

Self-Devaluation of Antibiotics as A Side Effect of their Use

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Abstract

Despite their long history of use, antibiotics remain the primary treatment for inflammatory diseases. However, it is often overlooked that these drugs are capable of killing only certain types of bacteria and do not directly affect inflammatory mechanisms. Moreover, long-term antimicrobial therapy leads to the development of side effects, including changes in the etiology of acute pneumonia. The prolonged and methodical eradication of common pneumonia pathogens forces nature to gradually replace them with agents unrelated to the spectrum of antimicrobial activity. It is this circumstance, and not microbial resistance, as is currently believed, that is the main reason for the decline in antibiotic effectiveness. This conclusion is supported by the prevalence of viral forms of pneumonia, while only a few resistant strains of pathogens are identified among the small number of bacterial infections. This latter statement indicates the need to reconsider the concept of disease and remove antibiotics from the list of miracle cures.

Keywords: Acute pneumonia; Etiology; Antibiotics; Side effects; Pathogenesis

Abbreviations: AP: Acute Pneumonia; MRSA: Methylene-Resistant Staphylococcus Aureus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; WHO: World Health Organization

Introduction

Antibiotics, rightfully considered one of the most remarkable discoveries of the 20th century and having saved millions of lives, continue to be the leading, and often the only, treatment for inflammatory diseases. The biological origin of these drugs and their selective action on associated but uncontrolled microorganisms naturally prompted nature to use its capabilities to correct the consequences of antibiotic use. The rapid development of microbial resistance to these drugs was noted even in the preclinical stage of their research [1,2], and the first side effects began to appear soon after the advent of antibiotics, the most striking example being acute pneumonia (AP).

Discussion

In the pre-antibiotic era, Streptococcus pneumoniae was consistently the predominant causative agent of AP, accounting for 95% or more of cases, regardless of region and time of study [3-7]. However, soon after the introduction of this therapy into widespread practice, new types of drugs were needed due to penicillin's ineffectiveness against a number of microorganisms, the proportion of which began to increase among the causative agents of the disease. Moreover, practice has shown that among host symbionts capable of causing AP, Staphylococcus aureus was distinguished by a more rapid ability to develop resistance [8].

which created conditions for the displacement of pneumococcus. The dynamics of AP etiology changed so rapidly and energetically that within one and a half to two decades, Staphylococcus aureus actually became the leading causative agent of the most severe and complicated forms of pneumonia, especially in children [8].

New antimicrobials for the treatment of inflammatory diseases have generated excitement and a storm of emotion since their introduction. Therefore, the development of resistance, the potential of which was already known in the microflora, primarily raised concerns about the future effectiveness of these drugs. This latter circumstance outweighed the importance of the role and influence of resistant microorganisms on the development of new problems. Since the initial focus was solely on the development of protective properties in individual members of the microflora, and antimicrobial therapy continued to ensure empirical compliance of the list of AP pathogens with the spectrum of activity of the drugs used, this situation did not cause particular concern. Practical medicine, having initially mastered the maximum number of currently known antibiotics [9], continued and continues for many years to invest in the early diagnosis of AP pathogens to expedite targeted antimicrobial therapy [10-12].

These efforts and attempts to improve the results of etiologic therapy reflected the established strategy for treating AP and the priority given to defining the basic principles of treatment. This approach could not ignore the professional perspective on the essence of the problems being addressed, consistently focusing on the causative agent of AP as the underlying cause of the disease, with antibiotics firmly established as the primary treatment method. Despite dynamic changes in the conditions for the development of AP, this professional understanding of the problem remained unchanged throughout the decades of the antibiotic era and has not been seriously revised, despite a number of contradictions and inconsistencies. This approach to the essence of the AP problem, which originated in the first half of the last century as the so-called microbial concept of disease [13], acquired a stable dominant position in subsequent years, defining modern strategy and tactics in this field of medicine.

Despite the strictly defined goals of early diagnosis of the etiology of AP, expert forums on this issue have deemed the obtained results irrelevant, and the principles of antibiotic prescription empirical [14,15]. However, the most significant omission that modern medicine has failed to address is the dramatic change in the composition of pathogens that, according to numerous statistical data, have become the leading causes of AP. Bacterial factors are no longer the primary cause, which, in turn, includes pathogens that are quite “exotic” for this disease [16,17]. Already a couple of decades ago, a significant increase in the incidence of viral forms of AP was noted, reaching almost half of all cases worldwide [18,19]. However, it was well known that in the early days of antibiotic therapy, such forms of the disease were rare.

In this situation, a radical rethinking of the leading role of the “microbe-antibiotic” tandem as the primary, but now irrelevant, goal of solving the problem seems justified and necessary, doesn't it? After all, nature has replaced the bacterial factor with viruses, and antibiotics in this situation cannot fulfill their intended purpose. However, as is already known, in recent decades, no obvious attempts have been made to bring the strategic basis for solving the problem closer to real circumstances. Ultimately, according to the logic of events in recent years, the emergence of the SARS-CoV-2 pandemic seemed a completely natural phenomenon. However, in the context of entrenched didactic misconceptions about the concept of an epidemic, this phenomenon was perceived as a catastrophe, accompanied by manifestations of professional depression [20,23], searches for the causes of so-called conspiracy theories [24], and attempts to shift professional responsibility to the shoulders of the government [25].

The current literature on this issue convincingly demonstrates that the lessons of the pandemic remain unexplored and unlearned. The etiologic profile of AP, transformed in the era of antibiotics, surprisingly has no impact on our current understanding of the problem. The “emergency,” unjustifiably widespread use of

antibiotics during the pandemic [26-28] also did not contribute to a critical analysis of these events. Currently, despite the changed realities, calls are increasingly being made for the development and release of new, more advanced generations of antibiotics [29-31]. This initiative is actively supported by the WHO and is developing against the backdrop of ongoing practical efforts to early diagnose the etiology of AP using the latest testing systems [10-12].

Given the actual end results, recent studies are more promotional than practical. Added to this is the often-cited assertion that pneumococcus remains the most common pathogen causing AP [32-34], which, as shown above, not only lost its prevalence in the early years of antibiotic use but has not even approached its previous levels since then [13,16]. Its current presence in overall statistics is too low for pneumococcus to play a significant role. However, such publications are usually accompanied by a rationale for continuing pneumococcal vaccination. These statements, attempting to emphasize the importance of previous vaccination efforts that failed to reduce the risk of severe AP, appear during a period of increasing viral pneumonia and reflect an undeniable bias. In addition to the currently observed trends, numerous studies are ongoing to find the most optimal antibacterial therapy options for patients with AP [35-37]. All this creates the almost complete impression that the biological conditions for the development of the disease are perceived today in the same way as in the early years of the development of this field, as if nothing has changed.

The prevailing climate of understanding the nature of AP continues to methodically and relentlessly dictate the rules of the so-called germ theory of disease, which has exerted a powerful didactic influence and dominated professional opinion on this issue throughout the long history of antibiotic therapy. Judging by a series of ongoing studies and the continuation of previous initiatives, freeing ourselves from the web of misconceptions that have already shaped this persistent worldview will not be easy, although it is urgently needed. The persistent influence of this concept on professional views and approaches to solving the problem of AP is emphasized by the identified explanation for the low effectiveness of treatment for this category of patients. Although the causative agent of AP remains unknown in half or more cases [30,38,39], and viruses are beginning to predominate among positive results, the main consequence of long-term antibiotic use should be considered the gradual creation of conditions in which their further use becomes unnecessary. This conclusion is consistent with modern realities, but it is not even taken into account in the current understanding of the problem of AP.

Microbial resistance has become the primary and only explanation for treatment failure. This side effect of antibiotics has been observed relatively unnoticed throughout the history of their use, without any significant discussions or major

decisions. Increased interest in this consequence of antibiotic use has emerged in the last couple of decades, reflected in a significant increase in the number of publications and special WHO documents on this topic, which, incidentally, coincided with the rise of viral forms of AP. However, the recognition of this side effect as a global scourge was somewhat unexpected and “surprisingly” announced at the peak of the SARS-CoV-2 pandemic [40]. Given all the known and aforementioned facts, the timing of declaring microbial resistance a global scourge in the midst of a viral pandemic (!) seems symbolic, consistent with the prevailing understanding of the nature of AP today.

The WHO’s recognition of resistant microflora as a global catastrophe logically fits into the understanding of the leading role of the pathogen and the lost hope for the effective use of antibiotics in the treatment of patients with AP. This assertion has found active support among the professional community, creating the image of a scientific explanation for the growing treatment failures. However, as an analysis of the actual state of microbial resistance shows, the overwhelming majority of opinions about the important and significant role of such microflora in solving the entire discussed problem of AP are declarative in nature and give rise to a new level of misconceptions and self-deception. Such publications are not supported by specific results or convincing evidence.

The stated danger of antibiotic-resistant microbes appears completely different when presented with statistics. It has been established that the etiologic role of such pathogens in AP is no more than 2% [41-43]. A logical question arises: how significant is the impact of resistant microorganisms on the outcome of the disease in the entire cohort of patients? This estimate is more the result of an adjustment based on the modern concept of AP than a critical analysis of the facts, isn’t it? Several obvious factors should be added to this. First, no one has presented evidence for such an important argument in this case as the increased virulence and aggressiveness of resistant bacteria. By developing their own defenses, such microorganisms do not become more dangerous from a microbiological perspective. They can become a serious obstacle only if antibiotics remain the primary treatment.

Secondly, no researchers or clinicians currently compare the prevalence of resistant microflora in patients with AP with the percentage of asymptomatic carriers of similar strains in the healthy population. For example, the prevalence of MRSA as a commensal pathogen in healthy individuals in the general population has been found to be higher than in patients with AP, reaching 3%, while screening results in some groups of healthy individuals have shown this strain to be prevalent at a frequency of 6-10% [44-46]. Attempts to explain the fact that the most medically dangerous microbial strains are found many times more frequently among healthy individuals, while posing little risk to them, would be futile, as there are no comprehensive explanations

for such comparisons. Moreover, doing so would undermine the entire framework that explains current treatment failures.

Finally, the danger of misconceptions arising from exaggerating the role of microbial resistance in reducing the effectiveness of therapy lies in the fact that, while maintaining adherence to the old concept of AP, many call for the development and release of new-generation antibiotics [29,47,48]. It is difficult to imagine what even more significant consequences the implementation of such ideas could lead to without a clear and consistent analysis of past events. Although expert reviews of the rationale for the use of antibiotics have been conducted in the recent past, the results of which showed excessive enthusiasm for this therapy, these materials in no way influenced the events of the coronavirus pandemic, when antimicrobials began to be prescribed to almost all hospitalized patients [26-28]. Currently, it is necessary to carefully analyze the number of patients with AP for whom the indications for the use of these drugs remain due to the changes in the etiologic list of pathogens that have occurred in the antibiotic era, and it is clear that the number of such cases remains small.

Conclusion

Thus, if we rely on objective facts and statistical data, rather than manipulation of generally accepted concepts, the most important biological effect of antibiotic use is the steady change in the etiology of AP, with a gradual devaluation of the role of these drugs as therapeutic agents. The importance of resistant strains is significantly exaggerated due to the interpretation of this side effect, which is based on an outdated understanding of the disease. Antimicrobials cannot serve as the primary treatment for inflammatory processes, since their action is aimed solely at suppressing the microbial factor but does not directly affect the mechanisms of inflammation. In aggressive inflammatory processes, the frequency of which is gradually increasing, even effective neutralization of the pathogen cannot significantly affect the emergence of inflammatory triggers and their mechanisms of action.

Despite extensive and compelling evidence supporting the presented assessment of antibiotic side effects, changing prevailing opinions on this issue depends on the didactic consequences of this therapy. Statements that developed over decades and were based on the belief in the exceptional therapeutic effect of antibiotics have lost their original meaning over time, and changes in the etiology of AP have created a complex problem that is becoming increasingly apparent with each passing year. To realistically assess the consequences of long-term antibiotic use, it is necessary, first and foremost, to align professional views on the problem of AP with the canons of medical science and the accumulated data on this issue. Such steps, requiring a fundamental rethinking of the disease concept, will allow us to understand the causes of existing misconceptions and pave the way for successful solutions.

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