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Associations and Reality in the Etiology of Acute Pneumonia

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Abstract

Modern AP concepts are focused exclusively on the infectious nature of the disease and the presence of certain pathogens. This belief determines the principles of treatment, the lack of effectiveness of which remains a concern of health professionals. The article presents a fragment of the study devoted to the etiology of AP.994 children aged 4 months to 14 years with various forms of so-called community-acquired pneumonia were examined and treated. Bacteriological examination of the material from the inflammation zone was carried out in 542 patients. Experiments on modeling AP and its pleural complications were performed on 44 animals. The obtained results and critical analysis of the literature data and scientific facts allow us to consider bacteria only as one of the etiological elements of AP, which is not mandatory in all cases of the disease. Scientifically based revision of existing ideas about the causes and mechanisms of AP development leads to the need for a radical change in the principles of treatment and is a strategic direction in solving the problem.

Keywords: Acute Pneumonia, Etiology, Symbiotic Microflora, Experimental Model of Acute Pneumonia, Pleural Empyema, New Doctrine

Introduction

Acute pneumonia (AP) has been one of the most acute health problems in all regions of the world for many years, occupying a leading position among the causes of morbidity and mortality [1-3]. At the same time, the justified concern of experts is a clear tendency to reduce the effectiveness of treatment of the disease. This concern is due to the increase in the number of cases requiring hospitalization and intensive care, as well as the gradual increase in mortality and the incidence of purulent complications, even in the best health systems of developed countries [4-10].

However, the main reason for deep reflection is not statistical reports, but the lack of reasoned scientific explanations of these negative trends and the lack of proposals for a radical strategic solution to the problem. The idea of the omnipotence of antibiotics as the main means of assistance in inflammatory diseases, which has developed in recent decades, is increasingly refuted by the results of daily practice. Equivalent treatment of patients with inflammatory processes having fundamental differences in localization, mechanisms of development and severity of clinical manifestations, has become a common norm. The increase in the group of strains resistant to antibiotics, and the periodic change of leaders among the pathogens of AP are accompanied only by tactical reforms and the release of more and more new antibacterial drugs, reducing the possibility of such maneuvers in the foreseeable future.

There is no doubt that the modern system of medical care for patients with AP requires not only an analysis of the situation, but also a deep and reasoned assessment of existing ideas about the nature of the disease and the scientific validity of the principles of its treatment. The first results of such research experience and clinical testing of the revised principles of AP treatment were obtained about three decades ago, but their relevance is not only not lost, but, on the contrary, in the light of the subsequent trends described above, is becoming increasingly important. In modern conditions, first of all, it is necessary to critically assess the reliability of information about the causative agents of the disease, as these data formed the basis of modern understanding of the nature of AP and they dictate the direction of therapeutic tactics. A small part of the previous work proposed below could be very useful for reflection in this regard and for starting a more in-depth analysis of current views on the issue.

Material and Methods

Studies were conducted in the Clinic of pediatric surgery at The State Institute for Advanced Training of Doctors (Novokuznetsk, USSR) in 1976-1985. During this period, the Department treated 994 children aged 4 months to 14 years with various forms of so-called community-acquired pneumonia and its purulent-destructive complications. Many patients from this number were selectively hospitalized in our Department in the initial period of the most aggressive forms of AP immediately at diagnosis. The reason for hospitalization of the last group of patients is that the surgical clinic was the only place of intensive care in our region with a population of about 2 million people. This group of patients was characterized by high mortality and rapid development of pleural complications. Unsatisfactory results of traditional treatment (massive doses of antibiotics, oxygen supply, methods of bronchial drainage, intravenous infusion) and a large concentration of very severe

patients are forced to look for effective solutions.

The work began with a review of theoretical ideas about the nature of AP, its causes and mechanisms of development. For this purpose, known scientific data from certain biomedical rules and laws were used. To clarify some of the nuances of the disease and obtain objective evidence of the measures taken, special studies and experiments were conducted. Here are only those materials that are relevant to the topic under discussion.

In bacteriological examination of patients, the importance was attached only to the material that was taken directly from the inflammation zone (542 patients). Therefore, the results obtained in patients with purulent complications of the main process were analyzed. It was in this category of patients there was a situation requiring removal of the contents of the lesion (pleural empyema, pleurisy, abscess), followed by microbiological examination.

Experimental research

4 series of experiments were carried out on 44 rabbits. The main experimental manipulation in all animals was endobronchial administration of various mixtures. These manipulations were performed under sterile conditions under intravenous thiopental sedation. A 0.6 mm diameter polyvinyl-chloride catheter was inserted using a puncture of the cervical trachea. The distal end of the catheter was moved to small bronchial branches in one of the lungs. After instillation, the catheter was immediately removed. The liquid mixture for instillation in each series of experiments differed in its composition. The following materials were ingredients for the preparation of the basic compound:

1. 1 billion microbial bodies of one-day culture Staphylococcus epidermidis in 1 ml of saline;
2. 1 billion Microbial bodies of one-day culture Escherichia coli in 1 ml of saline solution;
3. Sterile sunflower oil;
4. Horse serum is normal, which was not used only in the first series of experiments.

The culture of the above-mentioned microorganisms was chosen specifically for experiments, since these bacteria do not appear in the list of dangerous pathogens of AP and belong to the group of "harmless" symbionts. Therefore, the experiment had the following objectives:

- check the possibility of AP development involving trivial symbionts;
- To clarify the role and importance of microbial factors in the occurrence of nonspecific pneumonia.

Only the experimental conditions in series 1 and 4 are of interest for the topic of this article and the discussion below. Therefore, descriptions of 2 and 3 series of experiments are not given.

In the first experimental series (11 animals), a liquid mixture (1 ml of Staphylococcus epidermidis, 0.5 ml of Escherichia coli and 1 ml of sterile sunflower oil) was injected through a catheter into the bronchial tree. On the second and third day of the experiment, seven animals carried out jet slow intravenous infusion of rheomacrodex (30 CC/kg body weight). All animals were put to sleep on the fourth day.

All 15 rabbits 4 series of experiments received seven days before the main part of the experiment subcutaneous injection of 5 CC conventional horse serums. A week later, the above-mentioned composition of the mixture of ingredients, in which 0.05 CC of ordinary horse serum was added, was introduced into the bronchial tree. Later the animals were divided into 2 groups. Seven animals (series 4a) did not undergo additional procedures. The remaining 8 animals (series 4b) were obtained (3-4 hours after endobronchial procedures) intravenous slow infusion rheomacrodex and 0.9% sodium chloride (30 CC/kg body weight). These infusions were repeated once a day. Six animals from the last group (4b) received solutions with the addition of a dye (methylene blue). Euthanasia of all animals was performed on the fourth day after endobronchial instillations.

After euthanasia, the lungs of all animals were subjected to macro- and microscopic examination. Statistical evaluation of the study was carried out according to successive test plans, as well as by the method of controlling the average dispersion in pairs (Sachs L. "Statistics Auswertungsmethoden", Springer, Berlin, Heidelberg, New-York, 1972). These statistical methods made it possible to limit the amount of experiments to obtain reliable results.

Results and discussion

My generation grew up in fear of Staphylococcus aureus. Even at University, I received the first revelations that any pneumonia, accompanied by purulent and destructive complications, has a staphylococcal etiology. This was a period when in such situations the diagnosis of "staphylococcal lung destruction" was made confidently and without much thought. However, if the student had to take on faith the information provided, the practitioner could already critically evaluate the sources of such information. Treatment and monitoring of patients with AP allowed to note that the results of bacteriological examination of the material taken directly from the inflammation zone in some cases showed the presence of other microorganisms instead of the expected Staphylococcus aureus. In some cases, bacteria were not found in the purulent fluid at all. Yes, Staphylococcus aureus at that time was the leader among bacteriological findings in pleural empyema, but, as it turned out, he was not the only causative agent of the process. Statistics of such bacteriological data we carried out a little later in the period when there was a decrease in the frequency of detection of staphylococci. Analysis of the results of bacteriology of the material from the inflammation zone in 542 patients showed that Staphylococcus was detected in 32.7% of studies, other microorganisms-in 33.0%, and microbial flora-in 34.3% of studies were not revealed.

The results of clinical observations and statistics of bacteriological studies contradicted scientific explanations of the causes of purulent-destructive complications of AP. The main stimuli for the development of these complications were interpreted exclusively by the whole complex of pathogenic qualities of Staphylococcus. This microorganism was considered to be the main culprit of all troubles in AP. It is interesting to note that in the above analysis of bacteriological studies, pneumococcus was found only in 12.7%. Then it was difficult to imagine that in just a couple of decades the staphylococcal catastrophe will go down in history and not every certified specialist will be focused on these events, and pneumococcus will repeat the fate of Staphylococcus and will be presented at all levels as another Scarecrow.

But in fairness it should be noted that among the bacteriological findings of the pleural empyema were found other microorganisms (Proteus, E.coli, Klebsiella and others), which were considered less dangerous than staphylococci. However, purulent complications of AP still developed in the presence of less aggressive microflora, and their clinical and radiological signs had no fundamental differences. When the failure of treatment of AP and the development of its severe complications are trying to associate only with the presence of a certain pathogen, but in fact such a monopoly is not confirmed, then inevitably the question arises whether the value of certain properties of a microbe in the development and negative dynamics of the inflammatory process is not exaggerated. Finding an answer to this question becomes even more relevant if you try to explain the reason for the lack of microbes in the study of pus, which was extracted from patients with complications of AP. But patients with this result of bacteriological studies were no more and no less than a third of our observations.

The cause of the so-called sterile empyema of the pleura can be two possible factors. First, this circumstance can be a consequence of effective antibacterial therapy. Antibiotics are known to torpedo the microflora, but are not a means of direct impact on the mechanisms of the current inflammatory process. Second, it is now estimated that about a third of all AP cases worldwide have viral etiology [3]. If these data are true, antibiotics as the main modern means of treatment of AP have no reasonable application in such situations.

Some clarity in this discussion may be provided by the results of experimental studies on modeling AP and its complications. Such studies are usually resorted to in situations where it is not possible to clarify the details of the disease in clinical conditions, and animal experiments allow you to recreate a close panorama of the observed phenomenon.

Our experiments yielded the following results. In the first series of experiments, where the transbronchial infection of pulmonary tissue was combined with a violation of bronchial patency, the AP-model could not be obtained. Macro-and micro-studies of pulmonary tissue showed the presence of a stable pattern of atelectasis without signs of inflammatory reaction. Intravenous infusions carried out during this series did not make any changes to the final picture.

A fundamental change in the results was achieved in the fourth series of experiments. Preliminary sensitization of animals with horse serum and subsequent administration of a small dose of the same drug with simultaneous infection of lung tissue provoked an acute inflammatory reaction. Typical pattern of AP were detected in all observations of the series 4a.

The addition of intravenous infusions (series 4b) to such animals shortly after the start of the experiment showed the development of pleural changes. The dye, which was added in several cases, gave a color change in the area of inflammation. The presence of changes in the affected area against the background of infusions further emphasized the inflammatory nature of the observed tissue transformation. The increase in blood flow to the zone of inflammation by infusion stimulated an increase in edema and infiltration in conditions of increased vascular permeability. The results of the experiments were marked by obtaining a certificate for the invention [11].

It is necessary to emphasize a very important, in our opinion, element of experiments. Despite the strict observance of the conditions for the set of materials and performing manipulations, the degree of inflammatory changes in the lungs and the severity of the pleural reaction in each case had their differences. Inflammatory changes in pulmonary tissue ranged from infiltrative changes to small foci of necrosis or abscess. Both fibrin and purulent exudate accumulations were found in the pleural cavity. In one of the observations at the autopsy was found pyopneumothorax.

Thus, the results of the experiments allowed us to draw the following conclusions. First, the presence of a microbe is not the only condition for starting AP. Bacteria can be one of the components of the etiology of the process, and severe forms of damage can develop with the participation of representatives of the symbiotic microflora. Secondly, an important condition for the beginning of the inflammatory process in the lungs is the immune response of the sensitized organism to the repeated penetration of the allergen. Third, the development of an inflammatory reaction has individual characteristics and can differ in a wide range of manifestations.

The above data of our own research were only one part of all the work done, which was aimed at clarifying the nature and mechanisms of the development of AP and improving the results of treatment. Despite significant achievements in solving this problem, the results remained little known, as they were published only in Russian [12]. The past years have shown that the current understanding of the causes of the problem has not changed, but has focused even more on one narrow area.

Currently, all efforts in the process of diagnosis and treatment, and all proposals for the future are aimed at quickly checking the pathogens of AP for a more accurate choice of antibiotic. It should be noted that for many years all the troubles and failures in the treatment of patients with AP are considered as a result of the presence of infectious and dangerous pathogens. At the same time, the real and objective results of determining the AP agent in the early stages of the disease have not yet been obtained. The exception is a small group of patients with pleural complications, in which the material for bacteriological examination is extracted directly from the area of inflammation. In all other cases of this disease, the nature of the pathogen is tried to be judged indirectly [13].

For example, materials on the causes and etiology of AP published in the press release of the Center for Disease Control and Prevention are based mainly on the results of studies of the nasopharyngeal and oropharyngeal microflora, which were presented in one of the articles of the journal [14,15]. A similar approach to attempts to define the aetiology of AP is widespread and is also addressed in special manuals on this issue [16]. It does not mention a convincing counter-argument against the practical relevance of such data. It is well known that many healthy people have in the composition of the symbiotic microflora of the nasopharynx and oropharynx opportunistic microorganisms, which are described as predominant among the pathogens of AP [17]. But the presence of these bacteria in the body does not necessarily mean the development of acute inflammation in the lungs. In addition, to date, the list of identified AP pathogens has already exceeded 100 [18].

In the course of our studies, comparisons were started between the microflora found in the inflammation zone and the microflora

isolated from the oropharynx and nasopharynx, which were carried out in parallel in patients with complicated forms of AP. The initial results showed a discrepancy between the microbial composition of these sites, so further work in this direction was discontinued, and the data of the first results were not preserved. At present, I can only regret that I have not completed the study that is so necessary today.

The microflora of the upper respiratory tract, from my point of view, can not be a reliable reflection of the microbiological diagnosis of AP. At the same time, the material accumulated today on the study of the symbiotic microflora of the upper respiratory tract can give an idea of the dynamics of its composition under the influence of widely used antibacterial therapy in the world, if we analyze these data over the past decades.

Another surprising look at the causes of AP can be found in the World Health Organization documents on this issue." Pneumonia can be spread in a number of ways. The viruses and bacteria that are commonly found in a child's nose or throat can infect the lungs if they are inhaled. They may also spread via air-borne droplets from a cough or sneeze" [2]. In other words, AP is presented as a contagious infectious disease. However, this statement is not supported by any evidence, and most importantly, there is no further indication of the isolation of patients that is so necessary in this mode of transmission. By the way, it should be recalled that AP never belonged to the category of infectious diseases and did not require the isolation of such patients.

The chosen aspirations to solve topical issues of AP only through the prism of its causative agent are clearly manifested in the modern results of pneumococcal vaccination. Already the first results of this large company led researchers to confusion [19,20]. Contrary to the expected success after years of vaccination, the number of empyema of the pleura was statistically significantly increased. And the most depressing fact is not so much the end result as the lack of reasoned explanations of this phenomenon. But one explanation for these results is the fact that AP does not refer to diseases with strictly defined pathogens. Therefore, specific protection against pneumococcus cannot give the same effect against other bacteria. In this regard, it should be noted that the same analytical reviews provide, for example, data on a significant reduction in the number of cases of pneumococcal meningitis, for which the microbe is actually a specific pathogen.

The dominance of the concept of AP, based on the fatal role of infection in the nature of the disease, and the gradual decrease in the effectiveness of antibiotics as the main means of treatment, logically led to the emergence of another hypothesis that more justifies the failure of hospital treatment than reflects the real situation. In recent years, all cases of AP are divided into non-hospital and intra-hospital. In this case, nosocomial diseases are considered to be more dangerous and severe form of damage, this is explained by the concentration of more virulent and antibiotic-resistant microflora in hospitals. Such assumptions are based on the results of sanitary inspection of premises and medical equipment inside such institutions. However, the obvious logic of these fears requires reasoned objective evidence, and there is no such confirmation in the literature on this issue. Ideas about the causative agents of hospital pneumonia are based, as a rule, on the results of a study of the microflora of the oropharynx and nasopharynx, as if we are talking about sinusitis or tonsillitis, and not pneumonia. In addition, most publications on the development of AP during hospitalization of patients consider the onset of the disease as a contact transfer of certain microorganisms. The last conclusion logically assumes separate isolation of all hospitalized patients, but so far quarantine conditions use only for carriers of antibiotic-resistant strains. Naturally, with the prevailing ideas about hospital-acquired pneumonia, the severity of such patients is associated with the aggressiveness of the nosocomial microflora and little attention is paid to the initial state that caused hospitalization. Patients who are sent to the hospital are mostly sick people with reduced resistance of the body and other disorders of various organs and systems. In such circumstances, AP will be more severe and more likely to lead to serious complications. From my point of view, this direction requires separate monitoring and analysis depending on the nosology of the causes of hospitalization.

Unfortunately, all the conclusions and proposals in the existing publications on the future prospects of solving the problem of AP for a long time are very similar and are of a tactical nature. For example, "*Empirical selection of antibiotic treatment is the cornerstone of management of patients with pneumonia. To reduce the misuse of antibiotics, antibiotic resistance, and side-effects, an empirical, effective, and individualized antibiotic treatment is needed*" [21]. The existing treatment principles are based on the blind choice of antibiotic and cannot guarantee its adequate choice even by a very experienced doctor. This therapy is initially designed only for situations in which there is a bacterial element of etiology, but cannot have the same effectiveness, for example, in viral pneumonia, the frequency of which, according to the publications of recent years, is steadily increasing. Such conclusions rather urge to observe and try to improve the existing principles of treatment of patients with AP, but do not plan a radical solution to the problem. In this regard, it is appropriate to recall that the first experience of antibiotics was not due to the mandatory bacteriological examination of patients before treatment. However, at that time, the blind use of antibiotics was not an obstacle to their triumph. . Why today the shortcomings of rapid microflora studies in patients with AP have suddenly become one of the main reasons for failures in their treatment?

If tactics do not yield tangible results, especially for a long period, a serious revision of the disease strategy is necessary. It is the revision of the entire doctrine of the AP that made it possible to achieve significant success in subsequent treatment and to note the possibility of guaranteed prevention of complicated forms of the disease. Details of this work and its results have recently been published in English [22].

Thus, a purposeful look at the existing ideas about the origin and nature of AP suggests an excessive enthusiasm for the infectious concept of the disease. Further attempts to obtain methods for early recognition of the true pathogen of the process will go against the background of the emergence of new antibiotic-resistant strains, reducing the effectiveness of existing antibiotics and the need for periodic updating of this group of drugs. Analysis of the current state of the problem already indicates a gradual but steady increase in the number of complicated forms of the disease and the inability to quickly reduce its aggressiveness with the help of modern methods of treatment. Therefore, the continuation of research and efforts only in this narrow "infectious" direction leaves without due attention other important aspects of the disease and does not portend success in the future.

Conclusion

Modern AP concepts are focused exclusively on the infectious nature of the disease and the presence of certain pathogens. This belief determines the principles of treatment, the lack of effectiveness of which remains a concern of health professionals. The obtained results and critical analysis of the literature data and scientific facts allow us to consider bacteria only as one of the etiological elements of AP, which is not mandatory in all cases of the disease. Scientifically based revision of existing ideas about the causes and mechanisms of the development of AP leads to the need for a radical change in the principles of treatment and is a strategic direction in solving the problem.

If someone who reads this article is just beginning to perceive AP as an inflammatory process, and not as an infection, many of the shadow side of the issue, which there is no reasoned explanation, will begin to reveal its essence. Another perception of the nature of AP will help to understand why "antibiotics alone" are increasingly not enough to quickly stop the onset of inflammation, and the search and expectation of new drugs is a forced response to the growth of resistance of symbiotic microflora and the use of more advanced drugs is not able to bring this problem out of the impasse. A new look at the nature of the disease is important and necessary, but this is only the first step in the upcoming marathon to change the understanding of the causes and mechanisms of AP and the principles of its treatment. However, do not wait for the emergence of new resistant strains and postpone this process, because already in the course of such adjustments, you can notice a noticeable improvement in the results of treatment.

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