PRINCIPLES OF ANTIMICROBIAL THERAPY

By

Dr.Nashwa Abo-Rayah
Associate prof. (clinical &experimental pharmacology)
Mu'tah University- Faculty of Medicine
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OBJECTIVES

- TO EXPLAIN GENERAL PRINCIPLES OF ANTIBIOTICS
- TO CLASSIFY ANTIBIOTICS
- TO DESCRIBE AND UNDERSTAND MECHANISMS OF ACTION OF ANTIBIOTICS.
- GENERAL SIDE EFFECTS OF ANTIBIOTICS
- CLINICAL APPROACH TO PRESCRIBE ANTIBIOTICS

WHAT ARE ANTIBIOTICS?

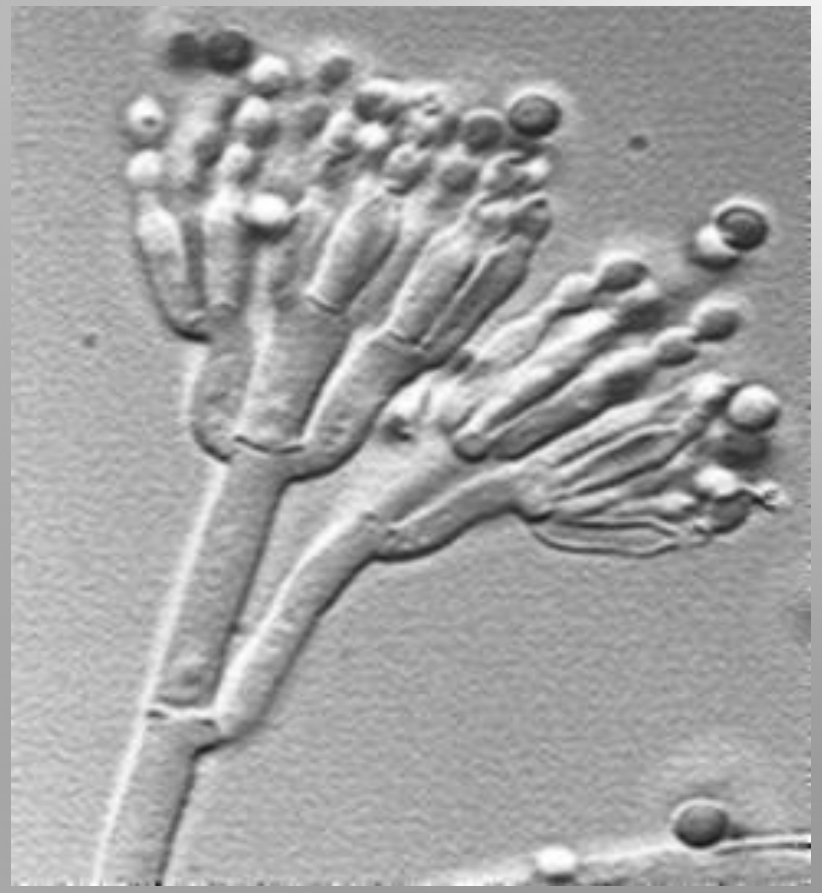
- IS A SUBSTANCE PRODUCED BY LIVING MICRO-ORGANISMS TO INHIBIT OR KILL ANOTHER LIVING MICRO-ORGANISMS E.G: PENICILLINS, CEPHALOPORINS , TETRACYLCINES AND CHLORAMPHICOL.
- **ANTIMICROBIAL AGENT**:
- IS ANY CHEMICAL SUBSTANCE WHICH KILLS THE ORGANISM OR INHIBITS ITS GROWTH E.G: SULPHONAMIDES, QUINOLONES
- TODAY THE TERM ANTIBIOTICS EXTENDS TO INCLUDE SYNTHETIC ANTIBACTERIAL AGENTS: SULFONAMIDES AND QUINOLONES

CLASSIFICATION OF ANTIBIOTICS ACCORDING TO SOURCE

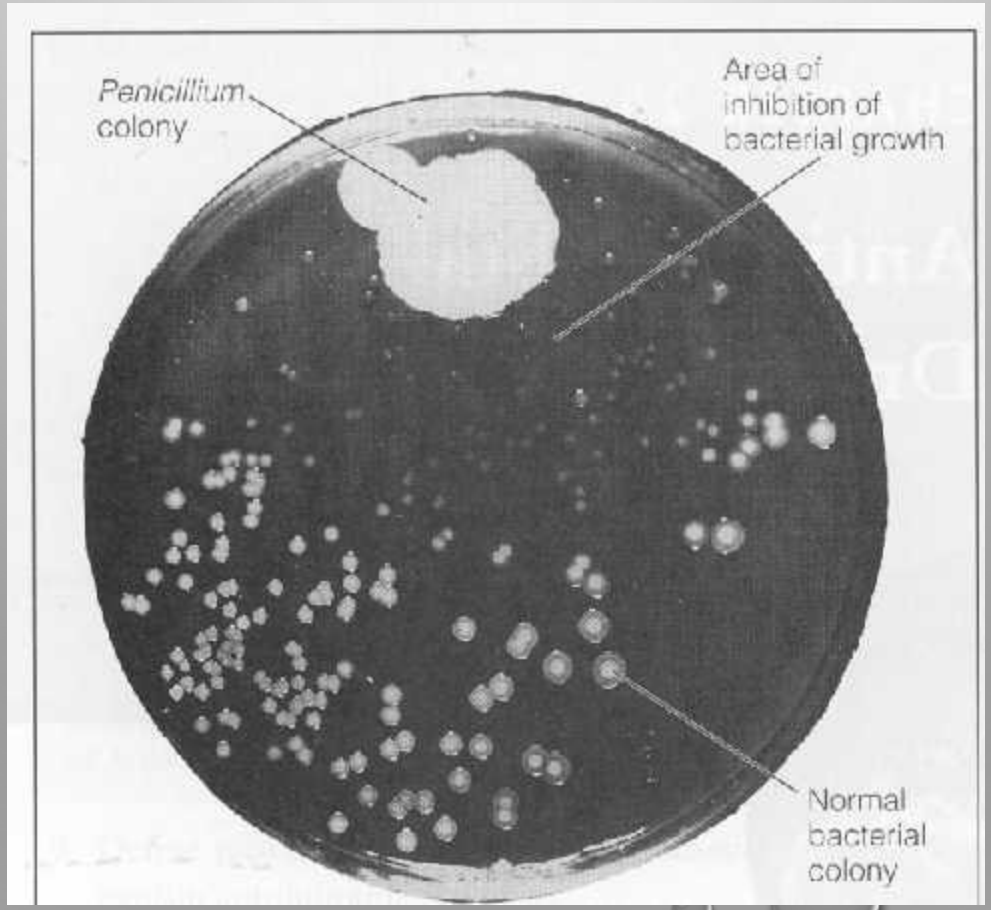
- 1- NATURAL: SEVERAL SPECIES OF FUNGI INCLUDING *PENICILLIUM* AND *CEPHALOSPORIUM*
- E.G. PENICILLIN, CEPHALOSPORIN
- NEW SOURCES EXPLORED: PLANTS, HERPS, FISH

- 2- SYNTHETIC: SULPHA DRUGS
- 3- SEMISYNTHETIC: AMPICILLIN

SIR ALEXANDER FLEMING



FLEMING'S PETRI DISH



SELECTIVE TOXICITY

- TO BE EFFECTIVE AND SAFE, ANTIMICROBIAL AGENT MUST HAVE **SELECTIVE TOXICITY**

يقتل البكتيريا وآمن على human.

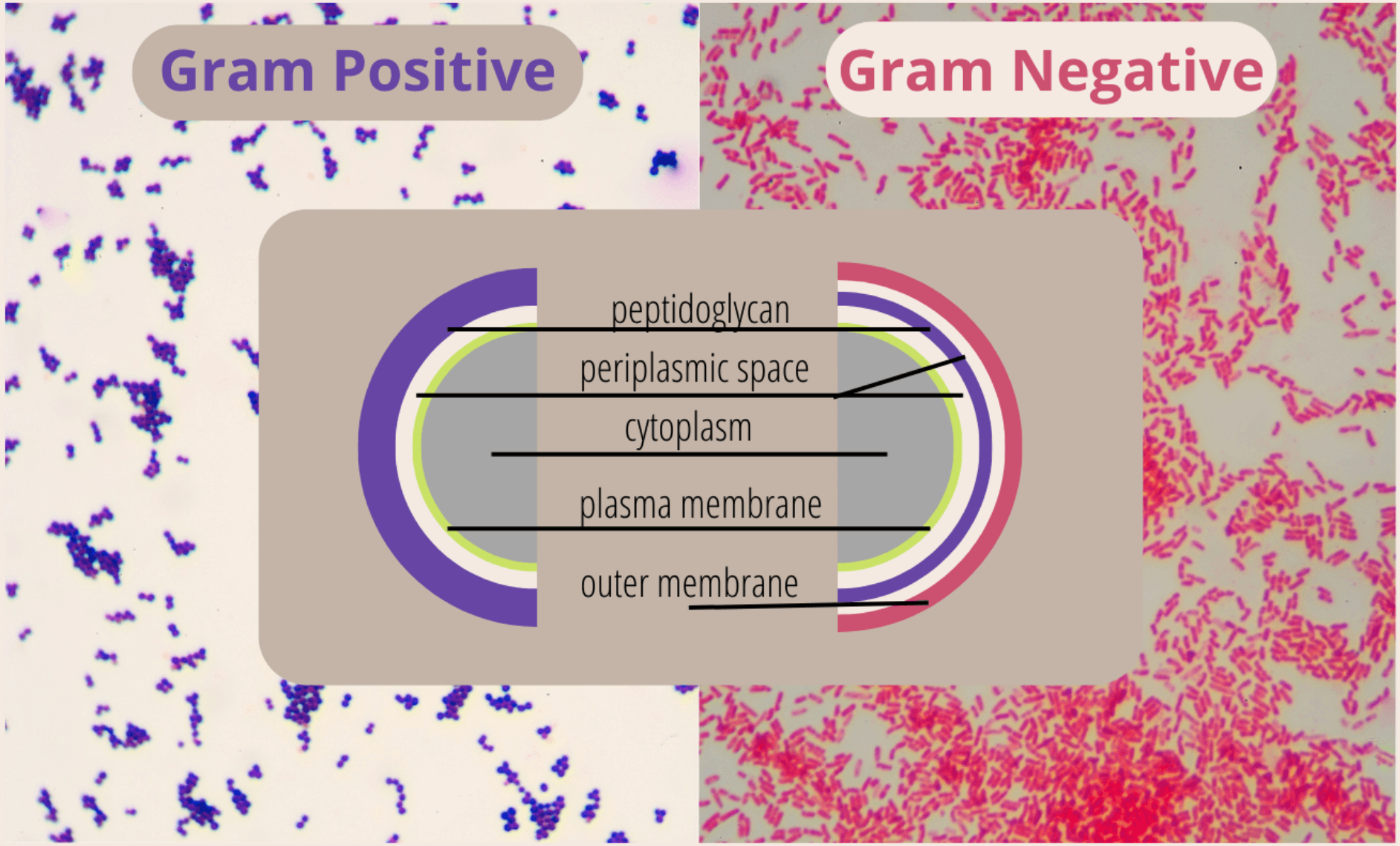
- SELECTIVE TOXICITY IS DUE TO THE DIFFERENCE IN STRUCTURE AND/OR METABOLISM BETWEEN THE PATHOGEN AND THE HOST.

PROKARYOTIC CELL	EUKARYOTIC CELL
Generally smaller in size than the eukaryotic cell (1-10µm)	Larger in size than the prokaryotic cell (5-100µm)
Membrane bound organelles are absent.	Membrane bound organelles are present.
The chromosome is singular.	More than one chromosomes are present.
The nuclear region is not very well defined and is called as the nucleoid.	The nuclear region is very well defined in form of separate membrane bound organelle called as the nucleus.

GRAM POSITIVE & GRAM NEGATIVE

- GRAM POSITIVE BACTERIA HAVE A THICK CELL WALL
  - PEPTIDOGLYCAN DIRECTLY ACCESSIBLE FROM ENVIRONMENT
- GRAM NEGATIVE BACTERIA HAVE A DIFFERENT WALL
  - THIN LAYER OF PEPTIDOGLYCAN
  - SURROUNDED BY AN **OUTER MEMBRANE** COMPOSED OF LIPOPOLYSACCHARIDE, PHOSPHOLIPIDS, AND PROTEINS
  - OUTER MEMBRANE IS A BARRIER TO DIFFUSION OF MOLECULES INCLUDING MANY ANTIBIOTICS
    - SOME LIPOPHILIC ANTIBIOTICS MAY DIFFUSE IN.
    - PORINS ALLOW PASSAGE OF ONLY SOME ANTIBIOTICS

Gram Positive vs Gram Negative Bacteria



ANTIBIOTICS ACCORDING TO THEIR MODE OF ACTION

- **BACTERIOSTATIC VS. BACTERICIDAL**
- ANTIBIOTICS DIFFER BY MODE OF ACTION
- BACTERIOSTATIC COMPOUNDS INHIBIT THE GROWTH OF BACTERIA
- HOST IMMUNE SYSTEM DOES THE KILLING
- BACTERICIDAL COMPOUNDS DIRECTLY KILL THE BACTERIA
- **BACTERIOSTATIC & CIDAL:**
- ACCORDING TO CONCENTRATION E.G: ERYTHROMYCIN AND ISONIAZIDE.
- LOCATION AND SEVERITY OF INFECTION AFFECT CHOICE OF ANTIBIOTIC
  - E.G. CNS INFECTION CALLS FOR BACTERICIDAL TREATMENT.

- cell wall Inhibitors
- cell membrane Inhibitors
- DNA Inhibitor
  ⇒ bacteriocidal.
- antimetabolite → sulfa drugs
  ⇒ bacteriostatic.
- protein synthesis Inhibitors
  ⇒ may cidal or static.

ANTIBIOTICS ACCORDING TO THE SPECTRUM

- **BROAD SPECTRUM:**
- EFFECTIVE AGAINST MULTIPLE GRAM +VE & -VE ORGANISMS E.G: EMEPENEM, TETRACYCLINE, QUINOLONES ,CHLORAMPHICOL.
- USED AS INITIAL EMPIRICAL TREATMENT TILL CULTURE AND SENSITIVITY RESULTS APPEAR.
  - ↳ patient with sever Infection like meningitis → we give blindly a broad spectrum antibiotic لحد ما نتيجة الفحص تظهر
- **NARROW SPECTRUM**
- EFFECTIVE AGAINST SPECIFIC ORGANISMS E.G: ANTIMICROBIAL AGAINST GRAM +VE BACTERIA: VANCOMYCIN AND PENICILLIN G.
- ANTIMICROBIAL AGAINST GRAM -VE BACTERIA: POLYMIXINE, BACITRACIN AND AMINOGLYCOSIDES.
- USED IN TREATMENT OF SUSCEPTIBLE ORGANISMS BASED ON CULTURE AND SENSITIVITY RESULTS.
- **MODERATE SPECTRUM:** E.G: MACROLIDS

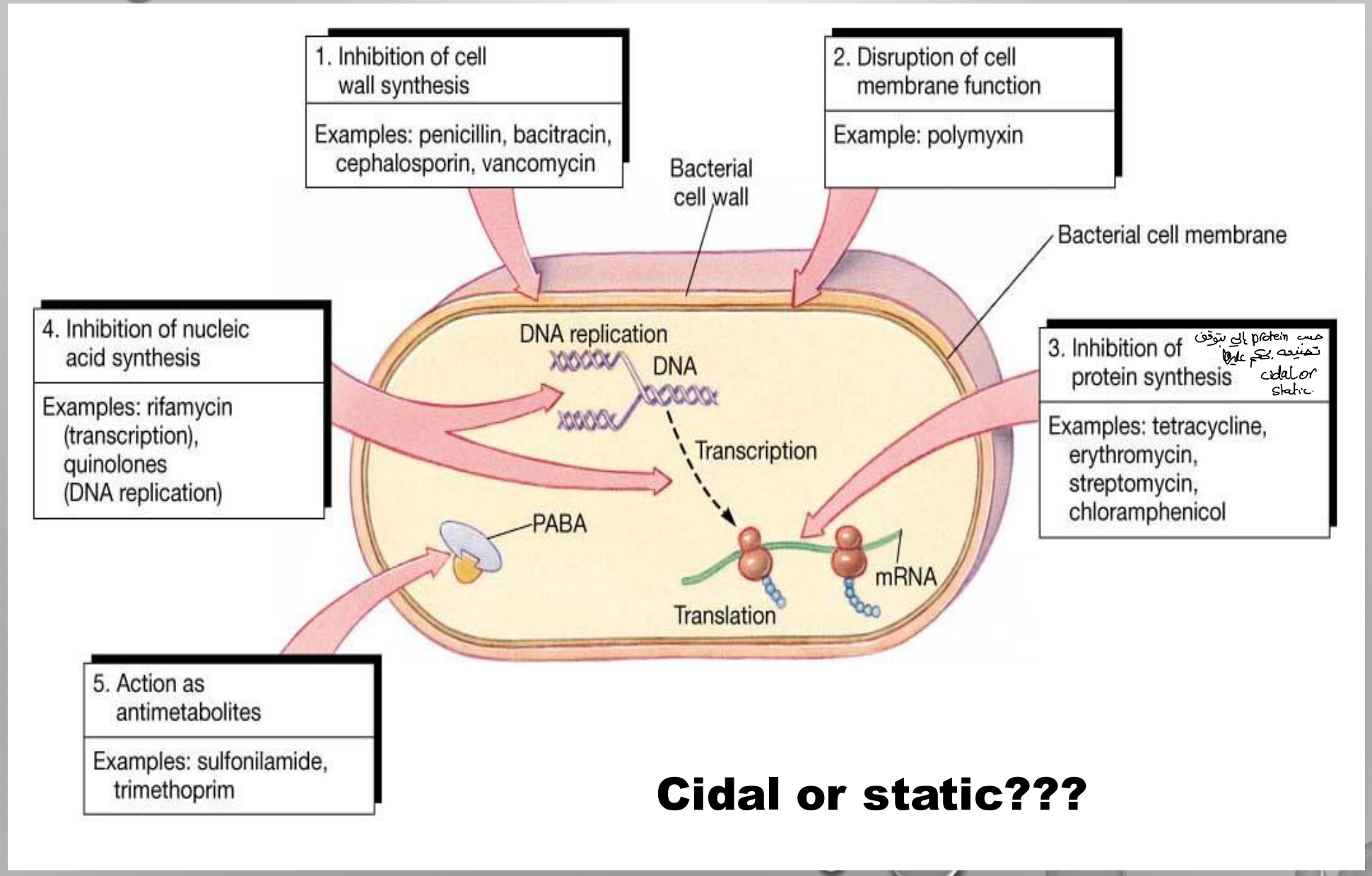
EXTENDED-SPECTRUM ANTIBIOTICS

- EXTENDED SPECTRUM IS THE TERM APPLIED TO ANTIBIOTICS THAT ARE MODIFIED TO BE EFFECTIVE AGAINST GRAM-POSITIVE ORGANISMS AND ALSO AGAINST A SIGNIFICANT NUMBER OF GRAM-NEGATIVE BACTERIA.
- FOR EXAMPLE, *AMPICILLIN* → semi-synthetic penicillin.

- **GRAM-POSITIVE AND GRAM-NEGATIVE COVERAGE**
- **ALL BUT 4 OF THE ANTIBIOTIC CLASSES** COVER BOTH GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA.
- **SPECIFIC COVERAGE CLASSES**
- THE 4 CLASSES THAT HAVE SPECIFIC GRAM COVERAGE INCLUDE GLYCOPEPTIDES, LINCOSAMIDES, AMINOGLYCOSIDES, AND MACROLIDES (GLAM).

- **GRAM-NEGATIVE COVERAGE ONLY**
- AMINOGLYCOSIDES PRIMARILY COVER GRAM-NEGATIVE BACTERIA (WITH SOME MINOR EXCEPTIONS AGAINST GRAM-POSITIVES, ESPECIALLY WHEN USED SYNERGISTICALLY).
- THE WORD AMI**NO**GLYCOSIDE HAS THE WORD **"NO"** IN IT. NO IS A NEGATIVE RESPONSE WHICH WILL HELP YOU REMEMBER GRAM-NEGATIVE.
- **GRAM-POSITIVE COVERAGE ONLY**
- THE OTHER 3 CLASSES (GLYCOPEPTIDES, LINCOSAMIDES, AND MACROLIDES) PRIMARILY COVER GRAM-POSITIVE BACTERIA ONLY (WITH MACROLIDES HAVING MINOR GRAM-NEGATIVE COVERAGE AS WELL).

CLASSIFICATION OF ANTIBIOTICS AGENTS ACCORDING TO SITE OF MECHANISM OF ACTION



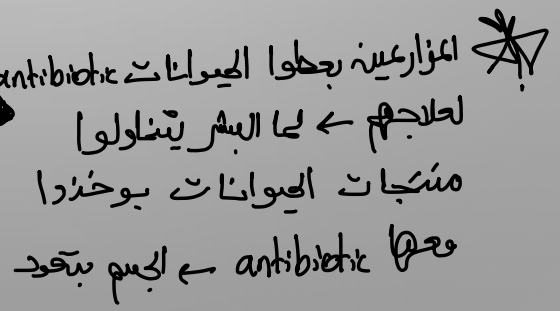
Cidal or static???

ANTIMICROBIAL RESISTANCE

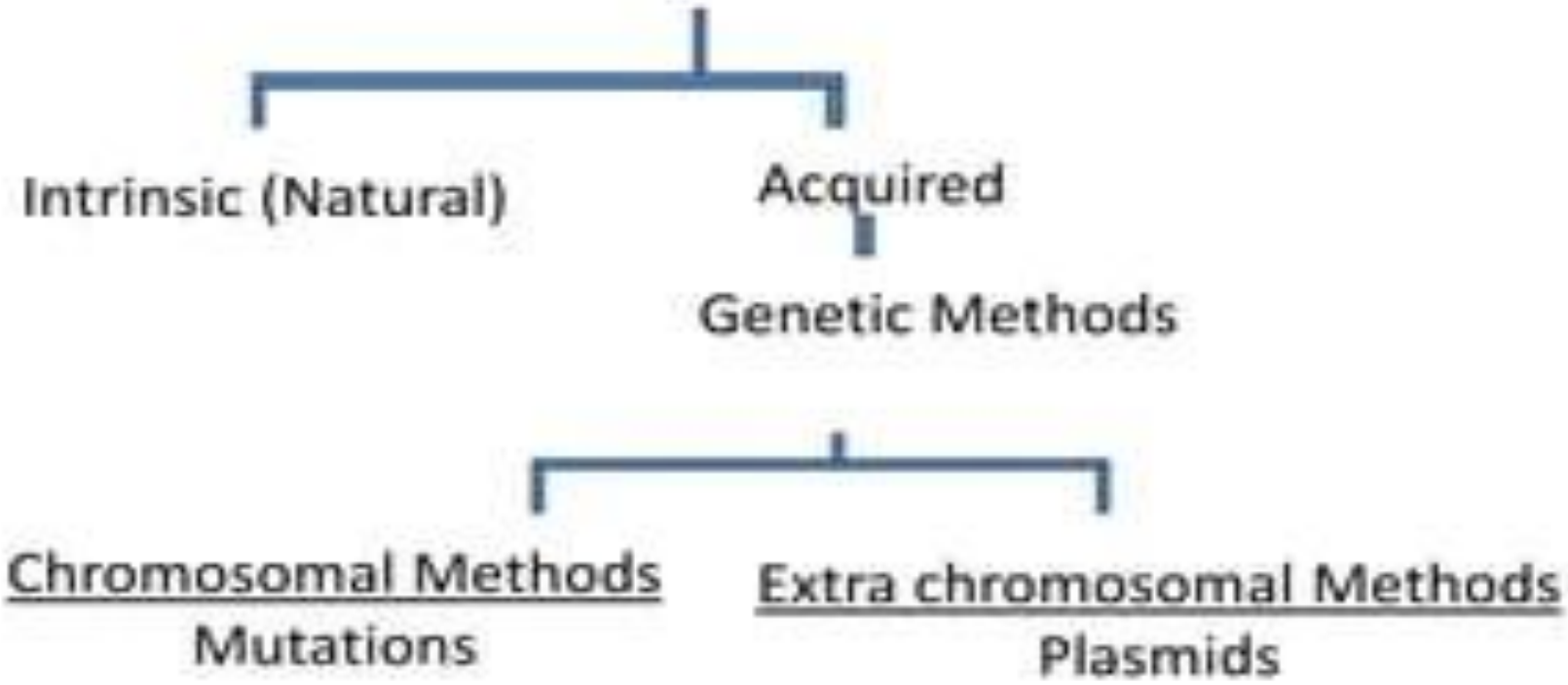
- THE ABILITY OF A MICROBE (GERM) TO RESIST THE EFFECTS OF A DRUG.
- ANTIMICROBIAL RESISTANCE INCLUDES ANTIBACTERIAL, ANTIFUNGAL, AND ANTIVIRAL RESISTANCE.
- DRUG RESISTANCE MAY BE PRESENT BEFORE TREATMENT IS GIVEN OR MAY OCCUR DURING OR AFTER TREATMENT WITH THE DRUG.

CAUSES OF THE ANTIBIOTIC RESISTANCE

- 1- OVERUSE
- 2- ANTIBIOTICS ARE UNREGULATED AND AVAILABLE OVER THE COUNTER WITHOUT A PRESCRIPTION
- 3- INCORRECTLY PRESCRIBED ANTIBIOTICS
- 4- EXTENSIVE AGRICULTURAL USE
- 5- AVAILABILITY OF FEW NEW ANTIBIOTICS



Mechanism Antibiotic Resistance



MECHANISMS OF ANTIBIOTIC RESISTANCE

- ANTIBIOTIC RESISTANCE MECHANISMS FALL INTO FOUR MAIN CATEGORIES:
- **(1) LIMITING UPTAKE OF A DRUG**
- **(2) MODIFYING A DRUG TARGET**
- **(3) INACTIVATING A DRUG** as
  - β-lactmase
  - acetyl transferase → Inactivate chloromphenicol.
- **(4) ACTIVE DRUG EFFLUX**

metronidazole/ vancomycin ← pseudomembranous colitis ← علاج ← مرض

GENERAL SIDE EFFECTS OF ANTIBIOTICS

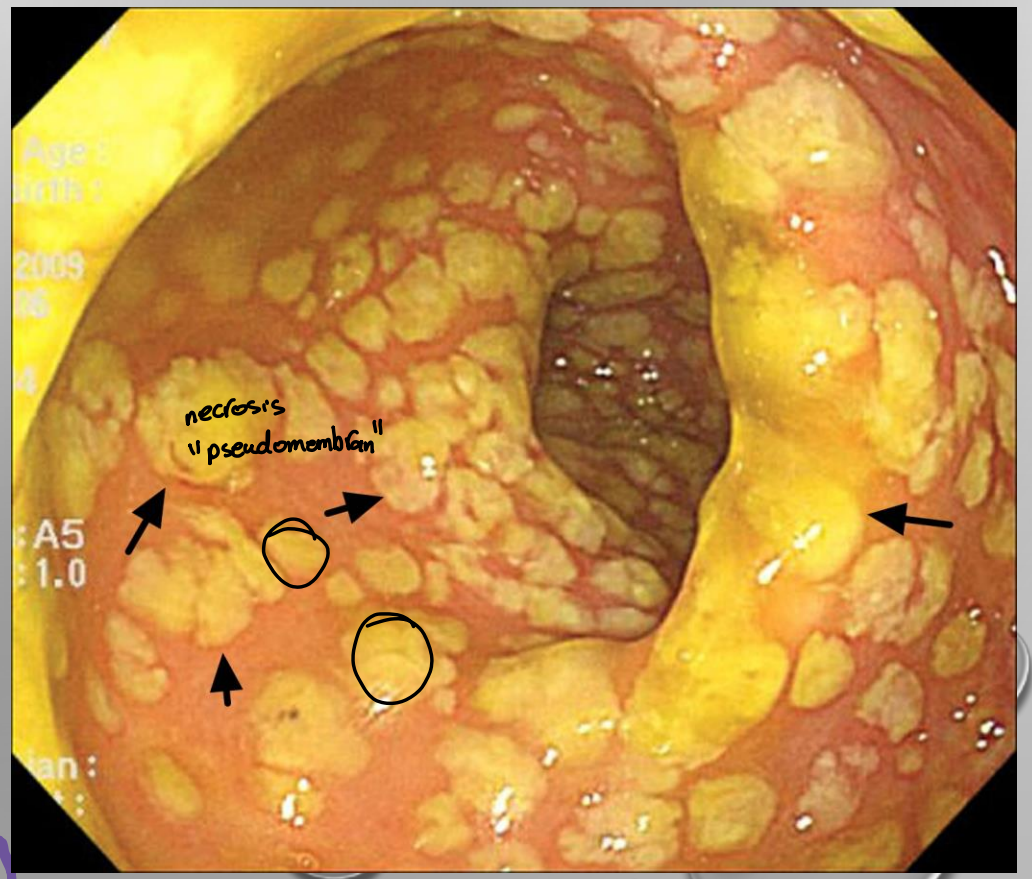
- 1- ALLERGY → Ranging from mild to sever (anaphylactic shock)
- 2- VITAMIN DEFICIENCY : K & B
- 3- SUPERINFECTION:
- PSEUDOMEMBRANOUS COLITIS: CLOSTRIDIUM DIFFICILE
  ← بقع بيضاء (تدل ع) فطريات في الفم.
- CANDIDA INFECTION: THRUSH, PHARYNGITIS

Using broad spectrum antibiotics will kill normal flora → harmful bacteria. → مضادات حيوية تقتل البكتيريا النافعة في الجسم وتؤدي لنقص vitamin K.

As a result.

- vitamin K & B reduced
  - responsible about making clotting factors
    - so deficient in them lead to bleeding problems.
- overgrowth of opportunistic ← C. difficle
  - cause damage and necrosis in intestin "pseudomembran"

العلاج: metronidazole & vancomycin



HOW TO PRESCRIBE ANTIBIOTICS?

- TO PRESCRIBE ANTIBIOTICS PROPERLY, YOU HAVE TO CHOOSE THE RIGHT:
- 1- PATIENT
- 2- DRUG
- 3- DOSE
- 4- ROUTE
- 5- DURATION

1- THE RIGHT PATIENT

* معلومة : كل bacterial Infection يرافقه fever وليس كل fever سببها bacterial Infection. الا Immunosuppressed patient ← عندهم Infection بدون fever ← WBCs ما عالية.

- **CONFIRM BACTERIAL INFECTION BY:**
- 1- FEVER: BODY TEMPERATURE MORE THAN 37.2 C
- 2- CBC: DIFFERENTIAL WBCS COUNT: NEUTROPHILIA INDICATES BACTERIAL INFECTION
- 3- SPECIFIC TESTS: EXAMPLE: WIDAL TEST FOR TYPHOID FEVER

* معلومة ارتفاع كل خلية ماذا يدل ↓

* neutrophilia → Indicate bacterial Infection.
WBCs ارتفاع بنسبة neutrophils بنسبة أكثر من ٦٠٪
* lymphocytosis → viral Infection OR TB
* basophilia → lymphoma, leukemia.

2- THE RIGHT DRUG

- SELECTION OF ANTIBIOTIC IS BASED ON:
- 1- THE CAUSATIVE ORGANISM 2- THE AFFECTED PATIENT 3- TISSUE PENETRATION
- **CAUSATIVE ORGANISM**:
- CULTURE AND SENSITIVITY OF INFECTED MATERIAL: E.G. SPUTUM, URINE, CSF IN MILD AND MODERATE CASES
- START EMPIRICAL ANTIBIOTIC THERAPY IN:
- ACUTELY-ILL PATIENTS, IMMUNOCOMPROMISED, MENINGITIS → symptoms :- neck rigidity, sever headache, photosensetivity.
  مرض أغراض التهاب السحايا
- **AFFECTED PATIENT**: FACTORS AFFECTING ANTIBIOTIC CHOICE: AGE, IMMUNE STATE, → if it suppressed we give them cidal
  PREGNANCY → some antibiotics cause tetratogenecity.
  - neonat & children → we can't give quinolone
    لـ يسبب تشوهات في الغضاريف.
  - old age patient → we can't give them Aminoglycoside because it make nephrotoxicity.
- **TISSUE PENETRATION:**
- CHRONIC PUS FORMATION REQUIRES IV ANTIBIOTIC ADMINISTRATION
- DIABETIC FOOT: ISCHEMIA DELAYS ANTIBIOTIC EFFECT
- BODY BARRIERS: BBB, VITREOUS HUMOR, PROSTATIC BARRIER
  - to treat meningitis → we should give lipophilic drugs to penetrate BBB
    - if the treatment can't penetrate BBB → we change the rout → as give the drug Intrathecal → directly to CSF

3- THE RIGHT DOSE

- MIC: THE LOWEST CONCENTRATION (IN MG/ML) OF AN ANTIBIOTIC THAT INHIBITS THE GROWTH OF A GIVEN STRAIN OF BACTERIA

post-antibiotic effect → antibiotics with this phenomenon as macrolides need single dose.

- The post antibiotic effect is the phenomenon of continued bacterial killing even though serum concentrations have fallen below the minimum inhibitory concentration (MIC) → that because it can penterat macrophage and neutrophilis and diver them to Infected tissue.

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Patterns of Microbial Killing

- Concentration dependent → It need multiple doses
  - Higher concentration ⟶ greater killing
    - Aminoglycosides, Flouroquinolones, Ketolides, metronidazole, Ampho B.
- Time-dependent killing → It need single dose.
  - Minimal concentration-dependent killing (4x MIC)
  - More exposure ⟶ more killing
    - Beta lactams, glycopeptides, clindamycin, macrolides, tetracyclines, bactrim

4- THE RIGHT ROUTE

- ACCORDING TO THE SEVERITY OF INFECTION:
- MILD- MODERATE CASES: ORAL
- SEVER CASES:PARENTRAL

5- THE RIGHT DURATION

- ACCORDING TO THE UNIVERSAL GUIDELINES FOR EACH CASE:
- TONSILLITIS: 3-5 DAYS
- UTIS: 10 DAYS
- PNEUMONIA: 7 DAYS
- MENINGITIS: 15 DAYS
- AFTER DISAPPEARANCE OF SYMPTOMS, ANTIBIOTIC SHOULD BE CONTINUED FOR 48-72HS???

that because when symptoms disappears the bacteria is in Inhibited state but not yet killed so when we stop antibiotic, the bacteria will develop a new mechanism for resistance.

ANTIBIOTIC COMBINATIONS

- **INDICATIONS:**
- 1- MIXED INFECTIONS: DIABETIC FOOT, PERITONITIS
- 2- SEVER INFECTION: MENINGITIS
- 3- HIGHLY RESISTANT BACTERIAL STRAINS: TB, PSEUDOMONAS
- **GOOD ANTIBIOTIC COMBINATIONS**:
- 1- SYNERGISM (COMPLEMENTARY): PENICILLIN AND AMINOGLYCOSIDES, PENICILLIN AND SULPHADIAZINE
- 2- ADDITION: TETRACYCLINE AND ERYTHROMYCIN
- WHAT ABOUT THIS COMBINATION: PENICILLIN AND TETRACYCLINE???

THANK YOU