PENICILLINS

Mechanism of action - bactericidal

Inhibition of the transpeptidase – cell wall synthesis inhibition

Inhibition of the activities of other PBPs can cause f.e.: spheroplast formation and rapid lysis or delayed lysis or the production of long filamentous form of bacteria

Classification of the Penicillins

Natural penicillins: Penicillin G and congeners.

Synthetic penicillins

Narrow spectrum

- The Penicillinase Resistant Penicillins (Izoxazolyl penicillins): methicillin, nafcillin, oxacillin, doxacillin, cloxacillin.

Broad-spectrum

- Aminopenicillins: ampicillin, amoxicillin, bacampicillin
- Carboxypenicillins: carbenicillin,ticarcillin
- Ureidopenicillins: mezlocillin, piperacillin

Natural penicillins

Pharmacokinetics

- poor absorption from GI tract (except penicillin V)
- widely distributed: in tissues (liver, bile, kidney, semen, intestine) and secretions (joint, pleural, pericardial fluid, bile), low concentration in: prosthatic secretions, brain tissue, intraocular fluid, phagocytic cells
- the concentration in CSF is increased only under inflame conditions
- eliminated rapidly - mainly by the kidneys (tubular secretion)

Preparations: Penicillin G (benzylpenicillin), Penicillin V (phenoxymethylpenicillin), Penicillin G Procaine, Penicillin G benzathine

Antimicrobial activity: both are effective mainly against gram-positive microorganisms. Many microbes previously susceptible to penicillins are now resistant.

- most Streptococci are susceptible, especially Str.pyogenes, excluding Strep. pneumoniae.
- 90% of strains of Staphylococci are resistant.
- the sensitivity to gonococci decreases
- effective against meningococci.
- some of the strains of Corynebacterium diph. and Bacillus anthracis are highly resistant.
- anaerobics: Clostridium sp. - highly sensitive, Bacteroides fragilis -resistant. The species of Leptospira - mostly susceptible, also Treponema pallidum, Borrelia burgdorferri, Actinomyces israelii, Pasteurella multocida and Listeria monocytogenes.

Therapeutic uses of natural penicillins:

- dental infections (results of carious lesions)
- not recommended for prophylaxis of endocarditis

Penicilllinase-resistant penicillins - isoxazolylpenicillins

- indicated to the treatment of infection that are known to be caused by staphylococci that elaborate the enzyme
- less active than penicillin G against other penicillin-sensitive organisms including nonpenicillinase-producing Staphylococci
- agents of choice for most staphylococcal disease, despite of the incidence of methicillin-resistant bacteria
- variable absorption from GI tract, but adequate.
- bound to plasma albumins to a great extend (90-95%)
- excretion: kidney and/or hepatic elimination

Broad-spectrum penicillins

<u>Aminopenicillins</u>

Antimicrobial activity similar to that of penicillin G including certain differences:

- A. are more active against gram-negative bacteria (but most strains of Pseudomonas, Proteus are resistant).
- A. are active against Haemophilus
- A. are active against Strep. from the viridans group.
- Entrococci are twice as sensitive to A. as they are to penicillin G.
- increasing resistance to: Neisseria gonorrhea, E. coli, Salmonella, Shigella

- Ampicillin and amoxicillin are readily absorbed from GI tract About

- Most of the dose is excreted in urine as an active form
- Ampicillin undergoes enterohepatic circulation.

Therapeutic uses of aminopenicillins
Infections caused by common intraoral pathegens:
  - Periapical or periodontal abscesses
  - Acute suppurative pulpitis
  - Toxix cellulitis
  - Postsurgical or posttraumatic infections
  - Suppurative infection of salivary glands
  - Ludwigs angina
  - Oral-antral or oral-nasal fistulas with sinusitis
  - Purulent osteitis
  - Osteomyelitis
  - Prevention of bacterial endocarditis

Antipseudomonal penicillins
Carboxypenicillins and ureidopenicillins
- active against some isolates of Pseudomonas and certain indole-positive Proteus sp (ureidopenicillins are more active)
- carboxypenicillines are ineffective against most strains of Staph., Klebsiella, Listeria
- ureidopenicillins - useful for treatment of infection with Klebsiella and Enterococcus faecalis
- both are sensitive to destruction by betalactamases
- mezlocillin, ticarcillin and piperacillin excreted in the bile in a significant degree, carbenicillin rapidly excreted as active moiety in the urine
- therapeutic indications: serious infections caused by gram-negative bacteria

Untoward reactions to penicillins
- hypersensitivity reactions

Management of the patient potentially allergic to penicillin
- evaluation of the patients history to avoid the use of penicillin
- use of benzylpenicilloyl polysine PRE-PEN
- desensitization

- bone marrow depression: granulocytopenia (aminopenicillins)
- hepatitis - oxacillin
- defect of hemostasis - carboxypenicillin
- hyperkaliemia - after high doses > 20 million U/24h of potassium salt of penicillin G
- neurological effects - high doses of penicillin G.
- allergic reaction to procaine
- pseudomembranous colitis
- Hoigne syndrome - pseudoanaphylactic reaction after i.m. injection of Penicillin G procaine

β-lactamase inhibitors
- Poor antimicrobial activity, bind beta-lactamases and inhibit them
- Active against plasmid-coded beta-lactamases, resistant to the chromosomal beta-lactamases induced by gram-negative bacilli
- Used in combination with beta-lactams to achieve wider spectrum of activity
- amoxicillin + clavulanic acid, ampicillin + sulbactam, ticarcillin + clavulanic acid, piperacillin + tazobactam

CEPHALOSPORINS
First-generation: Cephalotin (Keflin), Cefazolin (Kefzol), Cephalexin (Keflex)

good activity against Streptococci, Staph. aureus
modest activity against gram-negative
susceptible to beta-lactamase

Second-generation: Cefamandole (Mandol),Cefaclor (Ceclor), Cefuroxime axetil (Ceftin)

good activity against gram-negative bacteria
modest activity against gram-positive
active against Bacteroides
susceptible to beta-lactamase

Third-generation: Cefotaxime (Claforan), Ceftriaxone (Rocephin)

active against gram-negative
activity against gram-positive comparable to first-generation agents
more resistant to beta-lactamases
penetrate CSF

Ceftazidime (Fortaz), Cefoperazone (Cefobid)
Especially active against Pseudomonas

Moderately active against gram-positive bacteria

Fourth-generation: Cefepime (Maxipime)

Spectrum comparable to third-generation but more resistant to beta lactamases

Pharmacokinetics
- Excreted primarily by the kidney (exep. Cefoperazone)
- Penetrate CSF

Therapeutic use of cephalosporins
- drugs of choice for odontogenic infections caused by Klebsiella
- dental infection due to penicillinase-producing staphylococcal infection in patients who have a history of alergic responses of the nonimediate type to penicillin
- as alternative to penicillin in therapy of orodental infections caused by aerobic bacteria (acute celullitis)
- alternative drugs for the prevention of bacterial endocarditis

Adverse reactions:
- hypersensitivity reaction
- cross-reactivity with penicillins
- granulocytopenia
- nephrotoxicity
- diarrhoea
- intolerance of alcohol
- serious bleeding

CARBAPENEMS (imipenem, meropenem)

- Gram-positive aerobics: Streptococci, Enterococci, Staphylococci
- Gram-negative aerobics: Enterobacteriacae, most strains of Pseudomonas
- Anaerobes
- Highly resistant to beta-lactamases
- Treatment of nosocomial infections
- Adverse effects: nausea, seizures, hypersensitivity
- Pharmacokinetics: penetration CSF variable, excreted by the kidneys mainly as unchanged substance.Imipenem is hydrolyzed rapidly by dipeptidase.

MONOBACTAMS (aztreonam)
- Gram-negative aerobics, especially: Pseudomonas, Hemophilus, Gonococci
- Resistant to most of the beta-lactamases
- Therapeutic use: in selected instances (drug of the last choice) - in place of aminoglycosides
- Adverse reaction: generally well tolerated – allergy. No cross-reactions to other beta-lactams
- Pharmacokinetics: good tissue distribution incl. CSF, excreted mostly unaltered in urine.