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

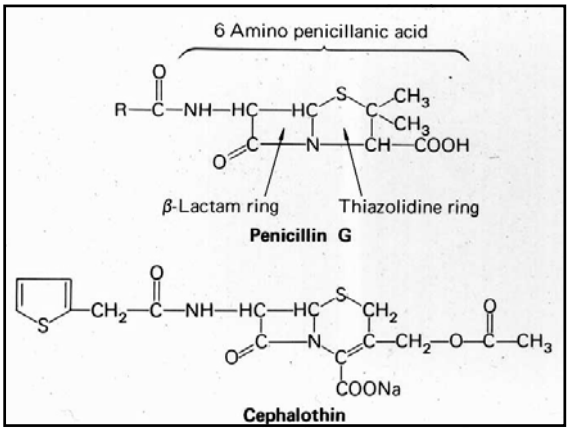
Development of C'sporins

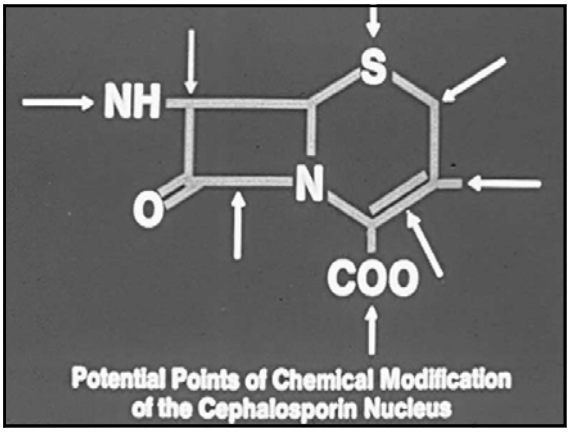
Generations - in response to clinical needs

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





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

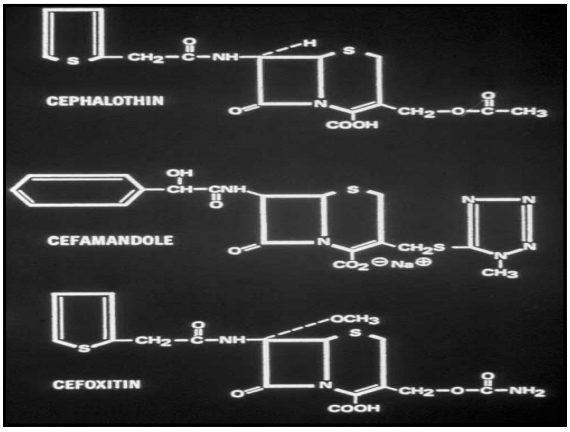
Second generation C'sporins

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



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

Kinetics of c'sporin binding

Affinity for receptor - PBP

Permeability characteristics of the porin

Beta-lactamase production - within periplasmic space

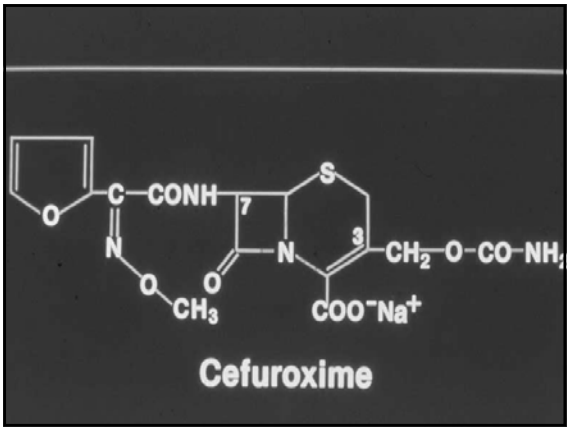
Third generation c'sporins

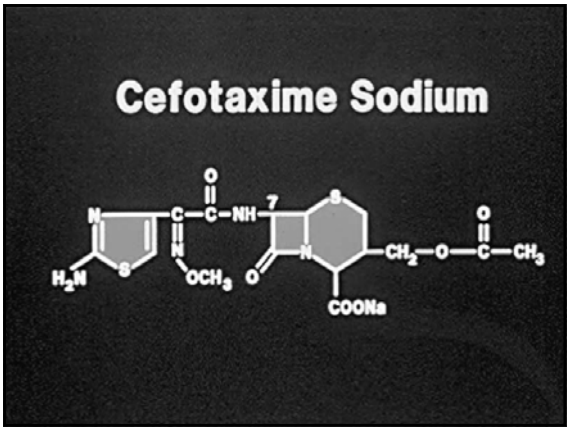
Cefotaxime
Ceftriaxone
Ceftazidime
Cefipime

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 -





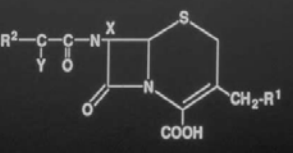
IMPORTANT PHARMACOKINETIC VARIABLES OF NEW CEPHALOSPORINS

Agent	Serum protein binding (%)	Metabolism	Peak serum levels (μg/ml) Ig*	Peak serum levels (μg/ml) 0.5g †	Half-Life (hours) Ccr>90	Half-Life (hours) Ccr>10	Vd (L)	Urinary recovery (%)
Moxalactam	50	-	60	24	2	19	19	75
Cefotaxime	38	+	42	12	1.1	2.5	27	55
Desacetyl cefotaxime	23	+	7	3	1.6	11	-	30
Ceftizoxime	31	-	87	14	1.4	25	18	85
Ceftriaxone	83-96	-	150	50	8	11-16	9	60*
Ceftazidime	17	-	80	18	1.8		16	75
Cefoperazone	90	-	125	26	1.9	2.5	12	25

*Based on intravenous infusion over 30 minutes.
†Intramuscularly

H.C. Neu, Bull. N.Y. Acad. Med., 60:327, 1984

β-LACTAMASE STABILITY OF CEPHALOSPORINS



X = O-CH_3 As in Cefoxitin

Y = N-OCH_3 As in Cefuroxime / Cefotaxime

Y = N-$C(CH_3)_2$-COOH As in Ceftazidime

TABLE 4. Spinal fluid bactericidal levels

Species	Ceftriaxone therapy: No. of patients	Ceftriaxone therapy: Geometric mean	Traditional therapy: No. of patients	Traditional therapy: Geometric mean
H. influenzae type b	13	1:512	13	1:8
S. pneumoniae	3	1:2,048	2	1:32
N. meningitidis	3	1:2,048	1	1:4
Group B streptococcus			2	1:32
E. coli	1	1:1,024		

PROPERTIES OF THIRD GENERATION CEPHALOSPORINS

- β lactamase stability
- Good penetration
- High affinity of lethal targets

WHY ARE ORGANISMS STILL RESISTANT?

- Altered permeability
- Altered targets (rare)

Ceftazidime/Cefepime - anti-*Pseudomonas*

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

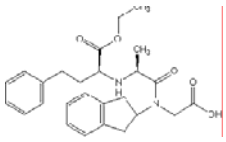
? Induction (low level) of chromosomal C'sporinase

Beta-lactamase stable -

less activity against gram positive organisms

Cefepime – Fourth generation

Increased beta-lactamase stability
Also better Gram positive -



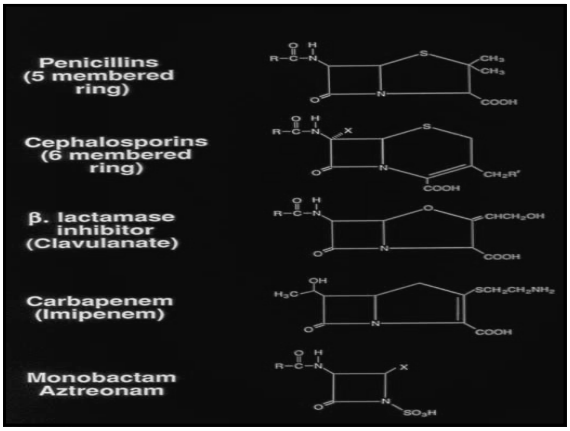
Carbapenems

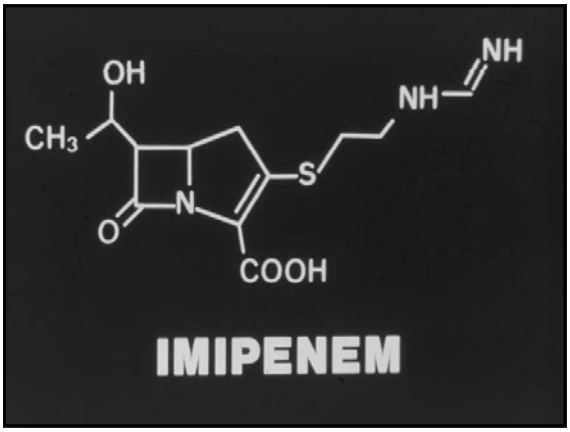
Imipenem
Meropenem

Beta-lactam class - PBP-2 major target
Permeability - separate porin

Huge spectrum - Aerobes, anaerobes
everything EXCEPT
Enterococci
Stenotrophomonas etc.

Concern - CNS side effects - Imipenem ??





Use of the cephalosporins:

First generation - Oral - surgical prophylaxis - skin soft tissue infections - taste good - "house cephalosprorin"

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

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

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

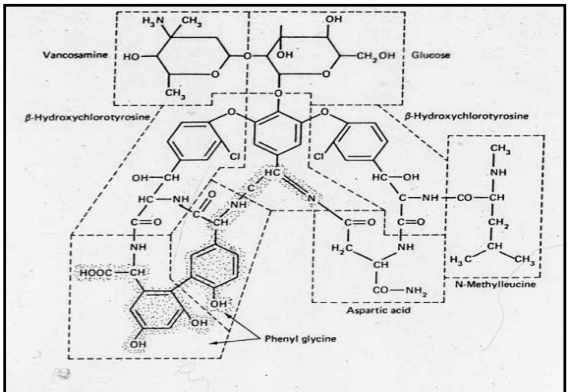
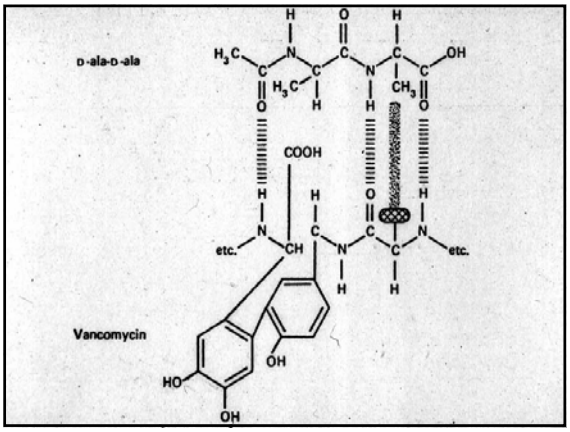


Figure 6.25 Structure of vancomycin. The stippled area indicates the residues involved in the interaction with the mucopeptide precursor.

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

Resistance - vancomycin resistant enterococcus (VRE)

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 - 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

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 alterative therapy

? Spread of genes involved to *S. aureus* and *S. epidermidis*

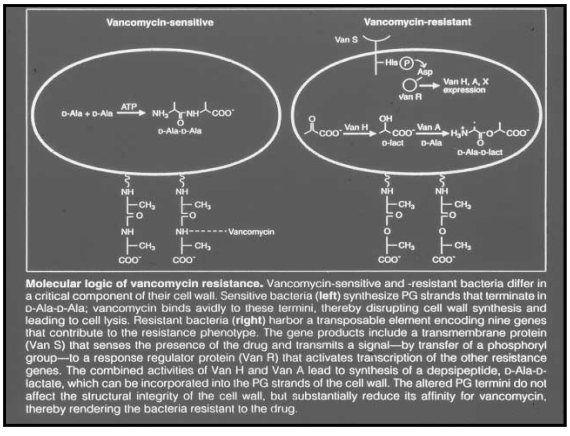
Side effects of vancomycin:

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.



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.

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