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Editorial

What is the Research Agenda in Ventilator-associated Pneumonia?

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Ventilator-associated pneumonia (VAP) diagnosis is a challenge because gold standard is lacking and confirmation is based on respiratory cultures and techniques with important limitations. Presentation with clinical signs of community-acquired pneumonia is unusual, bacteremia is uncommon, onset undetermined, and it usually presents as progressive hypoxemia (or increase in vasoactive drugs) in a ventilated patient with purulent respiratory secretions, being a post-hoc diagnosis after ruling out other infectious sites [1]. Half episodes are caused by unidentified organisms and heterogeneity in diagnosis is huge, with important geographical differences in strategies and pathogens [2,3]. Moreover, microbiologic tests may require hours to days of incubation and, classically, additional time is needed to identify organisms and further determination of susceptibility. For that reason, in general, antimicrobial therapy is empirical and often requires broad spectrum with subsequent emergence of antimicrobial resistance. Also, and more importantly, it is essential to develop fast diagnostic techniques and investigate airways microbe population that can immediately predict causative microorganisms without specimen processing. In this context, still remain many important research questions which need to be answered (Table 1).

In this issue of the International Journal of Infectious Diseases, Prat and Lacoma (ref) describe the clinical role of bacteria in the respiratory tract and review novel therapeutic approaches. Its excellent review is welcome because contains interesting considerations that can help to answer some of the formulated questions.

We agree with the authors that the role of clinical microbiologists is not limited to report a laboratory result; their expertise in laboratory diagnostic methods, susceptibility testing and interpretation of microbiological results go beyond that and should be taken for the optimal management of patients. In our opinion, a team working with fluent communication is highly recommended for optimal management; indeed, all microbiological results should be interpreted based on patient comorbidities, period of hospitalization, previous antibiotics and clinical presentation (hypoxemia) and images [4]. To detect bacteria in a respiratory sample does not mean an infection. Even if presumed, we have to translate it to the context patient before taking therapeutic decisions. We disregard decisions based only on microbiologic findings.

In this scenario, what is the optimal diagnostic approach for VAP? The recent Guidelines published by the Infectious Diseases Society of America/The American Thoracic Society (IDSA/ATS) provide recommendations for diagnosis and treatment of adults with Hospital-acquired (HAP) and VAP [5]. These guidelines suggest performing, with low quality evidence, noninvasive samples (endotracheal aspiration) with semiquantitive cultures for VAP diagnosis. Once again, a personalized approach is required; we agree with the recommendation in the use of noninvasive samples because there is low evidence of superiority on outcomes of invasive samples in non-immunocompromised patients; however, based in our experience, quantitative methods (that report number

Table 1
Top 25 Questions in the Research Agenda for VAP

1) What is the role of clinical microbiologists in VAP diagnosis?
2) What is the best diagnostic paradigm for VAP?
3) What time is acceptable for rapid diagnostic tests?
4) What is the duration of prior antibiotic exposure influencing identification and outcome?
5) How to differentiate between infection vs. colonization of lower respiratory tract?, 6) Is it relevant to differentiate VAP from ventilator-associated tracheobronchitis (VAT)?
7) What is the role of respiratory viruses in VAP?
8) Are chest-X rays needed or can be replaced by lung ultrasounds?
9) What is the role of biomarkers and 'omics', if any, in diagnosis?
10) Patients with tracheostomy and endotracheal tubes are comparable?
11) Adults data can be transferred to mechanically ventilated children?
12) What is the role of hypoxemia in the decision-process making?
13) How to stratify (for severity and benchmarking) different VARI and its influence in diagnosis?
14) How to optimize diagnosis to increase patient enrollment in randomized clinical trials?
15) What is the cost-efficacy of new diagnostic tests?
16) When is the VAP onset?
17) Does techniques used in reference centers can be applied in non-university hospitals.
18) What diagnosis strategy should be implemented in low-income and middle-income countries?
19) What is the contribution of identifying virulence factors in diagnosis of VAP?
20) Are new diagnostic tools improving outcomes and justifying increasing costs?
21) How predetermined colonization pressure influences diagnosis?
22) Is feasible to identify pneumonia onset with anticipation for pre-emptive therapy?
23) What is the contribution of surveillance to diagnosis?
24) Is diagnosis using a signature in breath expired metabolites a non-invasive technique contributing to better identification?
25) What are the responsible agents for episodes with unidentified organisms and how to reduce its prevalence?

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of bacterial colonies) should be preferred for VAP management because they are associated with high specificity and informs on bacteria burden which correlates with probability of infection [4]. However, immunocompromised patients require brochoalveolar lavage and lung transplants [6] might benefit of a transbronchial biopsy. We also endorse the use of E-test antibiotic strips applied directly to respiratory tract samples. Bouza et al., [7] reported that use of rapid E-test was associated with increased administration of appropriate antimicrobial therapy and reduced the report of antimicrobial susceptibility in 1.4 days (compared with 4.2 days for those using standard diagnostic methods). Then, the difficulty in the differentiation between infection vs. colonization remains a challenge nowadays. This represents, in our opinion, a key point in the research agenda in VAP. The introduction of polymerase chain reaction (PCR) tests has increased the ability to detect microorganisms in clinical samples, including those difficult to grow. Adding *mecA* identification to specimens with Gram-positive cocci (or *GenExpert®* to Gram-negative specimens) is already an advance [8] in this way. However, differentiation between colonization, active infection or excretion of non-viable microorganisms remains an open issue with newer molecular techniques. Novel technologies such as gene expression diagnostics [9] and also the study of respiratory microbiome are very promising tools that could allow us to enter into the era of ''personalized medicine''. Quantitative techniques might split colonization from infection. We strongly believe that only point-of-care tests, available within two hours, justify increasing costs, being able to modify outcomes. Introducing molecular tests require a new paradigm focusing on phenotypes rather than the organism, and trials are needed to measure the impact on appropriate antibiotic use, stewardship, time to resolution and period of MV as primary end-points. Microarrays are the most frequently used gene expression platform, being a promising tool for improving diagnosis in Lower Respiratory Tract Infection (LRTI), demonstrating its usefulness in the differentiation of bacterial and viral infections [10,11]. This technique is based on the immune response of the patient against the pathogen rather than detection of the microorganisms. The human microbiome is also a new non-culture-based technique that has been developed to characterize the entire population of microbes resident on the body surfaces. Recent studies have shown that investigation of the respiratory microbiome is an emerging field, and these findings may provide a different vision about respiratory diseases [12,13], suggesting that airways have a microbiome that varies from health to disease [14]. Understanding the factors that affect the composition of the lower airway microbiota in VAP will help us to look for new therapeutics and diagnosis challenges to improve outcome in this patients.

Another factor that should be considered in the research agenda in VAP is the differentiation between bacteria and respiratory viruses. What is the role of respiratory viruses in the development of VAP? This question has not yet been answered. After the 2009 influenza A (H1N1) pandemic it was established the importance of this virus causing pneumonia [15]. However, the role of respiratory virus in the development of VAP is still underestimated and only few studies analyze severe pneumonia and viral etiology. In the study performed in Finland by Karhu et al., [16], it was found a viral etiology of severe pneumonia in 24 patients (49%). Although, a viral etiology is currently recognized as a cause of severe pneumonia, no recommendation was done in the 2016 IDSA/ATS Guidelines [5]. In our opinion, we also need more studies to understand the role of cytomegalovirus and herpes virus [17,18] in ventilated patients.

Biomarkers are another piece of the VAP diagnosis that need more research effort. The 2016 IDSA/ATS guidelines recommended avoid performing biomarkers for diagnosis. Sequential use of old and newer biomarkers is more promising [19], particularly to anticipate poor resolution, and more studies are needed, enclosing metabolomics in breath condensate of the espiratory tube.

Current interest emerges in identifying ventilator-associated tracheobronchitis (VAT) and differentiating from VAP, because it is increasing MV period [6]. Indeed, it is treated with aerosolized antibiotics in many ICUs [20]. Chest radiographs are expensive, time-consuming and difficult to assess, and bedside ultrasounds [21] can replace it in trained sites, because they have additional benefits when performed bedside. We believe that the concept of ventilator-associated respiratory infections (VARI) has advantages and in the decision process it might be more important the degree of hypoxemia rather than chest images [1]. Finally, as documented by Peña-Lopez et al in children [22], where limited literature is available, differences between artificial airways (tracheostomy or endotracheal tube) should not be missed in VARI.

In conclusion, the research agenda should focus on a new paradigm focusing on antibiotic susceptibility rather than organisms. Speed is life, so in addition to Gram stain, what molecular tests (and biomarkers) can contribute to improve diagnosis with management implications within the first two hours after diagnosis need to be identified. This is not only of academic interest, due the current scenario of limited antimicrobial options and the urgent need to improve enrolment[23] in HAP/VAP clinical trials.

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