

# What Provokes Constant Changes in the Etiology of Pneumonia?

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## Opinion

Throughout the centuries-old history of acute pneumonia (AP), this disease was considered exclusively as an inflammatory process in the lung tissue, but in the second half of the 19th century, the intensive development of microbiology marked the beginning of the study of the etiology of AP. The first results of the study of pathogens of inflammation of the lung tissue have already identified the main etiological features of this disease. For example, C. Gram, the founder of one of the directions of microbiological diagnostics, in 1884, based on the results of his work, proved that AP can be caused by more than one microorganism, which excluded the specificity of inflammation in this disease [1]. 3 years after the publication of this article, materials appeared that pneumonia can be caused by opportunistic bacteria which are always present in the body, which confirmed the ancient postulate that people get pneumonia, not get infected with it [2]. And although *Streptococcus pneumoniae* (SP) or *Pneumococcus* (P) was isolated in 1886, which prevailed among the pathogens of AP and got its name because of this exceptional propensity [3], but the fundamental foundations of the etiology of this disease and its main properties - non-specificity and non-contagiousness - were formulated already at the dawn of the development of microbiology. It should be noted that the dominant role of SP among the pathogens of AP remained stable for a long period. Periodic statistics on the etiology of this disease consistently showed the presence of P as the causative agent in 95 percent or more of cases. Such figures were presented in 1917 [4], in 1927 [5], in 1933 [6], in 1939 [7] and in 1948 [8].

According to the materials of the presented statistical data, P remained the leader among the pathogens of AP for more than 30 years, without reducing the level of its prevalence is below 95%. And if we take into account the leadership of SP in inflammation of lung tissue since it was first discovered and, due to its superiority, received its name, then the duration of stable statistics of the etiology of AP exceeds at least six decades.

If we focus on the preserved statistics of the etiology of AP, then starting from the first results of studying this characteristic of the disease in the 19th century and up to the 40s of the last centuries, its main causative agent was SP, which consistently maintained almost one hundred percent participation in this inflammatory process. However, as the subsequent course of events has shown, the efforts of medicine to widely use etiotropic therapies have changed the usual proportions of the etiology of AP. In 1929, A. Fleming [9] reported the discovery of penicillin, but it was only in 1942 that he successfully used pure penicillin in clinical practice for the first time [10]. Even before the use of this drug in medical practice, the development of resistance of microorganisms to it was noted and proved. In early 1940, the developers of penicillin for its industrial release published data that the strain *E. coli* is able to inactivate penicillin by producing penicillinase [11], and in 1942 information was made public about the development of resistance of four strains of *Staphylococcus aureus* (SA) to penicillin [12].

Although the first report of tetracycline-resistant strains of P appeared only in 1963 [13], and to penicillin - in 1967 [14], the rapid

development of resistance of CA as part of the body's symbionts to penicillin contributed to an increase in its aggressiveness. Small outbreaks of staphylococcal infection began to be observed already in the late 40s, and in the 60s and 70s there was a peak in inflammatory processes of staphylococcal etiology, including severe pneumonia, especially in childhood. By this time, more than 80% of the CA strains were resistant to penicillin [15]. The increasing role of CA in the etiology of AP was so impressive in those years that severe forms of the disease were considered and began to receive treatment as conditionally staphylococcal even before receiving the results of microbiological studies at the initial diagnosis. With the increase in the number of cases of staphylococcal pneumonia, the percentage of SP began to decrease and, starting from this period, it no longer returned to its original indicator. It is very curious that in 1960 a synthetic analogue of penicillin, methicillin, appeared, to which CA had no resistance [16], but a year later a new form of the pathogen, Methicillin-Resistant Staphylococcus Aureus - MRSA [17] was described. In this situation, the SA showed its extreme aggressiveness, displacing SP from its usual leading positions among AP pathogens.

Moreover, if you wish, you can find data on this issue for the period when CA reached almost one hundred percent (mainly in children) among the pathogens of AP. In this case, we are not talking about presenting the details of the history of the etiology of AP, but about the causes that violated the primary persistent proportions between pathogens of acute nonspecific inflammation of the lung tissue and have since constantly maintained the dynamics of changing priorities in this list. SA was the first to break the hegemony of SP as the permanent leader of AP pathogens. In parallel with the increase in the aggressiveness of staphylococci and the increase in cases of staphylococcal pneumonia, antibiotic resistance of other microorganisms increased, which led to increased virulence and difficulty in neutralization. The frequency of detection of SP against the background of these processes was constantly decreasing and by the end of the 80s it had decreased to 15% [18]. However, by this time, as is known, SA had also ceased to play the role of a "leading monster" not only in the development of severe forms of AP, but also in the etiology of this disease as a whole. In the period preceding this time, the change of leaders among the pathogens of AP and the decrease in the effectiveness of the antibiotics used required the development and release of new drugs and periodic revision of therapeutic tactics.

The classic development of events "in a spiral" began to be noted in the 2010s, when, according to some statistics, SP in the etiology of AP increased to a third among all bacterial pathogens, but by this period it already occupied the second position after Haemophilus influenzae [19-22]. In the last specified period, long-term attempts continued to solve the problem of successful treatment of AP with the help of early microbiological diagnosis of the pathogen and targeted exposure to this disease factor using antibiotics. The stereotype that has developed over many decades about the dominant role of antimicrobial therapy has persisted and continues to dominate professional

ideas about the essence of the problem of AP. Only a few experts have begun to pay attention to the fact that changes in the etiology of AP are more profound than existing impressions. In fact, by this time, the problem of antibiotics losing their prescription in patients with AP began to worsen. More than two decades ago, some experts expressed concern about the growth of viral forms of AP [23-25]. Viral pneumonia was first described in 1938 [26], but for a long time remained a rare variant of the disease. However, already a decade and a half ago, the number of cases of viral pneumonia accounted for almost half of all cases of AP in the world [25].

Such a number of severe inflammatory processes that go beyond the traditional prescription of antibiotics and exclude hopes for the success of such therapy required new views on the problem and new solutions. Two epidemics of coronavirus at the beginning of this century (SARS and MERS) did not lead to a revision of the treatment strategy, although the coronavirus remained on the list of pathogens for all subsequent years, and pneumonia of this etiology continued to be registered until the outbreak of the SARS-CoV-2 pandemic [27,28]. In the light of significant shifts in the etiology of AP towards viruses and a steady decrease in the effectiveness of medical care for this contingent of patients, prolonged monitoring of changes in the conditions of development of this disease without attempts to radically revise the decision-making strategy is surprising and perplexing. However, the reason for the observed stagnation in solving the AP problem became more obvious with the onset of the SARS-CoV-2 pandemic and the referral of assistance to a large flow of patients with COVID-19 pneumonia. When a large number of patients with viral lung tissue damage were admitted, when bacterial coinfection was detected only in a few percent of cases, representatives of modern medicine did not find a better way to provide medical care, as a continuation of declarations of the undoubted need for the use of antibiotics, the rate of prescribing which in this group of patients approached almost one hundred percent [29-31].

Another landmark event that makes it possible to assess the cause of the stagnation in solving the AP problem is the official announcement of antibiotic-resistant microflora as one of the global health disasters [32]. The very fact of confirming these severe consequences of prolonged antibiotic use is welcome. But, from my point of view, the time for such a statement was not chosen by chance. As noted above, the development of microflora resistance to antimicrobial drugs was known even before the clinical use of antibiotics. The entire subsequent period of antibacterial therapy consisted of the generation and release of new drugs due to the development of resistance to previous drugs and a decrease in their effectiveness, which was especially intensively observed until 1970 [33]. The reason for such painstaking work of pharmacists and microbiologists was only the effect of antibiotics. The rapidly emerging resistance of microorganisms to the drugs used, as well as the replacement of some pathogens by others, which eventually led to the entry into the arena of viruses.

Thus, not only the fact of the development of microbial resistance was known, but also its specific manifestations were constantly subject to possible correction for at least 80 years. During this entire period, the obvious side effects of antibiotics were not taken as seriously as they were three years ago. The beginning of the SARS-CoV-2 pandemic showed the lack in modern medicine of not only effective ways to help patients with severe lung lesions, but also ideas for a way out of a situation where the basis of treatment was auxiliary and symptomatic means. The concentration of such patients in specialized departments significantly increased the burden on their staff and at the same time increased the feeling of ineffectiveness of the efforts made and the inability to avoid further deterioration and deaths during treatment. The studied and habitual hope for antibiotics, which in recent years have significantly lost their indications for use, has completely disappeared. Medical journals have even published articles accusing government officials of such a turn of events [34], as well as an unprecedented number of publications with confessions of authors in their depressive states that arose in the course of professional work [35-38]. It was a period when the opinion began to spread and strengthen that even in the most advanced health systems, medicine cannot guarantee a successful outcome in case of illness. The announcement of bacterial resistance as a global catastrophe explained the sudden loss of antibiotics as the main and usual treatment for pneumonia, while at the same time allowing the "honor of the uniform" to be preserved. At the same time, the described events of recent years have shown how narrowed the ideas of modern professionals about the problem of AP are by a learned template from the university about the complete dependence of the development of the disease on its pathogen and the decisive role of etiotropic drugs in achieving success.

Meanwhile, it is no secret to anyone that, despite significant transformations of the etiological list of AP, this disease has retained its unique features, and attempts to carry out differential diagnosis of variants based on etiological signs have failed and continue to fail [39-41]. The materials of a brief analysis of data on changes in the etiology of AP observed over several decades leave no doubt that the ongoing transformations among the active pathogens of the disease are the result of prolonged exposure to antibiotics on the microflora surrounding us. The purpose of antibiotics was initially to eliminate only pathogenic microorganisms, but not the inflammatory processes themselves. This allows us to consider antibiotics as a kind of "biological cleanser". For example, the spectrum of action of penicillin did not extend to all varieties of microflora. Some bacteria, as biological objects, have demonstrated their adaptive capabilities, avoiding complete destruction during the application of therapy. Since a vacuum cannot exist in the wild, more viable microorganisms begin to replace the destroyed microflora. The first manifestation of this antibiotic effect was a surge in staphylococcal infections, including severe forms of staphylococcal pneumonia. Subsequently, antimicrobial therapy was constantly improved, which was required due to a decrease in its

effectiveness and an expansion of the spectrum of resistant strains. All these efforts continued to support the dynamic process of changes in the etiology of AP. By now, the process of restructuring the primary relatively stable variant of the etiology of AP has reached a level where the influence of antibiotics on it as the main cause of such dynamics becomes less significant. A sharp increase in the proportion of viral variants of inflammation and their continued growth are a reaction of nature to external interference in its processes. If we return to the issue of microbial resistance from these positions, then this consequence of prolonged antibacterial therapy seems to be less significant than the observed shift in the list of leading pathogens of AP.

In addition, there are already quite a few real facts that the presence of antibiotic-resistant strains among the body's symbionts is not a sign of imminent disaster and such parity of existence can last indefinitely. The problem with resistant strains of microorganisms arises in the case of disease development, when such pathogens are the cause of inflammation, and etiotropic therapy continues to be considered as the only option for decent treatment. The last feature of the affected problem, when stable and significant side effects of the drugs used are not subjected to a full-fledged critical analysis, and the drugs themselves, contrary to the logic of the observed facts, continue to be considered as a life-saving panacea, indicates another consequence of the use of antibiotics, which is a persistent mental distortion of professional ideas about the essence of the whole AP problem. It is sad to state this, but there is simply no other explanation for several facts, except for the mental distortion of the problem under the influence of a firmly internalized belief in the therapeutic superiority of antibiotics. On the one hand, since the discovery of antibiotics, it has been well known that they can only act against bacterial pathogens, but do not have a direct effect on the emerging inflammatory process, which can progress in cases of aggressive development under the influence of their own mechanisms. On the other hand, long-term attempts at differential diagnosis of AP according to the etiological principle did not bring the desired results, but the AP clinic continues to maintain its uniqueness due to the localization of the lesion and its effect on the function of the affected organ, despite various pathogens of AP. Due to this feature, AP differs from other localizations of inflammation of the same etiology. In addition, in the current professional discussions on this topic, experts are trying to combine two mutually exclusive areas.

On the one hand, measures to reduce unjustified prescribing of antibiotics to reduce the further development of resistant bacterial strains are widely discussed, but, on the other hand, the search for the most effective antibiotics in the treatment of patients with AP and broad support for their use in viral pneumonia, when they have lost indications for their appointment, continues. If we summarize the available information on the problem raised, then such a consequence of prolonged use of antibiotics as the resistance of microorganisms seems to be much less of a nuisance than didactic deformations of professional ideas. In connection with the latter, it should be particularly noted that the WHO statement on microbial resistance as a

global catastrophe proposes a solution to this problem by developing more advanced forms of antimicrobials [32]. In other words, it is proposed to continue the development and improvement of the factors that caused the disaster under discussion.

Recently, despite the predominance of viral forms of AP in many statistical data, the search for means of rapid diagnosis of bacterial pathogens and determination of the most effective antibiotics for their neutralization continues, as it did many years ago [42-46]. There is a very clear impression that many experts have not revealed to themselves the deep meaning of the observed etiological changes in AP. As long as such points of view dominate professional perceptions of the essence of the AP problem, the hope of finding a rational and scientifically sound solution that can finally bring long-awaited success in the treatment of these patients will remain an unrealized dream. Only a radical revision of the concept of the disease will make it possible to move this problem off the ground. A ready-made example of such a solution can serve as excellent results in the prevention of complications and rapid elimination of the focus of AP, which the author of these lines received when he radically changed his own view of the problem and gave a leading role in the treatment process to timely pathogenetic therapy [47]. This work was carried out at a time when antibiotics still retained their former prestige, and viral pneumonia did not pose the tasks that have appeared today. Unfortunately, emigration delayed further research and earlier publication of data in the public domain. Summing up a brief analysis of the facts that are known and documented in available publications regarding the variability of the etiology of AP in recent decades, it should be noted that this phenomenon undoubtedly arose with the beginning of widespread use of antibiotics. To date, in fact, the only side effect of antibiotics remains the development of resistance of microorganisms and a steady decrease in the activity of these drugs.

A significant change in the etiology of the disease, which every year reduces the meaning of using this therapy in patients with AP, is a more severe consequence of taking antibiotics, but the causes and mechanism of this process remain beyond the due attention of specialists and are not subject to discussion. The efforts being made today in search of a solution to an ever-deepening problem repeat those attempts that have been made over the years and whose maximum success has been short periods of slowing down the development of the situation. However, in order to fully understand the scale and significance of the changes that have already occurred, it is necessary, first of all, to abstract from many years of training in the clearly exaggerated importance of antibiotics. The didactic role of this stamp today plays the role of the main brake in solving the problem.

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