CHEMOTHERAPY

GENERAL ISSUES RELATING TO CHEMOTHERAPY

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ANTI-MICROBIAL AGENTS

INTRODUCTION:

Anti-microbial agents are drugs that destroy or inactivate microbes:

- Antibacterial agents
- Antiviral agents
- Antifungal agents
- Antiprotozoal

ANTI-MICROBIAL AGENTS

INTRODUCTION .... CONT'D:

There are two categories of anti-microbial agents:

- Antibiotics: antimicrobial drugs produced by microorganisms
- Synthetic drugs: anti-microbial drugs synthesized in the laboratory

Clinical uses of anti-microbial agents:

- Curative
- Suppression
- Prophylaxis

ANTI-MICROBIAL AGENTS: GENERAL PRINCIPLES

LEARNING OBJECTIVES:

1. Describe the principle of selective toxicity of anti-microbial agents
2. Describe the mechanisms of action of anti-microbial agents
3. Describe the mechanisms of anti-microbial drug resistance (AMR) and measures that can be taken to reduce AMR
4. Explain the use of anti-microbial agents for empirical and definitive therapy of infections

ANTI-MICROBIAL AGENTS: GENERAL PRINCIPLES

LEARNING OBJECTIVES …. CONT'D:

5. Explain the factors considered in the selection of an appropriate anti-microbial agent
6. Explain the prophylactic use of anti-microbial agents
7. Explain the use of anti-microbial combination therapy
8. Describe super-infection/supra-infection that occurs with use of anti-microbial agents

INFECTIOUS DISEASE THERAPY

- Infectious disease therapy is based on the principle of selective toxicity: destroy the infectious organism without damage to the host
- Selective toxicity is achieved by exploiting basic biochemical and physical differences between the infectious organism and the host cells
- Chemotherapy is defined as the drug treatment for the diseases caused by bacteria and the other pathologic microorganisms, parasites, and tumor cells; without damaging host tissues

THE IDEAL ANTI-MICROBIAL AGENT

- Should have highly selective toxicity to the pathogenic microorganisms in host body and should have no or less toxicity to the host
- Should have low propensity for development of resistance
- Should not induce immunological reactions in the host
- Should have rapid and extensive tissue distribution
- Should be free of interactions with other drugs
- Should be relatively inexpensive

WHAT IS AN ANTIBIOTIC?

- The term “antibiotic” is from antibiosis, meaning against life
- Antibiotics are substances produced by various species of microorganisms: bacteria, fungi, actinomycetes - to kill or suppress the growth of other microorganisms
- Today the term antibiotic extends to include synthetic antibacterial agents such as sulfonamides and quinolones

ANTI-MICROBIAL SPECTRUM

Anti-microbial spectrum refers to the scope that a drug kills or suppresses the growth of microorganisms:

- Narrow-spectrum: The drugs that only act on one kind or one strain of bacteria e.g. isoniazid is effective against mycobacterial tuberculosis only
- Broad-spectrum: The drugs that have a wide antimicrobial scope e.g. tetracyclines and chloramphenicol

ANTI-MICROBIAL ACTIVITY

- Minimal inhibitory concentration (MIC): The minimum concentration of a drug required to inhibit the growth of bacteria in vitro
- Minimal bactericidal concentration (MBC): The minimum concentration of a drug required to kill bacteria in vitro

ANTI-MICROBIAL ACTIVITY …. CONT'D

Based on activity, anti-bacterial drugs may also be classified as:

- Bacteriostatic – Agents that suppress the growth of bacteria (e.g. sulfonamides, tetracyclines, linezolid, chloramphenicol, clindamycin)
- Bactericidal – Agents that kill the bacteria (e.g. penicillins, cephalosporins, aminoglycosides, flouroquinolones, rifampicin, metronidazole, vancomycin)

ANTI-MICROBIAL ACTIVITY …. CONT'D

- Some drugs may be bacteriostatic at low doses and bactericidal at higher doses e.g. erythromycin
- Some drugs may be bacteriostatic to some bacteria and bactericidal to others, e.g. chloramphenicol is bactericidal to H. influenzae, S. pneumoniae and N. meningitidis, while it is bacteriostatic to other organisms

MECHANISMS OF ANTI-MICROBIAL AGENTS

Inhibition of cell wall synthesis

- Examples: penicillins, cephalosporins, bacitracin and vancomycin
- Have excellent selective toxicity

Inhibition of functions of cellular membrane

Example: polymyxins increase of membranous permeability resulting in outflow of some important materials from bacterial cells thereby causing death of bacteria

MECHANISMS OF ANTI-MICROBIAL AGENTS

Inhibition of nucleic acid synthesis

- Inhibit DNA replication: e.g. quinolones and metronidazole
- Inhibit RNA synthesis: e.g. rifampicin

Inhibition of protein synthesis

- Occurs due to differences in ribosomes: eukaryotic cells have 80s (60s + 40s subunits) ribosomes while prokaryotic cells have 70s (50s + 30s subunits) ribosomes
- Examples: chloramphenicol, macrolides and clindamycin bind to the 50s subunit, and tetracyclines and aminoglycosides bind to the 30s subunit

MECHANISMS OF ANTI-MICROBIAL AGENTS …. CONT'D

Inhibition of folic acid synthesis and utilization

- The drug mimics a normal metabolite and acts as a competitive inhibitor. The enzyme in the microbial cell recognizes the drug instead of the normal metabolite and the pathway stops
- Examples: sulfonamides and trimethoprim inhibit folic acid synthesis

ANTI-MICROBIAL DRUG RESISTANCE

Drug resistance is the phenomenon that susceptibility of pathogenic microorganisms to drugs becomes lower or is even lost following exposure of the micro-organisms to the drugs

Types of resistance

- Intrinsic or natural resistance e.g. no target site in the micro-organism
- Acquired resistance: resistance is acquired by mutation (uncommon) or by transfer of genes (common and a very rapid method of acquiring resistance that often involves resistance to many anti-microbial agents)

ANTI-MICROBIAL DRUG RESISTANCE …. CONT'D

Cross resistance

This is the resistance seen among chemically related drugs. When a micro-organism develops resistance to one drug, it is also resistant to other drugs of the same group even when not exposed to it, e.g. resistance to one tetracycline means resistance to all other tetracyclines

TRANSFER OF ANTI-MICROBIAL DRUG RESISTANCE GENES AMONG BACTERIA

Many bacteria contain extra-chromosomal genetic material called plasmids in the cytoplasm. These carry genes coding for resistance (R-factors)

R-factors are transferred to other bacteria and spread resistance

TRANSFER OF R-FACTORS

Transfer of R-factors occurs by:

- Transduction: Plasmid DNA is transferred through bacteriophage, i.e. virus which infects bacteria
- Transformation: Resistant bacteria may release genetic material into the medium which is taken up by other bacteria
- Conjugation: The R-factor is transferred from cell to cell by direct contact through a sex pilus. This is the most important mode of spread of resistance.

MECHANISMS OF ANTI-MICROBIAL DRUG RESISTANCE

1. Production of enzymes that destroy the chemical structures of drugs
2. Change in cell membrane and cell wall permeability to the drug
3. Development of an altered structural target for the drug
4. Development of an altered metabolic pathways

MECHANISMS OF ANTI-MICROBIAL DRUG RESISTANCE …. CONT'D

Inactivation of antimicrobial drugs

- Bacteria acquire genes encoding enzymes that inactivate antibiotics
- Examples include: beta-lactamases that inactivate penicillins, aminoglycoside-modifying enzymes and chloramphenicol acetyl transferase

MECHANISMS OF ANTI-MICROBIAL DRUG RESISTANCE …. CONT'D

Altered uptake of anti-microbial drugs

- Results in decreased permeability to the drug and increased efflux of the drug
- Example, gram-negative bacilli can induce some special proteins to prevent entry of tetracyclines into the bacillus

Structural modification of target site

Example: the receptor protein on the 30s ribosomal subunit may be deleted or altered as a result of mutation resulting in failure of some aminoglycosides to combine with the bacteria

MECHANISMS OF ANTI-MICROBIAL DRUG RESISTANCE …. CONT'D

Development of altered metabolic pathways

- Microorganisms can develop an altered metabolic pathway that bypasses the reaction inhibited by the antimicrobial drugs
- Example, sulfonamide resistance may occur as a result of mutations that cause over-production of para-aminobenzoic acid (PABA) or cause production of a folic acid synthesizing enzyme that has low affinity for sulfonamides

METHODS OF AVOIDING RESISTANCE

- Antimicrobial agents should be used only when necessary
- Select the appropriate antimicrobial agent, whenever possible, using the narrow spectrum antimicrobial agents
- Correct dose and duration of treatment should be followed
- Avoid use of topical antimicrobial agents for prolonged periods of time
- Use a combination drug regimen where necessary to delay the development of resistance (e.g. in tuberculosis)

GENERAL PRINCIPLES OF ANTI-MICROBIAL THERAPY

Factors that influence the successful chemotherapy of an infection are:

- Site: the drug should reach the site of infection
- Concentration: the drug should attain adequate concentration at the site
- Host defense: active host defenses reduce the antimicrobial requirement
- Sensitivity: the micro-organism should be sensitive to the antimicrobial agent

GENERAL PRINCIPLES OF ANTI-MICROBIAL THERAPY …. CONT'D

Anti-microbial agents are used in two ways:

1. Empiric therapy: The drug must cover all the likely pathogens. A combination or a broad spectrum agent may be used. This therapy should be used only in some specific situations. Empirical therapy is usually commenced when results of bacteriological culture are not available.

2. Definitive therapy: When the definitive organism is identified, specific antibacterial agents should be given. Results of bacteriological culture should guide the drug selection.

GENERAL PRINCIPLES OF ANTI-MICROBIAL THERAPY …. CONT'D

Selection of an appropriate anti-microbial agent

- Identification of the infecting organism should precede anti-microbial therapy when possible
- The pathogenic micro-organism susceptibility to anti-microbial agents should be determined, if a suitable test exists

GENERAL PRINCIPLES OF ANTI-MICROBIAL THERAPY …. CONT'D

Factors that influence the choice of an anti-microbial agent or its dosage for a patient include:

- Age
- Renal and hepatic function
- Pregnancy and lactation status
- Site of infection

SELECTION OF ANTI-MICROBIAL AGENT

Selection of an anti-microbial agent is based on:

1. Pharmacodynamic factors: spectrum of activity
2. Pharmacokinetics factors: movement of drug through tissues of body
3. Patient factors: age, pregnancy and lactation status, allergies, co-existent diseases, immuno-competence

SELECTION OF ANTI-MICROBIAL AGENT …. CONT'D

Immuno-competence

- Immune system competence is necessary to eradicate microorganisms
- When there is immunosuppression there is need to kill the infecting organism rather than just inhibit growth. This often necessitates high dose prolonged therapy - increasing risk of toxicity and unwanted effects.

PROPHYLACTIC USE OF ANTI-MICROBIAL AGENTS

- Prophylaxis is the use of drugs in healthy individuals to prevent illness (e.g. infection)
- Chemoprophylaxis is the use of anti-microbial agents to prevent infection

CHEMOPROPHYLAXIS …. CONT'D

Chemoprophylaxis is recommended in the following situations:

- In medical care: to prevent infections in high risk patients (immune-compromised patients, neutropenic patients), prevent infection amongst contacts of patient with transmissible disease, suppression of infection before disease and prevention of exacerbation of chronic infection
- In surgery: where risk of infection is high (opportunistic infection), where risk of infection is low but outcome very serious and in patients increased susceptibility to infections

ANTI-MICROBIAL COMBINATION THERAPY

Use of a combination of antimicrobials may have synergistic, antagonistic or indifferent (no change) effects. Hence appropriate drugs should be used for combination.

Two bactericidal drugs given together are generally synergistic

Advantages of combination therapy

- Broadens the spectrum of activity
- Potentiation and synergism
- Reduces risk of emergence of resistance

ANTI-MICROBIAL COMBINATION THERAPY …. CONT'D

Disadvantages of combination therapy

- Drug interactions
- Toxicity (overlapping toxicity, toxicity of one drug may be enhanced by another)
- Selection of resistant strains – the few resistant mutants that remain may multiply unchecked
- Emergence of organisms resistant to multiple drugs
- Increased cost of therapy

USES OF ANTI-MICROBIAL COMBINATION THERAPY

- To obtain synergism e.g. β-lactam antibiotic plus aminoglycoside for endocarditis, anti-retroviral therapy
- Mixed infections or severe infections of unknown cause e.g. limb infections in diabetic patients, brain abscesses, intra-abdominal infections
- To prevent the emergence of resistance (e.g. HIV, tuberculosis and leprosy)
- Initial empiric therapy of severe infections e.g. bacterial meningitis, septicaemia
- To reduce adverse effects: the doses needed may be lower when a combination is used. This may reduce the incidence and severity of adverse effects.

WHY NOT USE TWO OR MORE ANTI-MICROBIAL AGENTS ALL THE TIME?

- Antagonism
- Cost
- Increased risk of adverse effects
- May actually enhance development of resistance: inducible resistance
- Interactions between drugs of different classes
- Often unnecessary for maximal efficacy

SUPER-INFECTION

- Super-infection/supra-infection is the appearance of new infection resulting from the use of anti-microbial agents
- Anti-microbial agents alter the normal microbial flora of the intestinal, respiratory and genitourinary tracts. The normal flora contribute to host defense mechanisms. They inhibit colonization of pathogenic organisms by producing antibacterial substances called bacteriocins and by competing for nutrients.
- When the normal flora are destroyed by antimicrobials, dangerous infections may result

SUPER-INFECTION …. CONT'D

- Chances of super-infection are highest with very broad spectrum antimicrobials, as they produce the greatest alteration of normal flora. Example: pseudo-membraneous colitis due to clostridium difficile when a patient is treated with clindamycin

END

Thanks for listening