Chemotherapeutic Drugs (Principles of Antimicrobial Therapy)

Introduction

Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity. In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration (CONC) of the drug be carefully controlled to attack the microorganism, while still being tolerated by the host.

Selection of Antimicrobial Agents (AMAs):

Selection of the most appropriate antimicrobial agent **requires knowing: Organism's identity, 2) Organism's susceptibility to a particular agent,3) Site of the infection, 4) patient factors, 5) Safety of the agent, and 6) Cost of therapy**. However, some patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

Identification of the infecting organism

Is essential step to select the proper drug. This process can be conducted by direct microscopic visualization and cultivation and identification, which are the most common techniques are used. Empiric therapy prior to identification of the organism Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established. However, in the critically ill patient, such a delay could prove fatal, immediate empiric therapy is indicated. For example, acutely ill patients with infections of unknown origin like a patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord) require immediate treatment.

Selecting a drug:

Drug choice in the absence of susceptibility data is influenced by the site of infection and the patient's history (for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, and whether the infection was hospital- or community-acquired).

For example, gram-positive (Gm+ve) cocci in the spinal fluid of a new-born infant is unlikely to be Streptococcus pneumoniae and most likely to be Streptococcus agalactiae (a group B streptococci), which is sensitive to penicillin G.

By contrast, Gm+ve cocci in the spinal fluid of a 40-year-old patient are most likely to be S. pneumoniae. This organism is frequently resistant to penicillin G and often requires

treatment with a high-dose third generation cephalosporin (such as ceftriaxone) or vancomycin.

Determining antimicrobial susceptibility of infective organisms

After a pathogen is cultured, its susceptibility to specific ABs serves as a guide in choosing antimicrobial therapy. Some pathogens like Streptococcus pyogenes usually have predictable susceptibility patterns to certain ABs. In contrast, most gram-negative bacilli and staphylococcal species often show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy.

Bacteriostatic versus bactericidal drugs:

- Bacteriostatic drugs arrest the growth and replication of bacteria, thus limiting the spread of infection until the immune system attacks, immobilizes, and eliminates the pathogen.

- Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill and immunocompromised patients.

Although practical, this classification may be too simplistic because it is possible for an AB to be bacteriostatic for one organism and bactericidal for another. For example, linezolid is bacteriostatic against Staphylococcus aureus and enterococci but is bactericidal against most strains of S. pneumoniae.

Minimum inhibitory CONC (MIC) is the lowest antimicrobial CONC that prevents visible growth of an organism after 24 hours of incubation, while minimum bactericidal CONC (MBC): is the lowest CONC of antimicrobial agent that results in a 99.9% decline in colony count after overnight broth dilution incubations.

Effect of the site of infection on therapy: the blood–brain barrier

Adequate levels of an AB must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues. The capillaries in the brain, which help to create and maintain the blood–brain barrier (BBB) can impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic. Drug properties can affect its penetration through BBB. These properties are:

a- Lipid solubility of the drug: The lipid solubility of a drug is a major determinant of its ability to penetrate into the brain. Lipids soluble drugs, such as chloramphenicol and metronidazole, have significant penetration into the CNS, whereas β-lactam ABs, such as penicillin, have limited penetration through the intact (BBB) under normal circumstances. b- Weight of the drug: A compound with a low molecular weight has

an enhanced ability to cross the BBB, whereas compounds with a high molecular weight (e.g vancomycin) penetrate poorly, even in the presence of meningeal inflammation.

b- c- Protein binding of the drug: A high degree of protein binding of a drug restricts its entry into the CSF.

Patient factors

In selecting an AB, attention must be paid to the condition of the patient. For example, the status of the patient's immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.

a- Immune system: Elimination of infecting organisms from the body depends on an intact immune system. Alcoholism, diabetes or advanced age can affect a patient's immunocompetence, as can immunosuppressive drugs. High doses of bactericidal agents or longer courses of treatment may be required to treat these patients.

b- b- Renal dysfunction: Poor kidney function may cause accumulation of certain ABs. Dosage adjustment prevents drug accumulation and therefore adverse effects. So, the direct monitoring of serum levels of some ABs (e.g vancomycin & aminoglycosides) is preferred to identify maximum and/or minimum values to prevent potential toxicities.

c- c- Hepatic dysfunction: ABs that are concentrated or eliminated by the liver (e.g erythromycin & doxycycline) must be used with caution when treating patients with liver dysfunction.

d- Poor perfusion: Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of AB that reaches that area, making these infections difficult to treat.

e- e- Age: Renal or hepatic elimination processes can be affected by patient's age. So, elderly patients may have decreased renal or liver function, which may alter the pharmacokinetics of certain ABs.

f- f- Pregnancy and lactation: Many ABs cross the placental barrier or enter the nursing infant via the breast milk. Although the CONC of an AB in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

Risk factors for multidrug-resistant organisms: Infections with multidrug-resistant pathogens need broader AB coverage when initiating empiric therapy. Common risk factors for infection with these pathogens include prior antimicrobial therapy in the preceding 90 days, hospitalization for greater than 2 days within the preceding 90 days, current

hospitalization exceeding 5 days, high frequency of resistance in the community or local hospital unit, and immunosuppressive diseases and/or therapies.

Safety and cost of the agent

ABs such as the penicillins are among the least toxic of all drugs because they interfere with a site or function unique to the growth of microorganisms. Other AMAs (e.g chloramphenicol) have less specificity and are reserved for life-threatening infections because of the potential for serious toxicity to the patient. Often several drugs may show similar efficacy in treating an infection but vary widely in cost.

Route of Administration

The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis. Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections. Some ABs, such as vancomycin and the aminoglycosides are so poorly absorbed from the GI tract that adequate serum levels cannot be obtained by oral administration.

Determinants of Rational Dosing

Rational dosing of AMAs is based on their pharmacodynamics and pharmacokinetic properties. Three important properties that have a significant influence on the frequency of dosing are CONC dependent killing, time-dependent killing, and post-AB effect (PAE).

A. CONC-dependent killing: Certain AMAs, including aminoglycosides and daptomycin, show a significant increase in the rate of bacterial killing as the CONC of AB increases. So, giving drugs that exhibit this CONC-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

B. Time-dependent (CONC-independent) killing: In contrast, β-lactams, macrolides and clindamycin do not exhibit CONC-dependent killing. The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood CONCs of a drug remain above the MIC. This effect is sometimes called CONC-independent or time-dependent killing.

C. Postantibiotic effect: The PAE is a persistent suppression of microbial growth that occurs after levels of AB have fallen below the MIC. Antimicrobial drugs exhibiting a long PAE (e.g aminoglycosides) often require only one dose per day, particularly against gram-negative bacteria.

CHEMOTHERAPEUTIC SPECTRA

A. Narrow-spectrum antibiotics

ABs acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, isoniazid is active only against Mycobacterium tuberculosis.

B. Extended-spectrum antibiotics

Extended spectrum is the term applied to ABs that are modified to be effective against Gm+ve organisms and also against a significant number of gram-negative bacteria (e.g ampicillin is considered to have an extended spectrum because it acts against Gm+ve and some gram-negative bacteria.

C. Broad-spectrum antibiotics

Drugs such as tetracycline, fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum ABs. Administration of broadspectrum ABs can drastically alter the nature of the normal bacterial flora and precipitate a superinfection due to organisms such as Clostridium difficile.

Combinations of antimicrobial drugs

It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism. This strategy reduces the possibility of superinfections, decreases the emergence of resistant organisms, and minimizes toxicity. However, some situations require combinations of antimicrobial drugs for e.g the treatment of tuberculosis benefits from drug combinations.

A. Advantages of drug combinations

Certain combinations of ABs, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately. Because such synergism among AMAs is rare, multiple drugs used in combination are only indicated in special situations (for example, when an infection is of unknown origin or in the treatment of enterococcal endocarditis).

B. Disadvantages of drug combinations

A number of ABs act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second. For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins. Another concern is the development of AB resistance by giving unnecessary combination therapy.

DRUG RESISTANCE

Bacteria are considered resistant to an AB if the maximal level of that AB that can be tolerated by the host does not halt their growth. Drug resistance can be occurred by two mechanisms:

1- Genetic alterations leading to drug resistance: Acquired AB resistance requires the temporary or permanent alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another.
2- 2- Altered expression of proteins in drug-resistant organisms: can be represented by different mechanisms, which are modification of target sites or enzymatic inactivation.

PROPHYLACTIC USE OF ANTIBIOTICS

Certain clinical situations, such as dental procedures and surgeries, require the use of ABs for the prevention rather than for the treatment of infections. Because the indiscriminate use of AMAs can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis should be closely observed to prevent the unnecessary development of AB resistance.

COMPLICATIONS OF ANTIBIOTIC THERAPY

Even though ABs are selectively toxic to an invading organism, it does not protect the host against adverse effects. For example, the drug may produce an allergic response or may be toxic in ways unrelated to the antimicrobial activity.

A. Hypersensitivity

Hypersensitivity or immune reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

B. Direct toxicity

High serum levels of certain ABs may cause toxicity by directly affecting cellular processes in the host (for example, aminoglycosides can cause ototoxicity).

C. Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections usually require secondary treatments using specific antiinfective agents.

SITES OF ANTIMICROBIAL ACTIONS

Antimicrobial drugs can be classified in a number of ways:

1- Chemical structure (for example, β-lactams or aminoglycosides)

2- Mechanism of action (for example, cell wall synthesis inhibitors (Figure 1).

3- Activity against particular types of organisms (for example, bacteria, fungi, or viruses).

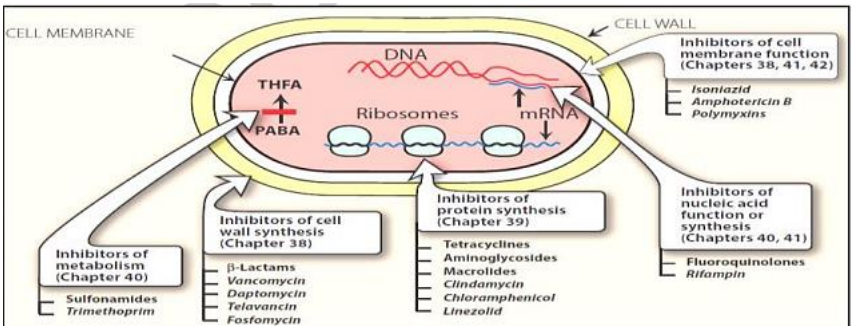

Figure 1: Classification of some AMAs by their sites of action. (THFA = tetrahydrofolic acid; PABA = paminobenzoic acid.)

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.