ISSN: 2577 - 8005

Opinion

Medical & Clinical Research

Why is Pneumonia Becoming Increasingly Atypical?

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Submitted: 21 Jan 2024; **Accepted**: 30 Jan 2024; **Published**: 15 Feb 2024

Citation: *Igor Klepikov (2024) Why is Pneumonia Becoming Increasingly Atypical? Medical & Clinical Research, 9(2), 01-05.*

Keywords: Etiotropic Agents, Lung Tissue, Microbiological Diagnostics, Inflammatory Processes, Antibiotics

For most of its centuries-old history, acute pneumonia (AP) has been considered by medicine as a single nosological form based on inflammation of the lung tissue and which had individual differences in severity and aggressiveness of its development. The lack of any information about the causative agents of the disease did not pose the task of searching for etiotropic agents, therefore, medical care for such patients was carried out for a long time mainly using pathogenetic methods found empirically.

At the end of the 19th century, the development of microbiology and the discovery of various pathogens of inflammatory processes made it possible to establish the participation of microbiological factors in the development of AP, initiating the study of the etiology of this disease. Back in 1884, C. Gram, the founder of one of the directions in microbiological diagnostics, proved by the results of his work that AP can be caused by more than one microorganism, thereby eliminating the concept of specificity of inflammation for this disease [1]. Just 3 years after Gram's article, materials were published that AP can be caused by opportunistic bacteria that are always present in the body [2]. In fact, in the materials and conclusions of these two articles, at the dawn of the development of microbiology, fundamental features of the etiology of AP were formulated, which over the years have received additional confirmation.

Despite the evidence that AP is not a monoetiological disease, and the inflammatory process in it is nonspecific, Streptococcus pneumoniae or pneumococcus was given a separate place in the early research materials of this section. This microorganism got its name as the leading etiological factor of AP, the frequency of which reached 90-95% among the pathogens of the disease until the middle of the last century [3,4]. Despite the questionable accuracy of the etiological diagnosis of AP, which was used almost a hundred years ago, in the first half of the last century it was assumed that severe inflammatory processes of the lungs (such as lobar lesions) were the result of the involvement of pneumococcus. A milder development of the disease and a smaller amount of damage to lung tissue were usually considered as a result of inflammation caused by other representatives of the microflora. This approach to the clinical interpretation of the etiology of AP was, in fact, the first attempt to divide all cases of the disease into typical ones, where pneumococcus was considered the causative agent, and atypical forms, the causative agent of which were considered other microorganisms [5]. In addition to the clinical and radiological differences, there was a difference in the effect of etiotropic treatment, which at that time began to use sulfonamide, but its effect was less noticeable in the so-called atypical forms [6].

Although the proposals to divide AP into typical and atypical forms were not widely recognized and widespread at that time, however, despite the absolutely obvious facts about the non-specificity of such inflammatory processes, attention could be drawn to the emergence of a tendency to hyperbolize the role of the pathogen in the development of this disease. With the accumulation of information about the microbiological features of the AP, such materials as, for example, the absence of infectious danger and epidemics of this disease or the likelihood of the participation of the commensal microflora as a pathogen, did not serve as a reason for discussion and attempts to understand the origins and mechanisms of the development of this nosology. At the same time, there was already a clear desire to find the dependence of the clinical picture of the disease on the type of pathogen and the desire to get effective etiotropic drugs at practical disposal.

Noticeable changes in the professional worldview began to manifest themselves by the time antibiotics appeared in medical practice. Thus, their primary effect has found fertile ground for their widespread use. The materials and warnings of the founders of antibacterial therapy about the danger of rapid development of side effects, such as microflora resistance [7,8], did not affect the choice and administration of these drugs. Not only the beginning, but also the further use of antibiotics was not distinguished by a strict justification of the indications for their appointment and compliance with the rationality of their administration. The decrease in the effectiveness of antimicrobial therapy and the emergence of resistant strains was accompanied by the need to

release new, more advanced drugs, the most intensive appearance of which was noted already in the first 3 decades of this therapy [9].

The priority of the therapeutic result over the risk of further side effects and the desire to constantly have active antimicrobials clearly prevailed in approaches to this therapy. The possibility of effective suppression of AP pathogens has been and remains the main topic of the discussed tasks for many years, while the fact itself and, most importantly, the reasons for the periodic change of leaders in the etiology of the disease did not belong to the category of issues of primary interest. The changes only affected the qualitative characteristics of the current leaders of inflammation and the most appropriate antimicrobial agents. At the same time, it should be noted that the number of observations with an unidentified pathogen of AP, according to numerous statistical data, has been growing for many years, and the reliability of the etiological diagnosis of the disease and its practical value have recently begun to cause reasonable doubts among many leading experts, which was assessed in recommendations on the leading role of the empirical (”blind”) choice of antibiotics [10,11].

In connection with the latter, it is very appropriate to pay attention to the frequency of detection of pneumococcus among the pathogens of AP in recent years, compared with the above-mentioned indicators in the pre-antibiotic period. Although in recent years publications have continued to appear that pneumococcus remains one of the leading pathogens of AP, and the continuation of anti-pneumococcal vaccination is presented as an important stage in the prevention of the disease, current statistics do not convince of the correctness of such statements. For example, in one of the most extensive and detailed studies of the etiology of AP on the eve of the pandemic, pneumococcus took a very modest position [12]. It was most often found among patients in intensive care units, whose examination is usually of the maximum possible nature. The frequency of its detection in this group was 22.5%, while the lack of information about the causative agent of AP was 46.7%. Among those hospitalized in general departments, these figures were 17.7% and 58.7%, respectively, and among outpatient patients - 10.9% and 68.7%. The presented figures raise more questions about the prevailing negative results of microbiological diagnostics than the relatively insignificant proportion of pneumococcus among the studies conducted.

Even earlier, information appeared that the etiology of AP is increasingly of viral origin. At the same time, statistical data that were presented about two decades ago indicated that viral forms of the disease at that time already accounted for almost half of all cases of AP in the world [13-15]. However, such reports reflected only experts' concern about the observed trend without analyzing the causes of the phenomena and, most importantly, without revising existing conceptual approaches to therapeutic recommendations. The first SARS epidemic, which was registered twenty years ago, was characterized by special severity and high mortality among patients, but the most noticeable changes in the standard approach to providing medical care to such patients affected, oddly enough, only terminology. To denote such forms of lung damage, the term "atypical pneumonia" reappeared, but now it denoted the most severe and unpredictable forms of the disease. The saddest result of that period and the years following it were the circumstances in which the principles of assessing the leading factors of the disease, the causes of the observed etiological transformations and, above all, the priorities of treatment were not logically reassessed.

Is it worth it, after such a long period of passive contemplation of the growth of viral forms of the disease, to be surprised at the approaches to the treatment of patients with COVID-19 pneumonia, which reflected the capabilities of modern official medicine in various health systems during the SARS-CoV-2 pandemic, and what are the natural results of such palliative care with aggressive development of the process? Continuing to strictly adhere to deeply rooted dogmas about the indispensable role of antibiotics in the treatment of patients with AP, modern medicine has lost its sense of reality and, contrary to its own recommendations and rules, continued to pin hopes on the widespread use of antimicrobials, knowing in advance about their ineffectiveness against viruses [16-20]. In such a situation, it is completely hopeless to expect specialists to critically evaluate the role of antibiotics that they have played in the transformation of the etiology of AP. As is known, the coronavirus did not disappear after its first epidemic of SARS at the beginning of this century and continued to remain among the pathogens of AP until the development of the pandemic [21,22], but this information was not critically evaluated, discussed, and even more so predicted.

The apparent surprise and suddenness with which the SARS-CoV-2 pandemic, which arose in 2019, continues to be perceived is actually deceptive, since the statistics of AP pathogens observed over the past decades show that this event itself may well be considered as expected and even inevitable. However, this phenomenon has revealed other important aspects of the general problem of acute nonspecific inflammation in the lung (ANSIL). In fact, ANSIL represents one nosology that has been known to medicine for almost its entire history as AP, but in the last period the desire to emphasize the etiology of the disease for the choice of etiotropic treatment has been accompanied by the emergence of new terms. SARS, which was observed during the first coronavirus epidemic 20 years ago, is an analogue of COVID-19 pneumonia. At the same time, the coronavirus strains changed not only during this entire period, but also strikingly quickly within the framework of the pandemic [23].Therefore, the observed approach to the analysis and explanation of the grandiose changes that have occurred over the past decades and continue to occur in the etiology of AP is surprising and perplexing, which is not based on the canons of medical and biological science, but is replaced by a search for causes not directly related to medicine. Many experts, considering the causes of the activation of viral infections and, in particular, the development of the SARS-CoV-2 pandemic, tend to ignore such an important factor as the biological effects of the drugs used.

For example, among the causes of the SARS-CoV-2 pandemic,

one of the variants of the so-called conspiracy theories began to be considered at the very beginning of its development. Studies on the deliberate or negligent spread of infection have been conducted at a high level, including the involvement of intelligence services, but have not confirmed the primary suspicions [24]. Another popular cause of many problems today, including medicine, is climate change, presumably capable of leading to global health emergencies [25]. Such statements, which do not have direct evidence, are rather declarative in nature. However, it should be emphasized that both the previous and this assumption were formulated by professionals at the most serious level.

The reason for the appearance of such extraordinary theories can be understood from the content of some other materials. So, even at the beginning of the coronavirus pandemic, an editorial in one of the authoritative medical journals explained medical failures in the treatment of a large flow of patients by the inadequate reaction of state leaders to this event, thus trying to explain not only the high incidence, but also the high mortality in the United States [26]. It would seem difficult to find a reason more distant from the biological essence of the problem under discussion, but the meaning and tone of this comment indicated that its authors had no medical ideas to explain and get out of the situation, and the opinion presented only reflected their professional confusion. Three years later, when the end of the pandemic was officially announced, the same editors of this journal in their new interview talked about the successes of medicine that she managed to achieve in the midst of infection, focusing on vaccination of the population, but bypassing medical care, where medicine clearly failed [27].

At first glance, it may seem that medicine has been able to solve the difficult task of dealing with a sudden disaster in a short time. However, the real facts do not give grounds for such optimistic conclusions. So, already at the beginning of the pandemic, it was known that contact with coronavirus does not always lead to illness, and 20 percent or more of those infected will find out about it only after passing testing [28-30]. According to some data, the proportion of asymptomatic infection during the pandemic reached 78.3%, depending on the regions [31]. Vaccination was of some importance as a preventive measure, but not as a therapeutic one. Today, numerous demonstrations against vaccination are already known, and some countries have abandoned strict epidemiological measures, which, nevertheless, have not made them leaders in morbidity and mortality. The gradual development of the so-called collective immunity, which many infectious disease specialists and immunologists talk about, also played its own specific and, perhaps, the main role.

To call a spade a spade, the main problem that the pandemic posed to medicine was not at all the danger of infection, which immediately and reasonably included anti-epidemic and preventive measures. Even the very fact of the development of clinical signs of contact with the pathogen did not indicate an imminent danger. But in the case of COVID-19 pneumonia, the lack of effective medical care has created an atmosphere of insecurity and fear of this disease. Such sentiments among professionals have significantly increased as a result of monitoring the ineffective treatment of a large number of serious patients concentrated in specialized departments, which was expressed in a series of unusual candid publications [32-35].

As the statistics of the coronavirus disaster showed, only 20% of those infected were hospitalized and only 5% were placed in intensive care units [28-30], but it was these groups of patients who needed emergency specialized care, and the results of their treatment reflected the potential of medicine in this difficult period. In this regard, the focus only on vaccination in the comments mentioned above is convincing evidence of distorted ideas about the nature of AP, which arose under the influence of excessive addiction to antibiotics. The established dominance of the pathogen as the main cause of the disease continues to determine the entire range of directions in solving the ANSIL problem, from professional views and setting tasks for ongoing research to attempts at therapeutic testing of various drugs.

Presenting COVID-19 pneumonia as a new specific form of inflammation of the lung tissue, modern medicine classifies it as an atypical variant of the disease primarily because it goes beyond the generally accepted stereotypes that are traditionally treated with antibiotics. On the one hand, such an interpretation is a catalyst for the vigorous development of effective antiviral drugs, which today is the leading direction in finding a solution to this problem. On the other hand, this point of view on the nature of viral pneumonia has already launched a new round of searching for decisive specific features of these forms of the disease, completely repeating similar studies in recent years, which did not bring the expected results. In recent decades, a lot of effort and money has been spent on early recognition of bacterial pathogens before specialists began to realize the futility of such research [10,11]. But, if earlier it concerned only the bacterial etiology of inflammation, now negative results are associated with attempts at differential diagnosis of bacterial and viral forms [36-39].

It would seem that now, when it is not possible to distinguish bacterial and viral pneumonia even with the help of an artificial intelligence algorithm (38), there are convincing arguments to look at this problem from a different angle. However, the fact that the hypnotic role of antibiotics continues to influence the professional worldview and is a serious obstacle in solving the ANSIL problem is convincingly confirmed in the basis of those studies that remain relevant. Against the background of the generally recognized trend of growth of viral forms of AP in recent decades, the development of the SARS-CoV-2 pandemic has elevated the so-called atypical pneumonia to the category of leading forms of the disease. In the context of a sharp change in the contingent of patients with acute pulmonary diseases, not only unjustifiably widespread use of antibiotics continued (16-20), but research on early identification of bacterial pathogens and elucidation of the most optimal antimicrobial drugs continued with the same activity (40-42).

A particularly striking example of the psychological dependence of decisions made during the pandemic on the exaggerated role of antibiotics has been demonstrated in the UK health system. All

patients with pneumonia caused by COVID-19 were automatically included in the community-acquired pneumonia (CAP) group, which implied routine therapy, including antibiotics [20]. At the same time, in another analysis of the material for this period, without providing evidence, it is stated that Streptococcus pneumoniae remains the main causative agent of CAP in England [43]. If we take into account the dubious value of bacteriological studies among such patients and the low reliability of the results obtained [10,11], then such conclusions are purely declarative, do not bring practical benefits and only support existing misconceptions.

Over the past few decades, relating to the period of antibiotic use, facts have been noted and recorded reflecting changes in the main characteristics of AP. The observed transformation is mainly related to the etiology of the disease. Having preserved the leading signs of the mechanisms of the inflammatory process and its dynamics, which determine the clinical picture of the disease and on which its diagnosis is based, AP has long lost the idea of its pathogens, the list of which corresponded to the proposed concept of "typical inflammation". In the last 2-3 decades, the proportion of so-called atypical forms of AP has been growing especially rapidly. If we critically carefully evaluate all the information about the historical dynamics of the etiology of the disease, then the observed changes acquire the features of inevitable ones.

Even at the dawn of the study of the etiology of the disease, it was noted that it does not have strictly specific variants and can be caused by more than one pathogen [44]. For most of the history of AP, this disease basically corresponded to the concept of bacterial inflammation, which was confirmed even after the start of antibiotic use, when the usual proportions of pathogens began to change and signs of microflora resistance appeared. Viral pneumonia, first described only in 1938 [45], was manifested for a long time by rare observations and did not present a noticeable clinical problem. However, the factual material of recent years shows that the conceptual ideas about this disease have ceased to correspond to the real situation in this section of medicine. All of the above information not only forces us to recognize the fact of significant changes in the spectrum of AP pathogens that occurred during the period of antibiotic use, but also provides a convincing basis for starting concrete actions to remedy the situation requiring emergency measures.

Funding

This manuscript is a full initiative of the author and does not have any funding.

Conflict of Interest

The author states that he has no conflict of interest.

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