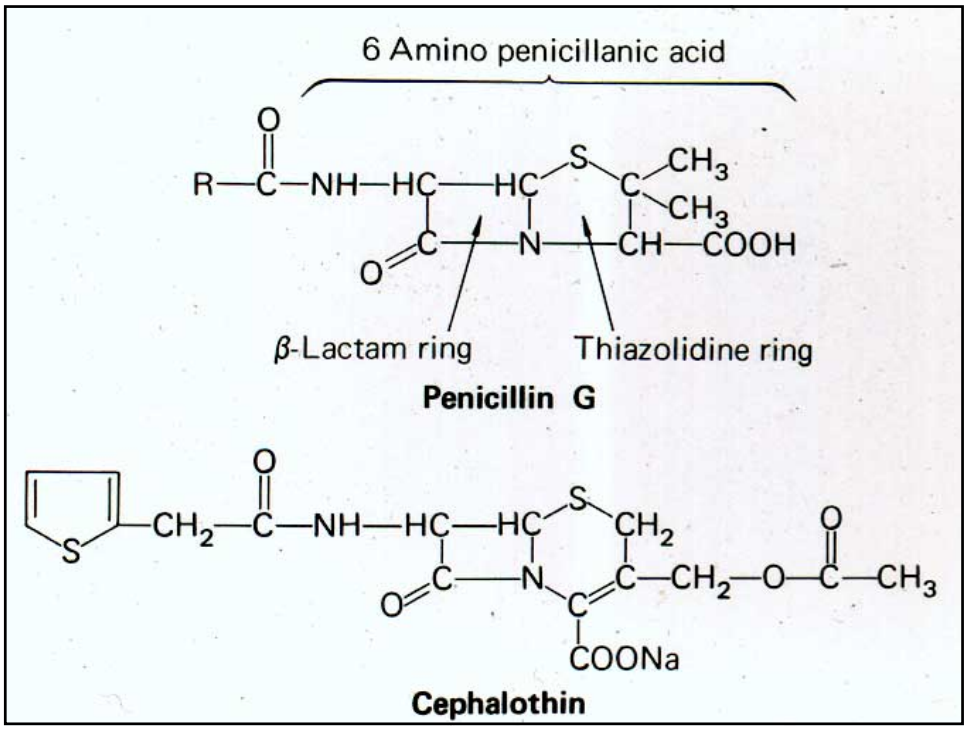
Beta-lactam antibiotics - Cephalosporins

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

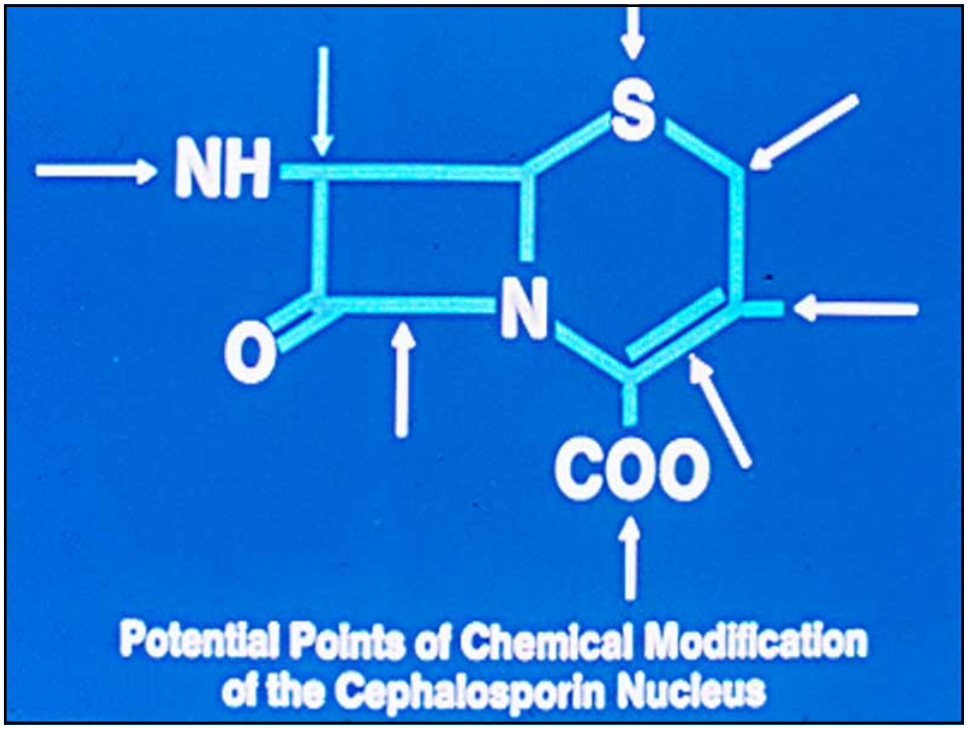
Development of C'sporins

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

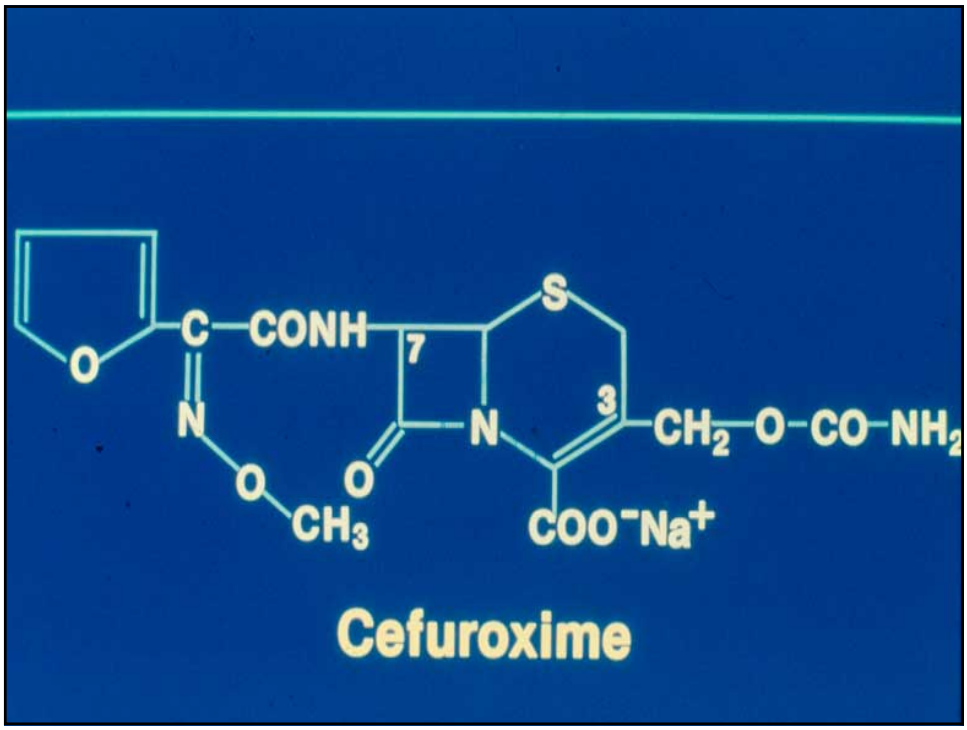
Cefuroxime - Respiratory tract infections -
community acquired

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

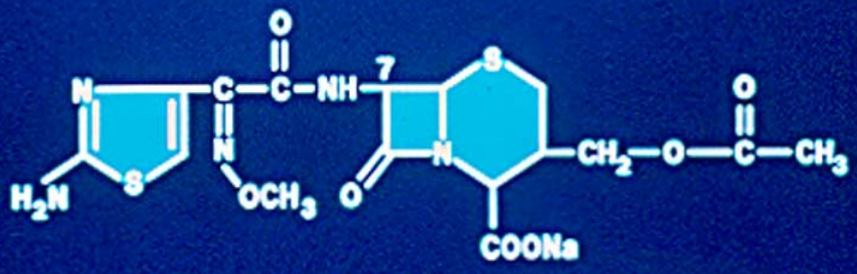
Cefotaxime
Ceftriaxone
Ceftazidime
Cefipime (4th?)

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



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

Ceftazidime/Cefepime - anti-*Pseudomonas*

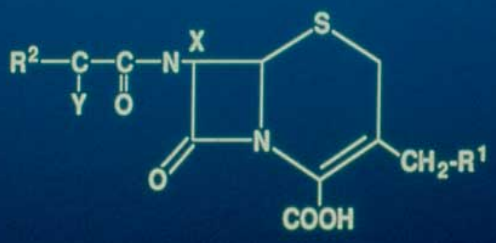
Used the side groups which have increased permeability through *P.aeruginosa* porins -

? Induction (low level) of chromosomal C'sporinase

Beta-lactamase stable -

less activity against gram positive organisms

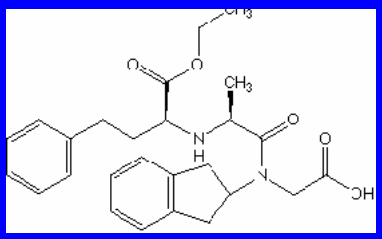
β-LACTAMASE STABILITY OF CEPHALOSPORINS



X = O-CH_3	As in Cefoxitin
Y = N-OCH_3	As in Cefuroxime / Cefotaxime
Y = N–O–$C(CH_3)_2$–COOH	As in Ceftazidime

Cefepime – Fourth generation

Increased beta-lactamase stability
Also better Gram positive -



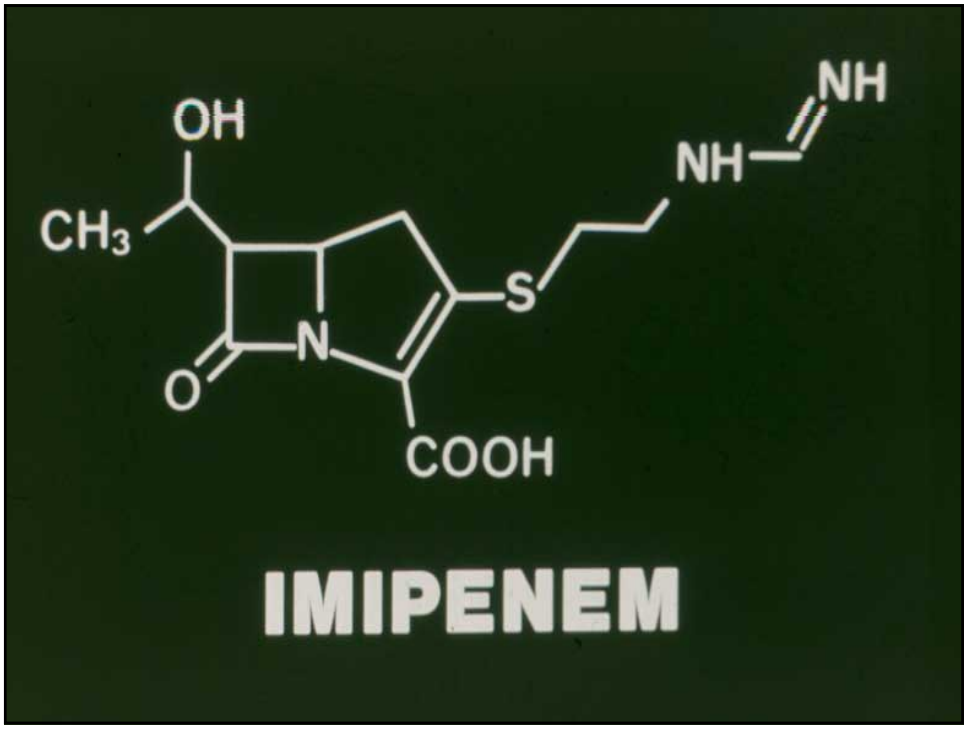
Carbapenems

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 ??

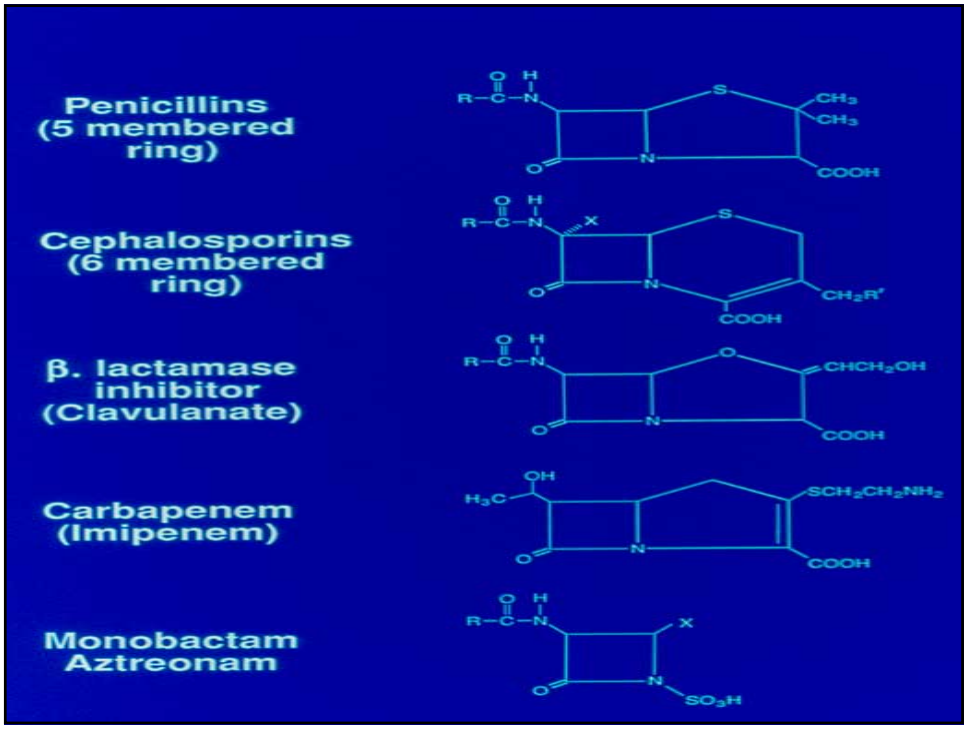


Monobactams - Aztreonam

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 cephalosprorin”

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		
Enterobacteriaciae	(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-ala-D-ala** - pentapeptide
blocks two steps in cell wall synthesis

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

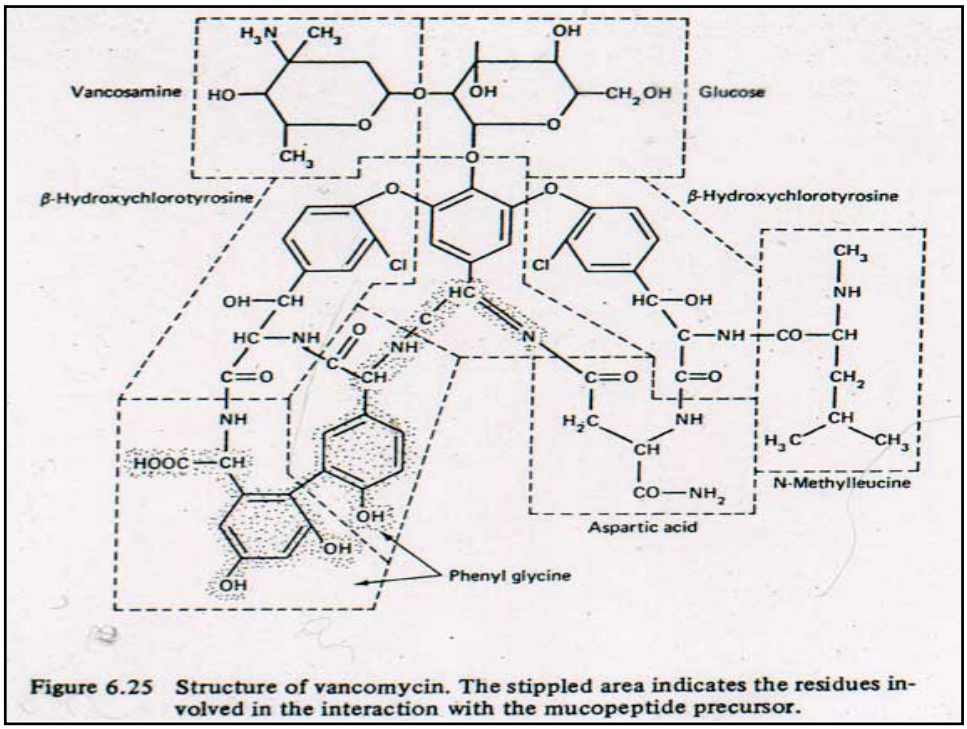
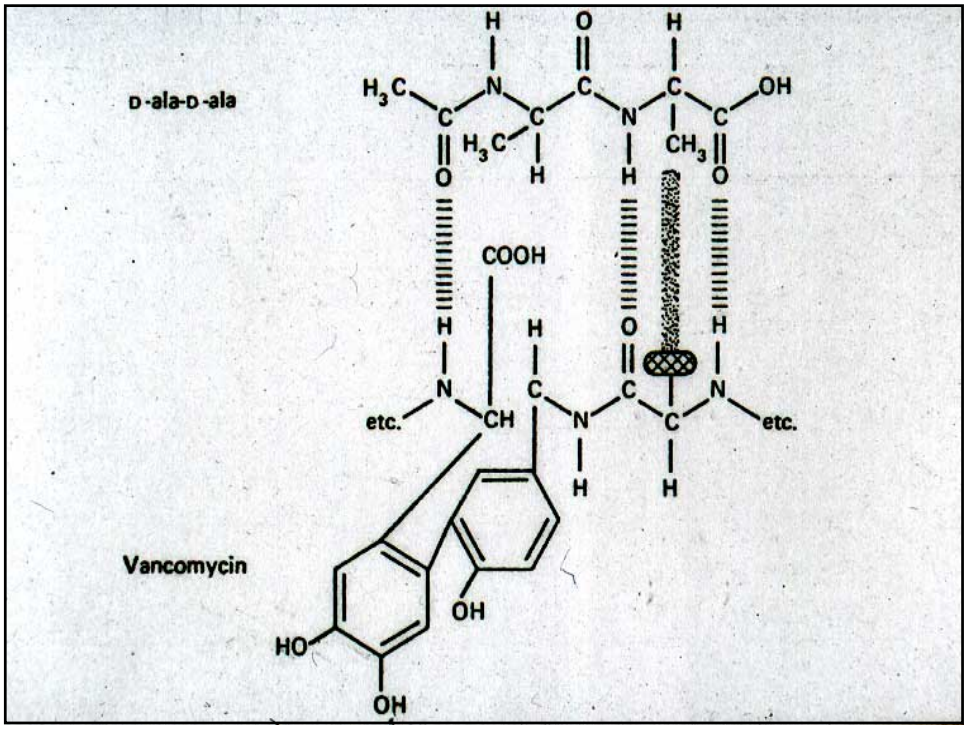


Figure 6.25 Structure of vancomycin. The stippled area indicates the residues involved in the interaction with the mucopeptide precursor.



Methicillin resistant *Staphylococci*

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

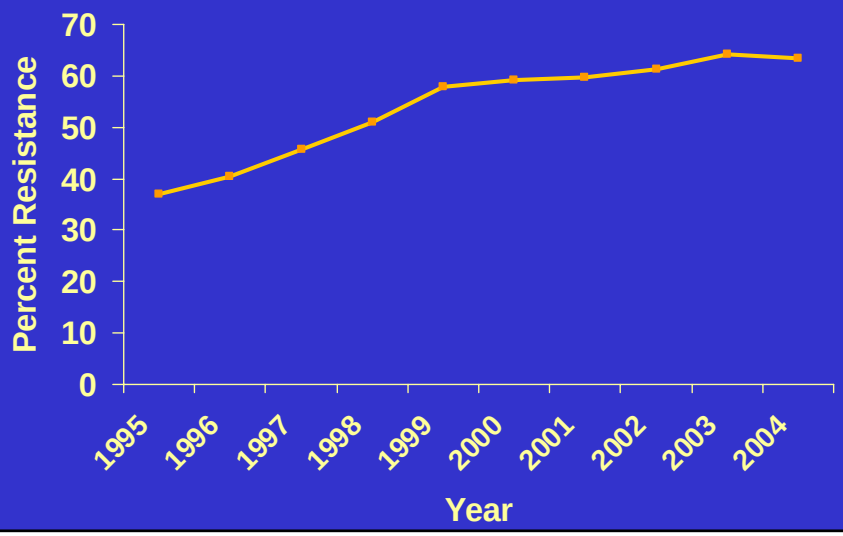
Use of Vancomycin

Staphylococci – resistant to penicillin –
"methicillin resistant - Altered PBP's

Coagulase-negative staphylococci – Catheter infection

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

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



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 ß-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

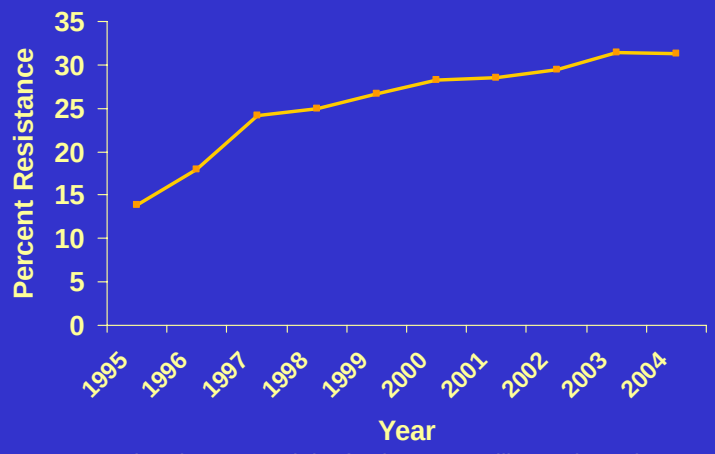
VRE = Vancomycin resistant enterococci
? From oral use of vancomycin

Selection of enterococci – altered cell wall structure

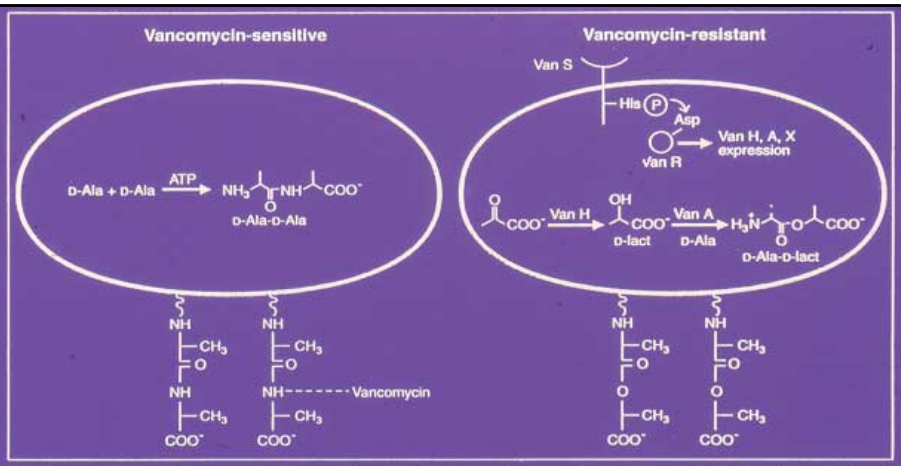
Several mechanisms:
D-ala-D-ala changed to a lactate
No metabolic cost

Several Vanco resistance cassettes

Vancomycin-resistant *Enterococci* 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.

Vanco resistant *S. aureus*

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

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