CHEMOTHERAPY; ANTIMICROBIALS

LECTURE (21)

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« المحاضرة برعاية ظلك احفظ لحد ما تموت »


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

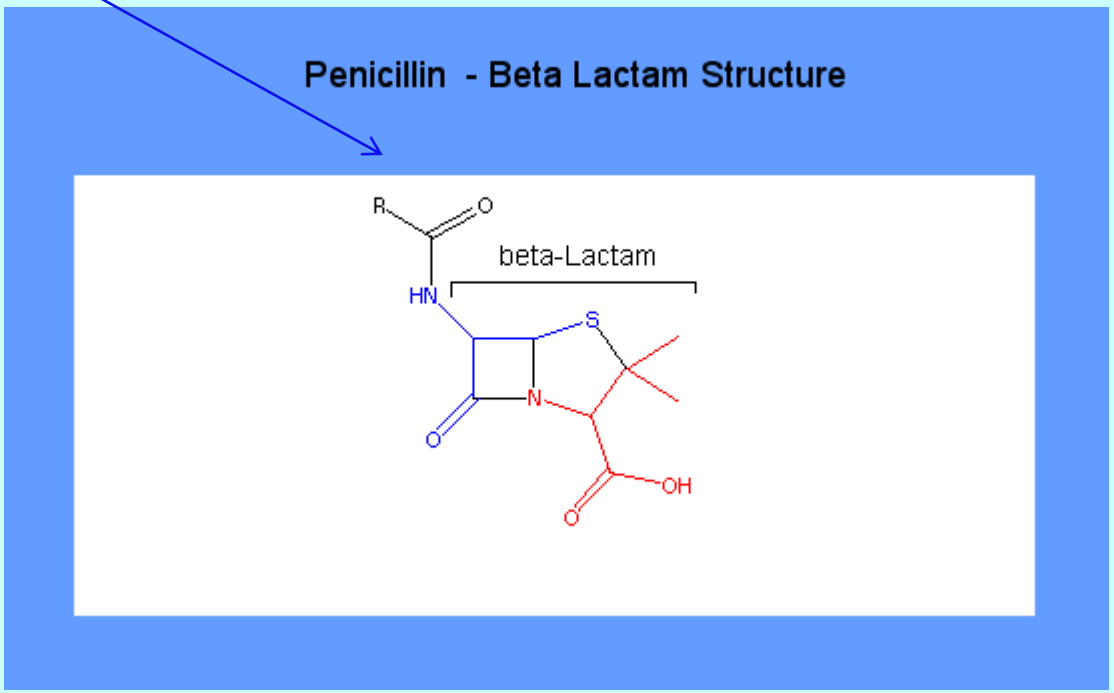
It must be intact otherwise the antibiotics lose its activity

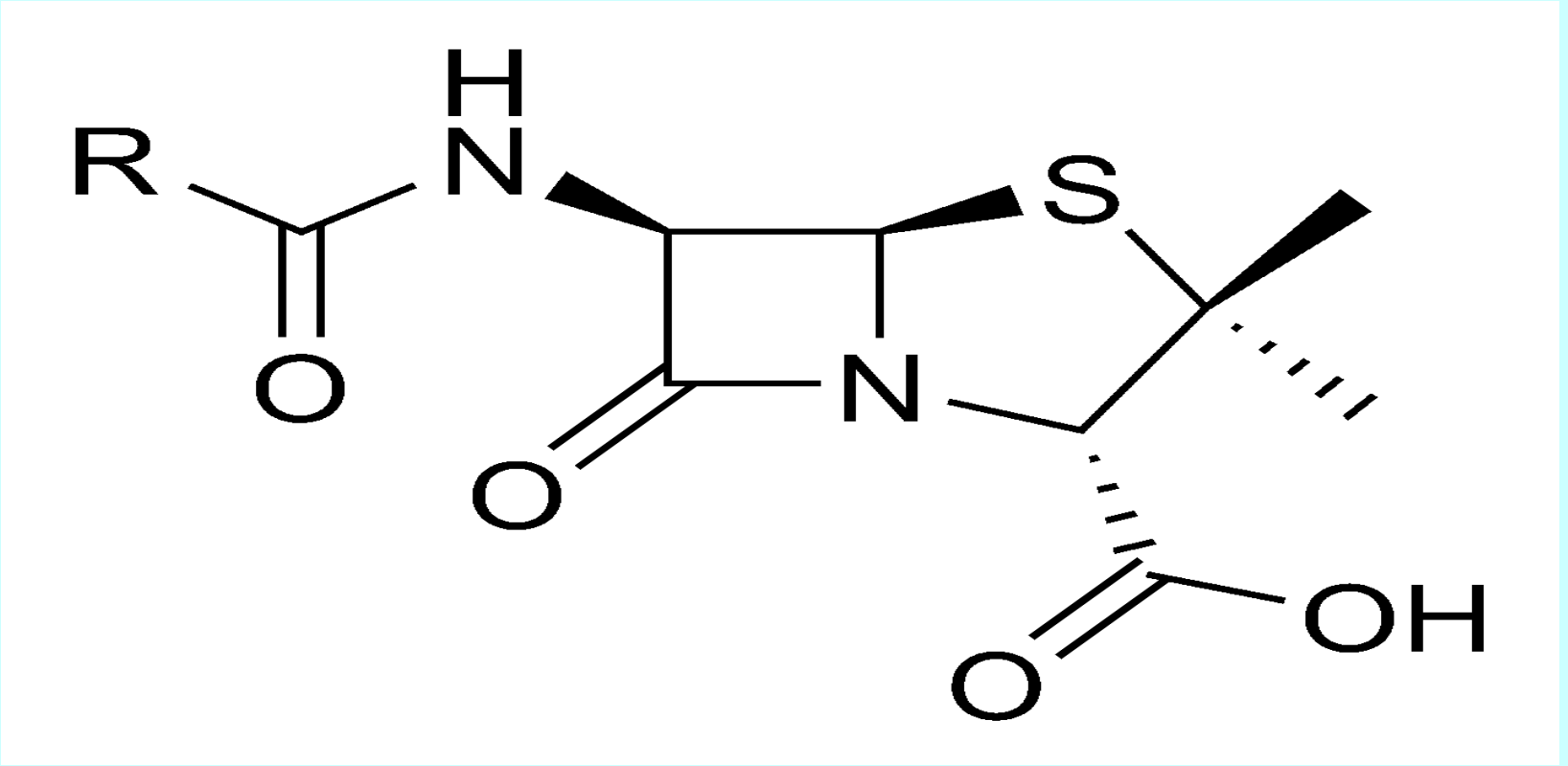
■Include: Penicillins, Cephalosporins, Carbapenems, Carbacephems & Monobactams

Supstitution on R group of the beta lactam determines the spectrum of activity

Structures are not for memorizing but you should recognize it

Any chemical modification on the R group usually results in differences in the pharmacokinetics




R
H
N
O
O
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S
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OH

-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 βlactamases..etc

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

**If the gasric acidity breaks down beta lactam ring , the drug is ineffected orally

■Beta Lactams Mechanism of Action:

■Inhibit synthesis of bacterial cell walls by binding to proteins in bacterial cell membranes e.g. PBP's

Penicillin binding proteins: they act as a receptors for antimicrobial agent

**Absence or mutation in these proteins make the drugs ineffective or make the bacteria more resistant to drugs

■Binding produces a defective cell wall that allows intracellular contents to leak out (lysis)

■Most effective when bacterial cells are dividing

Inhibitors of Cell Wall Synthesis

It is for memorizing

شوية ملاحظات على الجدول السابق :

لتسهيل الحفظ :

* كل ال penicillin بينتهوا ب cillin

كل ال first generation فيهم ph بالنص باستثناء ال

- cefazolin and cefadroxilهدول التنين ما فيهم ph لكنهم من ضمن ال first generation

* اي اشي بيحتوي على one---او ime--- بالنهاية فهو من ضمن ال third generation باستثناء ال cefuroxime هاد بيحتوي على ime لكنه مو من ضمن ال third generation

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 (PNC's)

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

-Derivatives of 6-aminopenicillanic acid (ß-lactam ring is important structure)

-Derived from a fungus

-Prototype is Penicillin G

important for antimicrobial activity

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

The distrubution of penicillin to the brain (due to BBB) and eyes is limmited.without infection>>the penetration of penicillin into the CSF is very low ~ 1%.with CSF inflammation>> can reach up to 10%.WITH improvment (after 2-3 days of using penicilln), the penetration will back again to 1%, BUT the drug will last 7 days at least>> thats why we should increase the dose after improvment:)

المفروض نقلل الجرعة بعد ما المريض يتحسن بس هون استثناء ولازم نزيدها لانه لما يتحسن المريض بيرجع بقل دخول الدواء لهيك لازم نزيد الجرعة

-Most serious complication is hypersensitivity

-Can cause seizures and nephropathy

+ also it is toxic to the kidney, this toxicity is synergistic to other antibiotics (the toxicity will be more when combined 2 antimicrobial agents

-Natural penicillins:

the doctor said: don't worry about the doses(numbers) and the drug if it is effective, orally... whatever :)

Benzylpenicillin=Penicillin G IM, IV

***Acid labile, short acting, given 4-6 times/day**

Depo IM forms to penicillin G

Procaine penicillin given IM twice/day, IV injection contraindicated (could lead to ↓ BP & convulsions)

Benzathine penicillin given IM mainly used for rheumatic fever prophylaxis

*** acid labile >> B-lactame ring is breaking down by the acid>> therefore it isn't effective orally.**

Rheumatic fever is a inflammatory condition which occurs after an tonsillitis caused by a specific bacteria specifically, a group A Streptococcus).It commonly affects the joints and heart specially in Children whose treatment was ignored

Those Children are treated by penicillin G and Asprin

Phenoxy methylpenicillin= Penicillin V Oral

It is similar to penicillin G but it is taken orally

Natural penicillins are narrow spectrum and penicillinase sensitive

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

Have little effect if any against G-ve bacteria

-Narrow spectrum penicillinase resistant

penicillins (anti Staph penicillins):

small number of microorganisms

Nafcillin IM, IV

Oxacillin IM, IV

Cloxacillin Oral

Dicloxacillin Oral

Flucloxacillin Oral & parenteral

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

Ampicillin IM, IV, Oral It has to be taken in empty stomach because the bioavailability affected by the food and is not an acid labile

Amoxicillin Oral More potent, has better bioavailability, longer DOA

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

Amino PNC's are widely used in tonsillitis, otitis media, gonorrhea, respiratory infections, shigella infections, UTI's…etc

Amoxicillin has good activity against Helicobacter pylori (+ PPI's +Clarithromycin +Metronidazole)

Proton pump inhibitors

To explain the Previous slide >>>>

Proton pump inhibitors (PPIs) greatly reduce the amount of acid produced by the stomach, which in turn reduces irritation of the stomach lining and allows an ulcer to heal. When used with antibiotics, PPIs also help treat Helicobacter pylori (H. pylori) infection.

-Antipseudomonal PNC's: Have great activity against pseudomonas microorganism such as G-ve bacilli

Piperacillin > Mezlocillin=Ticarcillin > Carbenicillin

Most potent — Least potent

All are synergistic with aminoglycosides against Pseudomonas

Pseudomonas causes urinary tract infection (UTIs)

-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

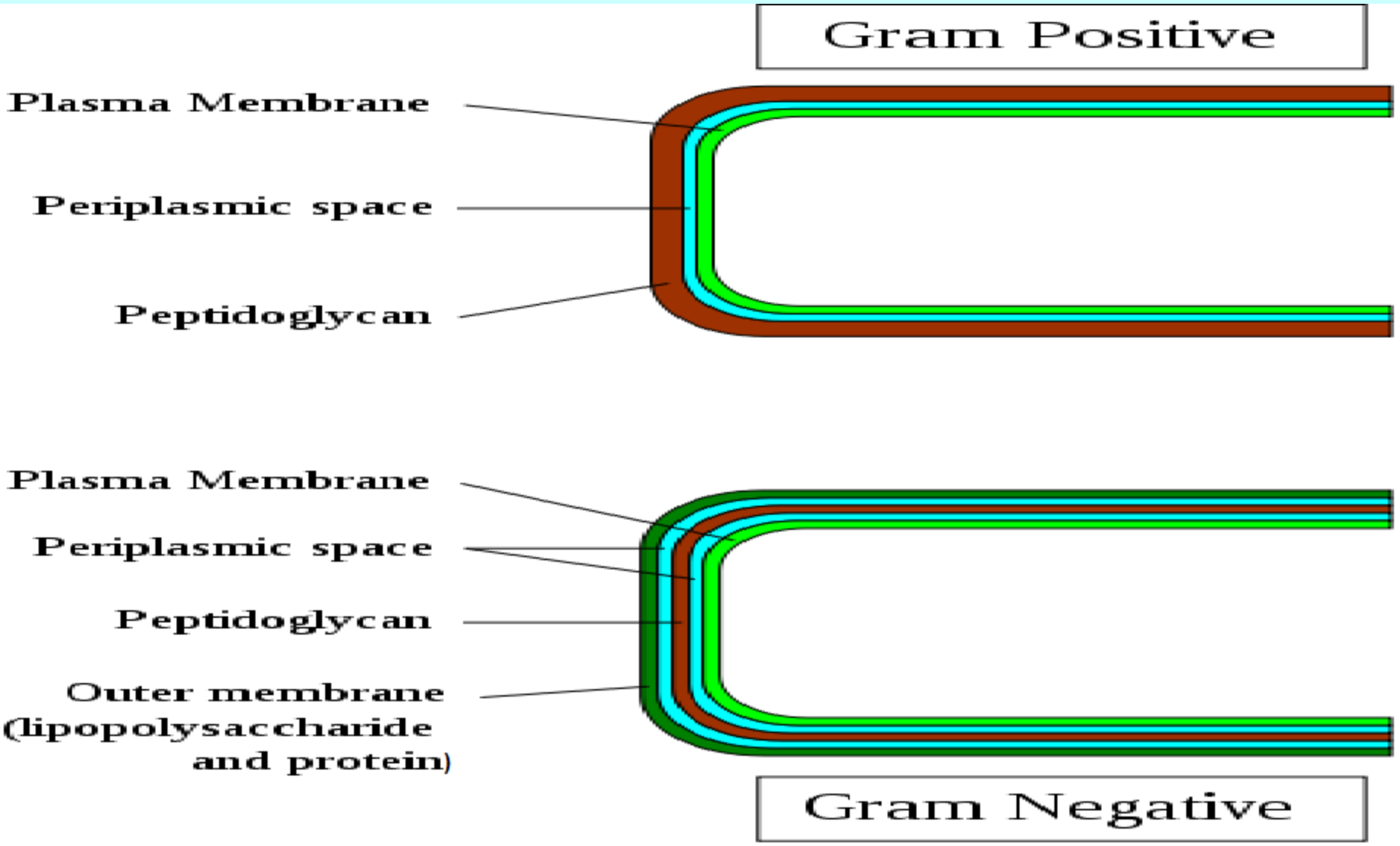
Penicillins are synergistic with aminoglycosides except amidinopenicillins

☐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 lysis of cell wall

Disruption of the cell wall causes death of the bacterial cell (Bactericidal Effect)


Gram Positive
Plasma Membrane
Periplasmic space
Peptidoglycan
Plasma Membrane
Periplasmic space
Peptidoglycan
Outer membrane
(lipopolysaccharide
and protein)
Gram Negative

Penicillin is more effective against Gram-positive bacteria because Gram negative bacteria have a lipopolysaccharide and protein layer that surrounds the peptidoglygan layer of the cell wall, preventing penicillin from attacking.

☐Pharmacokinetics of PNC's:

هون لازم ننتبه لل drug-drug interaction
لحتى ما يصيرالدواء سام اذا زاد تركيزه

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

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, GUS, GIT, respiratory tract and soft tissues

Genetourinary system

-Selection depends on the organism and severity of the infection e.g. anti-staph vs. anti-pseudomonal

These are specific agents that highly effective than other penicillins

** Combination of PNC's or a cephalosporin with a potent inhibitor of lactamases

■β-lactemase inhibitors:

Have no antibacterial activity, increase potency and spectrum of activity of combined antibiotic

Clavulinic acid, Sulbactam, Tazobactam

(Augmentin® =amoxicillin/clavulinate)

(Unasyn®=ampicillin/sulbactam)

(Zosyn®=piperacillin/tazobactam)…etc

-mechanisms of resistance to PNC's:

-Altered penicillin binding proteins (PBPs)

-Production of beta-lactamase (penicillinases)

-Decreased penetration/increased efflux (pseudomonas)

Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPS.The presence of an efflux pump can also reduce the amount of intracellular drug

Preparations to PNC's :

Oral, parenteral, intrathecal, topical, intra-articular

Inside joints

↓

مثل قطرات العين

■Side effects to PNC's:

-Allergy (Most frequent and dangerous) Type 1 more common than type 2

It is against any toxic material

Type I allergic reactions. Early onset (immune IgE mediated) Antigen-antibody reaction

Type II allergic reactions. Late onset (2-10 days). May manifest as eosinophilia, hemolytic anemia, interstitial nephritis or serum sickness (fever; ⟶ Pain in joints arthralgia; malaise…)

-Nonallergic ampicillin rash, occurs only once

After the rash occurs we should make test to make sure that the drud is safe and if we sensitive or not

(more common in pts with acute leukemias; mononucleosis, lymphomas, cytomegaloviral infections…)

-Neurotoxicity (more common with oxacillin)

-Hepatotoxicity (IV oxacillin)

-Bone marrow depression (reversible) (IV nafcillin)

-Nephrotoxicity (Methicillin)

■**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

-Absolute contraindications to all PNC's in pts with history of allergy

لحتى نتأكد من فعالية الدواء وانه غير سام وبنقدر نجربه على البشر لازم يخضع لل phases of clinical trials

GOOD LUCK