae* and *M. catarrhalis*, which are commonly associated with sinusitis.⁸

Pneumonia – when anaerobes are suspected

Amoxicillin clavulanate is appropriate for post viral/ influenza pneumonia where *S. aureus* is often implicated. It is also appropriate in aspiration pneumonia to cover anaerobes.

Patients with mild pneumonia are able to be managed at home, however, hospital admission should be considered for patients with two or more of the following features; age > 65 years, confusion, respiratory rate > 30/min, diastolic blood pressure < 60 mm Hg. Patients with these features have an increased risk of mortality.⁹

Mastitis in non-lactating women

S. aureus is usually the cause of mastitis in lactating women, and therefore flucloxacillin is the first-line antibiotic treatment. However, anaerobes are the most common pathogen implicated in non-puerperal mastitis, particularly in sub-areolar infections.⁵ Therefore it is appropriate to use amoxicillin clavulanate to treat mastitis in non-lactating women.

How does amoxicillin clavulanate work?

Amoxicillin clavulanate is a combination of the antibacterial agent amoxicillin and clavulanic acid. Clavulanic acid has minimal antibacterial action but is a potent inhibitor of beta-lactamase produced by some bacteria, including, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and some Enterobacteriaceae.³ It is also effective against a wide variety of anaerobes. In particular, clavulanic acid has good activity against plasmid mediated beta-lactamases which are often associated with transferred drug resistance.⁴ The combination of

amoxicillin and clavulanic acid prevents amoxicillin from being degraded by beta-lactamases therefore extending its spectrum of activity to include organisms which would normally be resistant to amoxicillin alone.

Clavulanic acid is generally less active against chromosomally-mediated beta-lactamases therefore organisms with these beta-lactamases such as *Enterobacter spp.* and *Pseudomonas aeruginosa* are resistant.³

Antibiotics for upper respiratory tract infections

(adapted from NICE, 2008)⁶

Antibiotics, including amoxicillin clavulanate, are often prescribed unnecessarily for self-limiting viral respiratory tract infections. Clinicians should avoid prescribing, or provide a delayed prescription, for patients with conditions such as acute otitis media, acute sore throat (unless high risk for rheumatic fever), common cold, acute rhinosinusitis and acute cough/acute bronchitis. The following groups of patients may be suitable for an immediate antibiotic prescription, depending on the severity of the condition and patient/carer preference:

- Children aged under two years with bilateral acute otitis media
- Children with acute otitis media with otorrhoea (discharge)


- Anyone with acute sore throat/acute tonsillitis when three or four red flags (see box) are present.

When patients are not given a prescription or are offered a delayed prescription, they should be reassured that antibiotics are not indicated and that they have little effect on the condition (i.e. length of illness and symptoms) and may cause adverse effects such as diarrhoea, vomiting and rash. Patients should be advised to come back if the condition worsens or becomes prolonged. Patients provided with a delayed prescription should be advised about when to use it, such as if symptoms do not settle in the expected time course of the illness or if a significant worsening of the illness occurs.

Red flags for sore throat:

- Temperature > 38 degrees celsius
- No cough or coryza (which may suggest a viral cause)
- Swollen anterior cervical lymph nodes
- Tonsillar swelling or exudate

All children presenting with sore throat who are of Pacific or Maori ethnicity, aged three years and over and who live in areas with high incidence of rheumatic fever (i.e. low socioeconomic areas of the North Island), should have a throat swab taken and should be prescribed empirical antibiotics (penicillin V [phenoxymethylpenicillin] or amoxicillin) if they have ANY of the red flags.

 See “Rheumatic Fever in Maori: What can we do better?” BPJ 37 (Aug, 2011).

All patients, whether they are provided a prescription or not, can be advised of the likely natural history of the illness, especially the average total length of time of an illness:⁶

- Acute otitis media: four days
- Acute sore throat/acute pharyngitis/acute tonsillitis: one week
- Common cold: seven to ten days
- Acute sinusitis: two weeks
- Acute cough/acute bronchitis: three weeks

It is appropriate for some patients to be provided with a prescription initially because they may be at greater risk of complications. These patients include:

- Those systemically very unwell
- Those with symptoms or signs of serious illness and/or complications
- Those with comorbidity that puts them at increased risk of serious complications, e.g. patients with significant heart, lung, liver or renal disease or those who are immunosuppressed
- Patients older than 65 years with acute cough and **two** or more of the following criteria, or patients older than 80 years with acute cough and **one** or more of the following criteria:
 - Hospitalisation in the previous year
 - Type 1 or type 2 diabetes
 - History of congestive heart failure
 - Current use of oral glucocorticoids

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