Beta-lactam antibiotics: Penicillins

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Penicillium chrysogenum +
Staph. Aureus


Beta-lactams bind to transpeptidase in place of D-Ala-D-Ala

Transpeptidase (a PBP) normally binds to the D-Ala-D-Ala at the end of peptidoglycan precursors to crosslink the peptidoglycan. Beta-lactams such as penicillin mimic D-Ala-D-Ala, occupying the PBP active site and inhibiting crosslinking of peptidoglycan peptide bridges. Cell wall is weakened and this allows autolytic enzymes that degrade the peptidoglycan network to dominate, leading to lysis of the cells. Bactericidal.
Beta-lactams bind to transpeptidase in place of D-Ala-D-Ala. The transpeptidase active site is occupied by beta-lactam and cannot bind D-Ala-D-Ala, thus crosslinking does not take place.

Beta-lactam antibiotics:

- **Amoxicillin** (penicillin)
- **Cephalexin** (cephalosporin)
- **Imipenem** (carbapenem)
- **Aztreonam** (monobactam)
Beta-lactam antibiotics

- **Penicillins**
  - Potent, safe, but alone generally narrow spectrum, and susceptible to beta-lactamases, allergy

- **Cephalosporins**
  - Less susceptible to penicillinases, less allergenic, broader spectrum in later “generations” (increased Gram- coverage)

- **Carbapenem**
  - IV, broad spectrum, resistant to most beta-lactamases; drugs of last resort

- **Monobactam**
  - IV, Gram- coverage (poor for Gram+), resistant to many beta-lactams

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Penicillins G and V

- **Penicillin G**
  - (benzylpenicillin)
  - Isolated directly from penicillium molds; fermentation produces large yields
  - Fairly narrow spectrum of coverage
  - Highly susceptible to beta-lactamase and penicillinase (e.g. *S. aureus*) activity

- **Penicillin V**
  - Penicillin VK, potassium salt
  - (phenoxymethylpenicillin)
Semi-synthetic penicillins

Cleave off natural sidechains with amidase to yield the 6-aminopenicillanic acid (6-APA) core, which can be synthetically substituted with other sidechains.

- Alter the spectrum, stability, bioavailability, resistance to penicillinases
- Examples: amino-penicillins (amox, amp), nafcillin, dicloxacillin, piperacillin

Penicillins general features

- Still widely prescribed and effective for bacteria that are not resistant
  - Amoxicillin still one of the most widely used antimicrobials (#5 drug overall)
- Very potent, bactericidal, if pathogen is sensitive, MIC~0.02µg/ml
- Fairly broad spectrum overall, especially for semi-synthetic derivatives in combination with beta-lactamase inhibitors
- Generally very safe (good selective toxicity); targets the cell wall, which is unique to bacteria
- Penicillin allergies:
  - One of the highest reported causes of a drug allergy, however actual incidence is believed to be somewhat lower than the 10% reported
10% of population claims to be allergic to penicillins


Older penicillin preparations <1970 included more contaminants that may have contributed frequency of allergic reaction. Newer preparations are more pure.

Infections themselves, including some viral infections (EBV, HIV, coxsackie, HBV, etc), can have associated rashes.

Thus, it may not necessarily be the case that every patient who presents with a rash close to penicillin administration necessarily has a penicillin allergy

If a patient presents a rash, they are generally considered allergic

Fortunately, skin tests are now commercially available again

Most small, simple drugs such as penicillins do not themselves directly cause allergic reactions; instead they first form covalent adducts (hapten + carrier complexes) with host proteins

These complexes present antigens that are recognized by IgE antibodies, leading to immune responses

The beta-lactam ring is unstable. It opens up when bound to the PBP active site. Normally this isomer covalently acylates an active site residue to irreversibly shut down the PBP activity
Penicillin allergy

- But an opened ring may also form an adduct with other proteins
- “Major determinant” of penicillin allergy involves conjugates forming with lysine side chains of host proteins. Penicilloyl lysyl antigen. IgE mediated response to major antigen.
- “Minor determinants” include adducts formed with cysteine and carboxyl residues. IgE mediated response directed against “minor determinants”
- Major vs minor only refer to the amounts of material observed, not to the immunological response

Penicillin allergy: major determinant

- Small fraction of penicillin is isomerized to penicillenic acid, which reacts with the terminal amino group on lysine side chains, yielding the penicilloyl lysyl major determinant
- 90% of modified proteins are of this variety
- Response occurs within 72h.
- Urticaria (hives), rash, pruritus (itch)
- If a patient presents a rash, they are considered allergic
Penicillin allergy: major determinant

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- Response occurs within 72h.
- Urticaria (hives), rash, pruritus (itch).
- If a patient presents a rash, they are considered allergic.

Penicillin allergy: minor determinant

- “Minor determinants”: Result from reaction of other breakdown products with cysteine residues on proteins to form penicillenyl and penicillamine conjugates.
- These determinants are associated with serious reactions such as anaphylaxis, shock.
- Usually appear within 1h of administration; immediate hypersensitivity (IgE).
- Anaphylaxis in 1:5,000-10,000 treatments (0.01-0.02%).
- ~0.0015% fatal outcome.
Penicillin allergy: testing

- What is available?
  - PrePen (AllerQuest); back on the market as of May, 2010
    - Skin test (puncture or intradermal) containing the benzylpenicilloyl major determinant on a polylysine carrier; those who show a positive test (wheal and flare on skin) to PrePen have IgE against the major determinant and are classified as penicillin allergic
    - PrePen does not include the minor determinant. Fresh, diluted PenG may be added to for the minor determinant.

- A patient may only exhibit an IgE-mediated response to the minor determinant
- Ideally a penicillin allergy test would include both major and minor determinants

Penicillin allergy

- For patients who have a positive skin test (PrePen+PenG), 40-70% may exhibit an anaphylactic reaction if penicillin were to be administered
- For patients who have a negative skin test, 1-3% may exhibit a reaction (usually mild) when penicillin is administered
- If minor determinants are not included (i.e. PenG), 3-10% of allergic patients may be missed by Pre-Pen

- Desensitization. If penicillin or beta-lactam is absolutely needed for patient with penicillin allergy, desensitization protocols are available (e.g. oral desensitization with PenV). Must be carefully monitored.
  - Examples where this might be indicated:
    - Strep. pyogenes is still sensitive to penicillins, and they are potent
    - Syphilis (caused by the spirochete Treponema pallidum) in pregnant women.

http://www.cdc.gov/std/treatment/2006/penicillin-allergy.htm
Penicillin allergy cross-reactivity

- Cross-reactivity with other beta-lactams:
  - If a patient has had a serious reaction (e.g. anaphylaxis), do not give other beta-lactams, except aztreonam (monobactam), which has no cross-reactivity
  - Allergy to penicillins does not necessarily correlate with allergy to cephalosporins, but 10% does occur; if a patient has a rash w/ penicillin, may switch to a cephalosporin
  - If a patient has shown an allergy to a cephalosporin, they are presumed to be allergic to penicillins as well
  - Oral administration gives fewer reactions than IV or IM, probably due to more gradual exposure of immune system to the drug
  - In general, the semi-synthetic penicillins show fewer allergic reactions
  - Ampicillin also has a separate rash associated with it; affects 9.5% of patients. Generally more allergenic than PenG or V

Comparative features of penicillins

- Stability of penicillins in stomach acid variable
  - PenG is destroyed by acid, PenV more stable
  - Newer derivatives such as amoxicillin have much better stability and bioavailability

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>PenG</td>
<td>15-30%</td>
</tr>
<tr>
<td>PenV</td>
<td>60%</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>30-50%</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>70-80%</td>
</tr>
</tbody>
</table>

- Susceptibility Gram+ penicillinas (narrow spectrum beta-lactamase) significant for PenG, PenV, amoxicillin, ampicillin
  - Dicloxacillin considered a “penicillinase resistant” penicillin
  - Highly susceptibility to Gram- beta-lactamases; combine with beta-lactamase inhibitors to get coverage of Gram- bugs
General features of penicillins

- Not significantly metabolized. Significant amounts are excreted in unmodified, active form in urine. PenG ~80% excreted within 3-4h.
- Can be effective therapeutic for urinary tract infections (UTI)
- Frequent dosing required
- Co-administered with probenicid to inhibit renal excretion. Increases plasma concentrations of penicillins and cephalosporins ~2x.
- Low penetration to cerebrospinal fluid unless inflammation is present

Properties of Penicillins

<table>
<thead>
<tr>
<th>type of penicillin</th>
<th>R group structure</th>
<th>oral absorption</th>
<th>route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &quot;Natural: Penicillin G&lt;br&gt;Penicillin V</td>
<td><img src="image" alt="Penicillin G structure" /> <img src="image" alt="Penicillin V structure" /></td>
<td>poor&lt;br&gt;60-70%</td>
<td>IV, IM&lt;br&gt;PO</td>
</tr>
<tr>
<td>2. Amino&lt;br&gt;Ampicillin&lt;br&gt;Amoxicillin</td>
<td><img src="image" alt="Ampicillin structure" /> <img src="image" alt="Amoxicillin structure" /></td>
<td>30-50%&lt;br&gt;70-90%</td>
<td>PO, IV, IM&lt;br&gt;PO</td>
</tr>
</tbody>
</table>

- Amino penicillins, more polar, better Gram-porin penetration

Courtesy Prof. Gary Elmer
## Penicillinase-resistant penicillins: “anti-Staph” (MSSA) penicillins

<table>
<thead>
<tr>
<th>Type of penicillin</th>
<th>R group structure</th>
<th>Oral absorption</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Penicillinase resistant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td><img src="image" alt="Structure" /></td>
<td>poor</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Oxacillin</td>
<td><img src="image" alt="Structure" /></td>
<td>poor</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td><img src="image" alt="Structure" /></td>
<td>good</td>
<td>PO</td>
</tr>
</tbody>
</table>

- Bulky side chains reduce binding of resistant penicillins to the penicillinase
- Methicillin was of this class, but no longer in use

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## Extended spectrum penicillins: “anti-Pseudomonas” penicillins

<table>
<thead>
<tr>
<th>Type of penicillin</th>
<th>R group structure</th>
<th>Oral absorption</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Extended spectrum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbenicillin (indanyl)</td>
<td><img src="image" alt="Structure" /></td>
<td>OK</td>
<td>PO</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td><img src="image" alt="Structure" /></td>
<td>poor</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Piperacillin</td>
<td><img src="image" alt="Structure" /></td>
<td>poor</td>
<td>IV, IM</td>
</tr>
</tbody>
</table>

- Charged, polar R-group improved permeability through Gm-porins
- Improved binding to PBP3 in Pseudomonas
- Used synergistically with aminoglycosides

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*Courtesy Prof. Gary Elmer*
## Antimicrobial spectrum of penicillins

<table>
<thead>
<tr>
<th>Penicillin type</th>
<th>Staph penicillinase resistance?</th>
<th>Gram- beta-lactamase resistance?</th>
<th>Useful coverage</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>no</td>
<td>no</td>
<td>Gram+; <em>S. pyogenes</em>, some <em>neisseria</em> (Gm-)</td>
<td>IV</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>no</td>
<td>no</td>
<td>Gram+; some <em>neisseria</em></td>
<td>PO</td>
</tr>
<tr>
<td>Ampicillin (aminopenicillin)</td>
<td>no</td>
<td>no</td>
<td>Gram+; some Gram- due to better porin penetration</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Amoxicillin (aminopenicillin)</td>
<td>no</td>
<td>no</td>
<td>Gram+; some Gram- due to better porin penetration</td>
<td>PO</td>
</tr>
<tr>
<td>Nafcillin (penicillinase-resistant)</td>
<td>yes</td>
<td>no</td>
<td><em>Staph</em> (not MRSA)</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Oxacillin (penicillinase-resistant)</td>
<td>yes</td>
<td>no</td>
<td><em>Staph</em> (not MRSA)</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Dicloxacillin (penicillinase-resistant)</td>
<td>yes</td>
<td>no</td>
<td><em>Staph</em> (not MRSA)</td>
<td>PO</td>
</tr>
<tr>
<td>Piperacillin (extended spectrum)</td>
<td>no</td>
<td></td>
<td>Gram+ anaerobes <em>Pseudomonas</em> Enterobacteriaceae (<em>Enterobacter, E.Coli, Klebsiella, Serratia, Salmonella, Shigella, Providencia, Citrobacter, Proteus</em>)</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Ticarcillin (extended spectrum)</td>
<td>no</td>
<td></td>
<td>similar to pip.</td>
<td>IV, IM</td>
</tr>
</tbody>
</table>
**Beta-lactamase inhibitors**

- Used to overcome beta-lactamase-related resistance to beta-lactams; **not effective against all beta-lactamases, however**
- Bind to beta-lactamase active site and irreversibly inactivate them by forming a covalent linkage to the active site serine
- Minimal antibiotic activity by themselves
- Combination therapy with beta-lactam antibiotics
  - Example: Augmentin (amoxicillin + clavulanic acid)

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**Penicillins combined with beta-lactamase inhibitors**

<table>
<thead>
<tr>
<th>penicillin type</th>
<th>Staph beta-lactamase (penicillinase) resistance?</th>
<th>Gram- beta-lactamase resistance?</th>
<th>useful coverage</th>
<th>route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin + clavulanate (Augmentin ®)</td>
<td>yes</td>
<td>yes</td>
<td>broad</td>
<td>PO</td>
</tr>
<tr>
<td>Ampicillin + sulbactam (Unisyn ®)</td>
<td>yes</td>
<td>yes</td>
<td>broad</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Ticarcillin + clavulanate (Timentin ®)</td>
<td>yes</td>
<td>yes</td>
<td>broad</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Piperacillin + tazobactam (Zosyn ®)</td>
<td>yes</td>
<td>yes</td>
<td>broad</td>
<td>IV, IM</td>
</tr>
</tbody>
</table>
Penicillins combined with beta-lactamase inhibitors

- Generally would like to use as narrow spectrum of antibiotic as possible so as to reduce impact on non-pathogenic flora and so as to maintain balance, prevent overgrowth (e.g. C. difficile, Candida yeast)

- But often we do not know the bacterial target, or may have a super-infection involving multiple species

Common infections

- Sinusitis
  - 30-40% S. pneumoniae
  - 20% H. influenzae
  - 20% M. catarrhalis

- Acute otitis media (middle ear infection)
  - By age 3, up to 70% of children have experienced at least 1 infection
  - 15-25% M. catarrhalis; 90-95% of these isolates produce beta-lactamases
  - 40% S. pneumoniae; 30% penicillin-resistant (PRSP)
  - 30% H. influenzae; 30% produce beta-lactamases

- Community-acquired pneumonia
  - 50-80% S. pneumonia
  - 2-18% H. influenzae
  - 2-5% S. aureus
  - ~5% anaerobes
  - ~5% other Gram-

- By comparison: Hospital-acquired pneumonia
  - Pseudomonas aeruginosa
  - Staph. aureus
  - Klebsiella pneumoniae
  - Enterobacteriaceae (Enterobacter, E. coli, Proteus, Serratia marcescens, A. baumanii)
Respiratory, sinus and ear infections: *S. pneumoniae*

- **Streptococcus pneumoniae:** Gram+
  - Pneumonia (500,000 cases/yr); *S. pneumo* the most common cause
  - ~40,000 cases/yr of invasive pneumococcal infection
  - 28% resistant to at least one antibiotic
  - 11% resistant to 3 or more antibiotics
  - Sinusitis and otitis media (7,000,000 cases/yr)
  - Sepsis (55,000 cases/yr)
  - Meningitis (6,000 cases/yr)
  - Penicillins front-line drugs, but now 30% is penicillin resistant (PRSP), also multi-drug resistance is observed
  - Vaccine helping to reduce prevalence of antibiotic resistance

Respiratory, sinus and ear infections: *H. influenzae*

- **Haemophilus influenzae:** Gram-, aerobe/facultative anaerobe
  - Opportunistic commensal bacteria
  - Pneumonia
  - Sinusitis
  - Otitis media (middle ear infection)
  - Vaccine (HiB conjugate vaccine) is available and has reduced frequency of invasive infections relating to encapsulated serotype B
  - 30% beta-lactamase producing
  - Some show modified PBPs conferring penicillin resistance, but ceph. may be effective, macrolides, fluoroquinolones
**Respiratory, sinus and ear infections: *M. catarrhalis***

- **Moraxella catarrhalis**: Gram-, aerobic, commensal found in upper resp. tract
  - Carriage in children up to 75%, in adults only 1-3%, esp in fall and winter
  - Emerged as pathogen, esp for children, adults w/ COPD, immune compromised
  - Otitis media (middle ear infection)
  - Pneumonia
  - Bronchitis
  - Sinusitis
  - Meningitis, sepsis more rare
  - Lower respiratory tract infections
    - COPD patients
    - Pneumonia in elderly
    - Hospital outbreaks

**Other common, big bugs**

- **Strep. pyogenes**: Gram+; “group A streptococcus” (GAS), beta-hemolytic
  - Sometimes part of flora, nonpathogenic, asymptomatic
  - Skin and wound infections
    - 10,000,000 cases/yr infection: impetigo, cellulitis
    - 4500 cases/yr invasive infection: necrotizing fasciitis
  - Strep throat
  - Scarlet fever
  - Streptococcal toxic shock
  - Acute rheumatic fever; autoimmune reaction triggered by Strep. pyogenes
  - Penicillin is the drug of choice, very little resistance has emerged; for those penicillin allergic, macrolides, clindamycin
Nosocomial infections and pathogens

- ~10% infection rate (between 48h of admission to 30d after discharge); ~90,000 deaths/yr
- Tend to exhibit greater frequencies and complexities of antimicrobial resistance
- Often related to insertion devices

Types of infections:
- Urinary tract infections (30%)
- Hospital-acquired pneumonia and respiratory infections (22%)
- Surgery-related (14%)
- Skin and mucosa (7%)
- Bacteremia 6%

Pathogens:
- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*
- *Staph. aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium*
- *Serratia marcescens*
- *Proteus mirabilis*
- *Enterobacter*
- *Citrobacter*
- *Stenotrophomonas maltophilia*
- *Acinetobacter baumanii*
- *Burkholderia cepacia*

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**Nosocomial pathogens: example *P. aeruginosa***

- *Pseudomonas aeruginosa*: Gram-, aerobic/facultative anaerobe, opportunistic
  - Minimal nutrient requirements, capable of colonizing wide range of environments
  - Frequent colonizer of medical device surfaces, e.g. catheters, ventilators
  - Burn and wound infections
  - UTI
  - Gastrointestinal
  - Bone and joint
  - Bacteremia (blood infection)
  - Respiratory infections, cystic fibrosis
  - 10% of hospital-acquired infections
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**Significant antimicrobial resistance**
- Biofilm formation
- Low cellular permeability to antibiotics
  - Selective porin channels and loss of expression of some porins
    - E.g. oprD porin deletion leads to lack of imipenem penetration, MIC goes from 1-2µg/ml to 8-32µg/ml
  - Overexpress outer-membrane protein (oprH) that stabilize lipopolysaccharide, which aminoglycoside usually interacts with to penetrate cell
- Efflux pumps; multi-drug efflux pumps transport across BOTH membranes
  - MexAB: beta-lactams, fluoroquinolones
  - MexXY: aminoglycosides
  - MexEF: carbapenems, fluoroquinolones

**P. aeruginosa** significant antimicrobial resistance (cont.)

- Beta-lactamase expression
  - AmpC “cephalosporinase” (not susceptible to inhibitors)
  - Extended spectrum beta-lactamas (cephs, pens), sensitive to inhibitors
  - Carbapenemases
- Modified targets
  - Mutated DNA gyrase to decrease fluoroquinolone activity
  - Altered ribosomal targets for streptomycin but anti-pseudomonal aminoglycosides are available
- These resistance mechanisms may be observed in various combinations, strain and isolate dependent

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Permeability and efflux</th>
<th>Inactivation</th>
<th>Changes in targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>++</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Quinolones</td>
<td>+++</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ most commonly encountered; ++ common; + reported but rare; – not reported

Penicillin G Spectrum:

- **Gram+ cocci**
  - *S. pyogenes*: minimal resistance observed, does not produce beta-lactamases
  - *S. pneumo*: modified PB in 30-40% gave rise to PRSP (penicillin resistant *S. pneumo*), not due to beta-lactamase
  - most common cause of CAP (community-aquired pneumonia) 50-80%
  - very common cause of otitis media ~35%
  - *S. viridans*: usually still sensitive
  - Endocarditis (heart valve infection)
  - *Enterococcus faecalis*: Pen G, amoxicillin generally effective
    - But note, *E. faecium*: highly resistant to Pen G (92%) and vancomycin

- **Gram+ rods**
  - *Clostridium tetani* (tetanus), *C. perfringens* (gangrene, food poisoning) sensitive, but *C. difficile* resistant

- **Gram- cocci**
  - *Neisseria meningitidis*: PenG can penetrate meninges due to inflammation, sensitive
  - But, *N. gonorrhoaeae* no longer sensitive due to beta-lactamases

- **Gram- rods: mostly resistant**
  - *E. Enterobacteriaceae, Pseudomonas, H. influenzae*

- **Helical and spirochetes**:
  - *Treponema pallidum* (syphilis): sensitive to Pen G still
  - *Helicobacter pylori* (stomach ulcers): not Pen G; amox + clarithromycin (macrolide) + PPI

### Notable UW formulary penicillins: Pen G

Penicillin G

**IM formulations:**

- **Procaine/Pen G**
  - IM shot (including the local anesthetic procaine)

- **Benzathine/Pen G** *(Bicillin® L-A and Bicillin® C-R)*
  - IM shot (not IV- cardiac arrest, black box warning)
  - Low levels of PenG (but close to MIC) persist for 14-20 days
  - **Bicillin L-A** has all Pen G bound with benzathine
  - **Bicillin C-R** has half of Pen G bound with benzathine and half with procaine

- *E.g. @ day 14, 0.02 mg/ml PenG, MIC for S. pneumo ~0.03μg/ml*
  - Syphilis (only **Bicillin L-A**: FDA warning on confusion with C-R, C-R not for syphilis)
**Notable UW formulary penicillins: Pen V**

**Penicillin V Spectrum:**
- Similar spectrum to Pen G, but PO; acid stable but food interferes w/ absorption
- Difficult to achieve as high concentrations as for Pen G (not PO), so primarily for more moderate infections
- Since PO, as w/ all self-dosed antibiotics, counsel to complete the full course
- Caution about allergies, diarrhea

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**Notable UW formulary penicillins: Ampicillin**

**Ampicillin Spectrum: note, w/o beta-lactamase inhibitor, similar to Pen G**
- Used in combination w/ aminoglycoside for *E. faecalis*
- Even though amp can penetrate the outer Gram- bacterial membrane, many Gram- bugs produce beta-lactamases that can degrade ampicillin. For example:
  - *E. coli* (80-90% of UTIs), 50% resistant to ampicillin due to beta-lactamase production
  - *Proteus mirabilis* (UTIs), 30% resistant
  - *N. meningitidis* generally sensitive, but some produce penicillinase
  - *N. gonorrhoeae* significant penicillinase production now
  - *H. influenzae* ~30% produce beta-lactamases
- Most nosocomial pathogens are resistant either due to innate impermeability or several resistance mechanisms including beta-lactamase production
- Note, significant enterohepatic recycling (as w/ bile acids): unmodified amp re-secreted into bile many cycles, leading to high intestinal levels of the drug. Potentially useful for *Shigella, Salmonella*, enteric infections. But, also greater risk of adverse effects such as diarrhea and *C. difficile* overgrowth.
Notable UW formulary penicillins: Ampicillin

**Ampicillin + Sulbactam spectrum (IV, IM):**
- Inclusion of beta-lactamase inhibitor (sulbactam) increases coverage of Gram- to also include:
  - *M. catarrhalis* (otitis media, pneumo, sinusitis)
  - *H. influenzae* (otitis media, pneumo, sinusitis)
  - *S. pneumoniae* (otitis media, pneumo, sinusitis)
  - Non-MRSA *S. aureus, MSSA.
  - *Klebsiella*
  - *Enterobacter*
  - *E. coli*
  - *N. gonorrhoeae*
- Good activity against anaerobes

Notable UW formulary penicillins: Amoxicillin

**Amoxicillin Spectrum: similar spectrum to ampicillin (PO):**
- Since oral absorption is better, less amox makes into enterohepatic recycling, less perturbation of gut flora, but also less effective w/ enteric infections than amp
- Ear, nose, throat infections, otitis media
  - *S. pneumoniae, S. pyogenes, H. influenzae*
    - Resistance to amox alone can be problematic; combination w/ inhibitor can be effective
    - Still widely prescribed for otitis media

**Amoxicillin + Clavulante spectrum (PO):**
- Similar spectrum to Amp + Sulbactam
Penicillin resistant and Extended Spectrum

Penicillin resistant penicillins:
- Nafcillin (IV, IM)
- Dicloxacillin (PO)
- Mainly used for sensitive *S. aureus* (not MRSA)

Extended spectrum penicillins: only used in combination w/ inhibitors
- Primarily used against *Pseudomonas* infections, for complex infections, or for empiric therapy where the pathogen is not known. Also generally good Gram- coverage.
- Piperacillin + Tazobactam (Zosyn ®)
  - More potent against Gram- than Ticarcillin, e.g. *Klebsiella*
  - *Pseudomonas aeruginosa* more sensitive, less resistance (15%) than for Timentin (30%)

Why use Pen G over a broader spectrum drug?

Table 1: Resistance to eleven antibiotics, *MIC* _{90} values, and *MIC* ranges of 263 *S. pyogenes* strains.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistant strains (n/%)</th>
<th><em>MIC</em> _{90} (µg/ml)</th>
<th><em>MIC</em> ranges (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>0/0</td>
<td><strong>0.0075</strong></td>
<td>0.0004-0.03</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0/0</td>
<td>≤ 0.125</td>
<td>≤ 0.125-0.25</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0/0</td>
<td>≤ 0.125</td>
<td>≤ 0.125-1.00</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0/0</td>
<td>≤ 0.125</td>
<td>≤ 0.125-0.50</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0/0</td>
<td>≤ 0.125</td>
<td>≤ 0.125-0.25</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0/0</td>
<td>1.0</td>
<td>≤ 0.50-1.0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0/0</td>
<td>≤ 0.25</td>
<td>≤ 0.25-0.50</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>8/3.0</td>
<td>0.25</td>
<td>≤ 0.25-2.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>10/3.8</td>
<td>≤ 0.125</td>
<td>≤ 0.125-2.0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>11/4.2</td>
<td>0.25</td>
<td>≤ 0.125-2.0</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>11/4.2</td>
<td>0.25</td>
<td>≤ 0.125-2.0</td>
</tr>
</tbody>
</table>