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New insights into pneumonia in patients on prolonged mechanical ventilation: need for a new paradigm addressing dysbiosis

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Ventilator-associated pneumonia (VAP) is related to poor outcomes and is most commonly treated with the use of antibiotic therapy in ICUs. The Infectious Diseases Society of America defined VAP as a new lung infiltrate of infectious origin occurring ≥ 48 h after endotracheal intubation.[1] Systemic antibiotic use may increase the risk of VAP by depleting commensal microorganisms and selecting gram-negative bacteria that may have multiple mechanisms of resistance. Traditional endotracheal aspirate cultures are unspecific and lead to widespread use of antimicrobial agents. As an alternative to systemic antibiotics, aerosolization has been suggested,[2] despite the current lack of evidence of reduction in mortality or in the number of days on mechanical ventilation (MV).[3]

In the present issue of the *Jornal Brasileiro de Pneumologia*, Núñez et al.[4] address the occurrence of VAP in tracheostomized patients on prolonged MV (median = 56 days). The authors reported 30-day and 90-day mortality rates of 30.0% and 63.7%, respectively. The SOFA score and the use of vasoactive drugs were significantly associated with 30-day mortality, whereas advanced age, SOFA score, use of vasoactive drugs and COPD were associated with 90-day mortality.[4] *Pseudomonas aeruginosa* was confirmed as the major pathogen isolated, especially in COPD patients. Interestingly, although *Acinetobacter baumannii* was isolated from microbiological cultures from various patients,[4] this was not associated with mortality, suggesting that patients die of pneumonia as an ultimate event rather than as a consequence.

The reason why most episodes of VAP develop within the first 10 days of MV is thought-provoking. Recent metagenomic technologies offer the potential to better the understanding of the interaction among the respiratory microbiota, immune response, and underlying conditions of individuals. Such advances call into question the traditional view of the pathogenesis of pneumonia—that is, the view that pneumonia is caused by a single organism and is a consequence of microaspiration. Metagenomic studies have revealed that other bacteria (anaerobes or "uncultivable" organisms) are frequently associated with the putative major pathogen[5] and, as a new concept, that the development of VAP is a combination of dysbiosis and failure of the host immune response. Because ARDS and VAP are associated with different respiratory microbiomes, a better understanding of this interplay should be of value for ARDS and VAP management strategies. Pathogens are introduced into a pre-existing complex microbial community, which facilitates or hinders pathogen growth and ultimately determines infection. A better understanding of the microbiota using metagenomics is required in order to improve treatment and for effective prevention of VAP.[6] The microbiome has a critical role in immune activation and host defense in patients on prolonged MV.

VAP should be differentiated from ventilator-associated tracheobronchitis,[1] which is more common and represents an intermediate step between airway dysbiosis and VAP development,[2] leading to the overuse of antibiotics, which, in turn, increases the risk of emergence of multidrug resistant pathogens.[5,7,8] In addition, most patients on prolonged MV have already had one or more episodes of infection or relapse caused by the same pathogen. Our group[9] assessed *P. aeruginosa* colonization in patients on MV using pulsed field gel electrophoresis and found that 18% of the individuals had recurrent pneumonia that were not reinfection cases, but relapses caused by the same clone with more resistant phenotypes. It remains to be determined whether this is also true for colonization with *A. baumannii*.

To break the cycle of antibiotic overuse, antimicrobial resistance, and dysbiosis of the host microbiome, a new paradigm is required. Changes in microbiota may be a lung response to chronic disease and may render the host most susceptible to infection. Flanagan et al.[10] were the first to sequence the *16s rRNA* gene from endotracheal aspirate specimens in ventilated patients with *P. aeruginosa* colonization: the most common bacteria belonged to the phyla Firmicutes, Bacteroidetes, and Proteobacteria. Antibiotic therapy reduced microbiota diversity and induced a predominance of *P. aeruginosa*.[10] According to most studies, there is an interaction between bacterial and fungal communities, and modifications in one community affect the other, whereas their interaction with the virome is yet to be elucidated. Although there is no impact on mortality, bronchial colonization by the phylum Ascomyta (*Candida* spp.) is a well-known independent risk factor for *Pseudomonas*-related VAP.[11]

In summary, the traditional paradigm of VAP (that it is a disease caused by a single bacterial pathogen acquired thorugh microaspiration) needs to be replaced by a hypothetical model in which VAP would be associated with dysbiosis. The gut microbiome contributes to protection against opportunistic pathogens. Enriching the microbiota with members of the phylum Proteobacteria, which are considered commensals, increases serum IgA levels.[12]

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Thus, lung dysbiosis combined with gut dysbiosis might induce local immunosuppression and lung dysfunction, facilitating the occurrence of VAP. The role of the Th17 response provoked by segmented filamentous bacteria, which provides protection from staphylococcal pneumonia, seems crucial. These observations are not only of academic interest. Early identification of patients with dysbiosis associated with a higher risk of developing VAP is an unmet clinical need, and this should lead to innovative, targeted preventive strategies.

Whereas whales and dolphins are protected from the consequences of pharyngeal and gut aspiration, both remain susceptible to pneumonia, a common cause of death among cetaceans. The time has come to consider the microbiome-regulated host immunity as a pivotal component of the physiopathology of VAP.

REFERENCES

1. Niederman MS. Hospital-acquired pneumonia, health care-associated pneumonia, ventilator-associated pneumonia, and ventilator-associated tracheobronchitis: definitions and challenges in trial design. Clin Infect Dis. 2010;51 Suppl 1:S12-S17. https://doi.org/10.1086/653035
2. Koulenti D, Arvaniti K, Judd M, Lalos N, Tjoeng I, Xu E, et al. Ventilator-Associated Tracheobronchitis: To Treat or Not to Treat?. Antibiotics (Basel). 2020;9(2):51. https://doi.org/10.3390/antibiotics9020051
3. Sole-Lleonart C, Roberts JA, Chastre J, Poulakou G, Palmer LB, Blot S, et al. Global survey on nebulization of antimicrobial agents in mechanically ventilated patients: a call for international guidelines. Clin Microbiol Infect. 2016;22(4):359-364. https://doi.org/10.1016/j.cmi.2015.12.016
4. Núñez SA, Roveda G, Zárate MS, Emmerich M, Verón MT. Ventilator-associated pneumonia in patients on prolonged mechanical ventilation: description, risk factors for mortality, and performance of the SOFA score. J Bras Pneumol. 2021;47(3):20200569.
5. Emonet S, Lazarevic V, Leemann Refondini C, Gaïa N, Leo S, Girard M, et al. Identification of respiratory microbiota markers in ventilator-associated pneumonia. Intensive Care Med. 2019;45(8):1082-1092. https://doi.org/10.1007/s00134-019-05660-8
6. Fromentin M, Ricard JD, Roux D. Respiratory microbiome in mechanically ventilated patients: a narrative review. Intensive Care Med. 2021;47(3):292-306. https://doi.org/10.1007/s00134-020-06338-2
7. Ahmed QA, Niederman MS. Respiratory infection in the chronically critically ill patient. Ventilator-associated pneumonia and tracheobronchitis. Clin Chest Med. 2001;22(1):71-85. https://doi.org/10.1016/S0272-5231(05)70026-5
8. Rello J, Lisboa T, Koulenti D. Respiratory infections in patients undergoing mechanical ventilation. Lancet Respir Med. 2014;2(9):764-774. https://doi.org/10.1016/S2213-2600(14)70171-7
9. Rello J, Mariscal D, March F, Jubert P, Sanchez F, Valles J, et al. Recurrent Pseudomonas aeruginosa pneumonia in ventilated patients: relapse or reinfection?. Am J Respir Crit Care Med. 1998;157(3 Pt 1):912-916. https://doi.org/10.1164/ajrccm.157.3.9703014
10. Flanagan JL, Brodie EL, Weng L, Lynch SV, Garcia O, Brown R, et al. Loss of bacterial diversity during antibiotic treatment of intubated patients colonized with Pseudomonas aeruginosa. J Clin Microbiol. 2007;45(6):1954-1962. https://doi.org/10.1128/JCM.02187-06
11. Azoulay E, Timsit JF, Tafflet M, de Lassence A, Darmon M, Zahar JR, et al. Candida colonization of the respiratory tract and subsequent pseudomonas ventilator-associated pneumonia. Chest. 2006;129(1):110-117. https://doi.org/10.1378/chest.129.1.110
12. Wilmore JR, Gaudette BT, Gomez Atria D, Hashemi T, Jones DD, Gardner CA, et al. Commensal Microbes Induce Serum IgA Responses that Protect against Polymicrobial Sepsis. Cell Host Microbe. 2018;23(3):302-311.e3. https://doi.org/10.1016/j.chom.2018.01.005