

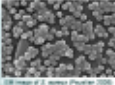
Why?

requires

S. aureus Prevalence

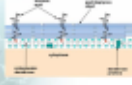
% Nasal Colonization of Population

- Permanent - 20%
- Transient - 60%
- Never - 20%



Cell Wall - Importance & Structure

- Mechanically supports the more flimsy cell membrane
- 20-40 nm thick
- Composed of
 - Peptidoglycan
 - Teichoic acids
 - Surface proteins




constructed

targeted by

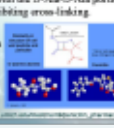
Cell Wall - Construction

1. Construction of peptidoglycan monomer
2. Addition of penicillamine cross-linker
3. Transglycosylation to outside of membrane
4. Transpeptidation to form cell wall



Cell Wall - Antibiotic Target

- β -lactams compete with the D-Ala-D-Ala portion of peptidoglycan inhibiting cross-linking.
- Bacteria fight back by degrading β -lactams ring



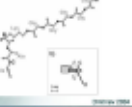
Vancomycin - "Drug of Last Resort"

- Vancomycin is a peptide-based antibiotic produced by *Streptomyces orientalis*, a soil bacteria.
- Unlike β -lactams, it cannot be administered orally but by IV.
- Toxic compound which requires blood levels to be constantly monitored in the hospital.

composed of

Peptidoglycan Activity

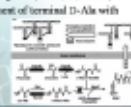
- See hand out for hands-on activity



fought by

Vancomycin - Resistance


- Naturally found in vancomycin producing bacteria as a set of 3 genes (VanA, H, and X)
- Involves replacement of terminal D-Ala with D-Lactate



structured as

Vancomycin Hands-on Activity

- See hand out

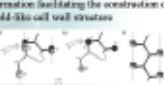


fit together by

integral to

Peptidoglycan Cross-linking

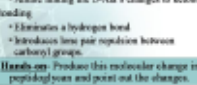
- Glycan chain adopts helical structure allowing the pentapeptide chains to adopt a ring conformation facilitating the construction of a well-ordered cell wall structure



results in

Effect of D-Lactate


- 1000 fold reduction in affinity!!!
- Structurally
 - Amino linking the D-Ala's changes to lactate
- Bonding
 - Eliminates a hydrogen bond
 - Introduces lone pair repulsion between carbonyl groups
- Hands-on: Produce this molecular change in peptidoglycan and point out the changes.



has key enzyme

VanX Mechanism

- Zn(II)-containing metalloenzyme which removes the terminal D-Ala



contributes to

Vancomycin - Mechanism

- folds into a bowl shaped molecule
- C-terminal L-Lys-D-Ala-D-Ala fits into this groove
- 5 hydrogen bonds are formed

