

Beta-lactam antibiotics

Penicillins

Target - Cell wall - interfere with cross linking
Actively growing cells

Bind to **Penicillin Binding Proteins**

Enzymes involved in cell wall synthesis

Activity of an Antibiotic

Affinity for target

Permeability properties
(ability to get to the target)

Stability to bacterial enzymatic degradation

Bacterial modifications:

- 1 - Mutate target - ? More than one protein
Importance of the target -
? Essential
2. Permeability - Size/charge considerations
? Substrate for an efflux pump
3. Selection for mutants that destroy the antibiotic

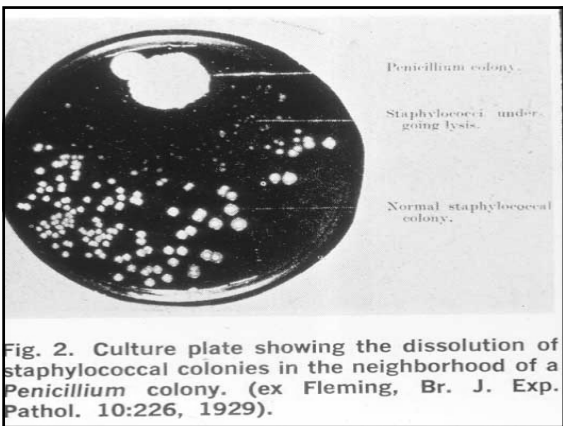
WHO discovered the penicillins??

Abess Hildegarde von Bingen ?

“Good things that grow on the sides of trees....”

Fleming -

Florey - WWII....



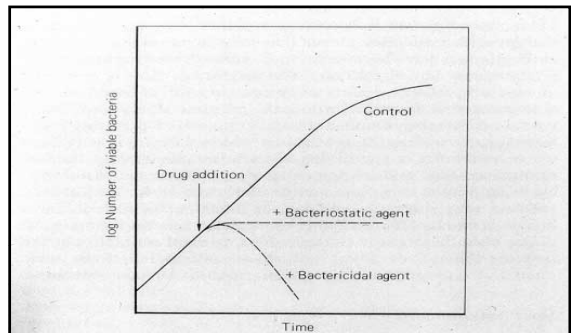
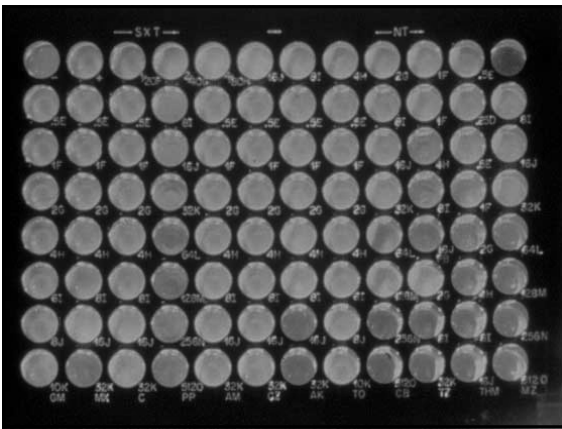
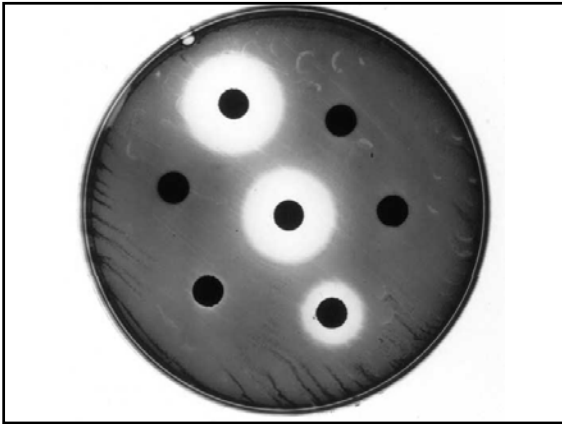
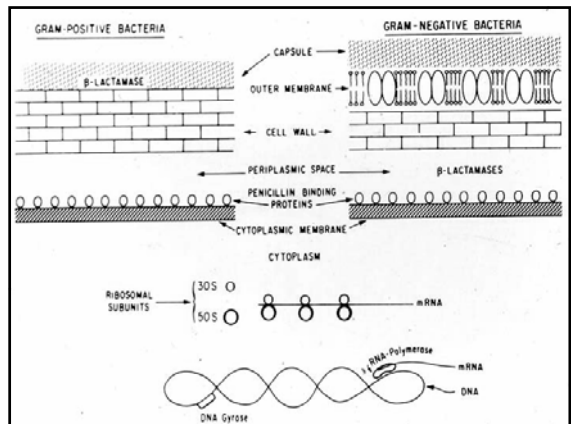
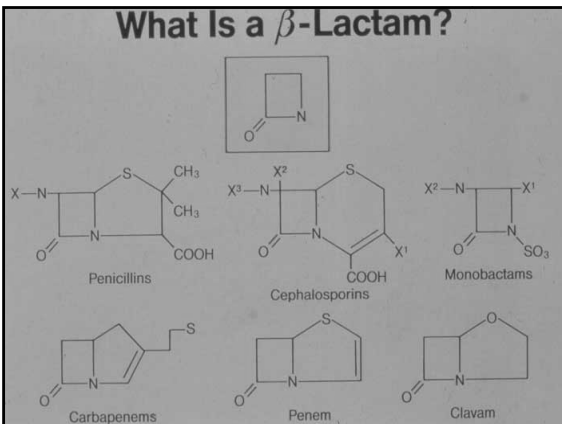


Figure 1-1 Bacteriostatic and bactericidal effects of antibiotics. A suspension of bacteria in the log phase of growth is divided into three parts. A bacteriostatic drug, such as chloramphenicol, is added to one culture and a bactericidal agent, such as penicillin, to another; the third is a control. At various times, samples are taken from each culture, diluted, and plated on agar with new growth medium. The number of colonies obtained is a measure of the number of viable cells per culture.

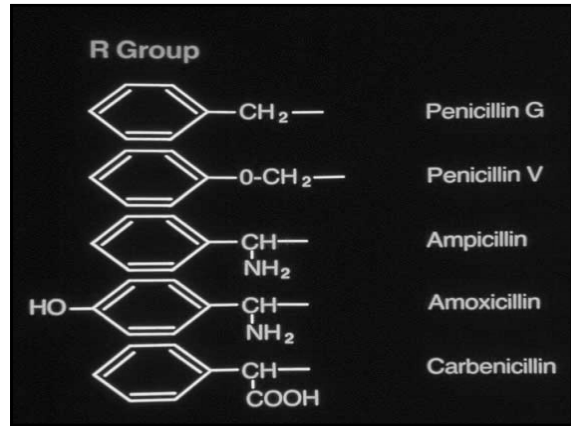


Activity of the beta-lactam antibiotic:

Affinity for critical PBP's (number of copies of the target)

Ability to get to the target (permeability properties – more of an issue for Gram negs)

Stability to beta-lactamases - degradation



Beta-lactamases - cleave the beta-lactam ring -
inactivate the drug -
Open ring - can't bind to the target

Co-evolved with the penicillin binding proteins

Share a ser-X-X-lys - binding site for interactions

Gram positives - Secreted into the environment
Gram negatives - Secreted into the periplasmic space

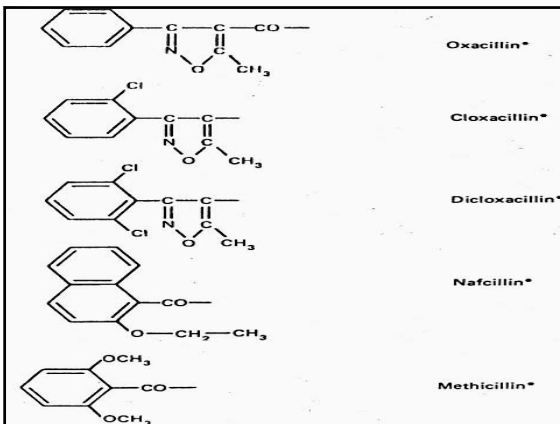
ANTI-staphylococcal penicillins

“semi-synthetic”

Add bulky side chains to provide

STERIC HINDRANCE to protect the
Beta-lactam nucleus –

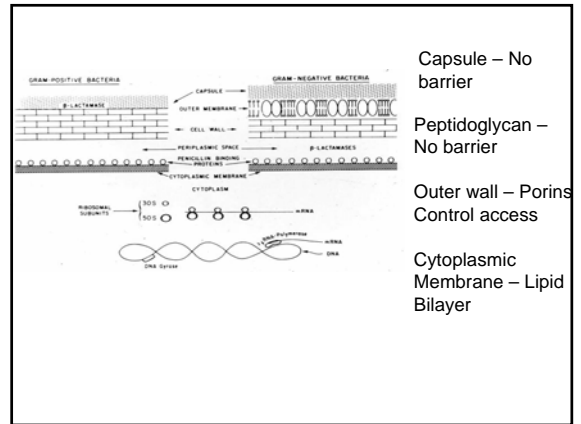
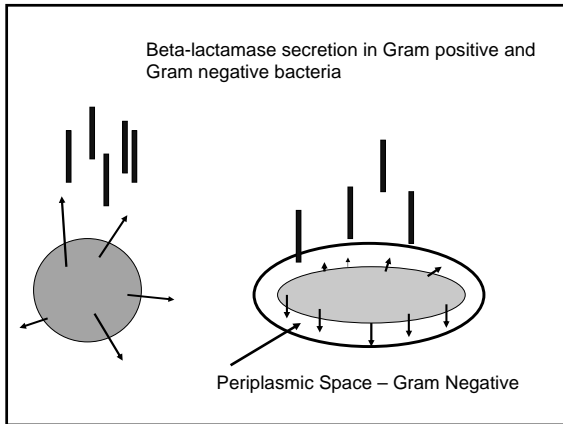
Gram positives – secrete bla's – “cloud”



Anti-staphylococcal penicillins

Strategy - Add a bulky side group to block beta-lactamase

(Methicillin) - renal toxicity
Nafcillin
Oxacillin
Cloxacillin (di-clox) - oral drugs



Beta-lactamases

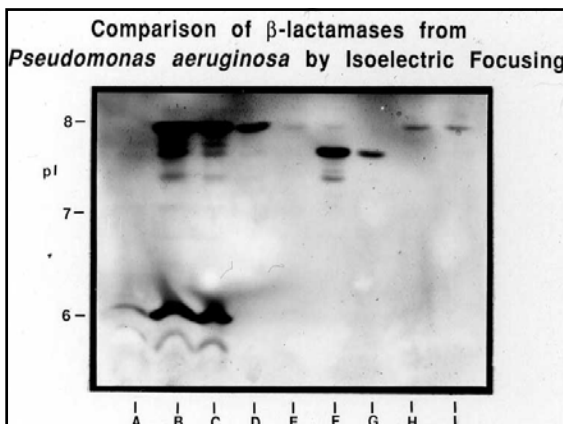
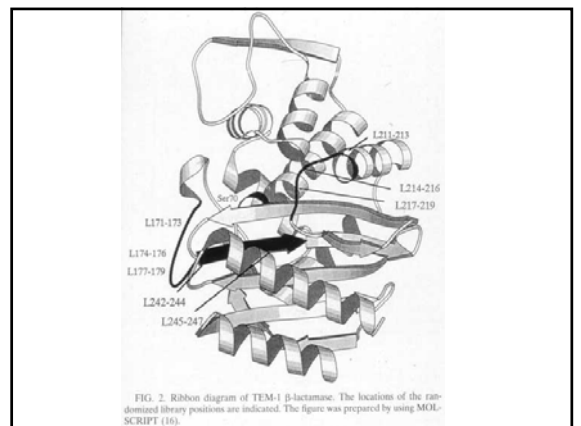
Regulation - Constitutive - Chromosomal (*E.coli*)

Plasmid mediated - copy number dependent

Inducible - chromosomal - SPACE organisms - as a model

2-component signaling - (*ampD*, *ampE*, *ampR*)

Sensor
Response regulator
Transcriptional activator



Drugs in clinical use:

Penicillin G, VK

Ampicillin (+) clavulanic acid (beta-lactamase inhibitor)

(oral or parenteral)

Piperacillin - anti-*Pseudomonas* (+tazobactam)

(parenteral)

Spectrum - gram positive and gram negative - Not inherently beta-lactamase stable

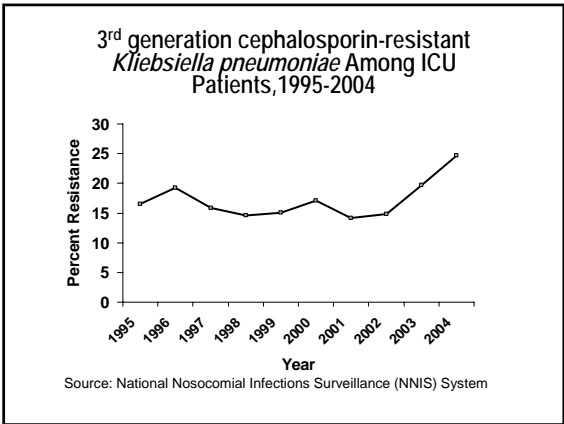
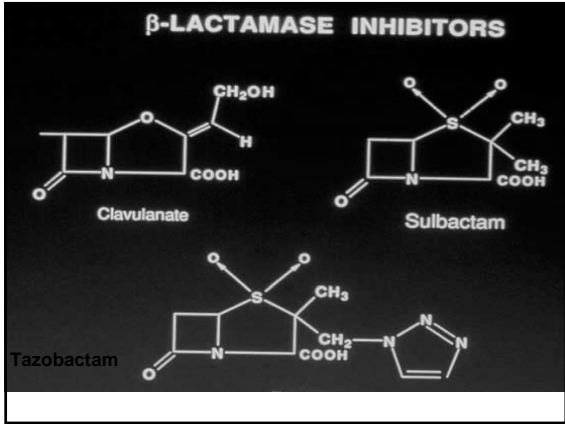
Spectrum - dependent upon permeability properties

Add a beta-lactamase inhibitor

Clavulanic acid -
Sulbactam
Tazobactam

Expands spectrum of activity
Anaerobes

NOT effective against the beta-lactamases of the
SPACE organisms



Pharmacology of the penicillins

Absorption - Amoxicillin - acid stable
dosing - give more - longer intervals
Augmentin - amox + clav - diarrhea

Metabolism - minor

Excretion - Renal - tubular secretion
Increase serum levels with probenecid
Biliary - only ureido penicillins
Nafcillin

Distribution - Anions - charged - extracellular space
CSF - with inflammation
Concentrated in urine