Scientific approaches to the development of new chemotherapeutic drugs

Chemotherapeutic Agents

Classification and Basic Mechanisms of Action

Resistance Issues

Part 1

ANTISEPTIC
DESINFECTION

Antimicrobials

ANTIBIOTICS

CHEMICAL STRUCTURE

1. Sulfonamides
2. Diaminopyrimidines
3. Quinalones
4. ß-Lactam antibiotics
5. Tetracyclines
6. Nitrobenzene derivative
7. Aminoglycosides
8. Macrolide antibiotics
9. Lincosamide antibiotics
10. Glycopeptide antibiotics
11. Oxazolidinone
12. Polypeptide antibiotics
13. Nitrofuran derivatives
14. Nitroimidazoles
15. Nicotinic acid derivatives
16. Polyene antibiotics
17. Azole derivatives:

MOA

1. Inhibit cell wall synthesis
2. Cause leakage from cell membranes.
3. Inhibit protein synthesis.
4. misreading of m-RNA code and affect permeability.
5. Inhibit DNA gyrase.
6. Interfere with DNA function.
7. Interfere with DNA synthesis.
8. Interfere with intermediary metabolism.

EFFECT ON BACTERIA

STATIC

1.Chloramphenicol
2.Sulfonamide
3.Tetracycline
4.Macrolide
5.oxazolidone

CIDAL

TIME

1.ß-Lactam
2.Isoniazid
3.Metronidazole
4.Pyrazinamide
5.Rifampin
6.Vancomycin

CONCENTRATION

1.Aminoglycoside
2.Bacitracin
3.Quinolones

STATIC/CIDAL

1.Macrolides
2.Lyncosamide
3.ß-Lactam

ANTIFUNGAL

ANTIVIRAL

ANTIPARASITIC

ANTIPROTOZOAL

Categories of antiseptic and disinfection

- **Microbicial and microbiostatic**

✓Chemicals that kill (fungicidal, bactericidal, virucidal)

✓Chemicals that reduce or inhibit growth (-static) – bacteriostatic, fungistatic

✓The difference between cidal and static is related to the concetration of the chemical used and the amount of the time it remains in contact with the surface

Categories of antiseptic and disinfection

- **Sterilization**

✓Complete eradication of all spores and microorganisms

✓Achieved by using high-pressure steam in autoclaves

✓Chemicals are used to disinfect a room

✓Disinfection and sterilization are different terms

✓Disinfection removes many microorganisms but does not remove spores

Categories of antiseptic and disinfection

- **Cleaning technique**

✓Surfaces must be cleaned thoroughly before applying a disinfectant

✓Combination of alcohol, phenols, or iodophors may washed over the area

✓Disinfectant –to surface contact time is important in cleaning

Clinical uses of antiseptics and disinfectants

antibiotics	antiseptics	disinfectant
Kill pathogens in the bloodstream Targetes at specific mocroorganisms Easily available	Cleanse and irrigate wounds, cuts, abrasions Prepare patiens' skin prior to procedures Do not cause skin sensitivity	Clean and store surgical instruments Disinfect operating room walls and floors Sterilize object through cold sterilization

Common chemicals that inhibit infectious microorganisms

- **Alcohol: ethyl and isopropyl alcohol**

✓Ethyl alcohol is bactericidal at all concentrations of less than 70%

✓Isopropyl alcohol is bactericidal at all concentrations

✓Alcohol can be used alone or in combination with other compound

✓Prep wipes contain isopropyl alcohol

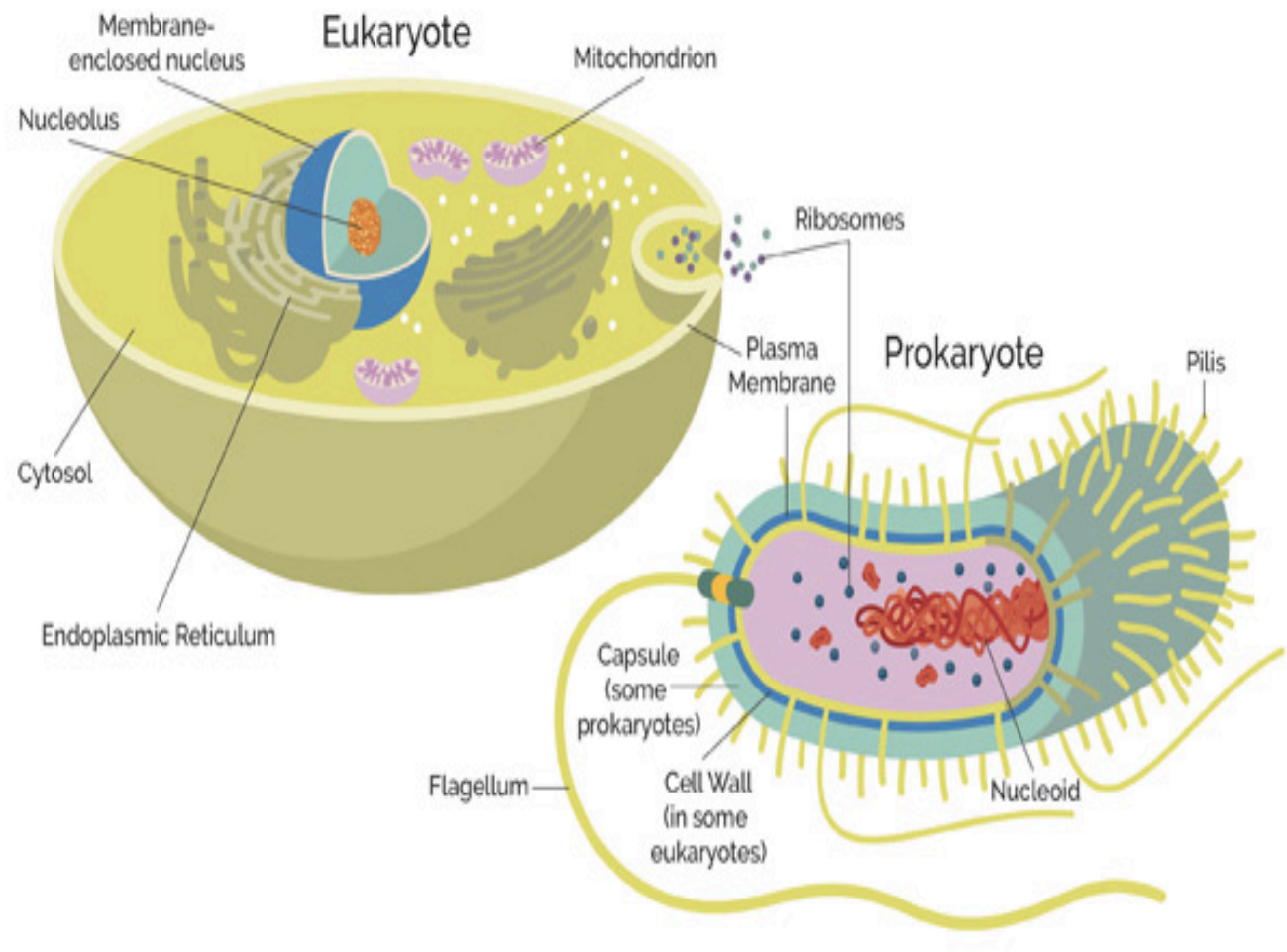
- Peroxides: hydrogen peroxide, benzoyl peroxide (used to medically clean wounds, to remove dead tissue, as an oral debriding agent), chlorhexidine (oral rinse and bleeding of gum)

The magic bullet is a scientific concept

Paul Ehrlich formed an idea that it could be possible to kill specific microbes (such as bacteria), which cause diseases in the body, without harming the body itself.

Differences between prokaryotes and eukaryotes

	Prokaryote	Eukaryote
Nucleus	Absent	Present
Membrane-bound organelles	Absent	Present
Cell structure	Unicellular	Mostly multicellular; some unicellular
Cell size	Smaller (0.1-5 µm)	Larger (10-100 µm)
Complexity	Simpler	More complex
DNA Form	Circular	Linear
Examples	Bacteria, archaea	Animals, plants, fungi, protists



Mechanisms of Antibiotics

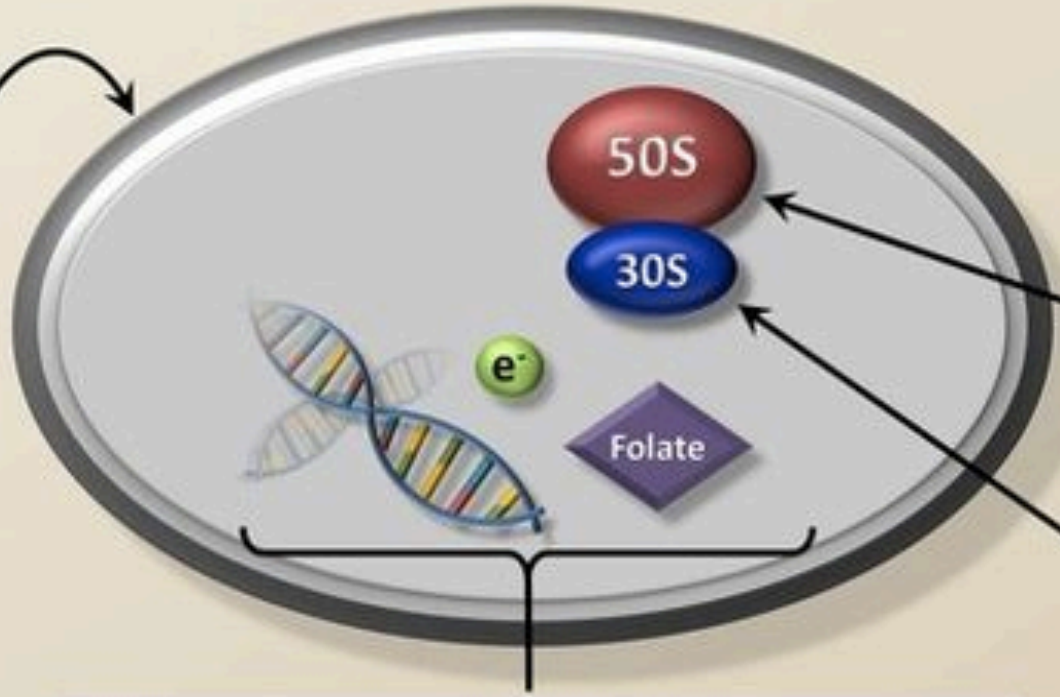
Inhibit Cell Wall Synthesis or Function

Beta Lactams
- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams

Vancomycin

Daptomycin

Polypeptides



Inhibit Protein Synthesis

Inhibit 50S subunit
- Macrolides
- Clindamycin
- Linezolid
- Streptogramins
- Chloramphenicol

Inhibit 30S Subunit
- Aminoglycosides
- Tetracyclines
- Tigecycline

Inhibit Nucleic Acid Synthesis or Function

Inhibit DNA Gyrase +/- Topoisomerase IV: Quinolones

Inhibits Folate Synthesis: Trimethoprim / Sulfamethoxazole

Create Free Radicals: Metronidazole, Nitrofurantoin

Bactericidal	Bacteriostatic
Bactericidal refers to agents that kill bacteria	Bacteriostatic refers to agents that prevent the growth of bacteria
Action is irreversible	Action is reversible
Inhibit the cell wall formation of bacteria	Inhibit DNA replication and protein synthesis of bacteria
Do not work with the immune system of the host	Work with the immune system of the host to prevent the growth and reproduction of bacteria
Minimal Bactericidal Concentration (MBC) refers to the concentration of the drug required to kill 99.99% of the bacterial population	Minimal Inhibitory Concentration (MIC) is the minimum drug concentration which inhibits the bacterial growth
Examples include betalactam antibiotics, cephalosporins, and vancomycin	Examples include tetracyclines, spectinomycin, chloramphenicol, sulfonamides, etc.

HOW ANTIBIOTIC RESISTANCE HAPPENS

1

There are lots of germs and a few are resistant to **antibiotics**.

2

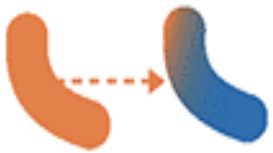
When **antibiotics** kill bacteria causing illness, they also kill good bacteria protecting the body from infection.

3

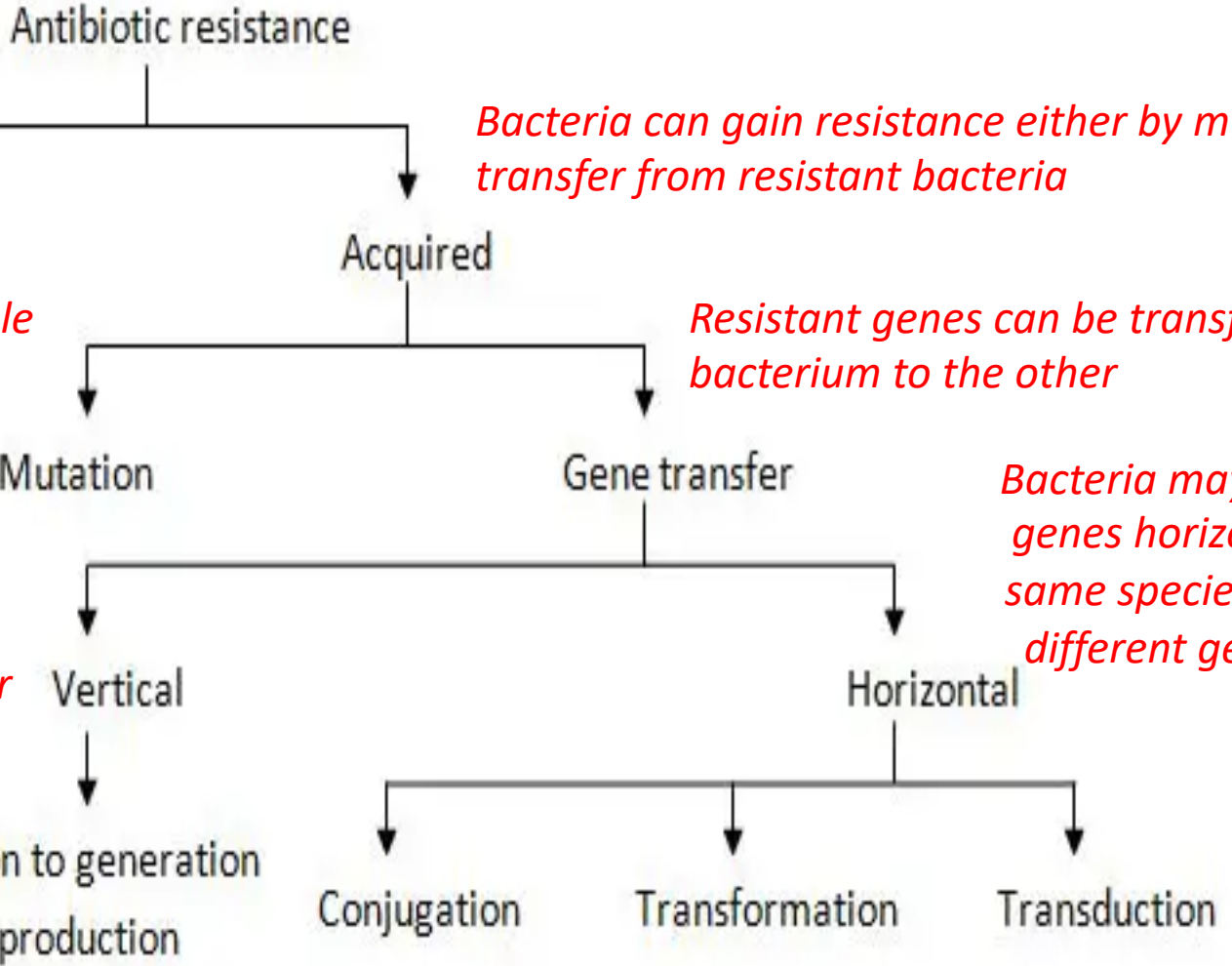
The **antibiotic-resistant** bacteria grow and take over.

4

Some bacteria give their **antibiotic resistance** to other bacteria, causing more problems.



Ways of gaining a resistant gene by bacteria



Bacteria can gain resistance either by mutation or a gene transfer from resistant bacteria

is a stable, heritable change of an organism's gene

Resistant genes can be transferred from one bacterium to the other

Bacteria may transfer resistant genes horizontally among the same species or even between different genera and species

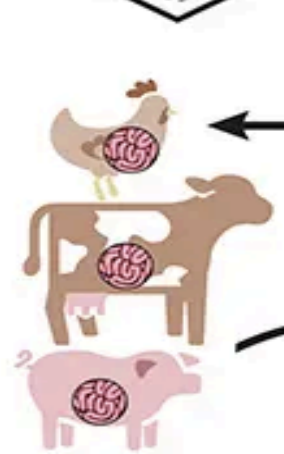
Resistant gene is transferred from one generation to another generation by reproduction.

Bacteriophage invades an antibiotic-resistant bacterium, the resistant gene of the bacterium is packaged into the head portion of the phage

is a mating process through which genes are transferred through the temporary fusion of the mating partners

Bacterium containing resistant genes dies, its DNA releases outside.

Examples of How Antibiotic Resistance Spreads



Animals get antibiotics and develop resistant bacteria in their guts.

George gets antibiotics and develops resistant bacteria in his gut.

Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.

George stays at home and in the general community. Spreads resistant bacteria.

George gets care at a hospital, nursing home or other inpatient care facility.

Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.

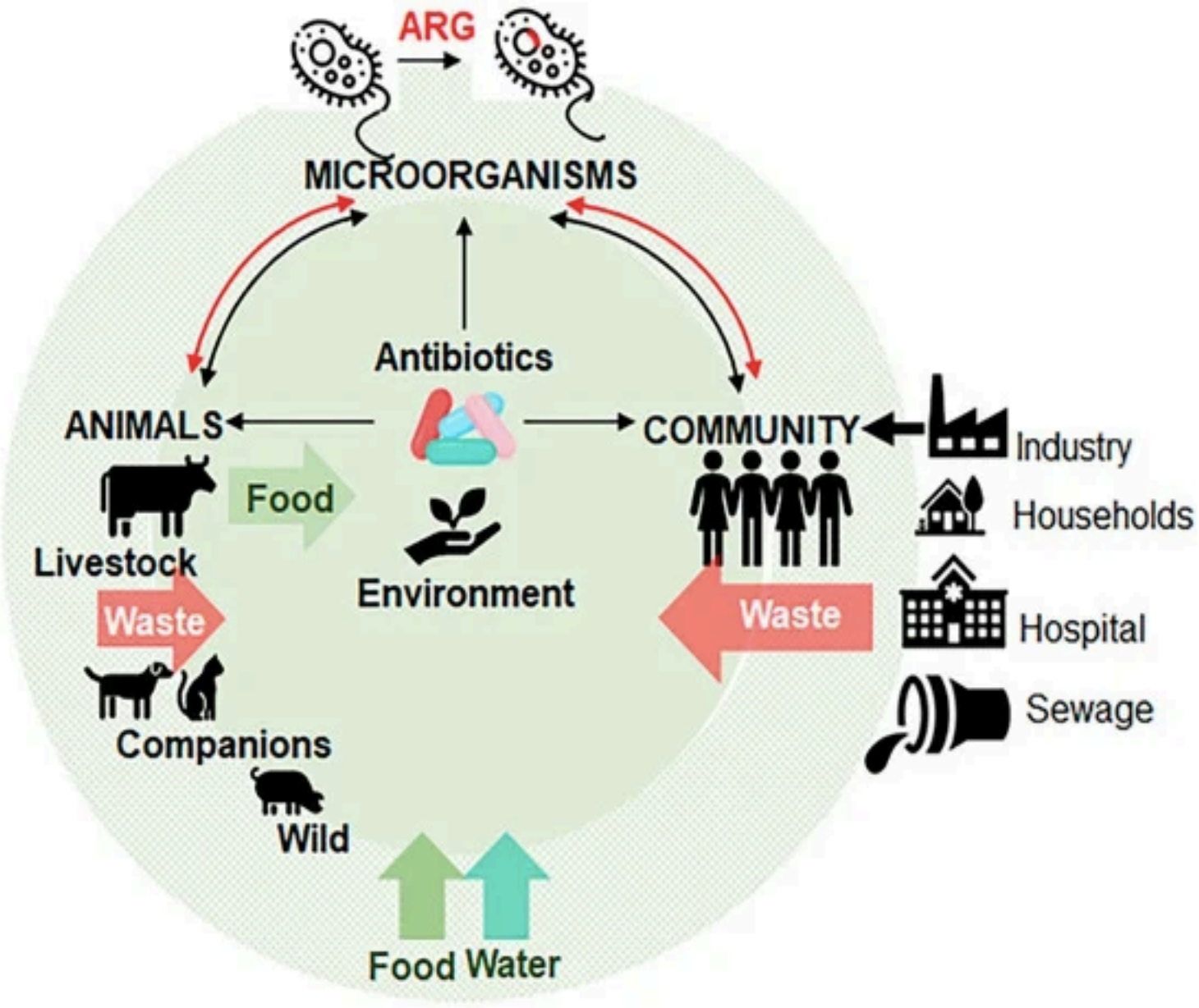
Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.

Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.

Patients go home.

Resistant bacteria spread to other patients from surfaces within the healthcare facility.

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



- Schematics of the major route of antibiotic resistance genes (ARG, a red inserted line) dissemination in environment.
- The diagram indicates the contribution of human communities to the production of antibiotics and their uses in hospitals, farms, and households.
- Generated antibiotic waste is released onto sewage, hence contaminating water, soil, and environment.
- Bacteria develop ARG mutations as a result of such exposure to antibiotics in the environment, and in human and animal hosts.
- ARG-containing bacteria spread in humans and animals through direct infections, food, or environment. The arrows indicate the putative transmission paths of entry of antibiotics and ARG.