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EDITORIAL

Antibiotics – Where To?



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The first antibiotic discovered was Penicillin, in 1928 and put on the market in 1943, replacing the older medicines, the sulphonamides[1]. After the discovery of Penicillin, people and specialists referred to it as a miracle, able to cure all the infections in the world. A large production determined the development of the "antibiotic era", where these substances became largely available in high-income countries.

Ever since the first discoveries of Alexander Fleming or Paul Ehrlich and others about the antibiotics, approximately 100 years ago, the advantages of the medicines in infections have been assimilated in the public health system[1]. Consequently, in 1967, the first bacteria resistant to Penicillin (*Streptococcus pneumoniae*) was reported. While in the 1970s it took almost 40 years to develop resistance to antibiotics, currently it happens that the resistance occurs in the same year as the release on the market[2].

This high speed in developing antibiotic resistance can be explained by their exaggerated use both in medicine and in agriculture, in combination with the bacteria's evolution capacity[3]. Nowadays, specialists are talking about a "post-antibiotic era", which is possible if proper measures are not taken at this moment. But, regarding the normal evolution, the antibioresistance is a clear adaptative reaction, based of Darwin's rules, which consists in developing complex strategies to combat the effects of the antibiotics.

Also, the concerns about the possibility of antibioresistance emergence first appeared in the early 1950s, when the pharmacologists recommended the rational use of antibiotics, instead of commercializing them only based on the verbal testimony. We must not forget that, in low-income countries, it is acceptable to largely prescribe antibiotics, in order to prevent severe complications of the diseases[1,4].

It is most probably to die in the near future of now potentially curable infections, due to the lack of medicines able to fight against them. The bacteria resistant to antibiotics are responsible for common infections (pneumonia, urinary tract infections, etc.), but especially for nosocomial infections, for example in the case of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), or multidrug-resistant Gram-negative bacteria resistant to every β-lactam antibiotic.

Consequently, the antibioresistance became a global health problem in the last ten years. Specialists predict that, by the year 2025, many of the most important antibiotics will become ineffective, which will have a severe impact upon the disease prognosis, being difficult to perform even basic surgery manoeuvres in a safe environment. It is also estimated that, by the year 2050, uncurable infections will be responsible for almost 10 million of deaths every year[5].

The magnitude of the incurable infections can be translated at the patient level into increased mortality and morbidity, while for the healthcare providers by increased utilization of the resources and costs[6]. Also, the next step in the general population would be prescribing broad-spectrum antibiotics to prevent severe complications. But these effects are even more obvious in patients undergoing surgical procedures, organ transplantation or patients with cancers.

The probability of discovering new molecules is considerably reduced. Currently, there are more than 270 molecules investigated, in order to determine their ability of acting as antibiotics. In the past years, since the 1970s, the pharmaceutical companies concentrated most of their efforts into other more profitable areas, instead of developing new

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antibiotic molecules, and the world runs out of options for infectious diseases. It is important to preserve the antibiotics we already have, in multiple ways, for example, by developing antibiotics adjuvants which are considered non-antibiotic structures that stimulate the antibiotic activity, blocking the resistance or boosting the immune response to infections, for example compounds which inhibit the β-lactamase enzyme, which determines the resistance to β-lactamines[7].

Most of the current studies are concentrated on developing better versions of the already existing substances, but most of these molecules have only a slightly better efficacy, with decreased susceptibility to bacteria resistance. Another possible pathway is searching for new molecules, derived from plants or other natural sources, but it is possible for the resistance to occur even in these cases. The most important step would be the exact understanding of the mechanism which allows the bacteria to be resistant to even aggressive antibiotics.

An international research identified a new possible substance which acts as an antibiotic, called Darobactin, which is able to bind the BamA protein, situated on the external membrane of the gram-negative bacteria. The effect is the disruption of the membrane and bacterial death, especially in case of Pseudomonas aeruginosa, E. Coli or Klebsiella pneumoniae resistant to antibiotics[8].

Ways of combating the resistance to antibiotics are related to individuals, healthcare providers and institutions. For the first time in the history, the World Health Organisation launched a warning in the year 2015, regarding the resistance to antibiotics and the possible risks involved, tackling that "we cannot allow hard-won gains for health to be eroded by the failure of our mainstay medicines". Since then, in every November, there is the World Antibiotic Awareness Week, with several campaigns. In the year 2016, the High-Level Meeting of the General Assembly on Antimicrobial Resistance concluded that antibioresistance is "the greatest and most urgent global risk"[9].

The most important thing is to understand what resistance to antibiotics means and the people will apply the measures, in order to reduce the use of medicines. Finding the proper strategies for antibiotic resistance prevention is a great challenge worldwide, because taking no action today means that tomorrow we might not have a cure for the infections.

A joint initiative between the World Health Organization and the Drugs for Neglected Diseases initiative, stimulates permanent research and it aims that, by the year 2023, the specialists should develop and deliver four new therapeutic molecules, either by improving the already existing antibiotics or by accelerating the discovery of new antibiotics.

The problem is global, this is why the measures should be globally understood and applied. In order to control and to prevent the extension of antibiotic resistance, doctors should prescribe antibiotics only when needed, in case of documented infections, according to antibiograms and guidelines. Healthcare industries should massively invest in research to develop new antibiotics, new vaccines to prevent diseases and to develop rapid diagnostic tools. Measures should be applied in the agriculture sector, where antibiotics must be given to animals only after veterinary recommendation, not for growth stimulation or to prevent diseases. Large campaigns should be made by Health Ministers in association with NGOs and Patients Associations through the media (TV, papers, online) in order to inform population about the correct use of antibiotics and the risks of antibiotic resistances.

The European Union aligns to the World Health Organization recommendation and, together with the European Centre for Disease Prevention and Control, the European Antibiotic Awareness Day is marked in November every year.

In Romania, a campaign regarding the antibiotic resistance was started in December 2019 – "Common cold is not treated with antibiotic. Inform yourself!" – and it was initiated by the Romanian Rhinologic Society along with the Romanian National Society of Family Medicine. Inside the European Union, 85% of the people are aware of the adverse effects of uncontrolled antibiotic use, whilst the percentage in Romania is much lower, of about 50%. Moreover, 93% of the Europeans get a medical prescription from a doctor, compared to Romanians (63%). On 11th of December 2019, in Bucharest, a meeting regarding prescribing antibiotics in viral respiratory infections "Antibiotic resistance – zero priority for public health" took place. It was attended by representatives of ten Romanian medical societies (Romanian Rhinologic Society, Romanian National Society of Family Medicine, Romanian Society of Pneumology, Romanian Society of Pediatrics, the Romanian Academic Society for Family Medicine, Romanian Society for Infectious Diseases and HIV/AIDS, Romanian Society for Pharmaceutical Sciences, Romanian Society of Epidemiology, Romanian Society for Microbiology, Romanian Society of Pediatric Otolaryngology) and MPs from the Committee for Health and Family of the Romanian Senate, representatives of the Ministry of Health and the General Directorate of Social Assistance and Public Health.

Secondary to this meeting, it was proposed to elaborate a clinical and therapeutic protocol in what the viral infections of the upper respiratory

tract are concerned in order to restrict antibiotic resistance in these diseases, in accordance to WHO recommendations.

CONCLUSIONS

Every organism has the ability to develop resistance to external factors and, in case of bacteria, it has implications in the human population. In the past 50 years, since the antibiotic discovery and use, resistance to bacteria has led to severe effects on the general evolution of infections.

Nowadays, multidrug-resistant bacteria are more frequently encountered, and the disease prognosis tends to be more severe. Due to the fact that most of the infections are not microbiologically proven, the real importance of etiologic resistant pathogens is underestimated, which generally underestimates the negative effects of the resistance.

It is in our hands, as specialists, to take part in the global prevention measure, to preserve the molecules we have today, in order to be able to cure the possible infections which may occur tomorrow.

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