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Review Article

Antibiotics and Etiotropic Mirages of Acute Pneumonia

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Abstract

Antibiotics, being one of the greatest discoveries of the last century, have rendered invaluable assistance in the treatment of many previously incurable conditions. However, for more than 80 years of practical application, the natural qualities of antibiotics have transformed the foundations of inflammatory processes in such a way that their own active capabilities are becoming increasingly unstable, and the need for their use is becoming less and less in demand. The observed transformations in these areas of medicine have long required fundamental analysis and reasonably radical solutions. The most indicative section for critical assessments of the problem under discussion is the state of medical care for patients with acute nonspecific inflammation of the lung tissue, allowing us to see the results of side effects of antimicrobial therapy and the disorientation they cause.

Abbreviations

ANSIL: Acute Non-specific Inflammation in the Lung; AP: Acute Pneumonia; ARDS: Acute Respiratory Distress Syndrome; MRSA: Methicillin-resistant Staphylococcus Aureus; SARS-CoV-2: Coronavirus Pandemic; COVID-19 Pneumonia: Coronavirus Pneumonia; WHO: World Health Organization

Introduction

For many years, practical medicine has been making every effort to treat patients with Acute Non-specific Inflammation in the Lung (ANSIL) or Acute Pneumonia (AP), which has not brought a tangible and stable solution to this problem. This nosology continues to be one of the leading causes of morbidity and mortality worldwide [1-3]. It is worth noting that with the same stability, medicine purposefully and persistently adheres to one system of views on these diseases, without subjecting it to logical analysis and radical rethinking. The so-called microbial theory, which originated with the development of microbiology in the late 19th - early 20th centuries [4], has become so entrenched in the professional worldview with the advent of antibiotics that obvious facts of inconsistencies and contradictions between the theory and practice of modern pulmonology remain without due attention and constructive discussion.

The discovery of antibiotics and their clinical use is rightfully considered one of the most significant discoveries of the twentieth century, and the appearance of these drugs in medical practice saved millions of lives on the planet. However, the nature and duality of this therapy slowly and steadily showed their peculiarities throughout the entire period of its use. By now, the long-term use of these biologically active drugs has significantly affected not only the usual foundations of inflammatory processes, but also the perception of such transformations. Among all diseases treated with antibiotics, AP is the most illustrative example for understanding the basis and structure of the transformations that have occurred over a long period of this therapy. The current state of this problem and the lack of expected results in its solution require a detailed analysis of the transformations that have occurred and the substantiation of optimal directions for achieving success.

Discussion

The above concept of AP considers the pathogens of the inflammatory process in the lungs as the main cause of the disease, and antimicrobial drugs as the main means of treatment. Since the advent of antibiotics in clinical practice, it has been known that these drugs have an exclusively antibacterial selective (!) effect and do not directly affect the mechanisms of inflammatory processes, in the treatment of which they initially demonstrated their enviable effectiveness. Thus, it was shown that the use of antibiotics, neutralizing one of the factors in the development of the inflammatory process,

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allows the body to more easily cope with an unexpectedly arising problem on its own. However, the first results of such therapy were assessed in the literal sense.

The first agent of this therapy, penicillin, brought rapid and remarkable results in the early phase of its use in AP, the prerequisite for which was the prevalence of pneumococcus, highly sensitive to this drug, in the etiology of the disease. The results of microbiological studies in patients with AP, conducted on the eve of the era of antibiotics in different regions of the globe for more than three decades, showed that pneumococcus consistently constituted 95% or more of the pathogens of these processes [5].

The cited indicators of the etiology of AP in that historical period should now quite reasonably raise doubts about their absolute reliability. On the one hand, the studies mainly concerned patients with so-called lobar or croupous pneumonia, which were always distinguished by the severity of their development and course, while mild forms of the disease fell out of sight. Conversely, the methods of microbiological diagnostics for AP have progressively improved in accuracy and precision over time. However, their results have become increasingly unsatisfactory to researchers. Indeed, the mere presence of a particular bacterial species within the body does not constitute definitive evidence of its involvement in the inflammatory process. Just as over time it became clear that many healthy people are passive carriers of strains that are considered the most virulent and dangerous, but this fact does not serve as a basis for an inevitable disease [6-13].

It would seem that during that period of the antibiotic era, a number of events and unambiguous facts became a clear message for a critical rethinking of the role and place of etiotropic drugs in the complex treatment of such patients. Unfortunately, official medicine did not take this step and the protracted process of chasing constant changes in the etiology of AP continued with the same efforts. Moreover, the irresistible desire to achieve success with the help of antimicrobial therapy exceeded rational limits. For example, such traumatic methods as transthoracic puncture of the lung [14] and even open biopsy of organ tissue [15] began to be used to identify pathogens of acute pulmonary inflammation. Such tactics did not bring any revolutionary achievements and, from my point of view, if we critically evaluate its dubious advantages and undoubted disadvantages, could not bring them. In turn, the choice of such tactics is a clear confirmation of a narrow approach to solving the problem from the standpoint of the "microbial concept". The lack of a positive result from such iatrogenic aggressions has not changed the system of professional views, and new attempts at open lung biopsy, the description of which can be found three decades after the previous "experiments" [16], look stunning.

The essence of antibiotic therapy is based on the principle of antagonism between the subjects of the microbial community. Microorganisms have natural adaptability, so the initial successes of therapeutic aggression against them could not continue indefinitely. Variability, self-defense and interchangeability of bacteria during their neutralization were demonstrated and proven at the stage of preclinical use of antibiotics [17,18]. Soon after the start of widespread use of this therapy, the share of other pathogens in the etiology of AP and the need for new drugs began to grow. The release of such drugs was most actively observed in the first decades of the antibiotic era and was dictated by the need to maintain the activity of this therapy [19]. Medicine in such competition remained in the role of catching up, and the introduction of new drugs cannot have an infinite continuation and prevent the subsequent steady decline in their effectiveness. At the same time, attempts at early detection of possible AP pathogens for the targeted use of antibiotics did not give the expected results.

Antibiotics have been used in medicine for over eight decades, and during this long period their use has gone far beyond strict medical indications. In an attempt to prevent the development of inflammatory processes, antibiotics began to be used for prophylactic purposes and continue to perform this function to this day [20-22]. However, there is another illustrative example of non-medical use of antibiotics, when they were introduced into the food industry to increase productivity in poultry, livestock and fish farming. As a result of such a campaign, the intake of antibiotics into the body of healthy people with food and their negative impact on the body's microbiome can have an unpredictably wide range and consequences. In recent years, many countries have established food quality control, but there is still no complete certainty that this channel for the distribution of antimicrobial drugs has been eliminated [23]. In addition, it has been established that natural emissions from farms and the spread of these drugs in the environment, even in small concentrations, can increase the resistance of microflora [24-26].

As evidenced by the accumulated information on the results of long-term use of antibiotics, these drugs are those pharmaceutical derivatives, the use of which implies the inevitable development of side effects. The consequences that antibiotics leave behind are a direct consequence of their potential. Now we already know that not all bacteria die under the influence of these drugs. Many microorganisms resist a sudden attack and survive, acquiring additional qualities in the form of resistance to certain types of antibiotics. In this context, there is no need to go into such nuances as differences in the sensitivity of different representatives of microflora and in the activity of the drugs used. These issues may be of interest to a greater extent from the standpoint of microbiology. In the clinical aspect, it is necessary to take into account two main directions in which antibiotic therapy acts, causing and leaving behind shifts in the initial indicators of our symbionts.

Firstly, the situation with the neutralization of individual pathogens cannot be maintained in such a state. Nature does not tolerate vacuum and absolute sterility. Therefore, other species capable of existing in a new environment inevitably begin to replace persistently destroyed bacteria. Such transformations are characteristic, according to existing postulates, of future AP pathogens, which are considered to be representatives of the commensal microflora and are part

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of the lung microbiome [27-29]. As is known, the earliest consequence of the clinical use of antibiotics was a steady decrease in the proportion of pneumococcus and an increase in other pathogens in the etiology of AP [5]. The phenomenon of changing the proportional ratios of various AP pathogens arose before resistant microorganisms began to be registered and accompanied the entire period of antibiotic therapy. At present, it is no longer justified and unreasonable to ignore the fundamental changes in the microbiological characteristics of AP that have occurred over a long period of antibiotic therapy.

On the one hand, in recent years the number of cases of AP in which it is not possible to identify the pathogen has increased, and the percentage of such cases exceeds half of all examined cases [30-32]. Therefore, hopes for achieving widely accessible and targeted antimicrobial therapy are beginning to decline over time. On the other hand, the number of viral forms of the disease has increased significantly, which, according to many specialists, are becoming the leading microbiological factor of AP [30,33-35]. The latter circumstance clearly shows us that such a transformation of the list of pathogens is one of the forms of self-defense of the accompanying microflora, in which, as we see, the proportion of pathogens resistant to antibiotics has begun to grow. This phenomenon can be interpreted and explained from different positions, however, from my point of view, it is the result of adaptive actions of the microflora against long-term aggression. This postulate is the most logical and explainable.

If we look at the number of cases of the disease in which the bacterial pathogen has been confirmed and in which there are still indications for the use of antibiotics from the standpoint of the changes that have already occurred in the etiology of AP and its modern statistics, we will see that the percentage of such observations in the total number of patients with AP is small and, as a rule, does not exceed a third of the entire contingent [30,36-38]. It is quite obvious that maintaining an emphasis on antibacterial therapy in the treatment of this nosology will not be able to solve the entire problem, is it not? In this regard, the unwavering desire of some researchers to prove the leading role in the problem of AP and the dominance of pneumococcus among the pathogens of the disease is surprising, which constitutes only a part of the positive results of microbiological tests [30,36,39,40].

The adherence to the firmly established conceptual framework of the "microbe-antibiotic" AP, which dominates the professional worldview despite changing basic circumstances, explains why microbial resistance is considered the most formidable and the only side effect of antimicrobial therapy. The recognition of this consequence of antibiotics as a global catastrophe occurred after 8 decades of their use [41], although the official registration of the emergence of such microflora and its spread began with the discovery of MRSA more than 6 decades ago [42]. Moreover, it is no coincidence that the WHO statement on the global significance of this side effect of antibiotics was published at the height of the SARS-CoV-2 pandemic. During this period, the number of patients with coronavirus pneumonia increased significantly. Medicine, deprived of the usual hope in the form of antibiotics, suddenly discovered the absence of any other means that could meet the established requirements. However, the WHO statement sparked a heated debate on the issue, as it helped to indirectly explain the failures in treating patients with COVID-19 pneumonia and reduce the tension that arose in society in connection with it.

The current discussion of resistant microflora, based on generally accepted and widespread ideas, only exaggerates concerns about the role of this phenomenon. In reality, resistant microflora has already become a common symbiont of healthy people. For example, the latent carriage of such a "monster" as MRSA reaches from 2-3% to 6-10% depending on the population group [9-13]. At the same time, among the causative agents of AP, such microorganisms are rare, not exceeding 2% [43-46].

Attempts to find an explanation for failures instead of finding successful solutions are obvious self-deception. In this case, the following example is very illustrative. At the beginning of the pandemic, the Global Health Security Index of 195 countries for the impending disaster was determined. According to existing standards, the US healthcare system was recognized as the most prepared [47]. In terms of the level of provision with the necessary means and equipment, as well as personnel training, this assessment is correct. However, as is known, by the end of the pandemic, the US turned out to be the undisputed leader, but only now in terms of morbidity and mortality [48,49]. Isn't this a reason to seriously think about the correctness and adequacy of the chosen ways to solve the problem?

In this regard, the professional assessment of this situation by well-known experts is quite indicative. Assessing the work of the US healthcare system during the pandemic, the editors of one of the leading American medical journals focused primarily on the spread of coronavirus, considering the widespread infection of the population to be a consequence of the shortcomings of the federal government [50]. At the same time, the authors did not touch upon such a relevant indicator as the mortality rate from COVID-19 pneumonia, for which the country was already a confident leader in the world. Such a selective approach to assessing the situation is not so much an attempt to shift the emphasis to the political plane (which seems logical), but a reflection of a deeply rooted professional belief in the primacy of the pathogen. In other words, coronavirus infection is perceived by modern specialists as a fatal phenomenon that can only be eliminated with the help of well-learned principles of etiotropic therapy. And since medicine did not have etiotropic drugs against coronavirus, the mortality results seem to be a logical fact depending on the spread of the infection.

The fact that most people infected with coronavirus cope with this problem on their own and only a small group requires hospitalization and additional care was known back in the first year of the pandemic [51-53]. However, these statistics often lack thorough interpretation and explanatory analysis, since the very fact of such a division of results in case of infection with one strain of the pathogen and the absence of effective

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medical care indicates shortcomings in the professional understanding of the problem. A couple of years later, in an interview towards the end of the pandemic, the editors of the same publication noted the successes (!?) of medicine in eliminating this scourge by vaccinating the population, but did not give due priority to the results of treatment, which simply require critical analysis when discussing this topic [54]. A surprisingly original explanation for the failures that have arisen in a medical problem, isn't it?

As for vaccination priorities, it should be noted that this area of care has a preventive, not therapeutic value. Therefore, there is no scientific basis for linking the introduction of vaccines and the treatment of those already ill. At the same time, when assessing the results of providing medical care to the population of a country in which the number of fatalities was the highest, this fact deserves to be the main and primary object of professional analysis. But in reality, it has not received due respect. It should also be recalled that, contrary to established ideas about mandatory compliance with anti-epidemic measures, the Swedish healthcare system did not resort to introducing these conditions. And although cases of illness and death were recorded in Sweden during the pandemic, ultimately some of the best results in the world were obtained [55-57]. Such an experiment in respiratory viral infections provides grounds for comparing the results between obtaining natural immunity and the effect of frequent re-administration of constantly modified vaccines.

Discussing at this stage the possibility of improving medical care for patients with AP, specialists continue to evaluate the problem of this disease primarily from the standpoint of the decisive role of its etiology. From this standpoint, the main prospect for achieving success today is based on the development of plans for the creation of new generations of antibiotics modified at the level of microstructures using artificial intelligence and nanotechnology [8,58-60]. In other words, without a thorough analysis of the rich legacy of side effects of this therapy and logically substantiated conclusions about the danger of further deepening of such consequences, the usual improvement of etiotropic drugs is proposed, which are the root cause of the discussed transformation of AP pathogens. If we take another look at the changes in the quality and redistribution of microflora that have occurred over the years of antibiotic use, it is scary to imagine what far-reaching and undesirable consequences the implementation of such plans and proposals can lead to.

And again, the assessment of events occurring in this section of medicine automatically returns us to the already mentioned axiom. Drugs that have the ability to neutralize individual pathogens of non-specific inflammation do not have the qualities of direct impact on the process itself. As a result of the hyperbolic perception of this type of therapy, one can observe how, in outpatient settings, with mild forms of inflammation, doctors literally share the same antibiotic between patients with different localization of inflammatory processes and incomparable clinical picture. At the same time, the antibiotic, perceived as a kind of panacea, according to existing recommendations, plays the role of the main, and often the only means of providing medical care. However, in more aggressive cases of the development of the process and hospitalization of patients, this therapy turns out to be increasingly powerless and additional methods do not improve the situation.

The ideology of AP, which has remained unchanged throughout the entire period of antibiotic use, has surrounded this therapy with a halo of myths that are passed down from generation to generation in the process of training professional personnel and support established misconceptions. It should be especially emphasized that the existing beliefs regarding the leading role of pathogens in the development of AP and the decisive importance of antibiotics in the treatment of this disease have long had a sufficient number of refuting facts and counterarguments, which only accumulate over the years and become more and more convincing [61]. The importance of such factors in this disease as individual characteristics of the body, reflecting the personal reaction of each of us to equivalent triggers, or the localization of the main lesion, the consequence of which is the unique pathogenesis of AP, are not the subject of this discussion. At the same time, only taking these circumstances into account can advance the solution to the problem of treating this disease and achieve the desired results [61].

The experience of the SARS-CoV-2 pandemic, which has convincingly demonstrated the mosaic nature of the results when the planet's population is widely infected with one pathogen, is still perceived rather timidly and cautiously. So far, only a few specialists, noting the difference in individual reactions of the body to the onset of the inflammatory process, are trying to use the possibilities of immunotherapy in combination with treatment [62,63]. However, attempts to correct the immune status of the body during the development of the disease do not bring the expected results, since in essence such methods are on the same level as vaccination and are more suitable for preventive than for therapeutic measures.

At the same time, such an important direction as the study of the pathogenesis of the disease and the use of pathogenetic approaches to providing medical care is not only real, but already proven direction to success [61]. Unfortunately, studies of the pathogenetic mechanisms of AP are currently focused on the cellular and molecular level, concentrating on the characteristics of the suspected pathogens of the disease. At the same time, the study of the mechanisms of AP development is increasingly delving into the ongoing transformations of cellular and molecular factors, while the condition of patients continues to be assessed and monitored by integral indicators of functional disorders [64,65]. These discrepancies are growing under the dominant influence of the goals set - to determine the type of pathogen and have adequate etiotropic agents at their disposal.

The result of the fascination with the virtual picture of pathogenesis in isolation from the parallel dynamics of the clinical condition of patients has been the emergence of new declarations, according to which AP is no longer a separate disease, but reflects the diversity of observed syndromes,

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representing a "burden of disease" [66-68]. In this regard, it is necessary to recall that, for example, such conditions as ARDS or multiple organ failure do not arise spontaneously and do not reflect independent nosologies, but are one of the links in the chain of pathogenesis and complications of AP, is not it? Therefore, there is no need to express concern that modern medicine has not been able to find adequate methods for the treatment of such conditions for many years [69]. With the development of these severe complications of AP, it should be recognized that precious time for pathogenetic action on the main focus and the cause of further progression of the disease has been lost. In such cases, the prospect of success lies not in finding methods for treating these critical conditions, but in assessing the adequacy of medical care at the early stages of the process.

Summarizing the above data, it should be noted that the use of antibiotics over a long period has formed a number of persistent side effects, each of which is a difficult problem to solve. At the same time, such consequences as the constant transformation of pneumonia pathogens and the formation of resistant strains of microorganisms are important only for the choice of etiotropic therapy. The commensal nature of inflammatory pathogens, including resistant strains, the proportion of which is increasingly growing among the symbionts of the body, reflects the auxiliary, rather than the main role of antibiotics in the treatment of this group of patients. The most significant and difficult to eliminate side effect of antibiotics is their negative didactic impact on the professional worldview, which determines both the assessment and essence of the problem under discussion, and the choice of further ways to solve it. The latter circumstance indicates the need for a radical revision of the AP concept, without which it is impossible to imagine a successful solution to the entire problem.

Conclusion

Antibiotics, which appeared in the arsenal of practical medicine as means of selective antimicrobial therapy, were accepted by the professional community as the main method of treating inflammatory processes, acquiring an aura of "miraculous" drugs that is not characteristic of them. The era of antibiotics left behind a number of side effects, and the transformation that occurred in the etiology of AP significantly reduced the indications for their own justified use. The natural decrease in the need for therapeutic use of antibiotic therapy and the growing need for additional medical care began to emphasize the limitations and fragmentation of the principles of the etiotropic approach to the treatment of AP. One of the characteristic features of the unshakable preference for this strategy is the focus on resistant microflora as the only remote result of antibiotic therapy. However, the main obstacle to a successful solution to the problem are the didactic consequences of antibiotic therapy with the continued dominance of the microbial model and a lack of critical reassessment of the efforts made.

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