Introduction to Chemotherapeutic Agents

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Antimicrobial Agents

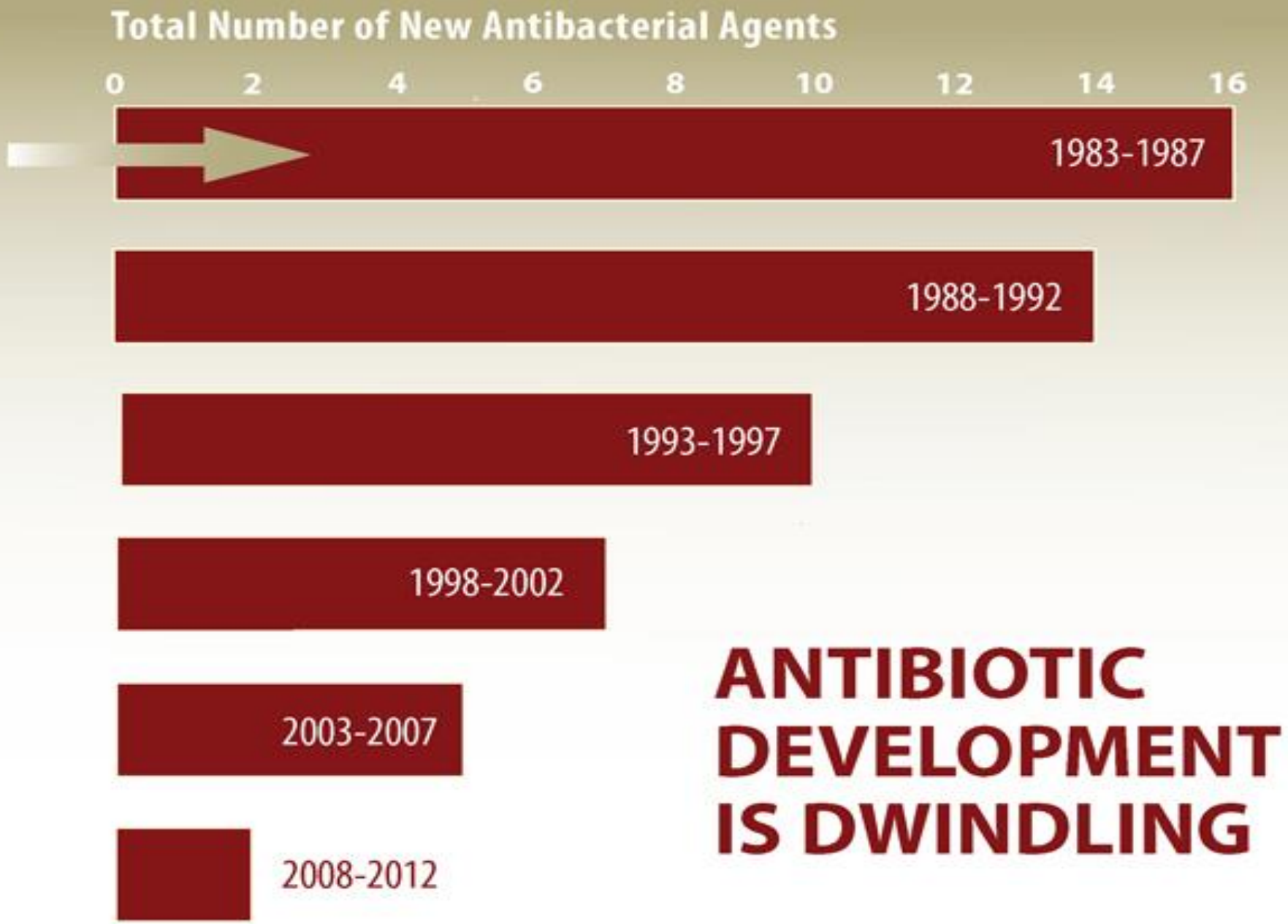
- **Substances that kill bacteria without harming the host.**
- **History:**
  - **Arsenic: 1800s for syphilis.**
  - **Sulfonamides: 1935.**
  - **Penicillin(Antibiotics): 1940.**
  - **Antimicrobials have revolutionized the treatment of bacterial infections as well as enhanced the advancement of medical and surgical treatment.**
  - **Patient's natural resistance plays a major role.**

Importance of Antimicrobials

- Helped control, treat, eradicate, and prevent many serious and very common diseases(syphilis, gonorrhea, TB).

  Military importance

- Enhanced the outcomes of many aggressive or new surgical and instrumental procedures(heart surgery, laparoscopy).
- Penicillin discovery was listed as the most important drug discovery in the 20th century.



Source: *The Epidemic of Antibiotic-Resistant Infections*, CID 2008:46 (15 January)
Clin Infect Dis. (2011) May 52 (suppl 5): S397-S428. doi: 10.1093/cid/cir153

Definitions

- **Chemotherapeutic agent:**
  - Any chemical compound that selectively acts on microbes or cancer cells.
- **Antimicrobial Agent:**
  - An agent(natural, semisynthetic, or synthetic) that selectively kills or slows down the growth of microbes *in vitro* and in *in vivo* when used in low concentration.
- **Antibacterial Agent:**
  - An agent that kills or slows down the growth of bacteria.
- **Antibiotic Agent:**
  - A natural substance produced by a micro-organism to kill another microbe.

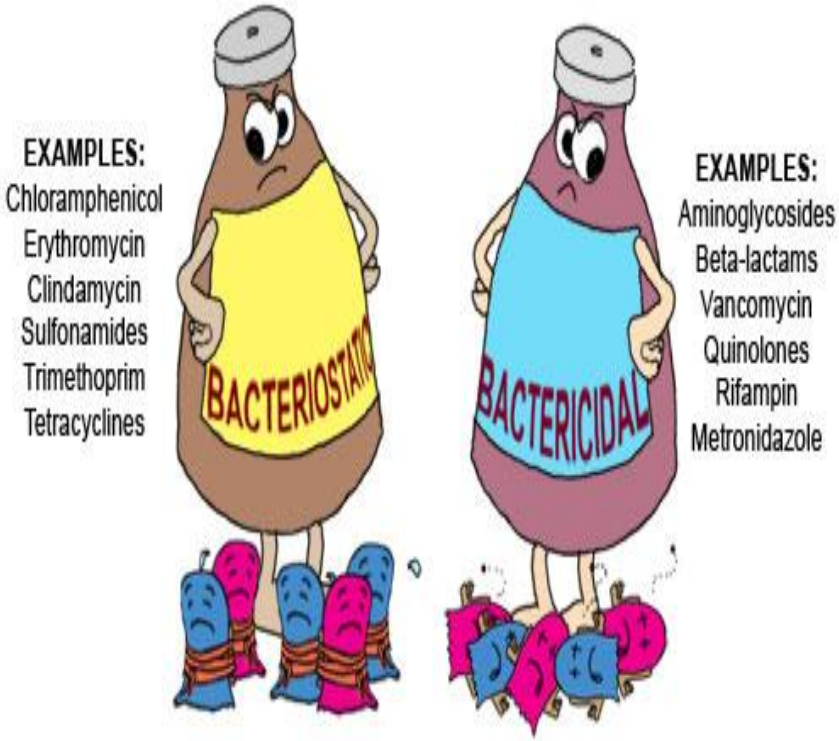
Definitions

- **Disinfectants:**
  - Agents that kill bacteria on the surface of objects like surgical instruments or floors:
    - Chemical: e.g. phenol which is too toxic for skin surfaces
    - Physical: ionizing radiation or high heat(sterilization and pasteurization)

- **Antiseptics:**
  - Agents used topically to affect bacteria on the surface of the skin, or mouth cavity. e.g. iodine or 70% alcohol

Classifications of Antibacterial Agents

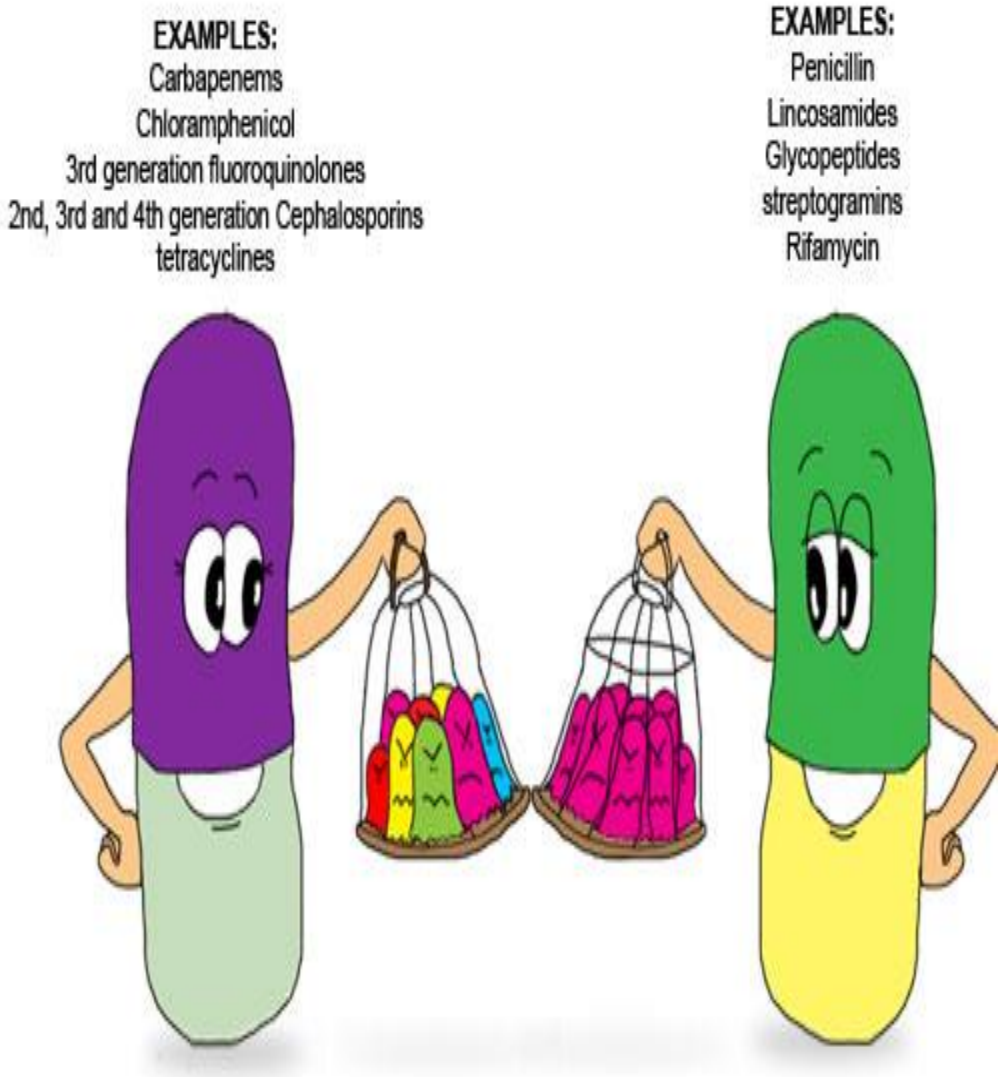
- *Antibacterials can be classified according to:*
- **Chemical Structures :**
  - Beta lactams, Aminoglycosides, Sulphonamides, Quinolones. Etc....
- **Mechanism of Action**
- **Type of Action:**
  - Bacteriostatic
  - Bactericidial .
- **Spectrum of Activity:**
  - Antistaph, Anti TB, Anti Richetsia
- **Width of the Spectrum:**
  - Broad or Narrow



Narrow Spectrum vs Broad Spectrum

- Relates to the number of microbes that are susceptible to the action of the drug i.e. Narrow (limited number) or Broad (wide)
  - Penicillin G is a narrow spectrum drug because it is only effective against gram-positive microbes
  - Tetracyclines are broad spectrum drugs effective against gram-positive and gram-negative microbes.
  - Wide spectrum drugs might cause *Superinfection*
  - *Wide spectrum antimicrobial, does not mean superiority.*
- ***Note: Never confuse these terms with potency levels of the drugs or efficacy (i.e. Narrow are weak, and Broad are strong).***

Narrow Spectrum vs Broad Spectrum



Narrow Spectrum vs Broad Spectrum

- Broad spectrum antibiotics are used when the infectious agent is unknown.

- Narrow spectrum antibiotics are prescribed when the micro-organisms have been identified from tissue samples.

Mechanisms of Action

- Inhibition of Cell Wall Synthesis
- Disruption of Cell Membrane
- Inhibition of Protein Synthesis
- Interference with Metabolic Processes

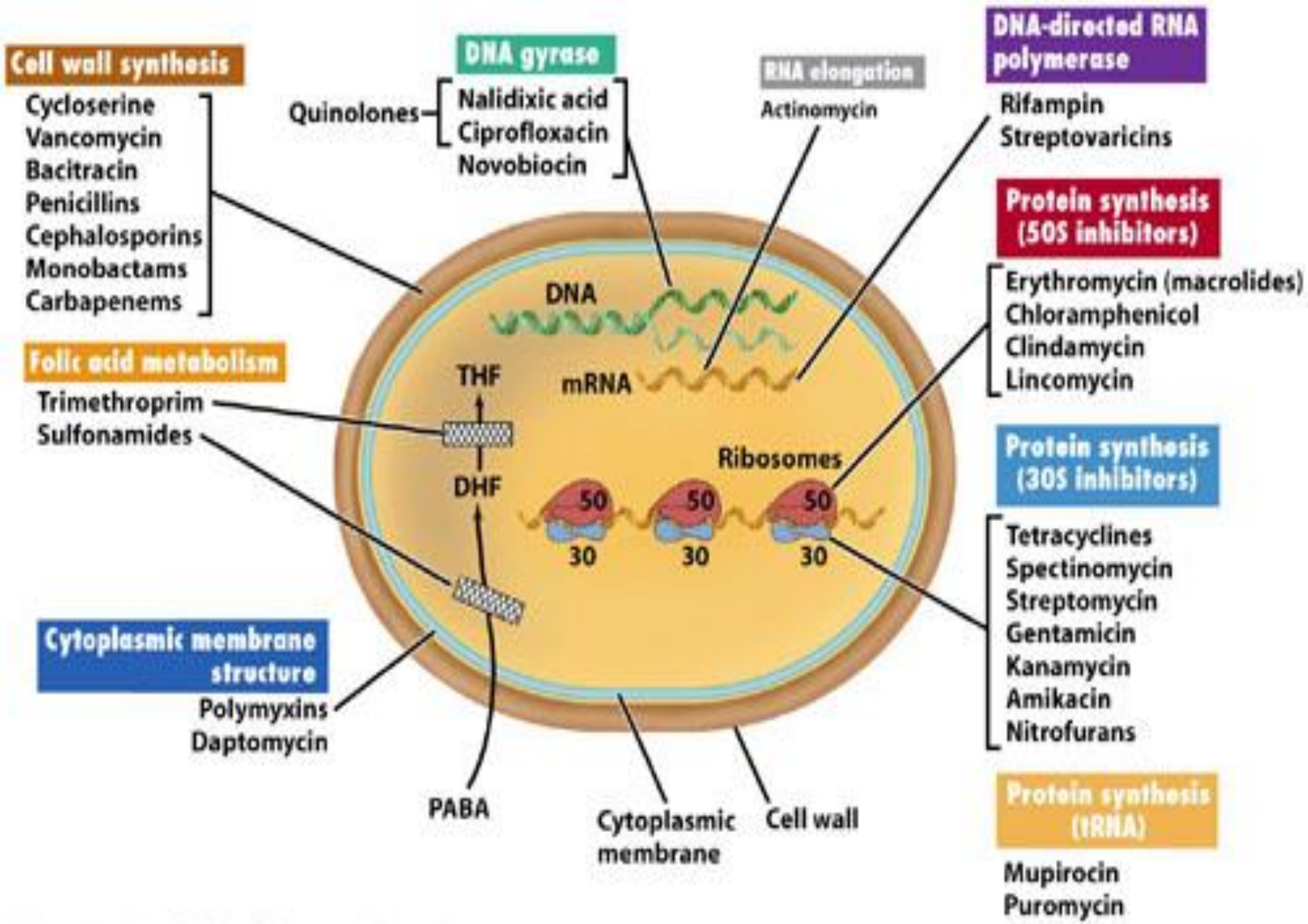
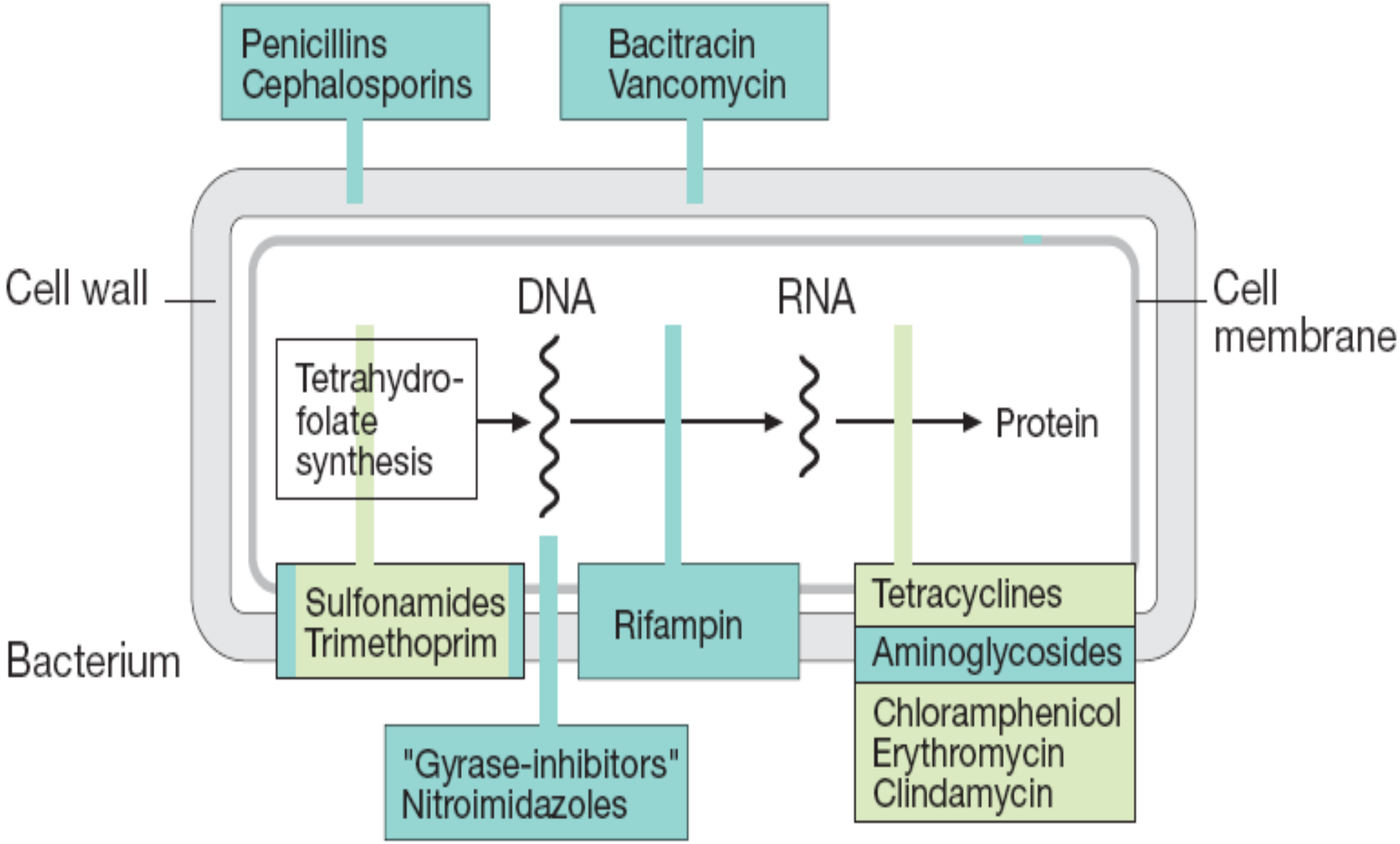


Figure 20-14 Brock Biology of Microorganisms 11/e

Main Targets of Antimicrobials



Summary of Common Antimicrobials

Beta-lactams (penicillins, cephalosporins)	**Broad-spectrum antibiotics. Flucloxacillin and co-amoxicillin are effective against some penicillin-resistant organisms.**
Aminoglycosides (streptomycin, gentamicin, tobramycin)	**Effective against gram negative bacteria e.g. *Pseudomonas*. Reserved for serious infections e.g. septicaemia, meningitis, hospital-acquired pneumonia.**
Glycopeptides (vancomycin, teicoplanin)	**Effective against *Staphylococci* resistant to other drugs, including many strains of MRSA.**
Tetracyclines (doxycycline, minocycline)	**Broad-spectrum antibiotics**

Summary of Common Antimicrobials

Macrolides (erythromycin)	**Broad-spectrum antibiotics, prescribed if patient is allergic to penicillins.**
Metronidazole	**Prescribed for surgical prophylaxis, bacterial vaginosis, pressure sores, leg ulcers.**
Quinolones (ciprofloxacin)	**Effective against gram negative bacteria, gonorrhoea, gastro-intestinal infections.**
Antitubercular drugs (rifampicin, isoniazid, rifabutin, streptomycin)	**Reserved for treatment/ containment of tuberculosis(TB).**
sulphonamides (co-trimoxazole, trimethoprin)	**Co-trimoxazole is reserved for serious infections associated with HIV/AIDS. Trimethoprin is prescribed for urinary tract infections.**

Inhibition of Cell Wall Synthesis

- Most bacteria possess a relatively rigid cell wall to protect from osmotic changes.
  - When bacteria divide, a new cell wall is synthesized.
  - Interruption of this synthesis, leads to new microbes which are susceptible(vulnarable) to external osmotic influences, causing cell rupture and death.
- Examples: Penicillins, cephalosporins, vancomycin and bacitracin

Disruption of the Microbial Cell Membrane

- This mechanism involves effects on cell membrane mechanisms of transportation leading to increased permeability of membranes, and consequently, external influences will have greater effect leading to death of the bacteria.
- Examples: Polymyxin, Colistin

Note: These agents are more toxic systemically than agents that inhibit cell wall synthesis.

Inhibition of Protein Synthesis

- Proteins are vital for growth and repair.
- These drugs act either at:
  - Site of protein synthesis (Ribosomes)
  - Within the nucleus by inhibiting synthesis of nucleic acids
    - DNA replication / RNA synthesis = TRANSCRIPTION
- Examples: Tetracyclines, aminoglycosides and macrolides (erythromycin)
- Drugs in this group exploit structural differences between microbial and human cells
  - **This effect inhibits growth, but does not lead to death.**
  - **High dose can lead to toxicity.**

Interference with Metabolic Processes

- Agents working through this mechanism are structurally similar to Para-aminobenzoic acid (PABA) which is a precursor of folic acid, which is necessary for nucleic acid and protein synthesis and consequently, bacterial growth.
  - Drugs in this group exploit microbial dependence on synthesizing their own folic acid, whilst humans get it from diet.
- Examples: Sulphonamides, Trimethoprim

Uses of Antimicrobials

- **Treatment of bacterial infections** in accordance with culture and sensitivity testing or knowledge of prevalent organisms.

- **Promoting growth of animal herds.**

- **Prophylaxis**:
  - surgery e.g. gastro-intestinal surgery, joint replacement.
  - meningitis contacts
  - surgical/ dental procedures in patients with artificial heart valves or heart valve lesions.

How Antibiotics Promote Animal Growth

- Stimulation of intestinal synthesis of vitamins by bacteria.
- Reduction in total numbers of bacteria in the intestinal tract with a lowering of competition between microorganisms and host animals for nutrients.
- Inhibition of harmful bacteria which may be mildly pathogenic or toxin-producing.

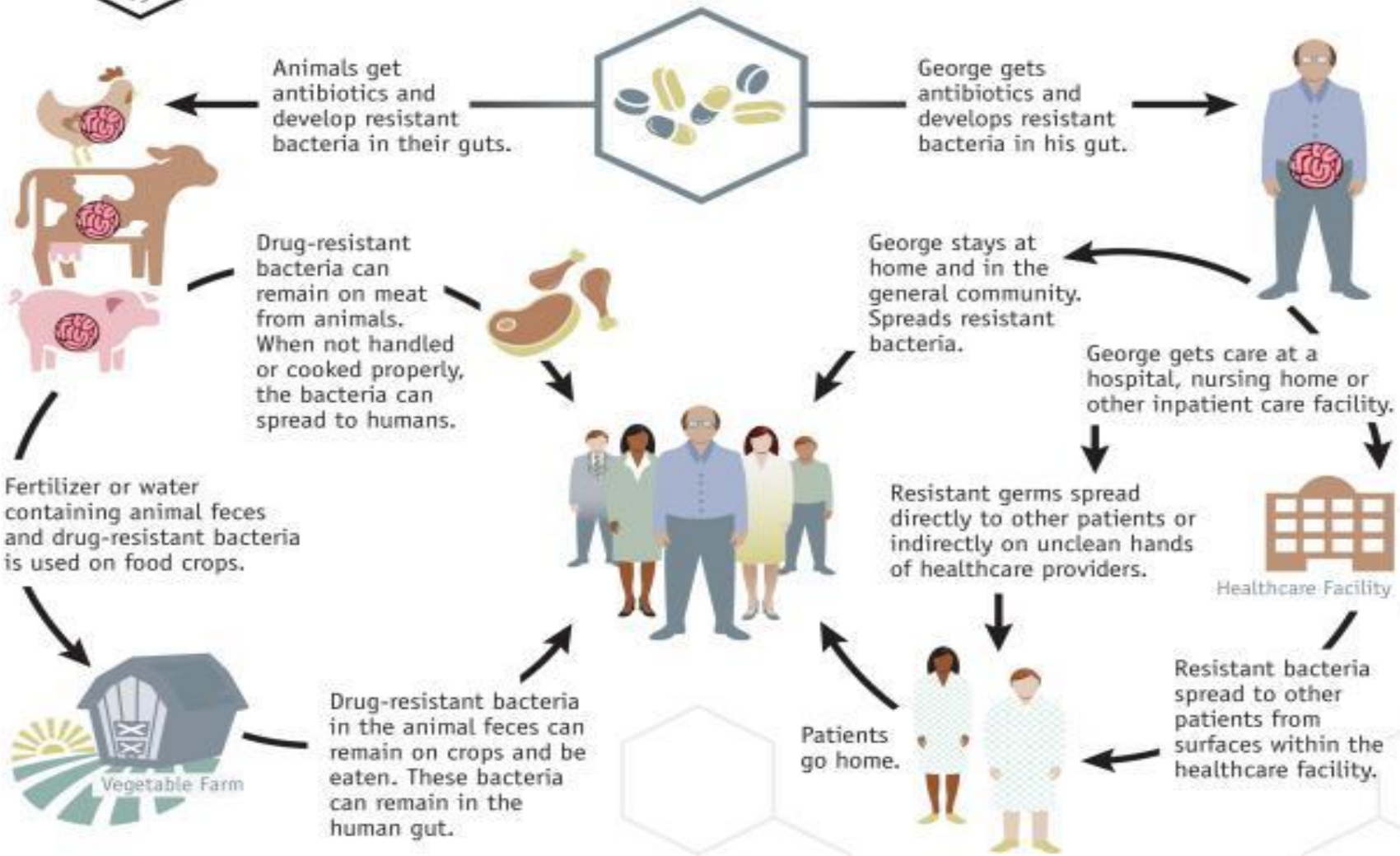
Antimicrobial Resistance

- **Primary Resistance:**
- **Acquired Resistance:**
  - By mutation (**about 1 in 10 million**)or by sharing the resistance genes of resistant organisms.
- **Clinical Resistance:**
  - Failure of an antimicrobial to eradicate infection, despite the apparent ability of the agent to kill the microbe ' in vitro.
  - May be due to impaired host immunity, inadequate drug delivery, and foreign material in the site of a wound.

Methods of Resistance

- **Diminished transport into the bacterium:**
  - The bacterium loses the porin that normally transports the antibiotic into the cell.
  - The bacterium has a pump that pumps out the drug.
- **Altered binding site:**
  - The PBP can still carry out its function, but the drug can no longer bind to it.
- **Enzymes that break down the antibiotic:**
  - Best examples are beta lactamases.
  - There are many other enzymes that break down aminoglycosides, chloramphenicol, and so on.
- **Multiple drug resistance involving all these mechanisms**

Examples of How Antibiotic Resistance Spreads



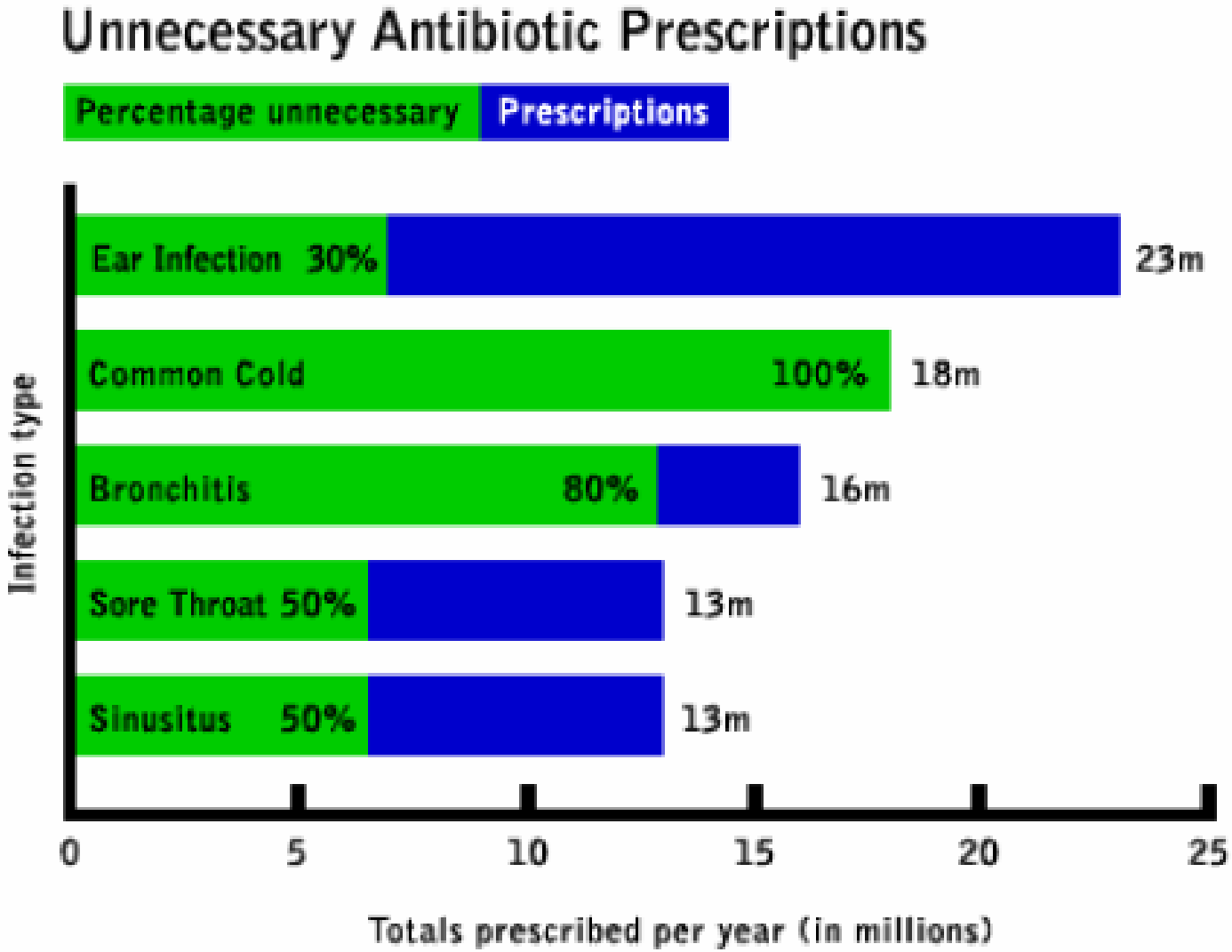
Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

Antimicrobial Misuse

- **Taking antimicrobials when they are not needed:**
  - **For undiagnosed fever**
  - **For viral infections**

- **Taking antimicrobials incorrectly:**
  - **Stopping treatment when symptoms disappear - not finishing the whole dose of the prescription to save for future use.**
  - **Sharing or using someone else's medicine.**
  - **Using a lower dose**

- **Antimicrobial misuse is the main cause for antimicrobial resistance.**



More than 50 million unnecessary antibiotic prescriptions are written each year in the United States for patients outside of hospitals, according the the Centers for Disease Control and Prevention

Choosing an Antibacterial

- The infecting organism.
- The correct antibacterial.
- Site of infection.
- Route of administration.
- Drug history of the patient.
- Complicating factors such as pregnancy.
- Cost.