

First aid and Prognosis for Acute Pneumonia

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Abstract

Acute pneumonia (AP) is one of the oldest nosologies known to medicine, but the causes of acute inflammation of the lung tissue, and even more so the mechanisms of its development, remained unknown for many centuries. And yet, observing these patients allowed ancient medicine to come to the conclusion, which remains relevant to this day, that people get pneumonia and do not become infected. Many years of empirical experience, based primarily on achieving quick and tangible results, have also made it possible in different parts of the world to develop various methods of providing first aid to this complex category of patients. Such approaches to the treatment of AP remained virtually unchanged until the first half of the last century, and their long-term relevance and prevalence reflect the presence of positive effects from the use of such techniques.

Keywords: nanotechnology; targeted drug childbirth; drug happening; nanoparticles; liposomes; polymeric micelles; dendrimers; controlled release; active point or direct at a goal; personalized cure

Introduction

The study and discovery of the causes of AP was facilitated, first of all, by the development of microbiology and its success in the discovery of the causative agents of this disease, starting from the end of the 18th century. The introduction of these achievements into practical medicine made it possible to establish and monitor that pneumococcus, which received its name due to its tendency to damage lung tissue, remained the main causative agent of AP for a long period, without reducing its activity to less than 95% [1-5]. The study of the mechanisms of development of the process in the lungs during this period has not yet yielded results that could directly affect practical approaches to treatment. At the same time, detailing the etiology of AP made it possible to establish and, with some success, begin to use sulfonamides in clinical practice as antimicrobial agents [6-7].

The appearance of sulfonamides in the general complex of treatment of AP was an example of the massive use of antimicrobial drugs and one of the first steps towards the spread of this direction. Therefore, by the time of the first clinical use of penicillin in 1943 [8], etiotropic drugs were already considered an important segment of medical care in the treatment of inflammatory diseases. The further introduction of antibiotic therapy brought amazing results in the early years, accompanied by a kind of euphoria, since the new type of therapy was considered an exceptionally miraculous method. The enthusiastic reception of the first effects of antibiotics has distorted a professionally balanced and scientifically based assessment of the basic principles and concepts. For example, it was initially known that the effect of antibiotics is directed only at pathogens and does not affect the mechanisms of the inflammatory process itself, but this did not prevent the treatment of AP from concentrating soon after the start of this therapy on the principle of “antibiotics alone”.

The entire course of subsequent events is evidence of the formation of views on the problem that do not correspond to and contradict the ever-growing facts of reality. On the one hand, this was due to a sincere desire to achieve effective care for seriously ill patients, when, first of all, efforts were aimed at constantly improving antimicrobial action, and information about side effects, known since preclinical studies [9-10], did not attract serious attention.

On the other hand, the emerging preferences and exaggerated assessment of the role and place of antibiotics in the complex treatment of AP continued to be replicated and taken root in the professional consciousness by making appropriate changes to educational programs. Over the past decades, numerous generations of doctors have been trained in the leading role of the AP pathogen in the occurrence and development of the disease, as well as the direct dependence of the success of therapy on its rapid and effective suppression. An example of such didactics can be sections of manuals and textbooks describing etiology, pathogenesis and treatment of AP, published in different periods. The difference between such presentations was that the lists of pathogens, their virulent properties and the most recommended antibiotics were only periodically updated in accordance with changes, but the essence of the approaches remained the same.

The growing desire to maintain the effectiveness of etiotropic therapy for AP has gradually and steadily moved away from the goal as a result of such obvious consequences of this treatment as increased microflora resistance, a decrease in the effect of existing antibiotics and the constant need to develop and produce more advanced drugs, periodic changes in the main pathogens and diversity of etiology. Of the listed consequences, only bacterial resistance caused serious concern among specialists, which was associated

primarily with a decrease in therapeutic results. In the early decades, the decline in the effectiveness of antibiotic therapy was supported by the release of new drugs, most of which were developed before 1970 [11]. Subsequently, the process of creating new drugs slowed down the pace of their generation, but the goal of these efforts remained the same. Antibiotics continued to play a major role in the treatment of AP, and efforts to effectively suppress the microbial factor were transferred to the development and application of methods for accurate diagnosis of the pathogen for the early targeted use of appropriate drugs. Over a long period, this company failed to achieve the expected success, and experts, including forums of societies on this problem, were forced to admit the absence of any influence of bacteriological diagnosis of AP on the results of its treatment, as well as the remaining empirical choice of antimicrobial drugs [12-14]. However, such recognitions did not lead to a logical revision and reassessment of the prevailing worldviews on the problem under discussion.

The decrease in the antimicrobial potential of antibiotics was accompanied by their gradual displacement from the list of drugs with reasonable indications for use in AP. The latter circumstance was associated with the growth of viral forms of the disease, the number of which reached almost half of all cases of AP in the world two decades ago [15-16]. The increase in the frequency of viral pneumonia in recent years has begun to be mentioned in discussions with recommendations for the inclusion of already known antiviral drugs in the etiotropic therapy of AP. However, the practical implementation of suppression of viral pathogens has not brought tangible results, since the effect of antiviral drugs can be expected only during the period of infection, until the virus has penetrated the cell, and not during the disease, when it is already surrounded by the cell membrane [17].

As a result of all the transformations described above, which changed the conditions for the emergence and development of AP, as well as the initial effectiveness of etiotropic therapy, in recent years there has been a clear trend toward an increase in the number of severe forms of CAP [14,18-19]. It is noted that the results of treatment depend on the clinical manifestations of the disease, and if the overall mortality from CAP has decreased slightly, in severe forms it continues to increase [18-19]. This circumstance was the reason for the active use of auxiliary and supportive methods of assistance. The choice and direction of action of such techniques completely depended on the currently dominant ideas about the main causes and mechanisms of the development of the disease. At the same time, to eliminate the pathogen and its supposed effect on the vital functions of the body in case of AP, methods of assistance began to be used, similar to the treatment of many other inflammatory processes.

Ultimately, the most standard scenario for caring for CAP patients admitted to hospitals in various parts of the world today is the following set of actions and decisions. The patient is initially insufflated with oxygen, trying to use techniques that give the best results, such as a nasal cannula or prone positioning. In parallel, based on an empirical choice, antibiotic therapy is started, which in a hospital setting is carried out by intravenous administration of drugs. This procedure is considered basic first aid, but its effect is usually assessed after 48–72 hours [12–14]. For this purpose, permanent access to the venous bed is established. In most patients, after antibiotics are prescribed, intravenous administration of solutions is continued, which is considered as a measure to reduce the risk of developing hypovolemia.

A decrease in systemic blood pressure in patients with AP is regarded as the development of sepsis or (depending on the clinic and indicators) septic shock. These factors serve as an indication for bolus infusions, and if there is no effect, for the use of vasopressors [12–14]. The latest additions to the therapeutic package are usually carried out in intensive care units, where the next step in case of further deterioration is to transfer patients to mechanical ventilation. A set of methods for helping patients with AP is currently considered scientifically based, so the surprise of a number of specialists that, despite early antimicrobial therapy and ventilation, mortality in this disease is increasing is quite sincere [20]. However, from my point of view, the described approaches to the treatment of AP, especially in the case of their

intensive use, practically program the development of subsequent stages of the disease, when the possibility of timely provision of successful pathogenetic assistance is lost.

The presented scenario for the treatment of patients with AP in a hospital setting is focused on the leading role of the pathogen in the nature of the disease and does not take into account a number of important factors and circumstances that inevitably affect the dynamics of the inflammatory process. Therefore, if we really want to achieve real success in the treatment of this category of patients, then we should completely transform the system of views on the problem under discussion and pay serious attention to the classical provisions of medical science, directly related to the topic under discussion. Such objects of attention should include the stages of development of the inflammatory process, the originality of its manifestation depending on the affected area in the body, the characteristics and originality of pulmonary blood flow, as well as its role and influence on the systemic circulation. This interpretation allows us to understand the reasons why modern therapy does not bring the expected results, and in publications one can increasingly find revelations about the progression of AP during and despite treatment [18,20-22].

The presented scenario for the treatment of patients with AP in a hospital setting is focused on the leading role of the pathogen in the nature of the disease and does not take into account a number of important factors and circumstances that inevitably affect the dynamics of the inflammatory process. Considering the pathogen as the main cause of the disease, and etiotropic drugs as the main hope for a cure, we must not forget that the laws of living nature will continue to influence current processes regardless of our ideas. In this regard, the most reasonable and rational step in understanding and solving the problem under discussion may be a thorough analysis of scientific information, already considered proven facts, which will expand and deepen our understanding of the unique features of AP.

First of all, numerous studies of AP in accordance with the basic concept of the disease “antibiotic versus microbe”, despite the lack of expected results, still provided answers to the essence of the problem being studied, but these indirect data did not attract the attention of researchers. For example, many years of attempts to differentiate AP depending on the pathogen proved futile not only among bacterial forms, but also in attempts to separate bacterial from viral forms [23-25]. The very fact that the same picture of the disease is preserved, regardless of the type of pathogen, suggests that the etiology of the disease does not have such an impact on the severity of clinical manifestations and the development of complications, which they always try to attribute to this.

On the other hand, all specialists are well aware that the same pathogen can cause diseases with completely different clinical manifestations. For example, it is impossible to imagine an equivalent clinical picture of the inflammatory process in pneumococcal meningitis and pneumococcal pneumonia, is it? And this fact brings us back to the assessment of those functional disorders that accompany damage to the corresponding structures of the body, and forces us to recall the fifth classic sign of inflammation - loss of function, which was first described by Galen at the beginning of our era and verified by centuries-old practice. If we take into account all the currently known information about the development of the accident, we will get a completely different scenario for the development of events.

The occurrence of inflammation in the lung tissue is associated not only with the presence of certain pathogens in the body, which, as is known, can be present in the microbiota of healthy people without causing any side effects. The latest confirmation of this rule is the statistics of the SARS-CoV-2 pandemic, when up to 20-40% of infected people did not have any clinical signs and learned about contact with coronavirus only on the basis of tests [26-29]. Currently, specialists in this field are only beginning to remember the long-known facts about significant differences in our reactions to the same situations and stimuli, paying attention to the individual characteristics of the course of AP and a wide range of protective and adaptive capabilities [30-31]. The results of recent reports once again indicate that the

development of AP can have a huge range of differences in its intensification, regardless of the type of pathogen. In the case of a relatively slow development of inflammation, the body has time to fully adapt to the emerging disorders without the use of etiotropic drugs, which could recently be observed in patients with Covid-19 pneumonia during the pandemic. Therefore, a description of a scenario with aggressive development of the disease will be more indicative and understandable.

The mechanisms of AP development were studied by the author of these lines more than 30 years ago. The reason for this work was reasonable doubts about the dominant role of the pathogen in the development of the disease and the leading importance of antibiotics for successful treatment, which arose as a result of our own observations and analysis of the dynamics of various examinations of seriously ill patients with AP during treatment. The purpose of the study, which refuted the generally accepted interpretation of the nature of the disease and the principles of its treatment at that time, was met with complete misunderstanding in the professional environment, but the work was continued and brought to its logical conclusion with excellent results of clinical approbation of pathogenetic methods of treatment of this category of patients. Since then, a lot of new information and facts have appeared confirming the main conclusions of the work done. Given the current importance of the AP problem in the world and the significantly increased amount of evidence indicating the possibility of solving it using already proven principles, the main fragments of the work in recent years have been published in numerous articles and summarized in two recent monographs [32-33]. Therefore, in this context, a brief overview of the pathogenesis of AP and the dependence of treatment results on various methods of medical care is presented.

The onset of inflammation is accompanied by a classic vascular reaction with increased blood flow to the affected area and a sharp increase in the permeability of the vascular walls. Excessive blood filling and slow blood flow increase blood pressure in the affected area, which is immediately accompanied by a response from the baroreceptors of the pulmonary vessels. The presence of baroreceptors in the vessels of the lungs has been known for a long time, and the role of the reflex emanating from them was proven back in the first half of the last century [34]. Currently, this reflex most often appears under the term “unloading reflex”, since it allows the vessels of the pulmonary circulation to unload during blood flow disturbances and overloads, in particular, due to the deposition of part of the circulating blood on the periphery.

Such reactions in our body act autonomously, without our conscious control, and turn on automatically when an appropriate stimulus occurs. Acting in this way, these reactions greatly facilitate our existence, quickly relieving us of many dangerous influences. The intensity of the development of subsequent pathological deviations is determined by the individual reaction of the body to a suddenly appearing trigger. In turn, at the same pace, defensive reactions develop, aimed at eliminating emerging violations and acting in the exact opposite direction. The more vigorously the violations develop, the more actively the defense counteracts. However, in the most aggressive cases of the development of the disease, the autonomous nature of such reactions does not prevent them from going beyond acceptable limits, when protective mechanisms begin to play a negative role.

A clear example of the negative role of protective mechanisms is the reaction of the vessels of the pulmonary circulation to the sudden involvement of their small segment in the inflammatory process. The zone of inflammation is capable of exerting its reflex effect on the pulmonary vessels of unaffected parts of the organ, and this influence intensifies and spreads in cases of intensive development of the inflammatory process. This fact was confirmed using cervical vagosympathetic blockades and comparative registration of rheopulmonograms in patients with aggressive development of AP [32-33]. Currently, new evidence of this fact has emerged. A study of tomograms of blood filling of the lung tissue in patients with COVID-19 pneumonia showed its significant decrease at the level of vessels with a diameter of 2 mm or less due to their generalized spasm [35-36]. However, the authors did not find parallels between these disorders and the size of the inflammation

zone. At the same time, attention was drawn to a greater oxygen requirement in patients with a more significant decrease in blood supply [36].

The above materials indicate that the severity of clinical manifestations of AP depends not so much on the volume of inflammation in the lung, but on the intensity of the process. At the same time, supplying patients with oxygen does not eliminate the cause of breathing disorders, which are caused not by the blockade of gas diffusion in the area of inflammation, as many believe today, but by the next link in gas exchange, which is the circulatory system. This is why AP should be considered primarily as a cardiovascular disaster rather than a respiratory one. Elimination of reflex spasm of the pulmonary vessels during this period of the disease and elimination of obstacles to the general blood flow at their level can bring a significant improvement in the condition of patients.

However, currently, pathogenetic approaches to emergency care for patients with AP are considered through the prism of the leading role of the pathogen and its aggressive qualities. Therefore, the main task that they try to solve when providing first aid to such patients is the selection and use of etiotropic drugs, mainly antibiotics. Since an immediate effect from etiotropic treatment is not expected, and the patient's condition in the initial period of the disease is variable and requires additional assistance with the rapid development of the process, such assistance is usually aimed at maintaining the volume of circulating blood to avoid possible hypovolemia. This plan of action is directly opposite to the mechanisms that arise in patients with AP. Intravenous administration of solutions to such patients additionally strains the pulmonary circulation and the right side of the heart. The result of the unloading reflex and signs of peripheral hypotension serve as a reason for bolus infusions.

Attaching importance to infusions in the acute period of AP and assessing the condition of patients according to the parameters of peripheral blood flow, no one remembers that blood pressure in the systemic and pulmonary circulation has an inverse proportion and its slightest changes in the pulmonary vessels affect peripheral parameters, which is due to their inextricable connection and general regulation. This “forgetfulness” is responsible for the overdiagnosis of sepsis and septic shock in these patients, although in fact such manifestations are pulmonary rather than septic in nature [32-33]. It is no coincidence that the bulk of “septic” patients today are patients with AP, the number of which exceeds the number of septic complications in all other localizations of inflammation combined.

By the time the first results of etiotropic therapy are assessed, on which great hopes continue to be placed, in the most aggressive cases of the development of AP and in this treatment scenario, precious time and the opportunity to provide timely and adequate assistance are lost. By this point, the situation for many patients may already be lost. Convincing confirmation of the hopeless and bleak results of treatment of severely ill patients with AP is currently the frank confessions of a number of specialists, which they shared in the open press [37-40]. When work carried out in accordance with all instructions and recommendations not only does not bring the expected results, but, on the contrary, leads to a state of confusion and depression, it is urgent and radical need to re-evaluate the validity of the existing system of views on this problem, isn't it? Giving antibiotics not only a leading role in the treatment of patients with AP, but also assigning them the function of providing first aid has long become a familiar and strictly observed rule of practical medicine. Possessing a biologically active effect, antibiotics during the period of their use have steadily changed the primary conditions under which this therapy began to be used. Today, the emergence of numerous resistant strains of bacteria, a significant decrease in the effectiveness of antimicrobial drugs, the steady growth of pathogens outside the spectrum of action of antibiotics, the variability and unpredictable severity of the etiology of the disease are the consequences of the use of these drugs, which have long and persistently demonstrated the need for a radical reassessment of their place and role in the treatment of this disease. However, all hopes are still placed on etiotropic drugs, among which the role of the main and most common drug continues to be played by antibiotics, the effectiveness of

which in this group of patients in recent years has begun to raise well-founded doubts.

In recent years, due to the growth of viral aggression, the search for antiviral drugs has been carried out, the intensity of which has especially increased during the SARS-CoV-2 pandemic. These efforts are aimed at developing agents that can replicate the initial results of antibiotic therapy. Such aspirations are based on the old concept of “etiotropic drugs against pathogens”, but do not take into account many important points, including the experience and consequences of antibiotic therapy. In addition, the very fact of the appearance of signs of a viral disease indicates the penetration of pathogens into the cells of the body, which is how a viral infection differs from a bacterial one. In the latter connection, as is already known, the effectiveness of antiviral drugs manifests itself with their early use, that is, we can talk more about prevention than about treatment.

Continuing to adhere to the old learned concept and trying to find a way out of the current situation, in modern medicine the popularity of a new direction is increasing every year. Many experts working in this field are now trying to find the most reliable prognostic indicators on which to triage patients at the onset of illness to determine the optimal level of care for them [14,18-20,41-43]. So far this endeavor has not brought significant success and, from my point of view, will not lead to the desired results. This confidence is based on the fact that the principles of treatment of AP, used since the advent of antibiotics, remain the same and there is no reason to expect that small tactical innovations will affect the strategy for solving the problem.

In fact, one of the main goals of developing such predictions is to determine the probability of death one month after the start of treatment and, based on these results, to admit patients at high risk of this outcome to intensive care units. The very formulation of the question indicates a submissive readiness to expect fatal results, and the guideline is a month, the limits of which are quite sufficient for the complete cure of patients with AP. Such a tactical method of distributing AP patients to the place of treatment is simply not capable of radically improving overall results if the principles and approaches to providing medical care remain the same. To ensure that such a conclusion is not considered unfounded, the following data must be provided. Finally, they began to pay attention to such a feature of the AP problem as an increase in adverse outcomes due to severe forms of pneumonia [14,18,19]. However, attempts to screen out such patients in order to intensify treatment do not bring satisfaction with overall results. In the total mass of such patients, there is always a group of patients who do not meet the applicable criteria, and at the same time, the unpredictability of the further development of their inflammatory process requires timely and effective assistance. In the event of a negative development of the AP, attempts to urgently make up for lost opportunities no longer allow them to be compensated for and bring unpleasant surprises. For example, Kolditz M. et al. [44] demonstrate results when mortality among patients with AP immediately admitted to intensive care units is 17%, and upon admission on days 4-7 of the disease it increases to 48%.

Thus, materials reflecting the current state of the AP problem clearly indicate the main reason preventing its solution. Attempts to further search for effective solutions to the problem will remain futile until ideas about the nature of the disease and the priorities for the development of such processes are brought into line with the laws of biomedical science.

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