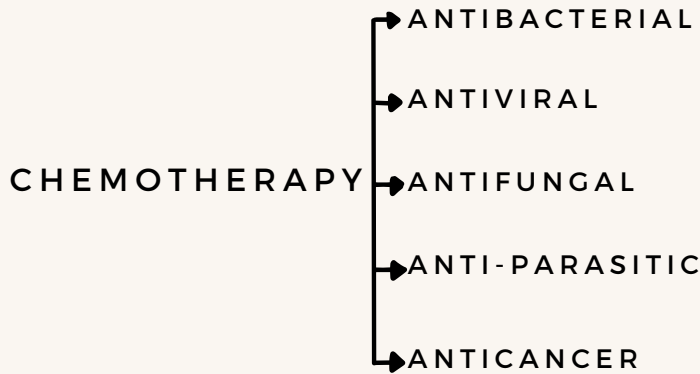


High yield

# Principles of antimicrobial therapy



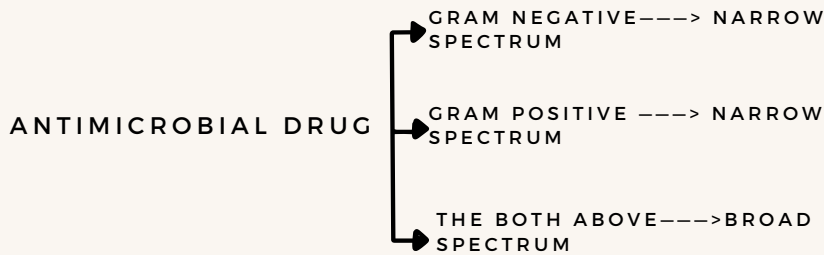
♥ **CHEMOTHERAPY: IS A TERM APPLIED FOR SYNTHETIC CHEMICALS THAT DESTROY INFECTIVE ORGANISMS**



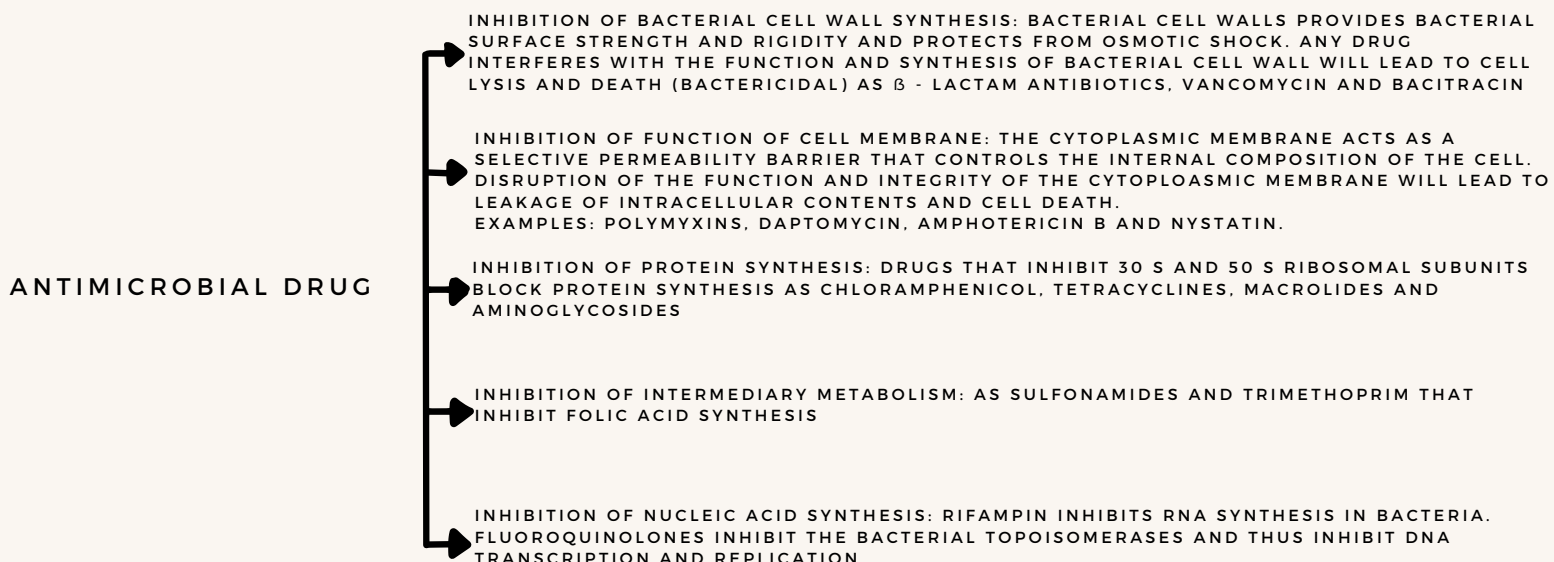
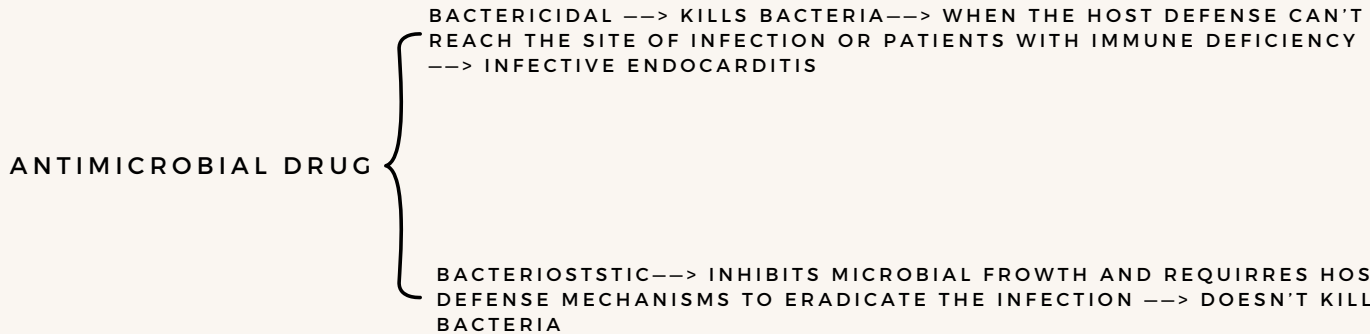
**SELECTIVE TOXICITY OF CHEMOTHERAPEUTIC DRUGS MEANS THAT THESE DRUGS CAN PRODUCE TOXIC EFFECTS ON THE ORGANISMS IN DOSES TOLERATED (NOT HARMFUL) TO THE HOST (HUMANS, ANIMALS, ETC.).**

**THE DIFFERENCES IN THE STRUCTURE, BIOCHEMICAL REACTIONS AND PHYSIOLOGY BETWEEN MICROORGANISMS AND HUMAN CELLS CONTRIBUTE TO THE SELECTIVE TOXICITY OF MOST ANTIMICROBIAL DRUGS.**

♥ **ANTIBIOTICS : ARE NATURAL PRODUCTS SECRETED BY ORGANISMS TO INHIBIT THE GROWTH OR KILL THE NEARBY ORGANISMS.**



♥ **CHEMICAL MODIFICATIONS ON THE CHEMICAL STRUCTURE OF ANTIBIOTICS CAN RESULT IN MORE EFFECTIVE OR MORE POTENT OR WIDER SPECTRUM CHEMOTHERAPEUTIC AGENT.**



FOR AN ANTIBACTERIAL DRUG TO BE EFFECTIVE, IT MUST REACH ITS TARGET IN AN ACTIVE FORM, BIND TO THE TARGET, AND INTERFERE WITH ITS FUNCTION. RESISTANCE IS SAID TO EXIST IF THE CONCENTRATIONS OF THE ANTIBACTERIAL DRUG NEEDED TO KILL OR INHIBIT THE BACTERIA CAN'T BE SAFELY ACHIEVED.

ACCORDINGLY, BACTERIAL RESISTANCE TO AN ANTIMICROBIAL AGENT IS ATTRIBUTABLE TO THREE GENERAL MECHANISMS:

- (1) THE DRUG DOES NOT REACH ITS TARGET.
- (2) THE DRUG IS NOT ACTIVE.
- (3) THE TARGET IS ALTERED.

### GENETIC DETERMINANTS OF ANTIBIOTIC RESISTANCE

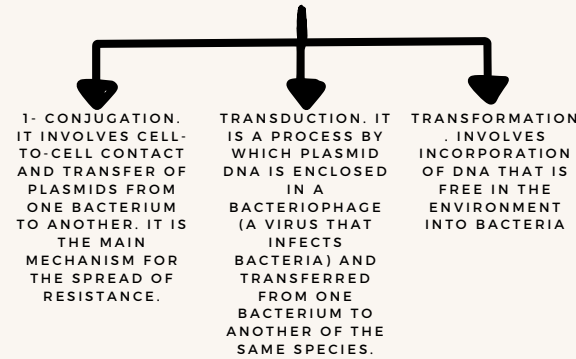
- 1) CHROMOSOMAL DETERMINANTS - MUTATIONS USUALLY THE MUTANTS ARE LESS PATHOGENIC EXCEPT IN MYCOBACTERIUM TUBERCULOSIS.
- 2) EXTRA-CHROMOSOMAL DETERMINANTS - PLASMIDS: PLASMIDS THAT CARRY GENES FOR RESISTANCE TO ANTIBIOTICS ARE REFERRED TO AS R - PLASMIDS.

### TRANSFER OF RESISTANCE GENES

1) BETWEEN GENETIC ELEMENTS WITHIN THE BACTERIUM:

SHORT DNA SEQUENCES WHICH CARRY FEW RESISTANT GENES CAN BE READILY TRANSFERRED (TRANSPOSED) FROM ONE PLASMID TO ANOTHER AND FROM PLASMID TO CHROMOSOME OR VICE VERSA.

2) BETWEEN BACTERIA: THE TRANSFER OF RESISTANCE GENES BETWEEN BACTERIA OF THE SAME SPECIES AND OF DIFFERENT SPECIES IS OF FUNDAMENTAL IMPORTANCE IN THE SPREAD OF RESISTANCE OF ANTIBIOTICS.



### MECHANISMS OF ANTIBACTERIAL RESISTANCE

- 1- BACTERIAL ENZYMES THAT INACTIVATE THE DRUG. EXAMPLES:  $\beta$  - LACTAMASES INACTIVATE PENICILLINS, ADENYLATING AND ACETYLATED ENZYMES INACTIVATE AMINOGLYCOSIDES.
- 2- DECREASED ENTRY OF THE DRUG INTO THE BACTERIAL CELL AS AMINOGLYCOSIDES OR INCREASED EFFLUX OF DRUG OUT OF THE CELL AS WITH TETRACYCLINE.
- 3- ALTERATION OF THE BINDING SITE FOR THE DRUG CHANGING THE AMINOGLYCOSIDE BINDING SITE OR DELETING IT OR CHANGING THE PENICILLIN BINDING PROTEIN.
- 4- DEVELOPMENT OF ALTERATIVE METABOLIC PATHWAY AS SULFONAMIDE RESISTENCE.
- 5- NATURAL RESISTANCE: SOME BACTERIA HAVE NO CELL WALL AND CELL WALL INHIBITORS CAN'T AFFECT THESE BACTERIA. MICROORGANISMS THAT ARE METABOLICALLY INACTIVE MAY BE RESISTANT TO DRUGS E.G. MYCOBACTERIA.

### ANTIMICROBIAL DRUG COMBINATIONS

MOST INFECTIONS SHOULD BE TREATED WITH A SINGLE ANTIMICROBIAL AGENT. ALTHOUGH INDICATIONS FOR COMBINATION THERAPY EXIST, ANTIMICROBIAL COMBINATIONS ARE OFTEN OVERUSED IN CLINICAL PRACTICE.

THE UNNECESSARY USE OF ANTIMICROBIAL COMBINATIONS INCREASES TOXICITY AND COSTS AND MAY OCCASIONALLY RESULT IN REDUCED EFFICACY DUE TO ANTAGONISM OF ONE DRUG BY ANOTHER.

THE RATIONAL (IDEAL) COMBINATION IS INDICATED TO:

- 1- BROADEN THE SPECTRUM.
- 2- DECREASE RESISTANCE.
- 3- OBTAIN SYNERGISM
- 4- TREAT POLY-MICROBIAL INFECTIONS.

### INDICATIONS OF ANTIMICROBIAL COMBINATIONS

- 1- TO PROVIDE BROAD SPECTRUM EMPIRICAL THERAPY IN SERIOUSLY ILL PATIENTS OR IN SEVERE INFECTIONS LIKE ENDOCARDITIS AND MENINGITIS.
- 2- TO TREAT POLY-MICROBIAL (MIXED) INFECTIONS SUCH AS INTRA-ABDOMINAL ABSCESES (AEROBIC AND ANAEROBIC ORGANISMS).
- 3- TO DECREASE THE EMERGENCE OF RESISTANT STRAINS. THE VALUE OF COMBINATION THERAPY IN THIS SETTING HAS BEEN CLEARLY DEMONSTRATED FOR TUBERCULOSIS.
- 4- TO DECREASE DOSE-RELATED TOXICITY BY USING REDUCED DOSES OF ONE OR MORE COMPONENTS OF THE DRUG REGIMEN.
- 5- TO OBTAIN ENHANCED INHIBITION OR KILLING (SYNERGISM).

MECHANISMS OF SYNERGISTIC ACTION

1. BLOCKADE OF SEQUENTIAL STEPS IN A METABOLIC SEQUENCE:

TRIMETHOPRIM-SULFAMETHOXAZOLE IS THE BEST-KNOWN EXAMPLE OF THIS MECHANISM OF SYNERGY. BLOCKADE OF THE TWO SEQUENTIAL STEPS IN THE FOLIC ACID PATHWAY RESULTS IN ENHANCED ANTIBACTERIAL ACTIVITY.

2. INHIBITION OF ENZYMIC INACTIVATION: ONE DRUG (E.G. CLAVULANIC ACID) PROTECTS AMOXICILLIN FROM DESTRUCTION BY  $\beta$ -LACTAMASES OF BACTERIA.

3. ENHANCEMENT OF ANTIMICROBIAL AGENT UPTAKE: PENICILLINS AND OTHER CELL WALL-ACTIVE AGENTS CAN INCREASE THE UPTAKE OF AMINOGLYCOSIDES BY A NUMBER OF BACTERIA WHICH ARE INTRINSICALLY RESISTANT TO AMINOGLYCOSIDES BECAUSE OF PERMEABILITY BARRIERS.

CHEMOPROPHYLAXIS

THE USE OF CHEMOTHERAPEUTIC AGENTS TO PREVENT RATHER THAN TO TREAT AN EXISTENT INFECTION

INDICATIONS

1- TO PREVENT RECURRENCE OF SYPHILIS, TO PREVENT RECURRENCE OF BETA HEMOLYTIC STREPTOCOCCAL INFECTION (WHICH CAN CAUSE COMPLICATIONS LIKE RHEUMATIC FEVER AND NEPHRITIS).

2- TO PROTECT CONTACT PERSONS FROM INFECTION: CONTACTS OF T.B PATIENTS, CONTACTS OF GONORRHEA, CONTACTS OF MENINGITIS CASE, ETC.

3- TO PREVENT SECONDARY BACTERIAL INFECTIONS IN PATIENTS RECEIVING CANCER CHEMOTHERAPY OR IMMUNOSUPPRESSIVE DRUGS AFTER ORGAN TRANSPLANTATION.

4- TO PREVENT BACTERIAL ENDOCARDITIS IN PATIENTS WITH VALVE DISEASE UNDERGOING SURGICAL, DENTAL OR ANY PROCEDURE THAT CAUSE BACTEREMIA.

5- TO PREVENT WOUND INFECTIONS IN SURGICAL PROCEDURES IN THE GIT, URINARY AND GENITAL TRACTS OR SURGICAL OPERATIONS THAT INVOLVE PROSTHETIC IMPLANTS (VALVE, ORTHOPEDIC DEVICE, ETC.).

FAILURE OF ANTIBACTERIAL (MISUSE OF ANTIBIOTICS)

1. TREATMENT OF NON-BACTERIAL INFECTIONS (MISDIAGNOSIS) AS IN THE TREATMENT OF VIRAL INFECTIONS AS VIRAL INFLUENZA BY ANTIBIOTICS.

2. TREATMENT OF FEVER OF UNKNOWN CAUSE (ABSENCE OF BACTERIOLOGICAL TEST)

3. SUBOPTIMAL USE OF THE DRUG E.G. DURATION OF THE COURSE IS TOO SHORT, DOSE IS TOO SMALL, INTERVAL BETWEEN DOSES IS TOO LONG OR THE ROUTE OF ADMINISTRATION IS UNSUITABLE (KINETIC FACTORS).

4. IMPROPER CHOICE OF ANTIBIOTICS E.G. THE USE OF A BACTERIOSTATIC IN CASES WHERE A BACTERICIDAL AGENT IS ESSENTIAL AS IN TREATMENT OF ENDOCARDITIS OR IN IMMUNOCOMPROMIZED PATIENTS.

5. NEGLECTING SURGICAL DRAINAGE OF PUS (ABSCESS) OR NECROTIC TISSUES.

6. DEVELOPMENT OF BACTERIAL RESISTANCE.

ADVERSE REACTIONS OF ANTIBACTERIAL AGENTS

1. TOXIC REACTIONS

2. HYPERSENSITIVITY REACTION.

3. SUPERINFECTION.

SUPERINFECTION

IT IS THE APPEARANCE OF BACTERIOLOGICAL AND CLINICAL EVIDENCE OF NEW INFECTION DURING THE TREATMENT OF A PRIMARY INFECTION.

IT OCCURS IN INDIVIDUALS WHO RECEIVE BROAD SPECTRUM ANTIBIOTICS OR COMBINATION OF ANTIBIOTICS AS THAT LEAD TO ALTERATION OF NORMAL BACTERIAL FLORA OF INTESTINAL, UPPER RESPIRATORY, GENITAL AND URINARY TRACTS.

SENSITIVE MICROORGANISMS ARE ELIMINATED AND THE DRUG RESISTANT MICROORGANISMS FREED FROM COMPETITION, PROLIFERATE AND PRODUCE SUPERINFECTION.

IT IS RELATIVELY DANGEROUS AS IT MAY LEAD TO SERIOUS NEW INFECTIONS BY PSEUDOMONAS, ENTEROBACTERIACEAE, OR CANDIDA (WHICH MAY BE DIFFICULT TO BE CURED).

EMPIRICAL THERAPY:

ANTIBIOTICS ARE GIVEN ONCE THE SYMPTOMS OF INFECTION APPEAR BEFORE CULTURE AND SENSITIVITY RESULTS.

PRE-EMPTIVE THERAPY:

IT IS AN EARLY PROPHYLACTIC THERAPY IN HIGH RISK ASYMPTOMATIC PATIENTS.

PROPHYLACTIC THERAPY:

PROPHYLAXIS MEANS PROTECTION AGAINST INFECTION DEVELOPMENT IN SUSCEPTIBLE INDIVIDUALS TO PREVENT POTENTIAL SERIOUS INFECTION DEVELOPMENT.

DEFINITIVE CURATIVE THERAPY:

IF THE MICROORGANISM IS ISOLATED AND SUSCEPTIBILITY TESTS WERE DONE.

SUPPRESSIVE THERAPY

CONTINUOUS TREATMENT TO SUPPRESSES MICROBIAL RELAPSE AFTER RESOLUTION OF INFECTION.