

Amoxicillin/clavulanate

A broad spectrum antimicrobial – overuse carries substantial risks for the community and the patient

- Amoxicillin/clavulanate is a broad spectrum antimicrobial that is overused. In the 2012/2013 financial year, CDHB used ≈42,000 vials for injection and 52,000 tablets. This is three times the volume of amoxicillin used.
- Compared with amoxicillin, amoxicillin/clavulanate is more likely to cause cholestatic jaundice, *C. difficile* associated infections and antimicrobial resistance.
- The UK Centre on Safety of Medicines advised that amoxicillin/clavulanate should only be used for infections thought to be due to amoxicillin resistant strains and that treatment length should match the indication (usually < 14 days).
- This bulletin outlines some of the indications for which amoxicillin/clavulanate is appropriate (**pink box**) and inappropriate (**purple box**), and highlights key complications that may result from its use (**blue box**).

When is amoxicillin/clavulanate appropriate?

Clavulanic acid is a β -lactamase inhibitor that extends the spectrum of amoxicillin by inhibiting its degradation by some enzyme producing bacteria such as *H. influenzae*, *S. aureus* and *B. fragilis*. It also inhibits most of the β -lactamases found in *E. coli* and *Klebsiella* species.

For **empiric** treatment, amoxicillin/clavulanate is reserved for situations when there is a high probability of β -lactamase producing organisms being present. A narrower spectrum agent should be used when susceptibility testing supports it. Examples of appropriate uses of amoxicillin/clavulanate for **empiric** treatment are (**page in the Pink Book, 2014**):

- Uncomplicated lower UTIs (p116)**. If trimethoprim and nitrofurantoin are not appropriate, amoxicillin/clavulanate should be used in preference to amoxicillin due to greater susceptibility of *E. coli* (83% vs 53%, respectively). Use amoxicillin alone if cultures prove susceptibility.
- Bites-animal and human (p141)**. These are usually polymicrobial and include β -lactamase producing anaerobes and *S. aureus*.
- Cellulitis-complicated/ulcers (p144)**. Chronic infections are often polymicrobial and may require amoxicillin/clavulanate to cover Gram-positive, Gram-negative and anaerobic organisms. However, acute infections in patients without recent antimicrobial exposure are usually due to *S. aureus* and streptococci so a narrow spectrum antistaphylococcal drug like flucloxacillin is usually suitable.
- Severe community acquired pneumonia (CAP) (p124)**. We recommend amoxicillin/clavulanate plus macrolide for severe disease (CURB-age 3-4) whereas for milder disease (CURB-age 0-2) amoxicillin or macrolide monotherapy is advised. For severe CAP, the immediate benefits (reduced mortality) of broader coverage for the individual patient outweigh the risks (**blue box**).
- Abdominal sepsis**. As an oral step-down from iv therapy.
- Other indications** – consult the **Pink Book, 2014**.

Examples of **inappropriate** indications for amoxicillin/clavulanate

- Empiric treatment of COPD (**p121**).
- Empiric treatment of mild to moderate CAP (**p124**).
- Amoxicillin sensitive urinary tract infections (**p116**).

Adverse effects

Compared with amoxicillin, amoxicillin/clavulanate has a greater risk of causing:

- Diarrhoea
- C. difficile* infection
- Thrush – vaginal, oral
- Antimicrobial resistance
- Cholestatic jaundice

Diarrhoea affects 5-39% of patients treated with antimicrobials. Amoxicillin/clavulanate causes diarrhoea twice as frequently as amoxicillin. It causes significant morbidity, and increases treatment costs and hospital stay.

C. difficile causes 10-20% of all antimicrobial associated diarrhoea, and is more likely with broader spectrum agents like amoxicillin/clavulanate. When hospitals decrease the use of broad spectrum antimicrobials, *C. difficile* infection rates fall dramatically.

Thrush is more likely to occur with broad spectrum agents.

Resistance. Amoxicillin/clavulanate promotes resistance by encouraging selection of non-sensitive species.

Cholestatic jaundice/hepatitis is six times more likely with amoxicillin/clavulanate than amoxicillin alone, and may be fatal. It affects one in 6000 patients treated. Liver injury may occur during treatment or up to 6 weeks after cessation. Risk factors include old age, male gender and long courses.

- To minimise risk for patients and the community, prescribers should avoid amoxicillin/clavulanate unless clearly indicated. Use antimicrobial guidelines in the Pink Book, 2014.
- Change to a narrower spectrum agent (eg. amoxicillin) if susceptibility testing supports this.
- If in doubt, consult with Infectious Diseases/Microbiology.