β-Lactam Antibiotics: Penicillins

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Spectrum of Activity Chart

- Bring to all antibiotic class lectures
- Classes of antibiotics along the top of the chart, with clinically-relevant bacteria listed in the left column
- List the spectrum of activity of each drug or drug class according to me
- Know general SOA of antibiotic classes
- Know activity of individual antibiotics against the target bacteria (shaded)
- Just because an antibiotic has activity against an organism does not mean it is used there clinically

Designed by Sharon Erdman, PharmD
Learning Objectives

Describe the general characteristics of the β-lactam antibiotics

Understand the differences in the penicillin groups with respect to:
- Spectrum of activity
- Pharmacokinetics – esp CSF penetration and route of elimination
- Sodium load
- Clinical uses
- Major adverse effects

β-Lactam Structure

β-Lactam Characteristics

1. Same MOA: Inhibit cell wall synthesis
2. Same MOR: β-lactamase degradation, PBP alteration, decreased penetration
3. Bactericidal in a time-dependent manner, except against Enterococcus spp.
4. Short elimination half-life of < 2 hours
5. Primarily eliminated unchanged by the kidneys (except nafcillin, oxacillin, ceftriaxone, cefoperazone)
6. Cross-allergenicity - except aztreonam
Penicillins

- Penicillin was accidentally discovered by Dr. Alexander Fleming in 1928 from a strain of *Penicillum notatum*.
- First used in 1941 for the treatment of staphylococcal and streptococcal infections.
- Semisynthetic derivatives were developed to enhance antibacterial activity and improve pharmacologic activity.
- All penicillins share a β-lactam ring attached to a 5-membered thiazolidine ring.

Penicillin Structure

The following structures can each be substituted at the R to produce a new penicillin.
Penicillins

Mechanism of Action

- Interfere with cell wall synthesis by binding to and inhibiting penicillin-binding proteins (PBPs) located in bacterial cell membranes.
- Number, type and location of PBPs vary between bacteria; PBPs are only expressed during cell division.
- Inhibition of PBPs leads to inhibition of final transpeptidation step of peptidoglycan synthesis.
- Are bactericidal (except against Enterococcus).

Bacterial Cell Wall Structure

PBPs are located in the cell membrane

Transpeptidase

Katzung, 11th Ed. p. 777
Penicillins
Mechanisms of Resistance

1. Production of β-lactamase enzymes
   - Most common mechanism where the enzyme hydrolyzes the β-lactam ring inactivating the antibiotic; over 100 β-lactamase enzymes have been identified
   - Produced by:
     - Gram-positive: Penicillin-resistant Staphylococcus aureus
     - Gram-negatives: Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, E. coli, Klebsiella pneumoniae, Enterobacter spp., etc
     - Gram-negative anaerobes: Bacteroides fragilis
Penicillins
Mechanisms of Resistance

2. Alteration in structure of PBPs leading to decreased binding affinity - methicillin-resistant
   *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP)

3. Alteration of outer membrane porin proteins leading to decreased penetration

Penicillins
Spectrum of Activity

- Natural and semisynthetic penicillins display different antibacterial activity
- Semisynthetic penicillins developed to provide enhanced activity
- Know the story behind the development of each group to understand the spectrum of activity of each group

Natural Penicillins

- First group of penicillins to be discovered and used clinically; other groups of penicillins are semi-
  synthetically derived from natural penicillin
- Naturally derived from *Penicillium notatum*
- Examples include:
  - Parenteral agents: Aqueous penicillin G (IV), Benzathine penicillin G (IM, long-acting), Procaine penicillin G (IM)
  - Oral agent: Penicillin VK
Natural Penicillins
( penicillin G, penicillin VK )

<table>
<thead>
<tr>
<th>Gram-positives</th>
<th>Gram-negative cocci</th>
</tr>
</thead>
<tbody>
<tr>
<td>pen-susc S. aureus</td>
<td>Neisseria spp.</td>
</tr>
<tr>
<td>pen-susc S. pneumoniae</td>
<td>Pasteurella multocida</td>
</tr>
<tr>
<td>Group streptococci</td>
<td>Anaerobes</td>
</tr>
<tr>
<td>viridans streptococci</td>
<td>Above the diaphragm</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>Clostridium spp.</td>
</tr>
<tr>
<td>Bacillus spp.</td>
<td>Other</td>
</tr>
<tr>
<td>Treponema pallidum (syphilis)</td>
<td></td>
</tr>
</tbody>
</table>

Penicillinase-Resistant Penicillins

- Developed in response to the emergence of penicillinase-producing *Staphylococcus*
- Semisynthetic derivatives of natural penicillin - contain an acyl side chain
- Examples include:
  - Parenteral agents: Nafcillin, Oxacillin, and Methicillin (not available)
  - Oral agent: Dicloxacillin

Penicillinase-Resistant Penicillins
(nafcillin, oxacillin, methicillin, dicloxacillin)

- Developed to overcome the penicillinase enzyme of *Staphylococcus aureus*, which inactivated natural penicillin

<table>
<thead>
<tr>
<th>Gram-positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>methicillin-susceptible S. aureus* (MSSA)</td>
</tr>
<tr>
<td>Group streptococci</td>
</tr>
<tr>
<td>viridans streptococci</td>
</tr>
</tbody>
</table>

* = target organism
### Antibiotic resistance in *Staphylococcus aureus*

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>Penicillin available</td>
</tr>
<tr>
<td>1942</td>
<td>Penicillin-resistance <em>S. aureus</em> &lt;br&gt; (beta-lactamase [penicillinase] which can be overcome with penicillinase-resistant penicillins, beta-lactamase inhibitors, or changing to cephalosporin core [cefa-zolin]; called methicillin-susceptible <em>S. aureus</em>, MSSA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>Methicillin available</td>
</tr>
<tr>
<td>Late 60s</td>
<td>80% of <em>S. aureus</em> pen-resistant</td>
</tr>
<tr>
<td>1968</td>
<td>First report of methicillin-resistant <em>S. aureus</em> (MRSA) caused by PBP alteration mediated by <em>mecA</em> gene which confers resistance to all beta-lactams except ceftaroline)</td>
</tr>
<tr>
<td>2015</td>
<td>99% of <em>S. aureus</em> pen-resistant and ~50% MRSA (varies)</td>
</tr>
</tbody>
</table>

### Aminopenicillins

- Developed in response to the need for agents with gram-negative activity
- Semisynthetic derivative of natural penicillin – addition of amino group
- Examples include:
  - Parenteral agent: Ampicillin
  - Oral agents: Ampicillin and Amoxicillin
### Aminopenicillins (ampicillin, amoxicillin)

Developed to increase activity against gram-negative aerobes

**Gram-positives**
- pen-susceptible *S. aureus*
- pen-susceptible *S. pneumoniae*
- Group streptococci
- viridans streptococci
- *Enterococcus spp.*
- *Listeria monocytogenes*

**Gram-negatives**
- *Proteus mirabilis*
- some *E. coli*
- *Salmonella, Shigella*
- βH. *influenzae*

* Better activity than natural penicillin

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### Carboxypenicillins

- Developed in response to the need for agents with enhanced activity against gram-negative bacteria
- Semisynthetic derivatives of natural penicillin – addition of carboxyl group
- Examples include:
  - Parenteral agent: *Ticarcillin* (not available)
  - Oral agents: None

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### Carboxypenicillins (ticarcillin)

Developed to further increase activity against gram-negative aerobes

**Gram-positives**
- Marginal

**Gram-negatives**
- *Proteus mirabilis*
- *Salmonella, Shigella*
- some *E. coli*
- βH. *influenzae*
- *Enterobacter spp.*
- *Pseudomonas aeruginosa*

* = target organism
Ureidopenicillins

Developed in response to the need for agents with even more enhanced activity against gram-negative bacteria
Semisynthetic derivatives of the amino-penicillins with acyl side chain adaptations
Examples include:
- Parenteral agent: Piperacillin (not available)
- Oral agents: None

Ureidopenicillins (piperacillin)

Developed to further increase activity against gram-negative aerobes

<table>
<thead>
<tr>
<th>Gram-positives</th>
<th>Gram-negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group strep</strong></td>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td>some Enterococcus</td>
<td><em>Salmonella, Shigella, E. coli</em></td>
</tr>
<tr>
<td>Anaerobes*</td>
<td><em>β</em>+ <em>H. influenzae</em></td>
</tr>
<tr>
<td>fairly good activity</td>
<td><em>Enterobacter sp.</em></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Serratia marcescens</em></td>
</tr>
<tr>
<td></td>
<td>some Klebsiella spp.*</td>
</tr>
</tbody>
</table>

* = target organism

β-Lactamase Inhibitors

- Potent inhibitors of many bacterial β-lactamases
- Protect penicillins from being hydrolyzed by some β-lactamases by irreversibly binding to catalytic site of β-lactamase enzyme
- Very weak to no antibacterial activity
- Examples include: clavulanate, sulbactam, tazobactam, avibactam (used in combo with cephalosporins)
**β-Lactamase Inhibitor Combinations**

- Developed to enhance activity of the penicillins against β-lactamase-producing bacteria
- Available only in fixed-dose combinations with specific penicillins
- Examples include:
  - Parenteral agents: Ampicillin-sulbactam (Unasyn®), Ticarcillin-clavulanate (Timentin®; not available), Piperacillin-tazobactam (Zosyn®),
  - Oral agent: Amoxicillin-clavulanate (Augmentin®)

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**β-Lactamase Inhibitor Combos**

(Unasyn®, Augmentin®, Timentin®, Zosyn®)

- Developed to gain or enhance activity against β-lactamase producing organisms

**Gram-positives**
- S. aureus (not MRSA)*

**Gram-negatives**
- H. influenzae
- E. coli
- Proteus spp.
- Klebsiella spp.
- Neisseria gonorrhoeae
- Moraxella catarrhalis

* = target organism

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**Penicillins Pharmacology**

- Time-dependent bacterial killing – Time above MIC correlates with efficacy
- No PAE for gram negative bacteria
- Synergy with aminoglycosides against Enterococcus spp., Staphylococcus spp., viridans strep, and gram-negative bacteria
Absorption
- Many penicillins are degraded by gastric acid
- Oral penicillins are variably absorbed and concentrations from oral formulations are lower than from IV formulations
- Oral penicillins cannot be used interchangeably for their IV equivalents (serious infections require IV)
  - Pen VK is best absorbed oral penicillin, but much less than IV
  - Amp/sulbactam achieves higher levels than amox/clav
  - Oral amoxicillin absorbed better than oral ampicillin

Distribution
- Widely distributed into tissues and fluids except eye, prostate, and uninflamed CSF
- Adequate CSF concentrations achieved ONLY in the presence of inflamed meninges with high-dose parenteral administration
- Variable protein binding

Elimination
- Most are eliminated unchanged by the kidney so that dosage adjustment is required in the presence of renal insufficiency; probenecid blocks tubular secretion
- The PRPs (nafcillin, oxacillin, and dicloxacillin) are eliminated by the liver – do not require adjustment in renal insufficiency or patients on dialysis
- ALL penicillins (except procaine penicillin G and benzathine penicillin G) have short elimination half-lives (<2h) and require frequent dosing.
Penicillins: Sodium Load

- Sodium is contained in some preparations of parenterally-administered penicillins
- Must be used with caution in patients with CHF or renal insufficiency
- Sodium content:
  - Sodium Penicillin G: 2.0 mEq per 1 million units
  - Ticarcillin: 5.2 mEq per gram
  - Piperacillin: 1.85 mEq per gram

Penicillins: Clinical Uses

Natural Penicillins

- Drugs of choice for penicillin-susceptible S. pneumoniae, infections due to other streptococci, Neisseria meningitidis, syphilis, Clostridium perfringens or tetani, Actinomyces, Bacillus anthracis (anthrax)
- Endocarditis prophylaxis; prevention of rheumatic fever

Penicillinase-Resistant Penicillins

- Infections due to MSSA such as skin and soft tissue infections, septic arthritis, osteomyelitis, bacteremia, endocarditis, etc.

Penicillins: Clinical Uses

Aminopenicillins

- Respiratory tract infections: pharyngitis, sinusitis, otitis media, bronchitis, urinary tract infections
- Enterococcal infections (often with an aminoglycoside) and infections due to Listeria monocytogenes
- Endocarditis prophylaxis in selected patients with valvular disease
### Penicillins: Clinical Uses

**Carboxypenicillins and ureidopenicillins**
- Serious infections due to gram-negative aerobic bacteria such as pneumonia, bacteremia, complicated urinary tract infections, skin and soft tissue infections, peritonitis, etc.
- Empiric therapy for hospital-acquired infections
- Infections due to *Pseudomonas aeruginosa* (esp. piperacillin)

### Penicillins: Clinical Uses

**β-Lactamase Inhibitor Combinations**
- Augmentin® (oral): sinusitis, otitis media, upper and lower respiratory tract infections, human or animal bite wounds
- Unasyn®, Zosyn®, Timentin® (IV) – used for polymicrobial infections such as polymicrobial pneumonia (aspiration), intra-abdominal infections, gynecologic infections, diabetic foot infections
- Empiric therapy for febrile neutropenia or hospital-acquired infections (Zosyn®)

### Penicillins: Adverse effects

**Hypersensitivity – 3 to 10%**
- Higher incidence with parenteral administration
- Mild to severe allergic reactions ranging from rash to anaphylaxis and death
- Antibodies produced against metabolic by-products (penicillin degradation products) or penicillin itself
- Cross-reactivity exists among all penicillins and even some other β-lactams
- Desensitization is possible
Penicillins: Adverse effects

**Neurologic – direct toxic effect**
- Especially in patients receiving high IV doses in the presence of renal insufficiency
- Irritability, jerking, confusion, seizures

**Hematologic**
- Leukopenia, neutropenia, thrombocytopenia – usually during prolonged therapy (> 2 weeks)
- Reversible upon discontinuation

**Gastrointestinal**
- Increased LFTs, nausea, vomiting, diarrhea, pseudomembranous colitis (C. difficile diarrhea)

**Interstitial Nephritis**
- Immune-mediated damage to renal tubules - characterized by an abrupt increase in serum creatinine, eosinophilia, eosinophiluria
- Can lead to renal failure
- Especially with nafcillin
- Others: phlebitis, hypokalemia, Na overload

**β-Lactam Antibiotics: Penicillins**

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