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Opinion

Stigmas of the Antibiotic Era in Acute Nonspecific Inflammation of the Lung

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Acute inflammation of the lung tissue of a non-specific origin has long been known under the terms "pneumonia" and "acute pneumonia" (AP). However, in the last three decades, this entity has been classified by the site and conditions of onset [1,2]. This classification principle was based on the assumption that pathogens in the environment, depending on their location, are capable of infecting a specific individual and contributing to the development of the inflammatory process in the lung. Classifying patients with AP according to different conditions of onset was proposed in the hopes of facilitating a more accurate selection of antibiotics and increasing their effectiveness.

Among the AP variants presented in this classification, some could not have been observed decades ago due to a lack of appropriate conditions, such as ventilator-associated pneumonia (VAP). Therefore, AP, which corresponds to the classic nosology of the disease, is presented in modern literature as community-acquired pneumonia (CAP), which, even in the presence of aggravating factors and comorbidities, develops outside of healthcare facilities. This group of patients is the most numerous, accounting for the vast majority of AP cases. In other cases, the patient's condition required hospitalization for observation and treatment even before the development of AP. In such cases, hospital-acquired pneumonia (HAP) may have developed, which is more of a clear complication of the underlying disease than an independent process, as is commonly believed.

This classification differs significantly from the main approaches to classifying various diseases due to its unusual and unconventional nature. Typically, a patient is first examined, and based on the results, the disease is assigned one of the generally accepted terms. In this case, the proposed classification has a completely opposite purpose, serving primarily an unusual diagnostic function. This patient classification is based on previously studied characteristics of the microbial composition under various conditions and the tendency for certain strains to predominate in the environment and medical equipment.

The discussed classification of AP has been in use for a long time, allowing us to assess its practical value. However, as the general state of the AP problem, as well as current results, demonstrate, this classification has not brought the expected benefits or significant changes in this field. Nevertheless, the established terminology has not only become generally accepted in official medical literature but has also recently been supplemented with new designations. For example, the term "intensive care unit-associated pneumonia" (ICUAP) has recently appeared [3-5]. The emergence of such terms pursues the same goals-an attempt to blindly define the presumed etiology of AP. The persistent persistence of this trend, despite the lack of obvious success in the practical application of such a classification [6], has its own stable prerequisites.

The objective conditions underlying the existing difficulties in diagnosing the etiology of AP include, first of all, the non-specificity of such inflammatory processes with a fairly extensive list of possible pathogens. This fact was established at the dawn of the development

of microbiology. Thus, in parallel with the discovery of the most active pathogen of lung tissue inflammation *Streptococcus pneumoniae*, which received the corresponding name [7], it was shown that such processes of this localization are not only its prerogative and can have more than one pathogen [8]. At the same time, it was established that opportunistic strains that are symbionts of the body can also act as a pathogen [9]. Subsequently, the list of potential pathogens of the disease was significantly expanded, due to the confirmation of new etiology options, including, in addition to bacteria, viruses and fungi.

The heterogeneity of the microbiological characteristics of AP against the background of the first successes of antimicrobial treatment methods, especially with the advent of antibiotics, contributed to the emergence of a biased system of views on this problem in the professional environment. It was during this period that the so-called microbial theory of disease [10] was formed and began to develop, in which the microbiological factor was considered the leading cause of its development, which involuntarily predetermined antimicrobial treatment as the main one. In the context of the widespread use of antibiotics, their side effects began to appear with the development of resistant microflora and a periodic change in the leading pathogens. The inconstancy and unpredictability of the etiology of AP awakened a desire for early diagnosis of pathogens for targeted antimicrobial treatment.

The biased subjective view of the problem under discussion has become the dominant point of view over time, despite the facts and evidence that refute it. Firstly, despite the periodic change of the leading pathogens of AP, the clinical manifestations of this disease remained relatively equivalent. Attempts at differential diagnostics of the disease depending on the type of pathogen have not yielded positive results over the entire long period of their implementation, including the desire to differentiate bacterial and viral forms of inflammation [11-13]. In modern literature, such a significant fact for the characterization of AP remains without reasoned scientific explanations, although the reason for the stability of manifestations of inflammatory transformation of lung tissue lies on the surface and is due to a classic sign of inflammation - dysfunction of the affected organ [14].

Secondly, long-term attempts at early diagnosis of AP pathogens do not give encouraging results, and the number of patients with unknown etiology continues to grow, accounting for half or more cases in recent years [15-17]. If in this situation we take into account the fact that the microbial factor is not decisive in the severity of the manifestations of the process, then the application of funds and efforts for microbiological diagnosis of AP can lead only to short-term success, but not to a victorious solution to the problem. The past SARS-CoV-2 pandemic clearly showed that infection of a large number of people with an identical strain of coronavirus gives exactly the opposite results, spreading from latent carriage to the development of severe COVID-19 pneumonia [18-20].

The new strain of coronavirus, unfamiliar to the body of most of the planet's inhabitants, was characterized by rapid spread, but even such a process of expansion confirmed the long-known postulate that pneumonia is not contagious, but it occurs as a disease. Isn't this a unique natural experiment, the results of which do not agree with the above-mentioned microbial theory and require an immediate revision of the entire concept of the disease? However, contrary to the logic and regularity of modern events in this section of medicine, recently published articles once again cite the assertion that CAP is a consequence of lung infection in out-of-hospital settings [21-23]. At the same time, among the positive results of etiological diagnostics, the prevalence of viral forms of inflammation over bacterial ones is noted [17,24-26], but if bacterial CAP is suspected, empirical use of antibiotics for at least 3 days is recommended [23,27]. A rather strange rationale for treatment approaches, which largely highlights the widespread blind faith and hope in antibiotics, despite the lack of rigorous justification for their use. At the same time, it ignores the fact that during the pandemic, the majority of people with severe COVID-19 pneumonia, despite the lack of etiotropic therapy, overcame this disease [18-20]. The latter phenomenon indicates an inflated idea of the role of etiotropic agents in general and antibiotics in particular in the treatment of AP.

Thirdly, at least over the last couple of decades, there has been a noticeable increase in viral pneumonias and parity between bacteria and viruses in the etiology of AP [28-30], and according to many recent statistics, viruses are beginning to top this list [17,24-26]. In this

regard, the question naturally arises about what hopes for the success of new generations of antibiotics the initiators of such plans expect to receive. At the moment, compliance with previous recommendations and guidelines without a radical revision of the basic principles does not bring noticeable success in achieving the main goal of the efforts - the final results. And this indicator, as is known, is far from the expected achievements.

Perhaps the latter circumstance is the reason why, when comparing the quality of medical care in three health care systems (USA, UK, Israel), the authors of the study came to the conclusion that the services of these countries do not pay enough attention to the results of treatment [31]. After all, patients and their relatives are interested not in hearing, but in seeing and feeling the success that further use of the methods offered today promises them. Such interests can only be served by a positive final result, preferably without consequences and with a certain guarantee of its achievement. However, over a fairly long period of increasing role of viruses in the etiology of AP, no attempts have been made to critically rethink the pathogenesis of these diseases, which continue to retain the basis of clinical manifestations, despite the radical change in pathogens. Meanwhile, it can be noted that monitoring of this category of patients and assessing the severity of their condition are based on integral functional indicators, whereas the study of the pathogenesis of AP is focused, first of all, on the virtual mechanisms of virulence of pathogens with damage to molecular and cellular structures [32-35].

Fourthly, demonization of the role of the microbiological factor in the development of AP has reduced the causes of the severe condition of patients with all inflammatory processes to a common denominator, regardless of their localization. The distribution of accents in the direction of the main efforts concerns both diagnostics and treatment. In this regard, we are talking about those situations when signs of septic complications appear and, in addition to the standard prescription of antimicrobial drugs, the use of auxiliary and supportive methods is required. In such cases, at the early stages of the disease, the most common standard prescription is intravenous infusions, which at first, as a rule, are considered as mandatory support for such patients and prevention of circulatory disorders. The volume of such starting infusions is not always subject to special control. Only in the case of sepsis or septic shock, intravenous infusions are significantly increased, taking on a strict bolus character.

It is quite obvious that in the latter case, patients with AP should be excluded from the list of indications for intravenous infusions, which are especially dangerous in the initial period of the disease, when edema and inflammatory infiltration of the lung tissue increase. The influence of the localization of the main focus in the pulmonary circulation is most clearly manifested in the aggressive development of the process [14]. Disturbances, first of all, of the pulmonary blood flow lead to compensatory, secondary, and not pathological, primary, as in other inflammatory diseases, changes in the peripheral circulation, the indicators of which are considered today as one of the cardinal signs of septic complications [36,37]. Such a mechanism in AP is a consequence of pulmonogenic, not septic shock and requires other approaches to its elimination [14]. The inevitability of this pathogenesis in patients with AP is due to the continuous cycle of general blood flow, which has opposite criteria in each of the two circulatory circles and must be preserved to maintain vital functions.

The situation that has developed over many years with approaches to the assessment and treatment of patients with AP cannot but draw the attention of medical specialists to the existing discrepancies. On the one hand, everyone knows from the university bench the initial differences and functional continuity of the two circles of blood circulation, and this information is one of the axioms of basic medical knowledge. On the other hand, the emphasis on the primacy of the microbial factor and its suppression in AP has left aside other important components of this disease. As a result of analogies with other inflammatory diseases, pseudosepsis is diagnosed in patients with AP, which provides grounds for pathogenetically unacceptable treatment methods. Such therapy is one of the significant reasons why sepsis and septic shock in AP often develop during and despite inpatient treatment [38-41]. A look at these phenomena from the standpoint of basic knowledge cannot leave any doubts about their causes.

Fifthly, the dominant ideas about the main causes of AP development and the necessary treatment methods in recent years have begun to generate a largely declarative campaign to form a negative image of resistant microflora. The active recent discussion of the role

and influence of resistant microflora on the severity of development and treatment results of AP is mainly presented as an indisputable negative fact, but without any convincing evidence. Thus, in most publications, the subjective assessment of this phenomenon appears as an indisputable factor [13,42]. However, objective materials, which are rare, show that resistant strains of pathogens are detected in less than 2% of cases [43,44]. And no one provides evidence that such strains, having acquired their own protection from certain types of antibiotics, have become more dangerous and aggressive.

The reason for the currently actively disseminated statements about the negative impact of resistant microflora on the development of AP and the results of its treatment is mainly the above-mentioned subjectivity of professional ideas about the nature of this disease. The established worldview about the leading role of the pathogen and the main therapeutic agent - antibiotics - involuntarily presents resistant microflora as an undoubted cause of therapeutic failures and suggests the development of new versions of antimicrobial drugs. Therefore, it is no coincidence that statements about the growing danger of resistant strains are usually accompanied by calls for the development and release of new generations of antibiotics [45-47]. Such reasoning only emphasizes the depth of ingrained common stereotypes that have turned into an instinctive tradition, leaving many facts from modern events without due attention. For example, no one is in a hurry to explain the fact that the number of resistant strains in the symbiotic microflora of healthy people can be several times (!) higher than the frequency of such pathogens in the etiology of AP [48-50]. But don't these comparisons refute the growing opinion about the extreme danger of resistant microflora?

Today, without a comprehensive understanding of the multifactorial changes that have already occurred in the era of antibiotics with the main characteristics of AP, further immersion in a concept of the disease that has long lagged behind real events continues. Calls for the development of new generations of antimicrobial drugs are devoid of expression of inevitable concerns about what even more severe consequences the implementation of such an expansion may lead to. At this stage, it is necessary first of all to realize that AP is not an infectious disease in the full sense of this terminology, and etiotropic therapy with its focus on one of the factors of inflammation cannot play the role of the main, and even more so the only method of treating this category of patients.

In addition, it should be realized that throughout the era of antibiotics, there was a change in the causative agents of AP, but the disease picture remained relatively stable, maintaining its correspondence to the classical term "acute pneumonia". At the same time, multiple attempts to find reliable differential diagnostic criteria depending on the etiology did not bring the expected results. The latter circumstances serve as a convincing argument for assessing the shifts in the indicators of various pulmonary functions and the integral causes of their impairment. This approach to revising the established worldview is the basis for understanding the pathogenesis of the disease and the logical justification of the necessary treatment principles. It is important to focus, especially in severe cases of the disease, on first aid methods that can directly affect the cumulative irritants of such disorders, and not on the counteractions sought today at the molecular-cellular level, which can only give an indirect and delayed effect.

Thus, at present, the main task on which the successful solution of the problem of AP depends is clearly defined. The primary need is to bring professional views on the nature of this disease into line with the fundamental canons of medical science. Narrowly specific ideas that have developed over a long period of antibiotic use and continue to be based largely on impressions of the exceptional role of these drugs obtained at the initial stages of this therapy have long lost their correspondence with real facts. Without eliminating this cause, any attempts to achieve success in solving the problem of AP will remain narrowly tactical, not strategic. Limited selectivity of research and repetition of already completed directions will only deepen the deviations that have arisen and delay the possibility of achieving the desired results.

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Conflict of Interest

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