Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 8 Issue 7 July 2024

Review Article

The Heavy Legacy of the Antibiotic Era

Igor Klepikov*

Professor, Retired, Renton, WA, USA

***Corresponding Author:** Igor Klepikov, Professor, Retired, Renton, WA, USA.

Received: April 24, 2024

Published: June 19, 2024

Abstract

The discovery and use of antibiotics in the treatment of patients with inflammatory diseases was one of the greatest medical achievements of the last century, saving millions of lives. However, eight decades have passed since the practical use of these drugs and their interference with the normal balance of nature led to the gradual and steady development of persistent side effects that eclipsed previous achievements and became complex and serious problems. These consequences include the development of microflora resistance, which is becoming an increasingly common representative of the microbiota of healthy people, the dynamics and variability of the etiology of acute pneumonia, an increase in the proportion of viruses and fungi as causative agents of pneumonia, a decrease in the effectiveness of antibiotics and a reduction in their justified use. Of all the listed consequences of antimicrobial therapy, only the resistance of microorganisms attracts the attention of specialists due to the loss of their former effectiveness by these drugs. The reason for such a narrowly focused assessment is the deep didactic distortion of professional ideas under the influence of antibiotics, which is their most serious side effect and requires correction in the first place.

Keywords: SARS-CoV-2; Acute Pneumonia (AP)

Since ancient times, it has been known about the positive effect of mold in inflammatory diseases [1], but only in the last century it was possible to detect and isolate penicillin from it [2,3], which marked the beginning of a new era in the treatment of patients. The clinical use of penicillin, which marked the beginning of the era of antibiotics, was marked by triumphant results combined with the ease of use of the new drug. All these fascinating features of the new drugs gave the impression of the appearance of a universal remedy for the treatment of inflammatory processes. However, with the direct continuation of this therapy, the prediction of its discoverer Alexander Fleming began to be confirmed, who in his Nobel speech pointed out the inadmissibility of using antibiotics for other purposes, which can lead to the development of microflora resistance [4].

A. Fleming's prophetic words were based on research materials available even before the start of clinical trials of penicillin and confirming the rapid development of resistance of microorganisms to the effects of new drugs [3,5]. Today, after eight decades of widespread use of antibiotics, we can confidently speak of the fateful confirmation of these warnings and forecasts, and the fact of the development of resistant microflora is recognized as a global catastrophe [6]. But the very fact that these severe consequences of the use of antibiotics are declared a serious problem does not give an idea of the important causes of this phenomenon.

There are many examples of the misuse of antibiotics, but the most revealing attitude of official medicine towards the prescription of antimicrobials is the experience of the SARS-CoV-2 pandemic. A huge flow of patients with coronavirus pneumonia, in whom the average incidence of concomitant bacterial infection did not exceed 10%, received antibiotics in 70-80 percent or more cases [7-11]. Despite the general professional awareness of the growth of resistant strains, the method of preventive use of antibiotics when the body is in full balance with its accompanying microflora remains widespread [12,13]. The availability of antibacterial drugs facilitates their use as self-medication, which does not always have reasonable indications [14].

The long-term and persistent side effects of antibiotics were significantly enhanced not only due to exceeding the rational indications for their prescription, but also due to the use of these drugs outside of medical purposes. Long-term disputes and discussions about banning the use of antibiotics in the food industry to increase production in areas such as livestock, poultry and even fishing have not yet led to unambiguous positive results [14,15]. This circumstance leaves open the question of the ingestion of these drugs into the body of a healthy part of the population. In this regard, in many countries, on the basis of separate regulations, they began to resort to appropriate labeling of the products offered. Examples of such designations are shown in the figure 1.

Figure 1: Food packaging with information about the use of antibiotics in the production process.

Unfortunately, the severe consequences of prolonged antibiotic use, which were belatedly announced as a huge global problem, are still focused only on microflora resistance. In fact, the side effects of antibiotics differ in a wider and more serious spectrum, which remains without discussion, but even proposals to solve the problem of resistant microflora do not leave hope for success. The proposals that appear in the public domain, including the recommendations of WHO experts [6,16], call for the creation of more effective antimicrobials, which means further development of the reasons that led to the solution of the problem under discussion. This approach to finding the necessary solution is also a reflection of the side effects of antibiotics, however, before discussing the details of the observed phenomena, it is necessary to note the following. Among the inflammatory diseases that can potentially be the cause of the use of etiotropic drugs, acute pneumonia (AP) occupies a special place. The unique feature of AP pathogenesis, which radically distinguishes it from the mechanisms of development of similar processes of other localization, is the reason that this disease seems to be the most suitable example for analyzing and understanding the negative effects of antimicrobial therapy.

The attention of researchers and practitioners was attracted by the first results of antibacterial therapy, which began in favorable conditions to combat microflora unfamiliar with antimicrobial aggression. Contrary to the evidence of the rapid development of resistance of microorganisms to these drugs and the impossibility of prolonged use of the same drugs with equivalent success, the belief continued to grow that the pathogen is the main factor in the occurrence and development of the disease and only antibiotics can bring the necessary therapeutic effect. Therefore, during the first decades of antibiotic use, a decrease in their effectiveness stimulated the development of new, more active drugs, the maximum appearance of which was noted in the period before 1970 [17].

In fact, attempts to implement the idea of early microbiological diagnosis in order to accelerate the targeted initiation of antimicrobial treatment have not stopped until now. In parallel, efforts were made to improve the results of AP treatment by prescribing antibiotics as early as possible and comparing the effectiveness of such hourly treatment from the moment of hospitalization [18-20]. All these goals remained unattainable to the extent that they implied a significant improvement in the results of AP treatment, and in recent years many experts have finally begun to recognize the long-obvious fact that there is no connection between the diagnosis of the etiology of AP in general

and the results of treatment, recommending an empirical choice of antibiotics [21,22].

In addition to these problems, which required at least maintaining the therapeutic effectiveness of antimicrobial therapy, a change in the list of leading pathogens of AP began to be observed. If for several decades before the clinical use of antibiotics Streptococcus pneumoniae remained the undisputed leader, which did not fall below the level of 95% of its participation, then in the era of antibiotics it quickly lost its leading position and did not return even close to the previous indicators [23]. The gradual and obvious decrease in the antimicrobial activity of antibiotics and the steady growth of resistant microflora imperceptibly, but quite logically, led to an increase in the number of diseases of viral etiology.

The latter phenomenon is a vivid demonstration of nature's reaction to prolonged interference in its habitual relationships. Initial attempts to maintain the same proportions between the microflora and the body were expressed in the development of bacterial resistance and the replacement of microbial pathogens. Later, as antimicrobial aggression continued, nature found a more rational way to protect its microcosm. The growth of viruses involved in the etiology of inflammatory processes has already stopped responding to contact with antibiotics. Moreover, in such cases, the latter lose their purpose and even theoretically lose touch with the hope of successful treatment results. Now that the etiological characteristics have completely changed, and the occurrence and development of AP has manifested itself as a selective disease of only a fifth of those infected with an identical pathogen during the pandemic [24-26], it would seem that the only correct and logical way out of this difficult situation remains, requiring a revision of ideas about the nature of this nosology and the principles of treatment strategy. However, the direction of the search for rational solutions indicates an additional and perhaps the most serious consequence of prolonged use of antibiotics.

Firstly, in recent years there has been a significant increase in the number of viruses in the etiology of AP, which a couple of decades ago were the cause of almost half of the cases of this disease in the world [27-29]. Secondly, the incidence of viral pneumonia began to grow due to the emergence of a tradition of annual seasonal epidemics of respiratory viral infections [30,31]. Thirdly, the lack of convincing differential diagnostic criteria between bacterial and viral forms of lung tissue inflammation indicates an insignificant role of etiology in the overall picture of the disease [32-35]. Finally, the severe SARS-CoV-2 pandemic, which cannot be considered sudden after two preliminary epidemics (SARS and MERS) and the subsequent preservation of the coronavirus in the list of pathogens of pneumonia for two decades [30,31], clearly demonstrated the potential of modern medicine in the treatment of such patients, which was expressed only in supportive and palliative care. The mentioned circumstances are enough to leave no doubt in the search for new ways of adequate solutions, isn't it? However, the efforts being made today to solve a long-overdue problem indicate that, contrary to the already indisputable facts, representatives of modern medicine are trying to succeed by further developing the learned stereotype about the main factors of "microbe - antibiotic" [36-39].

The acquired ideas about the essence of the nature of AP, in which the causative agent of the disease appears as the main cause, and etiotropic drugs are considered the main means of treatment, quite clearly represent an area beyond which clinicians and researchers do not venture. Given the abundance of facts that refute modern ideas about the disease, such a position can no longer be explained by simple misunderstanding. The job responsibilities of specialists are limited by administrative acts and conditions of insurance companies. However, these restrictions do not prevent the expression of their opinions and broad discussions, which currently continue to adhere to the previous guidelines. If, for obvious reasons, no practical changes are being made, then why are there no reasoned and scientifically sound explanations for the phenomena and changes that have been observed throughout the era of antibiotics? What is the logic of those statements that continue the line of the previous concept, having in front of them a lot of undeniable counterarguments? The reason for the latter phenomenon is the negative didactic effect of antibiotics on professional attitudes.

For many decades, the medical staff, generation after generation, consistently and persistently prepared for subsequent practical activities in an atmosphere of firm belief in the monopolistic leading role of antibiotics in the treatment of inflammatory diseases. At the same time, no alternatives to this principle of treatment were offered. In this regard, the period when the initial treatment of AP was designated by the term "antibiotics alone" looks quite logical. From such positions, a new perception of the epidemiology of this disease has become quite natural. AP, which for many centuries

was not considered a contagious disease and which has been said since ancient times that people suffer from pneumonia rather than become infected, suddenly, even before the growth of viral forms, began to belong to the category of infectious processes. Such interpretations, as well as a number of other features, reflect a deep didactic distortion and narrowing of the range of professional views. This reason should currently be considered as the main negative effect of antibiotics, since this factor is of paramount importance for choosing and justifying goals and ways to solve the problem.

In addition to the materials mentioned above, the dominant point of view on the issue raised today is much more important than it might seem at first glance. In this case, it is necessary to recall those patients with AP who, as a result of the aggressive development of the disease or the insufficient effectiveness of initial treatment, need additional help. Many publications on this topic draw attention to the growth of such a contingent. And here the problem of the discrepancy between the mechanisms of the main functional disorders in AP and the direction of action of the applied techniques is clearly traced.

On the one hand, the lack of clear differential diagnostic criteria for pneumonia, depending on their etiology, brings us back to the long-proven information that the unity and difference of inflammatory processes should be sought in their classic feature, which refers to the loss of function of the affected organ. It is on this basis, even in the case of a coincidence of etiology, AP will be radically different from inflammation of another localization. But, on the other hand, the idea of the pathogen as the main cause of the disease remains dominant in professional consciousness, which allows the use of general therapeutic techniques by analogy with other processes. In this aspect, there is a clear inattention to the functional features of pulmonary blood flow and its changes that occur during the development of AP. Misconceptions in this matter begin with diagnostics, where a violation of the parameters of blood circulation is assessed by indicators of peripheral rather than pulmonary blood flow [40,41]. This does not take into account the important fact that changes in systemic blood flow are secondary in patients with AP and reflect primarily compensatory shifts, rather than the severity of the disorders.

The inverse ratios of blood flow in the small and large circulatory circles, their complete interdependence, which maintains the parity of cardiac output between the two ventricles, and the leading role of pulmonary vessels in regulating total blood flow to maintain vital balance are unique factors that distinguish the pathogenesis of AP development from many other inflammatory processes. The main features of blood circulation are fundamental materials of medical science, and the importance of the existing differences between the two basins of the vascular system was confirmed not only experimentally, but also clinically four decades ago [42]. The importance of this information for understanding the mechanisms of AP and substantiating pathogenetic therapy is of paramount importance. But in this context, we are not talking about the features of the pathogenesis of AP, but about the fact that the superiority of the pathogen and the saving role of etiotropic drugs, despite numerous counterarguments, remain a persistent didactic consequence of antibacterial therapy. Such a psychological effect plays a leading role today in underestimating the mechanisms of pneumonia development and incorrectly justifying adequate treatment methods.

The presented remarks and explanations in modern medicine can relate only to the methods of additional and auxiliary medical care for patients with AP. This is due to the fact that, according to established standards, the main hope for success is placed on etiotropic therapy. Inattention to the pathogenesis of the disease excludes the search and application of pathogenetic techniques. However, the use of some additional methods of assistance cannot be considered as correction without aggravating consequences. Such techniques can literally play a crucial role. The logic of suppressing infection and eliminating its consequences allows the use of general therapeutic methods. Therefore, when the body of a patient with AP literally suffocates from a sudden relative excess of venous return [42-44], he begins to receive the most common and affordable type of medical care - infusion therapy, which only exacerbates the disorders that have arisen. At the same time, the more severe the patient's condition, the more intensive infusions are recommended. If we look at the discussed aspect from such positions, the reason for the progression of the disease, despite treatment, becomes clear [42].

The system of views on the problem of AP, which has developed under the influence of the exaggerated role of antibiotics in the

treatment of these patients, has much broader consequences than noted above. The first signs of this disease in the case of aggressive development and rapidly increasing severity of the patient's condition are usually assessed on the basis of one of the variants of the point scale, according to which the standard shifts in the main functional indicators of AP correspond to the currently generally accepted definition of sepsis [40,41]. This approach is the cause of overdiagnosis of septic conditions in patients with AP, and the determination of sepsis leads to intensive intravenous infusions. This circumstance explains the fact that the cause of sepsis in half or more cases is pneumonia [45], in which the pathogenesis features mimic a similar pattern [42]. In recent years, these criteria have been automatically applied to patients with viral forms of AP, the number of which has increased significantly, and at the same time, the percentage of diagnosis of sepsis and septic shock among this contingent began to exceed 60% [46,47], and in the case of concomitant oliguria, this figure increased to 82% [47].

It is very difficult and painful to admit one's own misconceptions when, despite the presence of irrefutable counterarguments, such beliefs continue to dominate the general professional worldview. In recent years, the problem of antibiotic-resistant microflora has attracted increased attention and concern, while other consequences of prolonged antibiotic use remain nameless. In this regard, it is necessary to pay attention to a rather strange and unusual circumstance. The development of bacterial resistance to antibiotics was known even before the beginning of their clinical use, and their practical implementation throughout this period was accompanied by a continuous increase in the diversity of resistant strains. This phenomenon, which has been observed for many decades, instead of a natural manifestation of anxiety and the implementation of measures to reduce such a burden, was accompanied by the development and release of new, more effective drugs. Throughout the entire period, maximum efforts were made to preserve and maintain the therapeutic activity of this therapy without any special measures against the growing resistance of the microflora. It was only after almost eight decades of practical use of antibiotics, when the process of formation and growth of resistant strains became quite obvious, that WHO finally declared this problem a global catastrophe. Why did this happen only in 2021 [6], and not in the 50s, 60s, and even more so in the 70s of the last century, when there were already quite good reasons for this?

The reason for such a belated official confirmation of the effects of antibacterial therapy, which have long become a well-known fact, is, in my opinion, the following circumstances. First, the didactic influence of antibiotics, which have strengthened a deep and unshakeable belief in their exclusivity and irreplaceability. Confirmation of this hypnotism can be found in a published WHO statement, in which bacterial resistance is declared a global catastrophe, and the solution to this problem is presented in the form of the development of new, more effective drugs [6]. But, the question is rhetorical, and what benefit can be expected from further improvement of the cause that gave rise to the problem under discussion?

Secondly, this document does not mention or analyze the effects of antibiotics, such as the constant change of AP pathogens that arose with their appearance. This sign was of no less important clinical significance than the formation of microflora resistance, since throughout the entire period of antibiotic use it was the reason for the constant correction of etiotropic treatment with the search and use of the most optimal drugs.

Finally, despite the lack of reasoned scientific explanations for changes in the etiology of AP in previous years, the importance of this phenomenon currently remains without proper comment. The targeted suppression of the leading microorganisms was accompanied by their replacement with other bacteria, and eventually nature found a more reliable way to protect its subjects - viruses began to appear on the scene. An increase in the frequency of viral forms of AP gradually reduced the likelihood of successful antibiotic use, but during this period no radical steps were taken to apply adequate medical care measures. Antibiotics have been and remain the main means of treatment, maintaining an unreasonable demand for them even during the period of the apparent predominance of coronavirus forms of the disease [7-11]. Nevertheless, it was the pandemic that accelerated the recognition of microbial resistance as a global catastrophe, since antibiotics lost their purpose during the apparent spread of viral diseases. However, the timing of the release of such a document and the lack of a logically and scientifically sound program of measures in such a situation are more reminiscent of a demarche to "save the honor of the uniform" than an urgently needed guiding treatise.

Thus, today, the effects of prolonged antibiotic use are associated only with resistant strains of bacteria. In the current stream of publications directly or indirectly related to the topic of antimicrobials and the treatment of inflammatory processes, the resistance of microflora caused by antibiotics is unanimously assessed as one of the most significant threats to health. At the same time, it is impossible to find descriptions in the literature, much less analytical comments and opinions on other effects of antimicrobials. In addition, published opinions on solving this problem are equally unanimous in considering the possibility of achieving success in resolving this situation only by developing new antibiotic options. With the current research potential of biomedical science, the creation of new antimicrobial drug options that can bring temporary success is quite acceptable. However, no one predicts a situation when the microcosm around us will create its own counteraction to this new aggression. If such an option is implemented and it inevitably happens, then we should not deceive ourselves with hopes of achieving a confident victory, since the consequences of such a step will undoubtedly be more serious and difficult to correct than those observed today.

The feelings of insecurity and fear that arise during the professional assessment of resistant microflora are quite understandable, since they belong to specialists who, despite the refuting facts, continue to consider the possibility of treating AP with antibiotics only. If we fully hope for the success of treatment only with the help of etiotropic agents, then the resistance of bacteria to drugs can be considered as a serious problem during the disease, right? But the possibility of the presence of such microorganisms in the microbiota of healthy people has been known for many years and is becoming an increasingly common condition, which does not necessarily mean the inevitability of the disease. At the same time, no one tries to criticize the failures of modern medicine in helping patients with AP, especially during a pandemic, and does not offer effective treatment for viral variants of the disease, which have become diagnosed in a large contingent of patients. The prevailing views on inflammatory diseases and their treatment also do not allow us to consider changes in the etiology of AP as a result of prolonged use of antibiotics. This explains why, at the professional level, there is an active search for the sources of outbreaks of infection using conspiracy theories and exploring options for deliberate infection [48].

In fact, the most important and serious consequence of prolonged use of antibiotics is their didactic effect on the formation of professional views on the problem under discussion. Limiting ideas about medical care for patients by concentrating efforts on suppressing the pathogen and maintaining these beliefs, despite the refuting facts, are currently the main obstacle to choosing optimal solutions to a problem that arose not without our participation. Ultimately, it is necessary to realize that a period has long come when it is necessary to reconsider one's own misconceptions and eliminate their consequences.

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.

Bibliography

1. Gould K. «Antibiotics: from prehistory to the present day». *Journal of Antimicrobial Chemotherapy* 71.3 (2016): 572-575.

2. Fleming A. «On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of B. influenzæ». *British Journal of Experimental Pathology* 10.3 (1929): 226-236.

3. Abraham EP and Chain E. "An enzyme from bacteria able to destroy penicillin". *Nature* 10.4 (1988): 677-678.

4. Fleming A. «The Nobel Prize in Physiology or Medicine 1945 - Penicillin: Nobel Lecture». NobelPrize.org (2020).

5. Rammelkamp T. "Resistance of Staphylococcus aureus to the action of penicillin". *Experimental Biology and Medicine* 51 (1942): 386-389.

6. Antimicrobial resistance (2021).

7. BD Huttner., *et al*. "COVID-19: don't neglect antimicrobial stewardship principles!" *Clinical Microbiology and Infection* 26.7 (2020): P808-810.

8. B Beović., *et al*. "Antibiotic use in patients with COVID-19: a 'snapshot' Infectious Diseases International Research Initiative (ID-IRI) survey". *Journal of Antimicrobial Chemotherapy*, dkaa326 (2020).

9. Rawson TM., *et al*. "Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing [published online ahead of print, 2020 May 2]". *Clinical Infectious Diseases* (2020): ciaa 530.

10. Lipman M., *et al*. "SARS-CoV-2 pandemic: clinical picture of COVID-19 and implications for research". *Thorax* 75 (2020): 614-616.

11. Puzniak L., *et al*. "A multicenter analysis of the clinical microbiology and antimicrobial usage in hospitalized patients in the US with or without COVID-19". *BMC Infectious Diseases* 21 (2021): 227.

12. M J Enzler., *et al*. "Antimicrobial Prophylaxis in Adults". *Mayo Clinic Proceedings* 86.7 (2022): 686-701.

13. Alsaeed OM., *et al*. "The Use of Antibiotics for the Prevention of Surgical Site Infections in Two Government Hospitals in Taif, Saudi Arabia: A Retrospective Study". *Cureus* 14.7 (2022): e26731.

14. Larson E. «Community factors in the development of antibiotic resistance». *Annual Review of Public Health* 28.1 (2007): 435-447.

15. Charles D. «Despite Pledges To Cut Back, Farms Are Still Using Antibiotics». *NPR* (2018).

16. Hoffman SJ., *et al*. "An international legal framework to address antimicrobial resistance». *Bulletin of the World Health Organization* 93.2 (2015): 66.

17. Aminov RI. «A brief history of the antibiotic era: lessons learned and challenges for the future». *Frontiers in Microbiology* 1 (2010): 134.

18. Yu KT and Wyer PC. "Evidence-based emergency medicine/ critically appraised topic. Evidence behind the 4-hour rule for initiation of antibiotic therapy in community-acquired pneumonia". *Annals of Emergency Medicine* 51 (2008): 651-662.

19. Dellinger RP., *et al*. "Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012". *Critical Care Medicine* 41.2 (2013): 580-637.

20. Noritomi DT., *et al*. "Implementation of a multifaceted sepsis education program in an emerging country setting: clinical outcomes and cost-effectiveness in a long-term follow-up study". *Intensive Care Medicine* 40 (2014): 182-191.

21. J P Metlay., *et al*. "Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America". *American Journal of Respiratory and Critical Care Medicine* 200.7 (2019): e45-e67.

22. Paula Peyrani., *et al*. "The burden of community-acquired bacterial pneumonia in the era of antibiotic resistance". *Expert Review of Respiratory Medicine* 13.2 (2019): 139-152.

23. Gadsby NJ and Musher DM. "The Microbial Etiology of Community-Acquired Pneumonia in Adults: from Classical Bacteriology to Host Transcriptional Signatures". *Clinical Microbiology Reviews* 5 (2022): e00015-22.

24. Z Wu., *et al*. "Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention". *JAMA* 323.13 (2020): 1239-1242.

25. Murad M and Martin JC. "Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages". *Nature Reviews of Immunology* 20 (2020): 355-362.

26. Zhou B., *et al*. "COVID-19 pathogenesis, prognostic factors, and treatment strategy: Urgent recommendations". *Journal of Medical Virology* (2021): 1-11.

27. Revised global burden of disease 2002 estimates (2004).

28. Rudan I., *et al*. "Epidemiology and etiology of childhood pneumonia". *Bulletin of the World Health Organization* 86 (2008): 408-416.

29. Ruuskanen O., *et al*. "Viral pneumonia". *Lancet* 377.9773 (2011): 1264-1275.

30. Visseaux B., *et al*. "Prevalence of respiratory viruses among adults, by season, age, respiratory tract region and type of medical unit in Paris, France, from 2011 to 2016". *PLoS One* 12.7 (2017): e0180888.

31. Shah MM., *et al*. "Seasonality of common human coronaviruses, United States, 2014-2021". *Emergency Infectious Dissease* 28.10 (2022): 1970-1976.

32. C Heneghan., *et al*. "Differentiating viral from bacterial pneumonia". April 8, 2020. The Centre for Evidence-Based Medicine. Evidence Service to support the COVID-19 response. *University of Oxford* (2020).

33. Kamat IS., *et al*. "Procalcitonin to Distinguish Viral From Bacterial Pneumonia: A Systematic Review and Meta-analysis". *Clinical Infectious Diseases* 70.3 (2020): 538-542.

34. Kamat IS., *et al*. "Procalcitonin to Distinguish Viral From Bacterial Pneumonia: A Systematic Review and Meta-analysis". *Clinical Infectious Diseases* 70.3 (2020): 538-542.

35. Lhommet C., *et al*. "Predicting the microbial cause of community-acquired pneumonia: can physicians or a data-driven method differentiate viral from bacterial pneumonia at patient presentation?" *BMC Pulmanory Medicine* 20 (2020): 62.

36. Kyriazopoulou E., *et al*. "BioFire® FilmArray® pneumonia panel for severe lower respiratory tract infections: subgroup analysis of a randomized clinical trial". *Infectious Diseases and Therapy* 10 (2021): 1437-1449.

37. Montes-Andujar L., *et al*. "Empiric antibiotics for community-acquired pneumonia in adult patients: a systematic review and a network meta-analysis". *Thorax* (2021).

38. Cilloniz C., *et al*. "Management of pneumonia in critically ill patients". *BMJ* 375 (2021): e065871.

39. Enne VI., *et al*. "Multicentre evaluation of two multiplex PCR platforms for the rapid microbiological investigation of nosocomial pneumonia in UK ICUs: the INHALE WP1 study". *Thorax* 77 (2022): 1220-1228.

40. Richards G., *et al*. "CURB-65, PSI, and APACHE II to assess mortality risk in patients with severe sepsis and community acquired pneumonia in PROWESS". *Journal of Intensive Care Medicine* 26.1 (2011): 34-40.

41. Singer M., *et al*. "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)". *JAMA* 315.8 (2016): 801-810.

42. I Klepikov. "The Didactics of Acute Lung Inflammation". Cambridge Scholars Publishing (2022): 320.

43. Thillai M., *et al*. "Functional respiratory imaging identifies redistribution of pulmonary blood flow in patients with COVID-19". *Thorax* 76 (2021): 182-184.

44. W Dierckx., *et al*. "CT-derived measurements of pulmonary blood volume in small vessels and the need for supplemental oxygen in COVID-19 patients". *Journal of Applied Physiology* 133.6 (2022): 1295-1299.

45. A Ceccato and A Torres. "Sepsis and community-acquired pneumonia". *Annals of Research Hospitals* 2 (2018): 7.

46. Cilloniz C., *et al*. "Pure viral sepsis secondary to community-acquired pneumonia in adults: risk and prognostic factors". *Journal of Infectious Disease* 220 (2019): 1166-1171.

47. Lin CK., *et al*. "Serum vascular endothelial growth factor affects tissue fluid accumulation and is associated with deteriorating tissue perfusion and oxygenation in severe sepsis: a prospective observational study". *European Journal of Medical Research* 28 (2023): 155.

48. LO Gostin., *et al*. "The Origins of Covid-19 — Why It Matters (and Why It Doesn't)". *The New England Journal of Medicine* 388 (2023): 2305-2308.