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Review Article

Resistant Microflora in Acute Pneumonia: Two Views on One Problem

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Abstract

One of the most exciting and disturbing topics in modern medicine is the growing threat of antibiotic-resistant microflora, the consensus plans to reduce the burden of which are proposed by the development of new generations of antimicrobial drugs. Such prospects are actually aimed at further development of the factor that was the cause and source of the phenomenon under discussion. At the same time, no one discusses the risk of implementing such a project, focusing only on the immediate therapeutic effect. At the same time, an analysis of the factual material on this topic shows that the role and significance of resistant microflora are clearly exaggerated, and among the consequences of long-term use of antibiotics there are those on which the nature of the assessment of the problem and the choice of ways to solve it depend.

Keywords: *Acute Pneumonia; Etiology of Pneumonia; Antibiotics; Side Effects; Antibiotic-Resistant Microflora*

Introduction

Recently, one of the most problematic topics, which has relatively suddenly acquired the character of active and topical discussion, has become the situation with antibiotic-resistant microflora (ARM). At the same time, it seems that this problem has developed and emerged in the last 1-2 decades, when disputes in this area began to intensify. Literally 3 years ago, the World Health Organization (WHO) declared this phenomenon a global catastrophe [1]. Now this topic has become a subject of increased interest and concern, and its mention is becoming a tradition in the analysis of the results of treatment of inflammatory processes. In this regard, various options for monitoring the prescription of these drugs are proposed, which, as their authors assume, should reduce the severity of this consequence of antibiotic therapy [2-4]. However, if we turn to the facts of the recent history of this therapy, then the initiatives that are proposed today are 80 years late. It was during this period that antibiotics began to be used and the formation of the discussed consequences arose. Such self-deception and obvious misconceptions regarding the timing of the occurrence of this side effect of antibiotics and, most importantly, the interpretation of the essence of this phenomenon are especially clearly seen in the example of the principles of treating patients with acute pneumonia (AP).

Discussion

First of all, it is necessary to remember that the clinical use of antibiotics had not yet begun, but the results of studies had already been published that showed and proved that bacteria were able to protect themselves by neutralizing the action of antibiotics and at the same time acquiring resistant qualities [5-7]. In 1945, there was not yet enough clinical experience and material to draw far-reaching

conclusions, but the discoverer of penicillin, Alexander Fleming, in his Nobel lecture warned against the widespread and unjustified use of drugs of this type, which could threaten the development of irreversible resistance of microflora [8].

How did practical medicine use such information and appeals? After all, A. Fleming's predictions began to come true already in the first years of clinical use of penicillin, when signs of a decrease in its therapeutic activity began to appear even in relation to those strains that were included in its spectrum of action. At the same time, the possibilities of this antimicrobial therapy were known, which extended only to certain types of pathogens, but did not have a direct effect on the mechanisms of the inflammation itself. However, the ease of use of this therapy and, most importantly, its amazing first experience prevailed over a balanced approach to its use. The main goal and tasks of medicine at that time turned out to be focused on maintaining the effectiveness of antimicrobial drugs. The development and release of new, more active agents was required not only as a result of a gradual decrease in the effectiveness of penicillin, but also in connection with the emergence of new pathogens of AP, for the neutralization of which other drugs were required.

The most intensive period of such work, when most classes of antibiotics appeared, was observed before the beginning of the seventies of the last century [9]. During this relatively short period, the intensive pharmaceutical race for constant dynamics in the etiology of AP contributed to the formation of professional views on the essence of this problem, in which the microbial factor acquired a leading role. Changes in the list of pathogens of the disease were of interest only from the standpoint of choosing the necessary drugs for their successful neutralization. The reasons for such changes were not the subject of special discussions, although there was a completely obvious reason for this. For example, the unshakable leadership of pneumococcus in the etiology of AP, which for several decades before the era of antibiotics did not fall below 95%, was lost with the advent of this therapy and subsequently did not approach the previous indicators [10]. However, no one was in a hurry to consider this phenomenon as a side effect of antibiotics. The process of intensive development and production of new antimicrobial drugs was aimed primarily at meeting the constantly changing therapeutic conditions and was not accompanied by parallel measures to reduce the side effects of antibiotic therapy. This period of intensive antibiotic production is now remembered as "the golden era of antibiotic discovery" [9].

However, the release of new, more effective drugs could not continue indefinitely, so this process slowed down. Nevertheless, the dynamics of the change of pathogens and their leaders in the etiology of AP, according to the established rules, required targeted antibiotic therapy. In this regard, the earliest possible bacteriological diagnostics and rapid prescription of appropriate antimicrobial drugs began to be considered as priority measures. Such a practice, as is known, did not bring the expected results, as did attempts at differential diagnostics depending on the type of pathogen. These results showed that the nature of the pathogen does not play a leading role in the disease, which retains its main symptoms regardless of the etiology. Unfortunately, these important data did not receive reasoned scientific explanations and did not influence the revision of established views. Many specialists continue to actively use early microbiological diagnostics and targeted use of antibiotics to this day and, making efforts in this direction, hope to achieve successful results [11-14].

All these data indicate that the established concept of the "microbe-antibiotic" disease had become widespread by that time and had a stable priority. The basis of such a system of views on the problem of AP was the leading role of the pathogen in the development of the disease and the undoubted belief in the exceptional therapeutic potential of antibiotics. Dissatisfaction with the results of bacteriological studies for emergency targeted prescription of antibiotics led to the division of AP into separate groups depending on the conditions and place of the process. Thus, such forms of the disease as community-acquired pneumonia (CAP), hospital pneumonia (HP), ventilator-associated pneumonia (VAP) appeared. It was assumed that the etiology of these disease variants has differences, which will accelerate and improve the empirical choice of drugs and, consequently, improve the results.

Today, it can be argued that the introduction of this classification had the psychological effect of supposedly better selection of antibiotics. However, the impact of such a gradation of the disease over the entire period of its use has not received convincing confirmation of its

significant impact on the final results, although it has nevertheless become a familiar terminology, and in recent years has even begun to be supplemented with new additions. For example, intensive care unit-acquired pneumonia (ICUAP) was added to the above-mentioned AP variants [15,16]. To the question of why such a classification continues to be used if it does not bring noticeable practical benefit, there is only one answer: a deeply rooted belief that antibiotics are of decisive importance in the treatment of patients with AP. To be convinced of this statement, it is necessary to simply look again at the brief historical background presented above. The red thread running through all these decades of antibiotic use is the prevailing and, in fact, fundamental desire to preserve and reproduce the therapeutic efficacy of these drugs, without much concern for the side effects of such efforts. However, in parallel with the gradual loss of antibiotic activity and significant changes in the etiology of AP, a steady emergence and increase in the number of resistant microorganisms was observed.

Currently, the galaxy of resistant bacteria represents a large group of diverse representatives of microflora, but the beginning of this phenomenon was laid soon after the appearance of antibiotics in clinical practice. The first microorganism to demonstrate its adaptability to unexpected aggression was Staphylococcus aureus (SA), which began to displace pneumococcus from the list of AP pathogens. Already by the 60s of the last century, it began to show resistance to penicillin [17] and in the next couple of decades it turned into one of the leaders in the etiology of AP, especially in childhood, where according to some statistics it reached almost one hundred percent.

The manifestation of resistance to natural penicillin led to the creation in 1960 of its synthetic analogue - methicillin, to which SA did not show resistance [18]. However, just a year (!) after the drug appeared, a new form of this pathogen was identified - methicillin-resistant *Staphylococcus aureus* (MRSA) [19]. From that time on, a new period in antibiotic therapy actually began, when attention began to be paid to the possible presence of resistant strains. Such interest in diagnostics was manifested in connection with the need to select antimicrobial therapy, but the prevention of further accumulation of such microflora relied mainly on anti-epidemiological measures. Antibiotics continued to be freely used, and there were no programs for strict control over their prescription.

The analysis of the situation on the growth and spread of resistant microflora has a large volume of information, since we are talking about a fairly large number of such representatives. Therefore, it will be quite enough to form an idea of this area using the example of MRSA, which appears in almost all reports and discussions.

SA is considered one of the most important microbes in our body, being part of the microbiome of 20-30% of healthy people [20]. However, the emergence of MRSA ultimately led to the fact that in the general population, carriage of this resistant strain is found in 2 - 3% of the population [21,22]. Among some layers of society that are associated with certain working conditions, this figure is significantly higher. Thus, among medical personnel, MRSA colonizes up to 4.1-6.4% [23] and among farmers working with livestock that receive antibiotics during the growing process, this strain is found in 10% [24,25]. It should be especially noted that in all these cases, we are talking about healthy people in whom MRSA carriage is an accidental finding detected during examination. However, these materials are one of the convincing evidences that the very fact of contact with a potential pathogen does not mean the inevitability of the disease.

Statistical data on colonization of workers in various fields of activity, as we see, have yielded unexpected results. Of course, most of us considered medical professions to be the most dangerous in terms of contact with patients, when medical personnel are exposed to an increased risk of colonization of their bodies with highly virulent microflora. This coincides with the established opinion that the internal environment and inventory of hospitals are a kind of concentration of the most virulent strains. This point of view was logically confirmed by the results of bacteriological studies. It was this information that formed the basis for the above-mentioned classification for identifying such forms of AP as HAP and VAP. However, comparative research materials have shown that MRSA colonization of workers on livestock farms, where antibiotics are used in the production process, is 2 times higher than this figure among medical personnel. At first glance, such data may seem erroneous, but there are enough arguments in favor of their reliability to treat these results carefully and assess their significance in the problem under discussion.

First of all, it is necessary to pay attention to the very fact of using antibiotics, which, as is already known, must inevitably lead to a change in the resistance of bacteria in the area of their distribution. At the same time, strict dosage of drugs is not assumed, and the dosages used remain unknown. In addition, it should be taken into account that animal husbandry cannot compete with medicine in terms of compliance with epidemiological and aseptic conditions. Finally, for a long time, no attention was paid to the use of antibiotics in the food industry (including poultry farming and fishing), but subsequently many countries approved requirements for mandatory labeling of products offered to buyers with information that antibiotics were not used in the manufacturing process of these products (See figure).

Figure: *Food packaging with information about the use of antibiotics in the production process.*

The above information reflects one of the options for protecting the unsuspecting consumer from unintentional intake of antibiotics that have found their way into food products. To what extent antibiotics could and can affect the healthy population, one can only guess. However, the introduction of food labeling does not solve the problem of free circulation of antibiotics in our environment. Just a few years ago, the World Organisation for Animal Health adopted a resolution in support of the campaign officially launched under the auspices of WHO a few months earlier to reduce the unnecessary use of antimicrobials [26]. However, the nature of such documents does not exclude a complete cessation of such practices, which continued in the subsequent period [27]. Today, no one can give an exact answer as to how many people on the planet continue to eat products containing antibiotics, but the problem in this case concerns not only the final products, but especially the disposal of waste from the process itself.

There is no special neutralization of antibiotics in livestock or poultry waste, so such components enter the free environment with wastewater, which is not accompanied by their automatic inactivation. Thus, monitoring of antibiotics released into the environment has shown that long-term exposure to these drugs, even in low concentrations, can affect the genetics of bacteria and increase their virulence [28-30]. Thus, antibiotics today can be compared to a genie that was thoughtlessly released from a jug. All segments of the microflora around us are under the influence of antimicrobial drugs. The degree of such influence depends not only on the conditions and concentration of the drugs, but also on the duration of their exposure. In any case, such information must be taken into account if a global program is planned to reduce the load of resistant microflora.

Analysis of the dynamics that have occurred in the etiology of AP and the constant search for suitable etiotropic treatment observed since the advent of antibiotics in clinical practice have shown that medicine has constantly tried to catch up with the changes that have occurred. In the initial period of the antibiotic era, the results of such a chase justified the efforts to a certain extent, although a slow and steady decline in the achieved successes remained an integral feature of antimicrobial therapy, which received a leading role. Parallel to this race and despite the results and accumulation of facts that contradict the chosen strategy and have not received reasoned explanations,

paradoxically, a professional worldview on the problem of AP was formed and strengthened in accordance with the chosen direction. The results of world practice in this section over time began to demonstrate a noticeable decrease in the effectiveness of antibiotics with the need for additional and auxiliary means of assistance. By this period, expert assessments of the causes of this phenomenon have already fully focused on the indispensable role of antibiotics in achieving therapeutic success.

At the beginning of this century, resistance of microflora began to be considered as one of the reasons for the decrease in the effectiveness of etiotropic treatment of AP. The increase in the number of new bacterial species in this list and the number of such observations was systemic. However, the essence of the initiatives that appeared in these years to reduce the burden of resistant microflora was the creation of new and more advanced antibiotics. The diversity of such plans included not only proposals to use other sources for the production of such drugs, but also the development of pharmaceutical forms capable of suppressing the virulence of specific microorganisms [31-33]. In essence, a new direction began to appear for strengthening and further developing the cause underlying the problem under discussion.

Such plans remained unrealized, but the principle underlying this initiative was further developed and supported by specialists, demonstrating the bias of existing views on the problem. For example, during the same period at the beginning of our century, viruses began to play a significant role in the etiology of AP. According to some statistics, including WHO data, viral pneumonia accounted for almost half of all cases of this disease in the world [34-36], which required a revision of the strategy, since antibiotics in such observations lost the meaning of their purpose. However, no attempts were made to revise the disease strategy and bring its concept into line with the canons of medical science. The emerging SARS-CoV-2 pandemic finally dispelled the illusion of the indispensability of antibiotics and demonstratively exposed the existing misconceptions and problems in this area of medicine, but, as reality has shown, these lessons remained unlearned.

Thus, during the pandemic, when the flow of patients with viral pneumonia increased sharply, and bacterial coinfection was determined in a small number of observations, patients with COVID-19 pneumonia were treated with antibiotics in 70-80 percent or more of cases [37-39]. In other words, official medicine was not ready for such a course of events and did not find anything better than to use the usual stereotype of treatment, which was losing its relevance. In severe cases, discussions began about the optimal options for palliative and supportive care for the treatment of such patients, but the achieved results created anxiety and tension not only in society, but also among professional doctors. A series of non-standard publications appeared in prestigious medical journals, presented by specialists who took part in the treatment of severe coronavirus pneumonia [40-43]. The unusualness of their content was more reminiscent of a kind of confession and a description of their own helplessness than a presentation of scientific information and proposals for real solutions.

Against the backdrop of growing global concern and alarm over the coronavirus outbreak and after many years of relatively passive observation of the gradual development of bacterial resistance, the WHO relatively suddenly declared resistant microflora a global catastrophe [1]. Such a statement, given the development of the situation in this segment of the problem, should, in my opinion, have appeared much earlier. However, simply declaring a problem is not enough for a leading medical institution. It is necessary to offer at least a plan for its real solution, which was absent, which, apparently, became one of the reasons for the wait-and-see attitude. Now, at the peak of the pandemic, a psychological maneuver was needed that would provide at least an opportunity for an indirect explanation for the failures of medical care. At a time when everyone's attention was focused on the viral infection, WHO experts focused on resistant bacteria as the cause of treatment failures and expressed hope that this situation could be corrected through the development and release of new antibiotics.

If we take the date of the description of the first resistant strain, MRSA, as the starting point, then the official countdown of the era of the development of such variants of microflora begins in 1961 [19]. WHO, as an organization authorized to monitor and act in the interests of global health, has been relatively passively observing the gradual development of this phenomenon for many years. Its periodic statements of the facts of the development of this process and the recommendations that have become more frequent in recent

years did not offer radical solutions to reduce this burden. During the last pandemic, general anxiety and concern began to grow, when not only in professional circles but also among the relatively educated part of the population, the opinion began to strengthen about the lack of adequate drugs for the usual treatment of coronavirus pneumonia. In this regard, the relatively sudden announcement by WHO of resistant microflora as a global catastrophe, which coincided with the peak of the pandemic, does not seem at all accidental [1]. At this difficult moment, WHO carried out a kind of psychological maneuver. The emergence of such a declaration, when everyone's attention was focused on the coronavirus infection, seemed like an opportunity to indirectly explain the failures of medical care and draw attention to resistant microflora. Having observed the emergence and development of resistant strains for many years and having an abundance of research results in this area, WHO experts could not find a more acceptable proposal to solve this problem than to correct the situation by developing and releasing new generations of antibiotics.

This WHO declaration, especially the recommendations to reduce the burden of AMR by further developing the underlying cause of the problem under discussion, is disappointing and regrettable. The experts of this organization do not notice the danger of the proposals made, especially against the background of the widespread hypnotic dominance of antibiotics in the professional worldview. All the information presented above, although it is in the nature of a brief excursion into the history of AMR, allows us to present a general picture of the problem based on widely known published data. At the same time, each of us's assessment of the current situation in this section depends entirely on how impartially we consider the available materials. And here one very significant pattern is clearly visible: without conducting a critical, comprehensive analysis of the consequences of long-term antibiotic therapy, without paying due attention to other types of side effects that are quite obvious, and without having a clear and comprehensive idea of the changes that have already occurred in this area, modern medicine continues to adhere to narrow, exclusively etiotropic approaches to solving this problem and actively act in the same direction.

The presented opinion and the directives of the leading world organization continue to stimulate persistent attempts to develop the earliest possible bacterial diagnostics of AP [11-14]. Such efforts have been made for several decades without achieving the desired success, and no one has critically assessed the illusory nature of this diagnostic principle. If someone tried to explain the fact that numerous variants of differential diagnostics by the type of pathogen turned out to be impossible not only for bacterial forms of inflammation, but also when separating bacterial and viral forms of AP [44-46], then the question of the benefits of early bacteriological diagnostics would make one think about its expediency. Moreover, what benefit can be expected from continuing these intentions if the indicators of unidentified pathogens of AP have long and consistently exceeded half of all observations [47-49]? At the same time, viruses began to play a key role in the etiology of AP [46,50,51]. In modern conditions, the causes and dynamics of which remain outside of critical analysis, the logic and validity of prescribing antibiotics in most cases of this disease raise serious doubts.

Currently, ARM is becoming a topic of rapidly growing rhetoric and is turning into one of the main reasons associated with difficulties in the treatment of AP. However, the analysis of modern materials on this topic shows that such conclusions are clearly exaggerated, lack convincing evidence and are declarative in nature. Modern studies of the etiology of AP usually provide the frequency of participation of certain types of pathogens, but such figures reflect only the proportion of positive results, which among the total number of patients began to make up a smaller part. In addition, in the current flow of publications on resistant AP pathogens, it is difficult to establish how many such patients were under observation. Only a few authors note that the number of AP patients with resistant pathogens, according to their data, is a small group among the total contingent [46,52]. Much less often in modern publications one can find real figures of ARM in patients with CAP, which can be as little as 1.4% [53] and the number of patients with AP, where the pathogen is MRSA, in terms of the entire contingent of observations is 0.7% [54].

If we compare the latest figures and estimates regarding the involvement of ARM in the etiology of AP with the frequency of latent carriage of such microflora, the data on which were presented above, then the question arises: what therapeutic problem are we talking about in this case, if the degree of colonization of healthy people significantly exceeds the percentage of lung tissue damage by resistant

bacteria? Without attaching importance to such surprisingly unusual statistics, some specialists quite seriously come to the conclusion about the need for preventive sanitation of latent carriers of ARM [55].

Public statements by many specialists that ARM poses a serious threat to public health and is a heavy clinical burden have no objective argumentation [56,57], but their motives and sources have only one basis for such a point of view. Long-term training of medical personnel with an emphasis on piety before antibiotics has formed an unquestionable belief in their exceptional therapeutic significance with a loss of attention to the perception of the real causes of this problem. If we continue to consider antibiotics as the main therapeutic agent for inflammatory processes, then it is quite logical that resistant microflora in the case of a disease turns into an extremely inconvenient and difficult to solve problem. The latter circumstance is a reason to search for new options of antimicrobial therapy that close this vicious circle.

Modern medicine, focusing not only its own attention, but also the attention of a wide audience on the discussed side effect of antibiotics, is currently seeking to revive the cause that is the source of these consequences. Such an interpretation of modern conditions creates an atmosphere of uncertainty, anxiety and fear of getting sick in society. At the same time, both solutions and explanations for the situations that have been observed recently are left aside. A similar atmosphere of reality is characteristic today of all regions of the globe, regardless of the country and the level of development of its medicine. A striking example is the results of medical care during the pandemic in the United States. Thus, in 2019, with the onset of the SARS-CoV-2 pandemic, the United States was recognized as the best prepared state among 195 countries in the Global Health Security Index [58]. But the most unexpected and incomprehensible for many was the final result. Contrary to expert estimates, the United States has become a leader in the negative consequences of the treatment of COVID-19 pneumonia! Such a striking and unexpected paradox simply obliges us to seriously think about a radical revision of the concept of AP in general and the problem of resistant flora in particular. This example shows that new strategic approaches to solving the problem are needed, without which a successful breakthrough is impossible.

Conclusion

Thus, today one of the most exciting and disturbing topics in medicine is the problem of antibiotic-resistant microflora. The relatively short-term antimicrobial effect of antibiotics was proven at the preclinical stage of their study, so the occurrence and progressive change in the conditions for the development of AP was a natural consequence of these drugs, since it was actually predicted even before their introduction into practice. The constant process of antagonism between antibiotics and pathogens was accompanied by such phenomena as a dynamic change in the etiology of AP, a decrease in the therapeutic capabilities of drugs and an increase in the resistance of microflora.

Antibiotics have been used in practice for over 80 years, and throughout this period, the phenomena noted continued to be observed and developed, but they were not analyzed in a timely manner, were not comprehensively assessed, and did not influence the strategy of the problem. Both scientific and especially practical medicine focused their attention and efforts on preserving and ensuring the therapeutic effect of antibiotics, which, despite the specificity of their etiotropic action, began to turn into the main means of treating AP. In this regard, the only consequence of this therapy that was noted and served as a goal for the development of new drugs was microbial resistance. Conversations and discussions about the rational use of antibiotics began to arise only in recent years, already in the current century. The reason for this trend was a noticeable loss of therapeutic activity by antibiotics, but global programs for the prevention and reduction of this burden were not implemented.

The dynamics of the etiology of AP, as a natural result of the influence of antibiotics, was not discussed at all, and its role and significance in the formation of new conditions for the development of the disease were not properly assessed. Therefore, the growth of viral forms of AP, which has been going on for several decades, was not promptly perceived as a prospect for the near future and naturally led to the development of those phenomena that we have been observing recently. Convincing confirmation of such widespread misconceptions are the reaction and actions of official medicine during the SARS-CoV-2 pandemic, the lessons of which remained unlearned. The fact that the

past global catastrophe did not lead to logical and expected conclusions and natural corrections is reflected today in the ongoing search for optimal bacteriological diagnostics of AP and new forms of antimicrobial drugs. By now, it is no longer possible to ignore the fact that the number of AP diseases that retain justifications for the use of antibiotics has significantly decreased, but, unfortunately, such dynamics are not reflected in the strategy for solving the problem.

The relatively short history of antibiotic therapy allows us to note that as this period lengthened, the severity of biological transformations also increased. At the same time, paradoxically, the professional conviction that antibiotics are the most important means of treating inflammatory processes also grew. Therefore, the reason for the persistent continuation of previous attempts to solve the problem of AP, in which antimicrobial drugs were assigned the role of a strategic factor, lies in a distorted, but deeply assimilated idea of the essence of the disease. This version of cause-and-effect relationships allows us to note that among the side effects of antibiotics, the main role is played by their didactic influence on the professional worldview. The possibility of getting rid of this consequence will allow us to look at biological transformations under the influence of long-term use of antimicrobial therapy from other positions. So far, the excessively exaggerated role of ARM creates an atmosphere for accelerated searches for new generations of similar drugs, but none of the participants in this process imagines what further risks and threats this path leads to.

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Conflict of Interest

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