Antimicrobial Stewardship Matters

Antimicrobial Stewardship | September 2025

Amoxicillin-clavulanate IV – Update

At a Glance:

- Amoxicillin-clavulanate should be used preferentially over piperacillin-tazobactam in community acquired polymicrobial infections where *Pseudomonas* spp are not involved (Table 2).
- When treating severe infections or when Gram negative coverage is required, the recommended dose is now amoxicillin 1000mg-clavulanate 200mg IV q6h (Table 1).
- Due to high oral bioavailability, oral amoxicillin-clavulanate is preferred over IV in patients with a functional gastrointestinal (GI) tract who can take oral medications.

About Amoxicillin-clavulanate

- Broad-spectrum antimicrobial that contains an aminopenicillin (amoxicillin) and a β-lactamase inhibitor (clavulanate) making it effective against some β-lactamase producing bacteria.
- Unlike piperacillin-tazobactam, amoxicillin-clavulanate has no activity against *Pseudomonas* spp and therefore exerts less selective pressure on this often multi-drug resistant organism.
- Compared to ceftriaxone and metronidazole, amoxicillin-clavulanate has a similar spectrum of activity but also has activity against ampicillin-susceptible *Enterococcus faecalis*. It is active against most clinically relevant anaerobes (see complete spectrum of activity.)
- The IV formulation is cost neutral compared to piperacillin-tazobactam at usual doses but is **more expensive** and **given more frequently** than ceftriaxone + metronidazole IV.
- Given good oral bioavailability (amoxicillin 80 per cent and clavulanate 30-98 per cent), patients can use oral amoxicillin-clavulanate if they are clinically improving, have a functional gastrointestinal tract and can take PO medications, facilitating hospital discharge. A dose of 875/125mg po BID (TID if osteomyelitis or bacteremia) of amoxicillin-clavulanate is recommended (doses should be adjusted for weight and renal function when necessary).

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Table 1. Amoxicillin-clavulanate IV Dosing

Amoxicillin-clavulanate IV	Normal Adult Dose	Dose and Interval Adjustment for Renal Impairment		
		Creatinine Clearance (mL/min)		
		30-50	10-30	<10 (Anuric, not on dialysis)
Skin & soft tissue (SSTI) and respiratory tract (RTI) infections	1000-200mg (1.2g) IV q8h	NO CHANGE NEEDED	Initial dose of 1000mg-200mg, then 500mg-100mg q12h	Initial dose of 1000mg-200mg, then 500mg-100mg q24h
All other infections	1000-200mg (1.2g) IV q6h*	NO CHANGE NEEDED	1000-200mg (1.2g) q8h	1000-200mg (1.2g) q12h

* For CrCl > 190mL/min, 1.2g IV q4h may be needed.

Table 2. When can amoxicillin-clavulanate be used instead of piperacillin-tazobactam

Infectious syndrome	Rationale for Amoxicillin-Clavulanate Use
Intra-abdominal infections [IAIs] (e.g. peritonitis, abscess, diverticulitis, appendicitis, cholangitis) (not tertiary/hospital acquired)	Amoxicillin-clavulanate has good coverage of gastrointestinal flora associated with IAIs[1]. *P. aeruginosa* is not a usual pathogen in IAI unless tertiary/hospital acquired so no need for piperacillin-tazobactam. ➢ *Use ceftriaxone + metronidazole if there is NO suspected or proven E. faecalis.* ➢ *If E. faecalis is involved, use amoxicillin-clavulanate.*
Polymicrobial skin and soft tissue infections (SSTIs) such as diabetic foot infections/ osteomyelitis where *Pseudomonas* spp are not involved.	Complicated SSTI: randomized controlled trial (RCT) data is available for the use of IV amoxicillin-clavulanate in complicated SSTIs[2]. Bone and joint infection: adequate bone penetration following a single dose in adults and clinical data in the pediatric population is available[3,4]. Consensus statement suggests oral amoxicillin-clavulanate for foot osteomyelitis[5].

Community acquired polymicrobial respiratory tract infections (CA-RTIs) such as aspiration pneumonia.	Multiple RCTs demonstrate clinical efficacy of amoxicillin-clavulanate when compared to ceftriaxone, IV cefuroxime, or moxifloxacin for CA-RTIs[6]. ➢ *Ceftriaxone (plus metronidazole if risk factors for anaerobes) remains first line.* ➢ *Reserve amoxicillin-clavulanate for polymicrobial RTIs not covered by ceftriaxone + metronidazole.*
Severe odontogenic infections	Oral amoxicillin-clavulanate is effective and well tolerated for odontogenic infections[7]. ➢ *If IV required, ceftriaxone + metronidazole is preferred over IV amoxicillin-clavulanate since it provides appropriate spectrum and more reliable anaerobic coverage at a lower cost.* ➢ *Reserve IV amoxicillin-clavulanate for those allergic to/intolerant of metronidazole.*
Gram negative or polymicrobial bacteremia	Studies looking at the use of amoxicillin-clavulanate were done in the setting of oral transition following IV therapy[8-10]. A higher dose of amoxicillin-clavulanate PO is suggested (875mg po TID with normal renal function) for bacteremia. ➢ *Ceftriaxone (plus metronidazole for anaerobes) remains first line.* ➢ *Reserve amoxicillin-clavulanate for polymicrobial bacteremias not covered by ceftriaxone + metronidazole.*

*Oral amoxicillin-clavulanate can be used instead of IV in the above clinical scenarios

Appendix

Amoxicillin-clavulanate or piperacillin-tazobactam?

- An RCT evaluating de-escalation from an empiric anti-pseudomonal β-lactam (most commonly piperacillin-tazobactam) to a non-pseudomonal β-lactam (such as amoxicillin-clavulanate IV) in patients with Enterobacterales bacteremia was non-inferior in efficacy to continuing with the empiric anti-pseudomonal β-lactam with no increased adverse events[11].
- A pilot study from Calgary evaluating General Surgery patients receiving IV piperacillin-tazobactam found the use of IV amoxicillin-clavulanate to be the more appropriate therapy in multiple patients (two of 25 cases in phase I and 12 of 28 cases in phase II) preserving the use of an anti-pseudomonal agent[12].

Why is q6h suggested for infections other than SSTI and RTI, i.e. for those involving Gram negative (Enterobacterales) organisms?

- In adults, the Canadian manufacturer recommended dosages for amoxicillin-clavulanate IV are 1.2g IV q8h (standard dose) and 2.2g IV q12h (high dose) which are lower than those recommended in Europe and Australia at 1.2g IV q6h (standard dose) and 2.2g IV q8h (high dose)[13,14].
- β-lactam antibiotics are effective when the percentage of time that the free/unbound serum concentration is above the minimal inhibitory concentration (MIC) (*f*T>MIC) of the pathogens 40-50 per cent of the time; even higher fT>MIC may be needed in critically ill patients[15].
- In pharmacokinetic-dynamic studies it has been shown that an increased frequency of amoxicillin-clavulanate IV administration is required to achieve these concentrations, particularly for Enterobacterales with MICs that are elevated but still within the susceptible range[13,15,16].
- An increased dosage of amoxicillin-clavulanate IV (q6h instead of q8h) is therefore recommended to prevent treatment failure and to prevent the development of antibiotic resistance in severe infections and/or those involving Gram negative (Enterobacterales) organisms.

Monte Carlo simulations of target attainment at *f*T>MIC 40% for wild-type *E. coli*[13,17]

	Amoxicillin-clavulanate dosing Probability of target attainment (per cent)	
MIC	1.2g IV q6h	1.2g IV q8h
0.5	100	100
1	100	100
2	100	100
4	100	98
8+	98	33
16+	6	0
32+	0	0

+CLSI breakpoints (used in Alberta Health Services) for Enterobacterales: ≤ 8mg/L is susceptible, 16 mg/L is intermediate, ≥ 32 mg/L is resistant[18].

The majority of isolates of Enterobacterales (*E. coli, K. oxytoca/pneumoniae* and *P. mirabilis*) in Central, Edmonton and North Zone had MICs ranging from ≤2mg/L to 8mg/L (Dr. P. van der Walt, personal communication, April 2, 2025).

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