Pharmacology

Subject:
Cell wall inhibitors

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- Beta lactam drugs:

  - Contain a beta-lactam ring that is part of their chemical structure.
  - Beta lactam ring is essential for antibacterial activity for some group of drugs such as: Penicillins, Cephalosporins, Carbapenems, and Carbacephems & Monobactams.

-Slide 2 + slide 3
  - Some people consider thiozoladin ring along with this ring as a beta lactam ring (slide 2)
  - But in fact the site or part which is attacked by gastric acidity or beta lactamases is this part (slide 3 “square ring”).
  - Dr may ask us in the exam “this structure belong to what ( slide 3 “square ring” ) ……… belong to beta lactam ring.

- Beta lactam ring is the site of attack by gastric acidity and lactamases.

- Any change in the R group results in wide range of different beta lactam drugs with different spectrum (narrow or broad ), with different sensitivity to beta lactamases (sensitivity or resistance) route of administration (oral or parental )…..

- The R in the structure of β-lactam antibiotic determines the characteristic of antimicrobial agent.

**Beta Lactams Mechanism of Action:**

- Simply, we have synthetic machinery to the cell wall of bacteria, If we understand the steps involved in the synthesis of bacterial cell wall we can manufacture many antibiotics that can inhibits cell wall synthesis.
- The cell wall is essential for the survival of bacteria.
- An interference with cell wall function could result in cidal, static...
- The Penicillin, Cephalosporin they act on cross linking of substances in the cell wall known as peptidoglycan
- Leading to the lyses of bacteria and the cidal effect. 

Most of the drug that act on cell wall are cidal in their nature

Slide 7:
- You should memorize all of them.
- Pay your attention on locally applied antibiotics (topically: Not systematic): vancomycin and bacitracin.

- B lactamase inhibitors are substances that have no antibacterial activity but could be combined with beta lactam antibiotic that is sensitive to beta lactemase resulting in more effectiveness of antibiotic in the management of bacteria producing beta lactamase.
- They are safe, don't have any side effect and they have alone NO bacterial activity.
- The most used is clavulanic acid.

- Bacteria that produce β-lactamase (hydrolyze β-lactam ring and hence inactivation of antimicrobial):
  - Staph aureus (cause frequent infection and it’s common)
  - Moraxella catarrhlis.
  - Neisseria gonorrhea.
  - Enterobacteriaceae.
  - Hemophilus influenza.
  - Bacteroides species.

Streptococcus doesn't produce lactamase
**Penicillin:**

- Most widely used antibiotics, most effective, least toxic and cheap (general characteristic).
- Derivatives of 6-aminopenicillanic acid (ß-lactam ring is important structure).
- Derived from a fungus.
- Prototype is Penicillin G.
- Widely distributed except in CSF (except if inflammation is present) and in intraocular fluid.
- Although penicillin is weakly cross BBB, it can be used in the meningitis (but isn’t the drug of choice).
- Most serious complication is hypersensitivity.
- Can cause seizures and nephropathy.

**Prototypic penicillin = penicillin G = Benzylpenicillin:**

- Ineffective orally because it’s acid labile.
- It is effective parentally (IM, IV).
- It’s mainly given by IM.
- You can give it by IV but should be carefully.
- Depo IM forms to penicillin G.
- This penicillin is given 4-6 times/day (short acting).
- So this penicillin is short acting and given parental.

**Note:** Antibiotic should be given in proper dose for proper duration of time otherwise bacterial resistance is more common.
Note: If tonsillitis occurs more than 10 times / year, you should remove the tonsils to avoid frequent used of antibiotic ((streptococcus cause tonsillitis, common in children)) .

- Procaine penicillin given IM twice/day.
- Benzathine penciling is given every month up to an age of 15 to treat for rheumatic fever prophylaxis (if tonsillitis is ignored it may develop to rheumatic fever).

**Phenoxy methylpenicillin= Penicillin V:**

- Considered drugs of choice to treat infections with G+ve Strep., β-hemolytic type A (most common microbe in tonsillitis).
- Natural penicillins are narrow spectrum and penicillinase sensitive.
- Most effect against gram positive, little effect against gram negative.
- Patient with severe tonsillitis we start with penicillin v but in certain condition Benzathine penicillin is better but it's cost is high and is inconvenient (IM).

- If the patient is ignored regarding treatment of tonsillitis this could affect the joint and the heart) leading to the condition known as  rheumatic fever.
- This condition is common through ages from 1 year up to 15.
- If its diagnosed even at age of 2 years the patient will be treated first for tonsillitis and then will be placed on an injection of Benzathine penicillin every month up to an age of 15 .
- It's very rare after age 15.
• Narrow spectrum penicillinase resistant penicillins (Anti Staph penicillins):
  - Nafcillin IM, IV.
  - Oxacillin IM, IV.
  - Cloxacillin Oral.
  - Dicloxacillin Oral.
  - Flucloxacillin Oral & parenteral.

• Broad spectrum penicillinase sensitive PNC’s (amino PNC’s):

<table>
<thead>
<tr>
<th></th>
<th>Duration of action</th>
<th>Bioavailability</th>
<th>Effecting by eating (ABSORPTION)</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>4 times /day</td>
<td>Less</td>
<td>Is affected</td>
<td>Oral, IV, IM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Should be taken 1 hr before or 2 hrs after eating</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>3 times /day (long duration)</td>
<td>More</td>
<td>Isn't affected (even if the stomach is full)</td>
<td>Oral</td>
</tr>
</tbody>
</table>

They are widely used.

Methicillin..No more used severe nephrotoxicity.

Although the amoxicillin is better than ampicillin, the ampicillin is still available because there is certain diseases that dont respond to the amoxicillin but it responds to ampicillin.
- These PNC’s have very little effect, if any, against PNCase producing bacteria e.g. H. influenza and against G-ve bacteria e.g. Ecoli, Proteus. No effect against Pseudomonas.

- Amino PNC’s are widely used in tonsillitis, otitis media, gonorrhea, respiratory infections, shigella infections, UTI’s…et

- Amoxicillin + PPI’s (proton pump inhibitors) has good activity against Helicobacter pylori.

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- Helicobacter pylori cause peptic ulcer disease.
- Such bacteria should treat by compound drug; Single drug isn't effective in eradication of helicobacter pylori.
- Peptic ulcer disease could be managed by those drugs which decrease acid secretion.

- Antibiotics those are used in the management Helicobacter pylori of disease: ((Amoxicillin, Clarithromycin)).
- The first combination discovered is (tetracycline + Clarithromycin + Metronidazole).
- Now, two antibiotic drugs (dual therapy) may be good enough when they discovered PPI's.

\[
\begin{align*}
\text{PPI's have antibacterial activity but not antibiotic and they have an effect against Helicobacter pylori} \\
- \text{PPI's} + \text{amoxicillin} \Rightarrow \text{Yes (have an effect against helicobacter pylori)} \\
- \text{PPI's} + \text{Clarithromycin} \Rightarrow \text{Yes} \\
- \text{PPI's} + \text{Metronidazol} \Rightarrow \text{No}
\end{align*}
\]

- **Antipseudomonal PNC’s:**
  - Piperacillin > Mezlocillin=Ticarcillin > Carbinicillin.
  - All are synergistic with aminoglycosides against **Pseudomonas.**

- **not an easy infection.**
• Amidinopenicillins:
  - Mecillinam (IM; IV) Pivmicillinam (oral).
  - Most potent PNC’s against enterobacteria.
  - (Salmonella, E. coli, Klebsiella, Shigella…), have little or no activity against G+ve cocci or pseudomonas.
  - synergistic with other β-lactams but not with aminoglycosides.
  - If you weaken the cell wall of bacteria you increase the rate of those drugs acting intracellular of bacteria.
  - Penicillin are synergistic in general with many aminodinopenicillins.

• MOA of Penicillins:
  - Most bacteria have rigid cell walls that are not found in host cells (selective toxicity).
  - PNC’s act by inhibiting transpeptidases, the enzymes that catalyze the final cross-linking step in the synthesis of peptidoglycan, thus leading to the lyses of cell wall. Disruption of the cell wall causes death of the bacterial cell (Bactericidal Effect).

Note: Any bacteria which is lacking cell wall it represent natural mechanism of resistance to penicillin, cephalosporin and other drugs that act on cell wall.
Pharmacokinetics of PNC’s:
- Bind plasma proteins, widely distributed, their concentrations in ocular fluid, joints and CSF are poor (do not cross BBB unless meninges are inflamed), do not cross the placenta (they are safe drug during pregnancy: amoxicillin and ampicillin).
- Metabolized by the liver and excreted by glomerular filtration and tubular secretion.
- Probenecid inhibits tubular secretion of PNC’s (nafcillin & oxacillin are mainly excreted by the liver).

indications for penicillin’s:
- More effective in treating gram+ infections.
- Used to treat infections of the skin, GU, GI, respiratory tract and soft tissues.
- Selection depends on the organism and severity of the infection e.g. anti-staph vs. anti – pseudomonal.
- Combination of PNC’s or a cephalosporin with a potent inhibitor of lactamases.

Lactemase inhibitors:
- make sensitive beta lactam drug resistance (extend spectrum of activity of combined antibiotic).
- enhance potency (amoxicillin alone: 500ml 3times/day amoxicillin/clavulinate: 250 ml 3times/day).

Examples:
- Clavulinic acid, Sulbactam, Tazobactam.
- 1. (Augmentin® =amoxicillin/clavulinate).
- 2. (Unasyn®=ampicillin/sulbactam).
- 3. (Zosyn®=piperacillin/tazobactam)...etc

You should memorize them.
Mechanisms of resistance to PNC’s:
- Altered penicillin binding proteins (PBPs).
- Production of beta-lactamase (penicillinases).
- Decreased penetration/increased efflux (pseudomonas).

Preparations to PNC’s:
- Oral, parenteral, intrathecal, topical, intra – articular.

Side effects to PNC’s:
- Allergy (Most frequent and dangerous).
  - Type I (immediate) allergic reactions. Early onset (immune Ig E mediated)(manifestation range between mild rash to severe anaphylactic shock).
  - Type II (delayed) allergic reactions. Late onset (2-10 days). May manifest as eosinophilia, hemolytic anemia, interstitial nephritis or serum sickness (fever; arthralgia; malaise…)
- Ampicillin has unique property that develops rash.
  - Ampicillin could produce rash, occurs only once (ampicillin rash) related to the ampicillin only.
    ((more common in pts with acute leukemias; mononucleosis, lymphomas, cytomegaloviral infections…)
- Hepatotoxicity (IV oxacillin).
- Bone marrow depression (reversible) (IV nafcillin)
- Nephrotoxicity (Methicillin) severe that's why withdraw methicillin from market

In general; Allergy is considered the major and most serious side effect to penicillin.

It's a type of allergy but not allergy that we talked about it (type 1 and type 2 ).seconed exposure doesn't cause rash, contrast to allergy reaction.
Penicillin isn't contraindicated.
• Other restrictions in the use of PNC’s:
  - Na+ penicillins → restricted use in pts with hypertension or heart failure.
  - K+ Penicillins → restricted use in pts with renal failure (because accumulation of K will happen)
  - Absolute contraindications to all PNC’s in pts with history of allergy.

• Cephalosporin:
  - Cephalosporin are never ever consider number one of choice for any condition although it's have broad spectrum; however they are highly effective in upper and lower respiratory infection, H. influenza, UTI’s, dental infections, severe systemic infection...
  - Derivatives of 7-aminocephalosporanic acid.
  - β-lactam antibiotics, Cidal.
  - Semisynthetic.
  - Broad spectrum.
  - Inhibitors of microbial cell wall synthesis.
  - Differ in pharmacokinetic properties and spectrum of activity.
  - classified into 1st 2nd 3rd 4th generations based on:
    - history.
    - Spectrum of activity.
    - Resistance / Sensitivity to beta lactemases.
    - Penetration to CSF.

1st narrow (are highly effective against gram positive)
2nd and 3rd (are highly effective against both)
4th (are highly effective against gram negative)

4th (are highly effective against gram negative)
1st generation is sensitive.
2nd resistant but less than 3rd and 4th.
3rd and 4th are resistant.

1st and 2nd don’t cross BBB as sufficient as 3rd and 4th.
- According to administration not much accurate.
- Not based on side effect.

- Slide 26 +27 +28 for the exam you should memorize the drug (which is yellow in the slides)
- (for the question: which the following is first generation drug?)
- All the following is second generation except?
- You should be familiar with all dugs of all generations.
- If there a bacteria produce lactemase you can't use first generation.
- 3rd cefixime widely used.

• Among cephalosporins:
  - Cefoxitin (2nd) has the best activity against Bacteroids fragilis.
  - Cefamandole (2nd) has the best activity against H. Influenza.
  - Cefoperazone (3rd), Ceftazidine (3rd) and Cefepime (4th) have the best activity against P. aeruginosa infections.

• Side effects to cephalosporins:
  - allergy is universal side effect for all antibiotic.
  - the patients which allergic to penicillin has a higher incidence of having an allergy to cephalosporin and vice versa (( cross linking )) not much but be careful 10 %.
  - Hepatotoxicity.
  - Nephrotoxicity.

You should memorize this.

Because there is a similarity in the structure of cephalosporins and penicillin (beta lactam ring)
- Hemolytic anemia

All cephalosporins are excreted by the kidney except Ceftriaxone (3rd) which is excreted by the liver

### Other β-lactam antibiotics:

- **Carbapenems** e.g. Imipenem, Meropenem
  - **Imipenem:**
    - Has the broadest spectrum of activity of all β-lactam antibiotics, effective against most G+ve & -ve bacteria and anaerobes, given IM, IV; β-lactamase resistant.
    - More potent against E. faecalis, B. fragilis and pseudomonas aeroginosa as compared to 3rd generation cephalosporin.
    - Some consider imipenem the drug of choice in the management of polymicrobial pulmonary, intraabdominal and tissue infections.
    - It's very quickly hydrolyzed or broken down by enzymes in the kidney called dehydropeptidase 1.
    - Seizures are major side effect to imipenem.
    - Imipenem isn't given alone... it's given usually with cilastatin.

  - **Meropenem:**
    - Has similar activity to imipenem; but resistant to metabolism by dehydropeptidase I (no need to combine it with cilastatin) and incidence of seizures is less than imipenem

  - **Carbacephems:** e.g. Loracarbef Oral
• Monobactams: e.g. Aztreonam IM, IV
  - Has excellent activity against G -ve bacteria
    
    Spectrum of activity similar to 2nd generation cephalosporin particularly cefaclor and cefprozil; effective orally; excreted renally.
  - little if any effect against G +ve MO’s
  - β-lactamase resistant.
  - Considered a substitute to aminoglycosides to treat G-ve infections (less toxic).
  - Rarely, causes allergic reactions in pts with type I allergy to other β- lactam antibiotics.

• Vancomycin & Teicoplanin:
  - Glycopeptide (Large Molecules).
  - Prevent crosslinking of peptidoglycans.
  - Bactericidal.
  - Narrow spectrum of activity effective against G+ve bacteria especially methicillin resistant Staph aureus (MRSA).
  - Alternatives to PNC’s to treat G+ve Strep & Staph infections in pts allergic to PNC’s.
  - Given IV (oral absorption is poor).
  - vancomycin alone is effective but in the condition of clostridium difficile colitis it's combine with metronidazole
  - pseudomembranous colitis=antibiotic associated colitis
    (Clostridium difficile colitis;
  - Staph enterocolitis)

  - The treatment:
- You should stop the drug (clindamycin, lincomycin).
- Then give vancomycin (and in this case vancomycin could be given orally (IV in life threatening cases).
- Improvement is excellent with vancomycin.
- Other drugs could produce pseudomembranous colitis but vancomycin are used in the treatment of pseudomembranous colitis caused by clincamycin and lincamycin only.
- Teicoplanin is given IM.

- Side effects:
  - Rapid IV → flushing, tachycardia, ↓ BP
  
  Thrombophlebitis, ototoxicity, circumoral parasthesia...

These side effects are not much common.