

Hidden Consequences of The Antibiotic Era

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Received: 📅 January 20, 2023; **Accepted:** 📅 January 27, 2023; **Published:** 📅 February 06, 2023

Abstract

The discovery of antibiotics in the last century allowed medicine to save millions of lives. However, the peculiarity of the action of these drugs does not even theoretically allow us to count on the stable and long-term effectiveness of antimicrobial therapy. To date, the consequences of the use of antibiotics require a thorough and comprehensive analysis of the transformations that have arisen and the development of measures to eliminate them. Along with the natural biological effect of antibiotics and the emergence of resistant strains of pathogens, it is important to eliminate distorted ideas about the nature of acute pneumonia that arose under the didactic influence of this therapy. In this situation, the choice of an adequate solution to the problem depends on the revision of the concept of the disease.

Keywords: *Antibiotics; Acute Pneumonia; Side Effects; Didactics of The Disease; The Doctrine of Acute Pneumonia*

The discovery of antibiotics in the middle of the last century was one of the significant achievements of medical science. The subsequent use of these drugs by practical medicine saved millions of human lives. However, now, after several decades of using this type of therapy, the World Health Organization (WHO) has declared the emergence and further growth of antibiotic-resistant microorganisms (ARM) one of the 10 global threats to public health [1].

During the period of the use of antibiotics, there was not only a transformation of the microflora, which no one doubts today and in relation to which antibiotics have long lost their former effectiveness, but also therapeutic stereotypes were formed and strengthened, in which etiotropic therapy plays the role of the main and, often, the only help with inflammatory processes of the lungs. Currently, the previous approaches to solving the problem of acute pneumonia (AP), which have taken the form of generally accepted standards, stimulate the desire to revive the former potential of antibiotics and return the successes of the past.

This is the solution to the problem, based on the development of new, more advanced antimicrobial drugs, is proposed today by WHO experts [1]. However, before, according to established traditions, continuing this process of competition between pharmaceutical companies producing new drugs and the microflora surrounding us, successfully resisting this aggression, which has already led to the situation, requiring urgent solutions, it would be more logical and rational, first of all, to understand the main causes of this phenomenon, wouldn't it?

Acute inflammatory processes of lung tissue of non-specific etiology during the period of antibiotic use have significantly

changed and continue to change the priority among their leading pathogens. This phenomenon was not observed in such a pronounced form in the pre-antibiotic period. In this regard, the appearance of many different terms to denote individual variants of inflammation in the lung should not change the essence of the problem, since we are still talking about one nosological form, which is called AP. The origin of the new terms is dictated by attempts to reflect the importance of the etiology of the disease, although in practice the number of observations in which the pathogen remains unrecognized continues to grow. At the same time, the basis of the disease, regardless of the pathogen, remains the inflammatory process of the same organ structures.

The emergence of antibiotic-resistant strains, which has been observed for many decades and which is only now beginning to be perceived as a very serious problem, is only one side of the action of these drugs. This phenomenon, as well as dynamic changes in the etiology of the disease, are associated with the initially inevitable biological effects of antibiotics. If we want to fully assess the negative consequences of this type of therapy, then it is necessary to take into account the whole complex of concomitant consequences. The coverage of this problem will be more scientifically justified if we present its state on the example of an analysis of the applied therapeutic principles.

Firstly, it is initially well known that antibiotics are a means of influencing only the microflora and do not have a direct effect on the mechanisms of inflammation. Despite the obvious and textbook nature of this pharmacological characteristic, these drugs throughout the entire period of their use are considered as the main means of treating AP, and at a certain stage the treatment of most patients with this disease

was designated by the term "antibiotics alone". At the same time, the situation has become familiar when one antibiotic drug as the main therapeutic agent is used in the treatment of inflammatory processes that are incomparable neither in clinical manifestations nor in severity of the course. For example, the same drug can be prescribed for the treatment of AP, acute otitis, pyelonephritis, soft tissue abscess, etc.

The latter circumstance serves as a convincing proof that antibiotics for many decades of their use have been considered as a universal means of treating inflammatory processes, and the medical approach to treatment has increasingly focused on the selection and distribution of the most optimal drugs. Focusing on the potential pharmacological capabilities of these drugs, it is not difficult to understand that the concentration of efforts on the etiologic variant of medical care, especially in the case of the application of the principle of "antibiotics alone", contributes only to neutralizing the causative agent of inflammation, but eliminating morphological and functional shifts remain the task of the body itself.

Secondly, the introduction of antibiotics into medical practice has opened up a fundamentally special section of drug therapy. Unlike most pharmacopoeia drugs that target chemical compounds and substances of the body itself, antimicrobials act against concomitant or externally penetrating biological micro-objects. Being separate biological entities, bacteria have the ability to adapt under the influence of external factors of aggression, which they have demonstrated with sufficient success over the past decades.

Thirdly, the resistance of microflora to antibiotics is not at all a diagnostic discovery of recent years, when changes in bacterial characteristics began to attract widespread attention of specialists. The first signs of this process began to manifest themselves after a short period of time after the introduction of antibiotics into practice in the form of a decrease in their effectiveness and the need to develop and release more advanced drugs. At that time, the assessment of the prognostic danger of strengthening these bacterial qualities did not have such a tragic connotation as it does today.

Fourth, in addition to the individual ability to increase antibiotic resistance, the microflora has been demonstrating for many years its ability to adapt to this external aggression by changing priorities between its representatives. Since its discovery in the 19th century, *Streptococcus pneumoniae* or pneumococcus has consistently remained the leading pathogen of AP, which is why it got its name. For example, before the appearance of antibiotics in medical practice, the proportion of pneumococcus in the etiology of this disease ranged from 90% to 95% [2-4].

In recent years, positive results of bacteriological examination of patients with AP account for only half of the observations, and among them streptococcal pneumonia is determined only from 10.9% to 22.5% (5). It should be remembered that in the interval between these time periods in the 60-70 years of the last century, pneumococcus practically disappeared from the etiology of AP and there was an almost undivided dominance of staphylococcus, which gave

reason to consider this phenomenon as a staphylococcal catastrophe. The subsequent return of pneumococcus to the list of AP pathogens occurred gradually without the use of special measures, but against the background of constant updating of antimicrobial drugs.

Against the background of the observed dynamics among microbial pathogens of AP, experts have been expressing concern about the growth of viral forms of the disease for more than a decade. About two decades ago, viral pneumonia accounted for a significant part of AP, reaching almost half of all cases of this disease in the world [6-8]. However, deep concern about this fact did not manifest itself in further correction of the principles of treatment. Moreover, with the onset of the SARS-CoV-2 pandemic and an increase in the number of patients with viral inflammation of the lung tissue, the senseless use of antibiotics against coronavirus continues to be defended as mandatory treatment in patients with so-called COVID-19 pneumonia [9-11].

In order to continue analyzing the causes of the observed dynamics among the pathogens of AP, it is not superfluous to recall that the widespread use of antibiotics applies not only to curative medicine. For a long time, these drugs could be widely and freely used in a number of food industries in order to increase the production of biological products, especially in such industries as poultry farming, animal husbandry and even fishing, and products containing antibiotics were automatically included in the diet of healthy people. This circumstance has led to the introduction in many countries of rules and laws on the special labeling of products sold [12].

Such a wide and long-term use of antimicrobials could not leave the microflora surrounding us untouched, so the consequences of using these drugs can be much more serious than we imagine. For example, one of the world's leading specialists in infectious diseases, Dr. Anthony S. Fauci, draws attention to the fact that it was in the last few decades that a relatively stable list of active infections began to change markedly with the emergence of new diseases and the return of some old ones [13]. The author considers climate change as one of the main reasons for this transformation. Unfortunately, the presented conclusion does not mention among the possible triggers such a specific factor as antibiotics, which directly affects the state of the microflora.

Finally, the most important, from my point of view, is another effect of antibiotics, which usually does not appear among their side effects, but its existence is clearly felt in the peculiarities of the interpretation of current events. The difficulty of confirming these consequences lies in their subjective nature, but it is their correction that will determine the choice of the most optimal solution to the whole problem. In this case, we are talking about the didactic influence of this type of therapy on the formation of professional ideas about the essence of AP. Long-term commitment to etiologic approaches in the treatment of this disease has created an unshakable and widespread opinion about the unique role and actual indispensability of antibiotics in the treatment process [9-11].

The long-term concentration of therapeutic efforts on achieving success with the help of antibiotics, in turn, accustomed to the idea of the absolute role of the pathogen of AP in its occurrence and development. This interpretation of the nature of diseases is characteristic of specific infectious processes that have not only an original pathogen, but also non-standard manifestations. AP differs from classical infections by a wide range of possible pathogens and in this respect fully corresponds to the concept of nonspecific inflammation.

The long-term tendency to determine the etiology of AP as early as possible was dictated by a decrease in the effectiveness of antimicrobial therapy and the desire to return it to its former success. It is only in recent years that leading experts on this issue have begun to recognize the futility of such efforts, which do not affect the final results in any way [14,15].

It would seem that the negative results of many years of attempts to differentiate inflammation of the lung tissue by the nature of the pathogen should be a reason to reconsider views and search for other directions in solving the problem. However, as the real situation shows, the experience gained did not lead to a reassessment of existing ideas about the essence of the disease. The beginning of the SARS-CoV-2 pandemic was marked by the continuation of the search for criteria for distinguishing between bacterial and viral forms of inflammation in order to select etiotropic agents. Much is said by the fact that, despite the lack of expected results, the authors of such studies consider it necessary to continue them [16-18], while antibiotics remain the main means in the treatment of patients with COVID-19 pneumonia [9-11].

The appearance of another type of AP in the form of COVID-19 pneumonia, which in clinical situations is indistinguishable from bacterial forms, is actually a continuation of the previous course of the supposed diagnosis of the pathogen, when the terminology of the disease depended on the conditions of its occurrence (community-acquired, aspiration, healthcare-associated, hospital-acquired, ventilator-associated pneumonia). Such a mini classification provided for the probability of the participation of various pathogens, depending on the circumstances under which the disease occurred. The introduction of this gradation into practice was designed to facilitate the choice of antibiotics, once again emphasizing the direction of the main attempts to move the problem off the ground. As is known, this technique has not brought noticeable success in the treatment of patients with AP but continues to be used in everyday practice.

It is quite natural and logical that with such a persistent desire to succeed only through the introduction of etiotropic approaches in the treatment of AP, the disease began to be considered as infectious, despite the fact that in its more than two-thousand-year history it has never had grounds for such a qualification. Currently, attention should be paid to the fact that unprecedented epidemiological measures that are being taken during the SARS-CoV-2 pandemic are associated with preventing infection of the population with a new type of pathogen with a potentially high risk of disease. However, these measures are not related to the prevention of the inflammatory process in the lungs, which is

very clearly demonstrated by the current statistics.

Thus, of those who contracted coronavirus during the current SARS-CoV-2 pandemic, in 80% of cases there are no signs of a lesion requiring referral to the hospital, and 20% of them learn about the fact of their own infection only on the basis of a test, since they have no signs of the disease. Inflammation of the lung tissue is observed only in 20% of the infected population, which requires their hospitalization, and the need to treat such patients in intensive care units occurs only in 5% of cases (19-21).

These figures show that the presence of coronavirus in the body does not necessarily mean the development of pneumonia. Carrying out sanitary and epidemiological measures during this period is aimed at reducing the rapid spread of the pathogen, but this is not at all a guarantee of the prevention of COVID-19 pneumonia. At the same time, the widespread feeling of fear of this infection is due to the fact that no one has any guarantees to avoid the inflammatory process in the lung tissue. This danger is confirmed by the results of observations of severe forms of the disease in all population groups, as well as the fear and uncertainty that accompany the pandemic due to the lack of effective medical care for pneumonia.

The elevation of etiotropic AP treatment to the rank of the leading method of helping these patients has become the main goal, the achievement of which is identified with the solution of the problem. It is this principle of solution that underlies the WHO experts' proposal for the further development of more advanced antimicrobials, as mentioned above [1]. Despite many years of unsuccessful attempts at early verification of the etiology of AP and the lack of clear differential diagnostic signs for various inflammatory pathogens in the lungs [14-18], such studies are continuing today, which their authors consider to be a priority for improving therapeutic results [22,23].

The reasons why etiotropic treatment of AP even theoretically cannot be a guarantee of effective care for this contingent of patients, especially in the case of aggressive development of the disease, were noted above. As the effectiveness of antibiotics decreased in the previous decades, the need for additional means of assistance grew. Narrowing the main therapeutic task to neutralize the pathogen completely depersonalized the unique pathogenesis of the disease and led to even greater misconceptions in its interpretation and choice of correction methods.

Such a classic sign of inflammation as a violation of the function of the affected organ, described many centuries ago by Galen and has passed the test of time, today, in relation to the assessment of patients with AP, is used only partially and with obvious distortions. Evaluation of functional disorders in patients with inflammation of the lung tissue mainly takes into account gas exchange disorders as a result of inflammatory blockade of the alveolar parts of the organ. The important role of pulmonary vessels in the general circulatory system of the body, as well as the features of blood flow and its regulation in a small circle remain unaccounted for in the modern concept of the disease.

It is well known that the blood pressure in the pulmonary vessels is several times lower than in the periphery [24]. Even a small increase in it, dangerous by pulmonary edema, leads through the small circle baroreceptors to an unloading reflex with a decrease in systemic blood pressure and a decrease in venous return [25,26]. This adaptive mechanism in the conditions of today's dominant ideas about the leading role of the microbial factor is considered as manifestations of sepsis and septic shock, and, as a rule, without bacteriological verification of the diagnosis [27-32]. The result of this interpretation is infusion therapy, which has an effect opposite to the compensatory reaction of the body.

Contrary to the sequence of shifts occurring in the vascular system of the body, one of the leading criteria for determining septic conditions in patients with AP is currently an indicator of peripheral rather than pulmonary arterial pressure (27,29,32). With this approach to diagnosis, it is not surprising that sepsis in AP is the main group among the general observations of this complication in all diseases (33,34). At the same time, it is in patients with inflammation in the lungs, as a rule, septic complications do not receive bacteriological confirmation [30,32], and against the background of subsequent medical efforts, these complications can develop during treatment [29,35].

If we analyze the affected problem from this angle and bring the ideas about the nature of AP in line with the basic provisions of medical science, then illusory hopes for solving the tasks based on a falsified system of views will become clear. This statement is based on the results of research and clinical application of pathogenetically based approaches to the treatment of aggressive forms of AP on representative material [12]. The results obtained convincingly indicate that the achievement of success in the treatment of this category of patients is determined, first of all, by a change in priorities in the choice of goals and objectives.

Currently, resistant strains of bacteria have actually become commonplace in the bacteriological examination of healthy people, being part of the accompanying microflora of the body and not showing independent aggression [1]. This acquired quality of microflora turns into a therapeutic problem in the case of a disease, when medical care is focused mainly on sterilization of the focus of inflammation. Current studies among patients with AP show that antibiotic-resistant strains are not more dangerous and dominant microflora in severe forms of the disease and may give way to less odious pathogens [23].

Thus, an analysis of the current state of the AP problem shows that the discovery and use of antibiotics brought not only improved results, but also initiated the occurrence of side effects of this therapy. To date, the consequences of the long-term implementation of this therapeutic direction have acquired the character of persistent phenomena, among which the most important is the didactic influence of antibacterial therapy on the formation of professional views regarding the characteristics of this disease. The distortion of the mental perception of the problem is less noticeable compared to the biological effects, but it is its correction that will determine the optimal directions of future solutions.

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