RECENT ADVANCES IN ANTIMICROBIAL THERAPY

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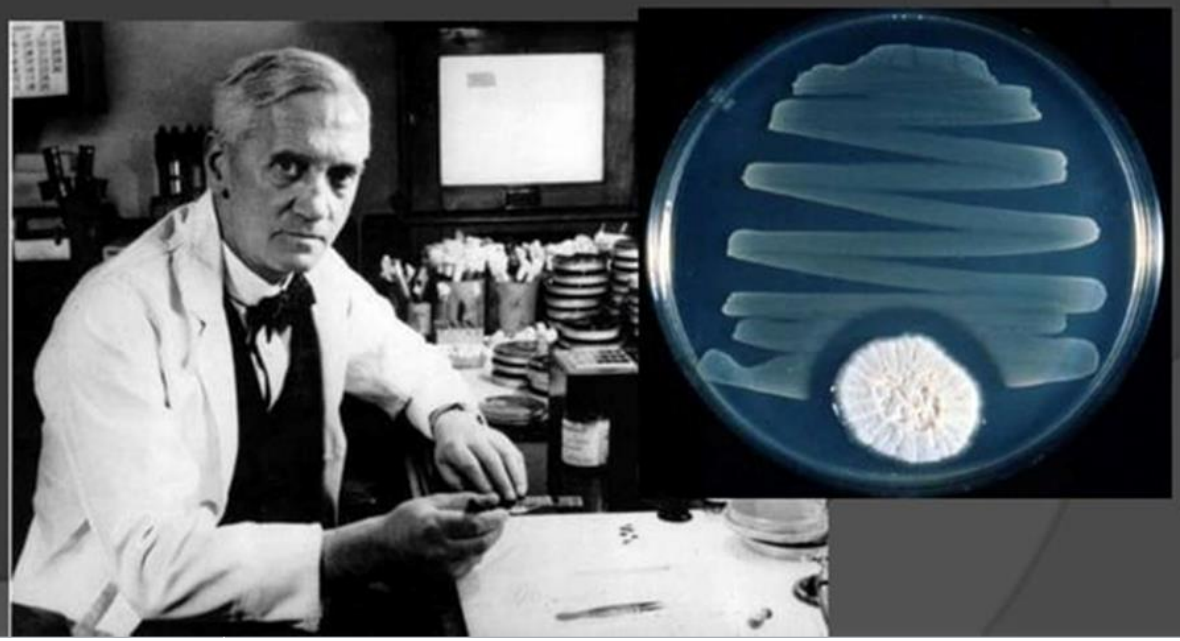
Introduction

- Modern medicine is dependent on chemotherapeutic agents
- Antibiotics are used to treat disease or prevent some types of bacterial infection
- Antibiotics destroy pathogenic microorganisms or inhibit their growth without damage to the host
- This selective toxicity is usually relative rather than absolute, requiring careful control of the drug concentration

- Drugs such as the sulfonamides are sometimes called antibiotics although they are chemotherapeutic agents, not microbially synthesized

.....History

Fleming and Penicillin



- Although penicillin was actually discovered in 1896 by a 21-year-old French medical student named Ernest Duchesne, his work was forgotten
- And penicillin was rediscovered (1928) and brought to the attention of scientists by the Scottish physician Alexander Fleming
- Selman Waksman announced in 1944 that he had found a new antibiotic, Streptomycin, produced by the *Streptomyces* griseus

- Waksman received the Nobel Prize in 1952, and his success led to a worldwide search for other antibiotic-producing soil microorganisms

Antibiotics based on their activity

- Chemotherapeutic agents, can be either cidal or static

- **Static agents** - Reversibly inhibit growth , if the agent is removed, the microorganisms can recover and grow again

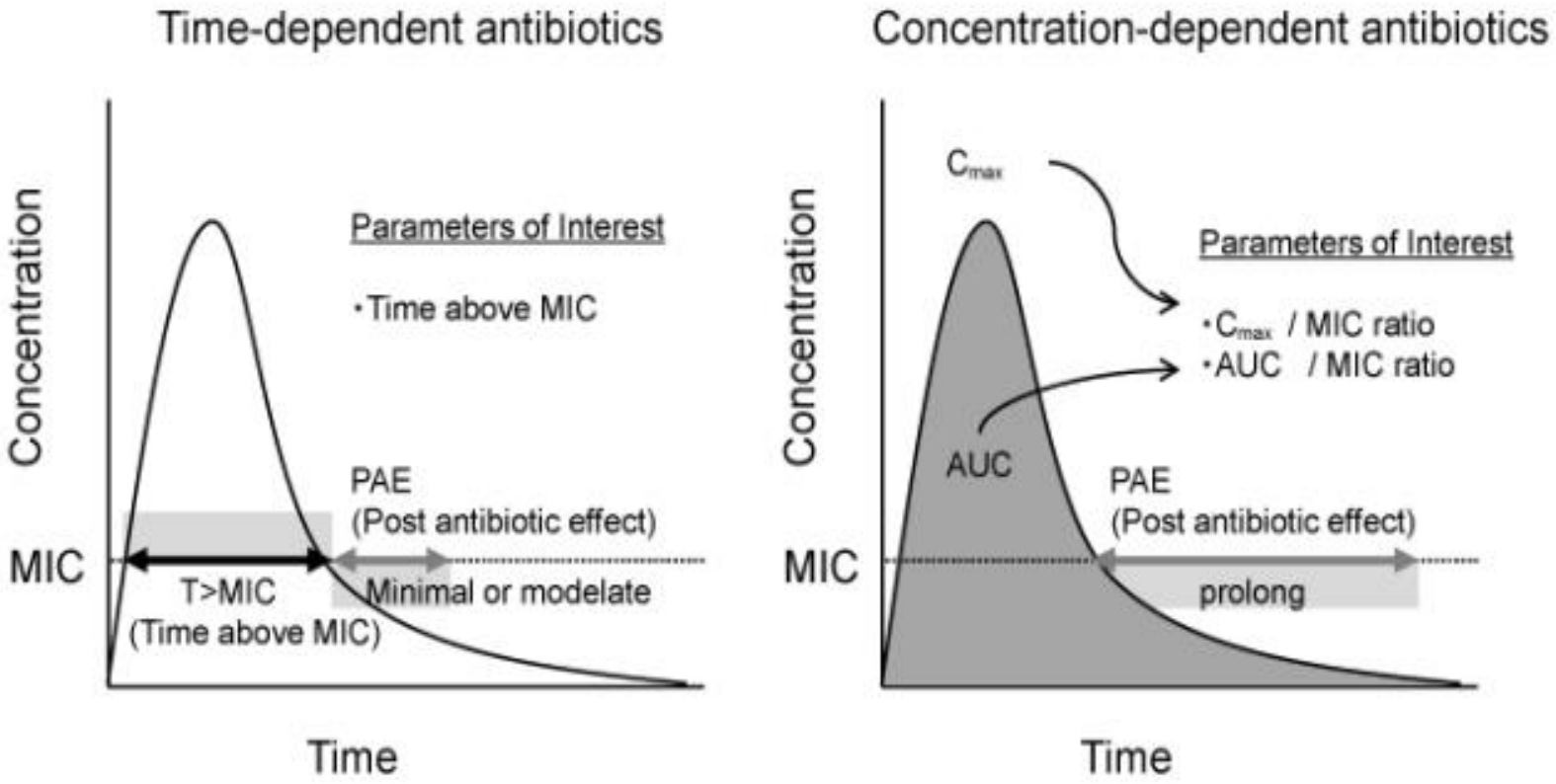
- **Cidal agents** - Kills the target pathogen, its activity is concentration dependent and the agent may be only static at low levels

- Chemotherapeutic agent against a pathogen can be obtained from the minimal inhibitory concentration

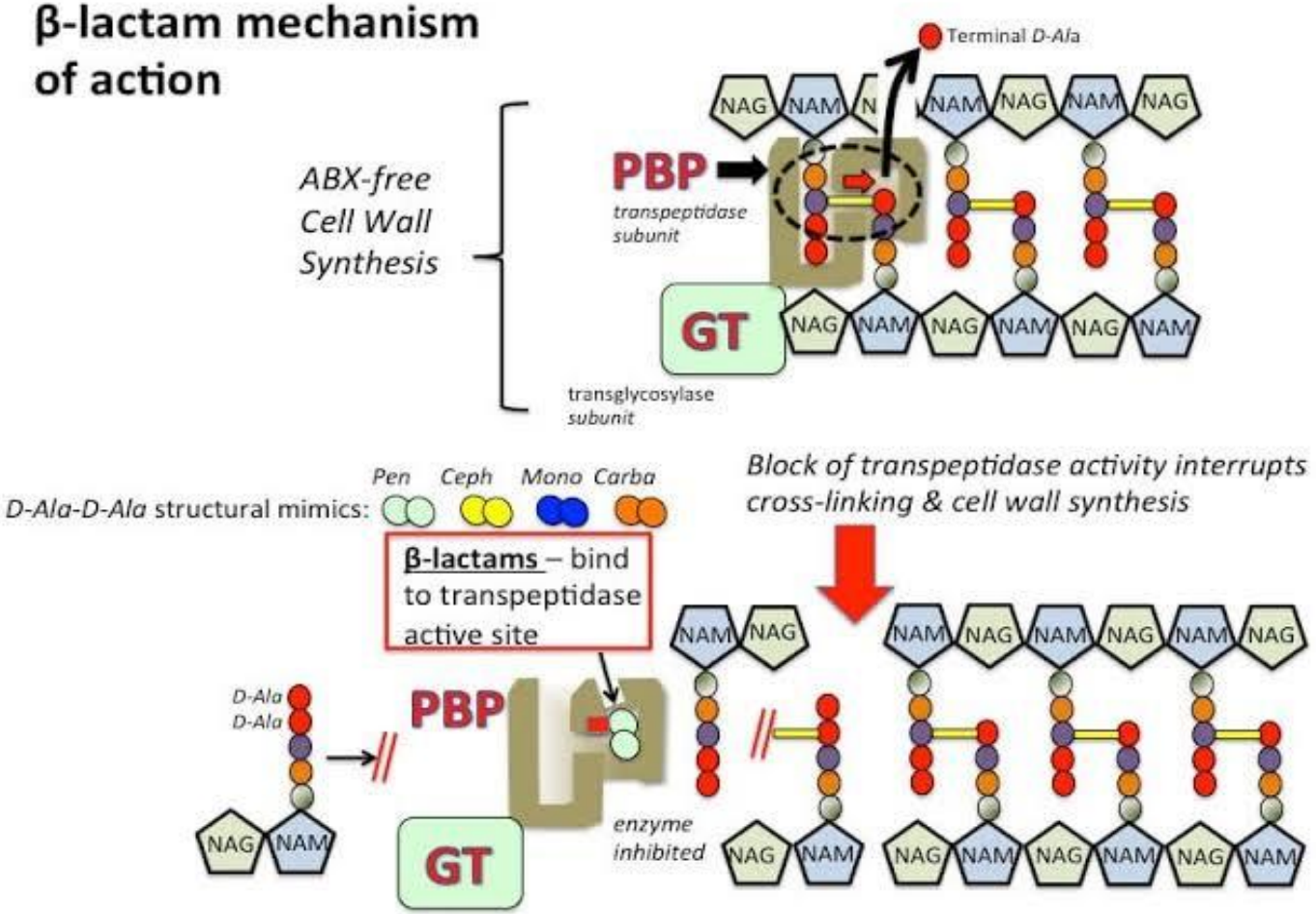
- **Minimum inhibitory concentration(MIC)** - The lowest concentration of a drug that prevents growth of a particular pathogen

- **Minimum lethal concentration(MLC)** - The lowest drug concentration that kills the pathogen

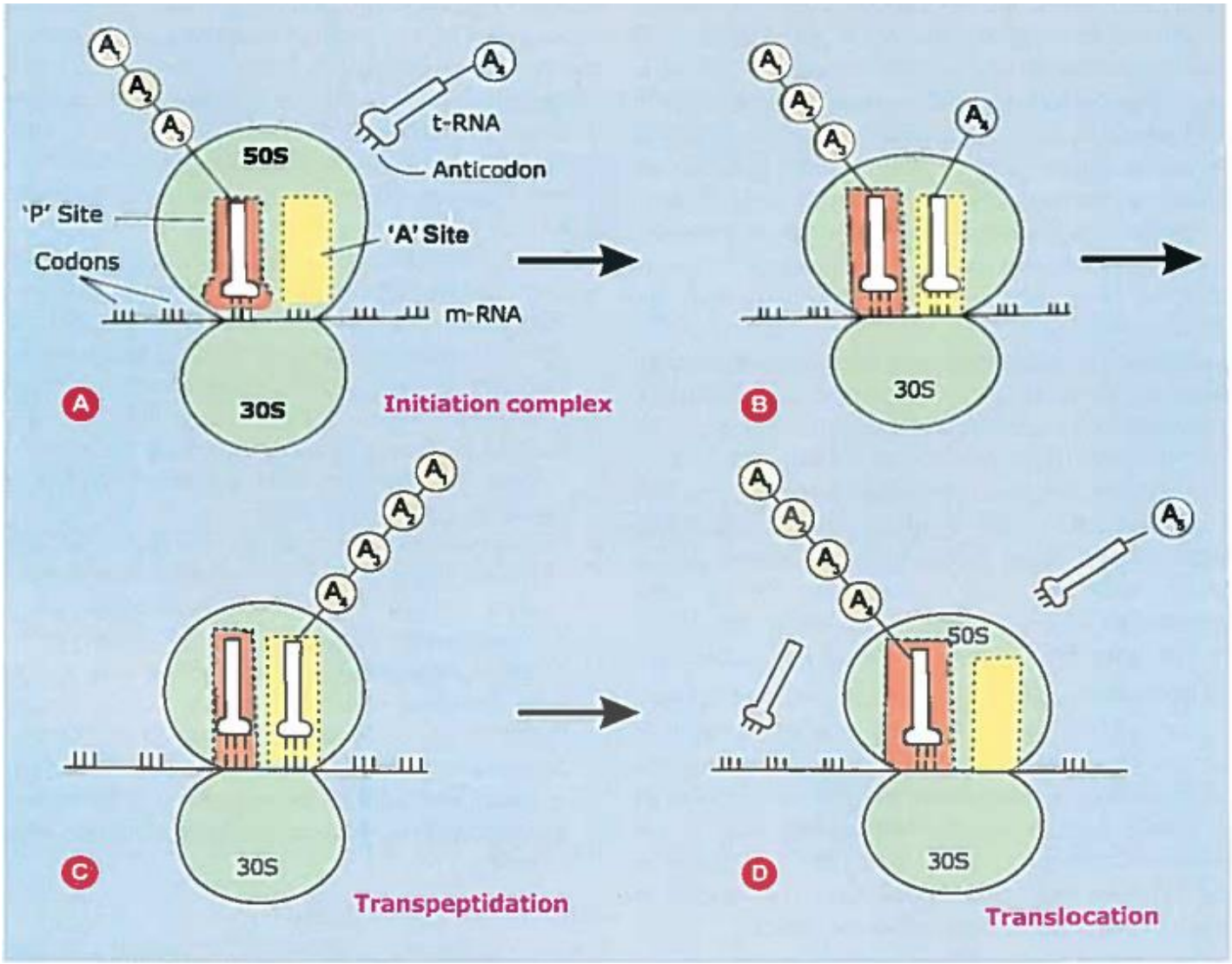
Postantibiotic Effect



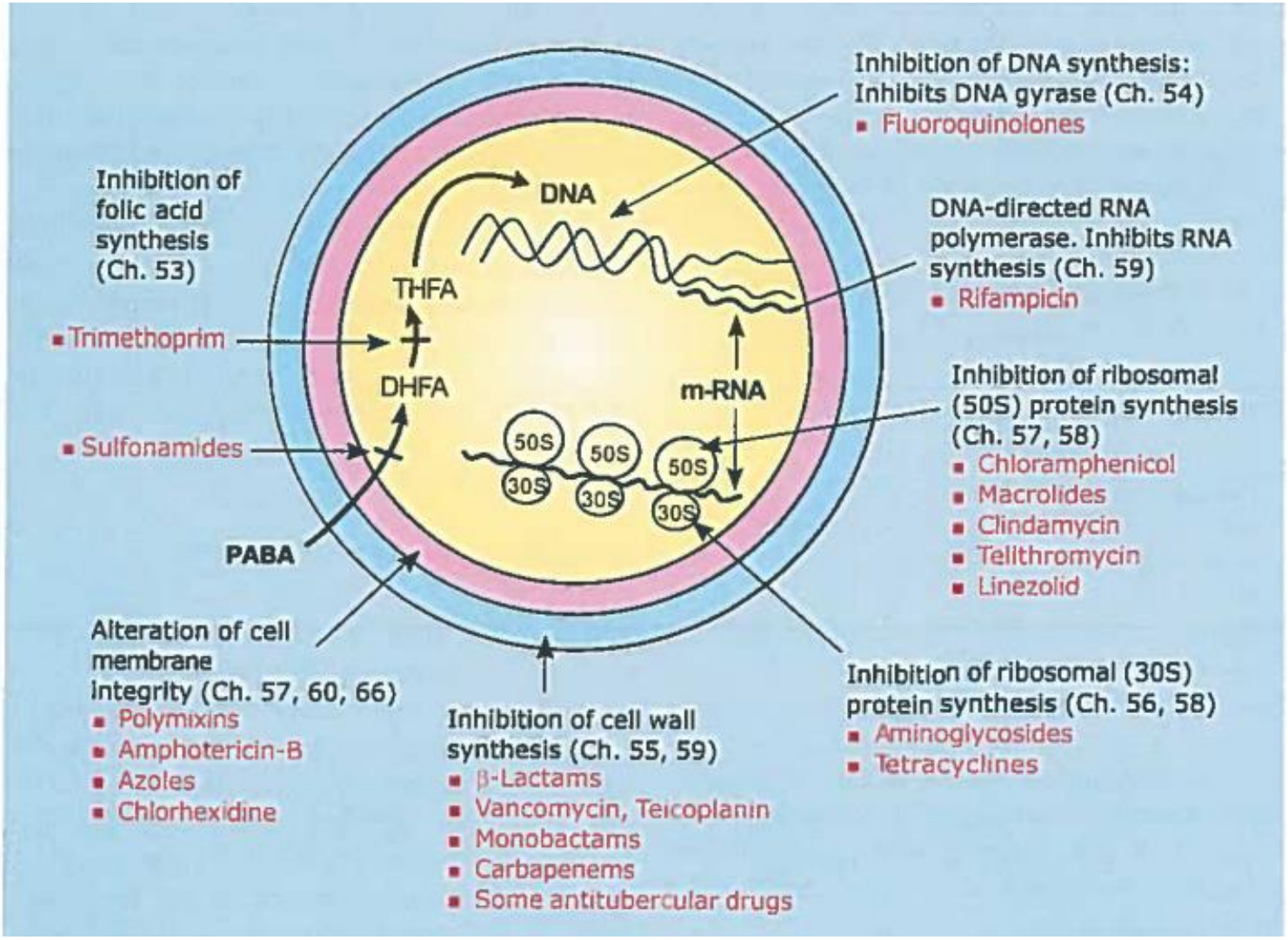
Biosynthesis of cell wall by the Bacteria



Steps in Bacterial Protein Synthesis



Classification of Some Antimicrobial Agents by Their Mechanism & Site of Action



- The biochemical processes commonly inhibited by Antimicrobial agents: -

a) Cell wall synthesis

a) Cell membrane synthesis

a) Ribosomal translation

a) Nucleic acid metabolism

- Recently, antisense antibiotics have been developed - **by inhibiting gene expression in bacteria in a sequence-specific manner**

Cell Wall Synthesis Inhibition

- Penicillin
- Ampicillin
- Carbenicillin
- Methicillin
- Cephalosporins
- Vancomycin
- Bacitracin

Protein Synthesis Inhibition

Streptomycin
Gentamicin
Chloramphenicol

Tetracyclines
Erythromycin and clindamycin
Fusidic acid

Nucleic Acid Synthesis Inhibition

Ciprofloxacin and other quinolones

Rifampin

Cell Membrane Disruption

Polymyxin B

Metabolic Antagonism

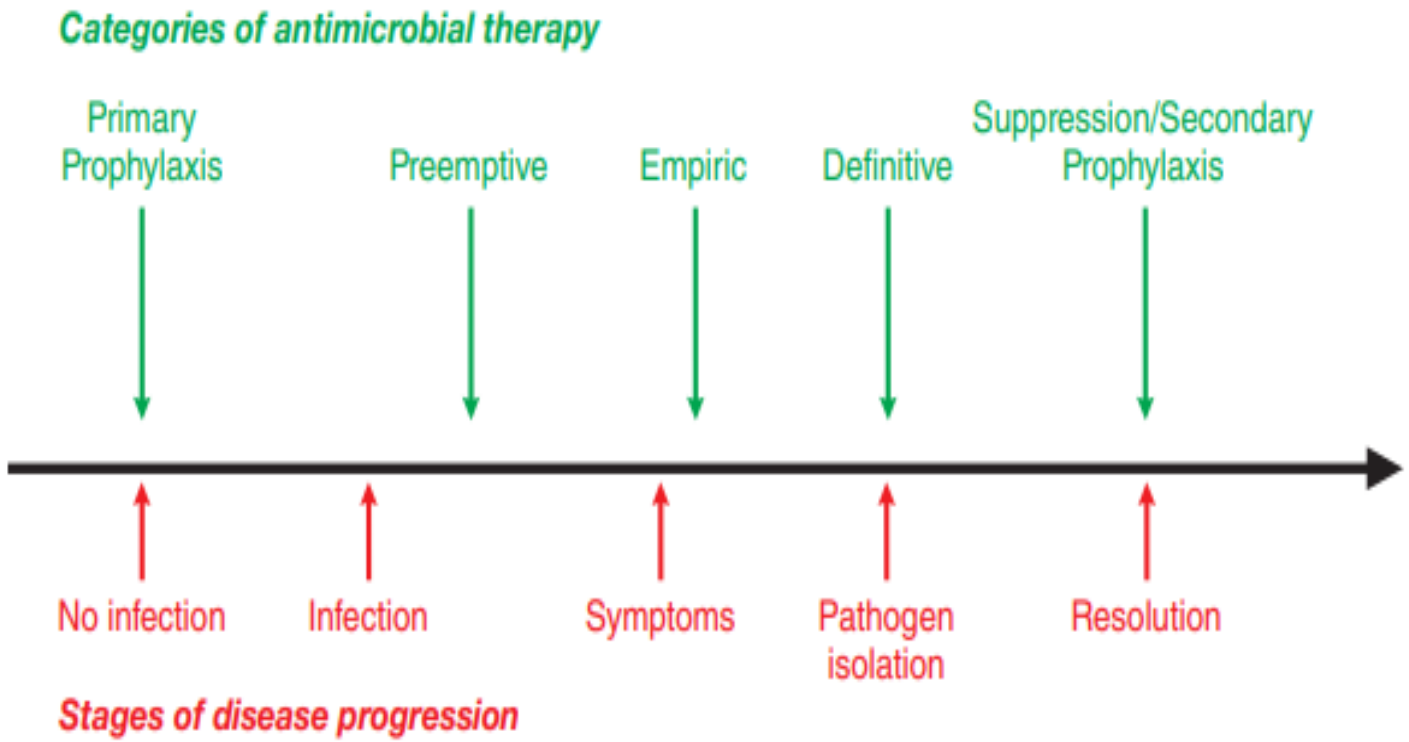
Sulfonamides

Trimethoprim

Dapsone

Isoniazid

Types and Goals of Antimicrobial Therapy



Antibiotic Resistance – WHO statement

- It is the biggest threats to global health, food security, and development today
- It can affect anyone, of any age, in any country
- Occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process

- A growing number of infections – such as pneumonia, tuberculosis, gonorrhea, and salmonellosis – are becoming harder to treat as the antibiotics used to treat them become less effective

- This leads to longer hospital stays, higher medical costs and increased mortality

Mechanisms of Resistance to Antimicrobial Agents

- Antibiotics were viewed as miracle cures when first introduced into clinical practice

- However, as became evident soon after the discovery of penicillin, resistance eventually developed

- Today, every major class of antibiotic is associated with the emergence of significant resistance

- Major mechanisms of antibiotic resistance include:

- Reduced concentration of the antibiotic at its target site

- Production of microbial enzymes that alter or destroy the antibiotic

- Alteration of antibiotic targets in ways that reduce antibiotic affinity

Why do we need newer antimicrobials

- Bacterial resistance to antimicrobials-health and economic problem
- Chronic resistant infections contribute to increasing health care cost
- Increase morbidity & mortality with resistant microorganisms

NEWER ANTIBACTERIALS

Oxazolidinones

- Considered to be the first truly new class of antibacterial drugs introduced in the past 3 decades

Linezolide-

✓ Approved for adults use in 2000

✓ Then approved for pediatric use in 2005

Newer Oxazolidinones

❑ **Drugs in pipeline:**

I. Radezolid

- Phase II clinical trial
- *Use*: uncomplicated skin and skin structure infections

II. Torezolid

- Phase II clinical trial
- *Use*: complicated skin and skin structure infections

❑ **MOA**: bind to the 23S portion of the 50S subunit of ribosome, preventing translation initiation

- **Advantage over Linezolid**:
  - Improved potency
  - Aqueous solubility
  - Reduced toxicity
- **Mechanism of resistance to older oxazolidinones**:- occurs due to mutations in ribosomal RNA (rRNA)
- **Resistance overcome by**:- additional hydrogen bond interactions with 23S rRNA

Newer glycopeptides

- Vancomycin , Teicoplanin & Telavancin are already in use

- **DRUGS IN PIPELINE**

✓ Oritavancin :- Phase III trial

✓ Dalbavancin :- Phase III trial

- **MOA**:

- Inhibits peptidoglycan biosynthesis by inhibiting transglycosylation plus transpeptidation

-Blocks utilization of D-Ala-D-Ala or D-Ala-D-Lac containing peptidoglycan precursors

Advantage over Vancomycin

- **Additional mechanism of action**:- increases cell membrane permeability causing rapid bactericidal activity
- Renal and hepatic excretion
- No known nephrotoxicity or dose adjustments
- Less frequent dosing
- Longer $t_{1/2}$ life

Mechanism of resistance to older glycopeptide

- Synthesis of low-affinity precursors in which C-terminal D-Ala residue is replaced by:

  D- lactate (D-Lac) or by D-serine (D-Ser)

- **Resistance overcome by**:- High binding affinity for both substrates(D-Ala-D-Lac precursor substrate OR D-Ala-D-Ala) due to presence of hydrophobic side chain

Lipopeptides

- New class of antibiotic
- Developed for the treatment of vancomycin-resistant enterococcal infections

❑ **Daptomycin**-Only drug in this class

- Approved in 2003
- Rapidly bactericidal
- No cross resistance

❑ **Indication**:-

- Treatment of complicated skin and skin structure infections

……Lipopeptides

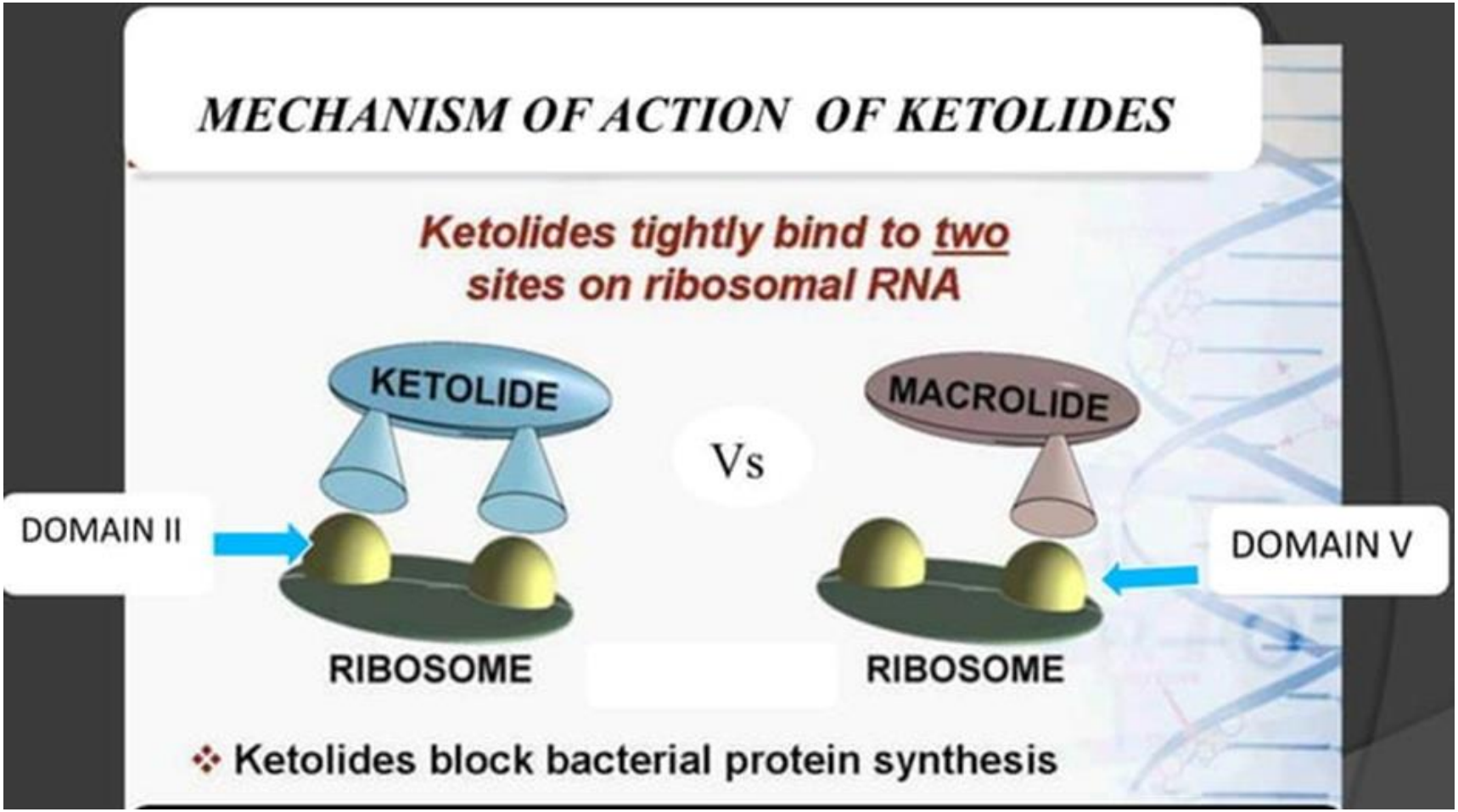
- **MOA:**
  - Binds to bacterial membranes and causes a rapid depolarization- Inhibition of protein, DNA, and RNA synthesis
  - Warning issued by FDA in July 2010-----can cause life-threatening eosinophilic pneumonia

Ketolides

- Drug resistance in community acquired respiratory tract infections:- discovery and development of ketolides
- Semisynthetic 14 membered ring macrolides
- Carbonyl group at the C3 position, responsible for sensitivity to macrolide resistant strains
- Telithromycin- Approved in 2004 for CAP
- **DRUGS IN PIPELINE**

✓ Cethromycin- Phase III trials

✓ Solithromycin- Phase III trials


MECHANISM OF ACTION OF KETOLIDES
Ketolides tightly bind to two sites on ribosomal RNA
KETOLIDE
MACROLIDE
Vs
DOMAIN II
DOMAIN V
RIBOSOME
RIBOSOME
Ketolides block bacterial protein synthesis

Glycylcyclines

- New class of antibiotics derived from tetracycline

- Designed to overcome two common mechanisms of tetracycline resistance
  - Resistance mediated by acquired efflux pumps
  - Ribosomal protection

- Only one glycylcycline antibiotic for clinical use:
  TIGECYCLINE

Tigecycline

- Approved in 2005
- **Indication**:
  - Complicated skin and skin structure infections
  - Intra-abdominal infections
- New Delhi metallo-β-Lactamase producing bacteria has also shown susceptibility to tigecycline
- Also active against MRSA
- **MOA:**
  - Bind to 30S subunit of bacterial ribosome
  - 20-fold more efficient than tetracycline

…..Tigecycline

- **DOSE:**
- Only I/V formulation available
- Slow I/V infusion of 100 mg followed by maintenance dose(50 mg)
- No dose adjustment in renal failure (in comparison to tetracycline)
- **DRUG IN PIPELINE: PTK0796**
- Oral formulation
- In a phase II trial

Newer carbapenems

- Beta-lactam antibiotics with a broad spectrum of antibacterial activity
  - Ertapenem: Approved in 2001
  - Doripenem: Approved in 2007
- **DRUG IN PIPELINE**:
  - Razupenem: Phase II clinical trial
- **Indication:**
- Complicated urinary tract infections
- Intra-abdominal infections

- **MOA**:
- Bind to penicillin binding proteins(PBPs) and inhibit cross-linking of the peptidoglycan structure
- **Advantage over older carbapenem**:

1) Spectrum of activity:-

- Similar to that of meropenem against gram-ve & similar to imipenem against gram+ve bacteria

2) Slightly better in vitro activity against P. aeruginosa
3) Not degraded by renal dehydropeptidase

- **Dose**: Available as I/V formulation only

Newer cephalosporins

❑ **Approved cephalosporins**

- Ceftaroline: Approved in 2010
- For the treatment of:

  -Community-acquired pneumonia &

  -Complicated skin and soft-tissue infections

❑ **Drug in pipeline**

✓ Ceftobiprole: Awaiting FDA approval

…..Newer cephalosporins

- **MOA**:

- Bind strongly to PBP2a of methicillin resistant Staphylococci

- Novel cephalosporin have-

- Broad spectrum activity against MRSA and multi-drug resistant S. pneumoniae

- **DOSE**: 600 mg IV every 12 hours

Novel Dihydrofolate reductase inhibitors

- Iclaprim
  - Diaminopyrimidine that inhibit DNA/RNA synthesis
  - Awaiting FDA approval
- **Indication**:
  - For the treatment of complicated skin and soft tissue infections caused by antibiotic-resistant bacteria
- Designed to overcome trimethoprim resistance
- Active against MRSA, penicillin resistant S. pneumoniae (PRSP)

Pleuromutilins

- Newer class of antibiotic
- **MOA**:
- Bind to 50S subunit of ribosomes inhibiting protein synthesis
  - Retapamulin:
- Approved in 2007
- Topical antibiotic
- Treatment of skin infections such as impetigo
- **Drug in pipeline**:
  - Azamulin

RIFAMYCINS

- Rifampin, Rifabutin & Rifapentine are already approved drugs
- RIFAXIMIN:
- Approved for:

  -Traveler’s diarrhea

  -Hepatic encephalopathy

  -Irritable bowel syndrome

  -Small intestinal bacterial overgrowth

  -Clostridium difficile infection

New Targets for the Next Generation of Antimicrobial drugs

- Targeting virulence factors
- Targeting bactericidal functions of bacterial proteins
- Modulating host response pathways
- Peptides derived from vertebrates, invertebrates and microorganisms

…..Future targets

1. Targeting virulence factors:- e.g.

    -Inhibition of bacterial adhesion

    -Inhibition of toxin production

    -Inhibition of toxin delivery

    -Inhibition of virulence regulators

…..Future targets

2) Targeting bactericidal functions of bacterial proteins

E.g:- Targeting enzymes like β-ketoacyl-acyl-carrier-protein synthase I/II

↓

Required for fatty acid biosynthesis in bacteria

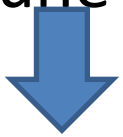
- DRUG IN PIPELINE:

✓ Platensimycin –preclinical trials in an effort to combat MRSA in a mouse model

…..Future targets

3) Modulating host response pathways

Innate immune response



Activation of TLR family of proteins

Produce antimicrobial peptides

- TLR activators and modulators could potentially have an antimicrobial role

…..Future targets

4) Antimicrobial peptides derived from vertebrates, invertebrates and microorganisms- Novel potential therapeutic target

- Examples:

✓ Dermaseptin------ frog skin

✓ Defensin & Crustin-------Crustacean

- **DRUGS IN PIPELINE**:

- Omiganan
- Pexiganan

New Strategies for Antibacterial Drug Discovery

- Therapeutic use of bacteriophages to treat pathogenic bacterial infections

- Common resistance mechanisms can be bypassed by producing antibacterial drug as- Prodrug microbe

- Production of hybrid antibacterial drugs- for high potency against two targets:

✓ Rifamycin-quinolone hybrid which is a RNA polymerase inhibitor and also a DNA gyrase inhibitor

- Improved formulation of alternative drug delivery methods, e.g; inhaled Amikacin nanoscale liposome formulation

Limitations of antimicrobial research & development pipeline

- Drug research and development is quite expensive and time-consuming
- Average cost per each new drug is estimated to be US$ 800 million to 1.7 billion
- Increasing number of pharmaceutical companies are withdrawing from the market of antibiotic development
- Few antibacterial agents in the pipeline

Antimicrobial Stewardship

- Antimicrobial stewardship refers to a program of interventions to monitor and direct antimicrobial use at a health care institution, thus providing a standard, evidence-based approach to judicious antimicrobial use
- It includes:-
- Infection control plus antimicrobial management
- Appropriate antimicrobial selection, dosing, route, and duration
- System selection of antimicrobials that cause the least collateral damage

Goals of Antimicrobial Stewardship

❖ Primary goal:

- Optimize clinical outcome/minimize unintended consequences of antimicrobial use
- Unintended consequences:

✓ Toxicity

✓ Selection of pathogenic organisms

✓ Emergence of resistant pathogens

❖ Secondary goal:

- Reduce healthcare costs without adversely impacting quality of care

Conclusion:

- There is a great need of newer antibiotics because of increasing microbial resistance
- Because of increase cost of development and increasing resistant, only few drugs are in pipeline
- We overuse antibiotics and often neglect to complete a full course of antibiotics once it has been prescribed, leading to the spread of antibiotic resistance
- Rational use of antibiotics remain the most important measure

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THANK YOU