

Amoxicillin/Clavulanate Review

Background: Clavulanate potassium (clavulanic acid) is a β -lactamase inhibitor with little intrinsic antibacterial activity as a single agent but combined with antibiotics such as amoxicillin which have a beta-lactam ring in their structure it expands the spectrum of activity of the antibiotic. The combination of amoxicillin and clavulanate potassium (A/C) is active against most β -lactamase producing *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, methicillin-susceptible *Staphylococcus aureus* and certain β -lactamase producing *Enterobacteriaceae*.^{1,2} In addition, clavulanate has a synergistic effect with β -lactam antibiotics against certain non β -lactamase producing bacteria. In combination with high dose amoxicillin it is effective for moderately penicillin-resistant *Streptococcus pneumoniae* infections.³

Indications: Health Canada-approved indications for A/C are sinusitis, otitis media, lower respiratory tract infections, skin and soft tissue infections, bite wounds and urinary tract infections.⁴ Note that A/C is second line to amoxicillin alone for many of the above conditions.

Product selection: Table 1 contains a list of the A/C products marketed in Canada.^{4,5} Dosing is based on and expressed as the amoxicillin content; however the ratio of amoxicillin to clavulanate varies between products. It is important to consider the ratio because using a product with the incorrect ratio could result in subtherapeutic clavulanic acid (compromising antibacterial effectiveness) or increased gastrointestinal (GI) adverse effects (risk of clavulanate-associated GI effects is dose dependent).^{6,7}

Table 1: Amoxicillin/clavulanate formulations available in Canada^{4,5}:

Products	Ratio	Dosing Interval	Amoxicillin	Clavulanate
Powders for Suspension				
125 F*	4:1	Every 8 hours (q8h)	125 mg / 5 ml	31.25 mg / 5 ml
250 F*			250 mg / 5 ml	62.5 mg / 5 ml
200	7:1	Every 12 hours (q12h)	200 mg / 5 ml	28.5 mg / 5 ml
400			400 mg / 5 ml	57 mg / 5 ml
Tablets				
250	2:1	Every 8 hours	250 mg / tablet	125 mg / tablet
500	4:1	(q8h)	500 mg / tablet	125 mg / tablet
875	7:1	Every 12 hours (q12h)	875 mg / tablet	125 mg / tablet

* Indicates the ratio of amoxicillin to clavulanate is "F"our to one.

Irrespective of amoxicillin dose, 125 mg of clavulanate per dose is sufficient to inhibit β -lactamases in adults.⁸ This extrapolates to approximately 3.5 mg/kg/dose in children < 35 kg. It is recommended not to exceed 10 mg /kg/day.⁹ Because of the varying ratio of amoxicillin to clavulanate (See Table 1), many products are not interchangeable. For example, both the 250 mg and 500 mg tablets contain 125 mg of clavulanate, so taking two 250 mg tablets together to make up a 500 mg amoxicillin dose would result in the dose of clavulanate being doubled (250 mg) and unnecessarily increase the risk of adverse effects.⁴

Dose recommendations: For mild to moderate infections, the recommended dose of A/C is 250 mg q8h or 500 mg q12h (20 to 25 mg/kg/day divided into 2 or 3 doses for children \leq 38/kg).⁴ For more severe infections and infections of the respiratory tract, the usual adult oral dosage is one 500 mg tablet q8h or one 875 mg tablet q12h (40 to 50 mg/kg /day in 2 or 3 doses for children \leq 38 kg; adult dose for children $>$ 38 kg).⁴ The 7:1 ratio oral suspension (A/C 200 or 400 mg) administered q12h is preferred at higher doses to minimize diarrhea risk.⁴ See Table 2 in online version at www.medsask.usask.ca for detailed dosing recommendations.

High-dose A/C (75 to 90mg/kg/day) is recommended if respiratory tract infections such as otitis media fail to respond to high dose amoxicillin within two to three days.⁸⁻¹⁰ At high doses, the available AC oral suspensions exceed the recommended limits for clavulanate doses increasing the risk of adverse effects. A 14:1 ratio AC formulation (Augmentin ES-600) has proven efficacy¹¹ but is not marketed in Canada. (It is available in the United States.) The preferred option in this situation is to divide the prescription into two parts, dispensing one-half as A/C 7:1 and one-half as amoxicillin.⁸⁻¹⁰ (See example prescription in side bar.) The total daily dose can be divided into two or three doses but twice daily administration (q12h) is preferred as it is equally effective, reduces the incidence of diarrhea and is more convenient.⁷ Alternatively, the entire prescription could be dispensed as A/C 7:1 but this option is more likely to cause diarrhea.¹¹

Example: Rx for amoxicillin/clavulanate 90mg/kg/day for a 30 kg child X 10 days

To minimize risk of side effects, dispense two products:

- 1) 45mg/kg/day A/C 7:1 suspension
- 2) 45mg/kg/day amoxicillin suspension

1. Daily dose A/C 7:1 = 45mg x 30 kg = 1350 mg
 - Using A/C 400/5 ml = daily dose 16.87 ml =
 - **8.5 ml q12h** or 5.5 ml q8h
 - **Dispense 200 ml of AC 400/5 ml**
2. Daily dose amoxicillin = 45mg x 30 kg = 1350 mg
 - Using amoxicillin 250 mg/5 ml = 27 ml/ day =
 - **13.5 ml q12h** or 9 ml q8h
 - **Dispense 300 ml of amoxicillin 250mg/5 ml**

Adverse Effects: Nausea, vomiting, and/or diarrhea are the most common adverse effects seen with A/C (up to 25% with 4:1 ratio).⁶ Diarrhea is more like to occur with A/C products than single ingredient amoxicillin (number needed to harm = 10).¹³ The mechanism responsible for this is largely unknown, although in one small study A/C was associated with a prokinetic effect.¹⁴ It is recommended to take A/C with food to reduce the risk of GI adverse effects and to enhance drug absorption.⁶

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References available in the on-line version of the newsletter (www.medsask.usask.ca)

Table 2: Recommended Doses of Amoxicillin-Clavulanate (A/C) by Age and Severity of Infection ^{4,6,7,10,12}

Age +/ or Weight (Full-term neonates and older)	Dosage range for mild to moderate infections (amoxicillin component)	Options for required dosage	High dosage range for more severe infections (amoxicillin component)	Options for required dose
<12 weeks	30mg/kg/day divided every 12 hours(q12h) Dosage is based on incompletely developed renal function affecting elimination of amoxicillin in	The 125mg/5 mL oral suspension is recommended. (4:1 A/C) There is limited experience with the 200mg/5ml oral suspension	Not applicable in this age group	Not applicable in this age group
12 weeks and older, ≤ 38kg	20mg/kg/day (q8h)	125mg/5ml – 250mg/5ml oral suspension (4:1 A/C)	40mg/kg/day (q8h)	125mg/5ml – 250mg/5ml oral suspension (4:1 A/C)
	25mg/kg/day (q12h)	200mg/5ml – 400mg/5ml oral suspension (7:1 amoxi/clav)	45 mg/kg/day (q12h) For high dose A/C. After initial treatment failure with amoxicillin alone, use 75 - 90 mg/kg/day A/C divided into 2 doses. (Not to exceed 4000 mg amoxicillin)*	200mg/5ml – 400mg/5ml oral suspension (7:1 A/C) For high dose A/C, A/C 7:1 formulation (200 mg/5 mL or 400 mg/5 mL) PLUS additional amoxicillin (e.g., for 90 mg/kg/day Rx give 45 mg/kg/day of A/C 7:1 formulation plus 45 mg/kg/day of amoxicillin).
12 weeks and older, > 38kg (Including adults)	500mg q12h OR 250mg q8h	500 mg tablet: if difficulty swallowing, use 125 mg/5 mL or 250 mg/5mL oral suspension (4:1 A/C)	875 mg q12h OR 500 mg q8h	850 mg tablet: If difficulty swallowing, use the 200 mg/5 mL or 400 mg/5 mL oral suspension (7:1 A/C) 500mg tablet: if difficulty swallowing, use the 125 mg/5 mL or 250 mg/5mL oral suspension (4:1 A/C)

*Canadian Pediatric society initiates high dose regimens at > 6 months⁹

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