Biomarkers to exclude the diagnosis of ventilator-associated pneumonia

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Ventilator-acquired pneumonia (VAP) is an important clinical problem that has been associated with substantial morbidity and mortality. However, the diagnosis of VAP can be particularly difficult, and surveillance programmes have not been markedly successful. The diagnosis of VAP can be difficult, in part, because new radiographic infiltrates can be secondary to aspiration, acute respiratory distress syndrome (ARDS) without pneumonia, or atelectasis. Typical criteria for the diagnosis of VAP include a new radiographic infiltrate, the presence of purulent tracheal secretions, hypothermia or hyperthermia, and/or a low or elevated peripheral white blood cell count. Some investigators and clinicians have used quantitative cultures of bronchoalveolar lavage (BAL) or tracheal aspirates with different thresholds of >10^3 or >10^4 colony-forming units to exclude VAP. Some investigators and clinicians have reported the results of an interesting paper with the title “Biomarkers to exclude the diagnosis of ventilator-associated pneumonia”. In this study, Hellyer et al° have reported the results of an interesting and well done clinical study to test the potential value of measuring biomarkers in BAL that may be useful in excluding pneumonia in patients with suspected VAP. The study was multicentre and prospective and was carried out in 12 intensive care units. VAP was diagnosed by bronchoscopy with culture of a pathogen in the bronchoalveolar lavage fluid at >10^4 colony-forming units. Several biomarkers were measured, including interleukin-1β (IL-1β), interleukin-8 (IL-8), matrix metalloproteinase (MMP)-8, MMP-9 and human neutrophil elastase.

In the current study by Hellyer et al, the biomarkers were tested for the diagnosis of VAP in a large fraction of the patients that were studied. These results are interesting and provocative, suggesting that it might be possible to enhance current clinical diagnostic efforts to exclude VAP at an earlier phase in the patient’s clinical course, thus preventing the unnecessary addition of new antibiotics to treat suspected VAP. The authors should be commended for doing a well-planned scientific study that included multiple sites. From a practical standpoint, in order to further test the utility of this approach, it would be necessary to have point-of-care assays for IL-1β and IL-8 that could be processed rapidly in the clinical setting within 2–4 h.

There is some earlier work on the potential use of protein biomarkers in BAL in patients with VAP from P. aeruginosa. In one study, plasminogen-activator inhibitor 1 (PAI-1) concentrations were correlated with higher mortality in ventilated patients with positive cultures for P. aeruginosa, and also correlated with the secretion of type III exotoxins by P. aeruginosa. In that study, PAI-1 concentrations in patients with ARDS were significantly higher than the concentrations measured in patients without ARDS. However, a significant difference between survivors and non-survivors in elevated BAL fluid PAI-1 concentrations persisted even after exclusion of patients with ARDS. However, in that study, PAI-1 was not useful for distinguishing patients with and without VAP. Several other biomarkers have been tested for the diagnosis of VAP with much success.

The most important limitation in the current study by Hellyer et al relates to the need to do fiberoptic bronchoscopy and lavage. The use of lavage was rational in this study because the investigators were able to direct the bronchoscope to the areas of the lung that showed maximal or substantial pulmonary consolidation. However, there were some patients who could not have bronchoscopy with suspected VAP because of a variety of safety issues that precluded bronchoscopy. Another limitation is that a substantial proportion of patients (73%) were treated with antibiotics at the time of the BAL, which may have caused false negative microbiology and, perhaps, even falsely reduced biomarker levels. However, in clinical practice, the reality is that the majority of patients in whom VAP is considered will already be receiving antibiotics. Another issue concerns the cut-off for defining VAP, namely >10^4 colony-forming units in the BAL fluid. The correct gold standard for diagnosis of VAP is not established, but this was a reasonable approach.

In summary, the study by Hellyer et al provides new data regarding the potential use of low levels of BAL concentrations of IL-1β and IL-8 to exclude the diagnosis of VAP in critically ill, ventilated patients. Reliable point-of-care measurements are now needed to test prospectively these two biomarkers in a multicentre study to determine the effect on reducing the unnecessary use of antibiotics in suspected VAP. A study of this kind could also assess the relative economic impact of more fiberoptic bronchoscopies versus reduced use of antibiotics in patients in whom VAP could be ruled out, postponing the results of microbiological cultures. This approach might have particular value also in ventilated patients who already have pre-existing pulmonary radiographic abnormalities from ARDS, pulmonary trauma and post-operative atelectasis.

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