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. pneumoniae
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. pneumoniae bacteremia

Use in meningitis -
**Cefotaxime Sodium**

![Cefotaxime Molecular Structure](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)</th>
<th>Urinary recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxalactam</td>
<td>50</td>
<td>-</td>
<td>60 24</td>
<td>2 19</td>
<td>19 75</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>38</td>
<td>+</td>
<td>42 12</td>
<td>1.1 2.5</td>
<td>27 55</td>
</tr>
<tr>
<td>Desacetyl cefotaxime</td>
<td>23</td>
<td>+</td>
<td>7 3</td>
<td>1.6 11</td>
<td>- 30</td>
</tr>
<tr>
<td>Ceftizoxime</td>
<td>31</td>
<td>-</td>
<td>87 14</td>
<td>1.4 25</td>
<td>18 85</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>83-96</td>
<td>-</td>
<td>150 50</td>
<td>8 11-16</td>
<td>9 60*</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>17</td>
<td>-</td>
<td>80 18</td>
<td>1.8</td>
<td>16 75</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>90</td>
<td>-</td>
<td>125 26</td>
<td>1.9 2.5</td>
<td>12 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

**Adverse Reactions to Cephalosporins**

**Table 1. Adverse Reactions to Cephalosporins.**

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Frequency</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>1.0–2.8</td>
<td>Norby, Sanders et al., Arndt and Jek, Platt*</td>
</tr>
<tr>
<td>Positive direct antiglobulin test</td>
<td>1.0–2.0</td>
<td>Sanders et al., Platt, Meyer*</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0.0001–0.1</td>
<td>Gadd et al., Sogn et al.</td>
</tr>
<tr>
<td>Fever</td>
<td>0.5–0.9</td>
<td>Sanders et al., Meyer*</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>2.7–8.2</td>
<td>Sanders et al., Platt*</td>
</tr>
</tbody>
</table>

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
Methicillin resistant *Staphylococci*

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

Use of Vancomycin

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

Coagulase-negative staphylococci – Catheter infection

*S. aureus* – MRSA – Methicillin Resistant *Staphylococcus aureus*
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 < 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.
Methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) Among ICU Patients, 1995-2004

![Graph showing the percentage of MRSA resistance from 1995 to 2004.](image)

**MRSA - types**

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

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

Epidemiology - few major types

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?
  Hemolysins
  Skin-soft tissue infections
  Fulminant pneumonias

Adolescents

Up to 70% of outpatient isolates !!!! At some centers

Invasive Methicillin-Resistant Staphylococcus aureus Infections in the United States

8987 observed cases of invasive MRSA

invasive MRSA was 31.8 per 100 000
Deadly Bacteria Found to Be More Common

ATLANTA, Oct. 16 — Nearly 19,000 people died in the United States in 2005 after being infected with virulent drug-resistant bacteria that have spread rampantly through hospitals and nursing homes, according to the most thorough study of the disease’s prevalence ever conducted.

Staph Infections Reported at Schools Across the Country

Students stand outside Staunton River High School in Moneta, Va., where a high school student infected with an antibiotic-resistant staph infection has died prompting Bedford County to close all 21 of its schools for a thorough cleaning.

Vancomycin resistance?
Widespread use - empiric therapy for *S. aureus* infection?

Development of resistance:

- *Enterococci*
- *Staphylococci*
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

**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)