**Chemotherapeutics I**

**Penicillins**

*Classification*

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 within tissues and secretions, low concentration in prostatic secretions, brain tissue, intraocular fluid, phagocytic cells
- the concentration in CSF is increased only under inflame conditions,
- eliminated rapidly - mainly by the kidney (tubular secretion, glomerulal filtration in 10%).

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

Antimicrobial activity

Aerobic Gram positive

most streptococci are susceptible, exc. of Strep. pneumoniae.

90% of strains of Staphylococci are resistant.

Aerobic Gram negative

sensitivity to gonococci decreases gradually

effective against meningococci.

Anaerobics

Clostridium sp. - highly sensitive, Bacteroides fragilis -resistant.

Others

Leptospira - mostly susceptible, also Treponema pallidum, Borrelia burgdorferri, Actinomyces israelii, Pasteurella multocida and Listeria monocytogenes.

Therapeutic uses

- streptococcal infections including streptococcal viridans and enterococcal endocarditis
- pneumococcal infections (pneumonia, meningitis) – definitive therapy
- infections due to anaerobes (pulmonary, peridontal)- definitive therapy
- meningococcal infections - drug of choice if bacteria are sensitive
- gonococcal infections - the effectiveness is dependent on geographical area
- syphilis (Jarish-Herxheimer reaction)
- diphteria
- anthrax, gangrene, tetanus
- fusospirochetal infections- gingivostomatitis
- listerial endocarditis
- Lyme disease

*The penicilllinase-resistant penicillins - isoxazolylpenicillins- antispahyloccocal penicillins*

- Empiric therapy – only in combination
- Well absorbed
- bound to plasma albumins to a great extend (90-95%)
- excretion: renal and hepatic elimination

The broad-spectrum penicillins

*Aminopenicillins*

Antimicrobial activity similar to that of penicillin G.

Main differences:

- A. are more active against Gram-negative bacteria (including Haemophilus, Neisseria, Salmonella, Shigella, but most strains of Pseudomonas, Proteus are resistant).
- Entrococci are twice as sensitive to A. as they are to penicillin G.

A. are active mainly against community-acquired strains

Aminopenicillins –pharmacokinetics

Readily absorbed from GI

Metabolized in the liver

Ampicillin undergoes enterohepatic circulation

Amoxicillin excreted by the kidneys

Therapeutic uses of aminopenicillins

- respiratory infections

- urinary tract infections
- prevention of bacterial endocarditis
- salmonella infections
- meningitis - are not indicate as a single agent to avoid resistance, excellent activity against Listeria meningitidis in immuno-compromised persons

Antipseudomonal penicillins
*Carboxypenicillins and ureidopenicillins*

- active against some isolates of Pseudomonas aer. and certain indole-positive Proteus sp.
- ineffective against most strains of Staph., B. fragilis
- ureidopenicillins - useful for treatment of infection with Klebsiella and Enterococcus faecalis
- 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
- bone marrow depression: granulocytopenia (aminopenicillins)
- hepatitis
- defect of hemostasis
- hyperkaliemia
- neurological effects
- allergic reaction to procaine
- pseudomembranous colitis
- Hoigne syndrome

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

*Second-generation: Cefamandole,Cefaclor , Cefuroxime axetil*
good activity against gram-negative bacteria
modest activity against gram-positive
active against Bacteroides
susceptible to beta-lactamase

*Third-generation:*
Cefotaxime , Ceftriaxone
active against gram-negative
activity against gram-positive comparable to first-generation agents
more resistant to beta-lactamases
penetrate CSF

Ceftazidime, Cefoperazone
Especially active against Pseudomonas
Moderately active against gram-positive bacteria

*Fourth-generation: Cefepime*
Spectrum comparable to third-generation but more resistant to beta lactamases
Better penetrate CSF.

Pharmacokinetics

- Well absorbed (depends on agent)
- Partially metabolized in the liver
- Excreted primarily by the kidneys (except cefoperazone)
- Penetrate CSF

Therapeutic uses of cephalosporins

- pneumonia (Pneumococci, Haemophilus, Staphylococci)
- serious infections caused by Gram negative aerobic bacteria

- cefotaxime and ceftriaxone - drugs of choice for the initial therapy of meningitis in nonimmunocompromised adults
- ceftazidime + aminoglycoside - treatment of choice for Pseudomonas meningitidis
- ceftriaxone - drug of choice for all forms of gonorrhoea
- typhoid fever - cefoperazone, ceftriaxone

Adverse reactions:
- hypersensitivity reaction
- diarrhea
- granulocytopenia
- nephrotoxicity???

- cross-reactivity with penicillins
- intolerance of alcohol
- 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 the urine.