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Review Article

Deduction and Induction in Solving the Problem of Acute Pneumonia

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Received: January 12, 2026; **Published:** March 04, 2026

Abstract

The antibiotic era has shaped the currently dominant view of their crucial role in treating patients with AP, attributing the main cause of inflammation to pathogenic microorganisms and their virulence. Prolonged use of antibiotics has led to a number of side effects that complicate the solution to the problem of AP, but not all of them are recognized and discussed. A detailed analysis of existing facts points to profound misconceptions and contradictions in attempts to find an optimal solution to this problem, the results of which continue to worsen. The path to achieving the stated goals in this area of medicine is not only realistic, but has even been successfully and convincingly tested. However, the main barrier, overcoming which requires significant effort, but which must be eliminated, is associated with a radical change in professional perceptions of the essence of the problem.

Keywords: *Acute Pneumonia; Etiology; Antibiotics; Side Effect; Pathogenesis; Disease Concept; Emergency Care*

Abbreviations

ANSIL: Acute Nonspecific Inflammation in the Lung; AP: Acute Pneumonia; ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit; MRSA: Methicillin-Resistant *Staphylococcus aureus*; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

Introduction

Acute nonspecific inflammation in the lung (ANSIL) or acute pneumonia (AP) is among the diseases known to medicine since ancient times, yet it remains one of the leading causes of mortality and a problem of deep concern to specialists worldwide [1-4]. Modern efforts to address this problem are not yielding the expected results, and an analysis of the principles underlying the approaches to finding a solution shows that professional understanding of the subject is stuck at the level of mid-20th-century ideology. The successes of microbiology and pharmacology, which at that time outpaced the development of physiology and pathophysiology, contributed to the emergence of the so-called microbial concept of AP, in which the main role in the development of the disease was assigned to the pathogen, and antimicrobial drugs were considered the main method of treatment [5]. With the widespread use of antibiotics, this concept became entrenched and dominant, and throughout the subsequent period it has not undergone a fundamental revision in accordance with the emergence of new facts and circumstances.

In this regard, it is necessary to consider and evaluate the reasons that currently act as factors supporting the state of stagnation in addressing the problem under consideration and hindering the elimination of even obvious, long-recognized, and significant contradictions.

Assessment of the practical significance of the etiology and etiotropic therapy of AP

In the first half of the last century, in the context of the widespread prevalence of pneumococcal pneumonia, but in the absence of clear treatment programs, the first options for etiotropic therapy appeared in the form of antipneumococcal serotherapy and sulfapyridine [5]. The improvement in treatment outcomes after the use of these agents instilled hope in the promise of this approach, giving rise to expectations of new successes in pharmacology. Therefore, the emergence of antibiotics, with their amazing effect on the virgin microflora, was perceived as a final victory. During that period, a number of important factors were overlooked and not subjected to critical evaluation, which subsequently led to a chain of new misconceptions.

Firstly, the focus shifted from inflammation of the lung tissue, which is the main symptom and basis of pneumonia, to the infectious factor acting as one of the triggers of this process. Secondly, the potential of new drugs, limited exclusively to selective action on specific strains of microorganisms, did not allow for direct intervention in the mechanisms of the inflammatory process. Nevertheless, the successful and rapid neutralization of the pathogen in the initial period of the antibiotic era inhibited the development of inflammation and yielded promising results. This quality of the new therapy became the main goal for preserving and reproducing its effect. Thirdly, even at the very beginning of antibiotic therapy, a decrease in its effectiveness was observed, not only and not so much due to the development of resistance in the microflora, but rather due to the dynamic shift in the causative agents of the disease [6]. This last circumstance led to the development and release of new classes of antibiotics with an additional and broader spectrum of action, most of which are known today and appeared in the first two decades [7].

Fourthly, the ongoing natural process of changes in the spectrum of pathogens and the development of resistant strains, on the one hand, and reaching a certain limit in the development of new classes of antibiotics, on the other hand, have shifted efforts towards early diagnosis of the disease etiology in order to apply targeted antimicrobial therapy as early as possible. Attempts to implement this approach continued for several decades, but the desired results were not achieved. Ultimately, authoritative recommendations emerged, recognizing the legitimacy of empirical antibiotic selection [8,9]. Despite the complete failure of many years of effort, attempts to achieve early diagnosis of the etiology of AP have continued actively in recent years with the emergence of new test systems [10-12], which underscores the deeply ingrained commitment to previous ideas. Although many researchers highly appreciate the quality of such diagnostic kits and express hope for success with their help, the actual evaluation of the results remains quite critical, requiring further refinement and improvement of the proposed methods.

Fifthly, for many years attempts have been made to diagnose the etiology of acute pneumonia based on clinical, laboratory, and radiological data, which have also not yielded the expected results. Moreover, it has not been possible to establish differences not only between bacterial forms of inflammation, but also between bacterial and viral pneumonias [13-15]. It would seem that this line of research could be considered unpromising. However, real events show that blind faith in previous ideas and the lack of alternative perspectives on the problem continue to stimulate such research [16,17].

Sixth, in recent years, a significant decrease in the effectiveness of antibiotic therapy in patients with pneumonia has become noticeable, leading to the declaration of antibiotic-resistant microflora as a global catastrophe at the peak of the SARS-CoV-2 pandemic [18]. The opportunistic and simultaneously narrowly focused nature of this statement is determined by at least two features. On the one hand, the development and spread of resistant microflora has been observed throughout the antibiotic era without any broad systemic countermeasures, and this call came almost 80 years after the start of the clinical use of these drugs, when the situation with providing medical care to such patients was approaching a critical point [18].

On the other hand, the change in the list of pneumonia pathogens was only of interest from the point of view of choosing antimicrobial drugs. Such a narrow pragmatic view of this phenomenon did not take into account the obvious circumstance that over the past 2-3 decades, changes in the etiology of pneumonia have actively increased the proportion of viral forms of inflammation [19,20]. Currently,

many clinicians note the predominance of viral forms of the disease [21-23]. This shift ultimately led to antibiotics, by influencing the spectrum of pneumonia etiology, contributing to a reduction in the number of cases where their use remained necessary. Thus, a phenomenon of self-displacement of antibiotics from the list of necessary medicines was observed.

Seventh, the declarative statements about resistant microflora as the cause of low treatment effectiveness in patients with AP correspond to the still dominant microbial concept of the disease, which explains the reduced activity of antibiotics, but does not reflect the real situation. No one has presented evidence of increased virulence of those strains that have developed their own defense against external aggression. These protective properties are only relevant if such a strain is the causative agent of the process, and antibiotic therapy is the main method of treatment. As statistics show, such microbial strains are found among the causative agents of AP in only 1 - 2% of cases, which does not confirm the seriousness of the problem [24-26]. At the same time, asymptomatic carriage, for example, of MRSA in some population groups significantly exceeds these figures, reaching 6 - 10%, and does not pose any problems for the body [27-29]. This kind of statistics reflects the prevalence of resistant strains among the body's symbionts and indicates that this reason for treatment ineffectiveness is clearly and significantly exaggerated.

The most intriguing aspect of the long history of establishing rapid and accurate diagnosis of pneumonia pathogens is the results of recent years, which show that more than half of cases remain of unknown etiology [8,30]. At the same time, the results of positive microbiological studies, despite improved methods, raise legitimate doubts among many clinicians, since some experts quite rightly consider bronchoalveolar lavage analysis to be the most reliable method, although even in this case a negative result is possible [31,32]. Therefore, some specialists quite reasonably consider modern antibiotic therapy, applied on the basis of microbiological research results, to be probabilistic [3,4].

Finally, continuing to adhere to the cognitively dominant "microbial concept" of pneumonia, modern medicine views antibiotics not only as the primary treatment but also as an integral and crucial component of first and emergency aid. This therapy is invariably considered first-line treatment [8,9]. Despite the lack of positive results after years of attempts to enhance the effect of antibiotic therapy by administering drugs as early as possible, such attempts continue to this day [33,34]. In my opinion, this persistence can only be explained by stereotypical views on the problem and a lack of critical analysis and evaluation of past experience.

However, the main misconception in emergency care using antibiotics is that the results of such therapy can only be assessed after 48 - 72 hours [8,9]. If the disease is not severe, the patient can continue treatment on an outpatient basis, and if successful, the entire treatment will be limited to antimicrobial drugs. When describing such situations, some specialists explain them by the success of antibiotic therapy, emphasizing that for many patients such assistance remains effective [3,4,35]. However, in this regard, it is worth recalling a similar situation during the SARS-CoV-2 pandemic, when many similar cases ended successfully without any specific treatment [36-38]. This comparison allows us to question the actual effectiveness of antibiotics, especially since in the case of aggressive development of pneumonia, this therapy does not bring success in many patients [3,4].

In addition to the materials mentioned above, there is a trend, which has intensified in recent years, towards reducing the use of antibiotics in the hope of mitigating the problem of antibiotic resistance. Moreover, many researchers present data indicating that this does not significantly affect the final outcomes [39-41]. Even more unconventional and unusual are reports of successful treatment of a certain category of patients with AP without the use of antibiotics at all [42,43]. Such results inevitably recall the outcomes of the recent coronavirus pandemic and encourage a more confident return to the question of the auxiliary role of etiotropic drugs.

In recent decades, specialists have begun to pay attention to severe forms of pneumonia, singling out this category of patients into a separate group for observation and analysis of results. The number of such patients is gradually increasing, and the ineffectiveness of initial treatment, which is essentially an assessment of the effectiveness of antibiotics, reaches 20 - 30% [3,4]. This proportion includes

patients who, due to the development of complications, primarily of a septic nature, are transferred to intensive care units (ICUs). Many clinicians consider such early transfer of patients an achievement, relying on the higher effectiveness of therapy provided in these units [44,45]. However, some very important circumstances in such cases remain without critical analysis and discussion. For example, in many patients, the development of complications of the underlying process is observed within the first 24 - 48 hours [46-48], which calls into question the adequacy of the initial therapy. Moreover, the therapy used in ICUs is traditionally syndromic, not pathogenetic [49], and mortality in these units has recently reached up to 40% [4]. Such recent data confirm the old postulate that if the therapy provided does not yield the expected results, then this form of treatment does not correspond to the nature of the disease, does it?

Thus, summarizing the data on the results of the etiotropic approach to solving the problem of AP, it can be stated quite clearly and unequivocally that this approach does not fully meet the challenges that have arisen during the long period of the antibiotic era and require solutions to achieve success. The logical connection between the primary focus and subsequent complications allows us to compare the development of AP to the flight of a multi-stage rocket, where the first stage plays only the role of etiological factors. At the same time, the narrowly targeted, specific action of antibiotics is in no way capable of serving as the main, let alone the only, means of treatment. The impasse observed today is a logical consequence of generally accepted recommendations, and further search for solutions must be shifted to a different plane.

The place and significance of AP pathogenesis in contemporary professional understanding

Representatives of modern medicine, persistently trying to solve the problem of pneumonia using etiotropic approaches, do not give sufficient importance to the fact that this disease, regardless of the type of pathogen, retains its main characteristics, which fundamentally distinguish it from the manifestations of all other inflammatory processes. Can the clinical picture of pneumonia, meningitis, or otitis be compared if the causative agent of all these diseases is pneumococcus? It is quite obvious that the similarity in the etiology of these diseases cannot be the reason for the identical clinical picture. This fact is a clear reminder from nature of the need to return to the forgotten fundamental rules of the inflammatory process, including its classic signs - redness, swelling, heat, pain, and loss of function. Among these signs, confirmed by medical practice for almost two millennia, the most important is the last one - impaired function of the affected organ, which determines the unique specificity of the disease. This circumstance dictates the need for a clear understanding of the pathogenetic mechanisms of the development of the inflammatory process in lung tissue and ways to effectively influence them. At the same time, the totality of the facts presented above indicates that antimicrobial therapy can, at best and when indicated, be considered an auxiliary method of treatment, but cannot be considered the leading and primary method of treating AP.

It should be noted that during the initial examination of a patient who, based on external signs, is highly likely to have acute inflammation of the lung tissue, the physician necessarily assesses and records the functional impairments of the affected organ. In other words, at this stage, the physician essentially becomes acquainted with and evaluates the external manifestations of the disease's pathogenesis. The initial damage to the organ at the microstructural level may not have obvious symptoms at first. However, as the process develops and the changes integrate, according to the law of dialectics, a transition from quantity to quality occurs, which at a certain stage leads to the appearance of one of the external signs of the disease. Each of these micromechanisms individually remains difficult to detect even with modern diagnostic achievements, but their subsequent integration leads to a quite tangible, qualitatively new change in the form of impaired function of the affected organ. The specificity of such manifestations depends on the localization of the inflammatory focus and the functional potential of the tissues in the damaged area. Thus, the development of the process must reach a certain level for the transformations to acquire external manifestations.

This simplified understanding of existing patterns is presented to clarify that deviations in functional parameters, used not only for assessing the patient's condition and further monitoring, but also as a target for therapeutic correction, are the result of complex pathogenetic micromechanisms. In turn, this postulate is necessary so that, when justifying and choosing initial therapy in patients with

AP, especially in cases of aggressive disease progression, priority is given to methods capable of directly and immediately affecting the main integral cause of the observed functional disorders.

The described approach to selecting effective first aid is far removed from the research currently being conducted in this field. Even the study of the pathophysiology of the AP is conducted depending on the type of pathogens [3,4,30,35], which reflects the continuing dominance of the etiological approach to acute infections in attempts to understand the mechanisms of the process and find its causes at the micro level. As practical results of such initiatives show, they do not bring the expected success. Examples of such failures include attempts to neutralize or correct factors such as the "cytokine storm," hormonal shifts, or decreased immune defense in patients with AP [50-52]. This data provides grounds for evaluating current research as unproductive and unpromising. Moreover, in such cases, the question of the need for supportive and supplementary therapy becomes acute, since the initial treatment does not bring relief to the patient, and the disease continues to progress. In this situation, as is known and generally accepted, the solution to this problem is also considered under the auspices of the dominant infection, and the choice of treatment methods does not go beyond general therapeutic procedures.

If we analyze the current situation in detail, we will see another striking example of a vicious cycle. And, given that inflammation, which always affects the blood vessels of the affected organ, is the only process occurring in the pulmonary circulation in AP, the question of why the diagnosis of these disorders and their correction with infusion therapy [8,9] continue to be carried out according to general principles for so many years becomes even more relevant. The regularity with which so-called sepsis and septic shock [46-48] develop during the first two days of inpatient treatment for AP should not be surprising. These results are a logical consequence of the general therapy applied in such situations.

The clinical and laboratory indicators that modern medicine relies on when choosing treatment methods in cases where the primary lesion is localized in the pulmonary vessels should be a mirror image, that is, the opposite, of the disturbances in systemic blood flow [53]. In this situation, one of the most important tasks for achieving success is understanding the differences between protective and adaptive mechanisms, on the one hand, and pathological changes, on the other, while maintaining a clear understanding of what is the cause and what is the effect in this case. Moreover, it is necessary to understand the permissible limits of adaptive processes, when certain therapeutic measures are required, and the boundaries of their transition into deviations that may require other interventions.

The observed patterns and the natural laws governing them determine the standards for observed deviations, which depend on the type of organism's response to pathogenic factors. Recently, studies have emerged that present criteria for recognizing variants of such responses [54]. However, this involves a retrospective assessment of possible organismal responses, which have not yet found practical application and are not supported by specific recommendations. Possible attempts to apply this data in practice may, at best, improve the prognosis of individual disease development, but will not provide specific recommendations for action. Therefore, to achieve real success in addressing the problem of AP, it is impossible to ignore the need for a consistent presentation of cause-and-effect relationships in the development of the disease's pathogenesis. This will allow not only to determine the nature of the necessary assistance at different stages, but also to identify the limits of reversibility of pathological disorders.

The dependence of modern views on the essence of the problem under discussion on the etiology of the disease and its microbiological factors has led to predictable complications of unresolved pneumonia, such as ARDS or multiple organ failure, being considered as separate syndromes depending on the nature of the pathogen [55]. Being a pathogenetic continuation of the development of the primary focus and its logical consequence, these syndromes are similar and indistinguishable in their main features regardless of the nature of the etiology. Interpreting individual stages of a single process as independent pathologies demonstrates how inaccuracy in defining the initial goal can lead to a chain of subsequent misconceptions. Such attempts to present the causes of the problem and ways to solve it through the details of individual links of the overall mechanism predetermine an approach that is unlikely to lead to success.

Example of profound misconceptions is the assertion by some specialists that AP is not a disease, but a group of syndromes caused by various microorganisms [55]. Such statements continue to be accompanied by the search for differences depending on the etiology, with the same approaches being repeatedly applied, only now at a new level. In my opinion, such views on the essence of the problem are not simply the result of misconceptions. Such assertions indicate deeply ingrained principles of an etiologically oriented ideology that continues to determine the strategy for solving the entire problem, despite contradictory facts. And this already relates to the mental level of professional orientation and poses more complex challenges in solving the problem.

Summarizing the results of the analysis

An analysis of the circumstances surrounding the treatment of pneumonia reveals that the currently dominant approach is a consequence of a persistent and unwavering focus on the microbial factor as the primary cause of the disease and on antibiotics as the only effective treatment method. The changes that have occurred over these decades under the influence of antibiotic side effects, which have fundamentally altered the conditions for the development of non-specific inflammatory processes and the qualitative aspects of etiotropic treatment, are not receiving adequate critical evaluation within the professional community. This observation is particularly important for lung diseases, in the etiology of which significant shifts have occurred towards viral agents.

At the same time, problems have arisen with underestimating the role of pathogenetic mechanisms of pneumonia, both in maintaining the classic signs of the disease and in determining the severity and extent of the resulting disorders. In the latter respect, the discrepancy between standard interpretations and the essence of the treatment methods used and the unique features of pneumonia pathogenesis has become particularly evident against the general background of inflammatory diseases. As the number of severe cases of pneumonia and the number of cases requiring supportive treatment methods increases annually, this contradiction becomes increasingly noticeable, yet there are still no signs of a revision of existing paradigms.

It is important to emphasize that the problem of AP in this context is considered and discussed as a clinical task, without delving into issues of prevention. Measures to prevent this disease of non-specific etiology, which does not belong to the category of contagious diseases, should be the subject of a separate discussion. Currently, the clinical (inpatient) aspect of providing care to this category of patients is of particular concern due to the increasing number of critically ill patients, the rising percentage of treatment failures, and fatal outcomes. The first step in solving the problem of AP, which will lay the foundation for real success, is a revision of the basic conceptual provisions, which will inevitably lead to a change in leading priorities and the replacement of etiotropic approaches with pathogenetic ones. The main principles of further actions involve the earliest possible neutralization of the initial integral (!) triggers of the disease, which are the main cause of the observed functional disorders and the source of progressive deterioration in the patients' condition.

Continuing the search for anomalies in patients with AP at the cellular and molecular levels, and obtaining evidence of one of the numerous micro-changes accompanying this disease, remains a realistic task with an achievable outcome. However, such micro-deviations, taken individually, represent a mosaic of metabolic, cellular, hormonal, and other manifestations of the disease. These micro-mechanisms lead to subsequent functional impairments only when they complement each other and reach a certain threshold. Attempts to correct individual micro-mechanisms that do not have their own clinical manifestations cannot yield a noticeable positive result. Currently, the results of such attempts and clinical studies are constantly being published, but they do not lead to the expected effects.

The effectiveness of emergency care lies in neutralizing the integral stimulus of functional disorders, which allows for an almost instantaneous positive effect. This requires an understanding of the nature and sequence of pathogenetic mechanisms. One of the first integral consequences of an inflammatory focus in the lung during aggressive development is a generalized reflex spasm of the vessels of the pulmonary circulation, which underlies the classic symptom complex [56-59]. On the one hand, this spasm represents an autonomous, uncoordinated defense of the lung tissue against rapidly increasing edema in the area of inflammation. On the other hand, it is accompanied by difficulty and reduction of blood flow in the pulmonary circulation, leading to an imbalance between perfusion

and ventilation. These circumstances stimulate respiratory excursions (dyspnea) and impaired gas exchange (hypoxemia), a decrease in vascular tone in the periphery with retention of part of the circulating blood (the so-called unloading reflex), and impaired tissue perfusion (a picture of pulmonogenic (!), not septic shock) [56-59].

The described integral mechanism of the initial manifestations of AP represents a stereotypical link in the pathogenesis of inflammation developing in the pulmonary circulation. However, the severity and intensity of this mechanism have a multifactorial individual dependence. The range of external manifestations of this mechanism has an infinite scale of individual variations. In many patients with a relatively mild course of AP, who continue outpatient treatment, changes in heart rate and respiration may not be observed. Methods for eliminating generalized spasm of pulmonary vessels become a pressing necessity in cases of severe disease development. Rapid restoration of the necessary proportions between perfusion and ventilation of lung tissue with objective confirmation of the results, a tendency towards normalization of respiratory and hemodynamic parameters, and immediate relief of the condition of patients with AP reflect, in my opinion, only a part of the positive results [56]. It would be very useful to conduct comparative studies of various immune, hormonal, and other parameters before and after the application of first aid methods. In this case, testing those indicators whose deviations have already been established, but previous attempts at their correction have been unsuccessful, may prove to be the most informative.

More than 40 years ago, several methods of emergency treatment for severe AP were tested and evaluated using comparative objective criteria. Among the methods tested were cervical vagosympathetic blockade, cupping therapy, and short-term general body cooling [56]. It should be noted that when these treatment methods were applied early, no general or systemic complications such as shock reactions, ARDS, or multiple organ failure were subsequently observed. This can be explained by the fact that eliminating disturbances in central hemodynamics contributes to the restoration of microcirculation both in the periphery and in the lung tissue, eliminating one of the main mechanisms for the development of these complications.

The described methods of emergency therapy undoubtedly have a positive, pathogenetically justified effect, allowing for the inhibition and interruption of the further development and formation of the chain of pathogenetic mechanisms. Shifting the main pathogenetic efforts to the initial stage of the disease makes it possible to contain the development of AP in its nascent phase. The results of such emergency therapy clearly demonstrate that modern trends in the search for prognostic criteria for the development of complications and fatal outcomes are an open acknowledgment of the hopelessness and ineffectiveness of existing treatment approaches.

The opposite effect is observed in the case of infusion therapy for severe AP. Intravenous infusions, which are the traditional standard of care, continue to be used in such patients immediately after hospitalization, with the volume and rate of administration increasing in parallel with the worsening of the patients' condition. The supposed goal of this therapy-replenishing fluid loss and reducing the risk of subsequent shock reactions-is actually a self-deception, and its implementation stimulates the development of the inflammatory process, accompanied by the appearance of pleural effusion [56].

Conclusion

An analysis of the facts concerning the state of the problem of ANSIL, accumulated during the antibiotic era, reveals a number of side effects of these drugs. However, the significance and evaluation of these changes are determined by the microbial concept of AP that has developed during this period and is currently dominant. Of all the changes that have occurred under the influence of antibiotics, only microbial resistance is currently considered significant, which is unjustifiably viewed as the cause of unsatisfactory treatment outcomes. At the same time, the complete disregard for the unique features of the pathogenesis of pneumonia and the clear inattention to changes in the initial conditions of AP development under the influence of antibiotics indicate clear didactic misconceptions and a state of cognitive dissonance in the professional community. Without eliminating these latter causes, a successful solution to the entire problem under discussion seems impossible.

Funding Support

This manuscript is a full initiative of the author and does not have any funding.

Conflict of Interest

The author states that he has no conflict of interest.

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