

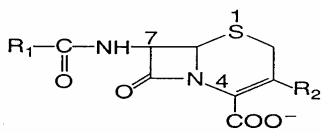
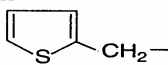
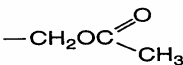
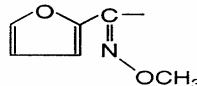
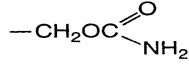
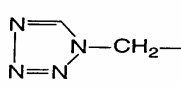
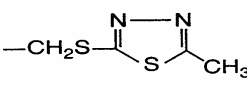
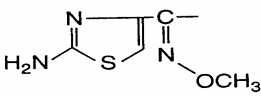
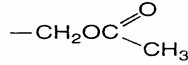
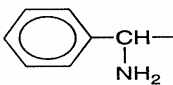

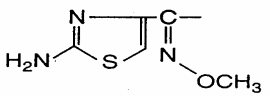
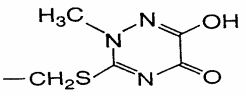
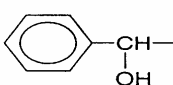
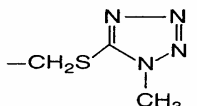
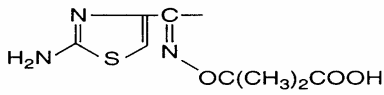
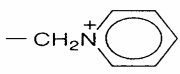
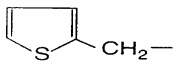
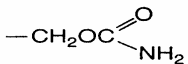
## CEPHALOSPORINS AND VANCOMYCIN

### CEPHALOSPORINS

These compounds are closely related in structure, mechanism of action, spectrum of activity and pharmacology to the penicillins. They are produced by fungi and synthetic modification.

#### I. CHEMISTRY

Contains 6-membered dihydrothiazine ring. Substitutions at position 3 generally affect pharmacology; substitutions at position 7 affect antibacterial activity, but this is not invariably true.

 <b>Basic structure of a Cephalosporin</b>					
Compound	R <sub>1</sub>	R <sub>2</sub>	Compound	R <sub>1</sub>	R <sub>2</sub>
Cephalothin			Cefuroxime		
Cefazolin			Cefotaxime		
Cephalexin			Ceftriaxone		
Cefamandole			Ceftazidime		
Cefoxitin					

II. MECHANISM OF ACTION

Cephalosporins are bactericidal. They inhibit enzymatic reactions necessary for stable bacterial cell walls by binding to PBPs. Bacterial cells must be growing.

III. PHARMACOLOGIC PROPERTIES OF CEPHALOSPORINS

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<b>Drug</b>	<b>Peak blood level (µg/ml)</b>	<b>Percentage Protein Binding</b>	<b>T<sub>1/2</sub> (hr)</b>	<b>[CSF] µg/ml</b>
Cefazolin 1g	188	70 - 85%	1.4	-----
Cefuroxime 1.5g	100	50%	1.3	1.1 - 18
Cefoxitin 1g	110	70%	0.7-0.9	-----
Cefotaxime 1g	100	13 - 38%	1.0	6 - 11 (2g)*
Ceftriaxone 1g	150	83 - 96%	5.8-8.7	1.3 - 44
Ceftazidime 1g	90	< 10%	1.9	2 - 42

*\*non-inflamed meninges CSF level 0.01-0.7 µg/ml*

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IV. MECHANISM OF RESISTANCE TO CEPHALOSPORINS

- A. Failure to reach receptor sites, permeability.
- B. Destroyed by β-lactamase. Some gram-negative bacteria produce large amounts of β-lactamase constitutively.
- C. Failure to bind to penicillin binding proteins, in gram negative and gram positive organisms.

V. ANTIMICROBIAL ACTIVITY

The cephalosporins have been grouped into "generations" corresponding to their development by the pharmaceutical industry in response to clinical needs. In general, the later generations of cephalosporins have greater gram-negative activity at the expense of gram-positive activity.

- A. First generation agents

- Cefazolin
  - Cephalothin
  - Cephalexin (oral)
  - Cefaclor (oral)

All of these drugs inhibit gram-positive cocci (S. pneumoniae, S. aureus, except enterococci), and some gram-negative rods such as E. coli, Klebsiella, Proteus mirabilis. None of these drugs are active against Enterococci which have PBPs with low affinity for the cephalosporin molecule.

These drugs are widely used for common infections, surgical prophylaxis, skin and soft tissue infections where the likely organisms are gram-positives (Streptococci or Staphylococci) or community acquired gram-negatives.

- B. Second generation agents  
Cefuroxime  
Cefoxitin  
Cefotetan

These are parenteral drugs with increased gram-negative activity.

Cefuroxime is stable to the common plasmid-mediated penicillinases, increasing its spectrum of activity beyond that of the first generation drugs to cover  $\beta$ -lactamase producing organisms of the upper respiratory tract such as Hemophilus and Branhamella.

Cefoxitin (and cefotetan) have increased activity against anaerobic organisms. They are often used to treat infections involving GI tract flora (gram-negatives such as E. coli, Bacteroides ).

- C. Third generation agents  
Cefotaxime  
Ceftriaxone  
Ceftazidime

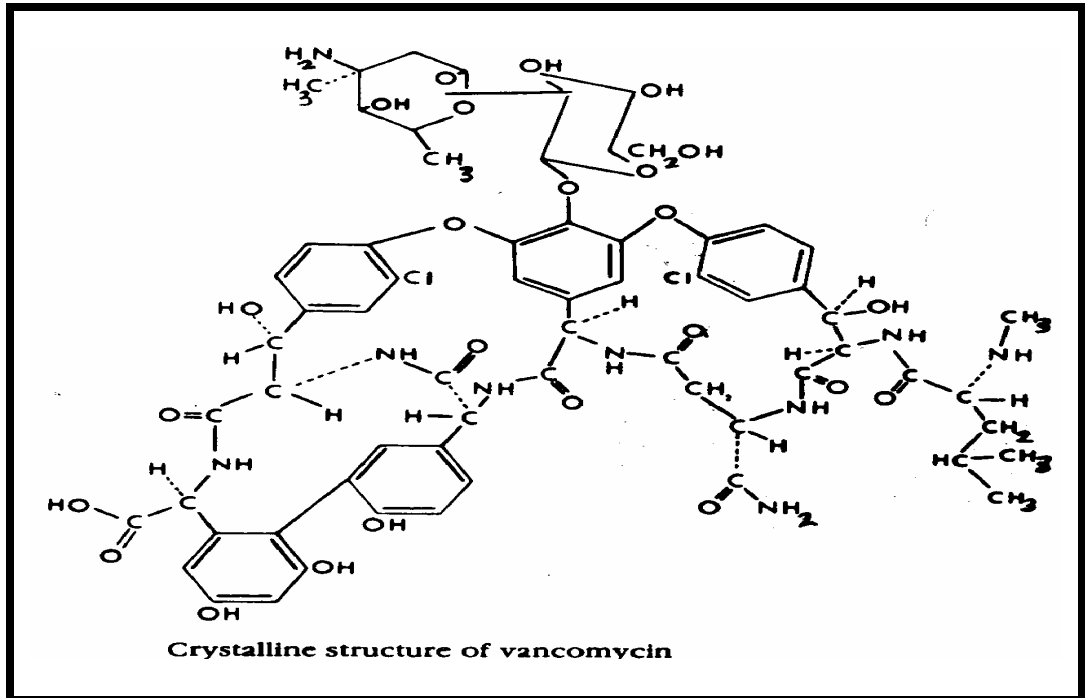
These are highly active drugs which are widely used for many different indications. They are stable to the common plasmid mediated  $\beta$ -lactamases and thus have a broad spectrum of activity.

1. Cefotaxime  
Cefotaxime was initially developed for gram negative infections but is also highly active against S. pneumoniae, particularly strains of S pneumoniae which are intermediately resistant to penicillin. It has good penetration into the CSF in the presence of inflammation, and thus, is currently the drug of choice for meningitis due to either Streptococci or gram negative organisms (N. meningitidis, H. influenzae) until susceptibility testing is available. It is active against most E. coli, Klebsiella, and many common gram negative rods, but not P. aeruginosa.
2. Ceftriaxone  
Ceftriaxone has a spectrum of activity very similar to that of cefotaxime, but has a much longer half-life and is more active. Thus, a single intramuscular dose can provide bactericidal activity in the blood against many organisms for 12-24 hours. This drug is extremely popular in an outpatient setting to cover potentially septic patients with pneumococcal infection (S. pneumoniae), as well as N. gonorrhoea which can be effectively treated in a single injection in many cases. Due to its high levels of activity, it is effective in the CSF and is often used to treat CNS infections, including CNS-Lyme disease.
3. Ceftazidime  
Ceftazidime has a side chain similar to piperacillin and hence, is particularly active against P. aeruginosa. It has less activity against gram positive organisms. It achieves adequate CSF levels.

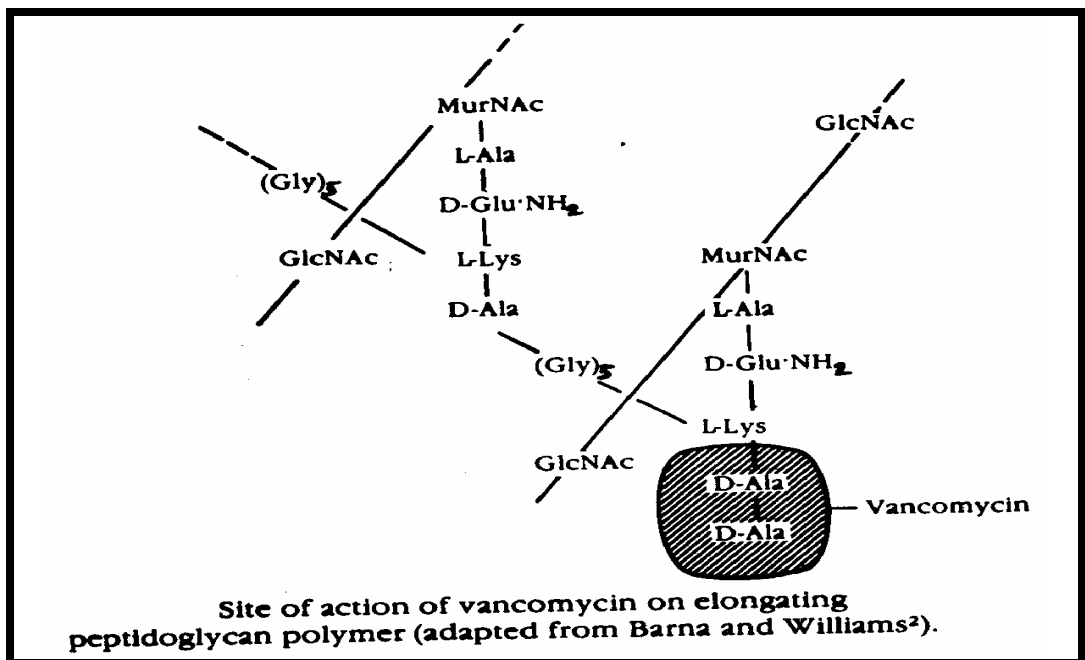
- A. Oral compounds  
A large number of oral cephalosporins are available. A prototypic drug is cephalexin. Cefaclor was developed to cover  $\beta$ -lactamase-producing H. influenzae which produce penicillinase. However, drugs with increased stability to  $\beta$ -lactamases have also been marketed. In general, these have longer half lives to increase the ease of administration, and are quite expensive.
- B. Distribution  
As hydrophilic molecules, these drugs do not penetrate into phagocytic cells. However, in other areas, such as in lung, kidney, muscle, bone, placenta, interstitial, synovial and peritoneal fluids, and in urine, excellent drug levels are achieved. The cephalosporins are also found in the bile.  
Cefotaxime, ceftriaxone, ceftazidime enter CSF in concentrations adequate to treat meningitis.
- C. Metabolism  
Cefotaxime is metabolized to desacetyl derivative, but this derivative has antibacterial activity and has longer half-life.
- D. Elimination  
By kidney - combination of active tubular secretion and glomerular filtration, varies with agent. Accordingly, probenecid blocks secretion of some compounds and some of the drugs can accumulate to varying degrees in presence of renal failure. Hemodialysis removes these drugs; peritoneal dialysis minimal effect.
- E. Adverse effects of Cephalosporins
1. Hypersensitivity  
Rash, urticaria, eosinophilia, fever, anaphylaxis (rare).
  2. Hematologic  
Leukopenia and rarely hemolytic anemia.
  3. Superinfection with fungi, resistant gram-negative organisms.
  4. Miscellaneous  
Phlebitis, false positive tests, e.g., Coombs, glucose.
  5. Agents with methyltetrazole side chain at position 3 cause Antabuse reactions and elevation of prothrombin levels due to effect on vitamin K synthesis (cefotetan).

## I. VANCOMYCIN

- A. Glycopeptide antibiotic - originally identified in the 1950s, but now widely used due to the increasing incidence of infections due to gram-positive organisms which are resistant to  $\beta$ -lactam antibiotics.



- B. Mode of action



Vancomycin interferes with lipid phosphodisaccharide-pentapeptide complex; no competition between penicillin and vancomycin for binding sites and no cross-resistance. Bactericidal.

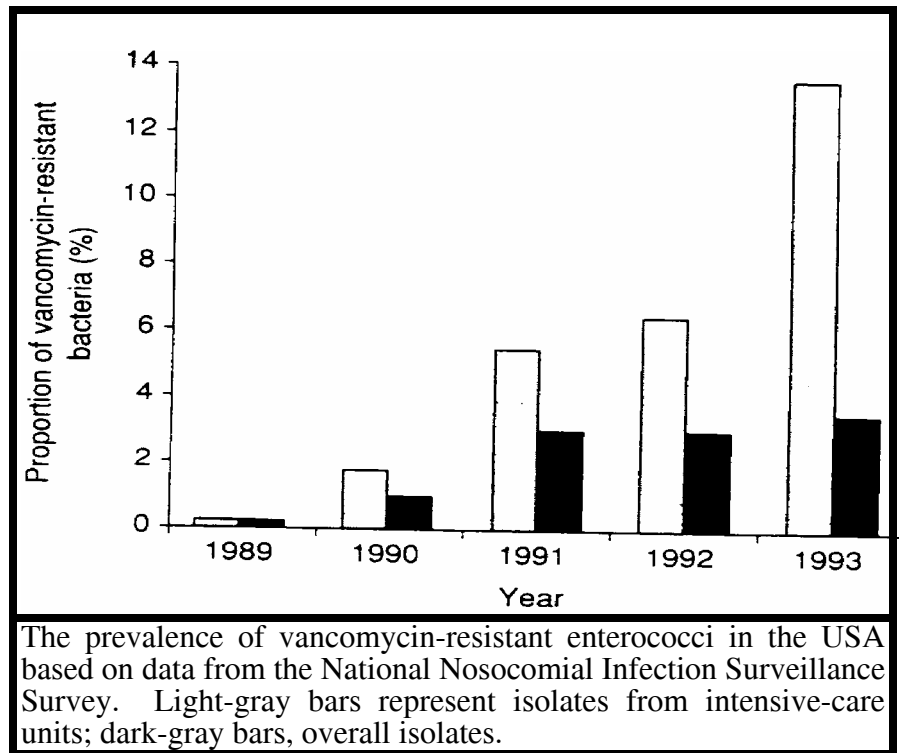
C. Spectrum of activity

Gram-positive bacteria: staphylococci, streptococci, enterococci, C. diphtheriae, B. anthracis, Clostridium difficile.

D. Vancomycin resistance

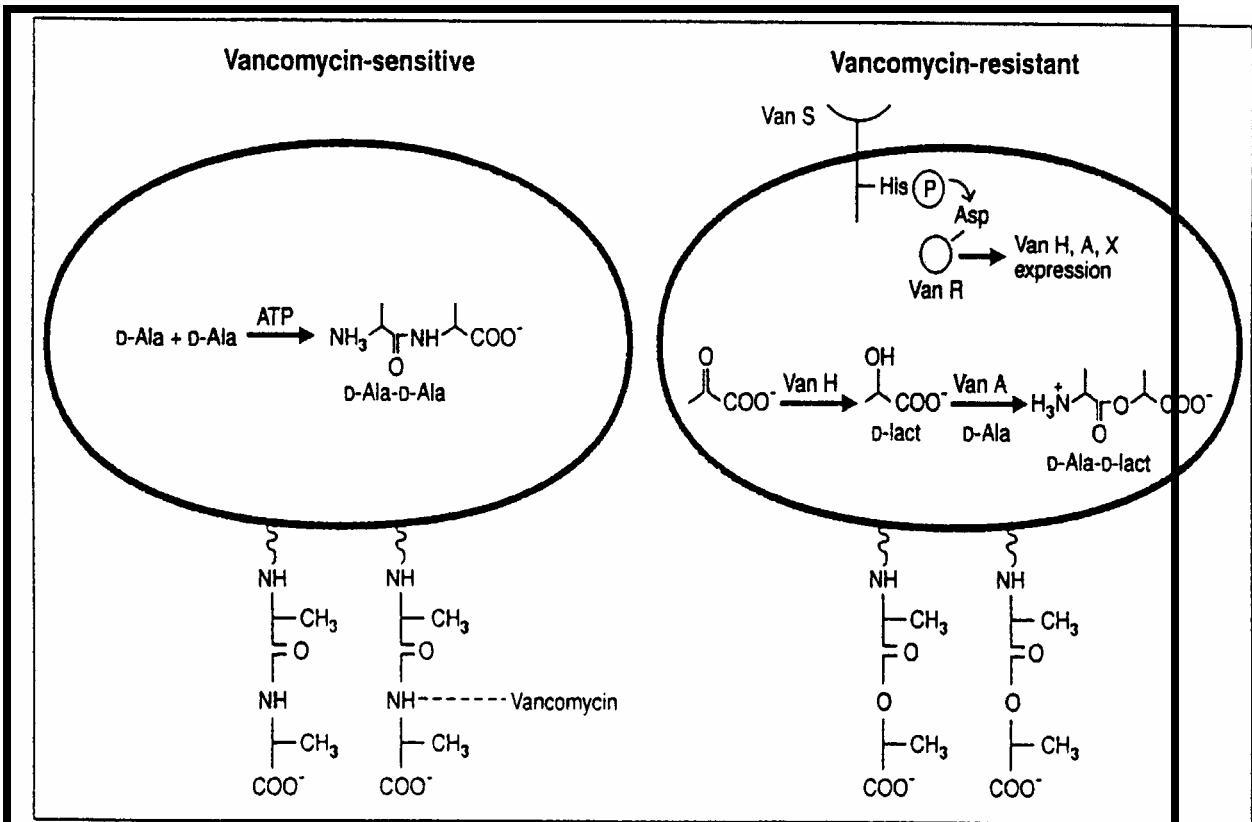
1. Epidemiology

Vancomycin resistance is becoming an increasingly common problem, particularly in the enterococci such as Enterococcus faecium. This is plasmid-mediated and readily transferable. Since these plasmids have been shown to be able to replicate in S. aureus, there is a very real concern that vancomycin resistant Staphylococci will eventually be selected.



2. Molecular Mechanisms

A transposable element encoding 9 genes allows the organism to "sense" vancomycin and activate transcription of the rest of the operon leading to the replacement of D-ala-D-ala with D-ala-D-**lactate**, which substantially reduces the binding of vancomycin to its target.



**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.

E. Pharmacology

1. Administration - parenteral (IV)
2. Distribution
  - a. Wide to tissues and infected pleural, pericardial, synovial, ascitic fluids.
  - b. Enters the meninges.
  - c. Protein binding - 55%.
3. Excretion
  - a. Excreted by glomerular filtration by the kidneys in unchanged form.
  - b. Accumulates in renal failure; normal  $t_{1/2}$  is 6 h;  $C_{Cr} < 10$  ml/min,  $t_{1/2}$  is 35-50 hr., anuria 7-9 days.
4. Toxicity
  - a. Nephrotoxicity - low risk, potentiates nephrotoxicity of aminoglycosides.
  - b. Phlebitis (frequent)
  - c. Generalized rash and urticaria with rapid infusion due to histamine release -- Red man syndrome.
  - d. ? Ototoxicity - never rigorously established if levels  $< 40$  ug/ml.
5. Clinical Use
  - a. Serious gram positive infections in penicillin-allergic patients.
  - b. Infections due to resistant S. pneumoniae or methicillin-resistant Staphylococci (either S. aureus or coagulase negative Staphylococci).