بسم الله الرحمن الرحيم

Principles of antimicrobial therapy

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CHEMOTHERAPY

- **Chemotherapy** is a term applied for synthetic chemicals that destroy infective organisms.

- They fall into four categories: **antibacterial**, **antiviral**, **antifungal** and **anti-parasitic** agents.

- The term "chemotherapy" has been broadened to include also antineoplastic (**anticancer**) agents.

(تعلق بالورم)

- **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.).

تقتل البكتيريا وتقتل الإنسان

الإنسان

- 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.

- Some antibiotics are **antibacterial**, others are **antifungal** and others are **anticancer** antibiotics.

- **Chemical modifications** on the chemical structure of antibiotics can result in **more effective** or more potent or **wider spectrum** chemotherapeutic agent.

Antibacterial drugs

Classification

A) According to the spectrum against bacteria

1. Drugs acting mostly against **gram positive organisms (narrow spectrum)** as **penicillin G**, β lactamase resistant penicillins, **vancomycin**, and some **macrolides**.

2. Drugs acting mostly against **gram negative organisms (narrow spectrum)** as **aminoglycosides** and **polymyxins**.

3. Drugs acting against **both** gram positive and gram negative organisms i.e. **broad spectrum** as **Chloramphenicol**, **Fluoroquinolones** and **tetracyclines**.

B) According to the fate of the organism: Bactericidal versus bacteriostatic

An antimicrobial drug that can eradicate an infection in the absence of host defense mechanisms (e.g. **kills bacteria**) is called a **bactericidal** agent. Therefore, in patients with **immune deficiency**, or when the host defense can't reach the site of infection (e.g. **infective endocarditis**), antibiotic selection for treatment of infection should be of **bactericidal activity.**

When the antimicrobial drug **inhibits microbial growth** and requires host defense mechanisms to eradicate the infection (i.e. does not kill bacteria), it is called **bacterioststic** agent

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C) According to mechanisms of actions

DNA أهم شي منها

1- 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 **β – lactam antibiotics**, **vancomycin** and **bacitracin**.

2- 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**.

not cell wall

Examples: **polymyxins**, **daptomycin**, **amphotericin B** and **nystatin**.

3- Inhibition of **protein synthesis**: drugs that inhibit 30 S and 50 S ribosomal subunits block protein synthesis as **Chloramphenicol**, **Tetracyclines**, **macrolides** and **aminoglycosides**.

4- Inhibition of **intermediary metabolism**: as **sulfonamides** and **Trimethoprim** that inhibit folic acid synthesis.

5- Inhibition of **nucleic acid synthesis**: **rifampin** inhibits RNA synthesis in bacteria . **Fluoroquinolones** inhibit the bacterial topoisomerases and thus inhibit DNA transcription and replication.

Resistance to antibacterial agents

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. *

تم تغييره

نعم، في العديد من الحالات، تؤدي الطفرات التي تجعل البكتيريا أكثر مقاومة للمضادات الحيوية إلى انخفاض قدرتها على الإمراض. السبب هو أن هذه الطفرات قد تؤدي إلى تغييرات في وظائف الخلايا أو بنيتها، مما يمكن أن يضعف من فعاليتها في التسبب بالعدوى.

ومع ذلك، هذا ليس صحيحًا دائمًا. فبعض البكتيريا، مثل المتفطرة السُلّية، يمكن أن تطور مقاومة دون أن تفقد قدرتها على التسبب في المرض.

Genetic determinants of antibiotic resistance

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.

ii- **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.

iii- **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: β – lactamases inactivate penicillins, adenylating and acetylating enzymes inactivate aminoglycosides.

لقدر أزيد الجرعة وبالتالي أقتل البكتيريا لكن الجرعة ستكون قاتلة لل [host cell]

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. (TB لازم أشتغل عليها بأكثر من antibiotic)

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.

1+1>2

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 Enzymatic Inactivation:** One drug (e.g. Clavulanic acid) protects amoxicillin from destruction by β-lactamases of bacteria. One drug protect the other
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

for protection not treatment

The use of chemotherapeutic agents to prevent rather than to treat an existent infection.

β-Hemolytic S.cocci - 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

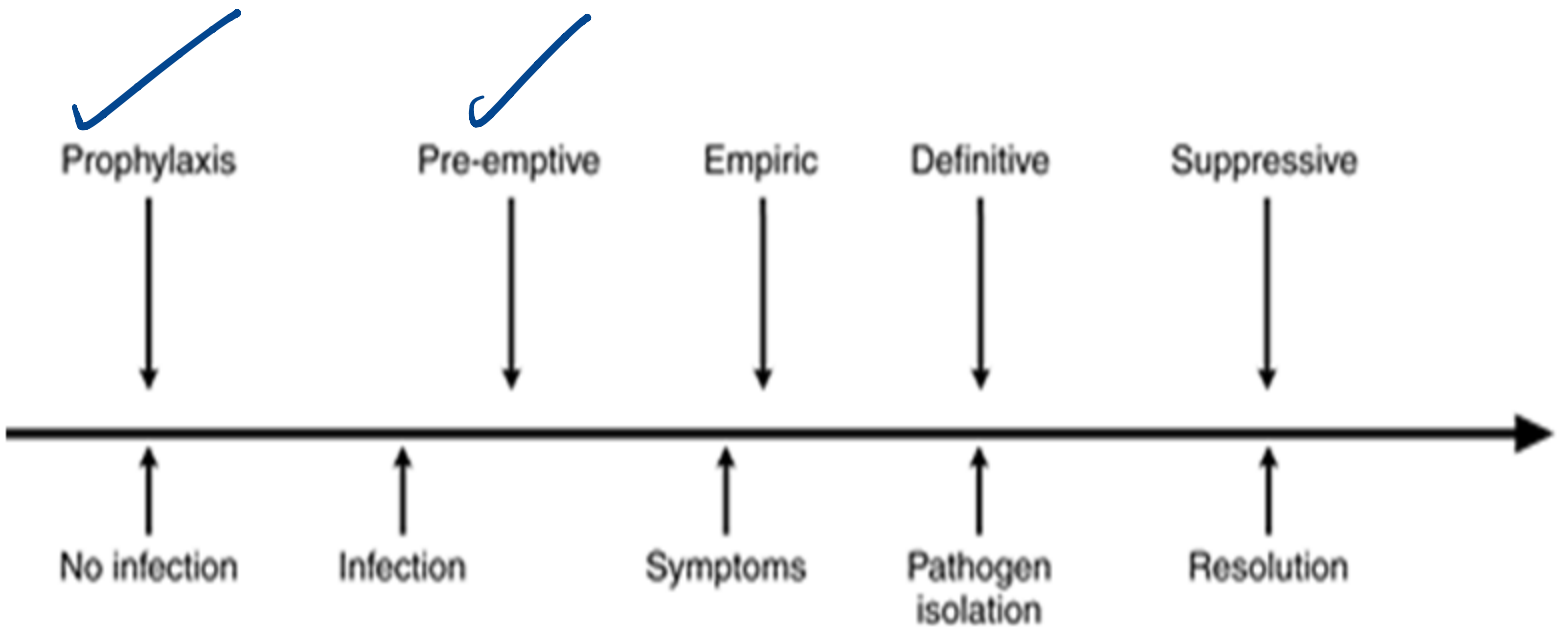
1. Toxic reactions.
2. Hypersensitivity reaction.
3. Superinfection.

Superinfection

بيطلع واحد وانا بعالج new infection أو تاني

- 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. يتم القضاء على الكائنات الحية الحساسة، وتتكاثر الكائنات الحية المقاومة للأدوية، التي تحررت من المنافسة، مما يؤدي إلى حدوث عدوى مفرطة.
- It is relatively dangerous as it may lead to serious new infections by Pseudomonas, Enterobacteriaceae, or Candida (which may be difficult to be cured).

Regimens of antimicrobial therapy



Empirical Therapy: علاج تجريبي

Antibiotics are given once the symptoms of infection appear before culture and sensitivity results.

Pre-emptive therapy: استباقي

It is an early prophylactic therapy in high risk asymptomatic patients.

Prophylactic therapy: وقائي

Prophylaxis means protection against infection development in susceptible individuals to prevent potential serious infection development.

Definitive curative therapy: علاجي نهائي

If the microorganism is isolated and susceptibility tests were done.

Suppressive therapy كابح

Continuous treatment to suppresses microbial relapse after resolution of infection.

العلاج التجريبي:
يتم إعطاء المضادات الحيوية بمجرد ظهور أعراض العدوى قبل ظهور نتائج الزراعة واختبار الحساسية.

العلاج الاستباقي:
هو علاج وقائي مبكر يُعطى للمرضى ذوي الخطورة العالية ولكن دون أعراض.

العلاج الوقائي:
الوقاية تعني الحماية من تطور العدوى في الأفراد القابلين للإصابة لمنع حدوث عدوى خطيرة محتملة.

العلاج العلاجي النهائي:
يتم هذا العلاج عندما يتم عزل الكائنات الدقيقة وإجراء اختبارات الحساسية.

العلاج الكابح:
علاج مستمر يهدف إلى كبح عودة العدوى بعد التعافي منها.


THANK
YOU