Antimicrobials (3)

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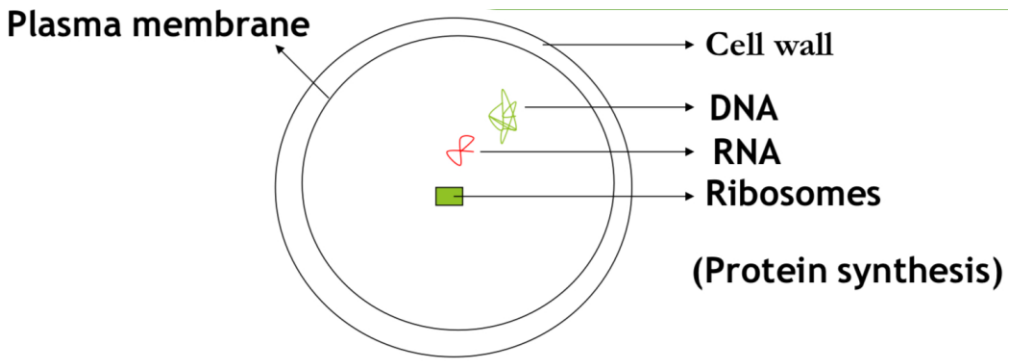
Bacterial resistance Occurs:

- When clinical condition of host is impaired.
- When normal flora have been suppressed.
- With interrupted or inadequate treatment.
- More frequently in certain types of bacteria (Gram negatives possess an outer membrane and cytoplasmic membrane preventing passage of antibiotic through pores).
- With widespread use of broad spectrum antibiotics. In poor environmental setting of host; usually we start with a narrow spectrum antibiotics or we used what is called the first drug of choice for specific microorganisms.



Mechanisms of bacterial resistance

Natural resistance:

Absence of a metabolic process or an enzyme or protein in the bacteria which is required for the action of the antimicrobial.

Absence or hard cell wall making the antimicrobial difficult to penetrate.

Bacterial Resistance

- We need the antimicrobial drug in large amounts at site of action above its concentration in the plasma, otherwise resistance emerges.
- To overcome this type of resistance the drug has to be given in very large doses which leads to severe side effects.

Mechanisms of bacterial resistance

Acquired resistance:

Development of resistance in a previously sensitive microorganism. This could occur in the following ways:

1. Mutation or genetic change; misuse or abuse of certain antibiotic.

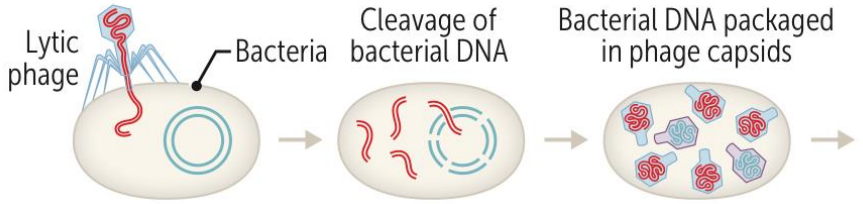
2. Adaptation: Production of enzymes breaking the antimicrobial e.g. β-lactamases; the bacteria adapts itself against the action of antibiotic.

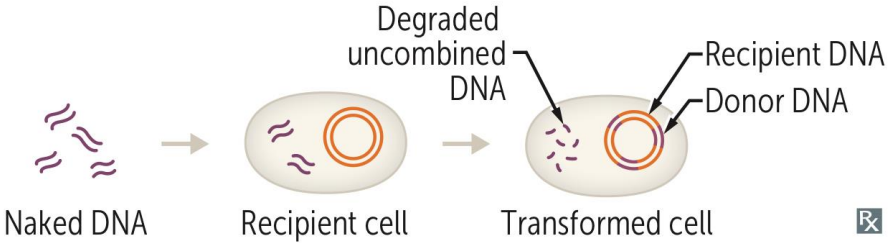
3. Infectious or multiple drug resistance:

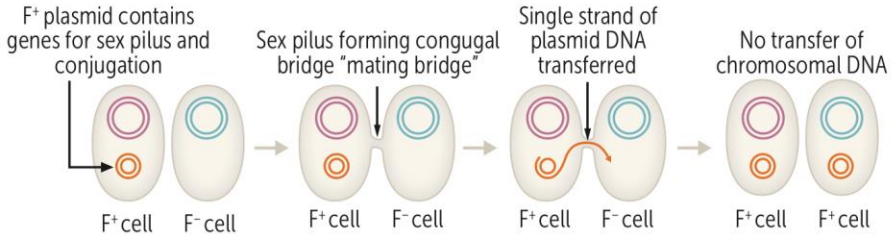
Transduction; bacteriophage which transfers chromosomal or extrachromosomal DNA (plasmid) to bacteria

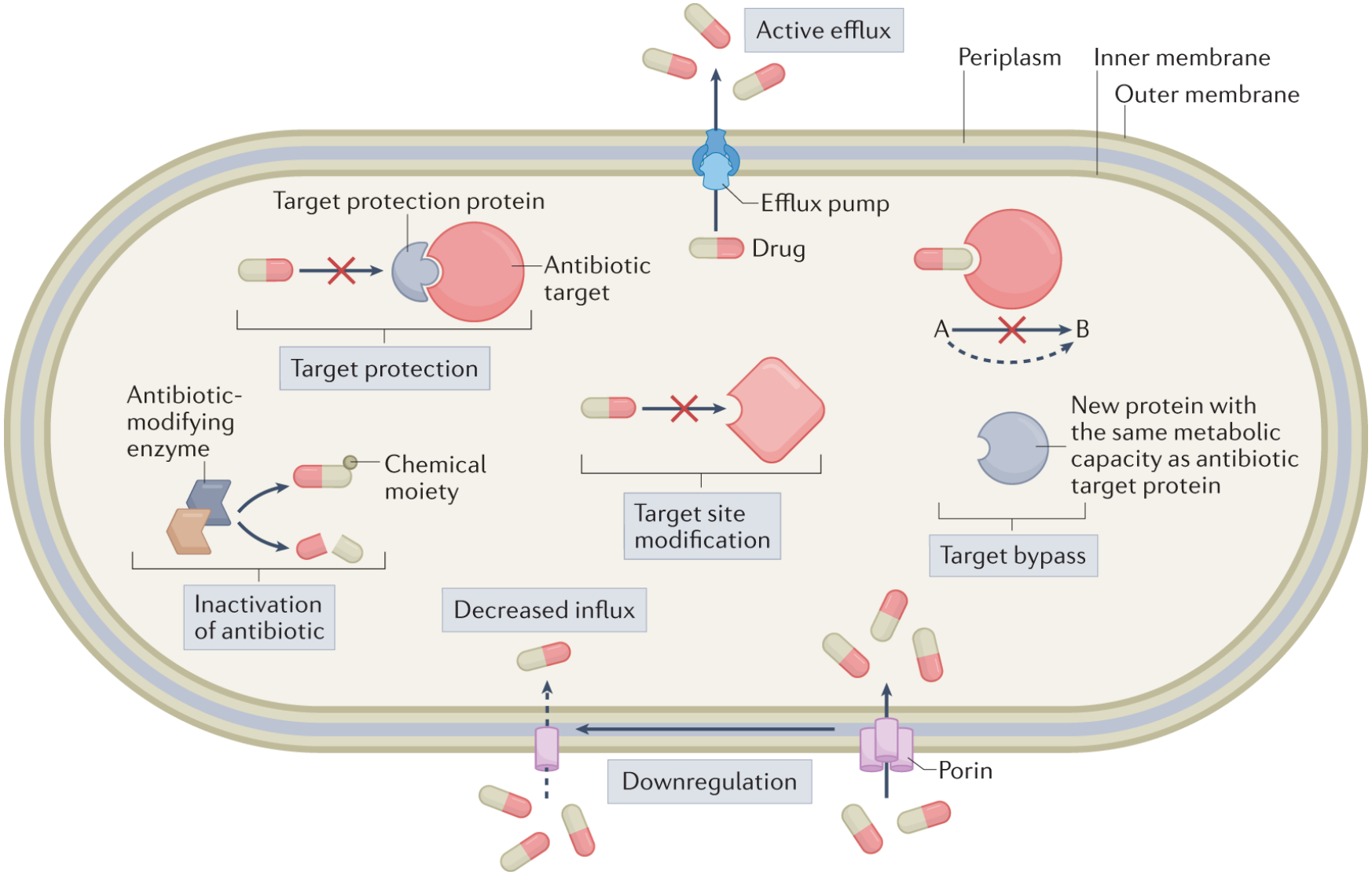
Transformation; transfer of DNA responsible for resistance from environment to bacteria.

Conjugation; Passage of resistant genes from cell to cell by direct contact



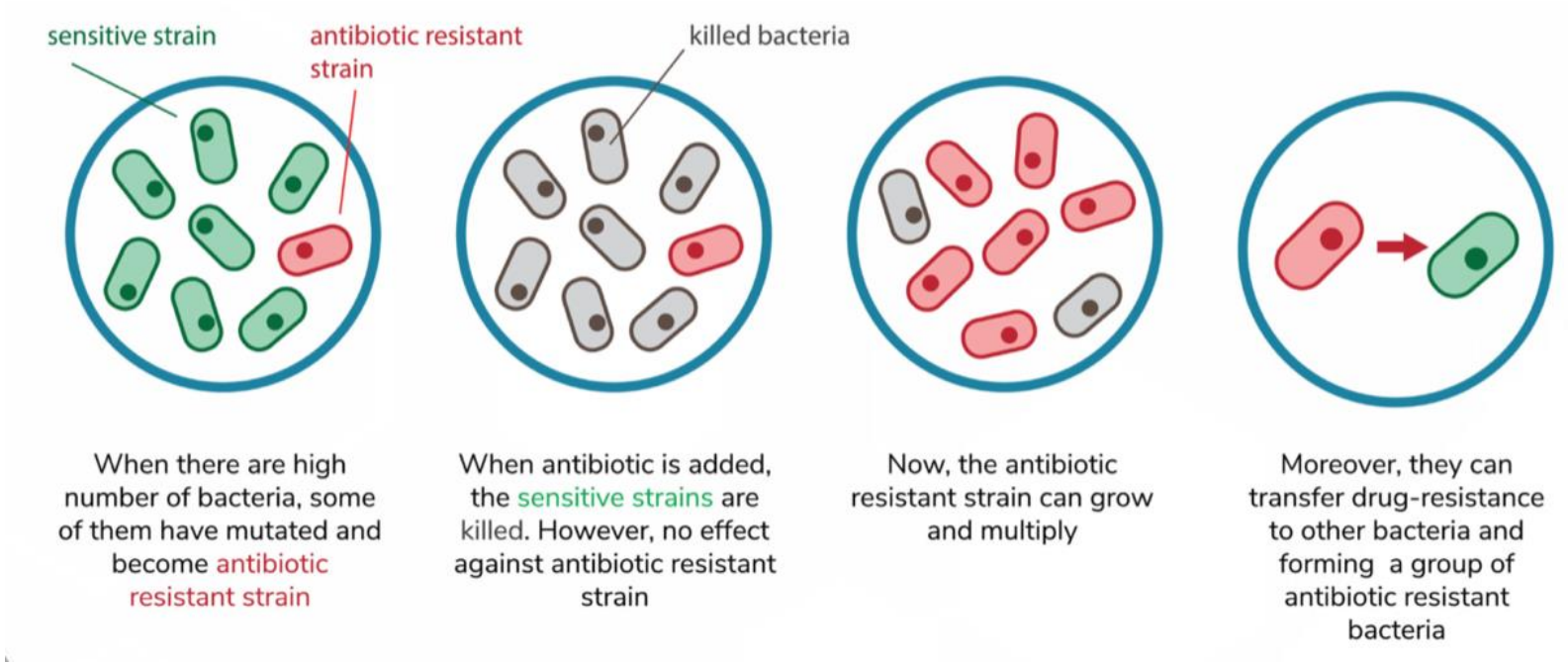





Active efflux
Periplasm
Inner membrane
Outer membrane
Efflux pump
Drug
Target protection protein
Antibiotic target
Target protection
A
B
Antibiotic-modifying enzyme
Chemical moiety
Inactivation of antibiotic
Target site modification
New protein with the same metabolic capacity as antibiotic target protein
Target bypass
Decreased influx
Downregulation
Porin

Examples on mechanisms of resistance:

- Generating enzymes that inactivate the antibiotic (beta lactamase).
- Changing structure of target site e.g. PBP's (beta lactams and aminoglycosides).
- Preventing cellular accumulation of antibiotic by altering outer membrane proteins or using efflux pumps e.g. G-ve.
- Changing the metabolic pathway that is being blocked (sulfa drugs).
- Overproducing the target enzyme or protein to overpower the effects of antibiotics.
- Mycoplasma lacks a cell wall making it resistant to penicillins.
- Sulfonamides have no impact on bacteria that obtain their folate from environment.



Bacterial Resistance

Most of resistance is acquired due to misuse or abuse of antibiotics e.g. improper dose & DOA, treatment of suppurative diseases, treatment of viral infections with antibacterial agents.

Misuse : use the drug in condition which is not indicated.

Abuse : the drug is indicated but we use it improperly.

Combined therapy Indications

To obtain synergism or reduce the dose of a toxic drug.

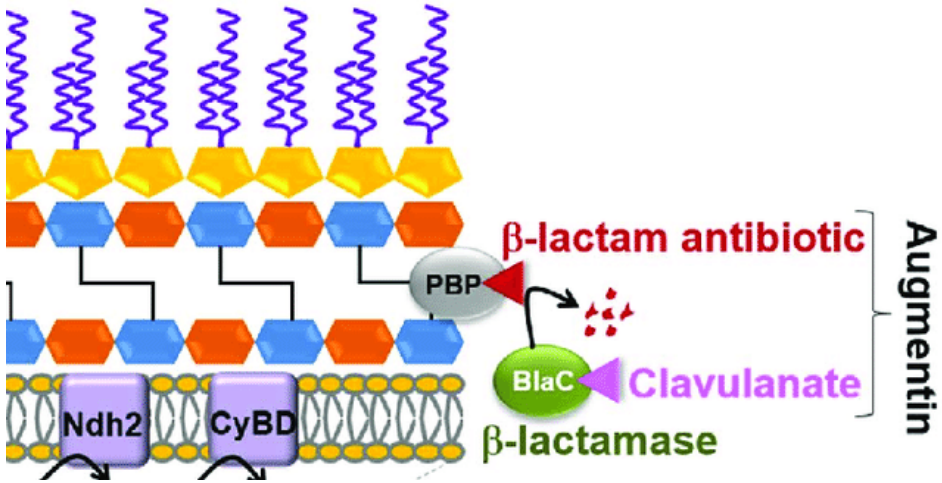
To reduce emergence of resistance.

Treat mixed infections with microorganisms of different sensitivities.

Treat infections at different anatomical sites (bile, CSF, eye).

Treat infections of unknown etiology especially in patients at high risk of developing infections e.g. AIDS patients or patients with agranulocytosis [Neutropenia].

TB is NEVER treated with a single drug, usually we start with three drugs.



Combined chemotherapy

- Outcome of combined chemotherapy:
- Indifference.
- Antagonism [Cidal + Static].
- Synergism (Penicillins+aminoglycosides): synergism happens to the desired effect and the side effect as well.
- Disadvantages of combined chemotherapy:
- Toxicity.
- Increased cost.

Prophylactic use of antibacterial agents:

Indications:

Protection of healthy individuals against highly contagious disease or infections.eg.syphilis, gonorrhea, T.B, meningococcal meningitis.

Prevent infections in very ill patients e.g. AIDS, before major surgeries, delivery, organ transplantation, recurrent UTI's…etc

Prophylaxis is successful if:

A single antibiotic is used.

The dose required for prophylaxis is less than the therapeutic dose.

The drug is needed or used for a brief period (chronic therapy or prophylaxis is not advised → bacterial resistance).

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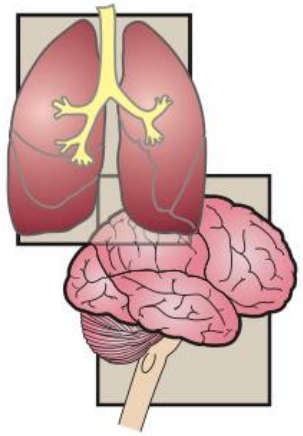
Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.



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Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.

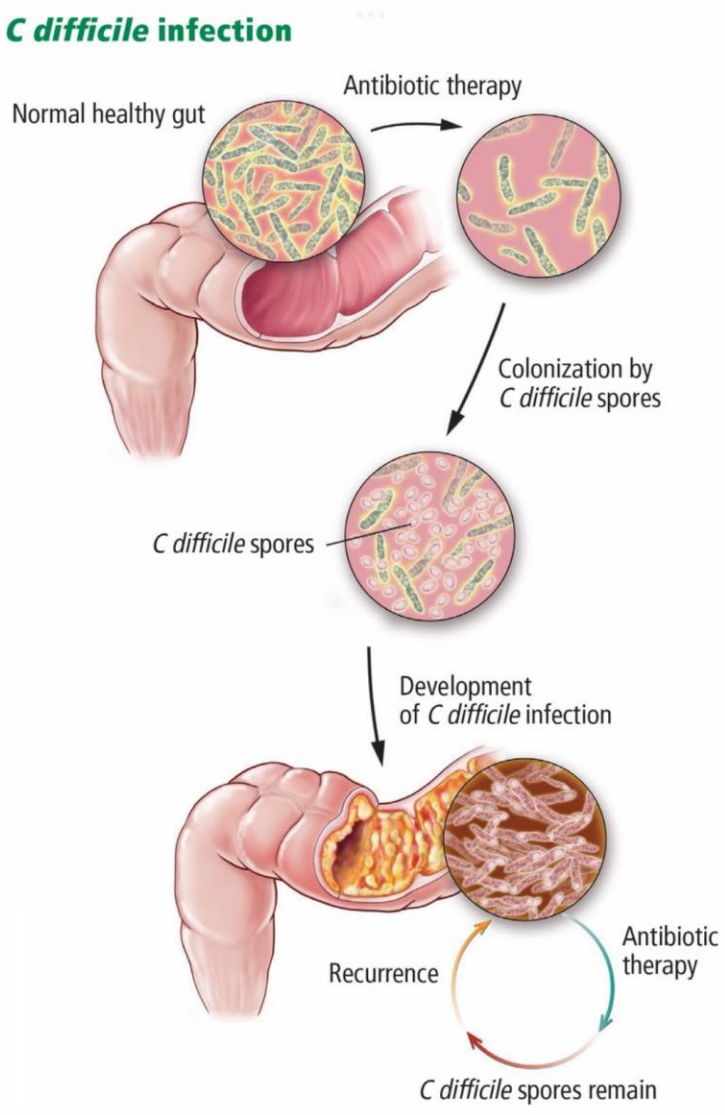
Complications of antibiotic therapy:

Hypersensitivity.

Direct toxicity; (toxic to certain site), There are some antibiotics that are toxic to the kidneys.

Super infection; When we use broad spectrum antibiotics.

Alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria.



Inhibitors of Microbial Cell Wall

β-lactam antibiotics:

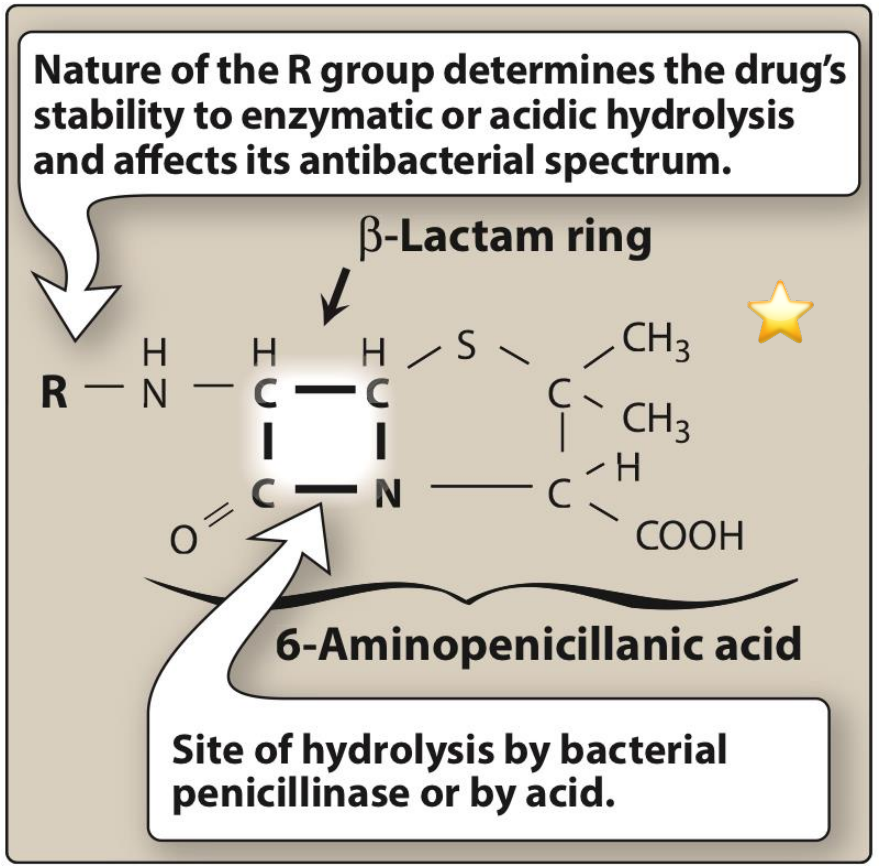
Contain a beta-lactam ring that is part of their chemical structure.

An intact beta-lactam ring is essential for antibacterial activity.

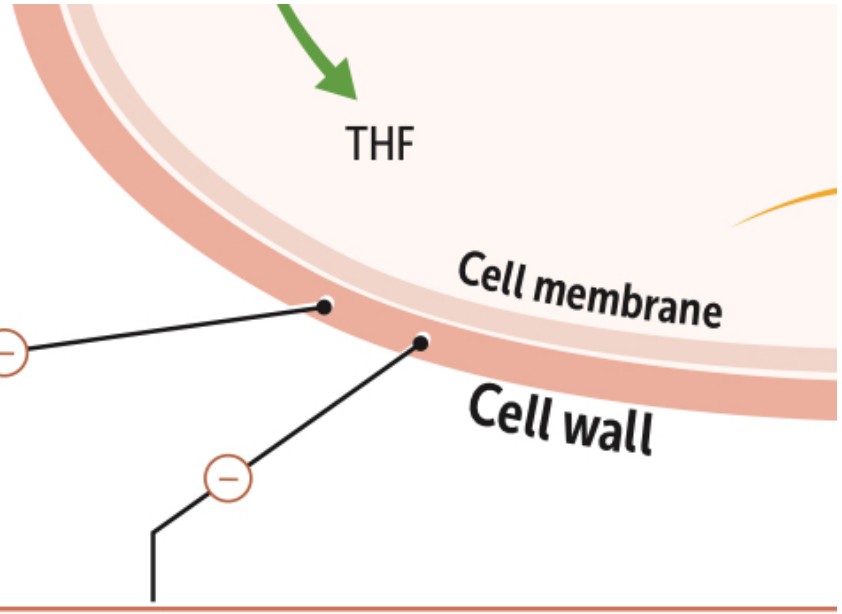
Include: Penicillins, Cephalosporins, Carbapenems, Carbacephems & Monobactams .

The R in the structure of β-lactam antibiotic determines the characteristic of antimicrobial agent e.g. narrow or broad spectrum; oral vs parenteral administration; sensitivity vs resistance to β lactamases..etc.

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



CELL WALL SYNTHESIS



PEPTIDOGLYCAN SYNTHESIS

Glycopeptides
- Vancomycin
- Bacitracin

PEPTIDOGLYCAN CROSS-LINKING

Penicillinase-sensitive penicillins
- Penicillin G, V
- Ampicillin
- Amoxicillin

Penicillinase-resistant penicillins
- Oxacillin
- Nafcillin
- Dicloxacillin

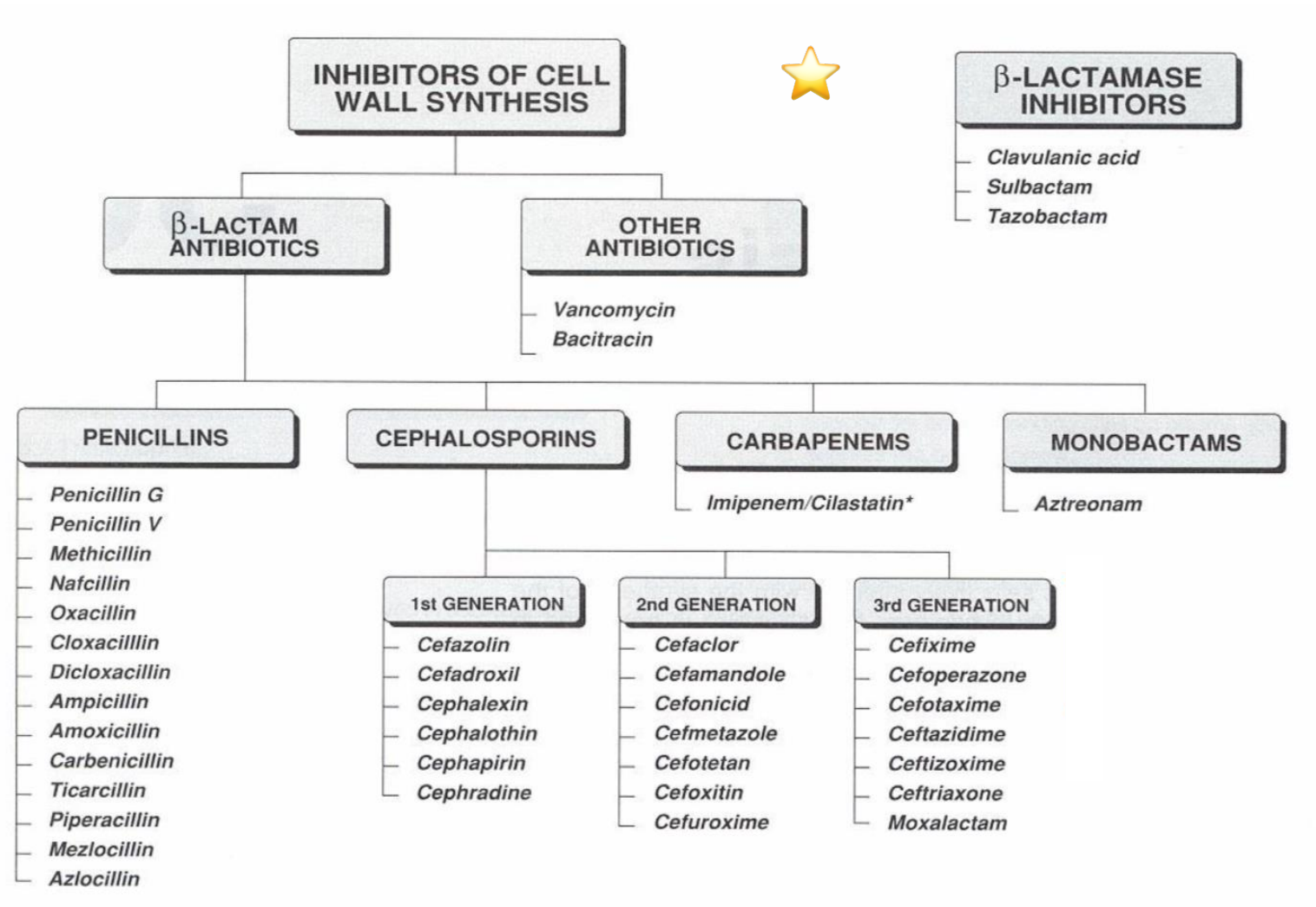
Antipseudomonal
- Piperacillin

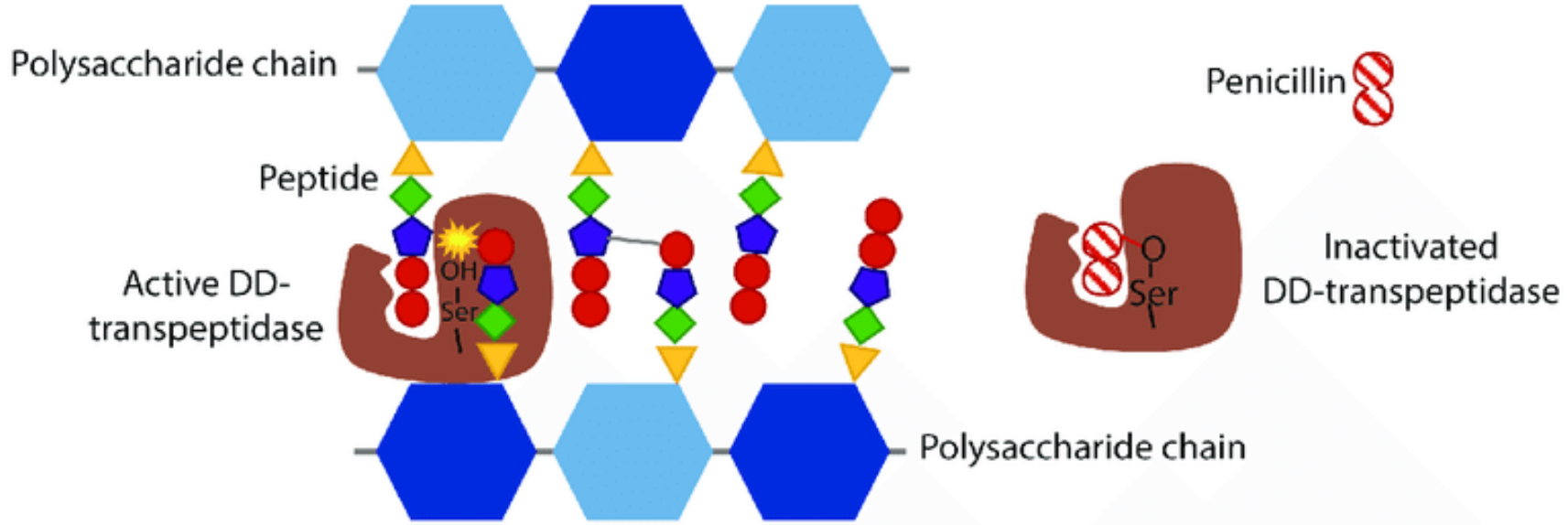
Cephalosporins (I-V)
- 1st—Cefazolin, etc
- 2nd—Cefoxitin, etc
- 3rd—Ceftriaxone, etc
- 4th—Cefepime
- 5th—Ceftaroline

Carbapenems
- Imipenem
- Meropenem
- Ertapenem
- Doripenem

Monobactams
- Aztreonam

Inhibitors of Cell Wall Synthesis





Beta Lactams MOA

1. Inhibit synthesis of bacterial cell walls by binding to proteins in bacterial cell membranes e.g. PBP's (Penicillin binding proteins).

2. Binding produces a defective cell wall that allows intracellular contents to leak out (lysis of the bacteria and death).

3. Most effective when bacterial cells are dividing.

Bacteria that produce β-lactamase

- Bacteria that produce β-lactamase (hydrolyze β-lactam ring and hence inactivation of antimicrobial activity):
- Staph aureus ✅.
- Moraxella catarrhlis.
- Neisseria gonorrhoeae.
- Enterobacteriaceae.
- Hemophilus influenzae.
- Bacteroides species.

Penicillins

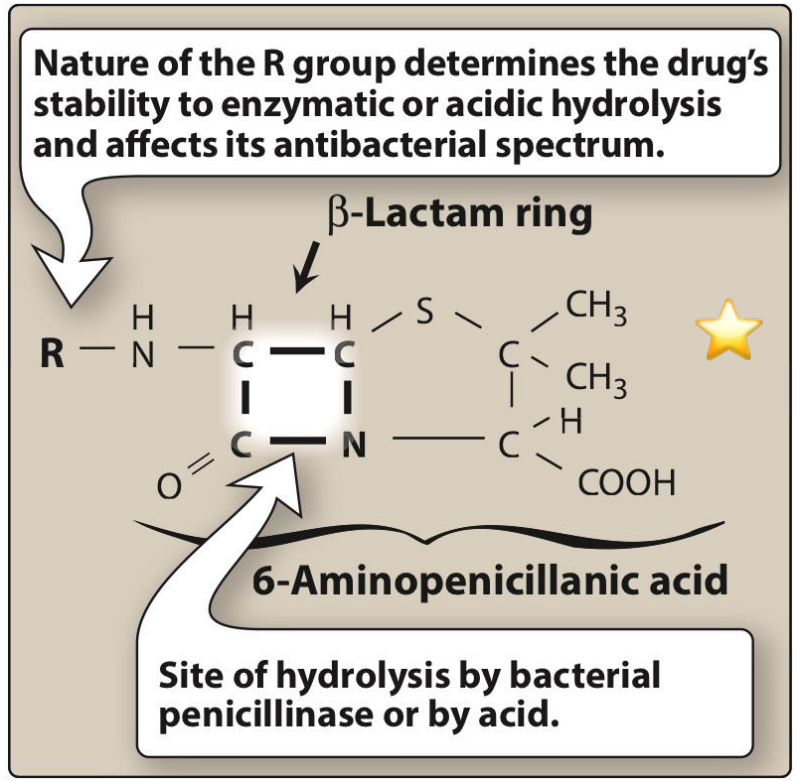
Most widely used antibiotics, most effective, least toxic and cheap.

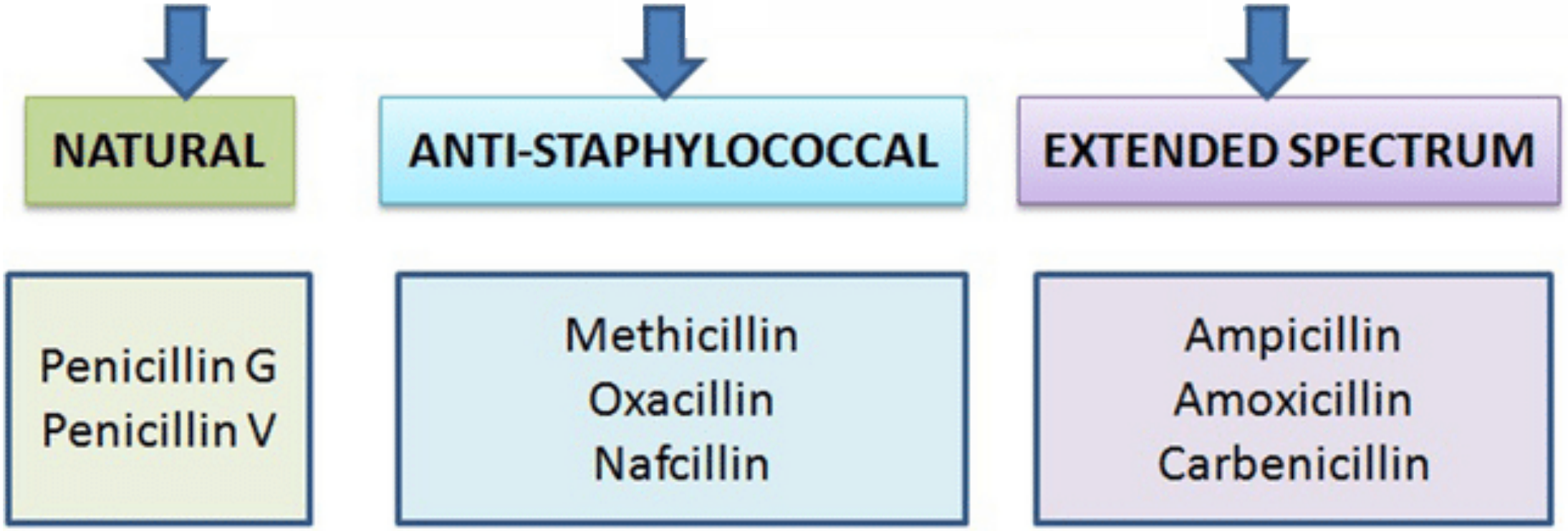
Derivatives of 6-aminopenicillanic acid (ß-lactam ring is important structure for antibacterial activity, breaking down such B-lactam inactivate the antibiotic whether by gastric acidity or by specific enzyme lactamase).

Derived from a fungus, Prototype is Penicillin G.

Widely distributed except in CSF (except if inflammation is present) and in intraocular fluid.

Most serious complication is hypersensitivity (most serious side effect are allergic reactions). Can cause seizures and nephropathy.





Penicillins

Natural penicillins:

Benzylpenicillin= Penicillin G [IV, IM].

Acid labile (the B-lactam ring will be broken down by the acidity), short acting, given 4-6 times/day.

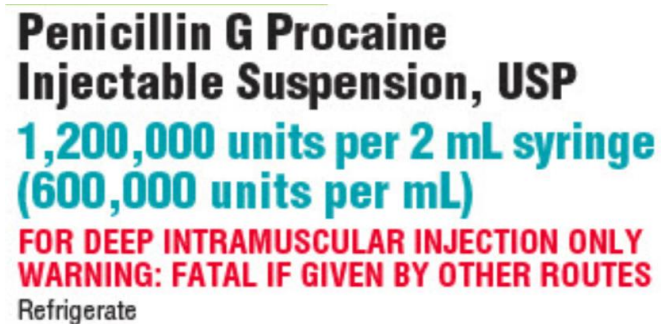
Depo IM forms to penicillin G:

Procaine penicillin:

It should be given IM twice/day, IV injection contraindicated (could lead to ↓ BP & convulsions).

Benzathine penicillin:

It should be given IM mainly used for rheumatic fever prophylaxis (Given or action taken to prevent disease).



Natural penicillins:

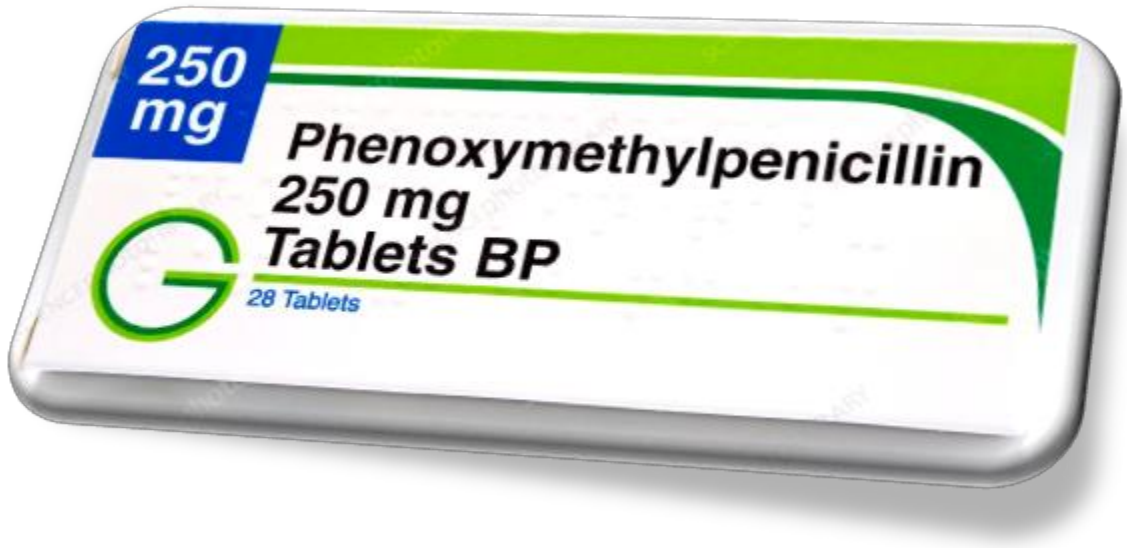
Phenoxymethylpenicillin=PenicillinV [Oral].

Natural penicillins are narrow spectrum and penicillinase [Beta-lactamase] sensitive.

Considered drugs of choice to treat infections with G+ve Strep. β-hemolytic type A (most common microbe in tonsillitis).

Have little effect if any against G-ve bacteria.

If the patient has an allergy to penicillin we use erythromycin.



Broad spectrum penicillinase sensitive penicillins

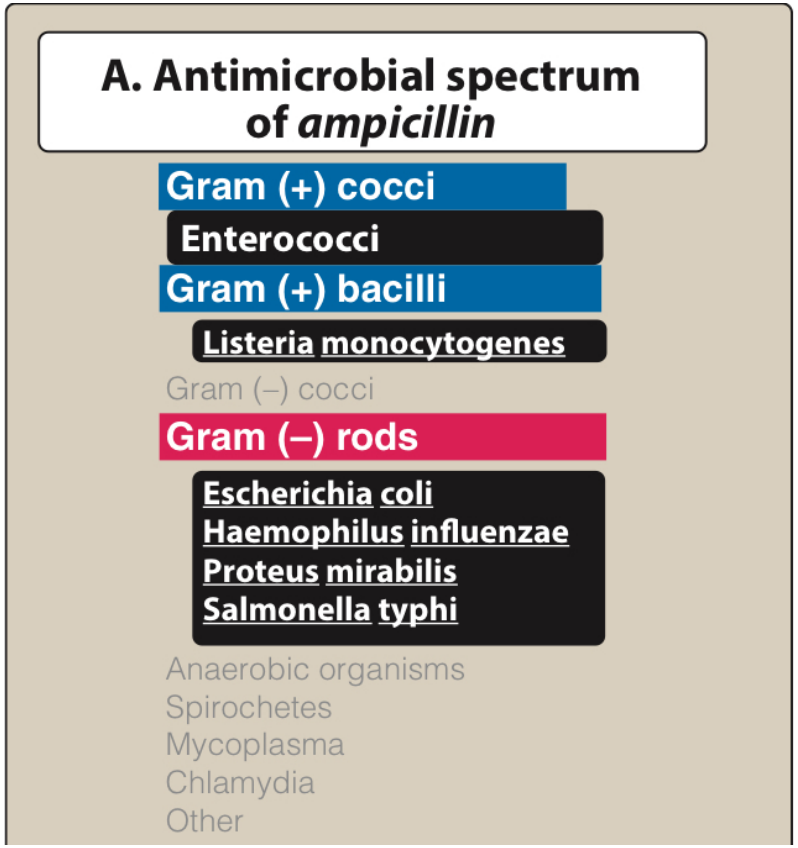
Broad spectrum penicillinase sensitive PNC's (amino penicillins):

Ampicillin (absorption affected by food) IM, IV, Oral.

Amoxicillin (absorption is not affected by food) Oral More potent, has better bioavailability, longer duration of action.

Ampicillin is given four times per day , amoxicillin is given three times per day so amoxicillin has longer DOA(duration of action).

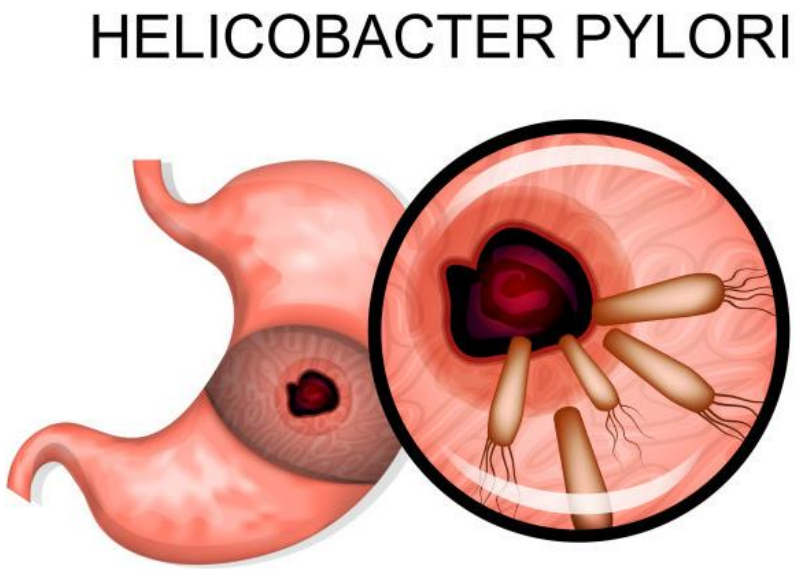
These PNC's have very little effect, if any, against PNCase producing bacteria e.g. H. influenza and against G-ve bacteria e.g. E. coli, Proteus. No effect against Pseudomonas.



Broad spectrum penicillinase sensitive penicillins

Amino penicillins are widely used in tonsillitis, otitis media ,gonorrhea, respiratory infections, shigella infections, UTI's (urinary tract infections)...etc

Amoxicillin has good activity against Helicobacter pylori (causes peptic ulcer) (+ PPI's (proton pump inhibitors) + Clarithromycin + Metronidazole).



Narrow spectrum penicillinase resistant penicillins

- Narrow spectrum penicillinase resistant penicillins (anti Staph penicillins):
- Nafcillin: IM, IV .
- Oxacillin: IM, IV.
- Cloxacillin: Oral.
- Dicloxacillin: Oral.
- Flucloxacillin: Oral & parenteral.

Penicillins:

Antipseudomonal Penicillins:

Piperacillin (the most potent) > Mezlocillin=Ticarcillin > Carbenicillin (the least potent).

All are synergistic with aminoglycosides against Pseudomonas.

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.