Opinion. Open letter to the Editor.

COVID-19: Target Selection

Igor Klepikov[1*]

Author information: [1]Professor of Medicine, Retired, USA

Received: 05-15-2021; Accepted: 06-20-2021; Published: 06-21-2021.

Keywords: pneumonia, COVID-19, adaptation, lungs, inflammation

For many, the history of coronavirus disease began with the current pandemic, although clinical medicine has been familiar with this type of infection for at least the past two decades [1,2]. Despite the information and experience in this area, a number of researchers consider COVID-19 as a new disease with clinical uncertainty (3). However, most specialists, based on the morphology and clinic of the main pathology of the current pandemic, define it as COVID-19 pneumonia. This term reflects another etiological variant of the disease, which belongs to the unified nosology "acute pneumonia" (AP).

The new diagnosis is mainly of epidemiological significance since, reflecting the etiology of the disease, it indicates the presence of a pathogen capable of rapid spread. However, the clinical meaning of this formulation is small. It is a consequence of the prevailing opinion about the leading role of the etiology of the disease in all its most important manifestations. In this regard, it should be recalled that the previous experience of classification of AP depending on the suspected pathogen did not bring the expected results [4,5]. Moreover, experts today claim that the differential diagnosis between COVID-19 pneumonia and bacterial forms of the disease is a very difficult task for practical medicine [6,7], highlighting the common basis of these two variants of inflammation.

Let us carefully and dispassionately analyze the current concepts that represent AP as a result of infection. The further development of the disease and the features of its manifestations are considered depending on the type of pathogen. At the same time, it is no secret that the features of each pathogen are studied mainly in vitro, and its true effect on the body is presented in the form of assumptions and analogies. The statistics of the current pandemic have dealt a crushing blow to such a simplistic view and have already clearly demonstrated the indisputable fact that the penetration of an equivalent infection into the body can provide an infinite range of clinical options and not necessarily lead to disease, right?

To date, no one can give a clear justification for the clinical manifestations of AP, which are due solely to its etiology. Many manifestations of inflammatory tissue transformation continue to be interpreted as the result of the action of the pathogen and not those processes and mechanisms that cascade as a result of acute pathology in the lungs. There are no effective drugs against the coronavirus, so modern medicine is trying to find ways to counteract its penetration into the cell. To this end, the microstructures of the virus and their interaction with the host organism at the cellular and molecular levels are studied (8-17). Such studies do not raise doubts about their importance and prospects, but we must call a spade a spade. The results of such studies may help prevent COVID-19, but not in the treatment of those who are already ill.

To help severe patients with COVID-19 pneumonia, significant efforts are being made today to eliminate the manifestations of an inflammatory reaction, which is considered a consequence of the aggression of the pathogen. For example, the" fashionable" trend in this direction is the desire to neutralize cytokines in patients' bodies [18-22]. Currently, the term "cytokine storm" is used to explain one of the main reasons for the severity of the condition of patients with AP. When suggesting options for reducing the activity of cytokines, no one focuses on the fact that these factors are not specific for lung damage but only serve as a reflection of the intensity of the inflammatory response [23]. Try to find an explanation for the fundamental differences between elevated cytokine levels in patients with AP and, for example, with psoriasis [24]. This is about the same task as finding differences in the causes of fever in these finding

Corresponding Author: Igor Klepikov: igor.klepikov@yahoo.com

differences in the causes of fever in these categories of patients.

The main omission in such searches and tests is the loss of real ideas about cause-and-effect relationships in the dynamics of AP development. The bogeyman of the etiology of the process dominates to such an extent that certain facts and circumstances go unnoticed. In this connection, there is an involuntary association with one of the heroes of the O'Henry novels, who asks: "Why the wind?" and without waiting for the other person to answer, he answers himself: "Because the trees are swaying!"

Even in the presence of effective drugs against coronavirus, it is necessary to anticipate the scenario of such treatment. Antiviral drugs must enter the affected cells and destroy the coronavirus before it ceases to show its pathological activity. During this entire period of treatment, the influence of the focus of inflammation on the functions of the lungs and the body as a whole will continue. This type of drug treatment can not directly affect the mechanisms of functional disorders. The body does not have a time resource for adaptation in the aggressive development of the process.

For acute inflammation to occur in the lung tissue, an infection alone is not enough. Only in combination with other factors, the pathogen plays the role of an "ignition system." Still, when a focus of acute pneumonia appears, the inflammatory process and its effect on the body come to the fore. Inflammation of the lung tissue means the appearance of new circumstances, which will undoubtedly depend on the volume of the lesion. Hardly anyone would disagree with the opinion that 50% of lung tissue damage, regardless of etiology, is accompanied by a more severe condition of the patient, compared to 5-10%, right? Even a visual representation, which cannot reflect the entire complex of pathophysiological mechanisms that occur in AP, allows us to assess the role of the focus of inflammation of the lung tissue for blood circulation in the body (see Figure 1).

Looking at this picture, it is impossible to deny that the inflammatory process in the lung tissue interferes with the general blood flow in the body, creating at least a physical obstacle to the movement and gas exchange of blood. The mechanisms of these disorders are not only purely mechanical, and violations of pulmonary blood flow go beyond the zone of inflammation. The development of such generalized blood flow disorders in the small circle of blood circulation is a protective and adaptive mechanism under blood circulation conditions. This mechanism reduces the load on the vascular system of the lungs, repelling the impending danger. However, as you know, any defensive reaction has its practical limit. Therefore, in the conditions of rapid development of events, we can observe a typical picture of a pulmonary shock, the cause of which is not the causative agent of AP [25].

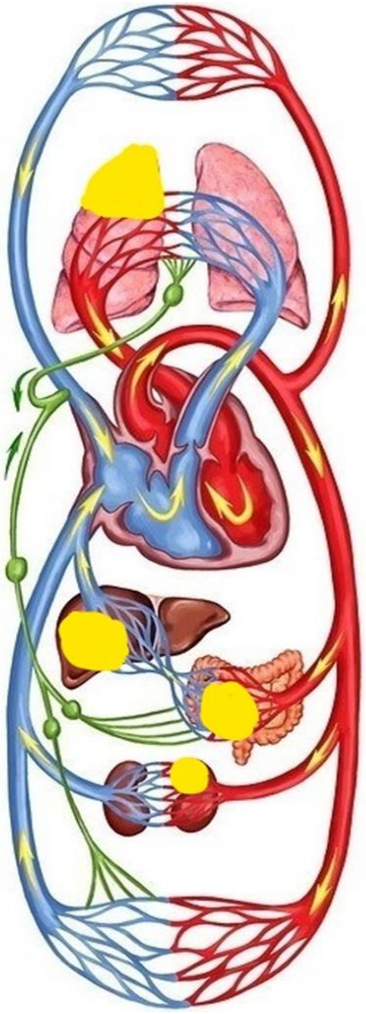

Figure 1. Schematic representation of the human circulatory system. Comparative value of foci of acute inflammation (yellow fields) for different departments and volumes of blood flow, depending on the possible localization.

The reflex nature of this mechanism has been known to medicine for more than eight decades as Schwiegk's reflex [26]. Indirect confirmation of generalized small-circle vasospasm activation has already been proven by computed tomography in patients with COVID-19 [27]. However, such circulatory transformations are more

complex since this process involves the baroreceptors of the pulmonary vessels and humoral factors. For example, it is known about the important role of the renin-angiotensin-aldosterone system (RAAS), which is an integral part of the complex of blood pressure regulation and blood redistribution [28]. Currently, many researchers are considering changes in this system in patients with COVID-19 pneumonia resulting from viral aggression and are trying to find an effective correction of these deviations [29-35].

And again, as in the previous example, the same dependence of existing approaches to studying the problem and the principles of medical care, which are focused on the etiology of AP, is traced. Both excessive cytokine release and changes in the RAAS can be observed in pathology that has nothing to do with inflammation (23,27). Therefore, detecting such abnormalities in patients with COVID-19 cannot be a specific reaction, characteristic only of AR, or be considered a sign inherent exclusively in coronavirus infection, right? Attempts to achieve success in the treatment of COVID-19 pneumonia by eliminating selective manifestations of the body's response to extreme circumstances go beyond logic and understanding.

In the search for a solution to this problem, the causal relationship of AP manifestations has been lost for many years. Currently, patients with AP, whose physicians carefully collect anamnesis and study their X-ray studies to assess the potential severity of the disease, are perceived in the further treatment process as a virtual picture of cellular and molecular transformations, but not as the main and unified macro-object of the study. At this stage, it is necessary, first, to have a broad and maximally objective view of the entire chain of mechanisms underlying the AP. In the meantime, the focus of research and therapeutic efforts brings us back to the aforementioned analogy with the question: "Why the wind?"

It is very unpleasant to talk about the low effectiveness of modern approaches to AP treatment, but the facts oblige us to be frank since the pandemic has already claimed more than 3.7 million lives. In a year and a half of coronavirus infection, no one in the world has presented relatively reliable ways to help these patients. In this case, we are not talking about vaccination of the population, but about targeted, but not palliative treatment of those already ill. It is quite logical that the costs of finding such solutions do not bring returns since the research goals are narrowed to small segments of the disease. For example, as of January 2021, the National Institutes of Health (NIH) has issued nearly a thousand awards totaling about $ 2 billion to support Covid-19 projects. However, the results of publicly funded research remain largely unknown, and at best, only 8% of completed or discontinued papers are sent for publication [36].

Experience in treating acute inflammation of the lung tissue has been accumulated for centuries by trial and error. The appearance of antibiotics in medical practice has created an atmosphere of general euphoria and short-sighted confidence in the possibility of successful treatment of this group of diseases with a single pill. The previous experience of treating such patients was discarded and forgotten as an unnecessary attribute [37]. But today, many experts not only in the field of medicine and biology are convinced that nature does not tolerate interference that violates its rules and the balance of its components. As the ancient proverb says: "Sow the wind and reap the whirlwind." Observing the progressive growth of viral lung lesions against the background of many years of fascination with antibiotic therapy, medicine has not yet fully realized that it is reaping the fruits of its own myopia and is persistently trying to correct the situation with the help of the principles and approaches that gave rise to this conflict.

Today, medicine has more opportunities to conduct objective research and tests than 4-5 decades ago, when there was a need to clarify and test various aspects of AP. At that time, it was already noticeable that antibiotics were losing priority in treating AP, and complications and high mortality inevitably accompanied aggressive forms of the disease. These circumstances gave rise to the search for optimal care for the most severe patients with AP.

As a result of many years of work, the materials of fundamental medical science were grouped, and additional information about the nuances of the development of AP was obtained. This section of the work allowed us to prove the fallacy of ideas about the crucial role of antibiotics in this category of patients. Against the background of the scientific justification of the nature of AP, the bet on the leading role of antibiotics in the treatment of this disease looks fragmentary and primitive. But to confirm such conclusions, first of all, requires a radical revision of the doctrine of the disease.

Only after changing their own views on the essence of the problem is there an understanding that other efforts are needed so that the patient feels the positive effect of this help. At the same time, to assess the effect of different

treatment methods, it is not enough to focus on analogies of their use in other diseases or on subjective impressions. Objective tests should be considered as a prerequisite for the introduction of new methods and areas of care. Then the final results of treatment of the most severe patients may exceed expectations [38].

Since this work was completed, the lack of effectiveness of antibiotics in the treatment of bacterial forms of AP has become more than obvious. Now a huge number of patients with viral lung diseases, where the use of antibiotics does not make real sense, have added to this undoubted problem. In the current situation, the most logical and reasonable step would be a strict revision of the strategy for solving the entire problem of the AP. However, contrary to logic and numerous facts, many experts do not find anything better than to continue the previous conceptual line. For example, what are the reasons why leading experts in this field insist on using antibiotics for COVID-19 pneumonia [6,39-45]? From my perspective, the main reason for such recommendations can only be the didactic influence of the lingering cult of antibiotics in the theory and practice of AP.

As the results of long-term use of antibiotics show, the medicine fight against bacterial pathogens is lost. The recognition of this fact is necessary for the future for the successful solution of the tasks set. The existing distortion of scientific ideas about the nature of AP hinders the rational search for solutions. Nature and time have convincingly shown us that the principle of "sterilization" of the focus of inflammation is not only a narrowly focused action but also has far-reaching consequences. Obviously, the further continuation of this strategy cannot lead to the desired success, and the side effects and negative consequences of such an ideology will only increase and worsen.

Various changes in the body of patients with AP, which are diagnosed and undergo therapeutic correction, are initially protective and adaptive in nature, so the desire to normalize such deviations cannot always achieve the intended goal. It is necessary to revive the old concept of "norm in pathology," which meant that there are deviations that reflect its adaptation to new conditions in the case of a disease in the body. Such shifts up to a certain limit are a positive phenomenon and do not require correction. At this stage, it is necessary to determine the line after which each compensatory-adaptive reaction of the body acquires the features of a pathological one that requires additional help. But before investigating the various manifestations of AP, it is necessary to adopt a general scheme of the relationship and sequence of these reactions and mechanisms in the pathogenesis of inflammatory transformation of lung tissue instead of ephemeral dependence on the pathogen.

REFERENCES:

1. Severe acute respiratory syndrome. https://en.wikipedia.org/wiki/Severe_acute_respiratory_syndrome
2. Middle East respiratory syndrome. https://en.wikipedia.org/wiki/Middle_East_respiratory_syndrome
3. Schaye VE, Reich JA, Bosworth BP et al. Collaborating Across Private, Public, Community, and Federal Hospital Systems: Lessons Learned from the Covid-19 Pandemic Response in NYC. NEJM Catalyst Innovations in Care Delivery 2020; 06, 1, 6, November — December 2020. doi: https://doi.org/10.1056/CAT.20.0343
4. Metlay JP, Waterer GW, Long AC at al.; on behalf of the American Thoracic Society and Infectious Diseases Society of America. 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 2019; 200, 7, 1, e45-e67. https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST
5. Klepikov I. How many pneumonias exist in nature? Eur J Clin Microbiol Infect Dis. 2020. https://doi.org/10.1007/s10096-020-03834-7
6. Heneghan C, Pluddemann A, Mahtani KR (2020). 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. https://www.cebm.net/covid-19/differentiating-viral-from-bacterial-pneumonia.
7. Kamat IS, Ramachandran V, Eswaran H, Guffey D, Musher DM. (2020). Procalcitonin to Distinguish Viral from Bacterial Pneumonia: A Systematic Review and Meta-analysis. Clin Infect Dis 2020; 16, 70(3): 538-542. doi: 10.1093/cid/ciz545. PMID: 31241140.
8. Zelba H, Worbs D, Harter J et al. A Highly Specific Assay for the Detection of SARS-CoV-2–Reactive CD4+ and CD8+ T Cells in COVID-19 Patients. The Journal of Immunology 2021; 1, 206 (3): 580-587. doi: 10.4049/jimmunol.2000811
9. Dzau VJ, Balatbat C. Strategy, coordinated implementation, and sustainable financing needed

for COVID-19 innovations. The Lancet Journal 2020; 396, 10261: 1463-1534, e73-e82. doi: https://doi.org/10.1016/S0140-6736(20)32289-3
10. Bohn MK, Hall A, Sepiashvili L et al. Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression. Physiology 2020; 35, 5: 288-301.
11. Cheepsattayakorn A, Cheepsattayakorn R. Pathogenesis and Pulmonary Pathology in SARS-CoV-2 (COVID-19) Host Cell Invasion. Acta Scientific Microbiology 2020; 3.11: 01-02.
12. Attaway AH, Scheraga RG, Bhimraj A. Severe covid-19 pneumonia: pathogenesis and clinical management. BMJ, 2021; 372: n436. doi:10.1136/bmj.n436
13. Grant RA, Morales-Nebreda L, Markov NS et al. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. Nature, 2021. https://doi.org/10.1038/s41586-020-03148-w
14. Zhou B, Kojima S, Kawamoto A, Fukushima M. COVID-19 pathogenesis, prognostic factors, and treatment strategy: Urgent recommendations. J Med Virol. 2021; 1– 11. doi:10.1002/jmv.26754
15. Loo J, Spittle DA, Newnham M. (2021). COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax 2021; 76: 412-420.
16. Stenmark KR, Frid MG, Gerasimovskaya E et al. Mechanisms of SARS-CoV-2-induced lung vascular disease: potential role of complement. Pulmonary Circulation, 2021; 11(2): 1–14. doi: https://doi.org/10.1177/20458940211015799
17. El-Shimy IA, Mohamed MM, Hasan SS, Hadi MA. Targeting host cell proteases as a potential treatment strategy to limit the spread of SARS-CoV-2 in the respiratory tract. Pharmacol Res Perspect. 2021; 9: e00698. doi:10.1002/prp2.698
18. Farah H, et al. Potential Anti-Inflammatory Approaches for the Management of SARS-CoV2 Infections. J Pulmon Respir Sci 2020; 5(S1): 000S1-001.
19. Ahmed I. Siddiqi. Cytokine flames of COVID-19. J. Archives of Medical Case Reports and Case Study 2020; 3(2). doi:10.31579/2692-9392/014
20. Mo Shehata. Covid-19; The Possible Medical Strategies. EC Pulmonology and Respiratory Medicine 9.6 2020: 03-07.
21. Cytokine Storm -to the Editor. (2021). April 22, 2021. N Engl J Med 2021; 384: e59. doi:10.1056/NEJMc2036236
22. Caramaschi S, Kapp ME, Miller SE et al. (2021). Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review. Mod Pathol. 2021. https://doi.org/10.1038/s41379-021-00814-w
23. Cytokine. https://en.wikipedia.org/wiki/Cytokine
24. Hülya Çiçek., et al. Serum Cytokine Profiles in Patients with Psoriasis. Acta Scientific Medical Sciences 2021; 5.5: 13-22.
25. Klepikov I. Acute Pneumonia is More Cardiovascular than Respiratory Disaster. J Emerg Med Care 2018; 1(1): 105
26. Schwiegk, H. Der Lungenentlastungsreflex. Pflügers Arch. Ges. Physiol 1935; 236, 206–219.
27. Thillai M, Patvardhan C, Swietlik EM, et al. Functional respiratory imaging identifies redistribution of pulmonary blood flow in patients with COVID-19. Thorax, 2021; 76: 182-184.
28. Renin–angiotensin system. https://en.wikipedia.org/wiki/Renin%E2%80%93angiotensin_system
29. Amraei R, Rahimi N. COVID-19, Renin-Angiotensin System and Endothelial Dysfunction. Cells 2020; 9(7):1652. doi: 10.3390/cells9071652.
30. Malha L, Mueller FB, Pecker MS, Mann SJ, August P, Feig PU. COVID-19 and the Renin-Angiotensin System. Kidney Int Rep. 2020; 5(5): 563-565. doi:10.1016/j.ekir.2020.03.024.
31. Wiese OJ, Allwood BW, Zemlin AE. COVID-19 and the renin-angiotensin system (RAS): A spark that sets the forest alight? Med Hypotheses. 2020, 144: 110231. doi:10.1016/j.mehy.2020.110231
32. Aleksova A, Ferro F, Gagno G, Cappelletto C, Santon D, Rossi M, Ippolito G, Zumla A, Beltrami AP, Sinagra G. COVID-19 and renin-angiotensin system inhibition: role of angiotensin converting enzyme 2 (ACE2) - Is there any scientific evidence for controversy? J Intern Med 2020; 288(4): 410-421. doi: 10.1111/joim.13101
33. Franz H. Messerli, George CM Siontis, Emrush Rexhaj. COVID-19 and Renin Angiotensin Blockers. Current Evidence and Recommendations. Circulation. 2020; 141: 2042–2044. doi: 10.1161/CIRCULATIONAHA.120.047022
34. D. Clark Files, Kevin W. Gibbs, Christopher L. Schaich et al. A Pilot Study to Assess the Circulating Renin-Angiotensin-System in COVID-19 Acute Respiratory Failure. American Journal of Physiology-Lung Cellular and Molecular Physiology 2021. https://doi.org/10.1152/ajplung.00129.2021
35. Christiansen CF, Pottegård A, Heide-Jørgensen U, et al. SARS-CoV-2 infection and adverse outcomes in users of ACE inhibitors and angiotensin-receptor blockers: a nationwide case-control and cohort analysis. Thorax 2021; 76: 370-379.

36. Kadakia KT, Beckman A.L, Ross JS. Leveraging Open Science to Accelerate Research; 2021. doi: 10.1056/NEJMp2034518
37. Klepikov I. Acute Pneumonia in Modern Healthcare and in the History of Medicine. Annals of Biological Research 2021; 12 (3): 31-34
38. Klepikov I. Acute pneumonia. New doctrine and first treatment results. Lambert Academic; 2020. Link: https://bit.ly/3uGDKhY
39. Huttner BD, Catho G, Pano-Pardo JR et al. COVID-19: don't neglect antimicrobial stewardship principles! Clinical Microbiology and Infection 2020; 26, 7: 808-810. doi:https://doi.org/10.1016/j.cmi.2020.04.024
40. Beović B, Doušak M, Ferreira-Coimbra J et al. Antibiotic use in patients with COVID-19: a 'snapshot' Infectious Diseases International Research Initiative (ID-IRI) survey. Journal of Antimicrobial Chemotherapy 2020; dkaa326. doi:https://doi.org/10.1093/jac/dkaa326
41. Rawson TM, Moore LSP, Zhu N, 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]. Clin Infect Dis 2020; ciaa530. doi:10.1093/cid/ciaa530
42. Kim D, Quinn J, Pinsky B et al. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA 2020; 323: 2085–6.
43. Guggenbichler S, Fey T and Guggenbichler JP Dramatic Increase of Multiresistant Microorganisms We are approaching the Postantibiotic Era? Integ Biomed Sci 2020; 6(1): 74-83.
44. Ocampo-Torres Moisés, et al. Characterization of Mortality by Covid-19 in a Health System in Central Mexico". EC Pulmonology and Respiratory Medicine 2020; 9.12: 20-22
45. Alejandro David Bendala Estrada, Jorge Calderón Calderón Parra, Eduardo Fernández Carracedo et al. Inadequate Use of Antibiotics in the Covid-19 Era: Effectiveness of Antibiotic Therapy 2021; PREPRINT (Version 1) available at Research Square. https://doi.org/10.21203/rs.3.rs-244297/v1