Ventilator associated pneumonia: asking the right question

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Everything about ventilator associated pneumonia is contentious. What is the microbial pathogenesis? How can it be prevented? How should it be treated? One strongly advocated preventive strategy consists of intensive topical and systemic antimicrobial prophylaxis. An opposing but equally strongly advocated approach is the use of conventional but firmly applied infection control measures together with limitation of antibiotic use. For treatment, questions abound. One drug or two? Which drug? For how long?

There are two main reasons which underlie our failure to move toward consensus on many of these questions. Firstly, the magnitude and nature of the problem varies widely between intensive care units. The incidence of pneumonia in mechanically ventilated patients ranges from as little as 5% in some units to more than 50% in others. This may represent, in part, differences in diagnostic approach, but most of the difference in incidence is probably real, reflecting differences in patient population, medical and nursing practice, and infection control practices. Because many studies of pneumonia are generated by intensive care units with high pneumonia rates, questions naturally arise about whether their conclusions are necessarily applicable to units with lower rates.

The second main cause of contention is the problem of definition. How is the diagnosis of ventilator associated pneumonia made? One point of view is that reliable diagnosis must rely on bronchoscopy combined with quantitative bacteriology of the specimens so obtained. An alternative view is that clinical and radiological evidence of infection combined with conventional semi-quantitative bacteriology is sufficient for diagnosis in most cases, and reduces morbidity caused by delay in treatment while waiting for quantitative bacteriological results.

Advocates of bronchoscopy point out that at least half of ventilated patients who might be diagnosed with pneumonia using a standard infection control definition (radiological pulmonary infiltrate, a fever, raised white blood cell count, or purulent tracheal secretions together with a cultured pathogen from endotracheal aspirates) do not, in fact, have an infection. The evidence for this comes from a series of studies showing that, in patients who meet the clinical definition of suspected pneumonia, use of a quantitative bacteriological threshold for diagnosis on a bronchoscopically obtained specimen (≥10^3 colony forming units (cfu)/ml in the case of protected specimen brush (PSB) samples, 10^3 cfu/ml for bronchoalveolar lavage (BAL) samples) resulted in a diagnosis of "no pneumonia present" in many of the patients and a more specific diagnosis of the cause of the pneumonia in many of the rest.

The main problem, of course, is determining what reference standard to use to define whether or not pneumonia is really present. Most of these studies have used some combination of blood cultures, clinical course (e.g. patient improves without antibiotics = no pneumonia), and post-mortem histological and microbiological examinations.

In this issue of Thorax Fàbregas and colleagues make a useful contribution to this debate. Quantitative bacteriological examination of endotracheal aspirates and bronchoscopic specimens (both PSB and BAL) from 25 recently deceased mechanically ventilated patients was performed and the quantitative diagnostic thresholds for pneumonia from these methods were compared with various clinical criteria and with an arguably rigorous reference standard for the diagnosis of pneumonia—namely, the presence of both histological and bacteriological evidence of pneumonia on one or more of 16 lung biopsy specimens obtained immediately after the airway sampling procedures. They concluded that, against this standard, all of the quantitative bacteriological methods (endotracheal aspirate at ≥10^3 cfu/ml, BAL at ≥10^4 cfu/ml, and PSB at ≥10^5 cfu/ml) performed similarly, and none were substantially superior to standard clinical definitions of pneumonia.

This study has some significant limitations. Most patients were receiving antibiotics so it is possible that lung bacteriology may have become negative in some patients with pneumonia while airway cultures were still positive for the offending organism, resulting in an underestimate of the specificity of the airway cultures. Alternatively, an antibiotic induced reduction in the number of bacteria in airway cultures, particularly PSB, may have reduced sensitivity. Further, since these patients were deceased, the results may not be representative of other patients still under active treatment. However, these are not major detractors from the main point of the study, which is a direct determination at a single point in time of how closely quantitative airway cultures correlate with the presence of the same organism in lung tissue from patients with histological pneumonia.

The few other similar post-mortem studies of ventilator associated pneumonia have reached a range of differing conclusions about the usefulness of the various diagnostic methods available. Only one, that of Chastre et al, concluded that PSB or BAL bacteriology correlated well with lung bacteriology of the same lung segment, and that in most cases this was associated with histological pneumonia. Kirtland et al also reported a good correlation between bronchoscopic bacteriology and lung bacteriology but found that this was a poor predictor for the presence of pneumonia, attributing this in part to non-standard definitions for histological pneumonia. Several other investigators have also concluded that PSB and BAL
are of limited diagnostic usefulness when tested against the lung histology reference standard.11-13 Methodological differences between these studies probably account for the differing conclusions. My analysis of the data is that, if bronchoscopic cultures are obtained from a lung segment with new clinical and radiological evidence of pneumonia in the absence of antimicrobial therapy, then examination of tissue from the same sampled lung segment has a strong probability of having similar bacteriology and histologically evident pneumonia. However, if the situation is confounded by prior treatment with antibiotics, previous pneumonia or lung inflammation, a time delay between bronchoscopic examination and taking biopsy specimens, or bronchoscopic sampling of a different lung segment from that from which biopsy specimens are later taken, then the correlation between the bronchoscopic bacteriology and biopsy proven pneumonia becomes less strong. This is generally in keeping with the results of Fàbregas et al in that their strict definition of pneumonia—namely, culture positive inflamed lung—would strengthen the association between airway cultures and pneumonia by avoiding the problem of including previously treated culture negative pneumonia in the pneumonia group, while the association would be weakened by the fact that airway cultures were not individually matched by segment to the biopsy specimens examined. In the real world of clinical diagnosis, in which not every suspect lung segment can be cultured quantitatively, the intermediate diagnostic usefulness of these specimens reported here probably represents what is practically achievable.

Of perhaps most interest in these data is the fact that quantitative culture of endotracheal aspirates was roughly equal to bronchoscopic methods in diagnostic accuracy, and none was significantly superior to clinical criteria alone. These data agree with most previous direct comparisons of the diagnostic value of endotracheal aspirates with those obtained by bronchoscopic methods in that, with appropriate adjustment of the pneumonia diagnostic threshold, the quality of the information obtained by the various methods was similar.14-16 Indeed, the question arises as to whether BAL and PSB are really just variable dilutions of the endotracheal aspirate specimen by 10–1000 fold, resulting in a shift in the diagnostic threshold value without a real difference in the quality of the specimen. If this were true, then we would expect that any improvements in test specificity associated with the methodology would necessarily be accompanied by deterioration in test sensitivity; this prediction is a fairly accurate description of the large body of literature on this subject. It also would agree with the common sense notion that specimens obtained from locations only 5–15 cm apart along a widely patent airway in continuous motion are unlikely to have substantially different bacterial populations. Most patients who receive mechanical ventilatory support for a protracted period develop microbial colonisation of the airway. A subset of these patients develops invasive infection requiring treatment with antibiotics. However, infection occurs along a continuum of severity, ranging from purulent tracheobronchitis to subclinical invasive peribronchial pneumonia to frank progressive bronchopneumonia.17 The onset of infection is accompanied by an increase in bacterial numbers in airway secretions but this, too, is variable and it now appears that, while quantitating bacteria in the airway has diagnostic value, further refinements of sampling or microbiological methods are not likely to lead to greater diagnostic precision.

Perhaps we have been asking the wrong question. Does the clinician most need a test which correlates reliably with the presence or absence of pneumonia defined by the best available histological and microbiological reference standard? Or do we most need a decision rule to guide us in prescribing antibiotics and in ensuring that patients’ treatment or prevention trials are evaluated using standardised methods? To be useful, such a rule would be tested, not using diagnostic reference standards, but by controlled trials in which patient morbidity and mortality, antibiotic use and resistance, and costs are the major outcome measures. Data of this kind are beginning to be collected and hold promise for the future. The most useful studies will carefully re-examine the usefulness of all the clinical data, tracheal aspirate microscopic analysis, and both quantitative and semi-quantitative bacteriology rather than focusing only on the latest bronchoscopic sampling method so that we obtain rules that are accurate but also, as far as possible, cost effective and accessible.