

KEY MESSAGES:

- **Amoxicillin-clavulanate IV** may be considered an alternative to: (refer to Table 3)
 - Ceftriaxone plus metronidazole, when *Enterococcus faecalis* coverage is **required**.
 - Piperacillin-tazobactam for polymicrobial infections, when *Pseudomonas aeruginosa* or **SPACE** organisms are of **low suspicion**.
- Usual dose: **amoxicillin-clavulanate 1000 mg IV Q8H**.
- For **severe** infections (e.g. invasive *Enterobacterales* infection): **amoxicillin-clavulanate 2000 mg IV Q8H**.
- Oral amoxicillin-clavulanate is preferred if patient is taking other oral medications, as it has good bioavailability (77-93%).

ASPIRES Tidbits: IV Amoxicillin-Clavulanate

1. **Background:** IV formulation of amoxicillin-clavulanate, a broad-spectrum, semi-synthetic aminopenicillin/beta-lactamase inhibitor antibiotic, is now available on the VCH formulary.
2. **Spectrum of Activity**
 - Comparable spectrum to ceftriaxone + metronidazole with additional activity against *Enterococcus faecalis*.
 - Narrower spectrum than piperacillin-tazobactam with **no activity** against *Pseudomonas aeruginosa*.

Table 1: Amoxicillin-clavulanate spectrum of activity

Gram Positives	Gram Negatives	Anaerobes
- <i>Streptococcus spp.</i> , methicillin-susceptible <i>S. aureus</i> , and <i>E. faecalis</i>	- <i>E.g. Escherichia coli</i> , <i>H. influenzae</i> , <i>Klebsiella spp.</i> (except <i>K. aerogenes</i>), <i>Moraxella spp.</i> , <i>Proteus spp.</i>	Gram-positive and negative anaerobes, including <i>Peptostreptococcus</i> and <i>Bacteroides fragilis</i>

- **No activity** against ampicillin-resistant *E. faecium*, *P. aeruginosa*, **Enterobacterales with AmpC** (e.g. **SPACE organisms** - *Serratia spp.*, *Providencia spp.*, *Acinetobacter spp.*, some *Citrobacter spp.* (*freundii* complex), *Enterobacter spp.*, *Morganella spp.*, *K. aerogenes*), *Stenotrophomonas maltophilia* and **atypical** pathogens (*Mycoplasma*, *Legionella*, *Chlamydia*).

3. **VGH Resistance Patterns¹**

Table 2: Common pathogens implicated in respiratory, gastro-intestinal tract and urinary tract infections

Common pathogens		Ceftriaxone	Metronidazole	Amoxicillin-clavulanate	Piperacillin-tazobactam
Gram Positives	<i>Streptococcus pneumoniae</i>	100%	0%	99%	99%
	<i>Staphylococcus aureus</i> – MSSA	100% ²	0%	100%	100%
	<i>Enterococcus faecalis</i>	0%	0%	100%	100%
Gram Negatives	<i>Escherichia coli</i>	83%	0%	85%	97%
	<i>Klebsiella pneumoniae</i>	80%	0%	88%	92%
	<i>Proteus mirabilis</i>	94%	0%	93%	99%
	<i>Enterobacter spp.</i>	45%	0%	0%	59%
	<i>Pseudomonas aeruginosa</i>	0%	0%	0%	87%
Anaerobes	<i>Peptostreptococcus</i>	≥85%	≥95%	99%	≥85%
	<i>Bacteroides fragilis</i>	0%	≥95%	92%	89%

¹Data per 2022 VGH antibiogram

²Ceftriaxone does not have reliable activity for severe MSSA infections; ceftazidime or cloxacillin should be used if appropriate.

4. **Dosing Considerations**

- **Amoxicillin-clavulanate 1000 mg IV Q8H** is sufficient for most infections.
- For **severe** infections (e.g. invasive *Enterobacterales* infection): **amoxicillin-clavulanate 2000 mg IV Q8H**.
- Oral amoxicillin-clavulanate is preferred (500 mg PO TID or 875 mg PO BID) and should be considered, when clinically stable and tolerating other PO medications.

5. **Cost**

- At usual doses, IV amoxicillin-clavulanate (\$\$) has a higher cost than ceftriaxone + IV/PO metronidazole (\$), but is lower than piperacillin-tazobactam (\$\$\$). Oral amoxicillin-clavulanate is the most-cost-effective option (\$).

6. Treatment of Infections

Table 3: Place in Therapy

Infection	Place in Therapy
Respiratory tract	
Esophageal Perforation	1 st line: Ceftriaxone 1 g IV Q24H ⁴ + Metronidazole 500 mg IV Q12H 2 nd line: Amoxicillin-clavulanate 1000 mg IV Q8H ³
Hospital-Acquired Pneumonia (HAP)	Mild: Amoxicillin-clavulanate PO, or Cefuroxime PO, or Ceftriaxone 1 g IV Q24H ⁴
	Moderate-Severe: Fewer than 5% of HAP patients have <i>Pseudomonas</i> 1 st line: Ceftriaxone 2 g IV Q24H 2 nd line: Amoxicillin-clavulanate 1000 mg IV Q8H ³ 3 rd line: Piperacillin-tazobactam 3.375 g IV Q6H ^{3,5}
	Aspiration Pneumonia
	Mild-Moderate: Amoxicillin-clavulanate PO, or Cefuroxime PO, or Ceftriaxone 1 g IV Q24H ⁴ Severe (hospital-acquired): 1 st line: Ceftriaxone 1 g IV Q24H ⁴ + Metronidazole 500 mg PO/IV Q12H 2 nd line: Amoxicillin-clavulanate 1000 mg IV Q8H ³
Pleural Infection (Community-acquired)	1 st line: Ceftriaxone 1 g IV Q24H ⁴ + Metronidazole 500 mg PO/IV Q12H or Amoxicillin-clavulanate PO 2 nd line: Amoxicillin-clavulanate 1000 mg IV Q8H ³ 3 rd line: Piperacillin-tazobactam 3.375 g IV Q6H ^{3,5}
Gastrointestinal Tract	
Community-associated Intra-abdominal Infection (IAI)⁶	Mild-Moderate: • <i>Uncomplicated:</i> Cefazolin 2 g IV Q8H ³ + Metronidazole 500 mg PO/IV Q12H • <i>Complicated:</i> Ceftriaxone 2 g IV Q24H ⁴ + Metronidazole 500 mg PO/IV Q12H
	Severe: Empiric coverage for <i>Enterococcus</i> & <i>Pseudomonas</i> is not necessary in community-associated IAI 1 st line: Ceftriaxone 2 g IV Q24H + Metronidazole 500 mg PO/IV Q12H 2 nd line: Amoxicillin-clavulanate 2000 mg IV Q8H ³ 3 rd line: Piperacillin-tazobactam (septic shock/ICU) 3.375 g IV Q6H ³
	Hospital-associated Intra-abdominal Infection (IAI)⁶
	Mild: Ceftriaxone 1 g IV Q24H ⁴ + Metronidazole 500 mg PO/IV Q12H Moderate: 1 st line: Ceftriaxone 1 g IV Q24H ⁴ + Metronidazole 500 mg PO/IV Q12H 2 nd line: Amoxicillin-clavulanate 1000 mg IV Q8H (if source-controlled and/or clinically stable) ³ Empiric <i>Enterococcus</i> coverage may be considered if: post-operative infection, recent cephalosporins or broad-spectrum antibiotic use, immunocompromised, valvular heart disease or prosthetic intravascular material Severe: 1 st line: Piperacillin-tazobactam 3.375 g IV Q6H ³ 2 nd line: Amoxicillin-clavulanate 2000 mg IV Q8H ³ for directed therapy based on culture results
Genitourinary Tract	
Urinary Tract Infection	Uncomplicated Cystitis: PO preferred: Nitrofurantoin, Sulfamethoxazole-Trimethoprim (SMX/TMP), Cephalexin
	Complicated Cystitis or Pyelonephritis: <i>Mild-Moderate (hospitalized):</i> PO preferred: Cefixime, Amoxicillin-clavulanate PO, SMX/TMP If IV therapy required: Ceftriaxone 1 g IV Q24H ⁴
	Severe (e.g. urosepsis): 1 st line: Piperacillin-tazobactam 3.375 g IV Q6H ³ 2 nd line: Amoxicillin-clavulanate 1000 mg IV Q8H ³ if AmpC organisms and <i>Pseudomonas</i> not suspected
Skin & Soft Tissue	
Diabetic Foot Infection	Mild: PO therapy preferred: Cephalexin If IV therapy required: Cefazolin 2 g IV Q8H ³
	Moderate: Ceftriaxone 2 g IV Q24H + Metronidazole 500 mg PO/IV Q12H or Amoxicillin-clavulanate PO
	Severe: 1 st line: Amoxicillin-clavulanate 1000-2000 mg IV Q8H ³ , Amoxicillin-clavulanate PO step-down as soon as eligible 2 nd line: Piperacillin-tazobactam 3.375 g IV Q6H ^{3,8} ⁸ Consider <i>pseudomonal</i> coverage if: tropical/warm climates, soaking of feet, failed non-pseudomonal therapy, or limb-threatening infection

³Dose may require adjustment for renal insufficiency

⁴If patient's weight >100 kg, may consider ceftriaxone 2 g IV q24h

⁵Consider piperacillin-tazobactam in patients with *Pseudomonas* risk factors: structural lung disease, cystic fibrosis, bronchiectasis, immunocompromised, or mechanical ventilation, etc.

⁶Amoxicillin-clavulanate PO is preferred for IV to PO step-down

⁷If purulent and MRSA suspected, add doxycycline PO or sulfamethoxazole-trimethoprim PO or vancomycin IV