Chapter 12

Topics:

- **Antimicrobial Therapy**
- **Selective Toxicity**
- **Survey of Antimicrobial Drug**
- **Microbial Drug Resistance**
- **Drug and Host Interaction**

Antimicrobial Therapy

- **Ideal drug**
- **Terminology**
- **Antibiotics**

An ideal antimicrobic:

- soluble in body fluids,
- **selectively toxic**,
- nonallergenic,
- reasonable half life (maintained at a constant therapeutic concentration)
- unlikely to elicit resistance,
- has a long shelf life,
- reasonably priced.

There is no ideal antimicrobic

Selective Toxicity - Drugs that specifically target microbial processes, and not the human host's.

Chemotherapy is the use of any chemical agent in the treatment of disease.

A **chemotherapeutic agent** or **drug** is any chemical agent used in medical practice.

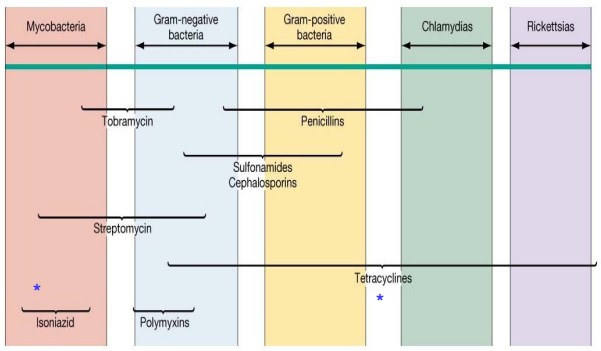
An **antibiotic** agent is usually considered to be a chemical substance made by a microorganism that can inhibit the growth or kill microorganisms.

An **antimicrobic** or **antimicrobial agent** is a chemical substance similar to an antibiotic, but may be synthetic.

Antibiotics

- Naturally occurring antimicrobials
  - Metabolic products of bacteria and fungi
  - Reduce competition for nutrients and space
- Bacteria
  - *Streptomyces, Bacillus,*
- Molds
  - *Penicillium, Cephalosporium*

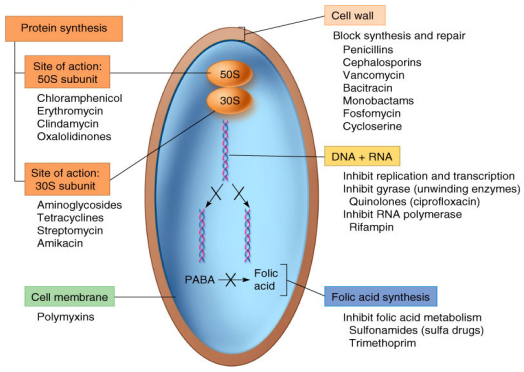
Spectrum of antibiotics and targets



5 General Mechanisms of Action for Antibiotics

- **Inhibition of Cell Wall Synthesis**
- **Disruption of Cell Membrane Function**
- **Inhibition of Protein Synthesis**
- **Inhibition of Nucleic Acid Synthesis**
- **Anti-metabolic activity**

The mechanism of action for different antimicrobial drug targets in bacterial cells



Cell wall synthesis

- Bactericidal
- Vancomycin – hinders peptidoglycan elongation
- Penicillin and cephalosporins – binds and blocks peptidases involved in cross-linking the glycan molecules

Antibiotics weaken the cell wall, and cause the cell to lyse.

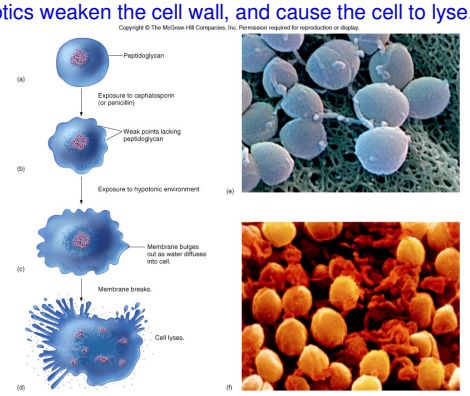


Fig. 12.2 The consequences of exposing a growing cell to antibiotics that prevent cell wall synthesis.

Affect cell wall synthesis

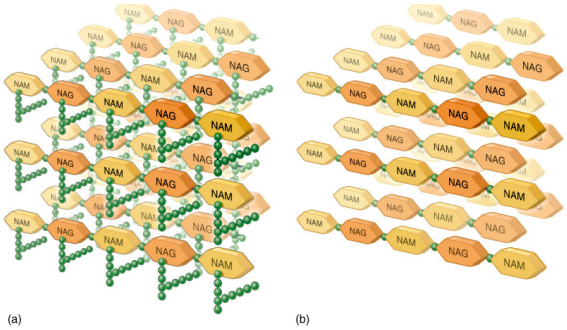
Penicillin – Figure 13.11

Penicillin G - drug of choice for streptococci, meningococci, pneumococci, spirochetes, clostridia, aerobic gram-positive rods treponemes - administered parenterally - other than by mouth - why?

Penicillin V, ampicillin or other analogues may be used for oral administration

Cephalosporins - similar to penicillins

The mechanism of cell wall inhibition by penicillins and cephalosporins

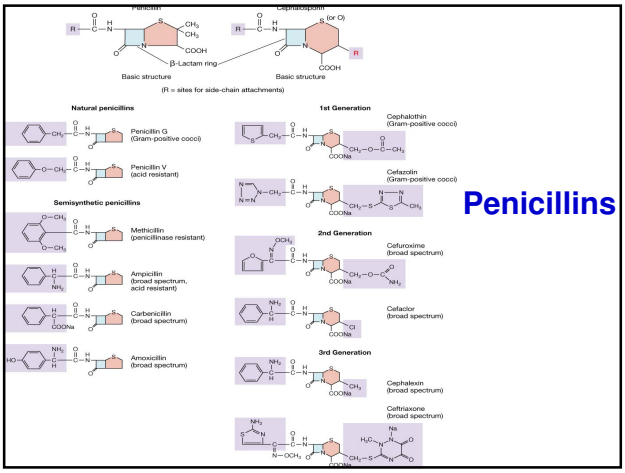


Penicillin

- *Penicillin chrysogenum*
- A diverse group (1st, 2nd , 3rd generations)
  - Natural (penicillin G and V)
  - Semisynthetic (ampicillin, amoxicillin)
- Structure
  - *Beta-lactam* ring
  - Variable side chain (R group)

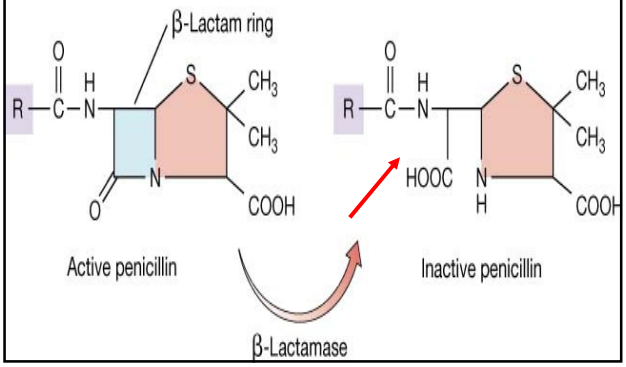
Penicillin continued

- Resistance – if bacteria contain penicillinases - β-lactamase
- Inhibits cell wall synthesis
- Effective against Gram+ bacteria



Penicillins

Effect of β-lactamase on penicillin

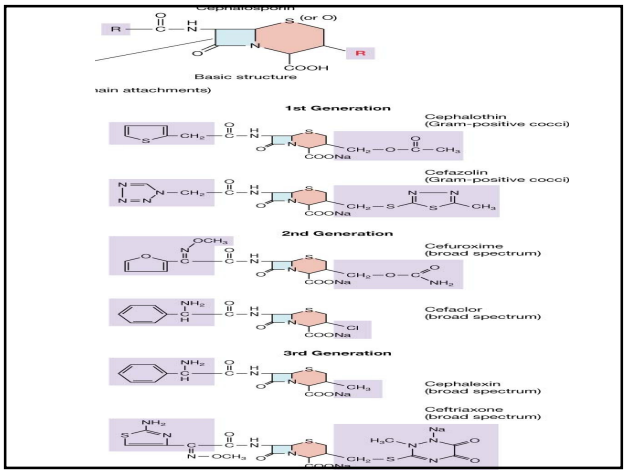


Cephalosporin - beta lactam

- *Cephalosporium acremonium* (mold)
- Widely administered today
  - Diverse group (natural and semisynthetic- 4th generation!)
- Structure
  - similar to penicillin except
    - Main ring is different
    - Two sites for R groups

Cephalosporin continued…

- Resistant to most pencillinases
- Broad-spectrum – inhibits cell wall synthesis
- 3rd generation drugs used to treat enteric bacteria, respiratory, skin, urinary and nervous system infections



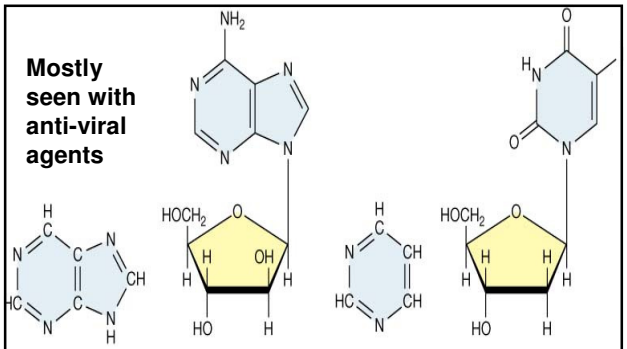
Nucleic acid synthesis

- **Chloroquine – binds and cross-links the double helix**
- **Other quinolones – inhibits DNA unwinding enzymes (gyrase) and block replication.** Ciprofloxacin is an example
- **Viruses**
  - **Analogs of purines and pyrimidines - sometimes considered antimetabolites**

Rifampin - blocks transcription - can cause red man syndrome - a result of accumulation of metabolic products of the antimicrobic in secretions

"Red Man Syndrome"

Mostly seen with anti-viral agents



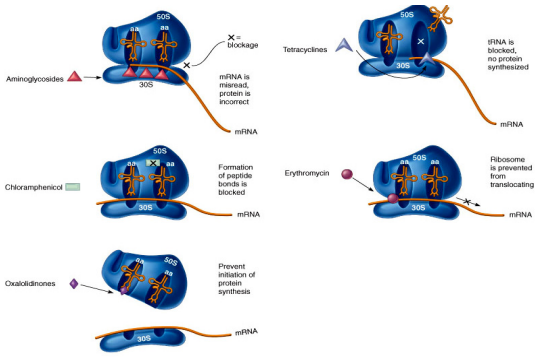
(a) purine

(b) purine analog

(c) pyrimidine

(d) pyrimidine analog

Examples of different antibiotics and their sites of inhibition on the prokaryotic ribosome



Protein synthesis

- Aminoglycosides
  - Binds the 30S ribosome
  - Misreads mRNA
- Tetracyclines
  - Binds the 30S ribosome
  - Blocks attachment of tRNA to A site
- Chloramphenicol
  - Binds to the 50S ribosome
  - Prevents peptide bond formation

Aminoglycosides

- *Streptomyces* and *Micromonospora*
- Broad-spectrum
- Commonly used to treat bubonic plague and sexually transmitted diseases
- Inhibits protein synthesis - bind 30S ribosomal subunit

Tetracycline

- *Streptomyces*
- Broad spectrum and low cost
- Commonly used to treat sexually transmitted diseases
- Side effects – gastrointestinal disruption, deposition in hard tissues
- Inhibits proteins synthesis - Binds the 30S ribosome and blocks attachment of tRNA

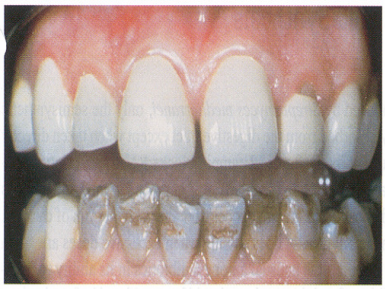


Figure 13.12 **Staining of teeth caused by tetracycline.** If the condition results from ingestion of the antibiotic during pregnancy, both the deciduous (baby) and permanent teeth will be affected, as both sets of tooth buds are forming in the fetus at that time.

Chloramphenicol

- *Streptomyces*
- Broad-spectrum
- Only made synthetically today
- Treat typhoid fever, brain abscesses
- Side effects – aplastic anemia
- Inhibits protein synthesis - binds 50S ribosome subunit - prevents peptide bond formation

Erythromycin

- *Streptomyces*
- Structure – macrolide ring
- Broad-spectrum
- Commonly used as prophylactic drug prior to surgery
- Side effects - low toxicity
- Inhibits protein synthesis - bind to 50S ribosome subunit- prevents translocation

Cell membrane

- **Polymyxins**
  - **Interact with membrane phospholipids**
  - **Distorts the cell surface**
  - **Leakage of proteins and nitrogen bases**
- **Anti-fungal - Polyenes**
  - **Amphotericin B and Nystatin- bind to sterols on cells membranes.**

Polyenes

- **Antifungal**
- **Commonly used for skin infections**
- **Targets the membrane - loss of selective permeability**
- **Polyenes – Amp B and Nystatin**
- **Amphotericin B - binds to ergosterol found in fungi and protozoa, but not in human cells - increases membrane permeability**
- **Side effects are numerous due to toxicity of the drug**

ANTIMETABOLITES

Act either through competitive inhibition or erroneous incorporation – molecular mimicry

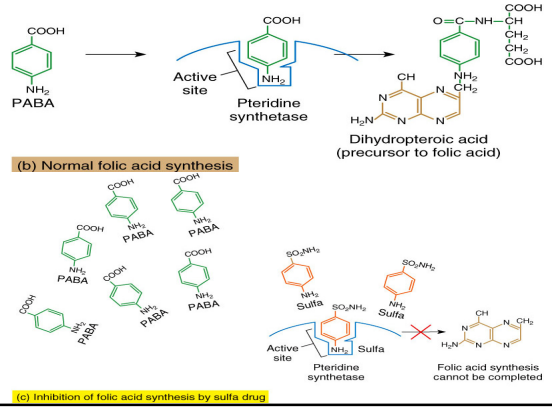
Sulfonamides - block synthesis of folic acid - and as a result, nucleic acid synthesis

Isoniazid - antimetabolite for two vitamins

Sulfonamides (sulfa drugs)

- **Synthetic drug**
- **Based on sulfanilamides**
- **Used in combination with other synthetics such as trimethoprim**
- **Commonly used to treat pneumonia in AIDS patients**
- **Inhibits folic acid synthesis**

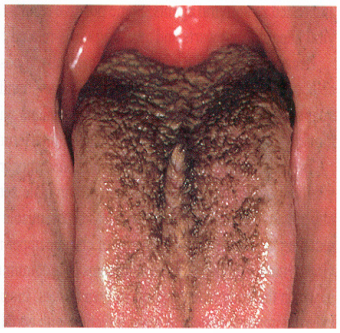
The mode of action of sulfa drug



Other types of antimicrobials

- **Antiprotozoan – metronidazole - most are fairly toxic - black hairy tongue**
  - **Treat Giardia and amebiasis**
- **Antimalarial – Quinine**
  - **malaria**
- **Antihelminthic – mebendazole**
  - **Tapeworms, roundworms**

Flagyl



➢ Figure 13.14 **Black hairy tongue, a reaction to the drug metronidazole (Flagyl).** The papilli on the tongue surface become elongated and filled with breakdown products of hemoglobin, which darken the tongue.

Antiviral

- Limited drugs available
- Difficult to maintain selective toxicity
- Effective drugs – target viral replication cycle
  - Entry
  - Nucleic acid synthesis
  - Assembly/release
- Interferon – artificial antiviral drug

Antimicrobial Resistance

- Resistance factors – R plasmids
- 5 main mechanisms of resistance
- New approaches

5 Mechanisms of Resistance

1) Alteration of Targets – usually affects ribosomes

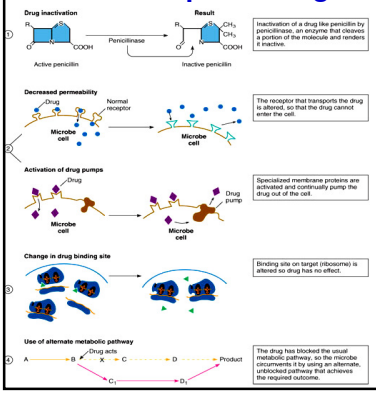
2) Alteration of Membrane Permeability- Change in the receptor that binds the drug

3) Development of Enzymes – β-lactamase

4) Efflux pumps – Memnbrane proteins many Gram negatives that pump out drug

5) Alteration of Metabolic Pathway – Development of alternate pathway

Examples of mechanisms of acquired drug resistance



β-lactamase

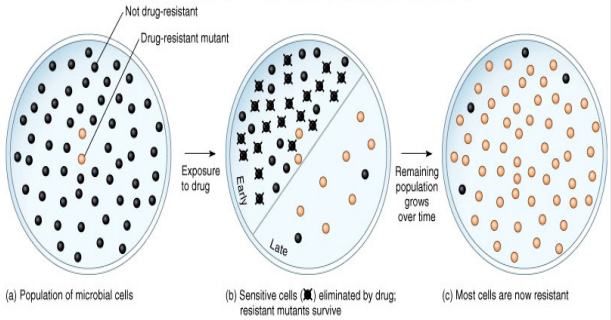
Membrane permeability

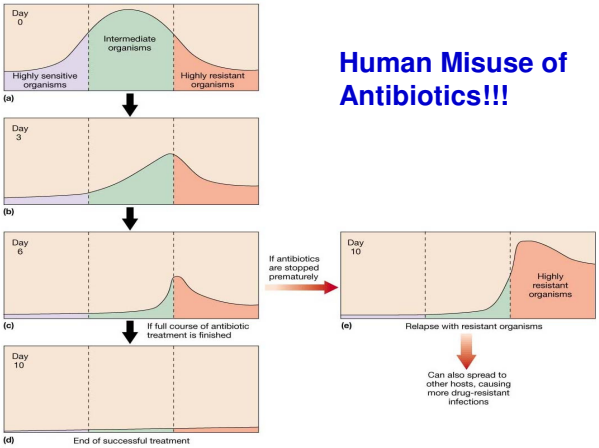
Efflux pumps

Alter targets

Alternate metabolism

Demonstration of how natural selection enables resistant strains to become dominant





Human Misuse of Antibiotics!!!

Limiting Resistance

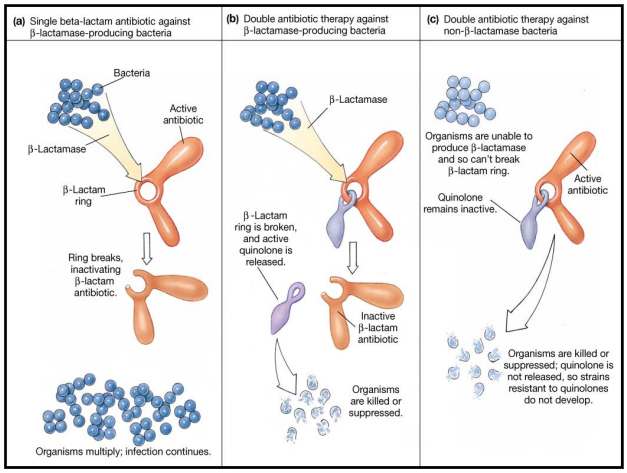
1) Constant exposure to high levels of antibiotic

2) Use of multiple antibiotics

3) Restricted use of antibiotics

New approaches

- **Increase drug resistance requires new approaches for developing effective antimicrobials**
  - **Prevent iron –scavenging capabilities**
  - **Inhibit genetic controls (riboswitches)**
  - **Probiotics and prebiotics**
  - **Combination therapy**
  - **Phage therapy**



Drug and Host Interaction

- **Toxicity to organs**
- **Allergic reactions**
- **Suppress/alter microflora**
- **Effective drugs**

Main Types of Side Effects Associated with Antimicrobial Treatment

1) Toxicity

2) Allergy – actual drug or breakdown products

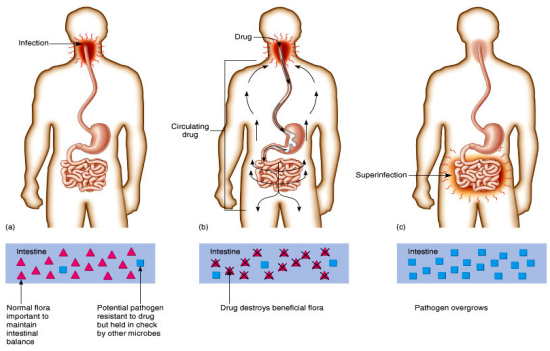
3) Disruption of Normal Microflora
Can Lead to SUPERINFECTIONS!!

Development of disease following broad spectrum antimicrobic therapy

Pseudomembranous colitis (antibiotic associated diarrhea) - often caused by *Clostridium difficile*

Yeast infection – after broad antibiotic use to treat UTI caused by *E. coli*

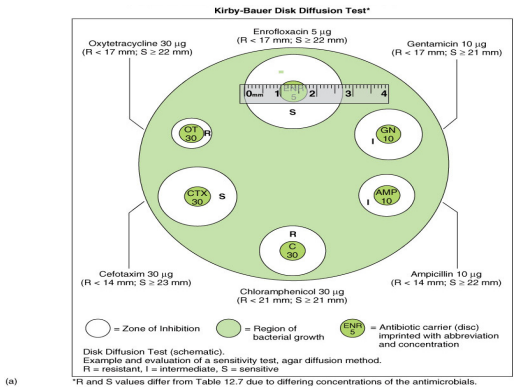
Disrupting the microflora in the intestine can result in superinfections



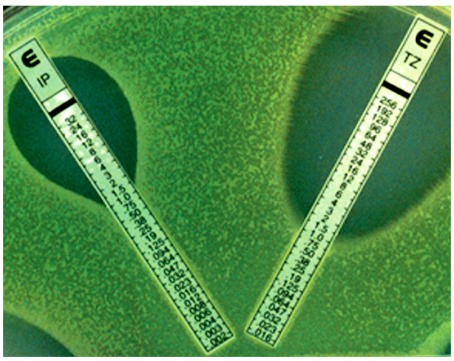
Effective drugs

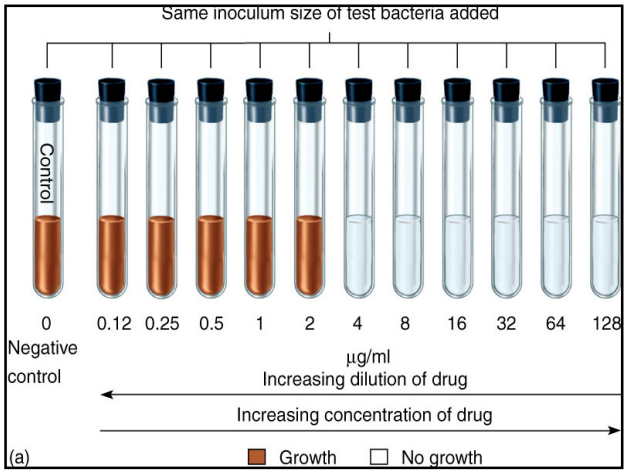
- **Identify infectious agent**
- **Sensitivity testing**
- **Minimum Inhibitory Concentration (MIC) – visual call**

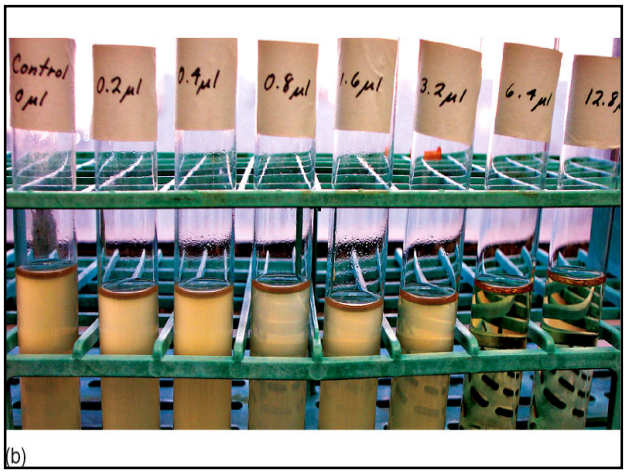
An example of the Kirby-Bauer Test



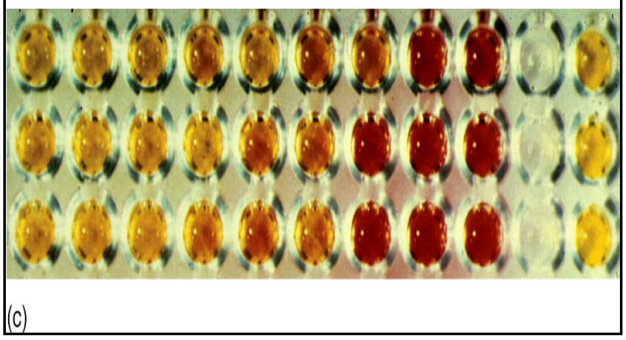
The E-test is an alternative to the Kirby-Bauer procedure

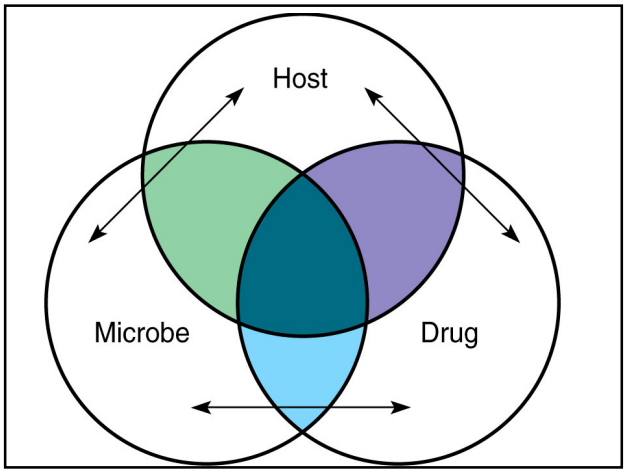






Multiwell plate to calculate several MICs





Antimicrobics have helped us deal with disease, but on the other hand, improper use of antimicrobics have created new difficulties.