



The host response in different aetiologies of community-acquired pneumonia: Potential new targets for adjunctive treatments?

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Lower respiratory tract infections, including pneumonia, are the leading infectious cause of death with more than 2.3 million deaths in 2016.¹ This has been a fact ever since Sir William Osler, in 1918, observed that pneumonia had replaced tuberculosis as the leading cause of death.² Since the emergence of the SARS-CoV-2 virus in Wuhan, China in November 2019, and the resulting pandemic with more than 1.4 million deaths worldwide one year later,³ the importance of acute respiratory infections for mankind has once again been emphasized.

Treatment failure in patients with pneumonia seems to be associated with an excessive inflammatory response and therefore several potential adjunctive therapies to the “conventional” antimicrobial agents has been investigated.⁴ Especially corticosteroids, which modulate a vast range of physiological processes, have been investigated as a potential adjunct to conventional community-acquired pneumonia treatment,⁴ but their efficacy in pneumonia treatment remain controversial and it is not recommended as routine use.

There may be several reasons why corticosteroid studies have shown divergent results, but a lack of knowledge of the immune host response to specific pathogens may be an important factor. This is illustrated by the fact that in hospitalized patients with Covid-19 who require oxygen, corticosteroid treatment improves survival³ while in patients with influenza corticosteroid treatment may be associated with significantly higher mortality.⁵

Due to the worldwide effect of the COVID-19 pandemic a vast amount of research has been performed including several trials focusing on immunomodulatory treatment.^{3,6} Simply, transferring findings from these studies to pneumonia due to other pathogens is tempting, but as illustrated above this may not be the correct approach. Therefore, studies directly comparing the pathophysiology response across different aetiologies are needed.

In a recent issue of *eBioMedicine* Schuurman et al. compared the pathophysiology response to common pneumonia pathogens, such as *Streptococcus pneumoniae*, Influenza and SARS-CoV-2.⁷ The authors measured 74 plasma biomarkers and stratified them into several pathophysiological domains-antiviral response, vascular response and function, coagulation, systemic inflammation, and immune checkpoint markers.⁷ Although the authors were challenged by the well-known fact that identifying the causative pathogen in pneumonia is notoriously difficult (120/265 patients without a known causative pathogen) the authors provide us with valuable new information on the pathophysiology response across different aetiologies.

In patients with COVID-19 a high incidence of venous thromboembolism has been reported.³ The occurrence of venous thromboembolism has been associated with hyperinflammation, leading to a pro-thrombotic state with increased D-dimer.³ Interestingly, Schuurman et al. found no indications of large differences in soluble coagulation biomarkers across aetiologies.⁷ This could be an indication that the activation of the coagulation system is an “universal” response during pneumonia. In fact, it has been reported that patients with pneumonia have a 5-fold increased risk of venous thrombosis within 1 year after the episode of pneumonia.⁸

Furthermore, the authors found a higher angiotensin-2/1 ratio in all aetiologies compared to COVID-19. Angiotensin 1 and 2 act through their tyrosine kinase receptors.⁹ A high level of angiotensin-2 is associated with vascular leakage while angiotensin-1 is associated with reduced vascular permeability and hence a high angiotensin-2/1 ratio is a marker of an impaired endothelial barrier.⁹ In patients with pneumonia (mixed aetiologies) a high level of angiotensin-2 has been associated with increased 28-day mortality¹⁰ and in mice with severe pneumococcal pneumonia treatment with angiotensin-1 prevented lung injury.¹⁰ In addition, blockade of angiotensin-2 with monoclonal antibodies reduced sepsis induced vascular leakage in mice.⁹ Treatment with Imatinib, a tyrosine kinase inhibitor, may lead to improved survival in patients with COVID-19.⁶ Therefore, it is possible that angiotensin-2/1 may represent a target for intervention across aetiologies and because of the higher ratio of angiotensin-2/1 observed in non-COVID-19 pneumonia

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it might be an even better target in patients with non-COVID-19 pneumonia.

One of the major strengths of the study by Schuurman et al. is the large number of measured biomarkers which allowed the authors to stratify the response into different pathophysiological domains. Further, the authors have compared the response across 3 "leading" pneumonia pathogens ensuring a high degree of generalizability. However, as mentioned previously, there is large part of patients without an identified causative pathogen which together with the relatively small sample size may have affected some of the comparisons.

The lung is an organ which is optimized for gas exchange and hence it is vulnerable for an excessive inflammatory response. To design future specific anti-inflammatory strategies and thereby improve the outcomes of patients with pneumonia there is a need for research focusing on differences and similarities in the immune response against both viral and bacterial pathogens. The present study has such a focus point and it contributes to our understanding of the pathogen-specific host response in pneumonia.

Contributors

AVJ has drafted and revised the manuscript solely.

Declaration of interests

None to declare.

References

- 1 Wang H, Abajobir AA, Abate KH, et al. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet North Am Ed*. 2017;390:11084–1150. [https://doi.org/10.1016/S0140-6736\(17\)31833-0](https://doi.org/10.1016/S0140-6736(17)31833-0).
- 2 Osler W, McCrae T. *The Principles and Practice of Medicine*. New York, London: D. Appleton and Company; 1920.
- 3 Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. *Eur Respir J*. 2021;57:2100048. <https://doi.org/10.1183/13993003.00048-2021>.
- 4 Sibila O, Rodrigo-Troyano A, Torres A. Nonantibiotic adjunctive therapies for community-acquired pneumonia (corticosteroids and beyond): where are we with them? *Semin Respir Crit Care Med*. 2016;37:913–922. <https://doi.org/10.1055/s-0036-1593538>.
- 5 Lansbury L, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2019;2(2):1–77. <https://doi.org/10.1002/14651858.CD010406.pub2>.
- 6 Aman J, Duijvelaar E, Botros L, et al. Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial. *Lancet Respir Med*. 2021;9:957–968. [https://doi.org/10.1016/S2213-2600\(21\)00237-X](https://doi.org/10.1016/S2213-2600(21)00237-X).
- 7 Schuurman AR, Reijnders TDY, van Engelen TSR, et al. The host response in different aetiologies of community-acquired pneumonia. *EBioMedicine*. 2022;81:104082. <https://doi.org/10.1016/j.ebiom.2022.104082>.
- 8 Ribeiro DD, Lijfering WM, Van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Pneumonia and risk of venous thrombosis: results from the MEGA study. *J Thromb Haemost*. 2012;10:1179–1182. <https://doi.org/10.1111/j.1538-7836.2012.04732.x>.
- 9 Joffe J, Hellman J, Ince C, Ait-Oufella H. Endothelial responses in sepsis. *Am J Respir Crit Care Med*. 2020;202:361–370. <https://doi.org/10.1164/rccm.201910-1911TR>.
- 10 Gutbier B, Neuhau A-K, Reppe K, et al. Prognostic and pathogenic role of angiotensin-converting enzyme 1 and -2 in pneumonia. *Am J Respir Crit Care Med*. 2018;198:220–231. <https://doi.org/10.1164/rccm.201708-1733OC>.