

## Antibiotics as a Cause of Stagnation in Solving the Problem of Acute Pneumonia

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### Abstract

The discovery and use of antibiotics is rightfully considered one of the greatest discoveries in medicine of the 20<sup>th</sup> century, which allowed saving millions of lives. However, it was initially known that this direction of treatment could not have a long-term, much less permanent effect, quickly accompanied by side effects. Unfortunately, medicine has long concentrated its attention and sought to support only the therapeutic activity of these drugs, without paying due attention to their side effects. At present, when the accumulated consequences of antibiotics have become completely obvious and serious manifestations, it turns out that there are no scientifically sound and hopeful and trustworthy plans to get out of the situation. Antibiotics still occupy a key place in the treatment of diseases, even despite the inadequacy of pathogens for their purpose. But the criticality of the situation and the need for its urgent analysis lies in the fact that the main prospect on the agenda today is the development of new generations of antimicrobial drugs at the molecular, nanotechnological and genetic levels. The likelihood of a further continuation of a trend that has already led to global consequences could have even more dire results.

**Keywords:** Acute Pneumonia; Etiology; Pathogenesis; Antibiotics; Side Effects; Disease Concept; Misconceptions

### Introduction

Acute non-specific inflammation of the lung tissue (ANSIL), known throughout its history as acute pneumonia (AP), has always been considered a serious, but not hopeless disease. Ancient and medieval medicine managed, through many years of empirical selection, to identify methods and techniques that brought relief to such patients, allowing many of them to cope with the sudden catastrophe. Such experience was acquired by trial and error, when the desired result was preceded by a series of dramatic events, but the lack of knowledge and opportunities for targeted research did not allow, even in case of success, to conduct an objective assessment and scientific justification. Nevertheless, the accumulated experience of helping patients with AP over a long period of time represented the «golden fund» of many medical generations and remained in demand until the middle of the last century. Such longevity of the use of a number of methods serves as an indirect, but clear confirmation of their positive effect.

The specificity of the solution to the problem of AP, which is currently dominant, became apparent 80 years ago with the advent of antibiotics in clinical practice. The first results of this therapy gave rise to exaggerated hopes for the unique and universal ability of these drugs to cure inflammatory processes. This perception of the new type of therapy in wide professional circles did not at all coincide with the qualities of antibiotics, which were established at the preclinical stage. For example, by the time of the first clinical use of antibiotics,

it was already known that they are capable of providing only a narrowly targeted antimicrobial effect, but do not have the ability to directly influence the mechanisms of the inflammatory process. In other words, by demonstrating their therapeutic ability in relation to the causative agent of non-specific inflammation and suppressing its activity, antibiotics are able to eliminate one of the factors of AP, providing an indirect effect on the inflammatory process and facilitating the further task of the body to overcome it.

Even before the clinical application of this therapy, the biological effect of these drugs was known, which are capable of losing their activity under the influence of microbial defense factors, while the microorganisms themselves, on the contrary, are capable of increasing their resistance to this external aggression [1,2]. Unfortunately, all these qualities and features of antibiotic therapy with severe remote consequences, which the pioneer of this direction A. Fleming warned about [3], did not receive due attention and professional foresight.

### Discussion

#### Unchanged principles of antibiotic use

The presented information was open and accessible to specialists using antibiotics in their practice, and provided a serious basis for making equally great efforts to reduce the burden of its side effects in parallel with the colossal efforts to preserve and support the effectiveness of antimicrobial therapy. It is regrettable that throughout the entire period of antibiotic use, all efforts and capabilities of medicine were aimed at achieving clinical success in the treatment of patients with AP, and only in recent years, when the situation regarding the consequences of this therapy became completely obvious, signs of concern about this have appeared with great delay. It is precisely signs, and not real actions, that are capable of solving the problems that have arisen as a result of many years of persecution of AP pathogens. After many years of such efforts, it remains only to state that AP remains one of the main problems of modern medicine [4]. At the same time, the situation as a whole and its individual segments continue to be viewed from the narrow positions of further improvement and use of antimicrobial agents.

The currently widespread approaches to assessing the effects of antibiotics in general and the treatment of patients with AP in particular cannot, in my opinion, lead to full conclusions and rational decisions, since they cover only a narrow segment of these problems. The ideology of the basics of acute nonspecific inflammation, which developed in the era of antibiotics and dominates in professional views, creates a false impression of scientific validity, but at the same time leaves many important circumstances and facts unclaimed. In this case, we are talking about the concept of the disease that has developed over a long period of antibiotic therapy, which in a condensed form can be represented by the tandem «pathogen - antibiotic», in which the first factor is considered the main cause of the disease, and the second is a symbol of the success of treatment. If in previous years a critical analysis of the changes that arose with the advent of antibiotics could cause certain difficulties in their assessment, as well as uncertainty and doubts about the reliability of the transformations that arose, then at present the transformation of the initial conditions in which the use of antibiotics began has reached such a state that requires from us a careful and balanced look at the circumstances that have arisen, primarily with the aim of preventing their further development.

#### Microbiology of AP in the pre-antibiotic era

The development of microbiology made it possible to establish the main features of the etiology of AP at the end of the century before last. Thus, the founder of one of the areas of microbiological diagnostics, C. Gram, in 1884 published the results of his work, in which he showed that AP can be caused by more than one microorganism, characterizing this inflammation as non-specific [5]. Three years after the publication of this article, materials appeared stating that pneumonia can be caused by opportunistic bacteria that are always present in the body, which confirmed the ancient postulate about why people get pneumonia and do not become infected with it [6]. And although *Streptococcus pneumoniae* (SP) or *Pneumococcus* (P) was isolated in 1886, which prevailed among the causative agents of AP and received

its name because of this exceptional tendency [7], nevertheless, the fundamental principles of the etiology of this disease and its main properties - non-specificity and non-infectiousness - were formulated precisely at the dawn of the development of microbiology.

In the first half of the last century, the etiology of AP was tracked dynamically over several decades on the eve of the antibiotic era. The results of these studies, conducted by different researchers, in different regions and conditions, demonstrated a convincing constancy of the list of causative agents of the disease. Thus, starting from 1917 and almost until the middle of the last century, the main causative agent of the disease remained pneumococcus, the detection rate of which did not fall below 95% [8-12]. However, after the widespread use of antibiotics, the situation began to change dramatically, and a relatively stable and familiar combination of causative agents of non-specific inflammation of the lung tissue began to demonstrate unprecedented dynamics. This process was accompanied not only by a change in the proportions between the already known causative agents of AP, but also by the appearance of new species in this list. Since then, the share of pneumococcus in the etiology of AP has significantly decreased and subsequently did not exceed even half of the observations [12].

### Increased microbial resistance and loss of constancy in the etiology of AP

Changes in the frequency ratios of various pathogens began to be noted soon after the beginning of the antibiotic era. Thus, in the first decades of using antimicrobial drugs, the role of *Staphylococcus aureus* (SA) among the causative agents of AP began to grow, resistance to which was rapidly increasing [14]. It is very curious that in 1960, a synthetic analogue of penicillin, methicillin, appeared, to which SA had no resistance [15], but a year later a new form of the pathogen was described - methicillin-resistant *Staphylococcus aureus* - MRSA [16]. The increase in the role of SA in the etiology of AP was quite impressive in the 1960-1970s, when severe forms of the disease were often considered and treated as staphylococcal even before the results of microbiological studies were obtained during primary diagnosis. During this period, according to some statistics, the frequency of SA in the etiology of severe pneumonia, especially in children, reached almost one hundred percent.

Despite such an important and obvious phenomenon as a change in the etiological characteristics of AP, it was not considered as a side effect of antibiotic therapy throughout the entire observed period, was not the subject of special discussions, and did not receive reasoned explanations for its occurrence. But we are talking about a reason that for many years forced us to look for new options for antimicrobial therapy and periodically revise the treatment tactics for this category of patients. At the same time, effective counteraction to new pathogens and the growing resistance of microflora required the development and release of new, more advanced forms of antibiotics, the most intensive production of which was observed in the first three decades of this therapy [17]. Such efforts were made to maintain the therapeutic effect of antibiotics, but the technological capabilities of that period did not allow this process to continue with the same productivity and success, so in the future, priority was given to early diagnosis of the pathogen and the earliest possible targeted therapy.

Despite the great difficulties in maintaining the effectiveness of etiotropic therapy at the proper level, which slowly but steadily continued to lose its previous positions, the role of antibiotics in the treatment of patients with AP in professional perception continued to paradoxically increase. By this time, the principle of treating patients with inflammatory processes, including AP, which was designated as «antibiotics alone» began to spread in practical medicine. At the same time, mainly in outpatient treatment of patients, antibiotics were the main and actually the only means of providing assistance. Treatment of inflammatory diseases in most cases began to be carried out according to a general template, regardless of localization and other features of the process. In fact, the treatment of patients with various inflammatory diseases gradually turned into a process of distributing antibiotics, which was accompanied by the addition of auxiliary and symptomatic methods in emergency cases and depending on the observed disorders. The nature of the treatment lost its specificity, often representing a course of prescribing one drug not only in cases with different, but also incomparable nosologies. Such a primitive and formulaic transformation of professional approaches to the treatment of inflammatory diseases did not cause any disputes or objections, including from pulmonologists and resuscitators. In this regard, in order to obtain a more complete and reasoned understanding of

the current situation in solving the problem of AP, it is necessary to find an answer to the inevitable question: how did antibiotics, the narrowly targeted antimicrobial action of which was known from the moment of their appearance, turn into a kind of panacea, on the use of which the fate of patients with inflammatory processes of non-specific etiology began to depend? In order to come to the most correct answer to this question, it is necessary to analyze in more detail the course of events, especially in recent years.

### The role of modern medical education in the formation of false ideas about the nature of AP

Of course, first of all, it is necessary to consider the system of initial training of medical personnel, which in each section lays the perspective of general ideas. The main direction of such concepts and recommendations can be found and assessed in manuals and reference books that serve as basic information for students of medical universities. A review of such publications over the past decades shows that the presentation of the proposed material on the AP section is based on the idea of the pathogen as the main cause of the disease, and the use of antibiotics is presented as a method of choice for achieving success. The difference between the versions of publications of different years consists only in a change in the list of the most likely pathogens of AP with a corresponding difference in the description of their aggressive qualities, as well as in the revision of the recommended set of antibiotics, which are proposed as the most acceptable for neutralizing the listed probable pathogens.

Unfortunately, when conducting a comparative analysis of such educational literature, which is often the result of the collective work of famous specialists from different countries and therefore has international recognition and authority, it is impossible to indicate the reasons for the persistent adherence to this narrow concept of the disease. Despite the events of recent years, which have already quite openly and frankly exposed the long-overdue inadequacy of theoretical ideas in relation to the developing circumstances, on the contrary, the generally accepted concept of AP is becoming an increasingly stable ideal in professional circles every year. Sufficient clarity in this paradox is brought by the decisions and measures that have been taken by various organizations and representatives of official medicine in response to the events of the new century. However, before analyzing these illustrative materials, it is necessary to return to the basic educational information. It should be noted that some data included in the mandatory list of materials intended for the training of future doctors, and already representing an axiom not only for students but also for experienced specialists, suddenly turn out to be consigned to complete oblivion, and the widely used methods of helping patients with AP have a mechanism of action that is completely inadequate for such situations.

One of the sections included in the range of mandatory disciplines for training medical personnel is information about the anatomical and functional features of the cardiovascular system. A general idea of the unique work of this system, which is presented to future specialists at the university, cannot do without explaining the inextricable connection and complete antagonism of the two circles of blood circulation. How else can a future specialist be trained without giving him the necessary ideas about one of the main systems of the body, right? Despite the diametrically opposite difference in indicators, the two halves of the cardiovascular system provide vital parity of cardiac output and synchronicity in the work of the right and left chambers of the heart in the most difficult situations. Such introductory information cannot but include data on the fact that blood pressure in the vessels of the pulmonary circulation is approximately 6-8 times lower than systemic pressure [18]. Causes that can increase pressure in the pulmonary vessels by only 5 mm Hg lead to interstitial pulmonary edema, and an increase of 10 mm Hg. already leads to complete edema of the organ tissues [19]. In setting out the fundamental differences between the two halves of the cardiovascular system, it is impossible not to explain, at a minimum, that the regulation of proportions, maintaining synchronicity in the work of the entire network and protecting the lung tissue from edema during overload of the pulmonary vessels is ensured by the so-called unloading reflex, which was discovered and first described almost a hundred years ago [20].

Information about the features of blood flow in the pulmonary circulation forces us to consider the mechanisms of pulmonary diseases from other positions, in contrast to pathology in the area of the systemic circulation. This concerns, first of all, inflammatory processes

based on the primary lesion of vascular structures with a local catastrophe of blood flow in the lesion. Knowing that the vessels of the pulmonary circulation not only have their initial blood flow indicators, but also have baroreceptors, due to which the so-called unloading reflex is triggered, changing the operating conditions of the entire vascular system, a comparison of the causes and mechanisms of disorders resulting from acute inflammation of tissues in the pool of two different circulatory circles is initially incorrect. The primary link in the lesion in AP are the pulmonary vessels, and a change in the indicators of systemic blood flow is a secondary reaction to the underlying cause. With aggressive development of the inflammatory process in the lung, the resulting protective reaction in the form of a generalized spasm of the entire network of pulmonary vessels creates a mechanism for their overload. The so-called unloading reflex, the action of which is especially evident in such situations, leads to pronounced secondary changes in peripheral circulation.

The mechanism of circulatory failure described above was attributed by us to a special form of the so-called pulmonogenic shock, which was confirmed by special studies and proven by objective tests in clinical trials four decades ago [21]. It is important to note that this form of shock is not associated with septic complications of AP and is relatively easily eliminated with timely pathogenetic care. The author managed to publish the results of the work done and its general materials and make them available to a wide range of specialists only recently [22,23]. However, as current circumstances show, the materials of this work have not only not lost their relevance, but, on the contrary, have become even more necessary for solving the problem that has deepened over this time.

### Reasons for overdiagnosis of sepsis

If we consider the pathogen as the main cause of the development of AP, then the development of the picture of general circulatory disorders should first of all be interpreted as a result of the generalization of the infectious onset and septic complications, right? This is exactly the definition that began to form many years ago, when the effectiveness of antibiotics began to decrease and cases of severe and complicated course of the disease began to be observed more and more often. Initially, to confirm the septic nature of complications, it was important to identify concomitant bacteremia, but at the same time, many specialists drew attention to a very unusual discrepancy in the results of studies. On the one hand, AP, according to statistics, was the main nosology in which generalized septic complications were diagnosed, but, on the other hand, it was in this group of patients that positive blood cultures were an extremely rare sign, not exceeding 10% [24,25]. This strange phenomenon, characteristic only of AP, has not received a reasoned explanation, but the diagnosis of sepsis and septic shock in this category of patients, by analogy with inflammatory diseases of other localizations, on the contrary, has advanced, finding new forms of justification.

In recent years, the diagnosis of sepsis in patients with pneumonia has fully complied with the principles of examining this complication in other inflammatory diseases. Now, mandatory blood testing for the presence of the pathogen is no longer required. The proposed schemes for assessing various body parameters and scoring systems, which are currently widely used as the main methods for diagnosing sepsis, include such important criteria as respiratory rate and pulse rate, as well as systemic arterial pressure [26]. If deviations in these indicators are assessed from the standpoint of suspicion of a generalized infection, then this seems to be a completely logical approach. Such a diagnostic system takes into account the important fact that dyspnea, tachycardia, and systemic hypotension are not characteristic early signs of most inflammatory diseases and appear at a late stage of the disease with the development of septic complications. However, continuing to concentrate efforts on suppressing the causative agents of AP, professional medicine has completely ceased to attach importance to such obvious circumstances that these signs are typical early manifestations of AP, especially in the case of an aggressive development of the process. Dyspnea and tachycardia are generally classic signs of AP, aren't they? Therefore, the assessment of the condition of patients with AP at the very beginning of the disease gives a set of points characteristic of septic processes.

In addition to the differences between dyspnea and tachycardia in patients with AP and the same symptoms in other localizations of inflammation, another common misconception is the equivalent assessment of systemic circulatory disorders in these two categories of

diseases that are incomparable in pathogenesis. Knowing the fundamental initial differences between pulmonary and systemic circulation and having an idea of the mechanisms that autonomously preserve and support vital parity and synchrony in the coordinated work of the two halves of the cardiovascular system, is it possible to consider arterial hypotension in AP and other inflammatory processes as a consequence of one mechanism and equivalent causes? This question is very relevant, since at present it is in this equivalent way that a decrease in systemic arterial pressure is assessed. If we now evaluate the quality and reliability of sepsis diagnostics from these positions, then the reasons why AP is today considered the main source of septic complications, actually forming a huge group of patients with a false diagnosis of «sepsis», should be clear.

Incorrect interpretation of the causes of the observed systemic circulatory disorders serves as the basis for the use of inadequate therapeutic measures. Treatment of patients with sepsis consists of intravenous infusions, the increase in intensity of which is especially enhanced in septic shock. However, if we consider this type of therapeutic care in the light of the pathogenesis of AP, then this type of therapy should be contraindicated in the initial period of the disease. Convincing clinical and experimental evidence of the negative role of infusions in the dynamics of AP development was obtained by us in previous years and as a result of replacing this therapy with other first aid means, the results were significantly improved [21-23]. Unfortunately, modern medicine does not pay due attention to the differences in the pathogenesis of inflammatory processes of various localizations. In recent years, there has been a tendency to consider sepsis as a separate syndrome, regardless of its underlying cause. For example, huge studies are being conducted in which researchers are trying to establish the reasons for the different effectiveness of intravenous infusions in sepsis [30,31]. The results of such studies, which do not provide a clear answer to the question posed, were, in my opinion, pre-programmed, since the authors do not analyze the results of the infusions performed depending on the localization of the underlying cause of sepsis. On the other hand, it is impossible to form an idea of the nature of the nosologies that served as the source of sepsis based on the materials of such studies.

This small digression from the main topic with the mention of septic complications of AP and the principles of their treatment, on the one hand, is an additional deepening into the problem under discussion. However, on the other hand, such information serves as a vivid example and an additional argument for understanding how deeply and thoroughly the «habit» of placing hopes on antibiotics has penetrated into professional consciousness and how vital decisions of official medicine depend on those factors that are the reasons for the further deepening of the problem. To complete this excursion regarding modern efforts to get out of critical situations in AP, it is necessary to provide additional information that has begun to appear in recent years and is a new confirmation of the sustainability of previous approaches.

### **The increasing role of viruses in the etiology of AP and the loss of antibiotics' usual prospects**

Firstly, the significant increase in viral forms of AP in recent times, which is associated not only with the SARS-CoV-2 pandemic and which can no longer be ignored to the extent and in the form observed since the beginning of this century, requires the development and implementation of effective actions. However, the lack of reliable antiviral therapy that could replace the usual etiologic role of antibiotics creates a tense atmosphere of uncertainty and confusion in the professional sphere. At the same time, the number of patients among those hospitalized with AP who have been diagnosed with sepsis in recent years has reached 61 - 82% [32,33]. Such figures and ratios should, first of all, raise reasonable doubts about the reliability of the diagnosis of «sepsis», which exceeds half of all cases of the disease, and under certain conditions is observed in 4 out of every 5 patients. The distrust of the diagnosis of sepsis in viral pneumonia is increased, in my opinion, by the fact that no one has presented objective evidence, including, first and foremost, microbiological studies confirming viral sepsis, and the diagnosis itself is based only on the analogy of clinical manifestations with bacterial forms.

Secondly, the phenomenon of the leading role of the pathogen in the development and dynamics of AP continues to hypnotically influence the choice of diagnostic and therapeutic measures. Thus, in the recent past, AP began to be divided by the place and conditions of its occurrence, believing that in different situations there is a difference in pathogens and this will help to use targeted antibacterial

therapy, and, consequently, improve the results. Time has shown that the use of such a classification did not have a significant impact on the treatment results, since initially we were talking about completely different categories of patients, whose initial condition has fundamental differences. Surprisingly, the results of this long-term practice, which did not bring the expected results, were not understood and learned, but the implemented classification remained a familiar working tool and continues to expand further. For example, recently, specialists began to note that the main problem in the treatment of patients with AP are cases of aggressive development of the process. This is a fair conclusion that should have been made long ago, since all the pathogenetic features of the disease are manifested precisely in such observations. However, the noted characteristic not only did not change the previous direction of interpretations of the disease, but also continued their further development. As the materials of the conducted works show, again continuing to hope for the phenomenon of the etiotropic action of antibiotics, at present, a gradation of severe community-acquired pneumonia (sCAP) has been introduced, suggesting the presence of special types of pathogens, which requires the selection of appropriate drugs [34].

Another new form of the disease began to be identified in patients whose high vulnerability to various complications was known long before the era of antibiotics. Thus, there were descriptions of AP that was absent at the time of hospitalization in the intensive care unit (ICU) - «ICU-acquired pneumonia» [35,36]. In addition, this form of the disease began to be identified in cases where AP was present at the time of admission to the ICU, but another bacterial or viral pathogen was superimposed during treatment [37,38]. The authors continue to explain the weakness of the prevention of this form of AP and the low efficiency of its treatment, first of all, by the virulence and antibiotic resistance of the microflora, which is believed to be concentrated in such departments. At the same time, such a remarkable fact draws attention to the fact that pathogens that were not previously included in this list are considered in the etiology of ICU-acquired pneumonia. At the same time, the authors of these studies openly admit the lack of convincing evidence of such a connection, but express the hope that it will be obtained in the course of further research [37,38]. This curiosity undoubtedly deserves attention, since it embodies the observed discrepancies between the prevailing ideas about the leading role of etiology and etiotropic therapy, on the one hand, and real practical materials, on the other.

Finally, we cannot ignore another important characteristic of AP, which has recently been used mainly as a statistical fact, but is practically not commented on and has no reasoned scientific explanations. In this case, we are talking about such an important indicator, from the point of view of prevailing professional views, as the frequency of diagnosis of AP pathogens. In recent years, this indicator has significantly decreased and, according to published results, in 60 percent or more of observations, the AP pathogen remains unidentified [36-38]. In this regard, without data on the etiology of inflammation in most cases, continuing to rely on the idea that the pathogen and its aggressive characteristics are the leading cause of the disease seems completely groundless and illogical. Moreover, in the presence of such conditions and circumstances, reasoning and discussions about the predominance of certain representatives of the microflora in the etiology of AP and their influence on the severity of the disease seem to be a sign of deeply learned stereotypes and assumptions abstracted from reality. Few clinicians and researchers admit to a lack of certainty about the etiology of the disease in these discussions. However, it is fair to note that major specialist forums, when discussing the diagnosis and treatment of patients with AP, add a standard “low quality of evidence” caveat to most of their recommendations, acknowledging that most of the issues discussed are far from resolved [31,39].

A brief mention of recent history allows us to note that against the background of those transformations that arose after the beginning of the widespread clinical use of antibiotics and were accompanied by a decrease in their antimicrobial activity, the priority direction was not simply the initial response to support and preserve the effect of this therapy. Over time, the desire to prolong the effect of this therapy as long as possible and to find the necessary ways for this continued to grow. Such motivation of interests over the past years has acquired a multifaceted system of special studies and clinical trials that have become familiar areas of professional activity with sufficient and reliable funding. However, such searches for solutions to the problem of AP not only continued, but also continue to consider the causative agent of the inflammatory process as the main cause of the disease, and its suppression as the main condition for successful

treatment. The formed ideology of the disease, which arose over the past period and remains dominant at the present time, continues to direct modern medicine to search for ways of early diagnosis of bacterial causative agents of AP and stimulate further improvement of antibiotics as the main therapeutic agent [40-42]. At the same time, the real and objective factors of environmental changes that occurred in the era of antibiotics remain largely underestimated.

At the beginning of this century, there were already serious reasons to take a closer look at the strategy for solving the problem of AP and to evaluate its scientific validity and usefulness. The feelings of concern that some experts began to express about the growth of viral forms of the disease were supplemented by materials showing the true situation in this area. Statistics of that period showed a significant increase in viruses among the causative agents of AP, and the number of acute viral inflammations of the lung tissue accounted for almost half of all observations of this disease in the world [43,44]. In addition, two coronavirus epidemics (SARS and MERS) occurred with a short interval, which, according to registered cases, were not of a threatening scale, but, judging by the identification of individual groups of patients on almost all continents [45,46], could claim to develop into a pandemic if they continued. In this regard, it should be noted that although these epidemics demonstrated a gradual attenuation of local outbreaks, the coronavirus not only remained present, but also continued to show its activity. For example, the results of outpatient tests among US residents who were in the other hemisphere from the said epidemics, in the period between MERS and the SARS-CoV-2 pandemic, revealed coronavirus in several percent [47]. During the same period, coronavirus continued to be registered among the causative agents of AP in 5.2% [48].

The presented information, regardless of our desires and aspirations, makes us take a fresh look at the ongoing changes in the initial conditions of the problem we are discussing and assess the adequacy of the efforts taken to solve it. If in previous years the main task was to try to identify the bacterial pathogen of the disease and choose the antibiotic needed in this case, now among patients with this nosology there are a large number of observations with viral forms of the disease, for which the main therapeutic agent in the form of antibiotics has lost its potential indispensability. What cardinal changes can be noted in recent years in the strategy for solving the problem and the principles of treating this category of patients, which should logically and inevitably occur due to the changed circumstances? This question is not at all idle, since the further results of providing medical care for this disease depend on the answer to it.

Modern medicine not only failed to timely assess the growth of viral forms of AP and conduct the necessary radical revision of its strategy in this area, but also, contrary to now completely obvious circumstances, continues to give priority to antibiotics in the treatment of these patients. It is the latest events that have exposed and emphasized the profound didactic influence of antibiotics on the formation of professional views on the problem under discussion. The attitudes about the absolute priority of this type of treatment, laid down from the university bench, were reinforced by the prevailing general atmosphere of ideas in work collectives. Therefore, when the fire of coronavirus infection, smoldering for a couple of decades, flared up, official medicine was simply not ready for this event, and the developing situation began to get out of control. The resulting confusion and uncertainty were reflected in the actions and measures that were taken during this difficult period.

### Have lessons been learned from the SARS-CoV-2 pandemic?

As recent history shows, in search of a way out of the current situation, experts consider outbreaks of infectious diseases from different positions. Thus, the famous infectious disease specialist Dr. Anthony S. Fauci, giving an interview during the pandemic [49], draws attention to the fact that the relative stability in the spectrum of infectious nosologies, which was observed in previous years, has changed dramatically in the last 2 - 3 decades, when new infections have appeared and some old ones are returning. He sees the reason for such changes in the negative impact of human activity on the environment and, in particular, as a result of climate change. At the same time, antibiotics, as the most aggressive factor in relation to the microcosm around us and the most likely cause of such dynamics, the author, unfortunately, does not note.



Not all experts bother to analyze the pre-SARS-CoV-2 pandemic conditions to understand its possible origins and causes. Moreover, in such an extreme situation, it is important for clinical specialists not to assess the unexpectedness of the virus invasion, but to determine the reasons for the lack of effective medical care for such patients, especially when they have the opportunity to widely advertise their opinion. However, the nature of such opinions and conclusions can sometimes have the most unexpected turns and directions. For example, the editors of a popular clinical medical journal in their editorial did not present their vision of the reasons why the mortality rate among patients with COVID-19 pneumonia in the highly developed health care system of the United States turned out to be the highest in the world [50]. Instead of a detailed analysis of the origins of the current situation, the authors declare the decisive role of omissions on the part of the federal authorities, which led to such catastrophic results [51,52]. A purely medical problem, which only professionals in this field can solve, was brought to the political arena.

In this regard, it is worth recalling a peculiar experiment that was conducted during the pandemic in Sweden. The authorities of this country abandoned strict anti-epidemiological measures, but this decision did not affect the incidence and mortality of the population from COVID-19 pneumonia [53]. It is interesting to note that these indicators in Sweden turned out to be among the lowest in the world, although in the European Union as a whole, they even exceeded the data for the United States [54]. These materials completely disavow the above statement about the involvement of the actions of the federal authorities in the catastrophic results of the provision of medical care during the pandemic, but on the other hand, they give reason to think about the reasons for the emergence of such declarations.

In addition, in the process of studying the spread of coronavirus, it was found that it is prone to rapid mutations [55]. The authors of this extensive study from different countries and continents found 82 mutations of the pathogen in just three and a half months. As a result of such transformations, vaccination of the population requires an unusually rapid repetition, but does not guarantee against the likelihood of disease. The actual results of vaccination of the population during the pandemic later confirmed this thesis. The tendency to such a dynamic transformation may be one of the additional explanations for why an outbreak of this already known infection occurred, which tended to spread quickly.

The interpretation of the latest outbreak of coronavirus infection as a fatal phenomenon, difficult to explain from the position of the prevailing theories, gave rise to another option for searching for causes. This direction was the study of the probability of so-called conspiracy theories with the assumption of the deliberate spread of virulent strains of this pathogen. The study of this issue was carried out at the highest level with the involvement of intelligence services in this work. The results of painstaking efforts of a large and diverse number of participants did not reveal any confirmation of the original assumption [56], but this does not mean that the authors of such generalizations came to certain conclusions.

Overall, the SARS-CoV-2 pandemic has provided medicine with very instructive trials and illustrative lessons that remain largely unlearned. The vast majority of decisions made and efforts undertaken remain inextricably linked to the use of antibiotics to varying degrees. For example, at the height of the pandemic, modern medicine had no choice but to continue the intensive use of antibiotics that are known to be inactive against the coronavirus. The frequency of prescribing these drugs to patients with COVID-19 pneumonia exceeded 70-80% or more, while bacterial coinfection was detected in only a few percent [68-70]. Some authors even included calls not to neglect this therapy in patients with coronavirus pneumonia in the titles of their reports [57].

### The reaction of official medicine to the events of recent years

Continuing the usual and standard principles of treating AP with the same emphasis on the antimicrobial segment of therapy, it is unlikely that any of the specialists hoped to achieve greater success, assuming in advance the futility of such efforts. However, systemic inertia and accepted stereotypes of treatment turned out to be stronger. At the same time, the awareness of the loss of the usual hope for

antimicrobial therapy and the lack of its adequate replacement grew not only in professional circles. A situation arose that required, if not the reproduction of suitable etiotropic drugs, then at least a worthy explanation for the failures of medical care for a large number of patients with viral pneumonia. Such a peculiar justification for this fiasco of modern medicine in this section was the official statement of the World Health Organization about microbial resistance as a global catastrophe [58]. Such an authoritative conclusion clearly indicates the source of the decrease in the effectiveness of antibiotics, partially explaining medical failures and reducing overall tension by switching attention to another, especially a long-known cause.

During the pandemic, some specialists faced another difficult and unexpected challenge. Due to the current epidemiological circumstances, patients with COVID-19 pneumonia were sent and isolated in certain departments. Such a concentration of seriously ill patients with a tendency for rapid negative dynamics of the process created unusually stressful working conditions for medical personnel. The low efficiency of modern therapy in this category of patients did not bring satisfaction to its performers and had a depressing effect on the moral atmosphere. A reflection of such situations was the publication of a series of unusual articles in professional medical journals, the authors of which described the depth of their shock while working in such departments and even disappointment in their chosen specialty [59-62]. However, as noted in ancient philosophical postulates, even in negative phenomena and events there are positive factors that should be discovered and, if possible, used.

A convincing example and direct evidence of a successful way out of such a situation is the author's own experience. 50 years ago, the author of these lines, a novice surgeon at a university clinic in a large Siberian city, found himself in an environment that completely replicated the working conditions in the above-mentioned departments for coronavirus patients. An outbreak of severe pneumonia with an aggressive course and high mortality forced the city health authorities to issue an order for the primary hospitalization of such patients directly to the surgical department. This decision was explained by the fact that only this department had resuscitation conditions and the necessary equipment. As a result of such a concentration, the department had, on average, at least 10-15 non-core patients. In this case, the situation that arose was perceived as a challenge to find a solution to this problem and here, oddly enough, the high concentration of patients played a positive role. Under these conditions, the attending physician could observe the dynamics of the disease and the reasons affecting its speed not on one or two patients, but by evaluating and comparing the results of a large group. In other words, in this case the so-called law of "transition of quantity into quality" was at work.

However, the described conditions were only a pretext and a kind of springboard for subsequent research and decisions. In any case, a detailed analysis of the observed phenomena and a detailed assessment of the compliance of efforts with the classical foundations of medical science were required. The final result of the work done, during which the widespread doctrine of AP was completely revised, became the possibility of talking about guaranteed prevention of the development of complications of the process. To implement the latter provision, it was necessary to use early pathogenetic therapy. The stages of this work encountered active objections and disagreements with its basic principles. This especially concerned the announcement of antibiotics, the priority of which at that time was not in doubt, not the main, but an auxiliary means of treatment.

In this case, the topic of the present report concerns the variety of side effects of long-term use of antibiotics as the leading method of treating AP. Therefore, repeating already published descriptions of the doctrine of the disease and pathogenetic principles of treatment is beyond the scope of the current discussion [21-23]. This mention is given only to show the probability of a way out of the current conditions. At the same time, modern circumstances in this section of medicine show a clear discrepancy between real facts and the direction of research, despite and in spite of the completely obvious transformations of the basic conditions in this area.

To summarize the above information, it should be noted with regret that of the side effects of antibiotic therapy, only microbial resistance currently attracts close attention and active discussion in professional circles. This consequence of the use of antimicrobial

agents can be traced throughout the entire period of their use, and in recent years it has become widespread. However, official statements about this phenomenon as a global catastrophe require, in my opinion, clarifying explanations. This factor causes tension and anxiety among specialists only because antibiotics continue to be considered the main means of treating AP. The latter circumstance forces us to consider resistant microflora as a kind of bogeyman and to advertise this opinion. This trend has arisen because in the case of admission of patients with AP, in whom the inflammation is caused by such pathogens, an explanation is given in advance why the treatment may be obviously ineffective. In fact, the correct explanation for the lack of success in treatment may be the latest information on the causative agents of AP, obtained using molecular testing [63]. The authors, referring to these data, note that viruses play a key role among the pathogens of the disease, while resistant microflora makes up only a small part of them.

The abundance of publications, including official statements, the number of which has been growing in recent years, devoted to the problem of resistant microorganisms, as a rule, do not focus on such an obvious fact as the tolerant and non-aggressive spread of resistant strains among the healthy part of the population. The actual results cited in the literature contradict the currently widespread discussion of the danger of antibiotic-resistant microorganisms, where the latter is clearly exaggerated by its real threat. The constant increase in the proportion of resistant strains has turned them into familiar representatives of the microbiota of healthy people. Thus, in the general population, MRSA carriage is 2 - 3% [64,65], among medical personnel this figure increases to 4.1-6.4% [66] and among farmers working with livestock receiving antibiotics during cultivation, this pathogen is detected in 10% [67,68]. These figures apply to healthy people in whom the presence of MRSA in the body did not manifest itself with any signs of disease. Few doubt that such free-living carriers of resistant strains, having entered the atmosphere of a medical institution, will be surrounded by sanitary and epidemiological measures, and in some cases may receive prophylactic treatment with antibiotics.

The tireless and prolonged concentration of attention and efforts on suppressing the supposed (!) causative agent of AP has been and continues to be accompanied by a distortion of professional ideas about the essence of this problem in relation to the principles and classical foundations of medical science. Many factors reflecting the inadequacy of the leading role of antibiotics in modern conditions are perceived without consistent critical analysis and reasoned explanations. Such circumstances and parameters include negative results of microbiological tests in more than half of the observations, empirical, that is, actually «at random», but has become habitual, choice of antibiotics, the growth of viral forms of the disease that are not amenable to the action of antimicrobial drugs. However, modern conditions, strangely enough, do not receive an adequate response. One of the many examples of such inadequate efforts are the materials of the article already cited above. The authors point to the key role of viruses in the modern etiology of AP, but discuss and strive to improve targeted antibiotic therapy, considering it the key to success [63].

Such paradoxes have recently become commonplace in addressing the problem discussed here, but are perceived by professionals through the prism of the dominant concept of the disease as quite logical and urgent aspirations. The above-mentioned intentions to shift responsibility for the unsuccessful results of helping the population during the SARS-CoV-2 pandemic to politicians and federal authorities have recently been further pursued. Now this trend has been joined by epidemiologists and medical lawyers, concerned about the “apparent inability of politicians to understand” the seriousness of the new (expected) pandemic and its difference from the previous one [69,70]. At the same time, the authors are convinced that health professionals should advocate for new investments in public health preparedness for a possible next pandemic. In this regard, it is very interesting to note that the demand for increased funding for the health care system is in no way consistent with the facts that have already been covered, but remained unanswered and without reasoned explanations. In 2019, with the onset of the SARS-CoV-2 pandemic, the United States was recognized in the Global Health Security Index as the best prepared among 195 countries [71]. The results of such preparation are widely known, in which the United States, unexpectedly for many experts, turned out to be the leader in negative consequences.

In the latest situation, the proposed approach to preparing healthcare for another pandemic is striking. On the one hand, despite the huge number of specialists in this field, no one has taken responsibility for conducting a detailed analysis and giving a thorough and

reasoned answer as to why inpatient care completely failed during the SARS-CoV-2 pandemic, if the country's healthcare system was better prepared than anyone else? Ultimately, as is already known, the negative results of this catastrophe were not determined by the number of infected and observed in outpatient settings, the share of which, according to numerous statistics, was 80% of the total [72,73]. At the same time, about 20 - 40% had no signs of the disease at all and learned about contact with the coronavirus only on the basis of tests [74]. The most important stage in the provision of medical care was the treatment of patients with COVID-19 pneumonia admitted to hospital. It is this segment of medical care that has once again demonstrated its imperfections, and the number of deaths in the country has significantly exceeded this figure in all other countries and on other continents.

On the other hand, it is quite obvious that increasing the volume of expenditure on the healthcare system in itself cannot change the results of medical care. In my opinion, specialists in this field are primarily obliged to conduct a deep critical analysis of the reasons why the treatment of patients with AP continues to stall, which was clearly demonstrated by the results of providing care to such patients during the past pandemic. In this regard, to claim that the healthcare system in the USA has achieved success (?) during the pandemic as a result of vaccinating the population, but not to touch on the results of treating patients in hospitals, looks like an attempt to «put a good face on a bad game» [75]. A retrospective assessment of vaccination against coronavirus, which required repeated injections after 3 - 4 months and was not a complete guarantee of avoiding a serious disease, generally raises great doubts about its positive role. At the same time, such an obvious and serious consequence of long-term use of antibiotics as a significant change in the causative agents of AP and a significant loss of the purpose of these drugs, have not yet received due attention.

Thus, the widespread use of antibiotics over eight decades has led to a number of serious and now probably irreversible consequences. The most noticeable and studied side effect is microbial resistance, which attracts attention only because it is perceived as an obstacle to the main therapeutic agent, which antibiotics continue to be considered. The inevitability of this biological action of antimicrobial agents was quite naturally accompanied throughout the entire period of exploitation of this therapy by a constant change in the etiology of AP. Ultimately, this led to a stunning increase in viral forms of the disease, significantly reducing the number of patients in whose treatment one can hope for the success of antibiotics. The listed and known transformations in the etiology of AP are a natural reaction of nature to interference in its usual relationships. However, as the materials of the conducted studies and proposed developments show, professional activity aimed at attempts to restore the former effectiveness of antibiotics continues to increase.

The paradoxical nature of the desire to revive and rehabilitate antibiotic therapy for AP is not only that in most cases the pathogen remains unidentified, and viruses begin to act as etiological leaders of the disease. In such conditions, even expecting the desired effect from antimicrobial agents seems very problematic. As D. Goldman., *et al.* [76] rightly note, when considering the problem of counteracting resistant microflora, such principles are easier to formulate than to implement, stating that the evolution of antibiotic-resistant microflora continues to outpace the introduction of new antimicrobial drugs.

### Conclusion

More importantly, the information about the basic canons of solving the problem under discussion testifies to the persistence and inflexibility that are observed today in attempts to revive etiotropic therapy. Continuing to follow this narrow path, researchers of the AP problem leave aside the most important features of this disease. The exorbitant task that was imposed on antibiotics from the moment they appeared in clinical practice was initially masked by their antimicrobial effectiveness. However, today, against the background of all those transformations that have occurred with the etiology of the disease and the appropriateness of using the drugs themselves, continuing to treat the process of inflammatory tissue transformation with agents that do not affect its mechanisms can no longer be considered a scientifically sound approach to solving the problem, can it?

The totality of the available data convincingly shows that the most important, most influential and difficult to eliminate consequence of long-term use of antibiotics is their powerful didactic effect on professional worldview in this section of medical knowledge. It is the existing limited understanding of the leading role of the pathogen in the development of AP and etiotropic therapy in achieving success that currently determines the principles of solving this problem. Without changing this point of view, the future solution of the AP problem looks very unpromising, and the proposed development of new forms of antimicrobial drugs at the molecular level, if they reach the clinical stage of implementation, may bring even more severe side effects.

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