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Letter to Editor

Etiotropic and Pathogenetic Therapy of Acute Lung Inflammation- ②

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From the moment of the first description of Acute Pneumonia (AP) to the present day, a huge period of time has passed with the change of a number of generations and epochs, during which the art of healing the sick has significantly advanced in many directions, achieving unprecedented success. Significant changes in medicine have taken place in the direction of its main goal, although the ideal of medical care has remained unchanged at all times, regardless of the depth of scientific knowledge and the range of means—the resolution of the disease in the shortest possible time and preferably without consequences.

Especially rapid reforms in the treatment of patients with AP were observed in the last century due to the success of Microbiology and the discovery of antibiotics. The emergence of new method of treatment of acute inflammatory processes has saved millions of lives and for many years was perceived as a universal way to treat many diseases. However, the disastrous consequences of long-term use of antibiotics exceeded all cautious predictions about their side effects.

Unlike drugs of classical pharmacology, which affect various activators and derivatives of the body itself, antibiotics are directed against pathogens as representatives of the microcosm around us. Acting in this direction, these drugs have an impact not only on the suspected pathogen, but also on the accompanying microflora of our body, changing its composition. The steady decline in the effectiveness of antibiotics, the need to constantly develop new, more effective forms of them, the appearance and growth of a group of antibiotic-resistant microorganisms, many of which are already becoming familiar to us as symbionts, are the most noticeable consequences of long-term use of this group of drugs.

A full-scale assessment of the effects of long-term antibiotic use is very difficult, but a rough idea of this process can be obtained from individual statistics. For example, in the United States alone, 41.2 million prescriptions are issued each year for antibiotics intended to treat acute respiratory infections. This results in a cost of \$ 1.1 billion [1]. According to the Centers for disease control and prevention, more than two million people are infected with antibiotic-resistant pathogens each year in the United States, and at least 23,000 people die as a result [2]. The dynamics of infection with antibiotic-resistant microorganisms has been analyzed based on data from more than 20% of all hospitalizations in the United States. The results obtained showed the overall stability of this task when changing the ratios between different types of these pathogens [3].

Despite a significant decrease in the effectiveness of antibiotics and an undoubted increase in their negative consequences, they are still considered as the main, “cornerstone” method of treating patients with AP [4,5]. Moreover, it is proposed to increase the insufficient effectiveness of this type of medical care by extending treatment courses to achieve a sterilizing effect (?) and reduce the long-term consequences of lung tissue inflammation [6]. Such recommendations only raise additional questions, since it is known that it is impossible to achieve complete sterility of a living organism even theoretically, and antibiotics act exclusively on microorganisms, but do not directly affect the mechanisms of inflammatory response in tissues. Current estimates of antibiotic therapy in patients with AP reflect the understanding that the success of treatment depends only on this type of care and without these drugs there can be no hope for a favorable outcome.

Unfortunately, the evaluation of antibiotics as a necessary treatment for AP does not take into account the very significant

and important prerequisites that were noted above and that are reflected in the evolution of numerous resistant strains and the need to update the drugs used. The long-term and unavoidable impact of antibiotics on the bacterial part of the body’s microbiome could not, even theoretically, not lead to tangible consequences. For example, in previous years, influenza and other viral infections were precursors of bacterial forms of AP, while viral pneumonia was extremely rare [7,8]. In recent years, there has been a trend towards an increase in the number of viral lung lesions, but these changes in the etiological orientation of the disease have not affected treatment approaches. Many experts express serious concern about the widespread and unjustified use of antibiotics for viral infections [4,9].

The total annual cost of treating patients with viral respiratory infections in the United States was estimated a couple of decades ago at about \$ 40 billion [9]. Attempts to limit these costs and reduce the number of unnecessary prescriptions of antibiotics for respiratory viral infections are more of a narrow psychological impact than a radical solution. So Meeker et al. [10] recognizing the powerful influence of established traditions and collective opinion on the prescribing of antibiotics for viral infections, applied a method of visual impact on primary health care doctors using campaign posters on this issue. In other words, we are talking about drawing the attention of treating doctors to the undeniable and well-known facts about the passive role of antibiotics in viral diseases. As a result of this work, prescribing antibiotics for viral infections has decreased, but not enough to be considered successful.

The preservation of the established traditions of treating patients with acute respiratory diseases is further confirmed by the experience of providing assistance to patients in the current pandemic. Thus, T.M. Rawson et al. [11], analyzing medical care for patients with coronavirus disease, found that bacterial and fungal co-infection was detected in only 8% of patients, but 72% received antibiotics.

The reasons for such a persistent return to antibiotics in viral infections have more psychological implications than a reasoned scientific justification, but any reasons will be used to continue this tradition, as long as the idea of the AP problem is based on the leading role of pathogens, and lung damage will be treated on the same principles as other inflammatory processes. The most significant causes of misperception and subsequent actions have, in my opinion, the following origin.

First, didactics in the treatment of patients with AP for many years has been determined by the exceptional value of antibacterial therapy. This type was the core of the medical complex for the care of this disease, and often its only means. Over a long period of use of antibiotics in medicine, a system of rules and regulations has developed, according to which it is easier and safer for every doctor in a dubious situation to prescribe an antibiotic without a clear justification, than to skip a situation when such treatment really makes sense. Therefore, when antimicrobials are taken as the main treatment for AP, it is necessary to have not only professional confidence, but also personal courage to refuse this type of assistance to a patient with severe respiratory pathology.

Second, the long-term focus on suppressing AP pathogens has pushed many important aspects of the problem into the background and even out of sight. For example, the clinical picture and laboratory diagnostics of AP correspond to the classics of the inflammatory process, and pathoanatomic and histological studies are an indisputable confirmation of this fact regardless of the type of



pathogen, is not it? In this case, medical care is aimed at destroying pathogenic microorganisms without taking into account the mechanisms of inflammation and does not have any effect on the ongoing process. Therefore, as a result of successful antimicrobial therapy against the background of ongoing inflammation, one can observe the development of such a fairly frequent complication as sterile pleural empyema. Perhaps, in such situations, there are other reasons for the formation of purulent effusion without the participation of microorganisms? And these reasons have irrefutable evidence?

Finally, what medical appointments and actions currently determine the specifics of providing medical care to patients with rapidly progressive lung inflammation? The insufflation of oxygen? However, this procedure is symptomatic and supportive, not affecting the mechanisms of the disease, but only correcting their consequences. Ventilation of the lungs, on which with the increase in the number of viral pneumonia and the loss of antibiotics from medical care, high hopes are placed? [12]. However, this procedure is also auxiliary-substitutive in the terminal stages of the disease, and to avoid such conditions, it is necessary to act before such a situation occurs, is not it? It is unlikely that anyone will object to the logic of treating such patients as early as possible, but hopes for primary care methods are again focused only on the prospect of creating etiotropic drugs [13].

It is easy to see that the General trend in the treatment of AP, which has developed over the past few decades under the hypnotic influence of the role of antibiotics, has formed a limited understanding of the dominant role of pathogens in the course and outcome of the disease. This prevailing doctrine continues to determine the direction of treatment efforts regardless of the etiology of lung damage, leaving without due attention the role of the body of patients and the nature of local inflammatory changes in the tissues of the organ.

Currently, in the current pandemic, when the usual characteristics of AP have changed significantly and the possibility of conducting etiotropic therapy has disappeared, distortions in understanding the basics of the problem have become even more noticeable. For example, the variability of clinical manifestations of coronavirus infection in the presence of an identical pathogen is considered primarily from the standpoint of epidemiology, without affecting the pathogenesis of the disease and individual characteristics of the body [14]. In the case of aggressive development of the process in the lungs, the care strategy is to monitor patients and determine the time for timely intubation and transfer to artificial ventilation [15]. To reduce the probability of intubation in viral pneumonia, attempts to supply oxygen in the supine position of the patient on the stomach are checked [16,17]. At the same time, anatomical studies of lung lesions in COVID-19 indicate inflammatory changes in the same lung structures as in bacterial processes and other viral infections, indirectly reflecting the generality of functional disorders [18-20].

All of the above publications state the fact of inflammation of the lung tissue, regardless of the etiology of the process. The histological nuances of the differences between bacterial and viral lung damage remain a reflection of one of the types of pathological processes that have always been classified and continue to be considered as "acute inflammation". This term appears directly or indirectly in all current publications on this subject, including analysis of materials with current coronavirus infection. However, if we are talking about the process of inflammation, why are the main concerns related to

the suppression of pathogens, and the dynamics and consequences of inflammatory tissue transformation are at best considered at the molecular and cellular level? But the inflammatory process, contrary to our estimates, is inevitably accompanied by five classic signs that were described by Celsus and Galen many centuries ago. Since the description of these signs, they have received additional justification and confirmation, but no one has questioned their role and significance in the clinic of inflammatory diseases. This is especially true for such a sign as a violation of the function of the affected organ, which determines, depending on the localization, the severity and uniqueness of each disease. However, this part of the problem remains insufficiently covered in relation to AP.

According to modern ideas about functional disorders in AP, we should expect violent objections at this stage of reasoning: "and then how to evaluate oxygen therapy, because edema and infiltration of lung tissue violate the gas exchange function and cause hypoxemia?" The presence of hypoxemia in severe patients with AP is objectively proven and is not in doubt, except for the causes and mechanism of these disorders. This question is based on seemingly logical assumptions, but it is necessary to ask a counter question: "why is a relatively small focus of acute inflammation in the lung, as a rule, able to cause more severe hypoxemia than atelectasis of the lobe or entire lung?"

To get a reasoned answer to this dilemma, it is necessary to remember that the lungs have not only their inherent gas exchange function. This organ has a number of so-called non-respiratory functions. First of all, the uniqueness of the lung tissue is the ability to pass through its vascular system all the blood that circulates in the body. The mechanisms of synchronous interaction between the two circulatory circles and its Autonomous regulation are well known and studied by fundamental medical science. In addition, the important role of violation of the relationship between the two circulatory circles in AP has been proved and the possibility of therapeutic effects on these shifts has been confirmed [21]. The AP pathogen acts as one of the triggers of the disease, but it is not its main and only cause. The included mechanism of inflammation develops further according to biological laws, where the pathogen recedes into the background, and etiotropic therapy no longer plays a decisive role, giving way to pathogenetic assistance.

Detailed consideration of the pathogenesis of AP and methods of influence on its links is not the purpose of this appeal. Some aspects of this problem were mentioned only as isolated examples. In this context, we are talking about the long-overdue need to review the AP ideology, on which all further actions to solve the problem fully depend. The subsequent re-evaluation of the priorities of the main directions of medical care in the AP will allow us to understand the possibility of using pathogenetically based methods of treating viral lesions today, which will be of invaluable importance for saving many lives. The prospect of developing antiviral drugs, even if successful, will not cancel these methods, since it will not be able to provide an absolute result in all observations. Therefore, pathogenetic approaches to the treatment of this category of patients should be considered as a natural specific treatment.

The results of treatment of patients with acute inflammatory processes of the lungs are characterized by negative dynamics for many years. However, the current situation in this section of medicine has already reached a critical level, basing the strategy of providing assistance to this category of patients only on symptomatic and



auxiliary methods. A huge layer of fundamental medical materials that can reveal the essence of the problem and give an impetus to its solution remains in the archives, and not at the forefront of science and practice. Returning to the basics of lung physiology and pathophysiology allows you to evaluate the unique features of this system and see the entire panorama of the problem.

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