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Principles of antimicrobial therapy

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

CHEMOTHERAPY
- ANTIBACTERIAL
- ANTIVIRAL
- ANTIFUNGAL
- ANTI-PARASITIC
- ANTICANCER

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.

ANTIMICROBIAL DRUG
- GRAM NEGATIVE---> NARROW SPECTRUM
- GRAM POSITIVE ---> NARROW SPECTRUM
- THE BOTH ABOVE--->BROAD SPECTRUM

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

ANTIMICROBIAL DRUG
- BACTERICIDAL --> KILLS BACTERIA--> WHEN THE HOST DEFENSE CAN'T REACH THE SITE OF INFECTION OR PATIENTS WITH IMMUNE DEFICIENCY --> INFECTIVE ENDOCARDITIS
- BACTERIOSTSTIC--> INHIBITS MICROBIAL FROWTH AND REQUIRRES HOST DEFENSE MECHANISMS TO ERADICATE THE INFECTION --> DOESN'T KILL BACTERIA

ANTIMICROBIAL DRUG
- INHIBITION OF BACTERIAL CELL WALL SYNTHESIS: BACTERIAL CELL WALLS PROVIDES BACTERIAL SURFACE STRENGTH AND RIGIDITY AND PROTECTS FROM OSMOTIC SHOCK. ANY DRUG INTERFERES WITH THE FUNCTION AND SYNTHESIS OF BACTERIAL CELL WALL WILL LEAD TO CELL LYSIS AND DEATH (BACTERICIDAL) AS ß - LACTAM ANTIBIOTICS, VANCOMYCIN AND BACITRACIN
- INHIBITION OF FUNCTION OF CELL MEMBRANE: THE CYTOPLASMIC MEMBRANE ACTS AS A SELECTIVE PERMEABILITY BARRIER THAT CONTROLS THE INTERNAL COMPOSITION OF THE CELL. DISRUPTION OF THE FUNCTION AND INTEGRITY OF THE CYTOPLOASMIC MEMBRANE WILL LEAD TO LEAKAGE OF INTRACELLULAR CONTENTS AND CELL DEATH.
  EXAMPLES: POLYMYXINS, DAPTOMYCIN, AMPHOTERICIN B AND NYSTATIN.
- INHIBITION OF PROTEIN SYNTHESIS: DRUGS THAT INHIBIT 30 S AND 50 S RIBOSOMAL SUBUNITS BLOCK PROTEIN SYNTHESIS AS CHLORAMPHENICOL, TETRACYCLINES, MACROLIDES AND AMINOGLYCOSIDES
- INHIBITION OF INTERMEDIARY METABOLISM: AS SULFONAMIDES AND TRIMETHOPRIM THAT INHIBIT FOLIC ACID SYNTHESIS
- INHIBITION OF NUCLEIC ACID SYNTHESIS: RIFAMPIN INHIBITS RNA SYNTHESIS IN BACTERIA. FLUOROQUINOLONES INHIBIT THE BACTERIAL TOPOISOMERASES AND THUS INHIBIT DNA TRANSCRIPTION AND REPLICATION

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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.

1- CONJUGATION. IT INVOLVES CELL-TO-CELL CONTACT AND TRANSFER OF PLASMIDS FROM ONE BACTERIUM TO ANOTHER. IT IS THE MAIN MECHANISM FOR THE SPREAD OF RESISTANCE.

TRANSDUCTION. IT IS A PROCESS BY WHICH PLASMID DNA IS ENCLOSED IN A BACTERIOPHAGE (A VIRUS THAT INFECTS BACTERIA) AND TRANSFERRED FROM ONE BACTERIUM TO ANOTHER OF THE SAME SPECIES.

TRANSFORMATION . INVOLVES INCORPORATION OF DNA THAT IS FREE IN THE ENVIRONMENT INTO BACTERIA

MECHANISMS OF ANTIBACTERIAL RESISTANCE

1- BACTERIAL ENZYMES THAT INACTIVATE THE DRUG. EXAMPLES: ß - LACTAMASES INACTIVATE PENICILLINS, ADENYLATING AND ACETYLATING 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 ABSCESSES (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).

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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 ENZYMATIC INACTIVATION: ONE DRUG (E.G. CLAVULANIC ACID) PROTECTS AMOXICILLIN FROM DESTRUCTION BY ß-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.

Done by : Boshra Algudah