Antibiotics

January 24, 2019 by Josh Farkas

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Antibiotics in the ICU are in some ways simpler than antibiotic therapy for less ill patients. IV access isn't an issue. Patients are critically ill, so we're justified in using broad-spectrum agents initially. There is considerable variation in this between different hospitals, so when in doubt consider your local antibiogram and consult with pharmacists and infectious disease specialists.

**when to start antibiotics?**

- Antibiotics shouldn't be started blindly (without a defined source of infection) unless the patient has septic shock or neutropenic fever.
- A positive culture may represent infection or *colonization* (bacteria present without causing disease). Colonization commonly occurs in the bladder of anuric or catheterized patients, or sputum of intubated patients. Don't treat colonization except in very specific situations (e.g. urinary colonization in pregnancy).
- If possible, get cultures before starting antibiotics.

**choosing drug & dose**

- Septic patients may have increased drug clearance, so antibiotics should generally be dosed on the higher end of dose ranges.
- Review which antibiotics patient has been exposed to recently; try to avoid these if possible.
- Review recent culture data. Try to choose antibiotics that cover pathogens that the patient has grown in the recent past.

**narrowing & discontinuing ASAP**

- Keep track in your notes of how long the patient has been on each antibiotic. Have some sort of plan regarding when to discontinue antibiotics and follow it.
- Use of procalcitonin has been shown to limit antibiotic exposure, while possibly improving patient outcomes.

**treatment failure**

- If a patient is failing antibiotic therapy, broadening coverage is usually not the answer.
- [Common causes of treatment failure](http://www.derangedphysiology.com/main/required-reading/infectious-diseases-antibiotics-and-sepsis/Chapter%202.1.5/causes-antibiotic-treatment-failure) include:
  - Wrong initial diagnosis
  - Under-dosing
  - Development of a new hospital-related problem (e.g. volume overload, superinfection at different site, drug fever)
  - Requirement for surgical/percutaneous drainage

**specific properties of various antibiotics**

- Antibiotics may be metabolized in the liver (often into inactive metabolites) or they may be excreted *unchanged* in the urine or bile.
• Hepatic metabolism/excretion is generally convenient, because this means the drug dose doesn't need to be adjusted based on renal function.
• Excretion of unchanged drug in the urine is ideal for treatment of urinary tract infections, because this will often produce very high drug concentrations in the kidney and bladder. Likewise, excretion of unchanged drug in the bile is ideal for biliary or intestinal infections.
  • Urinary drug concentrations depend on serum level, percent excreted in the urine, and how concentrated the urine is.

**bacteriocidal vs. bacteriostatic**

• An antibiotic which is bacteriocidal kills bacteria, whereas an antibiotic which is bacteriostatic stops bacteria from dividing.
• Traditionally it was believed that cidality was desirable for severe infections. However, cidality may actually be dangerous if this leads to rapid lysis of bacteria leading to a huge release of bacterial products (e.g. endotoxin) causing uncontrolled inflammation.
  • For example: Antibiotics which inhibit protein synthesis (e.g. clindamycin and linezolid) cause immediate cessation of toxin secretion in patients with toxic shock. They are used specifically for this reason – to shut down toxin synthesis (rather than necessarily immediately destroying all the bacteria).
• The concept that bacteriocidal antibiotics are superior is based on a *petri-dish model* of infectious disease, wherein the antibiotic is relied upon to kill the bacteria. However, this model isn't very accurate – in vivo, the antibiotic is just assisting the patient's immune system in containing the infection.
  • Severe neutropenia is one situation where the petri-dish model may actually be accurate, so cidal antibiotics might be desirable in that context.
• Overall, the focus on cidality is probably misplaced. In some situations this may be important, but other factors may be equally if not more important (e.g. tissue penetration, pharmacokinetics). Just because an antibiotic is bacteriostatic doesn't mean that it's not extremely effective.
  • A recent analysis of over fifty RCTs found no benefit of cidal antibiotics compared to static antibiotics, so the clinical superiority of cidal antibiotics may be mostly mythological.¹

**percent protein binding**

• Protein binding refers to the percent of drug in the blood which is bound to albumin. Only unbound drug is active against bacteria.
• A high percent protein binding (>90%) may have the following consequences:
  • Creates a reservoir of drug which is bound to albumin (which may extend the drug's half-life).
  • Reduces renal clearance (only free drug is cleared).
  • Reduces tissue penetration (only free drug is able to leave the bloodstream and penetrate tissues).
• Depending on the clinical context, a high percent protein binding could be helpful (e.g. long half-life extends dosing interval) or harmful (e.g. impaired tissue penetration).

**volume of distribution (Vd)**

• This is the effective volume into which the drug is diluted following administration. There are roughly three patterns of drug distribution:
  1) Drugs that stay in the extracellular fluid
    • The extracellular fluid has a volume of ~0.3 L/kg, so drugs that stay in the extracellular fluid will have a Vd of roughly 0.1-0.3 L/kg
    • Drugs with this pharmacology may work well for extracellular infections (e.g. bacteremia).
  2) Drugs that distribute throughout the total body water (intracellular and extracellular fluid).
    • The extracellular and intracellular fluids have a volume of ~0.7 L/kg, so drugs that distribute evenly through this volume will have a Vd close to this value.
    • Many drugs in this group have excellent tissue penetration (with the possible exception of vancomycin).
  3) Drugs that leave the blood.
    • Some drugs are absorbed avidly by the tissues, with a tendency to concentrate within tissues. This may be seen with lipophilic drugs which rapidly leave the blood and may form a depot in fat tissues. These drugs will have a Vd which is substantially greater than total body water (Vd >> 0.7 L/kg).
    • These drugs may have excellent tissue penetration, but may not be optimal for bloodstream infections.
The pharmacokinetics of treating meningitis depends primarily on three factors:

1. Serum drug level
2. What percent of the serum drug enters the meninges
3. How high a level is required to inhibit bacterial growth (minimum inhibitory concentration; MIC)

The table below shows the fraction of serum levels achieved in the meninges for different antibiotics. This is useful, but it's only one piece of the puzzle (#2 above). It's not intended to dictate which antibiotics may be used to treat meningitis, but rather to provide a general concept of relative CNS penetration.

For patients without CNS infection, having a low entry into the CNS may be desirable to avoid neurologic adverse events (the blood-brain barrier was designed for a reason!).

### meningal penetration of ICU antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Entry into un inflamed meninges</th>
<th>% Entry into inflamed meninges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides: Gentamycin</td>
<td>&lt;1</td>
<td>20</td>
</tr>
<tr>
<td>Aminoglycosides: Tobramycin</td>
<td>&lt;1</td>
<td>20</td>
</tr>
<tr>
<td>Aminoglycosides: Amikacin</td>
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<td>20</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Carbapenems: Eraspenem</td>
<td>10</td>
<td>5-20</td>
</tr>
<tr>
<td>Carbapenems: Meropenem</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Cephalosporin G1: Cefazolin</td>
<td>1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Cephalosporin G3: Ceftriaxone</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Cephalosporin G4: Cefepime</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Cephalosporin G5: Ceftaroline</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2</td>
<td>5</td>
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<td>Doxycycline</td>
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<td>70</td>
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<td>Metronidazole</td>
<td>30</td>
<td>100</td>
</tr>
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<td>PCNs: Penicillin G</td>
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<td>PCNS: Nafcillin</td>
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<td>20</td>
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<tr>
<td>PCNs: Ampicillin &amp; Ampicillin-Sulbactam</td>
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<td>20</td>
</tr>
<tr>
<td>PCNs: Piperacillin-tazobactam</td>
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<tr>
<td>Rifampin</td>
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<tr>
<td>Tigecycline</td>
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<td>8</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Vancomycin</td>
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<td>15</td>
</tr>
</tbody>
</table>

Antibiograms vary greatly in different geographic locales. The following antiobigram is intended only as a rough concept; whenever possible, it's preferable to use local data.
### key antibiotics in the ICU

<table>
<thead>
<tr>
<th></th>
<th>MRSA</th>
<th>MSSA</th>
<th>Strep &amp; Pneumococcus</th>
<th>Entero-coccus*</th>
<th>GNB</th>
<th>GNB, Inducible AmpC</th>
<th>GNB, ESBL</th>
<th>Pseud. aeruginosa</th>
<th>Anaerobes</th>
<th>CDiff</th>
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</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+++ (PO)</td>
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<tr>
<td>Linezolid</td>
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<td>+++</td>
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<td>+++</td>
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<tr>
<td>Cefazolin</td>
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<td>+/-</td>
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<tr>
<td>Ceftriaxone</td>
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<tr>
<td>Cefepime</td>
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<td>Ceftaroline</td>
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<td>Ampicillin- sulbactam</td>
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<tr>
<td>Piperacillin- tazobactam</td>
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<tr>
<td>Meropenem</td>
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<tr>
<td>Tigecycline</td>
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<tr>
<td>Azithromycin</td>
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<tr>
<td>Doxycycline</td>
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</tbody>
</table>

* The clinical significance of enterococcus in the context of polymicrobial abdominal/pelvic infection is unclear. It’s possible that they’re just along for the ride.


### First-Line agents for common gram-positive pathogens

- MSSA – Cefazolin or nafcillin. Nafcillin required for CNS penetration.
- MRSA – Vancomycin, linezolid (not preferred for bacteremia), or daptomycin (ineffective in pneumonia)
- Staphylococcus lugdenensis (“slug”) – Vancomycin empirically, narrow to oxacillin if sensitive.
- Enterococcus faecalis – Ampicillin preferred (99% sensitive), may be superior to vancomycin.
- Enterococcus faecium (VRE) – Linezolid is first-line, daptomycin 2nd line.
- Enterococcus faecium (non-VRE) – Vancomycin or linezolid
- Streptococcus anginosus – Penicillin G is 1st line, ceftriaxone is 2nd line
- Streptococcus pyogenes (Group A strep) or Streptococcus agalactiae (Group B strep) – Penicillin G is 1st line, cefazolin is 2nd line
- Streptococcus pneumoniae (not meningitis) – Ceftriaxone is 1st line, Vancomycin is 2nd line in severe allergy.
- Listeria spp. – Ampicillin is 1st line, trimethoprim/sulfamethoxazole is 2nd line.

### Commonly used agents for common gram-negative pathogens

- E. coli, Klebsiella pneumoniae, Klebsiella oxytoca
  - No risk factors for ESBL species: Ceftriaxone or cefepime
  - Risk factors for ESBL species: Carbapenem
- Proteus species: Piperacillin-tazobactam or cefepime
- Enterobacter or Citrobacter: Cefepime or carbapenem
- Pseudomonas: Piperacillin-tazobactam, cefepime, or meropenem

[aminoglycosides](https://emcrit.org/ibcc/antibiotics/)

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agents

- Gentamycin: Best gram-positive coverage
- Tobramycin: Workhorse aminoglycoside, good gram-negative coverage
- Amikacin: Best gram-negative coverage (often reserved for resistant pseudomonas)

spectrum

- Gram-positives: Covers MSSA and Enterococcus faecalis
- Gram-negatives: Excellent coverage (tobramycin and amikacin cover pseudomonas)

use

- Gentamycin is used for synergy against Enterococcus faecalis endocarditis, with other agents (at reduced dose of 1 mg/kg q8hr)
- Gram negative bacteremia with refractory shock
- Urinary tract infection

toxicity/contraindications

- Nephrotoxicity, otoxicity
- Neuromuscular blockade (may be an issue in severe hypocalcemia or myasthenia gravis)

pharmacology

- Administered only IV/IM.
- Excreted unchanged in the urine.
- Half-life (normal/ESRD) is ~2.5 hours.
- Plasma protein binding is low (~5-10%).
- Volume of distribution (Vd) is ~0.25 L/kg.
- Penetration
  - Lung penetration is borderline (bronchial secretion level is 2/3rds serum level, and drug may not function well in acidic environment within consolidated lung tissue).
  - Poor penetration of many tissues (brain, bile, prostate, meninges).
  - Excellent renal penetration.

dosing
In morbid obesity, consider using an adjusted body weight:

- Adjusted Body Wt = 0.6(ideal body wt)+0.4(actual body wt).

**Medscape monographs:**

**aztreonam**

**spectrum**

- Covers gram-negatives well (including pseudomonas), but nothing else.
- May fail in species that have *inducible AmpC beta-lactamases* ([AmpC_inducible_beta-lactamase](https://emcrit.org/ibcc/antibiotics/)), (citrobacter, enterobacter, morganella, proteus, providentia, and serratia).

**use**

- Excellent gram-negative coverage, safe for use in patient with anaphylaxis to penicillin (but might cross-react with ceftazidime).
- Can be used for many gram-negative infections (e.g. pneumonia, soft tissue, urinary tract, bacteremia).
- Logical choice for patient found to have gram-negative bacteremia.

**toxicity/contraindications**
Contraindication: Ceftazidime allergy (may be cross-allergic). However, overall seems to have low tendency to cause allergic reaction or side-effects.

- Abnormal liver function tests
- Thrombocytopenia
- Seizure

**pharmacology**

- Excreted unchanged in urine: 65%.
- Plasma protein binding: 56%
- Volume of distribution: 0.2 L/kg
- Tissue penetration: widely distributes throughout body including CNS. High levels in bile and urine.

**dosing**

- GFR >30 ml/min: 1-2 grams IV q8hr (meningitis or morbid obesity: consider 2 grams q6hr)
- GFR < 10-30 ml/min: 1-2 grams q12hr
- GFR < 10 ml/min: 1-2 grams q24hr
- CRRT 1 gram q12


**carbapenems (meropenem, ertapenem)**

**spectrum: meropenem**

- Gram-positives: Generally very good, but does miss MRSA and Enterococcus faecium.
- Gram-negative coverage:
  - Overall excellent (including pseudomonas, ESBL and Amp-C multi-drug resistant species).
  - Some carbapenem resistance is starting to emerge among enterobacteriaceae (especially among Klebsiella pneumoniae); this varies widely depending on geography.
- Anaerobic coverage: Excellent (but doesn’t cover Clostridium difficile).

**spectrum: ertapenem**

- Main differences compared to meropenem:
  1) Lacks coverage of pseudomonas and acinetobacter.
  2) Limited activity against enterococci.
- May be superior for non-pseudomonal gram-negatives (due to broad use of meropenem and development of meropenem resistance)

**use**

- Broad-spectrum beta-lactam antibiotics with a range of potential applications (e.g. pneumonia, intra-abdominal infections, urinary tract infections, bacteremia, soft tissue infections). Unlike most beta-lactams, carbapenems decrease lipopolysaccharide release from gram-negative bacteria, which could give them an advantage in the treatment of gram-negative septic shock.

https://emcrit.org/ibcc/antibiotics/
Front-line choice for multi-drug resistant gram-negative bacteria (e.g. bacteria with inducible AmpC beta-lactamases, ESBL bacteria).

Great for patient with history of anaphylaxis following penicillin exposure who requires broad-spectrum coverage. Carbapenems (especially meropenem) have an extremely low risk of allergic reaction. Using a carbapenem may be safer than a multi-drug regimen (e.g. vancomycin/aztreonam/metronidazole) and faster to administer in septic shock. Meropenem can actually be given as a bolus.

Meropenem has better tissue penetration (e.g. allowing it to be used in meningitis), whereas ertapenem has a longer half-life (allowing once-daily dosing).

toxicity/contraindications

Meropenem
- Seizure
- Thrombocytopenia
- Drug fever

Ertapenem
- DRESS syndrome
- Seizures, delirium, myoclonus/tremor

pharmacology

Meropenem
- Excreted unchanged in the urine (70%)
- Protein binding 2% (promoting wide distribution into tissues)
- Volume of distribution 0.35 L/kg
- Penetration: well distributed into most tissues including CNS.

Ertapenem
- Excreted unchanged in urine (40%)
- Protein binding of 95% – this creates a reservoir of drug in the blood, extending the half-life and allowing ertapenem to be given once daily.
- Volume of distribution 0.12 L/kg
- Penetration: higher protein-binding reduces its penetration compared to meropenem (e.g. giving ertapenem poor penetration of bile, peritoneal fluid, and prostate).

dosing

Meropenem
- GFR > 50: 1-2 grams q8 (higher end for pseudomonas, meningitis, or morbid obesity)
- GFR 30-50: 1-2 grams q12
- GFR 10-30: 500-1,000 mg q12
- GFR <10: 500-1,000 mg q24

Ertapenem
- GFR >30 ml/min: 1 gram IV q24hr (may consider higher dose in morbid obesity or severe illness)
- GFR <30 ml/min: 500 mg IV q24hr


cephalosporin G1: cefazolin

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spectrum

- **Gram-positives:**
  - MSSA, Staph saprophiticus, coagulase-negative staph which are sensitive to oxacillin.
  - All non-enterococcal streptococci (e.g. streptococcus groups A, B, C, G).
- **Gram-negatives**
  - Hits some, but not adequate for empiric therapy against gram-negative infections. May be used as step-down therapy once sensitivities available.

use

- **Empiric coverage before culture known:**
  - Cellulitis (often treatment of choice for cellulitis without evidence of abscess/purulence).
- **After culture/sensitivity known:**
  - Bacteremia, including MSSA (Increasing evidence that cefazolin is first-line therapy in MSSA bacteremia, superior to nafcillin).\(^5\) Note however that nafcillin has superior CNS penetration, so nafcillin might be better for endocarditis with brain emboli.
  - Pneumonia (e.g. due to MSSA or Group A streptococcus)
  - Urinary tract infection (e.g. due to sensitive E. coli or Proteus mirabilis)
  - Synergistic \textit{en vitro} with vancomycin against MRSA, with some supportive clinical evidence as well.\(^7\)

toxicity/contraindications

- **PCN allergy is not a contraindication.** Cefazolin has a unique side-chain, which isn't cross-allergic with any other beta-lactam.\(^8\) It can also be used in patients with hypersensitivity reactions to nafcillin.\(^8\)
- Drug rash, drug fever
- Transaminitis
- Neutropenia, thrombocytopenia
- Seizures, delirium

pharmacology

- Excreted unchanged by kidneys (90%)
- Protein binding: 80%
- Vd: 0.2 L/kg
- Penetration: Good penetration of lungs, joints, bone, prostate, and bile. However, poor CNS penetration is a major limitation of cefazolin.

doing

- GFR >50 ml/min: 1-2 grams IV q8 (2 grams for bacteremia; consider 2 grams q6hr in morbidly obese patient)
- GFR 30-50 ml/min: 1-2 grams IV q12
- GFR 10-30 ml/min: 0.5-1 gram IV q12

https://emcrit.org/ibcc/antibiotics/
GFR <10 ml/min: 0.5-1 gram IV q24

Medscape monograph: Cefazolin

cephalosporin G3: ceftriaxone

**spectrum**

- **Gram-positives**
  - MSSA: Does seem to cover, but *inferior* to cefazolin and *suboptimal* for MSSA bacteremia.
  - All non-enterococcal streptococci.
  - Streptococcus pneumoniae (resistant strains will usually still be cured clinically, with the exception of meningitis).
- Haemophilus influenzae, Moraxella catarrhalis
- Neisseria meningitidis
- **Gram-negatives**
  - Generally good coverage.
  - Misses: Pseudomonas, extended-spectrum beta lactamase organisms
  - Should be avoided in species that may have *inducible AmpC beta-lactamases* (#AmpC_inducible_beta-lactamase) (citrobacter, enterobacter, morganella, proteus, providentia, and serratia).

**use**

- Pneumonia
- Meningitis (covers nearly everything; will miss listeria and resistant streptococcus pneumoniae)
- Urinary tract infection without septic shock
- Bacteremia, endocarditis
- Peritonitis, prophylaxis in cirrhotic patients with GI hemorrhage.

**toxicity/contraindications**

- Cholecystitis (may crystallize in gallbladder causing pseudo-biliary lithiasis)
- Hepatitis
- Neutropenia, thrombocytopenia
- Drug rash, anaphylaxis
- Delirium

**pharmacology**
Roughly 50% excreted unchanged by kidneys, remainder excreted unchanged by liver. In renal failure, the liver picks up the slack so no dose adjustment needed. Achieves high levels in both urine and bile.

- Protein binding of 90% promotes an unusually long half-life of ~7 hours (longer than most beta-lactams).
- Volume of distribution 0.2 L/kg
- Good tissue penetration, including CNS (although higher doses needed to penetrate meninges).

**dosing**

- Generally 1 gram q24 (may use 2 grams q24 for severe infection, or in larger patients).
- Meningeal penetration: 2 grams q12.
- No renal adjustment.

**Medscape monograph:** [Ceftriaxone](http://reference.medscape.com/drug/rocephin-ceftriaxone-342510)

**cephalosporin G3: ceftazidime**

**spectrum**

- Gram-positive coverage is poor (ceftazidime loses activity against MSSA and penicillin-intermediate strains of Streptococcus pneumoniae)
- Haemophilus influenzae, Moraxella catarrhalis
- Good coverage of gram-negatives:
  - Does cover pseudomonas
  - Should be avoided in species that may have inducible AmpC beta-lactamases ([#AmpC_inducible_beta-lactamase](http://www.hosp.uky.edu/pharmacy/formulary/formtools/cephalosporins.htm)), (citrobacter, enterobacter, morganella, proteus, providentia, and serratia).

**ceftazidime is almost never the best antibiotic choice**

- Cefepime is usually a better choice
  - a) Cefepime has better activity against gram-negatives, including species with inducible AmpC beta-lactamases ([#AmpC_inducible_beta-lactamase](http://www.hosp.uky.edu/pharmacy/formulary/formtools/cephalosporins.htm)).
  - b) Cefepime has greatly superior activity against gram-positives, so it’s preferable for empiric therapy in septic shock (even in patients on vancomycin, as the vancomycin level is often subtherapeutic)
  - c) The safety profile of cefepime and ceftazidime are similar.\(^1\)
- For a mildly ill patient with definite gram-negative infection (e.g. gram-negative rods detected in urine or blood), aztreonam is a more logical choice.
- Ceftazidime seems to have a particularly strong tendency to select out for drug-resistant pathogens (e.g. MRSA, multi-drug resistant pseudomonas).
- Some hospitals have removed ceftazidime ([http://www.hosp.uky.edu/pharmacy/formulary/formtools/cephalosporins.htm](http://www.hosp.uky.edu/pharmacy/formulary/formtools/cephalosporins.htm)) from the formulary entirely, which is probably a good idea.
### toxicity/contraindications

- Transaminitis
- Drug fever
- Delirium, often with myoclonus
- Hemolytic anemia, neutropenia, thrombocytopenia
- Seizures
- Interstitial nephritis

### pharmacology

- Widely distributed with good penetration, including CNS.

### dosing

- GFR >50 ml/min: 1-2 grams IV q8hr (2 grams for severe infection, meningitis, or morbid obesity)
- GFR 30-50 ml/min: 1-2 grams IV q12hr
- GFR 10-30 ml/min: 0.5-1 grams IV q12
- GFR <10 ml/min: 0.5-1 gram IV q24


### cephalosporin G4: cefepime

- Gram-positives: Covers MSSA, most coagulase-negative staph, non-enterococcal streptococci, Streptococcus pneumoniae.
- Gram-negatives:
  - Covers species with [AmpC inducible beta-lactamases](#AmpC_inducible_beta-lactamase) (e.g. Enterobacter).
  - Covers pseudomonas
- Covers Haemophilus influenza, Neisseria meningitidis.

### spectrum

- Community-acquired septic shock (especially patients with PCN allergy who can't get piperacillin-tazobactam).
- Nosocomial infections (including meningitis)
- Likely safe in patients with PCN anaphylaxis (virtually no reported cases of cefepime-induced anaphylaxis).
**toxicity/contraindications**

- Drug fever
- Neutropenia, thrombocytopenia, positive Coombs test which is sometimes accompanied by clinical hemolysis.
- CNS: Seizure, delirium, often with myoclonus\(^{11}\)
- May cause more Clostridioides difficile than piperacillin-tazobactam.\(^{14,15}\)

**pharmacology**

- Excretion: 85% excreted unchanged in urine
- Protein binding: 20%
- Vd: 0.3 L/kg
- Penetration: Good tissue penetration, including the CNS. Positively charged R2 group gives the molecule a net even charge, improving penetration of gram-negative bacteria.

**dosing**

- GFR>60 ml/min: 2 grams Q8-12 hours (use 2 grams q8hr for pseudomonas or multi-drug resistant gram negatives or morbid obesity; using same dose and extending the duration of infusion may improve efficacy)\(^{12}\)
- GFR 30-60 ml/min: 2 grams Q12-24
- GFR 11-29 ml/min: 1-2 grams Q24
- GFR < 11 ml/min: 500-1000 mg Q24

Medscape monograph: [Cefepime](http://reference.medscape.com/drug/maxipime-cefepime-342511)

**spectrum**

- Gram-positives: Covers MSSA, MRSA, coagulase-negative staph, Streptococcus pneumoniae, non-enterococcal streptococci, Enterococcus faecalis.
- Gram-negatives: Generally good coverage, but misses pseudomonas and extended-spectrum beta-lactamase resistant organisms (ESBLs).
use

- Skin/soft tissue infection
- Pneumonia
- Endocarditis, bacteremia
  - Little evidence, but case series show ability to cure patients refractory to vancomycin or daptomycin.\textsuperscript{16}
  - Combination of ceftaroline plus daptomycin may salvage highly refractory MRSA bacteremia.\textsuperscript{16}
- Empiric antibiotic regimens designed to cover MRSA

toxicity/contraindications

- Nausea, diarrhea
- Rash
- Neutropenia (more problematic with longer courses)\textsuperscript{16}
- Clostridioides difficile colitis
- Seizure

pharmacology

- Excretion: 64\% excreted unchanged in urine
- Protein binding: 20\%
- Vd: 20 L/kg
- Penetration: Widely distributed, but only 10\% CNS penetration

dosing

- GFR > 50 ml/min:
  - Mild-moderate infections: 600 mg IV q12hr
  - Serious infections, endocarditis, staph bacteremia: 600 mg IV q8hr\textsuperscript{16,17}
- GFR 30-50 ml/min: 400 mg q12hr
- GFR 15-30 ml/min: 300 mg q12hr
- ESRD/HD: 200 mg q12hr
- Morbid obesity: no dose adjustment

clindamycin

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spectrum

- Gram-positives: Streptococcus pneumoniae, non-enterococcal streptococci, and staph (MSSA and some MRSA).
- Anaerobic coverage good, although increasing resistance among gut anaerobes (e.g. Bacterioides spp).
- Use caution if the bacteria is resistant to erythromycin, as some bacteria may be cross-resistant or have inducible resistance against clindamycin. This may be evaluated using the D-test.

use
Toxin suppression:
- Severe Group A strep infections (e.g. toxic shock syndrome, necrotizing fasciitis). The combination of clindamycin plus a beta-lactam is the gold standard therapy here.
- Clostridium perfringens: gas gangrene.
- Anaerobic coverage (however, metronidazole is generally superior for this).
- Clindamycin can be useful for lung abscess, due to combined coverage of anaerobes and oral streptococcal spp.

toxicity/contraindications
- High tendency to induce Clostridioides difficile infection.
- Rashes, fever, anaphylaxis, erythema multiforme.
- May block neuromuscular transmission, contraindicated in myasthenia gravis.

pharmacology
- High oral bioavailability (~90%); however, oral clindamycin may cause more Clostridioides difficile than IV clindamycin.
- Excretion: Metabolized by liver, only 10% excreted unchanged in urine.
- Protein binding: 90%
- Vd: 1 L/kg (widely distributed).
- Penetration:
  - Good penetration of most tissues, except the CNS.
  - Actively transported into neutrophils and macrophages, causing concentration in abscesses.
  - Dissolves biofilms on hardware.
- Mechanism: blocks protein synthesis by impeding release of protein from the 50S ribosome (same mechanism as macrolides).

dosing
- 900 mg IV q8.
- Generally no dose adjustment, but consider reduction in combined kidney & hepatic dysfunction.


daptomycin
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spectrum
- Very broad spectrum against gram-positives (including MRSA and vancomycin-resistant enterococci).
- Emergence of daptomycin resistance may occur while treating Staph aureus (especially if previously treated with vancomycin or large burden of bacteria).

use
- MRSA endocarditis, bacteremia
  - Be careful about using daptomycin if vancomycin MIC is >2 (increased rates of resistance).
  - Resistance can emerge during therapy, which might be avoided somewhat by co-administration of a beta-lactam (daptomycin plus ceftaroline might be ideal).
- Skin/soft tissue infection.
- Urinary vancomycin-resistant enterococcus infection (daptomycin secreted in urine, might be 1st line here).
- Note: Inactivated by surfactant in lung, so cannot be used for pulmonary infection.

toxicity/contraindications

- **Rhabdomyolysis**
  - Discontinuing statins might reduce risk.
  - Monitor creatinine kinase. Discontinue daptomycin if creatinine kinase increases >2000 U/L, or >1000 U/L with symptoms of myopathy.
  - False elevation of INR (lab artifact). This may be sorted out by repeating INR before an infusion when daptomycin is at trough levels.
- LFT abnormality
- Acute eosinophilic pneumonia
- Peripheral neuropathy

pharmacology

- Excretion: 80% excreted unchanged in urine
- Protein binding: 92%
- Vd: 0.1 L/kg (small Vd corresponds to plasma and interstitial fluid)
- Penetration: Distributes to bile and urine; CSF penetration poor.
- Dosed once daily with post-antibiotic effect and half-life of ~8 hours.

dosing

- Skin/soft tissue infection: 4-6 mg/kg IV daily
- Bacteremia: 8-10 mg/kg total body wt IV daily (consider 12 mg/kg for enterococcus or failure of lower doses)
  - Higher-dose daptomycin may reduce the likelihood of treatment-emergent resistance, is generally well tolerated, and is not associated with excess toxicities (2015 IDSA endocarditis guidelines).
  - For renal insufficiency (GFR <30), increase interval to q48.


doxycycline

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spectrum

- Gram-positives
  - Most streptococci
Streptococcus pneumoniae is increasingly resistant (~20% resistant).

Staph coverage is good (including coverage of ~80% of MRSA), but may fail to provide clinical cure en vivo.

Gram-negatives
- Some E. coli
- Haemophilus influenzae, Moraxella catarrhalis

Clostridia
- Atypicals: Mycoplasma pneumoniae, Chlamydia pneumoniae, legionella
- Listeria monocytogenes

Tick-borne illnesses (lyme, Rocky Mountain Spotted Fever, tularemia, ehrlichiosis, anaplasmosis).

Zoonotic organisms (Coxiella burnetti, Yersinia pestis, Chlamydia psittaci, Bacillus anthracis, leptospirosis, Pasturella multocida)

use
- Coverage for atypical organisms in patients with pneumonia, especially in the following situations:
  1) Patients who are at some risk for community-acquired MRSA pneumonia, but not enough risk to justify addition of linezolid or vancomycin (doxycycline has fair activity against community-acquired MRSA, but lacks evidence for efficacy in MRSA pneumonia).
  2) History of contact with animals.
- Coverage of almost all tickborne illnesses (e.g. anaplasmosis, Rocky Mountain Spotted Fever). Unfortunately, doxycycline will miss babesiosis, so if your tick-exposed patient has hemolysis then babesiosis may require further investigation and specific treatment.
- Staph aureus skin and soft tissue infections.

toxicity/contraindications
- Generally well tolerated (appears to reduce the risk of Clostridioides difficile).
- GI irritant: Nausea, vomiting if taken before/after meals; esophageal ulceration if taken orally without sufficient water.
- Vascular irritant: Can cause phlebitis when given IV.
- Pancreatitis reported in a few case reports.
- Stevens-Johnson syndrome.

pharmacology
- 100% oral bioavailability (however absorption impaired by aluminum, magnesium, calcium, iron, cholestyramine, or milk).
- Excretion: 30% excreted unchanged in the urine. Mostly eliminated by the liver.
- Protein binding: 82%
- Vd: 0.75 L/kg
- Penetration: Good penetration of most tissues (CSF reaches 25% serum level).
- Mechanism: Inhibition of protein synthesis through 30s ribosomal binding blocking aminoacyl-tRNA (same as tigecycline).

dosing
- Start with 200 mg loading dose in severe infection (otherwise steady-state drug levels won’t be reached for a few days).
- Usual dose: 100 mg q12 PO/IV (100% oral bioavailability)
- Meningeal dose: 200 mg q12.
- For moderate to severe legionella: 200 mg q12 hours for 72 hours, followed by 100 mg q12.


fluoroquinolones
Fluoroquinolones have little role in a modern ICU for the following reasons:

1) Increasing antibiotic resistance (e.g. >25% resistance of E. coli to ciprofloxacin in many locations).
2) Fluoroquinolones induce the emergence of multi-drug resistant bacteria to a much greater extent than most antibiotics. Removal of fluoroquinolones from the ICU may help control pathogens such as C. difficile and MRSA.
3) Fluoroquinolones have traditionally been used for patients with penicillin allergy, but we are increasingly realizing that cephalosporins are fine for such patients.

4) Fluoroquinolones cause delirium, likely to a greater extent than most antibiotics.

5) Fluoroquinolones have recently been implicated in causing persistent neurologic abnormalities, which may be especially problematic among intubated patients (who are unable to report neurologic side-effects). Fluoroquinolones can also cause connective tissue problems involving tendinopathy and possibly aortic aneurysm. Consequently, the FDA has recommended avoidance of fluoroquinolones when possible in a black box warning (https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm).

6) Fluoroquinolones add very little to beta-lactam antibiotics when used for double-coverage of pseudomonas.
   - The concept of double-coverage of pseudomonas just isn't supported by evidence (more on this here (https://emcrit.org/pulmcrit/double-coverage-vap/).
   - If you are going to double-cover for pseudomonas, the only antibiotic that adds substantially to a beta-lactam is an aminoglycoside. Adding a fluoroquinolone to an anti-pseudomonal beta-lactam is like adding a pistol to a cannon – it just doesn't add much (explained further here (https://emcrit.org/pulmcrit/double-coverage-of-gram-negatives-with-a-fluoroquinolone/)).

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**linezolid**

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**spectrum**

- Broad coverage of gram-positives (including MRSA, vancomycin-resistant enterococci, streptococcal species, coagulase-negative staphylococci).
- Listeria

**advantages of linezolid over vancomycin**

2. No nephrotoxicity.
4. Superior spectrum of activity against enterococci (including coverage of vancomycin-resistant enterococci).
5. Vancomycin is cleared by the kidneys, which makes therapeutic levels hard to achieve in patients with augmented renal clearance. In contrast, linezolid is cleared by the liver, making dosing and achievement of therapeutic levels easier.
6. MRSA is rapidly growing less sensitive to vancomycin (the phenomenon of "MIC creep"). This is forcing us to target higher vancomycin levels, leading to greater vancomycin nephrotoxicity. Over time this will become a more obvious problem (our evidentiary base of studies regarding linezolid vs. vancomycin lags 10-15 years behind current microbiologic trends).

**use**

- **Pneumonia**: Arguably front-line agent for MRSA pneumonia. Will also work for other gram-positive pneumonia (e.g. MSSA, Streptococcus pneumoniae).
- **Bacteremia**: In 2007, the FDA released a warning (https://emcrit.org/wp-content/uploads/2018/12/linezolidhcp_fdaletter.pdf) regarding the use of linezolid for catheter-related bloodstream infections (below). This seems to represent a statistical fluke, especially because subsequent
studies have shown that linezolid is effective for bacteremia. Currently, vancomycin remains preferred for MRSA bacteremia. However, linezolid is FDA-approved and potentially front-line therapy for treatment of bacteremia due to vancomycin-resistant enterococcus.

- **Urinary tract infection**: Although linezolid isn’t excreted in the urine, urinary concentrations greatly exceed serum levels. Linezolid may be used for definite or suspected infection with vancomycin-resistant enterococci.
- **Skin and soft-tissue infections**: Linezolid appears to be more effective than vancomycin.
- **CNS infections**: Linezolid has excellent CSF penetration and some limited evidence suggests that it may be used in meningitis.

<table>
<thead>
<tr>
<th>Type of organism</th>
<th>Linezolid</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus</td>
<td>37/222 (16.7%)</td>
<td>37/215 (17.2%)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>4/15 (26.7%)</td>
<td>1/11 (9.1%)</td>
</tr>
<tr>
<td>Gram positive and Gram negative</td>
<td>16/46 (34.8%)</td>
<td>7/39 (17.9%)</td>
</tr>
<tr>
<td>No organism</td>
<td>20/76 (26.3%)</td>
<td>12/92 (13.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>1/4 (25%)</td>
<td>1/6 (16.7%)</td>
</tr>
</tbody>
</table>

Data from 2007 FDA letter describing an RCT of linezolid versus vancomycin for treatment of catheter-related bloodstream infection. More patients in the linezolid group died, but this difference was not statistically significant (p=0.07). The mortality for patients with gram-positive infection was exactly the same between the linezolid and vancomycin groups (red box). Due to uneven randomization, more patients with gram-negative or mixed infection ended up in the linezolid group. Patients didn’t necessarily receive gram-negative coverage initially, possibly exploring poorer outcomes in gram-negative infection. This data actually suggests the equivalence of linezolid compared to vancomycin for bacteremia. Unfortunately, it gave birth to the dogma that linezolid must never be used for patients with bacteremia.

**toxicity/contraindications**

- **Serotonin syndrome** may occur if combined with other serotonergic medications (although safe in combination with fentanyl).
  - Ideally, serotonergic medications would be stopped and allowed to wash out prior to initiation of linezolid (especially fluoxetine, which has a half-life of several days). However, for critical infections it may be reasonable to simultaneously stop the serotonergic medications and initiate linezolid (with intensive monitoring for serotonin syndrome). Notably, when linezolid and serotonergic agents are co-administered, the rate of serotonin syndrome is <10%. Notably, when linezolid and serotonergic agents are co-administered, the rate of serotonin syndrome is <10%.
- **Nausea/vomiting** and diarrhea are most common side effects.
- **Prolonged courses** (>10-14 days) are difficult to tolerate due to a variety of toxicities which usually emerge late:
  - Thrombocytopenia, sometimes neutropenia and anemia (reversible)
  - Peripheral neuropathy (reversible) and optic neuropathy (can be irreversible if treatment isn’t stopped)
  - Lactic acidosis
- **Rarely**: Posterior reversible leukoencephalopathy (PRES), seizures, hypoglycemia.
- **Note**: protective against Clostridioides difficile.

**pharmacology**

- 100% oral bioavailability.
- Excretion: Mostly cleared by hepatic metabolism, but 30% is excreted unchanged in the urine.
- Protein binding: 31%
- Vd: 0.6 L/kg (approximately equal to total body water content)
- Penetration: Outstanding tissue penetration, including lung and particularly CSF (may reach 70% serum levels).

**dosing**

- 600 mg IV/PO q12hr (no adjustment for renal dysfunction; same dose provides meningeal coverage).
- Morbid obesity and severe infection, or co-administration with rifampin: consider 600 mg IV/PO q8hr.


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**macrolides (azithromycin, clarithromycin)**

[back to contents](http://reference.medscape.com/drug/zyvox-linezolid-342574)
spectrum

- Gram-positive coverage: some methicillin-sensitive staph aureus, some Group A/B/C/D/G streptococci, some pneumococcus. Clarithromycin may be superior for gram-positives.
- Haemophilus influenzae and Moraxella catarrhalis (azithromycin > clarithromycin).
- Atypical organisms (e.g. Mycoplasma pneumoniae, Chlamydiae pneumoniae, Legionella pneumophilia, pertussis, Coxiella burnetii).

use

- Atypical coverage for community-acquired pneumonia. Evidence suggests mortality benefit in severe community-acquired pneumonia, possibly due to anti-inflammatory effects.
- COPD exacerbation (although doxycycline may be preferable for patients recently on azithromycin).

toxicity/contraindications

- Extremely well tolerated; most common side effect is nausea or diarrhea with oral administration.
- Relatively low rate of Clostridioides difficile compared to most other antibiotics.
- Exacerbation of myasthenia gravis.
- Transaminitis; cholestasis (azithromycin)
- Clarithromycin:
  - May increase QTc and risk of torsade de pointes (not seen clinically with azithromycin [https://emcrit.org/pulmcrit/myth-busting-azithromycin-does-not-cause-torsade-de-points-or-increase-mortality/]).
  - May cause delirium (antibiomania)

pharmacology

- Azithromycin
  - Oral bioavailability of azithromycin is 37% (food decreases absorption).
  - Excretion in the bile, only 6% excreted unchanged in urine.
  - Protein binding: 50%
  - Vd: 30 L/kg
  - Penetration: Concentrates intracellularly within tissues, with a long half-life (2-4 days). Penetrates most tissues, but not urine or meninges.
- Clarithromycin
  - Oral bioavailability is 50%.
  - Excretion: Mostly excreted in the liver. 25% excreted unchanged in urine.
  - Protein binding: 60%
  - Vd: 3 L/kg
  - Penetration: Concentrates intracellularly (tissue concentration > serum concentration), poor CSF penetration.
  - Mechanism: blocks the protein from exiting the 50S ribosomal unit (same mechanism as clindamycin).

dosing

- Azithromycin
  - Community-acquired pneumonia, COPD: Most commonly 500 mg IV x1, then 250 mg IV daily x4 days. Alternative: 500 mg IV daily for three days (long half-life in tissues so will have biologic effect >>3 days).
  - Legionella pneumonia: 500 mg IV daily for 5-10 days.
  - Morbid obesity or severe illness: may consider 500 mg IV daily.

https://emcrit.org/ibcc/antibiotics/
Clarithromycin
- 500 mg PO twice daily (immediate-release formulation)
- GFR 10-30 ml/min: Reduce dose by 50%
- GFR < 10 ml/min: 250-500 mg q24hr
- No dose adjustment in hepatic dysfunction (kidneys pick up slack in drug excretion).


metronidazole

**spectrum**
- Best anti-anaerobic agent (better coverage & fewer problems with Clostridioides difficile compared to clindamycin).
- Only covers anaerobes.

**use**
- Anaerobic coverage (e.g. metronidazole plus cefepime produces broad-spectrum coverage). Can be used in broad range of infections (e.g. abdominal, CNS, gynecologic, respiratory, bacteremia, or soft tissue).
- Clostridioides difficile *(inferior to oral vancomycin)*; may be used as add-on agent in severe cases or in patients unable to take oral medications.
- Generally avoid adding it to piperacillin-tazobactam or meropenem (these agents have great anaerobic coverage; the only thing that metronidazole adds is Clostridioides difficile coverage).

**toxicity/contraindications**
- Nausea, diarrhea, dysgeusia
- Can cause encephalopathy, seizure, peripheral neuropathy, or aseptic meningitis (especially with prolonged use).
- Rarely: Stevens-Johnson syndrome, pancreatitis, hemolytic uremic syndrome.

**pharmacology**
- Oral bioavailability approaches 100%.
- Excretion: 20% excreted unchanged in urine, mostly excreted in bile.
- Protein binding: 20%
- Vd: 0.7 L/kg
- Penetration: Lipophilicity and low protein-binding cause metronidazole to distribute widely throughout the total body water (including abscess cavities and CNS).
- Mechanism: Trojan horse which is converted into bactericidal metabolites by the electron transport chain of anaerobic bacteria.

**dosing**
- 500 mg IV/PO q8 (no adjustment for renal function).
- Consider 50% dose reduction in Child-Pugh class C cirrhosis.

**spectrum**

- Gram positives:
  - Group A, B, C, G streptococci are susceptible
  - *Streptococcus pneumoniae*: generally susceptible for non-meningeal infections
- *Neisseria meningitidis*
- Anaerobes:
  - *Clostridia* (excluding *Clostridioides difficile*) are uniformly susceptible
  - Most oral anaerobes

**use**

- Rarely used for *empiric* therapy, but it is definitive therapy for susceptible organisms. Most common examples of this are as follows:
  - 1) Group A, B, C, G streptococci (uniformly susceptible)
  - 2) *Streptococcus pneumoniae* known to be PCN-sensitive
    - Infection outside CSF: Susceptible if MIC 2 mcg/ml or lower.
    - CNS infection: Susceptible if MIC is 0.06 mcg/ml or lower.
  - 3) *Neisseria meningitidis*
  - 4) *Clostridia perfringens*

**toxicity/contraindications**

- Hypersensitivity (rash, anaphylaxis, interstitial nephritis, hepatitis, drug fever)
- Neurotoxicity at high doses (myoclonus, seizure, confusion)
- Thrombocytopenia, leukopenia, hemolytic anemia (may also cause false-positive Coombs test without hemolytic anemia)

**pharmacology**

- Excretion: 80% excreted unchanged in the urine.
- Protein binding: 60%
- Vd: 0.3 L/kg
- Penetration: most fluids and tissues, including inflamed meninges.

**dosing**

- GFR > 50 ml/min: 2-4 million units (MU) q4 (4 MU for endocarditis or CNS infection)
- GFR 10-50 ml/min: 1-2 MU q4
- GFR <10 ml/min: 1-2 MU q6


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https://emcrit.org/ibcc/antibiotics/
spectrum

- Streptococci groups A, B
- Pneumococci (penicillin-sensitive)
- Methicillin-sensitive staph aureus (MSSA) & methicillin-sensitive staph epidermidis

use

- Main use is for known MSSA infection (including: endocarditis, hepatic abscess, skin/soft tissue infections, pneumonia).
  - Recent evidence suggests that cefazolin may be superior for many MSSA infections. However, cefazolin doesn’t penetrate the CNS, so nafcillin remains front-line for severe MSSA infections with CNS involvement (e.g. MSSA meningitis, MSSA endocarditis with septic emboli).
- Sensitive strains of coagulase-negative staph (Staph epidermidis, Staph haemolyticus, Staph lugdenensis)
- Synergistic en vitro with either vancomycin or daptomycin against staph aureus (clinical relevance to be determined).  

Toxicity/contraindications

- Rash (10% of patients), interstitial nephritis, drug fever
- Thrombocytopenia, leukopenia, hemolytic anemia (may also cause false-positive Coombs test without hemolytic anemia)
- Seizure or myoclonus may occur with high doses
- Phlebitis

Pharmacology

- Excretion: Mostly cleared by the liver and biliary tract. 10-30% unchanged drug is excreted in the urine.
- Protein binding: 90%
- Vd: 0.2 L/kg
- Penetration: Distributes widely, including inflamed meninges (20% serum levels).
- Mechanism: Inhibits cell wall synthesis by binding to penicillin-binding proteins (primarily 1a, 1b, and 2).

dosing

- Serious infections (e.g. endocarditis): 2 grams IV q4hr
- Dose reduce by 50% in decompensated liver failure. No adjustments for renal dysfunction.
- Monitor liver function tests every week


ampicillin & ampicillin-sulbactam
spectrum

- Ampicillin
  - Gram-positives: Enterococcus (~80% of E. faecalis, but only rarely covers E faecium); most Streptococci, most Streptococcus pneumoniae
  - Gram-negatives: Some E. Coli, Proteus mirabilis
  - Anaerobes: Covers many, including clostridium (but not Clostridioides difficile)
  - Listeria monocytogenes
- Ampicillin-Sulbactam
  - Gram-positives: Enterococcus (improved coverage of E. faecium compared to ampicillin); most streptococci, most Streptococcus pneumoniae, MSSA
  - Haemophilus influenzae, Moraxella catarrhals
  - Gram-negatives: Better than ampicillin but still mediocre coverage, increasing resistance (overall inferior to ceftriaxone).
  - Good anaerobic coverage

use

- Ampicillin may be drug of choice for:
  - Enterococcus faecalis
  - Listeria monocytogenes
  - Sensitive strains of E. Coli, Proteus mirabilis
- Ampicillin-Sulbactam
  - Community-acquired empyema (may easily transition to oral amoxacillin-clavulanic acid).
  - Epiglottitis (covers Haemophilus influenzae).
  - Diabetic foot infection, mild.

toxicity/contraindications

- Ampicillin
  - Skin rash (more common with mononucleosis, CLL, or allopurinol use)
  - Cytopenias (Coombs-positive hemolytic anemia, neutropenia, thrombocytopenia)
  - Acute interstitial nephritis, hepatitis, drug fever
  - Seizure, myoclonus (especially high doses in renal failure)
- Ampicillin-Sulbactam
  - Similar to ampicillin, increased risk of cholestatic hepatitis

pharmacology

- Excretion: 90% excreted in urine unchanged.
- Protein binding: 25%
- Vd: 0.25 L/kg
- Penetration: Widely distributed (e.g. urine, pleural fluid, lung), including inflamed meninges.

dosing
Ampicillin

- 1-2 grams IV q4-6 (q4 for meningitis or endocarditis)
- GFR 30-50 ml/min: extend dosing interval to q8
- GFR 10-30 ml/min: extend dosing interval to q8-q12
- GFR <10 ml/min: extend dosing interval to q12-q16

Ampicillin-Sulbactam

- 1.5-3 grams q6hrs
- GFR 30-50 ml/min: extend dosing to q6-q8
- GFR 10-30 ml/min: extend dosing to q12
- GFR <10: extend dosing to q24


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**Ampicillin-Tazobactam**

- **Spectrum**
  - Gram-positive coverage:
    - Covers: MSSA, non-enterococcal streptococci, vancomycin-sensitive enterococci
    - Misses: MRSA, vancomycin-resistant enterococci, coagulase-negative staph
  - Gram-negative coverage: Excellent (covers most pseudomonas)
    - Warning: Be careful with bacteria that are resistant to ceftriaxone and sensitive to piperacillin-tazobactam (especially E. coli & Klebsiella pneumoniae); this sensitivity pattern suggests extended-spectrum beta-lactamase resistant bacteria, which may be better treated with a carbapenem (see **ESBL** below).
  - Anaerobic coverage: Excellent (misses *Clostridioides difficile*)

- **Use**
  - Septic shock
  - Intra-abdominal infections, biliary sepsis, urosepsis
  - Nosocomial pneumonia

**Toxicity/Contraindications**

- Rash, drug fever
- Leukopenia, thrombocytopenia

https://emcrit.org/ibcc/antibiotics/
- Associated with lower rate of Clostridioides difficile than broad-spectrum cephalosporins (e.g. cefepime).

**pharmacology**

- Excretion: ~70% excreted unchanged in the urine.
- Protein binding: ~30%
- Vd: ~0.3 L/kg
- Penetration is excellent, including some entry into inflamed meninges. Extremely high levels in bile make this a good choice for biliary tract infections.
- Mechanism: inhibits synthesis of bacterial cell wall

**dosing**

- GFR >20 ml/min: 4.5g q8hr (extended infusion over four hours)
- GFR <20 ml/min: 4.5g q12hr (extended infusion over four hours)
- Morbid obesity: higher doses may be required.


**spectrum**

- Staph aureus (including MRSA), coagulase-negative staph
- Streptococcus pneumoniae, Group A streptococcus
- Acinetobacter baumanii
- Legionella, listeria
- Mycobacteria including tuberculosis

**use**

- *Note*: Rifampin is generally used as an adjunctive agent to avoid emergence of resistance.
- Prosthetic valve endocarditis
- Prosthetic joint infections
- Meningitis
  - Community-acquired: targeted especially at treatment of PCN-resistant Streptococcus pneumoniae.
  - Nosocomial: used in hardware-associated meningitis/ventriculitis.
- Legionella infections
- Tuberculosis

**toxicity/contraindications**

- Interacts with many medications.
- Discoloration of bodily fluids
- Hepatitis
- Nausea/vomiting, abdominal pain
- Rarely: Thrombocytopenia, leukopenia, hemolytic anemia
**pharmacology**

- Oral bioavailability: 95%
- Excretion: Hepatic metabolism, mostly excreted into bile. 15% excreted unchanged in urine.
- Protein binding: 80%
- Vd: 0.9 L/kg
- Penetration:
  - Good penetration of most tissues including bone, joint, and meninges (10-20% penetration of meninges; compare to vancomycin's 1-5% penetration).\(^{58}\)
  - Excellent penetration of biofilms, may help sterilize foreign bodies which cannot be removed (e.g. prosthetic valve endocarditis).
- Mechanism: Inhibits bacterial RNA polymerase

**dosing**

- Meningitis: 600 mg q12.\(^{59}\)
- Prosthetic valve endocarditis: 300 mg q8

**Medscape monograph:** [Rifampin](https://reference.medscape.com/drug/rifadin-rimactane-rifampin-342570)

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**tigecycline**

**spectrum**

- Covers all gram-positive cocci (including MRSA and vancomycin-resistant enterococci).
- Good gram-negative coverage (but misses Pseudomonas, most Proteus and Providencia, and some Morganella). Can be used against a range of multi-drug resistant gram negatives (e.g. ESBL, AmpC ([#AmpC inducible beta-lactamase](https://emcrit.org/ibcc/antibiotics/)), carbapenemase-producing enterobacteriaceae)
- Covers most anaerobes, including Clostridioides difficile.
- Covers listeria, Mycoplasma pneumoniae, Chlamydia pneumoniae.

**use**

- Add-on agent for fulminant Clostridioides difficile (suppresses toxin production by Clostridioides while simultaneously working against colonic flora which have translocated out of the bowel).\(^{60}\)
- Extremely drug-resistant bacteria (approved for community-acquired pneumonia, skin/soft tissue infection, and complicated intra-abdominal infection)
- FDA approved for soft tissue infection, complicated intra-abdominal infections, and pneumonia. However, they are generally not front-line, given concerns about potential of increased mortality (see FDA communication [here](https://www.fda.gov/drugs/drugsafety/ucm224370.htm)). This may reflect low drug levels in the blood.

**toxicity/contraindications**

- Nausea/vomiting (may avoid with slow infusion)
- Pancreatitis, hepatitis
- Coagulation abnormality, low fibrinogen level

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https://emcrit.org/ibcc/antibiotics/
Anaphylactoid reactions

**pharmacology**

- Excretion: Mostly excreted unchanged by the liver into the bile. 10-20% excreted unchanged in urine.
- Protein binding: 89%
- Vd: ~8 L/kg\(^{61}\)
- Penetration
  - Extensively enters the tissues (e.g. concentrated in alveolar macrophages, gallbladder, and colon).
  - Low levels in blood and urine (not good for bacteremia; maybe OK for urinary tract infection)
- Mechanism: Inhibition of protein synthesis through 30s ribosomal binding blocking aminoacyl-tRNA (same as doxycycline).

**dosing**

- Loading dose 100 mg, then 50 mg IV Q12hr (for serious infection 100 mg IV Q12 may be better).
- High-dose tigecycline (serious systemic infections): Loading dose of 200-400 mg IV, then 100-200 mg IV q24.
- No dose adjustment for renal dysfunction.
- In Child-Pugh Class C cirrhosis, reduce maintenance dose by 50%.
- Consider monitoring CBC, INR, lipase, and LFTs q48hr.\(^{60}\)


**trimethoprim-sulfamethoxazole**

[trimethoprim-sulfamethoxazole](#)

**spectrum**

- Gram-positives:
  - Group A and B streptococci
  - MSSA and >90% of MRSA isolates\(^{62}\)
  - ~70% Streptococcus pneumoniae
- Gram-negatives
  - Overall very good (better than ampicillin/sulbactam), but sensitivity of E. coli is falling
  - Misses pseudomonas
  - Avoid use for Klebsiella pneumoniae, even if sensitive *in vitro*.
- Anaerobes: Most gram-negative anaerobes, including Bacteroides
- Weird stuff: Legionella, Pneumocystis jirovecii, nocardia, Listeria monocytogenes, toxoplamosis

**use**

- Pneumocystis jirovecii
Listeria, toxoplasmosis, legionella

MRSA infections (particularly skin, appears inferior to vancomycin for MRSA bacteremia\textsuperscript{62, 63}).

Pneumonia (but limited by increasing resistance among streptococcus pneumoniae)

Urinary tract infections and prostatitis (due to sensitive organisms, not as empiric therapy)

**toxicity/contraindications**

- Overall generally well tolerated, but in context of HIV causes lots of hypersensitivity reactions.
- Hypersensitivity (rash, drug fever, aseptic meningitis, rarely Steven's Johnson Syndrome)
- Renal dysfunction (usually this is pseudo-elevation of creatinine, but can also cause interstitial nephritis or crystalluria with genuine renal dysfunction)
- Hepatitis, cholestasis, liver failure
- Hyperkalemia
- Methemoglobinemia in patients with severe G6PD deficiency
- Neutropenia, thrombocytopenia, leukopenia

**pharmacology**

- >90% oral bioavailability
- Excretion: ~50% excreted unchanged in urine
- Protein binding: 60%
- Vd: 1.8 L/kg trimethoprim; 0.3 L/kg sulfamethoxazole
- Penetration: excellent penetration of most tissues including CSF (40% serum levels).
- Extensively metabolized by liver, cleared by kidneys.

**dosing (dose based on trimethoprim component)**

- Basics:
  - Single-strength tablet = \textbf{80 mg trimethoprim} & 400 mg sulfamethoxazole
  - Double-strength tablet = \textbf{160 mg trimethoprim} & 400 mg sulfamethoxazole
- Pneumocystis jirovicii: daily dose of 15 mg/kg = 5 mg/kg q8 (~two double-strength tablets q8hr)
- Serious bacterial infection in ICU: daily dose of 10 mg/kg = 2.5 mg/kg q6 (~one double-strength tablet q6)
- Urinary tract or skin/soft tissue infection: daily dose of ~5 mg/kg (~one double-strength tablet q12)\textsuperscript{64}
- Renal dosing:
  - GFR 15-30 ml/min: use 50-75% of usual dose
  - GFR <15 ml/min: avoid unless Pneumocystis jirovicii; use 25-50% of usual dose
- Co-administration of folinic acid may prevent cytopenias without affecting anti-bacterial effects (except possibly against enterococci)


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**vancomycin (intravenous)**

(Back to contents)
spectrum: basically all gram-positives except VRE

- MSSA (but less effective than beta-lactams)
- MRSA (although efficacy depends on MIC)
- Enterococci except for vancomycin-resistant enterococci (VRE), which are usually Enterococcus faecium.
  - However, for E. faecalis bacteremia or endocarditis, add ampicillin or gentamycin for synergy.

interpreting vancomycin MIC in the context of MRSA

- MIC 1 ug/ml or below: Susceptible
- MIC 1.5 ug/mL is intermediate. Avoid vancomycin if possible. If vancomycin must be used, an AUC24 of at least 600 should be ensured to achieve efficacy (unfortunately this dose of vancomycin will increase the risk of nephrotoxicity).
- MIC 2 or higher ug/mL: Resistant

reasons vancomycin is often a sub-optimal antibiotic

- Nephrotoxic (rising resistance over time forces us to target higher vancomycin levels, which increases toxicity).
- Requires dose adjustment & monitoring of levels.
- For beta-lactam sensitive organisms, a beta-lactam is more effective (vancomycin provides broad-spectrum yet weaker coverage).
- Suboptimal penetration of lungs and meninges.
- Less effective for MRSA with a minimum inhibitor concentration (MIC) of 1.5 mg/ml or greater, a situation in which a different antibiotic may be more effective.
- Penicillin allergy is traditionally a major reason for the use of vancomycin. However, penicillin has a low rate of cross-allergy with cefazolin and third/fourth generation cephalosporins, so ‘penicillin allergy’ is a poor rationale for vancomycin use.
- Vancomycin should be avoided for empiric treatment of urinary tract infections or intra-abdominal infections. MRSA isn’t a common pathogen at these sites, whereas Enterococcus faecium may be more likely. If you’re really looking for an extended-spectrum gram-positive agent for infections at these sites, linezolid might be more appropriate (however, coverage with a single agent such as piperacillin-tazobactam is usually fine).

use

- Empiric coverage for MRSA in the context of septic shock, endocarditis, vascular catheter infection, skin/soft tissue infection.
- Known MRSA infections.
- Great choice for patients on chronic dialysis (the main drawback of vancomycin is nephrotoxicity).

toxicity/contraindications

- Nephrotoxicity is the primary concern.
- Fever/chills, phlebitis
- Cytopenias:
  - Neutropenia, especially with prolonged use
  - Thrombocytopenia: may cause acute, severe thrombocytopenia due to immune platelet consumption

https://emcrit.org/ibcc/antibiotics/
Red person syndrome: rapid infusion of vancomycin can cause histamine release with erythema and hypotension (anaphylactoid reaction). This is not an allergy, the drug may still be given at a slower rate.

Severe dermatologic reactions: drug rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP).

**Pharmacology**
- Excretion: 90% excreted unchanged in urine.
- Protein binding: ~50% protein binding
- Vd: 0.7 L/kg
- Penetration
  - Penetrates body fluids well, but limited penetration of lung or CSF.
  - Intravenous vancomycin has no meaningful activity against Clostridioides difficile (it must be given orally for that application).
- Mechanism: cell wall synthesis inhibited by binding to D-alanyl-D-alanine precursor and inhibiting peptidoglycan polymerization.

**Dosing**
- Loading dose of 25 mg/kg may be considered (critical illness, endocarditis, pneumonia, CNS infections).
- Maintenance dose is 15 mg/kg, with the conventional dosing interval dependent on renal function:
  - GFR > 70: q12
  - GFR 30-70: q24
  - GFR 20-30: q48
  - GFR <20: serially check levels, re-dose when sub-therapeutic (roughly q3-7 days)
- Conventional vancomycin dosing is based on trough levels:
  - Skin/soft tissue infection: target 10-15 mcg/ml
  - Bacteremia, endocarditis, pneumonia, meningitis: target 15-20 mcg/ml
  - Troughs <10 mcg/ml may promote emergence of resistant bacteria.
- It's probably preferable to dose vancomycin based on individual patient pharmacokinetics as explored [here](https://emcrit.org/squirt/vanco/).

Other options: Aminoglycosides, fluoroquinolones, or trimethoprim-sulfamethoxazole aren't susceptible to AmpC beta-lactamase.

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extended-spectrum beta-lactamases (ESBL)

ESBL refers to plasmids which confer resistance to most beta-lactams, except for cephamycins (cefoxitin, cefotetan, and cefmetazole) and carbapenems. They are generally susceptible to beta-lactamase inhibitors (e.g. sulbactam and tazobactam), potentially leaving these bacteria sensitive to combinations such as piperacillin-tazobactam.

diagnosis

- Most common among Klebsiella pneumoniae, Klebsiella oxyccoca, or E. coli. However, can occur in a variety of gram-negative bacilli.
- May be suspected on the basis of an unusual in vitro sensitivity pattern:
  - Sensitive to cephamycins (cefoxitin, cefotetan, cefmetazole)
  - Resistant to 3rd & 4th-generation cephalosporins
  - Often sensitive to beta-lactamase inhibitors (e.g. piperacillin-tazobactam)
- Many microbiology laboratories will recognize these patterns and report out that the species is an ESBL.

treatment

Caution: Most beta-lactam antibiotics shouldn't be used (regardless of whether they are reported out as "sensitive" by the laboratory).

carbapenems

- Meropenem or imipenem are the gold standard therapy for severe infection.
- Ertapenem: May be OK for less severe infection. Some studies have shown trends towards increased mortality with ertapenem. This may relate to inadequate dosing of ertapenem (the standard 1 gram/day regimen may fail to achieve adequate levels; 1.5-2 grams/day may be superior)(31369411).

beta-lactam/beta-lactam inhibitor combinations

- Observational studies show mixed results (no obvious increase in mortality vs. carbapenems).
- MERINO trial\(^\text{56}\):
  - RCT of bloodstream infections with E. coli or K pneumoniae resistant to ceftriaxone and "sensitive" to piperacillin-tazobactam.
  - 30-day mortality was 12% (23/187) in piperacillin-tazobactam group vs. 4% (7/191) in the meropenem group (p=0.002 with fragility index of five).
  - Limitations: Many deaths were ascribed to noninfectious complications of malignancy. Study seems to have combined ESBL organisms with inducible resistance due to AmpC production.
  - Overall this is the highest quality evidence available here, and it shows a potential signal of harm with piperacillin-tazobactam.
- It remains conceivable that piperacillin-tazobactam might be adequate in ESBL E. coli limited to the urinary tract, but overall this probably isn't a terrific idea.\(^\text{70–73}\)

other antibiotics:

- Trimethoprim-Sulfamethoxazole: May be used as oral step-down agent once patient recovering, if susceptible.
- Forsomycin and nitrofurantoin: May be used for uncomplicated cystitis (31369411).

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podcast


Double-coverage for pseudomonas is generally unnecessary and poorly supported by evidence.

- Over-utilization of:
  - Clindamycin – generally should be avoided except in toxic shock or severe group A streptococcal infections.

- Be careful for species with inducible AmpC genes (especially Enterobacter, Citrobacter, Serratia, Morganella, Proteus, Providentia). These may develop resistance to beta-lactams, causing treatment failure even if the antibiotic appears “sensitive” en vitro.

- Be wary for the presence of ESBL species if gram-negatives (especially E. coli or Klebsiella) appear sensitive to piperacillin-tazobactam but resistant to third and fourth-generation cephalosporins.

- For many non-MRSA gram positives, vancomycin is less powerful and has inferior tissue penetration compared to beta-lactams. Thus, vancomycin isn't optimal therapy for MSSA or streptococcal species.

References

Special Acknowledgement: Pharmacokinetics and doses listed above were largely drawn from the Hopkins Antibiotic Guide (https://www.hopkinsguides.com/hopkins) and Antibiotic Essentials 15th Ed. (https://www.amazon.com/Antibiotic-Essentials-2017-Burke-Cunha/dp/9385999079) by Cunha & Cunha. This chapter isn't intended to replace these resources, which I would fully recommend obtaining and consulting.

8. Blumenthal K, Youngster I, Shenoy E, Banerji A, Nelson S. Tolerability of cefazolin after immune-mediated hypersensitivity reactions to...


