

Lecture #19: Antimicrobial Chemotherapy

In what year was a chemical first intentionally used to selectively kill disease-causing bacteria in a human host?

- a. 1967
- b. 1542
- c. 1910
- d. 1983
- e. 1893

I. Terminology

- A. Chemotherapeutic agent = Any _____ that is used to treat a _____
- B. Antimicrobial drug = Any chemical used to treat a _____
- C. Antibiotics = Antimicrobial drugs
- D. Selective toxicity = Antimicrobial drugs must be selectively toxic against microorganisms and _____
- E. _____ = the level required for treatment
_____ = the level at which the drug is toxic to the host

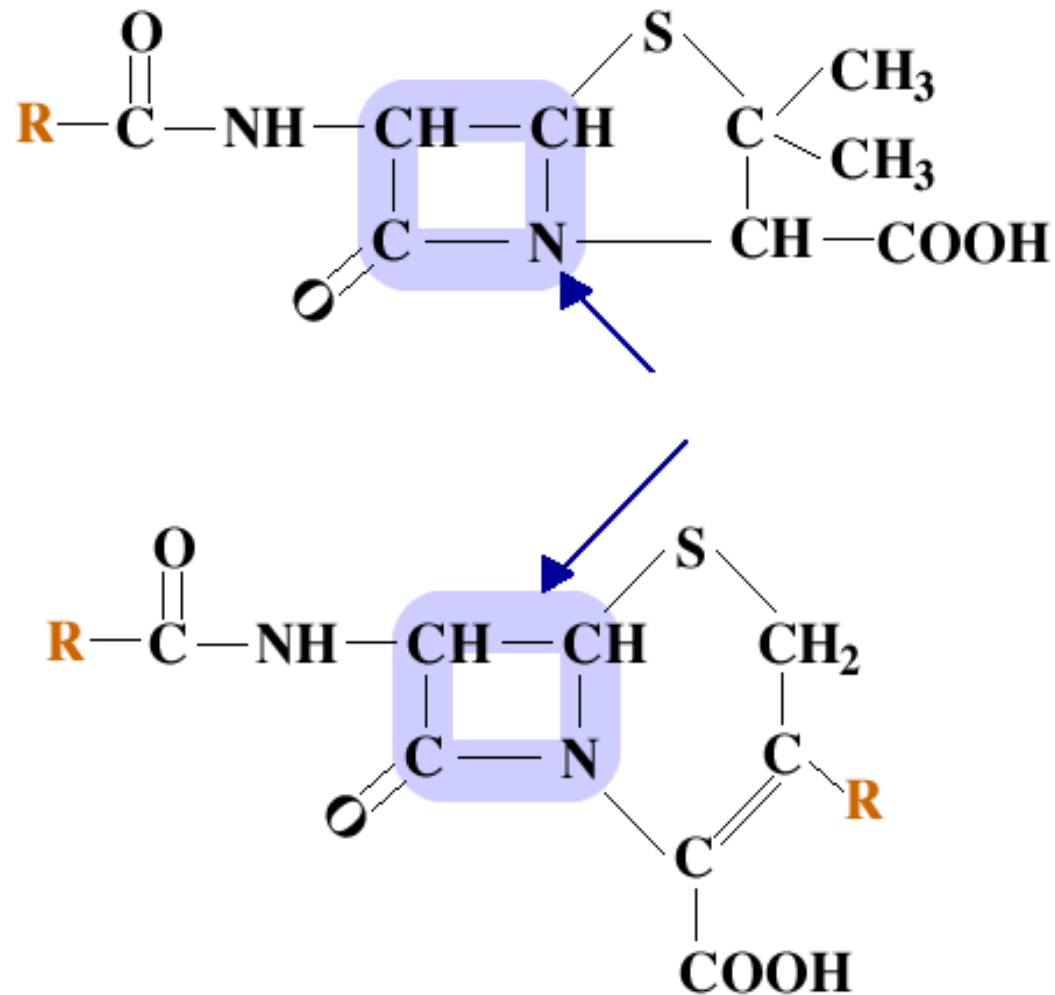
$$= \frac{\text{Toxic dose}}{\text{Therapeutic dose}}$$

***The _____ this is, the better (_____)
the antimicrobial drug**

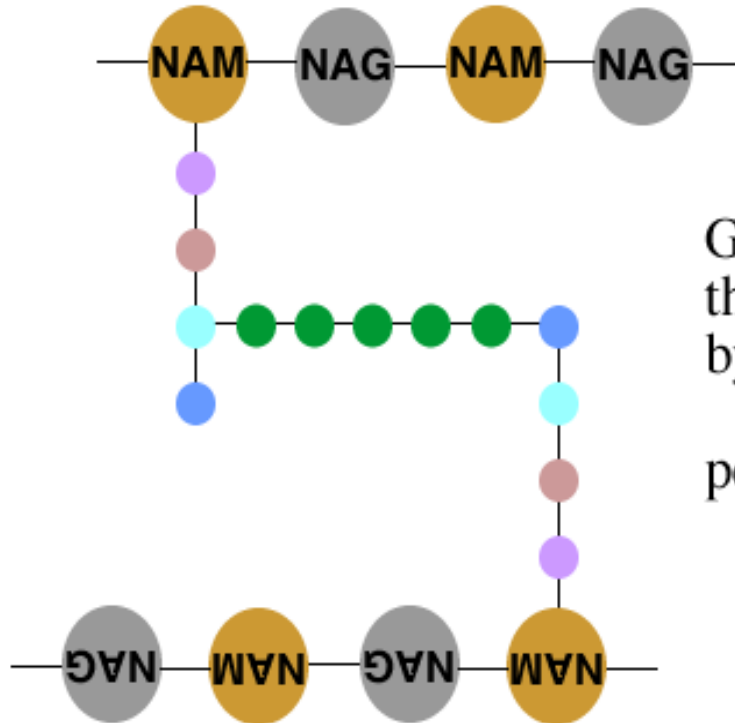
II. Mechanisms of Action of Antibacterial Drugs

A. Drugs that

1. The β -lactam drugs



β -lactam drugs:

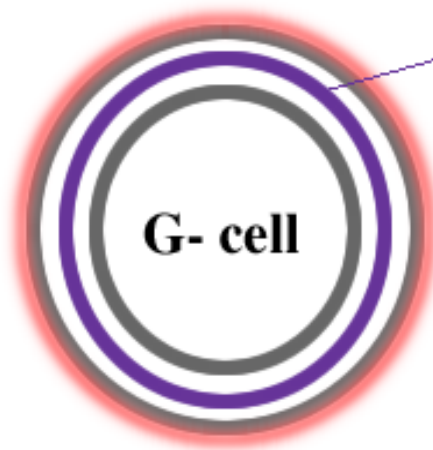


Generally thought to exhibit their antimicrobial activity by inhibition of synthesis of peptidoglycan*

*Although this is the most commonly proposed mechanism of action, the mechanism of the penicillins is still being debated. It has recently been proposed that they stimulate bacterial holins that form holes in the plasma membrane.

b. Affective only when cells are actively synthesizing their cell walls, when cells are

c.



The peptidoglycan layer of Gram-negative cells is by the outer membrane. Because of this, Gram-negative cells tend to be innately to β -lactam antibiotics.

Gram-negative cells are also more likely to produce enzymes called that can

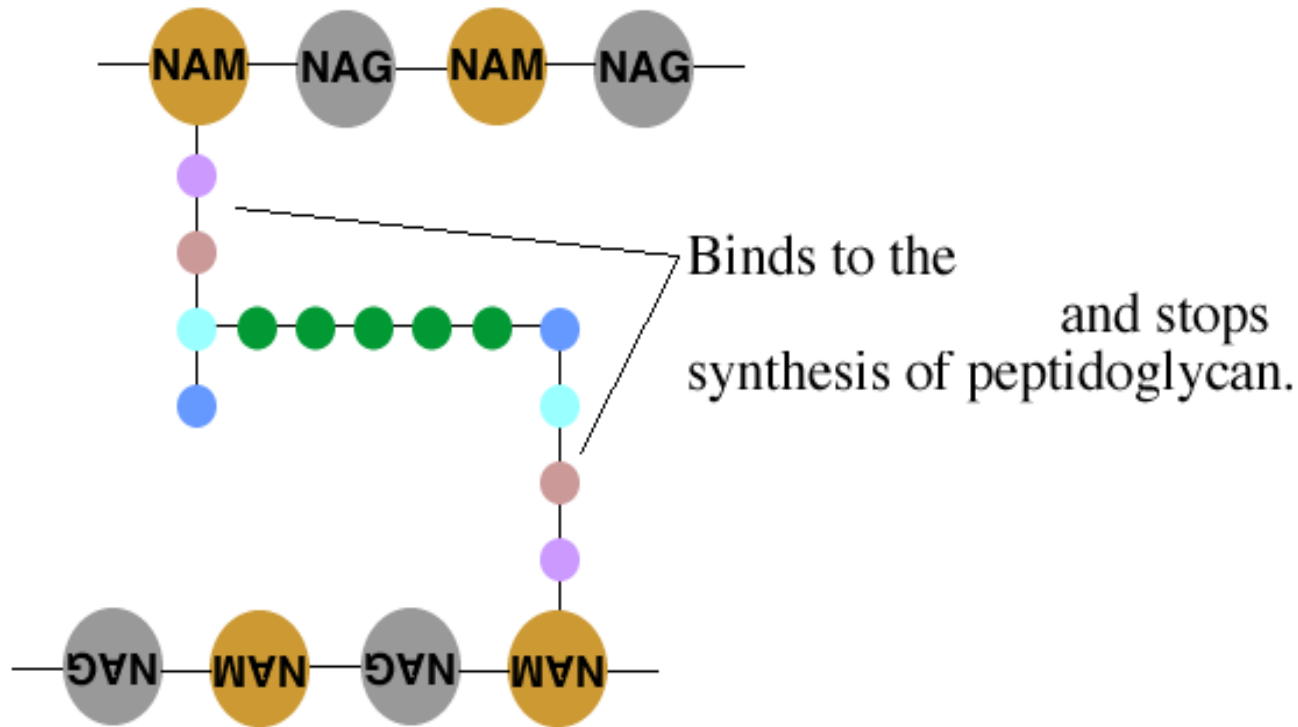
d. Other than allergic reactions, β -lactam antibiotics tend to have

e.

Types of β -lactam antibiotics:			
Antibiotic type	Source	Effective against	Example
	<i>Penicillium chrysogenum</i>	bacteria Some	Penicillin G Penicillin V
Broad-spectrum Penicillins	Partially	bacteria bacteria	
Extended-spectrum Penicillins	Partially synthetic	Some (e.g. <i>Pseudomonas</i>)	Ticarcillin Piperacillin
	<i>Acremonium</i> (More recent derivatives are partially synthetic)	Some G+ More recent derivatives are effective against	Cefepime

2. Vancomycin

a. Vancomycin:



- b. of Gram-negative bacteria so these organisms are innately resistant.
- c. Often good for treating Gram-positive infections if the β -lactam antibiotics are (e.g. antibiotic-resistant *Staphylococcus aureus*).
- d. Administered

3. Bacitracin

- a. Inhibits cell wall synthesis by interfering with the
of peptidoglycan precursors across the
cytoplasmic membrane.
- b. Used only in

B. Drugs that inhibit

Antibiotics that inhibit protein synthesis:			
Antibiotic type	Mechanism of action	Effective against	Example
Aminoglycosides	Bind to 30S ribosomal subunit causing it to	Mainly bacteria that (e.g. <i>Proteus</i> , <i>Escherichia</i> , and <i>Klebsiella</i>)	Gentamicin
	Reversibly bind to the and stop protein synthesis	Certain (rickettsias and chlamydiae)	Tetracycline Doxycycline
Macrolides	Reversibly bind to the and stop protein synthesis	A variety of bacteria, mainly , but also those that cause "walking pneumonia"	

C. Drugs that inhibit nucleic acid synthesis

The quinolones are a class of drugs that inhibit DNA gyrase and topoisomerase IV. They are effective against a wide range of Gram-positive and Gram-negative organisms (*E. coli*, *Klebsiella pneumoniae*, *Neisseria*, *Pseudomonas*, *S. aureus*, *M. tuberculosis*). Ciprofloxacin is an example.

D. Drugs that interfere with cell membrane integrity

Polymyxin B binds to the membrane of Gram-negative cells and disrupts the outer membrane. Cellular components are released and eventually the cell dies. Because this drug can also damage eukaryotic cells, it is used only as an active ingredient in

In general, which type of cell is easier to kill/inhibit with antibiotics?

- a. Gram-negative cells
- b. Gram-positive cells

Why??

**Because of the rise in antibiotic resistance, many efforts are under way to develop new drugs (e.g. Zyvox (linezolid) - in a new class of drugs that inhibit protein synthesis and is active against MRSA). Some efforts are focused on combination therapy in which the antibiotic is administered with a beta-lactamase inhibitor or a efflux pump inhibitor.
What other efforts are under way??**

Efforts are also underway to develop new antifungal and antiviral drugs. Why is this more difficult??