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Review Article

Sepsis Today: Diagnostic Misconceptions and Failure of Uniform Treatment Principles

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Abstract

Sepsis remains a major contributor to global hospital mortality, yet current diagnostic criteria and treatment protocols often fail to account for the complexity of its pathophysiology—particularly when sepsis originates from pulmonary infections such as pneumonia. This review critically examines longstanding assumptions in the classification and management of sepsis, challenging the conventional systemic interpretation and highlighting the overlooked role of pulmonary circulation and lung-specific mechanisms. Drawing from both historical clinical insights and contemporary data, the article underscores the limitations of uniform therapeutic approaches and the misapplication of sepsis definitions in respiratory contexts. The analysis calls for a reevaluation of diagnostic models and advocates for a differentiated, physiology-based treatment paradigm, offering preliminary considerations for future clinical strategies.

Introduction

In recent years, Sepsis (S) is increasingly recognized as a major global health issue of world health, as evidenced by the negative dynamics of its statistics, causing great concern among specialists. Just a few years ago, the total number of patients with S in the world was estimated at 30 million cases per year, of which 6 million were fatal [1,2]. Currently, according to the World Health Organization (WHO), the number of patients with S has increased to 48.9 million per year, and the number of deaths - to 11 million [3]. In the USA, the total number of S diseases has remained stable in recent years, amounting to 1.7 million cases per year, but it is noteworthy that the number of deaths over the past 6 years has increased from 270 thousand [4] to 350 thousand [5]. The level of hospital mortality among patients with S, which reached 20% a few years ago [2,6], has increased to 40% in recent years in Europe and North America, that is, in the most advanced health care systems [7]. At the same time, in the USA, S is the leading diagnosis of hospital mortality [8].

Discussion

S, as is known, is not an independent nosology that occurs against the background of complete well-being, and has its own sources of occurrence. The most common cause of S is acute nonspecific inflammation of the lung tissue or Acute Pneumonia (AP), confidently heading this list for a long time [9-11]. In recent years, the incidence of pneumonia as a source of S continues to grow, becoming the cause of generalized infection in more than 60% of cases [12,13]. Such a significant number of septic complications in patients with AP lacks a clearly established scientific explanation for this extraordinary statistics, which, of course, should be the subject of the search for an answer to such a shift in emphasis. To understand the reason for such a steady and progressive increase in septic complications among patients with acute inflammation of the lung tissue, it is necessary to pay close attention to the characteristics of this disease and the principles of modern diagnostics of S.

Although at present detection of the pathogen in the bloodstream is no longer included in the list of mandatory studies for the diagnosis of S, in this regard it is interesting to note one feature that was previously noted by a number of specialists. It was established that bacteriological blood tests in patients with AP with the clinical picture of S were characterized

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by an insignificant number of positive results, which reliably distinguished these data in comparison with similar studies in inflammatory processes of other localizations [14,15]. Such differences were mainly explained by the preliminary use of antibiotics in AP, as if such treatment was not used in other inflammatory diseases. Today, bacteriological blood tests in patients with S continue to be used, but now their results are used not for diagnosis, but for the correction of etiotropic therapy [16].

In recent years, there has been an increase in viral forms of inflammation, primarily with selective damage to the respiratory organs, marked by the emergence and growth of a group of patients with viral S [12,17-19]. At the same time, many clinicians note the almost complete identity of the bacterial and viral forms of S in patients with AP [20-22]. At the same time, we have no obvious evidence that the observed picture of the disease is due to the generalization of a viral infection, and no other causes, and the totality of the tests and evidence used indicates that viral S is simply a copy of bacterial S and its justification is based solely on analogies.

The SARS-CoV-2 pandemic highlighted to specialists in the field of pulmonary pathology a number of undeniable circumstances that do not fit into the concept of modern professional ideas about the nature of AP. First of all, the statistics of a colossal volume of observations in different regions of the globe once again confirmed the ancient postulate that people do not become infected with pneumonia, but rather fall ill. The fear of coronavirus that arose was in fact caused not by the danger of contact with a potential pathogen, but by uncertainty about a quick and complete cure in case of illness. Despite the relative novelty of this pathogen for most of the world's population, many of those infected with coronavirus had no signs of the disease and learned about this "surprise" only on the basis of tests, and the number of such observations reached 40% [23]. In cases where signs of the disease were observed, 81% of patients had a mild form that did not require hospitalization. The development of COVID-19 pneumonia, depending on the severity of manifestations, was subject to general hospitalization in 14% of cases, another 5% of patients were sent directly to Intensive Care Units (ICUs) [24]. According to the final data, it was this stage of health care systems in different countries that turned out to be the most vulnerable, and the results of inpatient treatment of such patients turned out to be unpredictable, which reflects the unreliability of existing and generally accepted treatment principles.

The period of antibiotic use was accompanied by significant and constant changes in the list of AP pathogens, which was not observed in the pre-antibiotic era [25]. Thus, by now not only have cases of viral pneumonia, which were previously extremely rare, become more frequent, but these forms of inflammation have also come to constitute a significant part of the total contingent of patients with AP. At the same time, viral forms of pneumonia are no less severe than bacterial ones. Thus, among hospitalized patients with viral AP, viral S is diagnosed in 61% of cases [21]. It is noteworthy that in 40% of patients hospitalized with the so-called community-acquired pneumonia of this etiology, S developed during treatment [19]. Among patients with AP, initially in general wards, up to 25% are transferred to the intensive care unit within the first two days due to a sharp deterioration in their condition [26]. Even such a critical condition as septic shock, in most of these observations in patients with AP, develops against the background of and despite intensive treatment [27].

The presented statistics of the results of modern AP treatment simply oblige one to think deeply, since for the majority of specialists reading it such events are not something new and unexpected. Similar AP events are observed everywhere to a greater or lesser extent depending on the proportion of severe forms of the disease, which in recent years, due to such uncontrolled dynamics, have begun to be singled out and analyzed separately [28,29]. The statement of the above facts is convincing evidence of the ineffectiveness of modern AP therapy, confirming the ancient postulate that if therapy does not give results, then this is a clear sign of the inadequacy of such treatment to the nature of the disease. Unfortunately, the presence of such numerous and diverse evidence is not accompanied by a logical critical analysis of the principles of treatment and a search for other ways to solve the problem.

At present, despite fundamental changes in the etiology of AP, antibiotics continue to be the main method of treating this group of diseases. In severe cases of the process, and especially in the presence of signs of S, the second important principle of treating AP is mandatory infusion therapy [30-32]. All other means and methods are auxiliary, symptomatic and supportive treatment measures that are used as needed. According to modern professional views, such approaches to treating AP create the impression of its full compliance with the causes of severe development of the disease. However, if we analyze the potential and purpose of such principles of therapy, we can understand the prerequisites for its ineffectiveness.

Firstly, the general picture of AP, reflecting the unique distinctive features of the disease, remains identical and does not acquire fundamental differences, regardless of the change of pathogens. This circumstance convincingly testifies to the decisive role of the pathogenesis of the process, and not its etiology, in the formation of the clinical features of the disease. In this regard, the observed stability of the disease picture returns us to the decisive role of the fifth classical sign of inflammation - loss of function, emphasizing the inevitable influence of this factor and raises questions about the added value of further pathogen-specific diagnostics..

Secondly, continuing to give preference to antibiotics as the main means of treatment, one should not forget the well-known axiom that these drugs can only have an antimicrobial effect and do not directly affect the mechanisms of the inflammatory process itself. This means that to obtain the expected therapeutic effect, not only the waiting time is required, but also the ability of the body to actually independently compensate for the functional deviations that have arisen.

Thirdly, continuing to place hopes on antibiotic therapy as the main method of treatment, modern medicine essentially

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considers these drugs as the only way to provide medical care. This approach to the choice of treatment methods assigns antibiotics not only the role of the main, but also an emergency type of care for patients with AP. In this regard, long-standing attempts continue to substantiate the importance of early microbiological diagnosis and early initiation of antibacterial therapy to improve the results of treatment of AP and S [33-35]. R. Cavallazzi and J.A. Ramirez [36], separately highlighting severe forms of AP, note that most patients with a mild course of the inflammatory process are successfully treated with antibiotics on an outpatient basis. At the same time, emphasizing the role of antibiotics, the authors forget to mention the favorable outcomes of coronavirus pneumonia with a similar course, in which patients did not receive specific pathogen-directed treatment, while in other observations, patients with the same etiology of pneumonia required hospitalization, including intensive care in ICU.

However, the main contradiction of using antibiotics as first and emergency aid in AP is their indirect action and the need to wait 48 - 72 hours to assess the effect of treatment [37]. In conditions of rapidly progressing inflammation, such a wait is a waste of precious time. This circumstance is one of the reasons for those observations when so-called septic complications arise during treatment [19,26,27].

Finally, the second mandatory method of providing care to patients with signs of S and Septic Shock (SS) is currently considered to be infusion therapy, the heterogeneous results of which have been discussed for many years, but the reasons for these differences remain an open question [38-40]. To understand the mechanisms of the observed differences in the effect of infusions, it is necessary to return to the prerequisites for their occurrence. The groups of analyzed patients with S represent observations with different sources of septic complications. As noted above, at least half of such materials are patients with AP, in whom the disease continued with the development of S and SS. In this regard, it is necessary to remember that AP is the only one of all inflammatory nosologies that is localized in the vascular pool of the pulmonary circulation.

Thus, when analyzing the results of treatment of patients with C, all observations should be divided into two groups of approximately equal numbers, fundamentally different in the localization of the primary focus. Now it is necessary to compare the functional differences in the vessels of the two circulatory systems in which the inflammatory process develops. Since constant blood flow and the maintenance of its diametrically opposed indicators in the pulmonary and systemic vessels are an indispensable vital condition, then in cases of aggressive development of the pulmonary process, the so-called unloading reflex, described almost a century ago [41], is activated. Unfortunately, the continuity of the connection and the reflex-humoral interdependence between the two circulatory systems is studied mainly by physiologists in experiments or on healthy volunteers, and is also occasionally noted in the clinic in pulmonary embolism [42-45].

At present, new data have appeared regarding the cause of general blood flow disorders in patients with severe AP, which occur in the pulmonary circulation in the form of generalized spasm of small-diameter pulmonary vessels [46,47]. Unfortunately, the authors of these studies limited themselves to merely stating this fact and drawing parallels with the severity of oxygenation disorders. However, these results are additional evidence for the materials that were obtained by the author of these lines four decades ago. The legal possibility of clinical trials, the details of these studies, and the objective results obtained are described in detail in published materials [48], including the presentation of individual fragments of this work in numerous articles.

In this context, we are not talking about the details of the work performed, but about general comments on the topic under discussion. Firstly, the obstruction of blood flow in the vessels of the pulmonary circulation increases their arterial pressure, which creates inevitable conditions for their unloading and equalization of the disturbed proportions between the two halves of the general circulatory system.

Secondly, the inclusion of the mechanism described above leads to a delay in part of the circulating blood on the periphery with a tendency to systemic hypotension. The observed changes in blood circulation in the systemic circulation imitate the picture that is today considered as manifestations of S and SS. In accordance with the mechanism of the emerging changes in blood circulation, we assessed this picture as pulmonogenic shock, and not the result of generalization of infection [48].

Thirdly, the use of such general diagnostic schemes as SOFA and qSOFA in modern conditions uses respiratory rate and arterial pressure as the main tests, which are usually characteristic early signs of severe development of AP. The positive nature of these tests already at the very beginning of the inflammatory transformation in the lung accelerates and increases the probability of diagnosing S and SS. At the same time, the fact that changes in arterial pressure in AP are secondary in nature, are not the result of other factors and mechanisms, but reflect the level of autonomous compensatory restructuring, which can go beyond its useful limits, is overlooked.

Fourthly, the use of intravenous infusions in such patients, which is currently generally accepted and widespread, produces an effect that is directly opposite to the expected one. When performing this procedure, solutions enter directly into the vessels that perform the function of venous return, further overloading the pulmonary vessels and the right half of the heart. In such cases, the predicted effect of infusions is absent, which serves as a reason for prescribing vasopressors, the action of which also does not correspond to the pathogenesis of the disease. It should also be noted that intravenous infusions have negative consequences in the area of inflammation, as they can contribute to pulmonary edema, impairing gas exchange, along with the rapid spread of edema and infiltration and the appearance of effusion in the pleural cavity. Such changes are most clearly manifested in the initial period of the disease, especially in its aggressive course, stimulating the development of the inflammatory process.

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All these conclusions were made on the basis of sufficiently convincing evidence on representative material, which served as the basis for refusing infusion therapy in each such case [48].

Finally, when we carried out our work, which was carried out more than four decades ago, when the views on the leading role of antibiotics in the treatment of inflammatory diseases were firm and significantly differed from modern assessments, their use in the treatment complex was given secondary and auxiliary significance. As an initial and emergency intervention for patients hospitalized with a severe onset of Acute Pancreatitis (AP), pathogenetically substantiated methods—some of which have historical or experimental significance—were employed to counteract excessive compensatory responses in the body. These included cervical novocaine vagosympathetic block, a regional nerve block technique, historically, and traditionally used for autonomic modulation; cupping therapy, a practice with historical roots in alternative medicine; and short-term general cooling of the patient's body, an approach explored experimentally for its potential protective effects against systemic inflammation. The results of such procedures, which was associated with rapid clinical improvement in historical cases with stabilization of the condition of such patients, were confirmed by objective tests [48]. It is very important to note in this regard that early intervention in the inflammatory process and its clinical manifestations was associated with more favorable outcomes, which were further reinforced by newly adjusted therapy.

The proposed analysis of the current state of the problem under discussion is presented as food for thought, not as a guide to action. Therefore, the text does not provide references to specific treatment methods, their descriptions and test results. If desired, this information can be easily found in the author's open-access articles, including the already mentioned monograph [48]. This version of the presentation of the material was chosen intentionally so that the readers' attention would be focused on the main defects of the established ideas about the nature of AP. The principles of treatment arising from our vision of the problem determine the main directions of treatment efforts and the choice of specific means and methods. Thus, the formed treatment complex for patients with AP is entirely shaped by the underlying ideology of the disease.

Antibiotics currently remain the leader in the treatment of patients with AP, thereby emphasizing how deeply the leading role of the pathogen in the development of the disease has taken root in professional ideas. The fact that the etiology of AP has been constantly changing over the past decades and has been radically transformed during the period of antibiotic use is not considered a natural side effect. Such a reality of recent years as the loss of the meaning of antibiotics in a large group of patients with AP, in whom "inappropriate" pathogens are detected, primarily viral ones, also does not affect the strategy of views. Therefore, at present, the main goals of solving this problem remain the earliest possible diagnosis of the causative agent of inflammation and the development of new types of antibiotics based on innovative technologies. All this indicates that the most serious side effect of long-term antimicrobial therapy is its negative didactic impact on professional ideas about the nature of the disease. This paradigm may remain under recognized within broader clinical discourse.

Today, it is no longer acceptable to ignore the unique differences in the pathogenesis of AP from the mechanisms of development of inflammatory processes in other localizations. The severe disruption of pulmonary blood flow that occurs during acute inflammation of the lung tissue requires the body to maintain vital parity between the two circles of blood circulation. "In a single diagnostic framework, the observed disease patterns and fluctuations in key indicators serve as the foundation for treating sepsis-like presentation, which manifests through a distinct cascade of circulatory changes. However, those treatment methods that are currently provided for generalized forms of infection naturally give the opposite effect in patients with AP.

Conclusion

Further change of the current situation in a positive direction and the beginning of the solution of the discussed problem is impossible without a radical revision of the concept of the disease. Such mental reform is the first and indispensable condition for solving the tasks set, but this step towards achieving the necessary result requires significant effort, as it shapes future strategies and outcomes.

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