Introduction to Chemotherapy

General Consideration

Assoc. Prof. Bilgen Başgut
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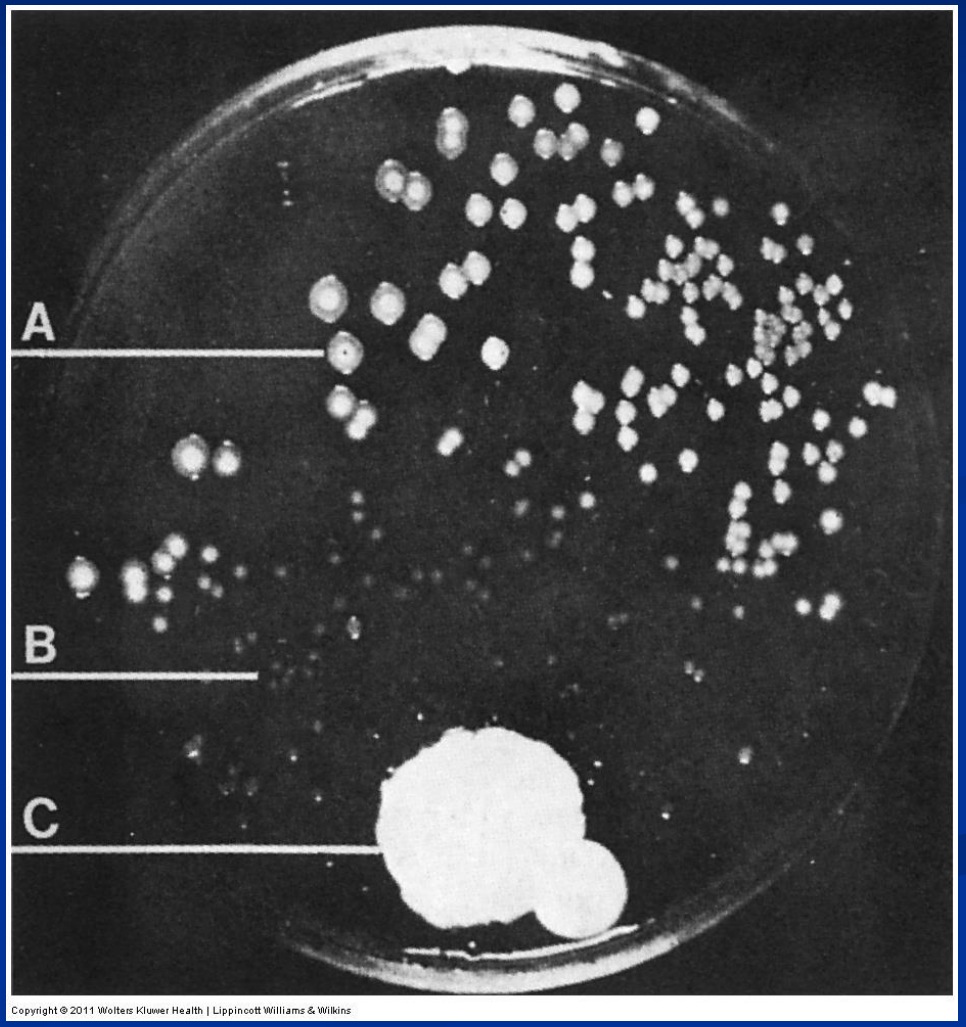
NEU-Medical College

History

- **Joseph Lister 1867 - Father of Antisepsis. Introduced use of carbolic acid.**
- **Paul Ehrlich 1908-10 - first suggest using chemical compounds to treat microbial diseases.**
- **Alexander Fleming 1928 - observed that the mold *Penicillium notatum* inhibited the growth of *Staphylococcus aureus* colonies - unable to purify the compound.**
- **Gerhard Domagk 1935 - Therapeutic value of sulfonamides against streptococcus and other organisms.**
- **Penicillin became available in quantities sufficient for clinical use in 1941.**

The discovery of penicillin by Alexander Fleming. (A) Colonies of *Staphylococcus aureus* are growing well in this area of the plate. (B) Colonies are poorly developed in this area of the plate because of an antibiotic (penicillin) being produced by a colony of *Penicillium notatum* (a mould), shown at C.



- After that， Streptomycin, chloramphenicol, and tetracycline were discovered. Since then, numerous classes of antimicorabial agents have been identified, and a lot of drugs are available for use today.

- Antimicrobials are among the most commonly used drugs.

Terminology

- *Chemotherapy* is the use of any chemical (drug) to treat any disease or condition.
- A *chemotherapeutic agent* is any drug used to treat any condition or disease.
- An *antimicrobial agent* is any chemical (drug) used to treat an infectious disease, either by inhibiting or killing pathogens in vivo. Some antimicrobial agents are antibiotics.

- An *antibiotic* is a substance produced by a microorganism that kills or inhibits growth of other microorganisms.
- Antibiotics that have been chemically modified to kill a wider variety of pathogens or reduce side effects are called *semisynthetic antibiotics*; examples include semisynthetic penicillins such as ampicillin and carbenicillin.

Classification of antimicrobial drugs

- Antibacterial drugs
- Antiviral drugs
- Antifungal drugs
- Antiprotozoal drugs

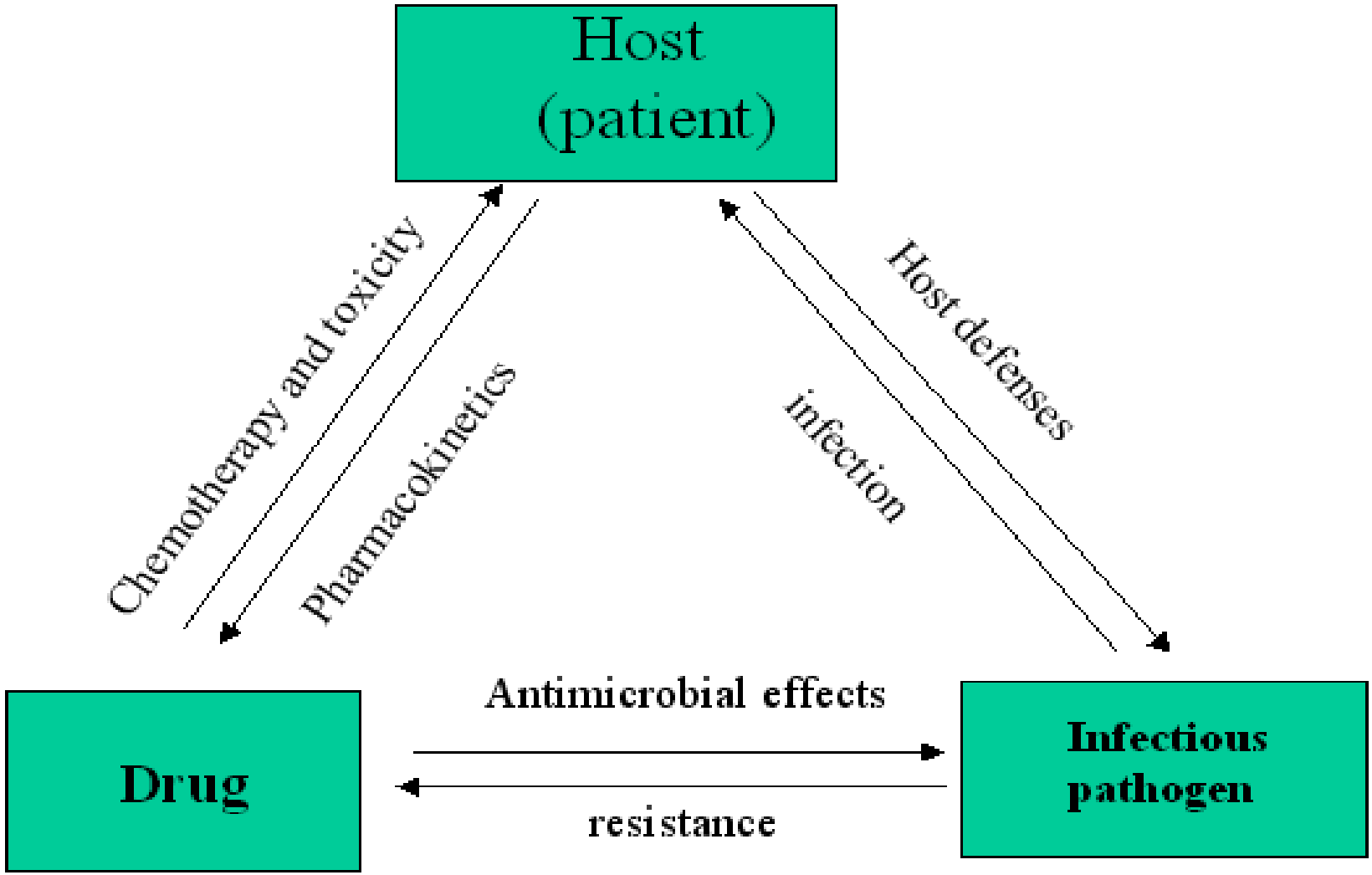


Fig.1 The relationship of Host-Drug-Pathogen in chemotherapy

Treatment & prophylaxis

- Prophylaxis - antimicrobial agents are administered to prevent infection
- Treatment - antimicrobial agents are administered to cure existing or suspected infection

Antimicrobial Therapy

Selective toxicity: bacterial infections provide differences in physiology that can be targeted for therapy

Special terms

Antimicrobial spectrum

Antimicrobial spectrum of a drug means the species of microorganisms that the drug can inhibit or kill.

1.Narrow spectrum

The agents act against a single or limited group of microorganisms, for example, isoniazid is active only against *mycobacteria*. *Penicilin G and V, macrolides*

2. Broad spectrum

- The agent affect a wide variety of microbial species and are referred to as broad spectrum antibiotics.

- For example, tetracyclines, chloramphenicol, quinolones, aminoglycosides, cephalosporines, penicillins (amoxycilin, ampicilin, carbenycilin)

- Using broad spectrum antibiotics interfere the nature of the normal bacterial flora and can precipitate a superinfection of an organism.

Special terms

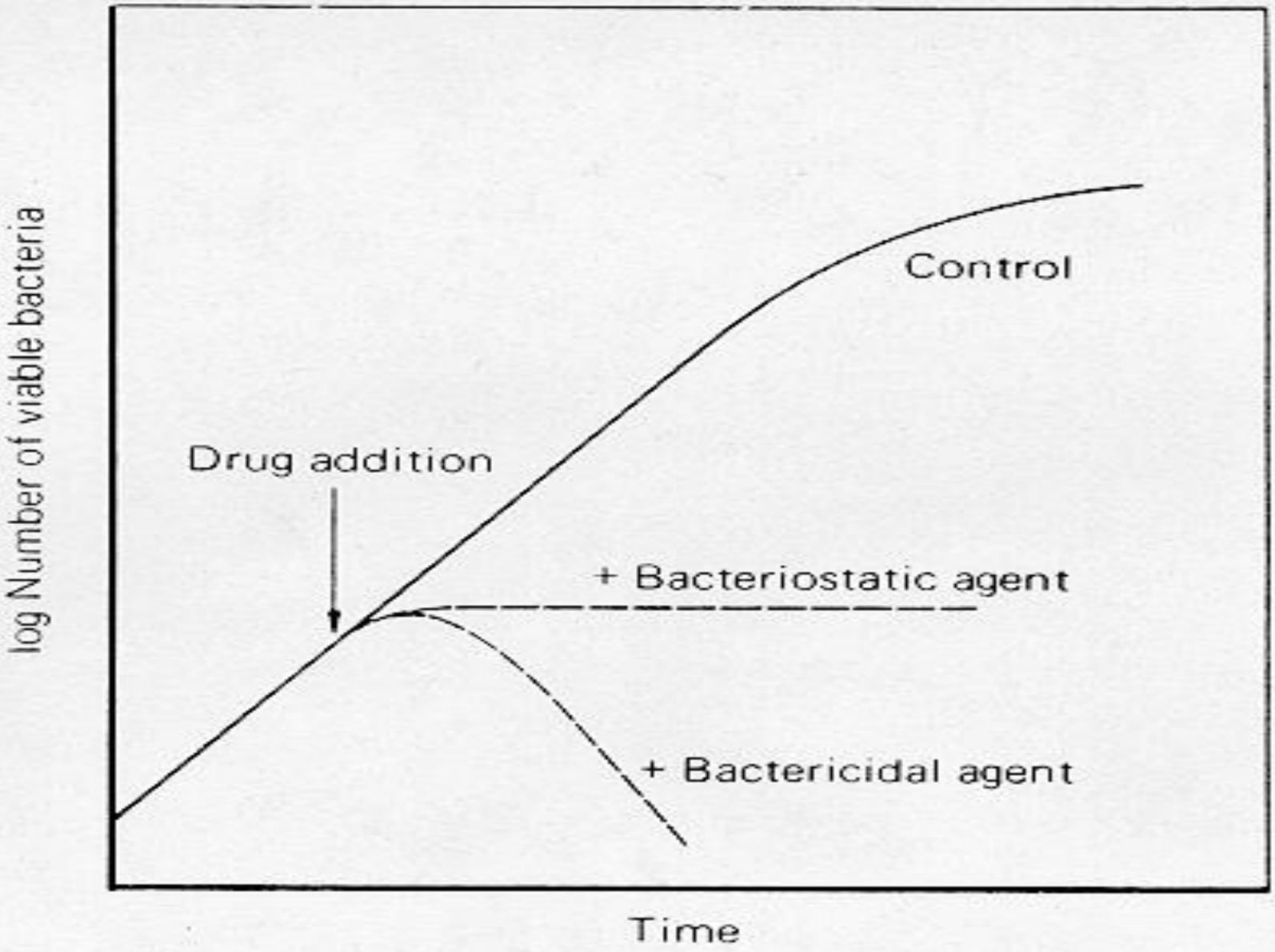
Bacteriostatic drugs

- Bacteriostatic drugs agents arrest the growth or replication of the microorganism, but cannot kill them.

Bactericidal drugs

- The agents which can kill the microorganisms are called bactericidal drugs. but also can destroy them.
- It should be noted that a drug may be bacteriostatic for one organism but bactericidal for another.

Bactericidal vs bacteriostatic



Bacteriocidal

- Penicillins
- Cephalosporins
- Aminoglycosides
- Vankomycin
- Amfoterisin B
- Rifampin
- Fluoroquinolons

Bacteriostatic

- Tetracyclins
- Sulfonamides
- Chloramphenicol
- Eritromycin
- Clindamycin
- Myconazol
- Metronidazol

Special terms

Chemotherapy index (CI) (therapeutic index of chemotherapeutic agents)

- CI is a term used to evaluate the safety of chemotherapeutic drugs, the value is LD50/ED50 or LD5/ED95.
- CI= LD50/ED50
- CI= LD5/ED95
- Larger the number = better

Special terms

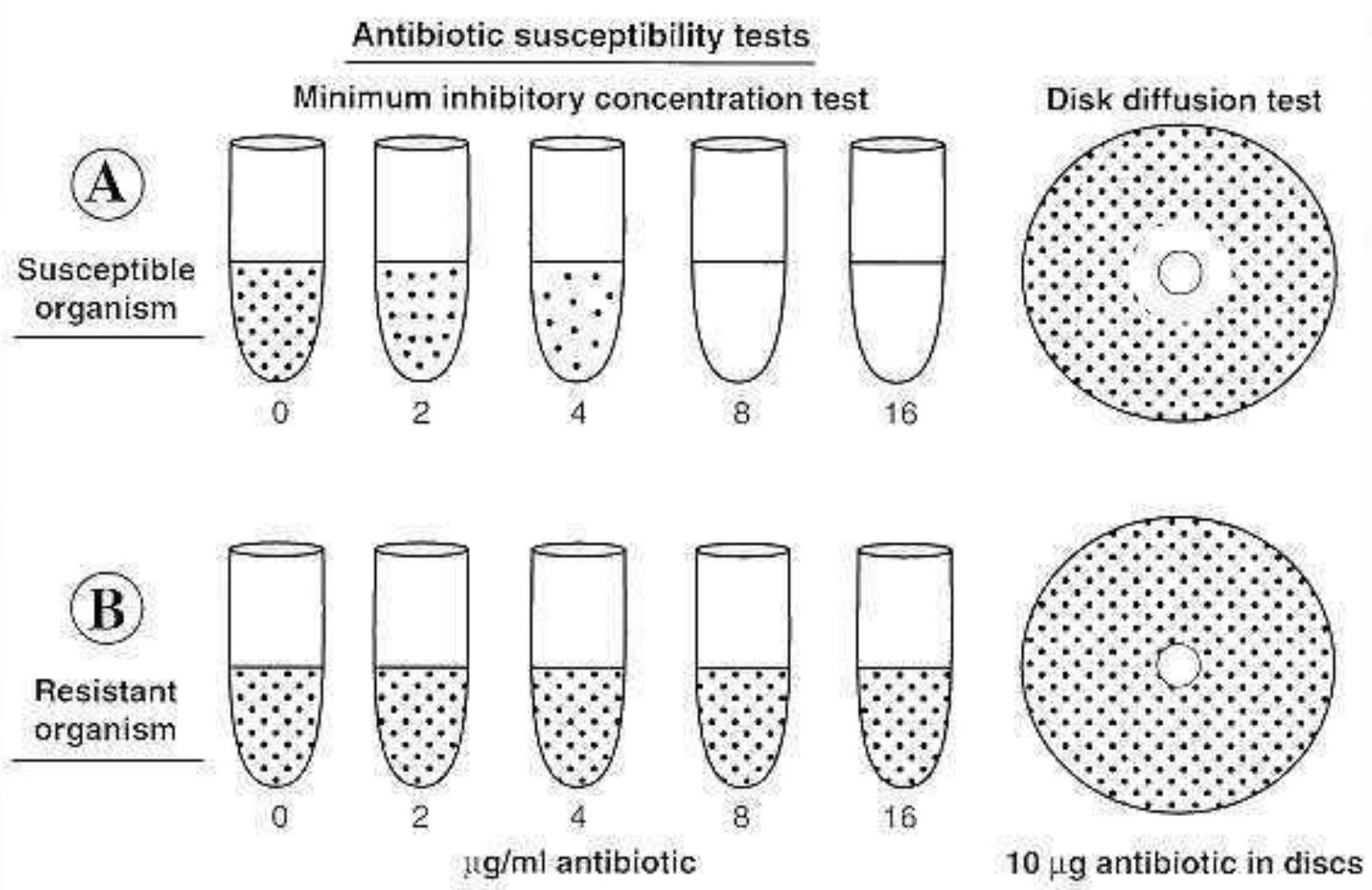
Minimal inhibitory concentration (MIC)

- MIC is the lowest concentration of antimicrobial agents that prevents visible growth in18-24 hours incubation.

- **Minimum Bactericidal Concentration (or minimal lethal conc.) (MBC)**

The minimum concentration needs for kill 99.9% of testing microorganisms.

- **If MBC≥32×MIC, it indicates that the microorganism has resistance to the drug.**


Antibiotic susceptibility tests
Minimum inhibitory concentration test
Disk diffusion test
A
Susceptible organism
0
2
4
8
16
B
Resistant organism
0
2
4
8
16
μg/ml antibiotic
10 μg antibiotic in discs

Special terms

Post-antibiotic effect (PAE)

- PAE shows the antimicrobial effect after the concentration decreased below MIC. (Aminoglycosides- 7 hr)

Characteristics of an Ideal Antimicrobial Agent

- *The ideal antimicrobial agent should*:
  - Kill or inhibit the growth of pathogens
  - Cause no damage to the host
  - Cause no allergic reaction in the host
  - Be stable when stored in solid or liquid form
  - Remain in specific tissues in the body long enough to be effective
  - Kill the pathogens before they mutate and become resistant to it

Mechanism of action

Antimicrobial agents can be classified into five major groups:

- (a) inhibitors of cell wall synthesis
- (b) inhibitiors of synthesis of cytoplasmic membrane
- (c) modification in synthesis or metabolism of nucleic acids
- (d) inhibitors of protein synthesis
- (e) modification in energy metabolism

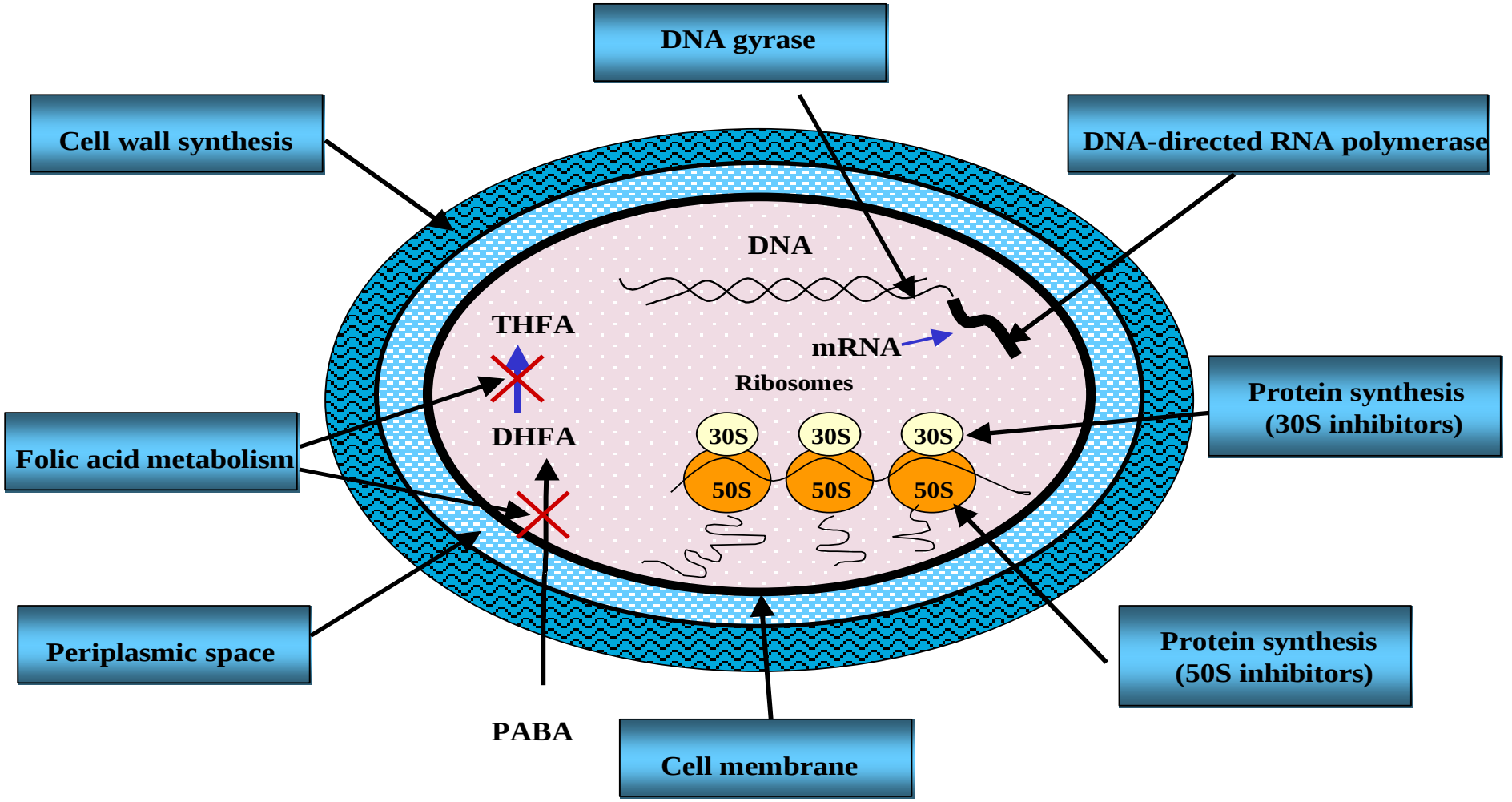


Fig. 2 antimicrobial site of action

Inhibit the biosynthesis of the cell wall.

- The cell walls of bacteria are essential for their normal growth and development.
- Stages of peptidoglycan synthesis

Inhibitors of cell wall synthesis

- Penicillins
- Cephalosporins
- Aztreonam
- Carbapenems
- Bacitracin
- Vankomycin

Inhibition of protein synthesis

- Tetracyclines, streptomycin and other aminoglycosides, clindamycin act on 30s ribosomal subunit.

- Chloramphenicol, lincomycin and eritromycin act on 50s ribosome subunit.

Interfere the metabolisms of nucleotides

- Rifampicin specifically inhibits DNA-dependent RNA-polymerase (DDRP), interfere mRNA synthesis.
- Quinolones inhibits DNA gyrase, reducing DNA duplication and mRNA transcription.
- Mitomicin
- Actinomisin
- Doxorubicin
- Metronidazol

Inhibit folic acid metabolisms

- Sulphonamides inhibit dihydrofolic acid synthase (DHF).
- Trimethoprim inhibit dihydrofolic acid reductase.
- Isoniazid

Resistance

- an adaptive response in which microorganisms begin to tolerate an amount of drug that would ordinarily be inhibitory

Resistance of antimicrobial agent

1. Type of resistance:

(1) Intrinsic resistance----It is a nature resistance existing on chromosome. Gram-negative bacilli to basic penicillins.

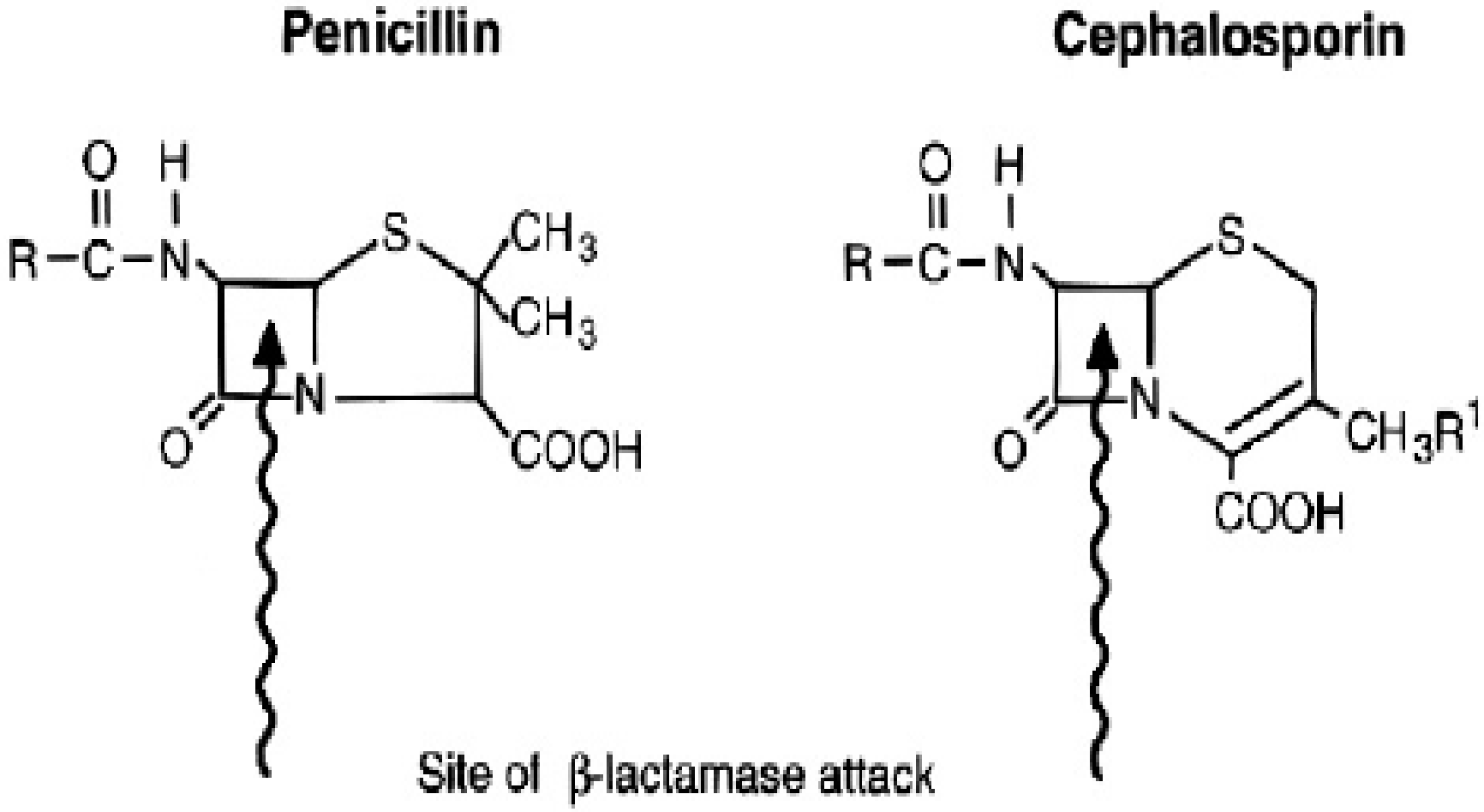
(2) Acquired resistance----It is induced by antimicrobial agents.
It is more often plasma-mediated, sometimes chromosome-mediated.

Resistance of antimicrobial agent

1. Enzymic inactivation

- The ability to destroy or inactivate the antimicrobial agents can confer resistance on microorganisms.

- For example, β-lactamases destroy many penicillins and cephalosporins



Splits the amide bond hydrolyzing the β-lactam ring

2. Modification of target sites

- The β-lactams can resist to organism by alteration of the target site that is penicillin binding protein(PBP) and mutation of dihydrofolate reductase which is less sensitivity to inhibition in organism resistant to trimethoprim.

3. Decreased accumulation

- Antibiotics are unable to gain access to the site of action due to the presence of an **efflux system** that pumps out the drug.
- Another situation is that gram-negative bacteria show a special membrane (lipopolysaccharide layer) and decrease penetrability of antibiotics.

4. Genetic alterations leading to drug resistance

1. Mutations

- Specific genetic mutations are the molecular basis for resistance to streptomycin (ribosomal mutation), to quinolones (DNA gyrase gene mutation) and to rifampin (RNA polymerase gene mutation).
- For example, the mutation to rifampin (Rimactane) is a single-step mutation: in this case, E. coli or Staph. Aureus's exposure to rifampin results in highly resistant strains due to a point mutation in the RNA polymerase gene, causing the polymerase protein no longer binds rifampin.

Genetic alterations leading to drug resistance

Transduction

- The resistance occurs when a bacteriophage which includes bacterial DNA in its protein coat infects the bacteria.
- This bacterial DNA may contain a gene confirming resistance to antibacterial drugs.
- For example, *Staphylococcus aureus* strain resistance development to penicillin may occur by transduction.
- Some bacteriophages carry plasmids that code for penicillinase, Other phages can transfer genes which confer resistance to tetracycline, erythromycin and chloramphenicol.

Genetic alterations leading to drug resistance

3. Conjugation

- Conjugation is another mechanism for single and multi-drug resistance development.
- In conjugation, direct passage of resistance-conferring DNA between bacteria proceeds by way of a bridge.
- The genetic material transfer in conjugation requires two elements: an R-determinant plasmid which codes for the resistance and a resistance-transfer factor (RTF) plasmid which contains the genes necessary for the bacterial conjugation process.
- For example most resistance of gram-negative bacilli is mediated by conjugation

TABLE 9-7 Mechanisms by which Bacteria Become Resistant to Antimicrobial Agents

MECHANISM	EFFECT
A chromosomal mutation that causes a change in the structure of a drug binding site	The drug cannot bind to the bacterial cell
A chromosomal mutation that causes a change in cell membrane permeability	The drug cannot pass through the cell membrane and thus cannot enter the cell
Acquisition (by conjugation, transduction or transformation) of a gene that enables the bacterium to produce an enzyme that destroys or inactivates the drug	The drug is destroyed or inactivated by the enzyme
Acquisition (by conjugation, transduction, or transformation) of a gene that enables the bacterium to produce a multidrug-resistance (MDR) pump	The drug is pumped out of the cell before it can damage or kill the cell

Some Strategies in the War Against Drug Resistance

- Education of healthcare professionals and patients
- Patients should stop demanding antibiotics every time they are, or their child is, sick
- Physicians should not be pressured by patients and should prescribe drugs only when warranted
- Clinicians should prescribe a narrow-spectrum drug if lab results indicate that it kills the pathogen
- Patients should destroy any excess or out-dated medications
- Antibiotics should not be used in a prophylactic manner
- Healthcare professionals should practice good infection control
- Patients should take drugs in manner prescribed

Undesirable Effects of Antimicrobial Agents

- Reasons why antimicrobial agents should not be used indiscriminately:
  - Organisms susceptible to the agent will die, but resistant ones will survive; this is known as *selecting for resistant organisms*.
  - The patient may become allergic to the agent.
  - Many agents are toxic to humans and some are *very* toxic.
  - With prolonged use, a broad-spectrum antibiotic may destroy the normal flora, resulting in an overgrowth of bacteria known as a *superinfection*.

Superinfection

- When beneficial species are destroyed, microbes that were once kept in small numbers can begin to overgrow and cause disease- a **superinfection**
  - Using a broad-spectrum cephalosporin for a urinary tract infection; destroys lactobacilli in the vagina; without the lactobacilli *Candida albicans* can proliferate and cause a yeast infection
  - Oral therapy with tetracyclines, clindamycin, and broad-spectrum penicillins and cephalosporins is associated with antibiotic-associated colitis

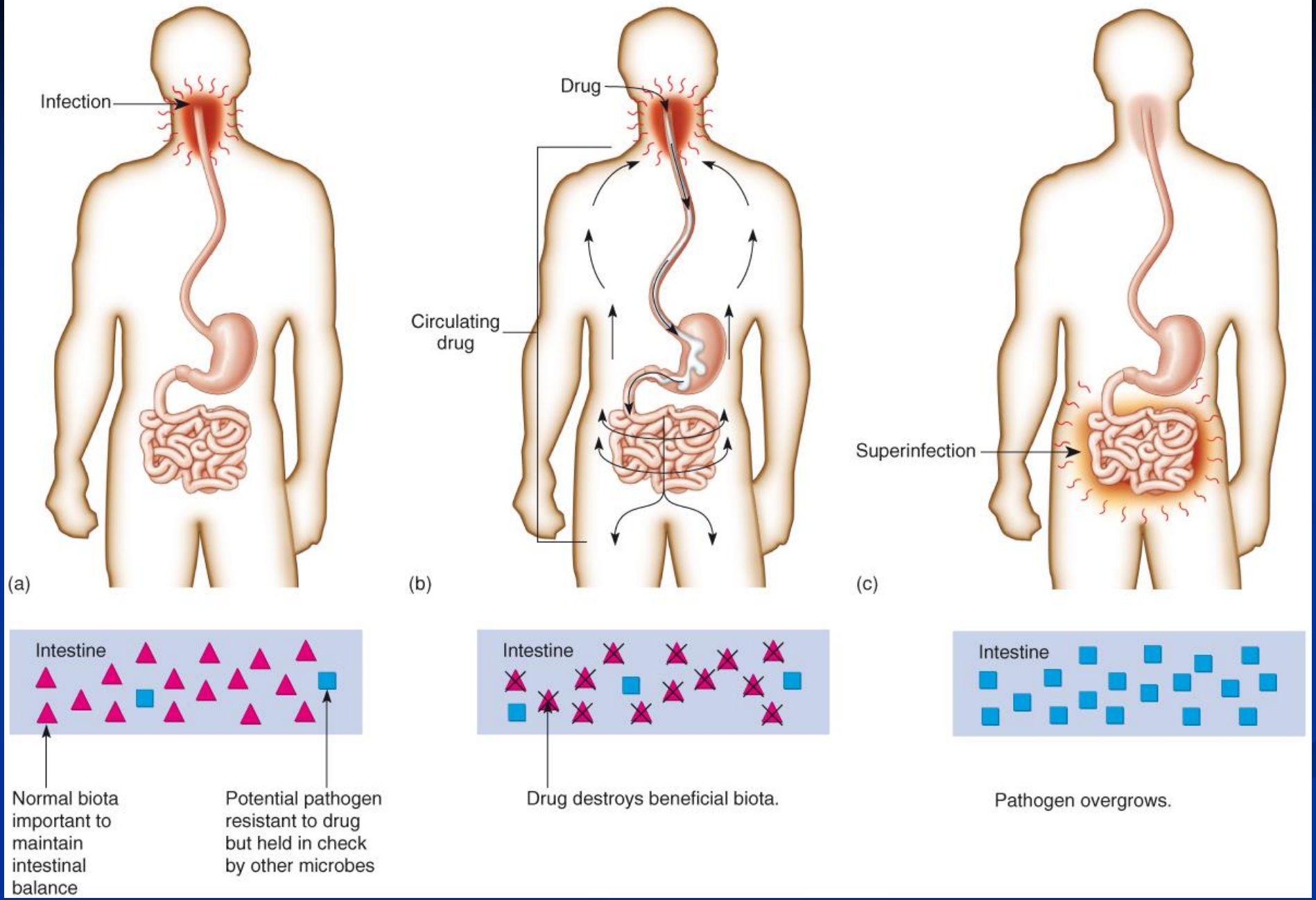


Figure 12.16

Side effects of antimicrobial agents

- Allergic reactions (Penicillin)
- Superinfection
- Nefrotoxicity (amfoterisin B, aminoglycosides, vancomycin)
- Hepatotoxicity (erytromycin, isoniazid, rifampin, ketakonazol)
- Neurologic disorders (aminoglycosides, etambutol, isoniazid)
- Myelosuppression (chloramphenicol, macrolides, flusitozin)
- Teratogenity (aminoglycosides, quinolones, tetracyclins, sulfonamides, chloramphenicol)

Empiric Therapy

- *Empiric therapy* is when drug therapy is initiated before laboratory results are available (i.e., before the pathogen is identified and/or before susceptibility test results are available).
  - Empiric therapy is sometimes necessary to save a patient's life.
  - Clinicians make an "educated guess" based on past experience with the type of infectious disease and the most effective drugs.
- Clinicians must take a number of factors into consideration before prescribing antimicrobial agents.

Empiric Therapy Selection

- **Patient Characteristics**
  - age, immune function, other disease states, pregnancy, renal/hepatic function
- **Site of Infection**
- **Drug Characteristics**
  - efficacy, side effects, tissue penetration, cost

Considerations in Selecting an Antimicrobial Drug

- Three factors must be known
  - The nature of the microorganism causing the infection
  - The degree of the microorganism's susceptibility to various drugs
  - The overall medical condition of the patient
- Identifying the Agent
  - Direct examination of body fluids, sputum, or stool is a rapid initial method
  - The choice of drug will be based on experience with drugs that are known to be effective against the microbe: the "informed best guess"
- Testing for the Drug Susceptibility of Microorganisms

Host factors to be considered in selection of antimicrobial agents

- Renal and hepatic function
- Age
- Genetic variation
- Pregnancy and lactation
- History of allergy or intolerance
- History of recent antimicrobial use

Prophylactic Therapy

The antibiotic given when there is likelihood of microorganisms being present and used to PREVENT infection

- Presurgical antimicrobial prophylaxis-

(a single dose cephalosporin (such as cefazoline) administered within 1 hour before the initial incision)

- Antimicrobial prophylaxis in immunocompromised patients-

(those with HIV infection, those who are undergoing chemotherapy for cancer, or those who are receiving immunosuppressive therapy after organ transplant)

- Antimicrobial prophylaxis to prevent transmission of communicable pathogens to susceptible contacts-

(for example macrolides can be prescribed to reduce transmission of pertussis, ciprofloxacin can be given to close contacts of a patient with meningitis caused by N. Meningitidis)

- Antimicrobial prophylaxis before dental and other invasive procedures in patients susceptible to bacterial endocarditis
- Traumatic injuries with a high probability of infectious complications

Combination Therapy

- To prevent the emergence of resistance

-M.tuberculosis

- To treat polymicrobial infections
- To give prompt treatment in desperately ill patients suspected of having a serious microbial infection.
- To achieve bactericidal synergism or to provide bactericidal action

When two antimicrobial agents act simultaneously on a homogeneous microbial population, the effect may be one of the following:

(1) indifference, ie, the combined action is no greater than that of the more effective agent when used alone;

(2) addition, ie, the combined action is equivalent to the sum of the actions of each drug when used alone;

(3) synergism, ie, the combined action is significantly greater than the sum of both effects; or

(4) antagonism, ie, the combined action is less than that of the more effective agent when used alone.

Disadvantages

(1) The physician may feel that since several drugs are already being given, everything possible has been done for the patient, leading to relaxation of the effort to establish a specific diagnosis. It may also give a false sense of security.

(2) The more drugs that are administered, the greater the chance for drug reactions to occur or for the patient to become sensitized to drugs.

(3) The cost is unnecessarily high.

(4) Antimicrobial combinations usually accomplish no more than an effective single drug.

(5) Very rarely, one drug may antagonize a second drug given simultaneously

Misuses of antibiotics

- Treatment of untreatable infections
- Therapy of fever of unknown origin
- Improper dosage
- Inappropriate reliance on chemotherapy alone
- Lack of adequate bacteriological information

Reasons for Treatment Failure

- Delay in diagnosis or therapy
- Wrong or incomplete diagnosis
  - No infection
  - Nonbacterial infection
  - Polymicrobial infection
- Errors in susceptibility testing
- Decreased activity at site of infection

Reasons for Treatment Failure

- Inadequate concentration of antibiotic at the site of infection
  - Improper dose
  - Decreased absorption from food or drug interaction
  - Increased elimination of agent
  - High protein binding
  - Poor delivery (eg. shock, vascular diseases)

Reasons for Treatment Failure

- Other host factors
  - Collection requiring drainage
  - Necrotic tissue
  - Foreign body
- Impaired immune defenses
- Development of drug resistance
- Superinfection

References

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