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 (4th?)

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 -
## Cefotaxime Sodium

![Cefotaxime Sodium molecule](image)

## IMPORTANT PHARMACOKINETIC VARIABLES OF NEW CEPHALOSPORINS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Serum protein binding (%)</th>
<th>Metabolism</th>
<th>Peak serum levels (µg/ml)</th>
<th>Half-Life (hours) Ccr&gt;90</th>
<th>Half-Life (hours) Ccr&gt;10</th>
<th>Vd (L)</th>
<th>Urinary recovery (%)</th>
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</thead>
<tbody>
<tr>
<td>Moxalactam</td>
<td>50</td>
<td>-</td>
<td>60 24</td>
<td>2</td>
<td>19</td>
<td>19</td>
<td>75</td>
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<tr>
<td>Cefotaxime</td>
<td>38</td>
<td>+</td>
<td>42 12</td>
<td>1.1</td>
<td>2.5</td>
<td>27</td>
<td>55</td>
</tr>
<tr>
<td>Desacetyl cefotaxime</td>
<td>23</td>
<td>+</td>
<td>7 3</td>
<td>1.6</td>
<td>11</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Ceftriaxime</td>
<td>31</td>
<td>-</td>
<td>87 14</td>
<td>1.4</td>
<td>25</td>
<td>18</td>
<td>85</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>83-96</td>
<td>-</td>
<td>150 50</td>
<td>8</td>
<td>11-16</td>
<td>9</td>
<td>60*</td>
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<tr>
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<td>17</td>
<td>-</td>
<td>80 18</td>
<td>1.8</td>
<td>16</td>
<td>16</td>
<td>75</td>
</tr>
<tr>
<td>Ceferonazone</td>
<td>90</td>
<td>-</td>
<td>125 26</td>
<td>1.9</td>
<td>2.5</td>
<td>12</td>
<td>25</td>
</tr>
</tbody>
</table>

*Based on intravenous infusion over 30 minutes.

† Intramuscularly

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
Ertapenem

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 – community acquired infections

**Parenteral - Third generation**

  Increased - due to resistant *S. pneumoniae* -
  *susceptible* to cefotaxime and ceftriaxone

  Gram negative infections - hospital acquired - selection of resistant organisms
Resistance Rates

MYSTIC program (USA 199-2006)
>100 medical centers

Resistance to carbapenems
Enterobacteriaceae (9,396 organisms) 0.5%
_Pseudomonas aeruginosa_ (3,100 organisms) 7.2%

All (20,051) 2.8%

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-aladala - pentapeptide
    blocks two steps in cell wall synthesis

Cidal - Only gram positives - Highly resistant S. pneumo
Methicillin resistant *Staphylococci*

- *mecA* mutations - altered PBP's
- often linked to overexpression of beta-lactamase
- Use different class of antimicrobial agent
Use of Vancomycin

Staphylococci – resistant to penicillin – “methicillin resistant - Altered PBP’s

Coagulase-negative staphylococci – Catheter infection

*S. aureus* – MRSA – Methicillin Resistant *Staphylococcus aureus*

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**Methicillin (oxacillin)-resistant Staphylococcus aureus (MRSA) Among ICU Patients, 1995-2004**

![Graph showing the percent resistance of Methicillin (oxacillin)-resistant Staphylococcus aureus (MRSA) from 1995 to 2004.](Image)

- **Percent Resistance**: 0, 10, 20, 30, 40, 50, 60, 70

- The graph shows an increasing trend in percent resistance from 1995 to 2004.
MRSA - types

Nosocomial – Multi-resistant – large chromosomal insertions – *mecA* cassette

Community – SCC’s (small covalent circles)  
Integrated elements along with the recombinases

Very common – moving back into the hospital

Community Acquired MRSA

Increasingly common – smaller mobile genetic unit

Still susceptible to other antibiotics (unlike hospital – acquired)

Often relatively virulent – Panton-Valentine toxin  
Skin- soft tissue infections  
Fulminant pneumonias

Adolescents

Up to 70% of outpatient isolates !!!! At some centers
Vancomycin - properties

Small glycoprotein (MWt @ 1,450) derived from *Nocardia orientalis*

Activity - most G(+) bacteria including Streptococci, Corynebacteria, 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

Vancomycin - Pharamacokinetic 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 < 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 resistance

VRE = Vancomycin resistant enterococci
? From oral use of vancomycin

Selection of enterococci – altered cell wall structure

Several mechanisms:
D-ala-D-ala changed to a lactate
No metabolic cost

Several Vanco resistance cassettes
Vancomycin-resistant *Enterococi* Among ICU Patients, 1995-2004

Source: National Nosocomial Infections Surveillance (NNIS) System

**Molecular logic of vancomycin resistance.** Vancomycin-sensitive and -resistant bacteria differ in a critical component of their cell wall. Sensitive bacteria (left) synthesize PG strands that terminate in d-Ala-d-Ala; vancomycin binds avidly to these termini, thereby disrupting cell wall synthesis and leading to cell lysis. Resistant bacteria (right) harbor a transposable element encoding nine genes that contribute to the resistance phenotype. The gene products include a transmembrane protein (Van S) that senses the presence of the drug and transmits a signal—by transfer of a phosphoryl group—to a response regulator protein (Van R) that activates transcription of the other resistance genes. The combined activities of Van H and Van A lead to synthesis of a depsipeptide, d-Ala-d-Lactate, which can be incorporated into the PG strands of the cell wall. The altered PG termini do not affect the structural integrity of the cell wall, but substantially reduce its affinity for vancomycin, thereby rendering the bacteria resistant to the drug.
Vancomycin-resistant S. aureus

- VISA – Vanco intermediate –
  MIC’s 4-16 micrograms/ml

Multiple point mutations
Thickened peptidoglycan layer
? Sponge effect
(GISA = glycopeptide-intermediate strains)