Basic principles in antibiotic therapy

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ABSTRACT

In 1877, Louis Pasteur studied the phenomenon of antibiosis, that is, the disharmonious interspecific relationship; however, only years later, the first antibiotic substance was developed, in 1929, by Alexander Fleming, which consisted of a yeast-like colony that reproduced in the vicinity of a petri tree. The antimicrobial spectrum can express the range of action of the drug, that is, it expresses the percentage of bacterial groups sensitive to the drug. The resistance of microorganisms represents a phenomenon of their evolutionary adaptation, which can be natural or acquired. The increase in the number of resistant bacteria may be linked to the mechanism of "induced selection", i.e., antibiotics lyse sensitive organisms, leaving resistant ones unharmed; or through dissemination, which happens through ingestion and/or contact with foods composed of antimicrobials.

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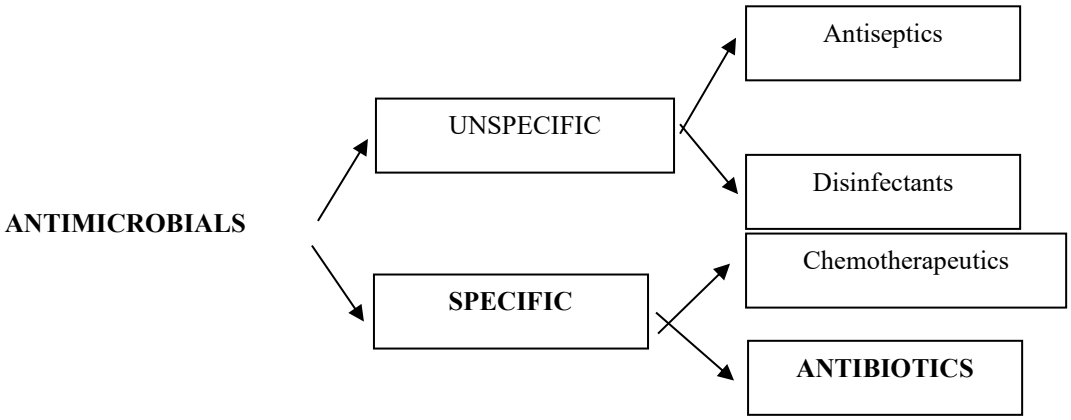
INTRODUCTION

In 1877, Louis Pasteur studied the phenomenon of antibiosis, that is, the disharmonious interspecific relationship; however, only years later, the first antibiotic substance was developed, in 1929, by Alexander Fleming, which consisted of a yeast-like colony that reproduced in the vicinity of a petri tree. Penicillin was developed. This drug had clinical application only in 1941 with the scientists Chain and Florey, concluding that penicillins – despite being the first antibiotic drugs developed – did not inaugurate the clinical prescriptions of this group of drugs, noting that sulfonamides were the first to be used six years earlier, in 1935. It will be seen later that antibiotic therapy has revolutionized medical therapeutics, demonstrating a subversion of the scourges of humanity, not least because these drugs, if they are correctly administered, have a selective toxicity to the invading parasite, sparing – as much as possible – the host. See Figure 1 for the defining origin of antibiotics.

Figure 1. Defining origin of antibiotics and their distinction between antiseptics, disinfectants, and chemotherapeutics.



SOURCE: The Authors, 2024.

Antibiotics and chemotherapy are words that are very present in a large part of the population. However, they do not refer to the same definition, so much so that the main divergence consists in their origins, since a chemotherapy always has a chemical origin; An antibiotic, on the other hand, has a biological matrix, which – when necessary – can be modified in the laboratory, receiving the nomenclature of *symptobiotic*; as is the case with most penicillins. Thus, it can be said that chemotherapeutic drugs consist of chemical substances artificially obtained for the treatment of non-infectious diseases, such as neoplasms, however, the same has as a side effect the action on the host's own cells.

Referring in this chapter exclusively to the study of antibiotic therapy, it should be known that there are two general types of mechanisms of action of these drugs: those that destroy pathogenic microorganisms and, on the other hand, those that act only in the paralysis of their reproductive process. However, there is a similarity between these two "classes": both act as chemical molecules

that interfere with the metabolic pathway of the therapeutic target, whether in the reaction of protein synthesis, peptidoglycan, nucleic acids, or folates. Thus, antibiotic action can be classified into two major groups:

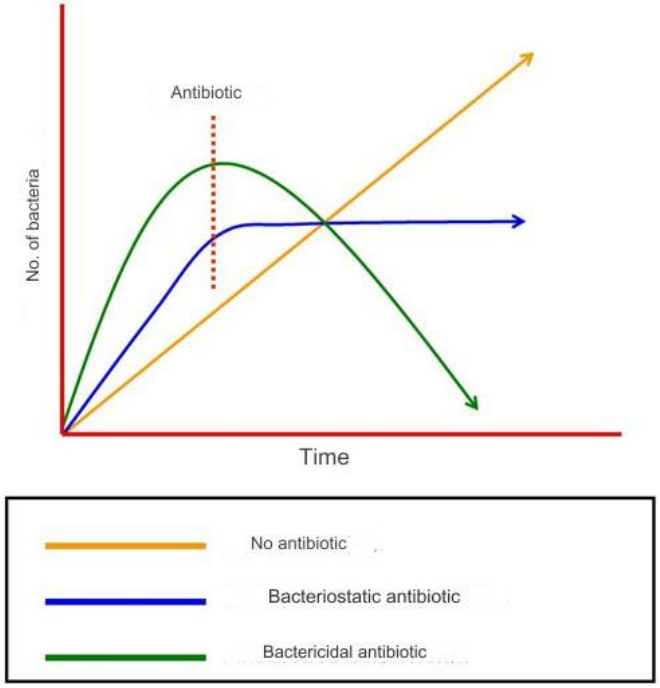
- **Bacteriostatic:** Drugs characterized as *bacteriostatic* inhibit bacterial multiplication, but do not destroy it. Based on this, it is possible to state that the suspension of this type of drug is more prone to the development of new growth of the microorganism (OM) and, consequently, greater resistance to these drugs. In this way, the use of a bacteriostatic drug causes its active substance to be stored inside the cell wall of the bacteria, but as will be seen below, OMs can expel it, by means of integral evasion proteins, transforming it into an ineffective drug.
- **Bactericidal:** bactericidal drugs have a total and lethal action on bacteria, having an irreversible effect on sensitive invaders, as opposed to bacteriostatic drugs.

These concepts, suffixed with *–cida* and *–static* , are also applied to the study of drugs that act to combat fungi and viruses: fungicides and fungistatics; virucidal and viriostatic; respectively. The *evidence of the action of antibiotics on the bacterium* is verified from the IMC (minimum inhibitory concentration) and AMC (minimum bactericidal concentration). The former is conceptualized as "the lowest concentration of antibiotic capable of completely inhibiting, *in vitro*, the visible growth of this living being"; while AMC refers to "the lowest concentration of drug that, after 18 hours of contact with the bacterial population, is capable of eliminating 99.9% of it". c

Therefore, it is possible to establish the dosing regimen of the drugs, because from the IMC and AMC, the sensitivity of a given drug to a certain microorganism will be ascertained – in vitro, that is, the OM may be sensitive, intermediate or resistant to the drugs tested. Sensitivity occurs when the MIC is clearly lower than the blood concentration obtained after administration of a dose known to conventional therapies, i.e., the lower the MIC, the greater the potency of the antibiotic, so the higher its potency, the greater the difficulty in developing resistance. On the other hand, it refers to a resistant OM when the MIC is found to be higher than the maximum concentrations that can be obtained *in vivo* without the administration of toxic doses.

Knowing the characteristics exposed above, it is possible to develop a graph that shows the difference in bacterial growth without and with the use of antimicrobials, as can be seen in Figure 2.

Figure 2. Graph showing the growth of the bacterial population in colony-forming units (CFU) without the use of ATB, with the use of a bactericidal ATB and a bacteriostatic ATB (the death of OM requires the action of the immune system, even because this antibiotic modality only blocks bacterial proliferation).



ANTIMICROBIAL SPECTRUM

The antimicrobial spectrum can express the range of action of the drug, that is, it expresses the percentage of bacterial groups sensitive to the drug. A small-spectrum drug is able to target a small number of bacteria, such as only gram-positive or gram-negative. A broad-spectrum drug, on the other hand , is endowed with the ability to inhibit both gram-positive, gram-negative, as well as other MO, such as anaerobes.

An important point, since the subject refers to infections, is the differentiation between *Community-acquired infections* and *Hospital*, because the correct discernment of them is helpful, *in retrospect,* in diagnostic and therapeutic approaches. Those are found to be acquired outside the nosocomial environment, i.e., they are not related to the patient's maintenance in the hospital. It is also accepted that a community-acquired infection can be contracted at the time of an individual's admission to this environment.

Nosocomial infections, on the other hand, have characteristics of incubation after hospitalization, being related to procedures, to the hospital environment itself, altering the normal microbial flora, that is, for practical purposes they are acquired after 48 hours of hospital admission or 24 hours if an invasive procedure has been performed (central venous access, for example).

BACTERIAL RESISTANCE

There is no way to talk – correctly – about antibiotics without mentioning resistance. Since this pharmacological class emerged, its use has been on a large scale, leaving a large part of its users resistant to these drugs, that is, when they really needed the drug, it would not have the desired effect. For this reason, "don't turn an ally of your health into an enemy." In 2011, Anvisa decreed through RDC 20/2011 the commercialization of these drugs only with the retention of the medical prescription by the establishment, which had – and still has – the objective of reducing the number of self-medications.

There has been so much talk about *bacterial resistance*, but it has not been defined. The resistance of microorganisms represents a phenomenon of their evolutionary adaptation. Over time, they have acquired mutations and structural changes that maintain their survival, so that resistance can occur naturally (without the occurrence of mutations, as is the case of *Moraxella catarrhalis* against penicillins, due to the production of beta-lactamases). However, the resistance may be acquired, i.e., the bacterium that was sensitive, due to numerous reasons (inadequate therapy, livestock – tetracyclines in feed) ended up becoming resistant.

There are some important biochemical mechanisms of antibiotic resistance by microorganisms. To begin with, we have the *production of an antimicrobial inactivating enzyme*, such as beta-lactamases, which destroy the beta-lactam rings of penicillins (99.9% of the *M. catarrhalis* and 50% of *Haemophilus influenzae* and 30% of the *Streptococcus pneumoniae*), making it possible to observe bacteria that produce these enzymes in the culture plates; Some bacteria are able to *alter your ATB-sensitive sites* by means of chromosomal mutations, as occurs with aminoglycosides: OMs modify the site of action of these drugs, altering the 30S subunit of the ribosome.

Another mechanism of bacterial evasion consists *of integral efflux proteins*, i.e., microorganisms are able to reduce the accumulation of drugs inside them through the expulsion channels created in their plasma membrane. In addition, some OMs are able to create an *alternative metabolic pathway* to prevent the inhibition of a certain metabolic reaction, modifying it. Trimethoprim (TMP) ends up having to face this problem throughout its mechanism of action, even because its target bacteria are capable of transferring, via plasmids, this information to daughter cells: "such an enzyme will be the therapeutic focus of such a fighter", in this way there will be an alteration of the conventional metabolic pathway.

Antibiotics are used on a large scale all over the world, and in some cases they require their association, but for this to happen, a consensus must be stipulated, as in the case of tuberculosis, for example. Therefore, it is determined as possible to combine two or more antibiotics when there are:

- Serious infections without diagnosis;

- Mixed infections;
- When it is desired to reduce the dose of an antimicrobial due to its toxicity, it can be associated with another antimicrobial (s) in order to avoid possible bacterial resistance.

It should be known that the antimicrobial association can occur between a bactericide and a bacteriostatic, generating an associative antagonism, in such a way that the bactericide will act in the destruction of the multiplying bacteria; and the bacteriostatic will act by inhibiting the multiplication of OM. However, that antibiotic will not be able to act on the bacterium under latent multiplication (paralyzed) by the action of this drug. A synergistic association will occur between two or more bactericidal drugs, such as the treatment for tuberculosis composed of the following representatives: isoniazid; Rifampin; and pyrazinamide. To conclude the study on the associations, there is the so-called *additive*, that is, between two bacteriostatics. This type of alliance is used as a possibility for the treatment of UTI (Urinary Tract Infection): sulfamethoxazole (SMZ) + trimethoprim (TMP).

It can be clearly seen that choosing the ideal antimicrobial is not an easy task. For this reason, a series of questions should be asked in order to safely prescribe these drugs.

- Is it really necessary to use an ATB?
- What bacteria are most likely to occur in this case?
- If there are several ATBs to choose from, which is the best choice?
- Is the association between ATB adequate?
- What are the important host factors that can determine whether or not to use a particular antimicrobial?
- What is the best route of administration?
- What is the appropriate dose?
- Does the initial treatment need to be modified after the culture result?
- How long is the therapy? Is there a possibility of resistance during prolonged treatment?

ANTIBIOTIC SUSCEPTIBILITY TESTING (TSA)

It has already been seen that some bacteria can become resistant to certain drugs by accumulation of genetic mutations, which can be transmitted to the descendant population through plasmids, from the processes of transduction, transformation or conjugation. The increase in the number of resistant bacteria may be linked to the mechanism of "induced selection", i.e., antibiotics lyse sensitive organisms, leaving resistant ones unharmed; or through dissemination, which happens through ingestion and/or contact with foods composed of antimicrobials. Thus, in some cases, it is necessary to perform the TSA or antibiogram in order to verify the *in vitro behavior* of a given microorganism in relation to some antibiotics.

The professionals responsible for choosing the ATB tested to verify the *in vitro* behavior of the bacteria are infectologists, microbiologists, members of the hospital infection control committees (HICC), hospital pharmacists, emphasizing that this task is extremely relevant, even because a TSA plate, for a MO, most of the time contains only 12 (twelve) antimicrobials.

In addition, it is important to know *when* to request the antibiogram, because OM with constant sensitivity to a certain ATB does not require the preparation of the antibiogram, as is the case with *Streptococcus pyogenes* against benzylpenicillin, for example. On the other hand, there are bacteria with varying sensitivity, such as enterobacteria, staphylococci – among others – which, in a way, impose the need for a supporting TSA, in order to know which ATB will be more effective in combating these representatives of the Monera Kingdom.

Only in 2016, Brazil created a regulatory document on what *to do with each OM and each specific infectious process*. Until then, TSA tests were based on American and European regulations, a fact that could generate *biases* in the results obtained, since the epidemiology varies in these different locations. In this way, the data obtained in an antibiogram are emitted "in groups":

- **Group A:** represents the cheapest and least resistant drugs to combat the OM in question: they are the first choice, tested and reported;
- **Group B:** are the second-choice drugs, used in situations where the administration of group A representatives is not feasible: selectively tested and reported;
- **Group C:** refers to supplemental and selectively reported drugs. They are the most expensive drugs with the greatest possibility of resistance;
- **Group U:** drugs tested in urine isolates.

CLASSIFICATION OF ANTIBIOTICS

The classification of the various classes of antibiotics can be made based on several criteria: mechanism of action, spectrum of action, chemical structure, sources of origin, organelles affected. However, this chapter will obey the division established from the mechanism of action of drugs.

- **Inhibition of cell wall synthesis:** beta-lactams;
- **Inhibition of protein synthesis:** tetracyclines, macrolides;
- **Provocation of erroneous reading of RNA with consequent erroneous coding of proteins:** aminoglycosides;
- **DNA gyrase inhibition:** quinolones;
- **Interference with intermediate metabolism:** sulfonamides.

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