Penicillins are often preferred over other antibiotics because of:
1. their safety
2. the fact that no adjustment is need in the face of renal impairment
3. their reliable efficacy in the treatment of staphylococcal infections
4. low rates of resistance to this class

Amoxicillin/clavulanate has is a very popular antibiotic for treatment of common respiratory infections because:
1. it is the least expensive oral antibiotic available for such infections
2. it is active against most *H. influenzae* and *M. catarrhalis*
3. of low rates of penicillin resistance in *S. pneumoniae*
4. of very low rates of GI side effects

The spectrum of activity of the carbapenems is very similar to that of:
1. vancomycin
2. 1st generation cephalosporins
3. aminoglycosides
4. 3rd generation cephalosporins
5. azithromycin
Penicillins and Miscellaneous β-lactams
John A. Bosso, Pharm.D.

**Mechanism of Action**

- Bind to penicillin binding proteins resulting in:
  - Loss of cell wall integrity
  - Osmotic fragility
  - Cell lysis and death

**Penicillin: Mode of Action**

**Penicillins: ADME**

- Administration: IV, IM, PO
- Distribution: variable, but in general, well distributed in body water; distribution into CSF is marginal
- Metabolism: minor, although some are excreted in bile
- Elimination: most eliminated in unchanged form by the kidneys
**Penicillin G (Benzyl Penicillin)**

**Spectrum** - *Clostridium perfringens*, *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, *N. meningitidis*, *Streptococcus pneumoniae*, non-penicillinase producing *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*

**Specific indications** - any susceptible gram-positive infection

**Side effects** - allergic reactions; hypersensitivity in 1 to 10%, anaphylaxis in 0.004 to 0.015%

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**Special Clinical Considerations:**

Be aware that significant amounts of sodium (1.7-2 mEq/1 million units or potassium (1.6 mEq/1 million units) are administered with parenteral penicillin

The long-acting penicillins (procaine, benzathine) have few indications.

- streptococcal pharyngitis or impetigo
- prevention of rheumatic fever
- acquired syphilis

Combinations of procaine and benzathine penicillins are probably no more effective than benzathine alone.

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**Phenoxymethyl Penicillin**

(Penicillin V, Potassium Penicillin V)

- **Spectrum** - same as pen G
- **Specific indications** - same as pen G
- **Side effects** - same as pen G
- **Special Clinical Considerations**
  
  This preparation is not susceptible to acid breakdown, prefer it over pen G for oral administration

---

**Ampicillin**

**Spectrum** - most Gram-positive organisms (excluding penicillinase-producing staphylococcus), *Proteus mirabilis*, *Salmonella*, *Shigella*, and some strains of *Escherichia coli*, *Haemophilus influenzae* and *Klebsiella*.

**Specific indications** - infections caused by susceptible strains of *E. coli*, *Proteus*, *H. influenzae* and *Shigella*

**Side effects** - allergic, diarrhea (~20%) and rash (~10%)
Penicillins and Miscellaneous β-lactams
John A. Bosso, Pharm.D.

**Ampicillin**

Special Clinical Considerations

1.) implications of diarrhea
2.) implications of rash
3.) Bacampicillin (Spectrobid®) is an ampicillin prodrug; it has no advantages and is more expensive.
4.) Ampicillin/Sulbactam is a parenteral combination conferring activity against many organisms inherently resistant to ampicillin based upon β-lactamase production. (Unasyn®)
5.) Ampicillin/Probenecid fixed combinations available in single dose containers for treatment of uncomplicated forms of gonorrhea (e.g. Polycillin-PBR® etc)

**Amoxicillin**

Spectrum - same as ampicillin
Indications - same as ampicillin (PO)
Side effects - similar to ampicillin (less diarrhea)

**Penicillin Resistance in S. pneumoniae**

- Resistance is typically mediated by an alteration in the penicillin-binding proteins (PBPs) caused by a series of mutations
- PBPs interact with beta-lactams by forming a relatively stable covalent complex, which by deacylation, results in a biologically inactive derivative
- Resistance mutations reduce the affinity to beta-lactams rather than affecting deacylation

**Amoxicillin/Clavulanic Acid (Augmentin®)**

Spectrum - same as ampicillin/amoxicillin plus β-lactamase producing strains of *H. influenzae, E. coli, Proteus, Klebsiella pneumoniae, S. aureus and Moraxella catarrhalis*

Side effects - mainly diarrhea although drastically reduced from original product

Indications - an alternative for otitis media and other URI’s, UTI’s and some pneumonia
Penicillins and Miscellaneous β-lactams  
John A. Bosso, Pharm.D.

<table>
<thead>
<tr>
<th>Amoxicillin/Clavulanic Acid (Augmentin®)</th>
<th>Amoxicillin/Clavulanic Acid (Augmentin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2:1, 4:1 or 7:1 ratios of amoxicillin and clavulanate</td>
<td>• Available as oral suspensions of:</td>
</tr>
<tr>
<td>• Available as</td>
<td>– 125 and 250mg/5ml as 4:1</td>
</tr>
<tr>
<td>– 125 &amp; 250mg chewable tabs in 4:1 ratio</td>
<td>• Given q 8 h</td>
</tr>
<tr>
<td>– 200 &amp; 400mg chewable tabs in 7:1 ratio</td>
<td>– 200 and 400mg/5ml as 7:1</td>
</tr>
<tr>
<td>– 250mg coated tab in 2:1</td>
<td>• Given q 12 h (less diarrhea but contains aspartame)</td>
</tr>
<tr>
<td>– 500 mg coated tab as 4:1</td>
<td>– 600mg/5ml as 14:1 (Augmentin-ES 600)</td>
</tr>
<tr>
<td>– 875 mg coated tab as 7:1</td>
<td>• Meant to deliver doses of 90mg/kg/d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amoxicillin/Clavulanic Acid (Augmentin XR®)</th>
<th>Penicillinase-Resistant Penicillins</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1000 mg amoxicillin &amp; 62.5 mg CA per tab</td>
<td>Spectrum - most gram-positive organisms</td>
</tr>
<tr>
<td>– 16:1 amox:CA</td>
<td>including most penicillinase-producing staphylococci</td>
</tr>
<tr>
<td>– Contains both immediate &amp; extended release amoxicillin</td>
<td>Specific indications - infections caused by penicillinase-producing Staphylococcus aureus</td>
</tr>
<tr>
<td>• Administered q 12 h</td>
<td></td>
</tr>
<tr>
<td>• Indicated for acute bacterial sinusitis and CAP in adults when pen-resistant S. pneumoniae is a concern</td>
<td></td>
</tr>
</tbody>
</table>
Penicillins and Miscellaneous β-lactams
John A. Bosso, Pharm.D.

Penicillinase-Resistant Penicillins

Oral - nafcillin, oxacillin, cloxacillin and dicloxacillin. *Dicloxacillin* is preferred due to superior antibacterial activity and absorption.

Parenteral - methicillin, nafcillin, oxacillin and cloxacillin. These agents vary in activity and extent of protein binding, but not enough to be important. Presently preferred agents are nafcillin and oxacillin.

Unique side effects:
- nafcillin - thrombophlebitis
- methicillin - interstitial nephritis

Extended-spectrum Penicillins

- Ticarcillin
- Mezlocillin
- Piperacillin
- Ticarcillin/clavulanate
- Piperacillin/tazobactam

Ticarcillin
(Ticar®)

Spectrum - most Gram-positive organisms (excluding penicillinase producers), *proteus, Pseudomonas aeruginosa* and some strains of *E. coli, Aerobacter and Salmonella.*

Specific indications - none

Side effects - similar to other penicillins plus clotting abnormalities

Special clinical considerations
1.) Resistance arises rapidly
2.) Expensive
3.) Contains 5.2 mEq Na per gram
4.) Synergistic with aminoglycosides but physically incompatible

Mezlocillin
(Mezlin®)

Spectrum - similar to ticarcillin with increased activity against Gram-positive organisms including enterococci and Gram-negatives such as *Proteus, Enterobacter, Klebsiella* and anaerobes such as *Bacteroides fragilis.*

Indications - similar to ticarcillin

Side effects - as with ticarcillin

Special clinical considerations
1.) Synergistic with aminoglycosides
2.) Marked inoculum effect
3.) Contains about 2 mEq Na per gram
Penicillins and Miscellaneous β-lactams
John A. Bosso, Pharm.D.

**Piperacillin**
(Piperacil®)
- Spectrum - similar to mezlocillin with greater activity against *Pseudomonas aeruginosa* and anaerobes
- Indications - similar to ticarcillin
- Side effects - similar to ticarcillin
- Special clinical considerations
  1. similar to mezlocillin

**Ticarcillin/Clavulanate**
(Timentin®)
- Spectrum - similar to mezlocillin with greater activity against some Gram-negatives, staphylococci and anaerobes
- Indications - similar to ticarcillin
- Side effects - similar to ticarcillin
- Special clinical considerations
  1. consider when broader coverage needed

**Piperacillin/Tazobactam**
(Zosyn®)
- Analogous to ticarcillin/clavulanic acid with better activity
- Due to intrinsic superiority of piperacillin

**Carbapenems**
- Imipenem
- Meropenem
- Ertapenem
- Experimental
  - Faropenem
Penicillins and Miscellaneous β-lactams
John A. Bosso, Pharm.D.

Carbapenems

- Broadest spectrum of activity of all β-lactams
- Generally reserved for serious nosocomial infections
- Parenteral only
- Eliminated unchanged by the kidneys

Activity of Carbapenems

<table>
<thead>
<tr>
<th></th>
<th>Enterococcus</th>
<th>E. coli</th>
<th>E. cloacae</th>
<th>E. aerogenes</th>
<th>C. freundii</th>
<th>P. aeruginosa</th>
<th>MSSA</th>
<th>K. pneumoniae</th>
<th>E. faecium</th>
<th>L. monocytogenes</th>
<th>B. cepacia</th>
<th>S. maltophilia</th>
<th>E. faecium</th>
<th>L. monocytogenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>0.08 / 0.08</td>
<td>0.14 / 0.36</td>
<td>0.17 / 0.49</td>
<td>0.59 / 1.85</td>
<td>2.0 / 8.0</td>
<td>2.0 / 4.0</td>
<td>22.7 / 162</td>
<td>0.12 / 0.25</td>
<td>0.02 / 0.02</td>
<td>0.02 / 0.02</td>
<td>2.0 / 16</td>
<td>0.02 / 0.5</td>
<td>0.02 / 0.13</td>
<td>0.5 / 4.75</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.3 / 0.55</td>
<td>0.01 / 0.13</td>
<td>0.02 / 0.05</td>
<td>0.02 / 0.02</td>
<td>0.01 / 0.04</td>
<td>0.00 / 0.00</td>
<td>0.13 / 13</td>
<td>0.13 / 1.0</td>
<td>0.03 / 0.03</td>
<td>0.12 / 0.23</td>
<td>2.0 / 10</td>
<td>0.02 / 0.06</td>
<td>0.13 / 11</td>
<td>0.32 / 0.23</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>2.0 / 10</td>
<td>0.02 / 0.02</td>
<td>0.02 / 0.05</td>
<td>0.02 / 0.02</td>
<td>0.02 / 0.02</td>
<td>0.02 / 0.02</td>
<td>0.32 / 8.5</td>
<td>0.5 / 4.75</td>
<td>0.18 / 0.36</td>
<td>0.08 / 0.48</td>
<td>2.0 / 4.0</td>
<td>0.02 / 0.06</td>
<td>0.13 / 11</td>
<td>0.32 / 0.23</td>
</tr>
<tr>
<td>Faropenem</td>
<td>0.12 / 0.25</td>
<td>0.02 / 0.02</td>
<td>0.02 / 0.02</td>
<td>0.12 / 4.0</td>
<td>0.02 / 0.02</td>
<td>0.02 / 0.02</td>
<td>1.23 / 8.88</td>
<td>0.12 / 4.0</td>
<td>0.02 / 0.02</td>
<td>0.02 / 0.02</td>
<td>2.0 / 10</td>
<td>0.02 / 0.06</td>
<td>0.13 / 11</td>
<td>0.32 / 0.23</td>
</tr>
</tbody>
</table>

Imipenem (Primaxin®)

Spectrum - broadest spectrum of activity of any β-lactam including most aerobic and anaerobic, Gram-positive and Gram-negative pathogens. Notable exceptions include MRSA, B. cepacia, S. maltophilia, E. faecium and L. monocytogenes.

Indications - unclear, not really the drug of choice for anything, perhaps most useful in nosocomial infections caused by multi-drug resistant bacteria.

Side effects - similar to other β-lactams (hypersensitivity, etc), seizures in predisposed patients.

Special clinical considerations
1.) Potent β-lactamase inducer
2.) Very β-lactamase stable
3.) adjust dose with renal insufficiency

Meropenem (Merrem®)

Spectrum - similar to imipenem with slightly greater activity against Gram-negative organisms and slightly less activity against Gram-positive organisms.

Indications - complicated intra-abdominal infections and meningitis.

Side effects - similar to imipenem except less propensity to cause seizures.

Special clinical considerations
1.) stable to renal dehydropeptidase
2.) very stable to most β-lactamas
3.) adjust dose with renal insufficiency
Penicillins and Miscellaneous β-lactams
John A. Bosso, Pharm.D.

Ertapenem (Invanz®)
Spectrum - similar to imipenem & meropenem but lacking in activity vs. *P. aeruginosa*, *A. baumannii*, & enterococci

Indications - CAP, complicated intra-abdominal infections, complicated UTI, complicated SSSI, and acute pelvic infections

Side effects - diarrhea, phlebitis, nausea

Special clinical considerations
1.) stable to renal dehydropeptidase
2.) adjust dose with renal insufficiency

Experimental
• Faropenem
  – Phase III
  – Potential indications for community-acquired infections
  – Oral

Aztreonam (Azactam®)
Spectrum - Gram-negative, aerobic organisms including *P. aeruginosa*; no Gram-positive or anaerobic activity

Indications - not drug of choice for any infection; may be used as aminoglycoside substitute in certain situations and as an extended-spectrum penicillin substitute in others.

Side effects - rare, very low risk of hypersensitivity, transient hepatic transaminase elevation

Special clinical considerations
1.) relatively β-lactamase stable
2.) must be used in combination in many clinical situations
3.) adjust dose in renal insufficiency