Article received on October 23, 2019 and accepted for publishing on February 13, 2020.

ORIGINAL ARTICLES

Antibiotherapy: latest current affairs – state of the art 2019

Viorel Ordeanu[1,2], Lucia E. Ionescu[1], Victoria G. Dumitrescu[1], Roxana G. Pricop[1], Răzvan Neagu[1], Diana M. Popescu[1]

Abstract: *Given the continuous growth of the bacterial resistance phenomenon, the appropriate choice of antibiotherapy represents an important step in the treatment and prophylaxis of infectious diseases. Depending on the symptomatology, the dose required for the effective treatment of an infection may vary. Inadequate dosing not only reduces the effectiveness of the antibiotic, but also promotes the emergence of resistant bacterial strains. Also, too high of a dose increases the toxic side effects of antibiotics. Therefore, a personalised antibiotherapy according to: the patient's clinical status, body mass, associated chronic diseases, etc. represents a promising approach in the treatment of infectious diseases.*

The purpose of this study is to present the most important current affairs regarding the emergence of new antibiotics, the maximum doses recommended by the latest version of the "European Committee on Antimicrobial Susceptibility Testing" (EUCAST - version 9/2019) and providing an indication on whether these antibiotics are used in Romania.

Keywords: *antibiotics, antibiotherapy, maximum recommended dose, antimicrobial chemotherapics*

INTRODUCTION

Antibacterial chemotherapics (antibiotics) have become the emblematic drugs of the 20th century starting with the first antibacterial chemotherapic, Salvarsan (invented by Paul Ehrlich, of German origin, in 1909) and the beta-lactamase Penicillin (discovered by the American Alexander Fleming, in 1929). Currently, there are hundreds of antibacterial antibiotics (AB), of which 269 have been approved for antibiotherapy (ABT). It was believed that bacterial diseases could be eradicated, but the practice has shown since the middle of the last century that the phenomenon of bacterial resistance to antibiotics emerges, that much higher doses are now needed, with modified conditioning and dosage, targeted use, in phases and combined or associated, even the use of new antibiotics, as far as they can be produced [1-7].

[1] Military Medical Research Center, Bucharest, Romania
[2] "Titu Maiorescu" University, Bucharest, Romania

ANTIBIOTHERAPY

Over time, the efficacy of ABT has been reduced, despite advances in medicine in general and pharmacology in particular. Resistant, multi-resistant and all-resistant bacteria create the most serious problems in medical practice and more and more patients die from infections or over-infections that do not respond to treatment. This worrying phenomenon has been thoroughly investigated, starting with the application manner of ABT. Thus, the website www.longitudeprize.org published in 2014 an international medical statistic [6] having as results the inappropriate use and prescription of ABs:

• 90% of the physicians prescribed AB under the pressure of the patient who wanted a certain AB (namely, "Customers is King?!");

•70% of the physicians prescribed AB without being sure

Corresponding author: Ionescu Lucia
ionescu.lucia@gmail.com

that the etiology of the disease is bacterial or viral;

• 49% of the physicians prescribed AB for a week or more, without a prolonged treatment being needed;

•44% of the physicians prescribed AB only preventively, after discharge from surgery.

Following the highlight of the multiple factors that lead to the irrational use of ABs, medical and especially non-medical, in 2017 UN/WHO launched a new conception on prophylaxis and treatment – One health – and officially formulated recommendations for the Member States, with the goal of maintaining the efficiency of ABT worldwide. Based on these recommendations, each country sets its own research directions for medical and pharmaceutical scientific research. In this respect, a prize was established worldwide, Longitude Prize (2014). It has a prize pool of £ 10m to reward a competitor who will develop a test targeted on the rapid diagnosis of the diseases that require ABT. Through the rational use of ABs, the test would lead to the conservation of efficiency and shall revolutionise healthcare worldwide. The test should be accurate, fast, inexpensive, easy-to-use and accessible to anyone, anywhere in the world. By this test, shall be identified which ABs are needed and which shall be used. But these requirements seem utopian in the current stage of development of science and technology, it being unlikely to discover something that corresponds at least partially. Therefore, the prize has not been awarded so far.

Inventing new ABs is costly and difficult. These must meet divergent conditions: high toxicity for microorganisms (thus, antimicrobial efficacy), but little or no toxicity for the treated macroorganism; also, it must not have significant side effects; it must be produced industrially with reasonable costs; it must be stored and managed conveniently etc.

For the in vitro evaluation of the antibacterial effect of the AB, the Minimum Inhibitory Concentration (MIC) testing is performed on the respective bacterium (Breakpoint by determination in microdilutions in liquid culture medium) and the Kirby-Bauer diffusimetric antibiogram (ABG) with the measurement of the diameter of the Inhibition Zone (IZ) on the solid culture medium [2, 7]. One can choose from theoretically efficient ABs [1, 3, 4, 5] those that inhibit isolated and identified bacteria from the patient, by interpreting in the SIR system (Susceptible, Intermediate and Resistant) the diameter measured in millimeters, compared to EUCAST tables [2]. Because often the result obtained in vitro was between susceptible and resistant, this is noted as intermediate and for clinicians it was equivalent to resistant, because it would not have the desired therapeutic effect. In the current conditions of spread of the bacterial resistance phenomenon towards antibiotics, it is recommended to increase the dose of ABs, where the pharmacological properties allow, so that the bacteria pass from the intermediate to the susceptible area. By this approach of bacterial susceptibility, the intermediate bacteria pass from the resistant group to the susceptible group, and the SIR system gains another significance. The paraclinical findings become a practical indicator for the guidance of the clinician:
S = susceptible to standard dosing regimen (usual dosage)
I = intermediate, susceptible to high exposure (high doses, where possible)
R = resistant (therefore, useless for use).

As a result, the most handy method of combating bacterial resistance is the justified increase of the consumption of ABs, by increasing the single dose, daily or per cure, the frequency of administration or the duration of treatment, where the pharmacological characteristics allow (for example, in order not reach the toxic dose). The maximum recommended doses can be per dose, per day or per cure, and the cure can be short (1-5 days), medium (5-10 days), long (10-15 days) or very long (15-60 days). The doses are approximated depending on the conditioning of the drug (single antibiotic package or fixed combination), as well as the body mass of the patient. Any drug is theoretically dosed for an average patient, with a net body weight of 70 kg; so for a patient over 140 kg it should be double dose and for one below 35 kg it should be half dose. Some drugs, including ABs, are given by calculating in mg/kg body weight, especially in paediatrics, where children may have very different weights. When choosing ABs and in determining the dose, one must take into account, in addition to the pharmacological criteria imposed by antibiotherapy (which are well known), also: the general and particular contraindications, the age, the general patient status, the associated diseases, possible allergies or intolerances, the need for combinations with anti-beta lactamases or combinations with ABs or other anti-infective or adjuvant drugs. Consideration should also be given to possible antagonisms, inactivation with drugs and food, unwanted adverse or secondary phenomena as well as possible Herxheimer-type reactions. All this leads to a bi-unequivocal personalized ABT: depending on the needs and characteristics of the patient as well as the susceptibility of the pathogenic bacterium [8-13].

THE CLASSIC RECOMMENDATIONS

Professor Balș, the professional owner of the hospital that bears his name formulated the basic principles of antibiotherapy (also called antibiotic therapy) regarding: indications, contraindications, errors, associations of ABs,

which are still valid today. These principles have been applied in Romanian medical practice by Prof. Angelescu and his students, with undeniable successes. But at present, although all these principles have remained valid, their effectiveness in ABT practice is progressively diminished, due to the the spread of bacterial resistance to ABs, worldwide. As a result, we must complement these principles with new observations and discoveries in order to maintain the effectiveness of ABT. The most important news for ABT are not the new ABs, but the increased doses of those already known and their grouping by type of bacterial resistance.

MAXIMUM DOSES CURRENTLY RECOMMENDED

The new maximum doses are recommended by EUCAST 2019, p.96-99, systematized on AB groups, International Common Names (DCI) and with mentions for different clinical situations (2), and in the following we shall provide a summary, with the mention, „*" If used in Romania:

Penicillins: Benzylpenicillin* 1.2 g (2MU) x 4-6 iv, or 2.4 (4 MU) x 6 iv in meningitis and pneumonia; Ampicillin* 2 g x 4 iv, or 2 g x 6 iv in meningitis; Ampicillin+Sulbactam* 3 g x 4 iv; Amoxicllin* iv 2 g x 6 iv; Amoxicllin - oral 1 g x 3; Amoxicllin+clavulanic acid* iv 2.2 g x 3 iv; Amoxicllin+ clavulanic acid - oral 1 g x 3; Piperacillin* 4 g x 4 iv; Piperacillin+tazobactam* 4.5 x 4 iv; Ticarcillin* 3 g x 6 iv; Ticarcillin+clavulanic acid* 3.1 g x 6 iv; Phenoxymethyl-penicillin 2 g x 4 oral; Oxacillin* 1 g x 6 iv; Cloxacillin 1 g x 4 oral or 2 g x 6 iv; Dicloxacillin 2 g x 4 oral or 2 g x 6 iv; Flucloxacillin* 1 g x 4 oral or 2 g x 6 iv; Mecillinam 0.4 g x 3 oral.

Cephalosporins: Cefaclor* 0.25-1 g tidpo; Cefadroxil* 0.5-1 g bidpo; Cephalexin* 0.25-1 g bid-tid po; Cefazolin* 1 g tid-qid (or 2 g tid) iv; Cefepime* 2 g tid iv; Cefixime* 0.2- 0.4 g bid po, or 0.4 g po in gonorrhea; Cefotaxime* 2 g tid iv, or 2 g qid in meningitis; Cefpodoxime* 0.1-0.2 g bid po; Ceftaroline* 0.6 g tid iv (slow infusion – 2 hrs); Ceftazidime* 2 g tid iv or 1 g x 6 iv; Ceftazidime+avibactam* 2.5 g tidpev (2 hr infusion); Ceftibuten 0.4 g po; Ceftobiprole 0.5 g tid iv (slow infusion – 2 hrs); Ceftolozane+tazobactam* 1.5 g tid iv (slow infusion – 1 hr); Ceftriaxone* 2 g bid iv, or 4 g iv in meningitis; Cefuroxime* 1.5 g tid iv; Cefuroxime 0.5 g bid po.

Carbapenems: Ertapenem* 1 g x 1 iv; Imipenem* 1 g qid iv (30 mins perfusion); Meropenem* 2 g tid iv (3 hrs perfusion), or in meningitis 2 g tid iv; Meropenem+vaborbactam 4 g tid iv.

Monobactams: Aztreonam 2 g qid iv.

Fluoroquinolones: Ciprofloxacin* 0.75 g bid po, or 0.4 g tid iv; Levofloxacin* 0.5g bid po, or 0.5g bid iv; Moxifloxacin* 0.4g x 1 po, or 0.4g x 1 iv; Norfloxacin* 0.4g bid po; Ofloxacin* 0.4 g bid po, or 0.4 g bid iv.

Aminoglycosides: Amikacin* 30 mg/kg x 1 iv; Gentamicin* 7 mg/kg x 1 iv; Netilmycin* 7 mg/kg x 1 iv; Tobramycin* 7 mg/kg x 1 iv.

Glycopeptides and glycolipopeptides: Dalbavancin* 1 g x 1 iv; Oritavancin 1.2 g x 1 iv; Teicoplanin* 0.8 g x1 iv (single dose in slow infusion – 3 hrs); Telavancin 10 mg/kg x 1 (slow infusion – 1 hr); Vancomycin* 0.5 g qid iv, or 1 g bid iv, or 2 g x 1 in perfusion.

Macrolides, lincosamides and streptogramins: Azithromycin* 0.5 g x 1 po, or 0.5 g x 1 iv, or 2 g po in single dose; Clarithromycin* 0.5 g bid po; Erythromycin* 1 g qid, or 1 g qid iv; Roxithromycin 0.15 g bid po, Telithromycin 0.8 g x 1 oral; Clindamycin* 0.3 g qid po, or 0.9 g tid iv; Quinupristin+dalfopristin 7.5 mg/kg tid iv.

Tetracyclines: Doxycycline* 0.2 g x 1 po; Eravacycline 1 mg/kg bid iv; Minocycline* 0.1 g bid po; Tetracycline* 0.5 g qid po; Tigecycline*0.1 g followed by 50 mg bid iv.

Oxazolidinone: Linezolid* 0.6 g bid po, or 0.6 g bid iv; Tedizolid* 0.2 g x 1 po.

Other antibiotics: Chloramphenicol* 2 g qid po, or 2 g qid iv; Colistin* 4.5 MU bid iv; Daptomycin* 6 mg/kg x 1 iv; Fosfomycin* 8 g tid iv or 3 g x 1 po in a single dose; Fusidic acid* 0.5 g tid iv; Metronidazole* 0.5 g tid po, or 0.5 g tid iv; Nitrofurantoin* 50-100 mg tid-qid po; Nitroxoline* 0.25 g tid po; Rifampicin* 0.6 g bid po, or 0.6 g bid iv; Spectinomycin 2 g x 1 im; Trimethoprim 0.16 g bid po; Trimethoprim+ sulfamethoxazole* 1.44 g bid po, or 1.44 g bid iv.

CLINICAL GROUPING OF ABs

Changing the posology and increasing the doses of ABs, where necessary and possible, contributes to maintaining a reasonable susceptibility of pathogenic bacteria, maintaining the efficiency of ABT. Clinicians should rationally use ABs and shall apply, where appropriate, the new recommendations, which move the category of bacteria with intermediate sensitivity, from resistant to susceptible [2]. Consideration should also be given to the recent clinical classification of ABs in the three groups: for infections with common bacteria (Access group antibiotics), with resistant bacteria (Watch group antibiotics) and the reserve (Reserve group antibiotics), as well as special antibiotics (eg anti-tuberculosis, anti-leprosy), according to the WHO Model List Essential Medicines, no 20/2017 and 21/2019 [1]. The practical advantage for medicine is immense, but if in medical practice it is found that many clinicians still do not

follow the rules of good practice of ABT, action will have to be taken. One of them could be, in extremis, that according to the recommendations of WHO 2017 and 2019, ABs from the therapeutic groups should be prescribed according to the competence of the doctor:

ABs group I, usual, by any doctor with the right to free practice,

ABs group II, for resistant or multidrug-resistant bacteria, by specialized clinicians,

ABs group III, reserved, by primary care clinicians,

Special ABs, by the clinicians, according to their specialty.

Obviously, "off-label prescriptions" could represent the exception, in justified cases; As an example, it has been found that the antiparasitic Metronidazole is also the most effective antianaerobic AB.

There are also some ABs, which, although authorized, are so little used in national medical practice that they could be considered as new ABs. It is interesting to see how many new ABs will be authorized in the coming years. It is very important to discover new anti-infective drugs, both with new molecules, and by highlighting antibacterial and/or antibiofilm properties in pharmaceuticals known for other pharmacological effects. This type of applied research involves smaller investments, and the results can be faster, going up to the patenting of new innovative anti-infective drugs, in the near future.

CONCLUSIONS

Antibiotherapy is constantly dynamic, in order to keep up with the adaptation of pathogenic bacteria to the selection of pressure exerted by ABs, We must be aware of these trends, apply new acquisitions in the field of drugs, dosage conditioning and dosage, to help maintain an effective ABT, and abandon, where appropriate, the old methods and habits. Unfortunately, it is possible that some healthcare workers may continue to prescribe ABs, not for treating the patient, but for their own peace of mind and as well as their patients' or for any other reasons.

References:

1. *** WHO Essential Medicine List 21, 2019 (EML)
2. *** EU European Committee on Antimicrobial Susceptibility Testing, version 9, 2019 (EUCAST)
3. *** Farmacopeea Romana ediția X 1993, Editura Medicala, București, reeditat 2017, si suplimentele (FR X)
4. *** European Pharmacopoea, ediția 7, 2016
5. *** Nomenclatura internațională a medicamentelor (Anatomic, Terapeutic, Clinic) cu codul ATC J01
6. *** Antibiotics www.longitudeprize.org
7. Ordeanu V. „Consideratii privind medicamentele antiinfectioase esentiale" Viata Medicala nr. 33(1231) 2013
8. Ordeanu V, Necsulescu M, Ionescu LE, Popescu DM, Bicheru SN, Dumitrescu GV, Hertzog RG, „Anti-infective Therapy Principles in Diseases Caused by Bacterial Biological Agents" Journal of Pharmaceutical Research International, 23, 5, 2018
9. Necsulescu M, Coculescu BI, Bicheru S, Popescu D, Ionescu L, Dumitrescu G, Ordeanu V. „General considerations regarding the infections with the Escherichia coli patogen" Romanian Journal of Military Medicine, 120, 1, 15-21, 2017
10. Dragomiroiu GTAB, Popa DE, Velescu BS, Andries AA, Ordeanu V, Nicolae AC, Dragoi CM, Barca M, Ginghina O. „Synthesis, characterisation and microbiological activity of novel hard gelatine capsules with cefaclor and piroxicam" rev. Farmacia, 64,6, 887-895, 2016
11. Serban C, Mitrea N, Ordeanu V. „Statistical study on the bacterial sensibility tested in sanitary microbiology laboratory" rev. Farmacia, 60, 5, 652-661, 2012
12. Serban C, Mitrea N, Ordeanu V. „Research on bacterial resistance to antibiotics, in suspicion of nosocomial infections, in major hospitals in Bucharest" rev. Farmacia, 60, 3, 350-357, 2012
13. Marica D, Ordeanu V, Ciocalie I, Iordachescu I, Trasculescu S, Rapunteanu G, Buia E, Agapi D, Constantinescu C. „A comparative study of the interference of sulfamides in peptone media. A concept concerning the masking of sulfamide sensitivity by peptones" Bacteriologia, virusologia, parazitologia, epidemiologia, 37, 1-2, 81-86, 1992