EDITORIAL

Pneumonia in the face of COVID-19

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In this issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology the Global Coalition Against Pneumonia draws attention to World Pneumonia Day on November 12 in two accompanying editorials (12, 28). This annual event recognizes the global burden of what William Osler once called not only the most widespread and fatal of all acute infectious diseases, but the “captain of the men of death” (26). While this statement has probably been true since the beginnings of humankind, the threat of pneumonia tends to receive specific attention during global outbreaks such as the ongoing coronavirus disease 2019 (COVID-19) pandemic or the Spanish flu 1918–1920. However, it is important to recognize that even before severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), pneumonia was already the most frequent cause of death among all infectious diseases in both adults and infants (30).

Unavailability of vaccines and antimicrobials for the prevention and treatment of pneumonia contributes to high morbidity and mortality in developing countries. Further, antimicrobial drug resistance, particularly in pathogens causing pneumonia (27), is a growing challenge worldwide. As a result of new resistance mechanisms and their rapid distribution, multidrug-resistant bacteria are spreading globally. Recent studies estimate that within the United States and the European Union, ~23,000 and 33,000 patients, respectively, die each year from an infection with a resistant pathogen (8, 9). As far more people are infected, the socio-economic impact of multidrug resistance is enormous and growing steadily. While novel antibiotics are thus in dire need, respective research and development programs in infectious diseases have been minimized by the pharmaceutical industry in the past years (23).

Importantly, however, in most fatal cases pneumonia is caused by bacteria without antimicrobial drug resistance and despite patients being treated with appropriate antibiotics. In these cases, killing of bacteria is not sufficient to prevent lung injury as a result from the abundance of pathogen-associated molecular patterns (PAMPs) and exotoxins, the infiltration and activation of inflammatory cells, the release of cytokines, lipid mediators, and extracellular traps, and the activation of complement and coagulation cascades. The resulting disruption of the alveolo-capillary barrier causes extravasation of proteinaceous fluid into the alveolar space, impairing lung mechanics and gas exchange and culminating in the clinical picture of the acute respiratory distress syndrome (ARDS) with mortality rates of 35–46% (2). Simultaneously, barrier failure promotes the systemic dissemination of infection and inflammation, the development of sepsis, and progressive multiorgan involvement. Even in the absence of overt ARDS, pneumonia may result in distinct acute or chronic systemic organ injury, evident, e.g., as direct cardiac damage by bacterial invasion into the myocardium and formation of microscopic lesions finally leading to cardiac scarring (25) or as atherosclerotic plaque formation in systemic arteries that can be causally linked to pulmonary inflammation (4).

Notably, this sequence of events also adequately describes disease progression in the current COVID-19 pandemic. Following initial infection of the airways with SARS-CoV-2, an inflammatory response emerges that—if uncontrolled—can disseminate throughout the body and cause systemic organ involvement. While occasional reports have highlighted the detection of viral RNA or virus-like particles in systemic organs such as the kidney or the gastrointestinal tract (5, 24), it is important to note that viral infection of and replication in systemic organs has so far—to our knowledge—not been demonstrated. The presence of viral RNA or particles in systemic organs may in fact be attributable to infiltration of macrophages with a positive SARS-CoV-2 signal from the lung, e.g., into the heart, which however does not implicate that these viral particles may be infectious (18). As such, systemic dissemination of COVID-19 and acute or chronic injury and functional impairment of the heart, kidney, or central nervous system are likely the result of an out-of-proportion immune response that involves the parallel activation of related cascades such as the complement and coagulation system. Consistently, biomarker studies by us and others have identified cytokines such as interleukin-6 or complement factors as circulating biomarkers in COVID-19 with plasma concentrations increasing as a function of disease severity (15, 19).

At present, COVID-19 is more deadly than influenza, and in contrast to the latter no SARS-CoV-2 vaccine has yet been proven to be both efficacious and safe. But even when a vaccine
would become broadly available, this would likely not be the end of the present pandemic—because not all people would get vaccinated, because vaccination may not be effective in a considerable percentage, and because immunity may only be temporary. Notably, vaccines against influenza virus or Streptococcus pneumoniae have been available for many years, yet people still die from influenza or pneumococcal pneumonia. Hence, the problem of pneumonia will not be solved by antimicrobial strategies and vaccines alone. It is fair to assume that the same holds true for COVID-19. As such, it becomes ever more important to understand the “physiological” basis of pneumonia and to utilize this knowledge for the development of targeted adjunctive therapies to fight disease manifestation and dissemination. Besides aiming to control excessive inflammation and coagulation such adjunctive therapies may and should comprise strategies to stabilize the alveolo-capillary barrier and thus, not only to prevent permeability-type lung edema and subsequent hypoxemia, but also to limit the invasion of bacteria and the development of sepsis.

Barrier protection may in principle follow one of three general strategies: First, barrier-disruptive mediators may be antagonized by, e.g., neutralizing antibodies or receptor blockers. While this approach seems intuitive, it has proven not effective in clinical trials targeting specific cytokines or lipid mediators, presumably because barrier failure is not caused by a single disruptive agent but a combination of endogenous (and exogenous) factors acting on the alveolar epithelium and capillary endothelium. To overcome this limitation, a second strategy aims to target common cellular pathways of barrier disruption. This approach has been effectively realized, e.g., by antagonists against the multimodal cation channel transient receptor potential vanilloid 4 (TRPV4). Activation of TRPV4 seems to constitute a critical event in alveolo-capillary barrier failure in response to a range of different infectious or injurious stimuli including acid or chlorine gas induced injury, ventilator-induced lung injury, pneumococcal pneumonia, or cardiogenic lung edema (1, 20, 21, 32, 33). While an abundance of preclinical data highlight the potential of this approach, clinical studies still have to prove the validity of this concept in patients with pneumonia, COVID-19, or ARDS (17). Third, a group of endogenous mediators or derivatives have been identified that seem to exert barrier-protective effects largely independent of the underlying disease. These include but are not limited to sphingosine-1-phosphate, adrenomedullin, angiotensin-(1–7), or angiopoietin-1 (13, 14, 22, 29). Accordingly, several clinical trials presently aim to exploit this strategy for the fight against COVID-19 (NCT04375124, NCT04417036).

Importantly, barrier stabilization may no longer be effective once ARDS has occurred. Hence, it will be critical to identify patients at risk for barrier failure at an early disease stage. Of late, patient stratification by subphenotyping using latent class analyses has provided promising results in ARDS patients in that it allowed to differentiate patients who may or may not profit from specific interventions including ventilatory (6), fluid management (11), or pharmacological strategies (7). Similarly, the relatively slow development of COVID-19 from initial SARS-CoV-2 infection to overt ARDS has fueled the search for predictive biomarkers of disease progression and severity (10, 31). Yet at present, C-reactive protein and procalcitonin are still the most widely used biomarkers in community-acquired pneumonia, even though their shortcomings are well recognized (16). As such, better and innovative strategies for the stratification of pneumonia patients remain in dire need. Notably, such strategies should not focus primarily on the pathogen but on the individual host and its response to infection. Heterogeneity in genetic predisposition, comorbidities, medication, infectious pathogen, and the ensuing host response, however, make the discovery of a single common biomarker rather unlikely. As such, systems-medicine approaches based on -omics data (including genomics, epigenomics, transcriptomics, proteomics, lipidomics, glycomics, metabolomics, and microbiomics) may help identify composite signatures that better reflect this complexity and assist not only in patient stratification, but also in guided therapy and monitoring of treatment responses. In parallel, appropriate preclinical models including small and large animal models, human tissue, and human organoids are required to mimic all aspects of the disease, allowing for rigorous testing of novel treatment strategies in multidimensional systems (3).

Up to now, therapeutic concepts for the treatment of pneumonia have been largely driven by a pathogen-centric view based on the individual antibiotic spectrum. In contrast, the role of the host has been largely underestimated. The relevance of this role has become strikingly evident in the present COVID-19 pandemic where the same virus causes a wide range of disease severities that spans from asymptomatic infections to severe ARDS and fatal multiorgan dysfunction. The development of a more host-centric view, however, requires better mechanistic insights into pneumonia in terms of host defense, injury, and repair versus aggravation. In brief, we need to apply physiology to get a better understanding of pathology that may, hopefully, fuel novel therapies.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.W. and W.M.K. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

REFERENCES

1. Balakrishna S, Song W, Achanta S, Doran SF, Liu B, Kaelberer MM, Yu Z, Sui A, Cheung M, Leishman E, Eidam HS, Ye G, Willette RN, Thorneloe KS, Bradshaw HB, Matalon S, Jordt SE. TRPV4 inhibition counteracts edema and inflammation and improves pulmonary function and oxygen saturation in chemically induced acute lung injury. Am J Physiol Lung Cell Mol Physiol 307: L158–L172. 2014. doi:10.1152/ajplung.00065.2014.

2. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A. LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315: 788–800, 2016. doi:10.1001/jama.2016.0291.

3. Bonniaud P, Fabre A, Frossard N, Guignabert C, Inman M, Kuebler WM, Maes T, Shi W, Stampfli M, Uhlig S, White E, Witzenrath M, Bellaye PS, Crestani B, Eickelberg O, Feirenbach H, Guenther A, Jenkins G, Joos G, Magnus A, Maitre B, Maus UA, Reinhold P, Vermyo JH, Richeldi L, Kolb M. Optimising experimental research in respiratory diseases: an ERS statement. Eur Respir J 51: 1702133, 2018. doi:10.1183/13993003.02133-2017.

4. Brack MC, Lienau J, Kuebler WM, Witzenrath M. Cardiovascular sequelae of pneumonia. Curr Opin Pulm Med 25: 257–262, 2019. doi:10.1097/MCP.0000000000000584.
9. Centers for Disease and Control Prevention. Antibiotic/ Antimicrobial Resistance (ARC/AMR) (Online). https://www.cdc.gov/drugresistance/

10. Del Valle DM, Kim-Schulze S, Hsin-Hui H, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz T, Madduri D, Stock A, Marron T, Xie H, Patel MK, van Oeelen O, Rahman A, Kovalchuk P, Aberg E, Jagannath S, Mazumdar M, Charney A, Firpo-Betancourt A, Bories-Coulet P, Sigel K, Cordon-Cardo M, Parekh S, Merad M, Gnjatic S. An inflammatory cytokine signature helps predict COVID-19 severity and death (Preprint). medRxiv 2020. doi: 10.1101/2020.05.28.2115758.

11. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, Caffee CS. ARDS Network. ARDS Network. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy [Erratum in Am J Respir Crit Care Med 198: 1590, 2018]. Am J Respir Crit Care Med 195: 331–338, 2017. doi:10.1164/rccm.201603-0645OC.

12. Greenshade L. World Pneumonia Day during a global pneumonia pandemic: 12 November 2020. Am J Physiol Lung Cell Mol Physiol. In press. doi:10.1152/ajplung.00462.2020.

13. Guttber H, Neuhall AK, Ruppe K, Ehrler C, Haberberger R, Dietert KR, Gruber AD, Kummer W, Michalik L, Kuebler WM, Hocke AC, Szymanski K, Letsiu E, Lüth A, Schumacher F, Kleusner B, Mitchell TJ, Bertrams W, Schmeck B, Treue D, Klauschen F, Bauer TT, Tomnies M, Weissmann N, Hippenstiel S, Nitschke M, CAPNETZ and PROGRESS Study Groups. Prognostic and pathogenic role of angiopoietin-1 and -2 in pneumonia. Am J Respir Crit Care Med 198: 220–231, 2018. doi:10.1164/rccm.201710-1733OC.

14. Guttber H, Schönrock SM, Ehrler C, Haberberger R, Dietert KR, Gruber AD, Kummer W, Michalik L, Kuebler WM, Hocke AC, Szymanski K, Letsiu E, Lüth A, Schumacher F, Kleusner B, Mitchell TJ, Bertrams W, Schmeck B, Treue D, Klauschen F, Bauer TT, Tomnies M, Weissmann N, Hippenstiel S, Nitschke M, CAPNETZ and PROGRESS Study Groups. Sphingosine kinase 1 regulates inflammation and contributes to acute lung injury in pneumococcal pneumonia via the sphingosine-1-phosphate receptor 2. Cell Physiol Biochem 258: 267–28, 2017. doi:10.1007/978-3-030-00873-1.

15. Herold T, Junirinovic A, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, Klein M, Weinerberger T. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol 146: 128–136e24, 2020. doi:10.1016/j.jaci.2020.05.008.

16. Karakiolou M, Stolz D. Biomarkers in pneumonia-beyond procalcitonin. Int J Mol Sci 2020; 20: 2020. doi:10.3390/ijms20082003.

17. Kuebler WM, Jordt SE, Liedtke WB. Urgent reconsideration of lung edema as a preventable outcome in COVID-19; inhibition of TRPV4 represents a promising and feasible approach. Am J Physiol Lung Cell Mol Physiol 318: L1239–L1243, 2020. doi:10.1152/ajplung.00161.2020.

18. Lindner D, Fitzek A, Bräuning H, Alesheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, Blankenburg S, Pfeiffer M, Westermann D, Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol. doi:10.1001/jamacardio.2020.3551.

19. Messner CB, Demichev V, Wendisch D, Michalik L, White M, Freiwaldb A, Textoris-Taube K, Vernardis SI, Egger AS, Kleidt M, Ludwig D, Kilian A, Agostini F, Zeleznikai A, Thibeault C, Pfeiffer M, Hippenstiel S, Hocke A, von Kalle C, Campbell A, Hayward C, Forster DJ, Maroni M, Cilley KS, Kuebler WM, Mulleder M, Drosten C, Sittau M, Witzenrath M, Kurth F, Sandner LE, and Ralser M. Ultra-high-throughput clinical proteomics reveals classifiers of COVID-19 infection. Cell 171: 11–24e14, 2020. doi:10.1016/j.cell.2020.05.012.

20. Michalik L, Erfindana L, Weichtl U, van der Giet M, Liedtke W, Kuebler WM. Transient receptor potential vanilloid 4 and serum glucocorticoid-regulated kinase 1 are critical mediators of lung injury in overventilated mice in vivo. Anesthesiology 126: 300–311, 2017. doi:10.1097/ ALN.0000000000001443.

21. Michalik L, Kuebler WM. TRPV4-A missing link between mechanosensation and immunity. Front Immunol 11: 413, 2020. doi: 10.3389/fimmu.2020.00413.

22. Müller-Redetzky H, Lienau J, Sittau M, Witzenrath M. Therapeutic strategies in pneumonia: going beyond antibiotics. Eur Respir Rev 25: 516–524, 2015. doi:10.1183/20936496.2014.2013.

23. Norry SR, Nord CE, Finch R. European Society of Clinical Microbiology and Infectious Diseases. Lack of development of new anti-microbial drugs: a potential serious threat to public health. Lancet Infect Dis 5: 115–119, 2005. doi:10.1016/S1473-3099(05)70086-4.

24. Pelleg VIG, Laighehtemann M, Lindemeyer MT, Sperkache JP, Wong MN, Allweiss L, Chilla S, Heinemann A, Wanner N, Liu S, Braun F, Lu S, Pfeiffer S, Schröder AS, Edler C, Gross O, Glatzer M, Wichmann D, Wiech T, Kluge S, Puech K, Aeffebach M, Huber TB, Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med 383: 590–592, 2020. doi:10.1056/NEJMc2011400.

25. Reyes LF, Restrepo MI, Hinjosa CO, Soni NJ, Anzueto A, Babu BL, Gonzalez-Mendez A, Caruana N, Rodriguez A, Jhingran A, Chalmers JD, Aliberti S, Sibilia O, Winter VT, Coabon JL, Giavedoni LD, Dela Cruz CS, Waterer GW, Witzenrath M, Sittau M, Dube PH, Orihuela CJ. Severe pneumococcal pneumonia causes acute cardiac toxicity and subsequent
cardiac remodeling. Am J Respir Crit Care Med 196: 609–620, 2017.
doi:10.1164/rccm.201701-0104OC.

26. Reynolds AR. Pneumonia: the new “captain of the men of death”: its increasing prevalence and the necessity of methods for its restriction. JAMA XL: 583–586, 1903. doi:10.1001/jama.1903.92490090031001k.

27. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. Euro Surveill 13: 13, 2008.

28. Swedberg E, Shah R, Sadrudin S, Soeripto J. Saving young children from forgotten killer: pneumonia. Am J Physiol Lung Cell Mol Physiol. In press. doi:10.1152/ajplung.00471.2020.

29. Walther T, Kuebler WM. Don’t judge too RASHly: the multifaceted role of the renin-angiotensin system and its therapeutic potential in COVID-19. Am J Physiol Lung Cell Mol Physiol 318: L1023–L1024, 2020. doi:10.1152/ajplung.00118.2020.

30. World Health Organization. Pneumonia. Fact Sheet (Online). https://www.who.int/en/news-room/fact-sheets/detail/pneumonia [2 August 2019].

31. Yang Y, Shen C, Li J, Yuan J, Wei J, Huang F, Wang F, Li G, Li Y, Xing L, Peng L, Yang M, Cao M, Zheng H, Wu W, Zou R, Li D, Xu Z, Wang H, Zhang M, Zhang Z, Gao GF, Jiang C, Liu L, and Liu Y. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. J Allergy Clin Immunol 146: 119–127e14, 2020. doi:10.1016/j.jaci.2020.04.027.

32. Yin J, Hoffmann J, Kaestle SM, Neye N, Wang L, Baehrle J, Liedtke W, Wu S, Kuppe H, Pries AR, Kuebler WM. Negative-feedback loop attenuates hydrostatic lung edema via a cGMP-dependent regulation of transient receptor potential vanilloid 4. Circ Res 102: 966–974, 2008. doi:10.1161/CIRCRESAHA.107.168724.

33. Yin J, Michalick L, Tang C, Tabuchi A, Goldenberg N, Dan Q, Awwad K, Wang L, Erinhanda L, Nouailles G, Witzenrath M, Vogelzang A, Lv L, Lee WL, Zhang H, Rotstein O, Kapus A, Szaszi K, Fleming I, Liedtke WB, Kuppe H, Kuebler WM. Role of transient receptor potential vanilloid 4 in neutrophil activation and acute lung injury. Am J Respir Cell Mol Biol 54: 370–383, 2016. doi:10.1165/rcmb.2014-0225OC.