deliver a definitive trial examining the efficacy of HFCWO.

There is unlikely ever to be a perfect airway clearance regime. Decisions regarding the optimal airway clearance regime for patients are not easy, and are complicated by the various clinical phenotypes of patients with CF and the number of options available. It is probable that all airway clearance regimes work by different mechanisms to enhance airflow and reduce mucus viscosity, both of which are important for optimal airway clearance. Before new devices become available, research needs to provide clear evidence that the new device can become available, research needs to provide non-productive of sputum) or in specific (eg, patients with large sputum volumes or non-productive of sputum) or in specific situations (eg, in stable disease or during an exacerbation). There is a high demand on patients with CF to take part in both pharmaceutical and non-pharmaceutical studies so much and is now as low as 1%, so it is unlikely that future airway clearance trials will be able to show any clear benefit in terms of lung function. This has been highlighted in a recent European Cystic Fibrosis Society (ECFS) consensus conference report on clinical trials which stated that new alternative outcomes need to be used.20 Physiological measures such as lung clearance index, cough monitors and sputum viscosity show promise as outcome measures, although consensus is needed on standardising the methodologies for these outcomes. Data are also needed on what magnitude of change is needed in these outcomes to translate into an important change in a clinical outcome. More emphasis needs to be put on how best to capture patients’ experiences of different treatments in trials (both positive and negative), and data on adherence will be particularly important.

In conclusion, appropriately designed trials of adequate size using new alternative outcomes will ensure that future airway clearance trials provide us with the information we need to make informed decisions on the options for effective airways clearance techniques.

Competing interests None.

Provenance and peer review Commissioned; not externally peer reviewed.


doi:10.1136/thx.2009.122663

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Novel pulmonary biomarkers in the diagnosis of VAP

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Ventilator-associated pneumonia (VAP) is reported to occur in up to 20–27% of mechanically ventilated patients, and impacts healthcare in terms of patient morbidity, mortality and expenditure.1–3 The concept of VAP seems straightforward— that is, alveolar inflammation due to an infectious agent that was not present at the time of initiation of mechanical ventilation. However, the diagnosis remains difficult. Importantly, this difficulty in diagnosis of VAP leads to potential over-/underprescription of antibiotics and misguided treatment.

The American Thoracic Society guidelines of 20053 suggest that the use of readily available clinical data is adequate to inform the diagnosis of VAP. However, while such an approach has the advantage of being straightforward to apply, when compared with postmortem histological specimens the resultant sensitivity and...
extensively reviewed and, while C-reactive protein, procalcitonin, and soluble cytokines to distinguish patients with or without VAP, while waiting for microbiological cultures, while a higher IL-8 would support the decision towards antibiotic prescription. The authors argue that while confirming a negative culture can take up to 48 h BAL cytokine results can be made available by 4 h, allowing more targeted decision making.

However, as the authors acknowledge, there are some potential limitations. To validate a novel biomarker requires confidence in the reference standard. The study uses quantitative BAL as the reference standard to confirm the presence or absence of VAP, against which the biomarkers are then validated. However, not all studies have confirmed that it is superior to clinical diagnosis alone (reviewed in Rea-Neto et al.), nor that it gives a consistent diagnosis. However, the authors point out, histological confirmation of pneumonia is not a practical reference for validation, and quantitative microbiological samples are increasingly accepted by the critical care community.

A further limitation of the study is the exclusion of patients who had had an antibiotic change within 72 h. The BAL cytokine data are not necessarily applicable to this group, and the discriminatory value of IL-8 and IL-1β in such a cohort has not been addressed. In addition, more patients in the “non-VAP” group were already on antibiotic treatment at the time of bronchoscopy and BAL. It is possible that the pre-existing antimicrobial treatment may lead to a false-negative microbiological diagnosis, misclassifying patients with VAP as “non-VAP”.

The authors argue that the higher IL-1β and IL-8 responses occurred only in the true VAP cohort—that is, with cfu >10⁵/ml—but it remains difficult to be confident that the “non-VAP” group (with positive cultures but at lower cfu) are not in fact true patients with VAP in evolution: this study did not include follow-up of the patients in each group to give their emerging clinical course. In addition, it would be interesting to know about the use of corticosteroids or immunomodulatory antibiotics such as tetracyclines or macrolides in each of the groups as these might affect measured cytokine profiles.

The ecology of the bacteria isolated in the cohort is a little unusual in that no Pseudomonas species were identified in the VAP group: the applicability of the cytokine data in the absence of a highly typical intensive care unit (ICU) pathogen therefore needs to be considered, and reproduced in other ICU cohorts. In addition, the study did not include viral...
Is vitamin D deficiency important in the natural history of COPD?

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Vitamin D consists of a group of fat-soluble prohormones, the most important of which are vitamin D2 and D3, with measurement of 25-hydroxyvitamin D (25-OHD) closely representing a person’s vitamin D2 and D3 status. D2 (ergocalciferol) is plant and fungal derived, while vitamin D3 (cholecalciferol) is made from 7-dehydrocholesterol in the skin. This conversion of 7-dehydrocholesterol to previtamin D3 is governed by both the intensity and appropriate wavelength of the ultraviolet (UV) B irradiation reaching 7-dehydrocholesterol. Adequate amounts of vitamin D3 can be made in the skin after only 10–15 min of sun exposure at least twice a week without sunscreen. However, with longer exposure to UVB rays, equilibrium is achieved in the skin and the vitamin degrades as fast as it is generated. Serum concentrations of vitamin D have been found to vary with age, race, sex,