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LASTING LEGACY IN INTENSIVE CARE MEDICINE

Bronchoscopy for diagnosis of ventilator-associated pneumonia

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The debate regarding invasive diagnostic techniques for the diagnosis of ventilator-associated pneumonia (VAP) has been alive for (too) many years. Recent major guidelines differ in the approach to the diagnosis of VAP. While American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines suggest the use of endotracheal aspirate samples [1], other major international guidelines advocate the use of bronchoscopy and invasive techniques for improvement of diagnosis accuracy [2]. This has resulted in various countries, healthcare systems, and individual clinicians being still in doubt in identifying the best method for the diagnosis of ventilator-associated pneumonia (VAP). Therefore, practicing a more individualized approach would ultimately benefit patient's care. A recent meta-analysis [3] found that endotracheal aspirate (ETA) had a higher sensitivity than bronchoalveolar lavage (BAL) (75.7 vs. 71.1%), but a much poorer specificity (67.9 vs 79.6%).

The crux of the debate, acknowledged by the proponents of both recommendations, is that clinical findings suggesting infection (fever, leucocytosis, changing radiographic infiltrates, etc.) are frequently observed in ventilated patients both with and without VAP, making clinical diagnosis neither specific nor sensitive. Lung histology, recognized as the best standard for determining the presence of pneumonia, requires documentation inflammation of the alveolar spaces with an intense infiltration of neutrophils, fibrinous exudates and cellular debris, particularly around terminal bronchioles. Because bronchoalveolar lavage (BAL) collects cells and fluid that line the bronchioloalveolar compartment of a large lung area (approximately one million alveoli when using a 120 mL BAL), it is currently the only tool capable of documenting the presence or absence of an infection at this level, as well as the presence of a potential pathogen. Assessment of alveolar neutrophilia helps to rapidly exclude bacterial pneumonia in critically ill patients with a negative predictive value approaching 100% when a BAL neutrophil percentage of less than 50% is paired with a negative Gram stain. The presence of intra- and extracellular bacteria in neutrophils and macrophages adds further early support to the presence of pneumonia, while high BAL levels of mediators, such as interferon and IL-8, correlate with the host inflammatory response [4].

A growing number of rapid diagnostic techniques (RDTs) using biomolecular approaches, including quantitative and/multiplex polymerase chain reaction and/or matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), are now available for endotracheal aspirates (ETA) and BAL specimens [5]. These RDTs allow rapid detection of a broad array of respiratory pathogens, including bacteria, yeast, moulds, viruses, and mycobacteria, with the potential to optimize empiric antimicrobial treatment. These platforms are now marketed by several companies and can be routinely used in most microbiological laboratories [6]. These new technologies, when applied to a BAL specimen and coupled with strong antibiotic stewardship programmes, might have the potential to reduce the time to appropriate antimicrobial therapy in patients infected with multidrug-resistant (MDR) pathogens, as well as help to prescribe more targeted antibiotics while avoiding broad-spectrum regimens. To date, no prospective interventional studies have documented that these

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tests lead to better outcomes (lenght of stay, mortality). A finite panel of pathogens and resistance markers will not allow RDTs to completely supplant traditional microbial identification methods and antimicrobial susceptibility testing. However, RDTs are complementary to traditional quantitative culture methods for pathogens requiring specialized media (e.g. *Legionella* spp., *Mycoplasma* spp.) and for samples obtained after initiation of antibiotics, in which quantitative cultures may be negative or grow below diagnostic thresholds.

Two major challenges for routine use of BAL to diagnose VAP have been brought out by research. The first and easiest to address is technical issues. Bronchoscopy is one of the most transformative diagnostic techniques in pulmonary medicine (among the stethoscope, pulmonary function tests, and chest radiography); however, it suffers from less attention to detail than the others. Earliest criteria for BAL were developed for use in assessing interstitial lung diseases, but standards for VAP diagnosis have been established for decades. Several components are critical for accuracy when used for VAP: (1) wedging into a bronchus with complete isolation of that airway from the rest of the central airways. This allows the instilled saline to fill the distal airways down to the alveolar level; (2) discarding the return from the initial 20–30 ml aliquot of saline which disproportionately contains bronchial secretions contaminating the bronchoscope channel during passage through the endotracheal tube and proximal central airways. Minimizing suctioning during passage and delaying airway inspection until after the BAL is obtained also minimize this contamination. These proximal secretions are more likely to have growth on culture due to airway colonization and even increased proportion of neutrophils compared to a true BAL sample. This aliquot can be used for diagnosis of purulent tracheobronchitis and for fungal, tuberculosis, and viral studies, which are not affected by tracheal colonization; (3) using a minimum of 120 ml (including the initial aliquot) to fill the entire airway down to the alveolar level. Larger volume instillations before retrieval optimize sampling the alveolar space; small aliquots risk only filling the proximal airways and returning fluid with a few cells that may be unrepresentative of the alveolar space ("bronchial washing"). The BAL cell count and differential offer quality control for BAL technical adequacy—few cells and lack of either neutrophils (with infection/inflammation) or macrophages suggest poor return from the lavage procedure; many ciliated epithelial cells suggest poor wedging of the bronchoscope or inclusion of the bronchial aliquot.

Bronchoscopy has many advantages beyond infection issues. For instance, cytopathological examination of BAL fluid in the diagnosis of certain conditions such as pulmonary alveolar proteinosis and pulmonary haemorrhage. The occasional finding of high proportions of eosinophils, lymphocytes, or other cells point toward unsuspected VAP mimics such as acute eosinophilic pneumonia or hypersensitivity pneumonitis. BAL also continues to play a key role in research, being the only tool capable of retrieving the cells and fluids lining the alveoli sequentially over the course of the illness. This sampling at the alveolar level allows critical insights into the early pathogenesis and progression of many acute respiratory diseases, including severe SARS-CoV-2-pneumonia.

An early criticism of BAL diagnosis of VAP was that bronchoscopy represented a technique only available to some centres, as the equipment and the process of disinfection and preparation were costly in terms of money and time and well-trained practitioners were not always available. Currently, the availability of disposable bronchoscopes requiring minimal setup has minimized cost and made bronchoscopy much more widely available. Different European societies have incorporated competency in bronchoscopy for critical care training programmes, such as the recently published CoBaTrICE (Competency-Based Training in Intensive Care Medicine in Europe) regulatory project under the leadership of the European Society of Intensive Care Medicine (ESICM) [7]. In other countries, bronchoscopy is part of training not only as a respiratory diagnostic procedure, but also for difficult airway intubation. In other countries, such as the United States (US), where the specialty has dual roots in respiratory and intensive care medicine, training with different levels of supervision has been defined for many years. We therefore need to work toward a training framework to provide the quality standards for bronchoscopy among different training bodies.

The second major challenge preventing routine use of BAL to diagnose VAP is the question of whether the results modify management often enough and to a sufficient extent that they justify the small, but finite risks of complications associated with the procedure. Therefore, benefit for the diagnosis of VAP results only from subsequent antibiotic management, withholding/withdrawing, de-escalation to fewer or narrower-spectrum agents, or escalating treatment. In addition, exclusion of VAP should prompt further diagnostic exploration of alternative causes of the clinical findings suggestive of VAP. The various alternative strategies for response to a diagnostic test for VAP are listed in Table 1.

Several important randomized trials to determine the benefit of an invasive diagnostic approach to suspected lower tract respiratory infection were completed around the year 2000. All sought to determine the best approach to diagnose VAP and to infer a subsequent survival

Table 1 Study designs on the approaches to antibiotic management in randomized trials of ventilator-associated pneumonia (VAP) diagnosis

Approach	Example(s)
Test; treat only positive	Baker, Meredith, Haponik AJRCCM 1996
Test; screen and start empirical; stop or modify based on cultures	Fagon et al. Ann Intern Med, 2000 [8]
Test; start empirical; stop or modify based on cultures	Singh et al. Am J Respir Crit Care Med, 2000 [15]
Test; start empirical; modify only based on cultures	Sanchez-Nieto et al. Am J Respir Crit Care Med, 1998 [10]
	Ruiz et al. Am J Respir Crit Care Med, 2000 [9]
	Sole-Violan et al. Crit Care Med, 2000 [11]
Test; start empirical; escalate only based on cultures*	Canadian Crit Care Trials Group, N Engl J Med 2006 [12]

*If the culture showed no growth, study antibiotics were discontinued, except at the discretion of the physicians, in patients with a high pretest likelihood of VAP

benefit. However, antibiotic management differed significantly. The study that mandated withholding or discontinuation of subsequent antibiotic therapy for negative bronchoscopy results was associated with lower 14-day mortality for invasive diagnosis [8]. Others [9–11] did not discontinue antibiotics for negative cultures, but escalating therapy for unsuspected pathogens or resistance. Several other large studies in Canada and the United Kingdom (UK) did not protocolize subsequent antibiotic at all and even allowed continuation of broad-spectrum antibiotics for patients with both low pretest probability of VAP and sterile cultures for either diagnostic strategy [12]. Since the clinical benefit of BAL diagnosis of VAP is entirely dependent on subsequent antibiotic management, it is not surprising that the published meta-analysis of comparing invasive strategies with non-invasive found no differences in mortality, reduced time in ICU and on mechanical ventilation, or higher rates of antibiotic change.

The ongoing debate regarding BAL and invasive diagnosis of VAP raises the greater issue: whether an alternative diagnostic technique determines subsequent mortality and other VAP outcomes an appropriate question to ask? In other words, the most serious mistakes are not the result of wrong answers; the truly dangerous thing is asking the wrong questions. The coronavirus disease 2019 (COVID-19) pandemic offers an illustrative example. Despite the aforementioned ATS/IDSA guidelines and meta-analysis [1], routine implementation of bronchoscopy has been extremely useful. Pickens et al. [13] found in patients with COVID-19 that BAL-based management was associated with significantly reduced antibiotic use compared with guideline recommendations. We learned that co-infection at the time of intubation occurred in a low proportion of cases. Despite knowing this information, the overuse of unnecessary antibiotics was the norm even though withholding or narrowing antibiotics was demonstrated to be safe in these critically ill patients. Moreover, due to (sometimes) prolonged antibiotic administration and prolonged duration of ventilation, we discovered the rising emergence of MDR pathogens. Finally, the development of invasive pulmonary aspergillosis (IPA) has been recognized as a major complication in patients with COVID-19. As angio-invasion was uncommon and the majority of these patients were not severely immunosuppressed, BAL galactomannan, rather than serum, was the best way to diagnose COVID-19-associated pulmonary aspergillosis (CAPA).

The final consideration is regarding the complications and risk–benefit balance. Despite being an invasive procedure, when compared with other invasive procedures, the risk of complications is quite low. Old published registries (some with more than 50,000 patients) have shown an extremely low mortality rate (0.01–0.04%) and a complication rate below 0.3% [14]. The greatest risk of BAL alone (without brushing or biopsies) is hypoxemia, with lower risks of airway bleeding and pneumothorax. Hypoxemia is induced by the increased airway resistance of bronchoscope passage through the airway leading to higher airway pressures. If the high pressure limit alarm is not adjusted, the ventilator breath is aborted and relative hypoventilation occurs. The increased airway resistance also often results in auto-positive end expiratory pressure (PEEP) and air trapping, which may add to hypoxemia and increase the risk of barotrauma. Careful adjustment and monitoring of the ventilator, appropriate sedation, and short procedure time can minimize risks. Compared to the risk of inappropriate antibiotics, selection for MDR pathogens, and antibiotic toxicities with less accurate diagnostic approaches, the trade-off favours invasive diagnosis.

We acknowledge that it would be desirable to determine the implications of molecular testing in invasive and not invasive respiratory sampling methods. Bronchoscopy with BAL for the diagnosis of VAP has a long legacy in intensive care medicine, with a reborn interest due to the unprecedented pandemic times. Done correctly and

safely, with antibiotic treatment decisions based on direct examination of samples, RDT results, and quantitative cultures, BAL provides clinicians with greater clarity in deciding whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy. Compared to the risk of inappropriate antibiotics, selection for MDR pathogens, and antibiotic toxicities with less accurate diagnostic approaches, the trade-off in our opinion favours invasive diagnosis.

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Declarations

Conflicts of interest
IM-L is a consultant to and speaker for bioMerieux and consultant for Qvella and Accelerate diagnostics. His institution has received research funds from Grifols. RGW is a consultant to and speaker for bioMerieux. His institution has received research funds from Curetis and Helixbind. JC is a consultant to Aridis, Inotrem, and PharmaMar. His institution has received research funds from AstraZeneca/Medimmune.

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