Beta-lactam antibiotics - Cephalosporins

Targets - PBP's

Activity - **Cidal** - growing organisms (like the penicillins)

Principles of action - Affinity for PBP's
- Permeability properties
- Stability to bacterial enzymes

Cephalosporins

Development - Giuseppe Brodtzu - Sardinian sewage

Cephalosporin C - Cephalothin
- No meningeal penetration
- Failed in meningococcal meningitis
- Painful to give IM

**Advantages**

- Cephalosporin nucleus - resistant to Staphylococcal penicillinase
- Cephalosporin nucleus - more readily modified

Development of C'sporins

**Generations** - in response to clinical needs

**First generation** - Cephalothin (not used)
- Cefazolin oral - Cephalexin, cefaclor

- Activity - Broad spectrum:
  - Gram positive Streptococci, *S. aureus*
  - Gram negative - *E.coli*, *Klebsiella*
- No activity against *Enterococci* - different PBP's

Second generation C'sporins

**Cefuroxime**
**Cefoxitin**
**Cefotetan**

70's - Beta-lactamase's recognized (*H. influenzae*)
- Anaerobic infections

- Cefoxitin - Methoxy group - conferred beta-lactamase stability
- Induction of chromosomal beta-lactamases
- *Bacteroides fragilis* - enteric anaerobes

- Cefuroxime - Respiratory tract infections - community acquired
Kinetics of c'sporin binding

Affinity for receptor - PBP
Permeability characteristics of the porin
Beta-lactamase production - within periplasmic space

Third generation C'sporins

80's - Intensive care - nosocomial infections
Multi-Resistant Gram negative organisms
Chromosomal beta-lactamase - C'sporinase
Inducible
Plasmid mediated enzymes - mutants with both Penicillinase and C'sporinase activity
Permeability limitations

Third generation c'sporins

Cefotaxime
Ceftriaxone
Ceftazidime
Cefipime

Highly active - Cefotaxime - S. pneumo
N. meningitidis, gets across BBB

Ceftriaxone - even more active - Single dose IM
get meningeal levels - Long half life !!!
N. gonorrhoeae, use in unreliable patients - Cover S. pneumonia bacteremia

Use in meningitis -
Ceftazidime/Cefepime - anti-
Pseudomonas

Used the side groups which have increased permeability through
P.aeruginosa porins -

- Induction (low level) of chromosomal C’sporinase

- Beta-lactamase stable -

- less activity against gram positive organisms

Cefepime – Fourth generation

- Increased beta-lactamase stability
- Also better Gram positive -
Carbapenems

**Imipenem**
**Meropenem**
- Beta-lactam class - PBP-2 major target
- Permeability - separate porin
- **Huge spectrum** - Aerobes, anaerobes
  - everything EXCEPT
  - *Enterococci*  
  - *Stenotrophomonas* etc.
- Concern - CNS side effects - Imipenem ??

Monobactams - Aztreonam

- Only binds to Gram negative PBP’s
- No real beta-lactam ring - therefore beta-lactamase stable
- Narrow spectrum - Only aerobic gram negative rods
  - Use - instead of an aminoglycoside

Use of the cephalosporins:
- First generation - Oral - surgical prophylaxis - skin soft tissue infections - taste good - “house cephalosporin”
- Second generation - Some oral - some parenteral
  - Selected uses
- Parenteral - Third generation
  - Increased - due to resistant *S. pneumoniae* - susceptible to cefotaxime and ceftriaxone
  - Gram negative infections - hospital acquired - selection of resistant organisms

Pharmacology

- Charged - hydrophilic - do not enter phagocytic cells
- Variably protein bound (Ceftriaxone - highly bound)
- Variable half-lives
- Metabolism - Cefotaxime - Liver - desacetyl derivative - active
- Excretion - Renal - Tubular secretion and glomerular filtration
Beta-lactams – side effects
- penicillin – c’sporin cross reactivity – 3-7% (depending on the drug)
- Hypersensitivity – Rash
  - IgE-mediated allergy – Anaphylaxis
- Major determinants – minor side effects
- Minor determinants – MAJOR reactions
- Diarrhea
- Neutropenia
- CNS – high doses – especially the carbapenems

C’sporins
- Intrinsic resistance - enterococci - different targets
- Acquired resistance - active change
  - Acquisition of an enzyme
  - Induction of an enzyme
  - Selection of a mutation
  - Alteration in permeability

Vancomycin
- History - Developed in the 50’s - anti-Staph drug
- Re-“discovered” - MRSA - and MRSE - *Staphylococci* with altered PBP-2A
  - *mecA* gene - no longer binds penicillin (C’sporins don’t bind either)
- Target - D-ala-D-ala - pentapeptide
  - blocks two steps in cell wall synthesis
- Cidal - Only gram positives - Highly resistant *S. pneumo*

**Figure 6.25** Structure of vancomycin. The stippled area indicates the residues involved in the interaction with the pentapeptide precocci.

Methicillin resistant *Staphylococci*

- *mecA* mutations - altered PBP’s
- Often linked to overexpression of beta-lactamase
- Use different class of antimicrobial agent
Small glycoprotein (MWT @ 1,450) derived from *Nocardia orientalis*

Activity - most G(+) bacteria including Streptococci, Corynebactria, Clostridia, Listeria, and Bacillus species.

Bactericidal at levels 0.5 - 3 mg/L

Staphylococci including β-lactamase producing and methicillin resistant species are killed at levels <10 mg/L

Resistance - vancomycin resistant enterococcus (VRE)

**Vancomycin - properties**

**Vancomycin - Pharmacokinetic properties**

Vd @ 0.7 L/kg

Protein binding @ 55%

Elimination: > 90% renal

Half-life @ 7 hrs (with normal Clcr)

Vancomycin is not removed by standard HD or PD, but it is removed by CVVH

**Side effects of vancomycin:**

Red man syndrome - histamine-mediated erythematous flushing of the face, neck and trunk, a reaction which occurs during the infusion, and may be associated with hypotension.

Nephrotoxicity and ototoxicity may occur in < 1% of pts especially those receiving other "toxic' drugs like aminoglycosides.

A relationship between vancomycin level and nephrotoxicity or ototoxicity has not been established.

It is now widely believed that the earlier reports of nephrotoxicity may have been related to impurities in the product.

**Vancomycin and Resistant *S. pneumoniae***

Penicillin MIC’s <0.1 - S; 0.1-1= RR; >2.0 Resistant

Alternate therapy - Pneumonia/Bacteremia - Cefotaxime or Ceftriaxone

? Meningitis - Can’t achieve levels -

Vancomycin - high doses - gets into CSF

**Vancomycin resistant enterococci**

Increased 34 fold from 0.3% to 7.9% NISS 1989 - 1993

Initially associated with ICU’s → Non ICU’s

Larger hospitals

Lack of alternative therapy

? Spread of genes involved to *S. aureus* and *S. epidermidis*
Cephalosporins - what to remember

Developed in response to clinical needs -
   Grouped by “generation”
   Learn properties of a prototype from each generation

Extremely widely used -

   Safe - Side effects specific to individual members of the family
         as well as the family as a whole
   Not necessarily cross reaction with penicillin
   hypersensitivity
   Aztreonam - Gram negs - narrow
   Imipenem/Meropenem - everything “except”
   Vanco - need to know well