Antimicrobial Agents

INTRODUCTION

A. DEFINITIONS

1. Antimicrobial vs. Anti-infective vs. Antibacterial vs. Antibiotic

2. Bactericidal vs. Bacteriostatic

B. HISTORY

500 B.C. - China

1877 - Pasteur

1876-90 - Koch

1929 - Fleming

1930's – Domagk (Bayer)

1939-41 - Florey & Chain

C. IMPACT OF ANTIMICROBIALS ON HEALTH CARE

1. Infectious disease - first drugs to actually result in a "cure"

2. Usage & Market share

3. Cost/Benefit ratio - complex issue

D. PRODUCTION, ISOLATION, AND PURIFICATION

1. Natural Antibiotics - produced by fermentation

2. Semi-Synthetic

3. Synthetic

E. NECESSARY INFORMATION

To fully understand antimicrobial therapy and provide the best pharmaceutical care to our patients, pharmacists and physicians need to be able to answer several questions to select the most appropriate drug for treatment of infection. Selection of the optimal antibiotic also requires a fundamental basis in medical microbiology in order to identify the most likely causative agent of infection.

Table 1. What Do we Need to Know about Antimicrobials?

What is it ?	Chemical structure and class natural or synthetic product
How does it work ?	Target site Mechanism of action
When is it used ?	Spectrum of activity and important clinical uses
What are the problems ?	Side Effects/Toxicity Microbial Resistance
Where does it go ?	Absorption, Distribution, Metabolism, & Excretion
How do we get it there ?	Route of administration Product formulation
How much does it cost ?	Cost effectiveness

Adapted from Mims, Playfair, Roitt, Wakelin, & Williams, *Medical Microbiology*, Mosby Europe Ltd., London, 1993.

F. EMPIRIC VS. DEFINITIVE THERAPY

1. Empiric therapy - based on treatment of most likely organisms for a specific infection

2. Definitive therapy - after organism is identified. May or may not have information on susceptibility & resistance.

Mechanisms of Action of Antimicrobial Agents

Antimicrobial agents take advantage of the differences between animals cells and bacteria (prokaryotes), fungi, or protozoa. The goal is to have highly selective toxicity towards these microbes with minimal or no toxicity in humans. Table 2 shows the basic differences between eukaryotes and prokaryotes.

Table 2. Characteristics of Eukaryotes and Prokaryotes

Characteristic	Eukaryotes	Prokaryotes
Major Groups	Algae, Fungi, Protozoa, Plants, Animals	Bacteria
Size (approximate)	5 μm	0.5 - 3.0 μm
Nuclear Structure		
Nucleus	Classic nuclear membrane	No nuclear membrane
Chromosomes	Double Stranded DNA arranged in multiple chromosomes	Single, closed strand of genomic DNA. Additional DNA found in plasmids
Cytoplasmic Structures		
Mitochondria	Present	Absent
Golgi bodies	Present	Absent
Endoplasmic reticulum	Present	Absent
Ribosomes (sedimentation coefficient)	80S (60S and 40S subunits)	70S (50S and 30S subunits)
Cytoplasmic membrane	Contains sterols. In animals, membranes contain cholesterol. Egosterol present in fungal membranes.	No sterols present*
Cell Wall	Absent or composed of cellulose (plants) or chitin (insects, fungi)	Complex structure containing lipids, proteins, and peptidoglycan
Reproduction	Sexual and asexual	Binary fission (asexual)
Movement	Usually none. If present, flagella are complex	Simple flagella, if present
Respiration	via mitochondria	via cytoplasmic membrane

* except in *Mycoplasma sp*.

Adapted from Murray, Kobayashi, Pfaller, & Rosenthal, *Medical Microbiology, 2nd ed.,* Mosby, St. Louis, 1994.

The most common targets for antimicrobial drug actions fall into 5 basic categories:

A. Inhibition of Cell Wall Synthesis

B. Inhibition of Protein Synthesis

C. Inhibition of Nucleic Acid Synthesis

D. Effects on cell membrane sterols (antifungal agents)

E. Inhibition of unique metabolic steps

Table 3. Specific Mechanism of Action of Antimicrobial Agents

Mechanism of Action	*Drugs*
Inhibition of Cell Wall Synthesis	
Inhibit cross-linking of peptidoglycan by inactivating transpeptidases (PBPs)	Penicillins, Cephalosporins, Aztreonam, Imipenem
Bind to terminal D-ala-D-ala & prevent incorporation into growing peptidoglycan	Vancomycin, Teicoplanin
Inhibition of transglycosylation	Oritavancin, Teicoplanin, lipophilic vancomycin analogs, ramiplanin
Inhibit dephosphorylation of phospholipid carrier in peptidoglycan structure	Bacitracin
Prevents incorporation of D-alanine into peptidoglycan	Cycloserine
Inhibition of Protein Synthesis	
Bind to 50S ribosomal subunit	Macrolides, Chloramphenicol, Clindamycin
Bind to 30S ribosomal subunit	Aminoglycosides, Tetracyclines
Inhibition of Nucleic acid synthesis	
Inhibition of DNA gyrase & topoisomerase	Quinolones
Inhibition of nucleic acid biosynthesis	Flucytosine, Griseofulvin
Inhibition of mRNA synthesis	Rifampin, Rifabutin, Rifapentine
Alteration of Cell Membrane Function	
Inhibition of ergosterol biosynthesis	Imidazole antifungals
Bind to membrane sterols	Polymyxins, Amphotericin B, Nystatin
Alteration of Cell Metabolism	
Inhibition of tetrahydrofolic acid production (cofactor for nucleotide synthesis)	Sulfonamides, Trimethoprim, Trimetrexate Pyrimethamine
Inhibition of mycolic acid biosynthesis	Isoniazid
Interference with ubiquinone biosynthesis & cell respiration	Atovaquone
Bind to macromolecules	Metronidazole, Nitrofurantoin

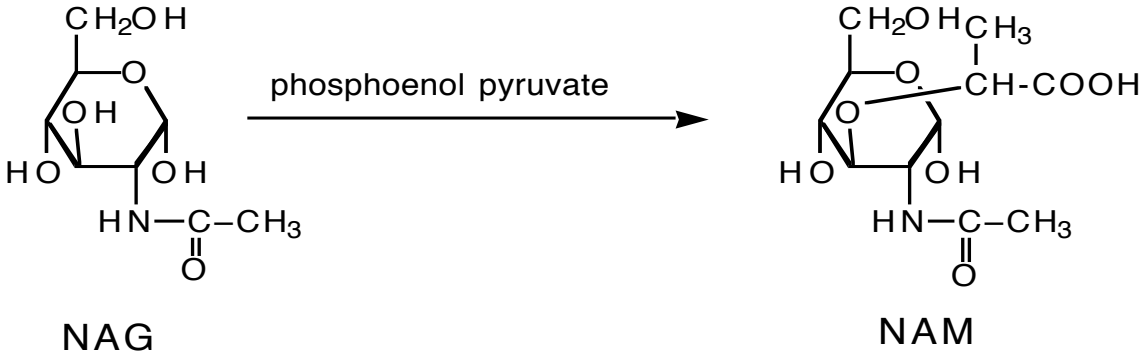
I. INHIBITORS OF BACTERIAL CELL WALL BIOSYNTHESIS

e.g. Penicillins, Cephalosporins, Vancomycin, Bacitracin, Fosfomycin

A. CELL WALL BIOSYNTHESIS

1. **Peptidoglycan layer** -Basic Building Blocks of

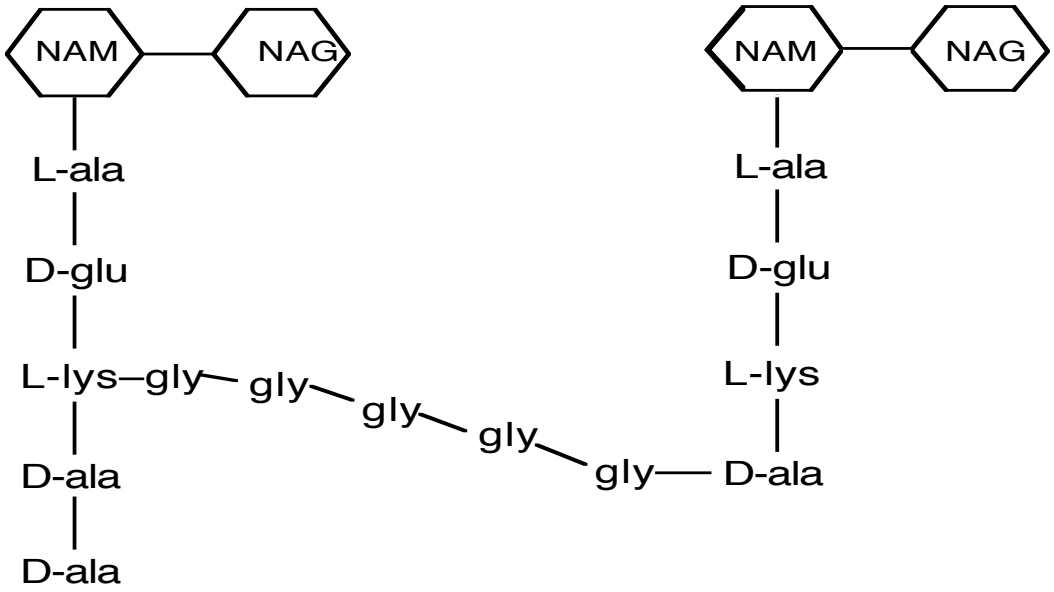
a. N-acetyl glucosamine (NAG) and N-acetyl muramic acid (NAM)



NAG NAM

b.) Transglycosylation – attachment of sugars to pentapeptide and membrane. C55-phospholipid - (Lipid A intermediate) involved in anchorage of peptidoglycan to membrane by connection through NAG via a pyrophosphate bond.

c.) Transpeptidation. Crosslinking of Amino-acid pentapeptide

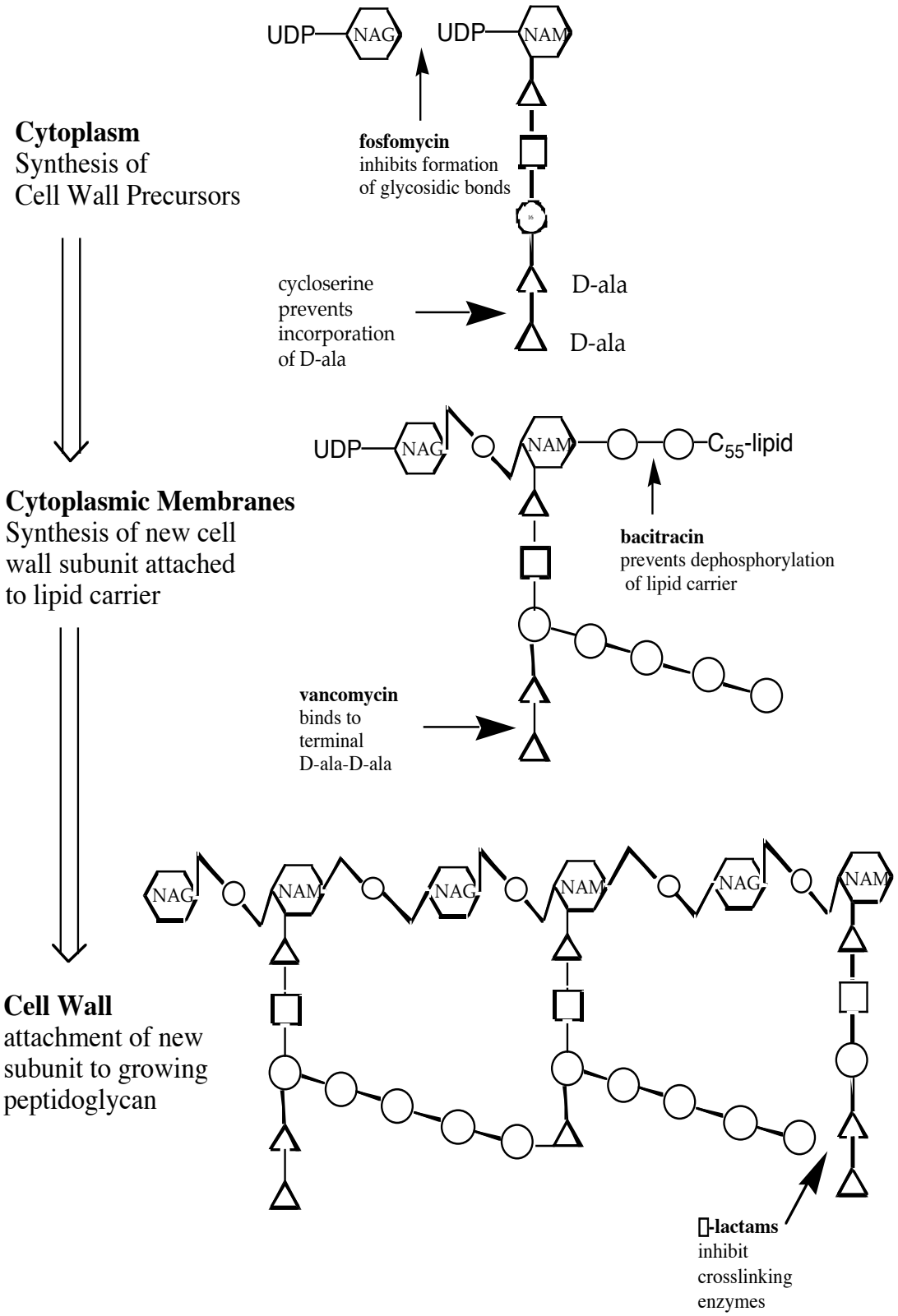


Peptidoglycan of Staph. aureus

i. Composition of amino acids may vary from one bacterium to another

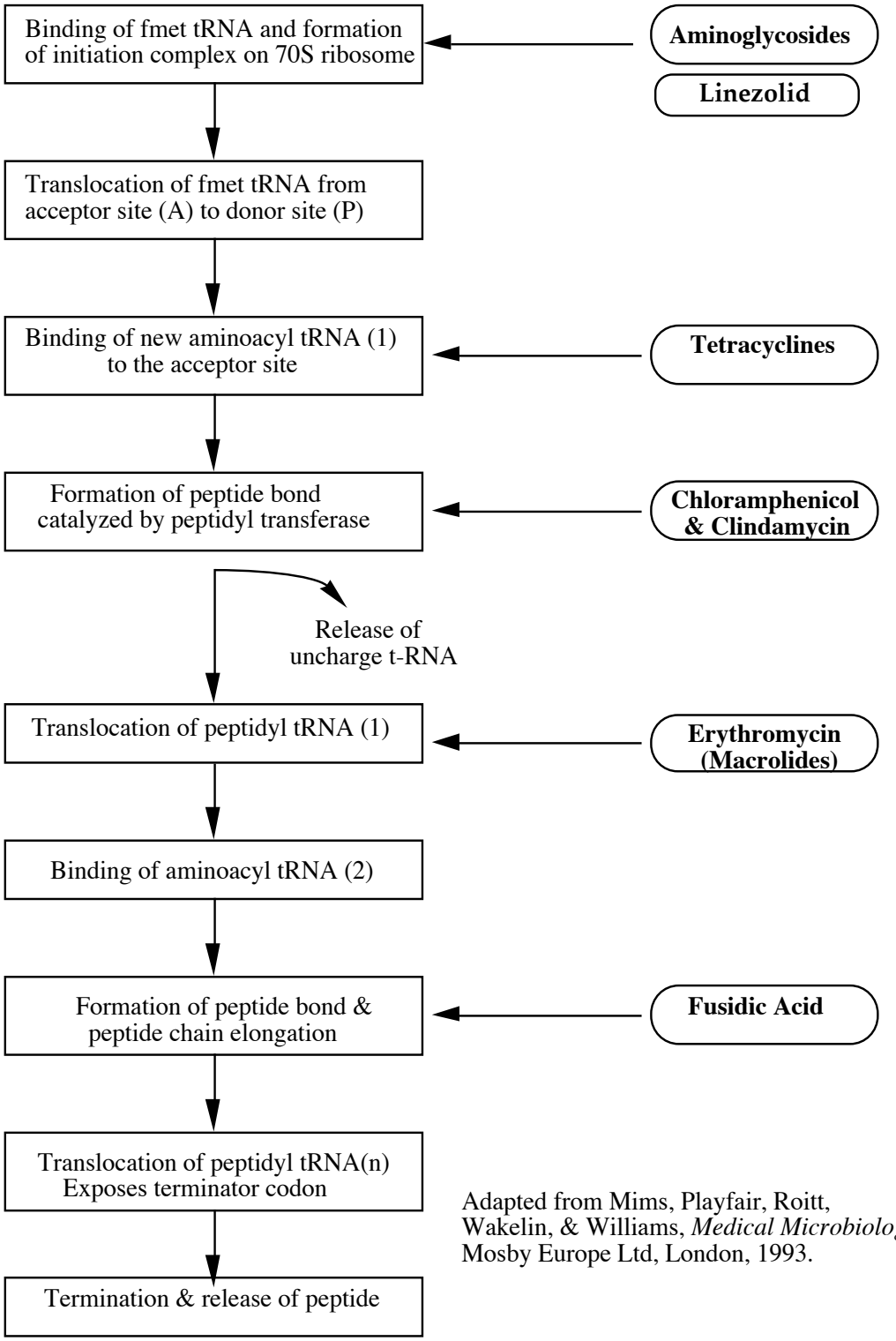
ii. Unusual D-amino acids are present. D-alanine and diaminopipelic acid are unique to bacteria.

Bacterial Cell Wall Biosynthesis and the Steps blocked by Antibiotics



II. INHIBITION OF PROTEIN BIOSYNTHESIS

A. Interaction with 30S ribosomal subunit - Aminoglycosides & Tetracyclines
B. Interaction with 50S ribosomal subunit - Chloramphenicol, Macrolides, Clindamycin



Adapted from Mims, Playfair, Roitt, Wakelin, & Williams, *Medical Microbiology,* Mosby Europe Ltd, London, 1993.

III. INHIBITION OF NUCLEIC ACID BIOSYNTHESIS

A. **Quinolones** - inhibit DNA gyrase & topoisomerase

B. **Flucytosine** - converted to 5-Fluorouracil in fungi. 5-FU inhibits thymidylate synthetase. Incorporated into fungal RNA.

C. **Griseofulvin** - binds to RNA of actively growing fungi

D. **Rifampin & Rifabutin** - inhibition of DNA dependent RNA polymerase

IV. ALTERATION OF CELL MEMBRANE FUNCTION

A. **Amphotericin B, Nystatin, Polymyxin B** - bind avidly to membrane sterols. Higher affinity for ergosterol (present in fungal membranes) than for cholesterol (in mammalian membranes).

B. **Imidazole antifungals** e.g. ketoconazole, fluconazole - inhibit 14-demethylation of lanosterol to ergosterol (essential component of fungal membranes).

V. INHIBITION OF CELL METABOLISM (ANTIMETABOLITES)

A. **Sulfonamides -** p-aminobenzoic acid (PABA) analogs that competitively inhibit incorporation of tetrahydropteroic acid, an initial step in the synthesis of folic acid.

B. **Trimethoprim, Trimetrexate, Pyrimethamine** - inhibitors of dihydrofolate reductase in bacteria (trimethoprim) or protozoa (pyrimethamine, trimetrexate).

C. **Atovaquone -** inhibits ubiquinone biosynthesis & cell respiration in protozoa

D. **Isoniazid, Ethionamide -** inhibit mycolic acid biosynthesis in Mycobacterium sp.

E. **Metronidazole, Nitrofurantoin** - reduced to highly reactive metabolites. Bind to cell macromolecules.