Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies

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Abstract

**Background**—A study was undertaken to assess the diagnostic value of different clinical criteria and the impact of microbiological testing on the accuracy of clinical diagnosis of ventilator associated pneumonia (VAP).

**Methods**—Twenty five deceased mechanically ventilated patients were studied prospectively. Immediately after death, multiple bilateral lung biopsy specimens (16 specimens/patient) were obtained for histological examination and quantitative lung cultures. The presence of both histological pneumonia and positive lung cultures was used as a reference test.

**Results**—The presence of infiltrates on the chest radiograph and two of three clinical criteria (leucocytosis, purulent secretions, fever) had a sensitivity of 69% and a specificity of 75%; the corresponding numbers for the clinical pulmonary infection score (CPIS) were 77% and 42%. Non-invasive as well as invasive sampling techniques had comparable values. The combination of all techniques achieved a sensitivity of 85% and a specificity of 50%, and these values remained virtually unchanged despite the presence of previous treatment with antibiotics. When microbiological results were added to clinical criteria, adequate diagnoses originating from microbiological results which might have corrected false positive and false negative clinical judgements (n = 5) were countered by a similar proportion of inadequate diagnoses (n = 6).

**Conclusions**—Clinical criteria had reasonable diagnostic values. CPIS was not superior to conventional clinical criteria. Non-invasive and invasive sampling techniques had diagnostic values comparable to clinical criteria. An algorithm guiding antibiotic treatment exclusively by microbiological results does not increase the overall diagnostic accuracy and carries the risk of undertreatment.

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Keywords: ventilator associated pneumonia; clinical diagnosis; sampling; lung biopsies

Clinical criteria have repeatedly been considered as inappropriate for the diagnosis of ventilator associated pneumonia (VAP). Necropsy studies conducted in the early 1980s suggested that the use of clinical parameters to diagnose VAP leads to overdiagnosis4 or, even worse, underdiagnosis, particularly in patients with adult respiratory distress syndrome (ARDS).2 More recently, additional evidence for this view has been put forward from evaluation of clinical criteria by microbiological3 or post-mortem histological reference tests.4,5 As a consequence, some authors have argued that the diagnosis of VAP should be guided by the quantitative culture results of bronchoscopically retrieved lower respiratory tract samples.7 A corresponding algorithm would imply that patients with a clinical suspicion of pneumonia but negative microbiological results would not receive antibiotics. Clinical criteria for the suspicion of VAP continue to form the starting point of diagnostic evaluation. It therefore remains important to determine the accuracy of these criteria.

A major methodological problem in this regard is the accuracy of the reference test. During the last five years several immediate post-mortem studies have validated diagnostic techniques using histological or microbiological examination of lung tissue samples.4,5,8–10 These studies have established considerable limitations in the diagnostic accuracy of quantitative cultures of lower respiratory tract samples and have raised concerns about using these techniques as a reference for clinical criteria. Clinical parameters have been validated in a previous report from our group in which the histological examination of a single lung biopsy sample was used as the reference test.4 However, as other workers have shown,1 a single lung biopsy sample may frequently under-diagnose pneumonia. Moreover, histological evidence of pneumonia may reflect any stage during its evolution but not necessarily the active inflammation responsible for clinical symptoms.

We therefore chose to validate clinical criteria by both the presence of histological pneumonia and positive quantitative lung tissue cultures as reference tests most probably reflecting clinically symptomatic pneumonia.
We included clinical criteria as defined by Johanson et al as well as the clinical pulmonary infection score (CPIS) as proposed by Pugin et al. To determine the impact of microbiological criteria on the accuracy of the diagnosis of pneumonia we compared the performance of clinical criteria and different sampling techniques and also analysed the diagnostic results when adding the microbiological results to the clinical diagnoses. This approach allows an estimate of the potential diagnostic contribution of sampling techniques in everyday practice when evaluating patients with clinically suspicious VAP.

Methods

Patients

Twenty-five patients whose lungs had been mechanically ventilated for more than 72 hours and who died in our Respiratory Intensive Care Unit were included in the study. Patients with immunosuppression (organ transplantation, HIV infection and AIDS, severe neutropenia <1.0 × 10⁹/l, steroid therapy equivalent to prednisone in a dose of >20 mg/day) were excluded. All patients received treatment with antibiotics during their stay in the ICU. Eight subjects (32%) did not receive antibiotics during the 48 hours before death and 17 (68%) received antibiotics until the day of death. The mean duration of antibiotic treatment was 9.5 (7.9) days. General characteristics of the study population and causes of ICU admission and death are presented in table 1.

The study was approved by the local ethical committee and family members gave written informed consent for the study to be performed.

Clinical and Radiographic Evaluation

All clinical and laboratory data were recorded on the day of death. The chest radiographs were also reviewed by one of the investigators and an independent radiologist on the day of death.

Sampling Methods

Non-invasive and invasive sampling was performed 0–90 minutes after death without discontinuing mechanical ventilation. Three fragments were obtained from both lungs, one by fiberoptic bronchoscopy from the middle lobe giving an overall sample of 16 biopsy specimens per patient (two guided in addition to 14 blinded). The total number of biopsy specimens was 375 (in three patients only one lung was sampled). In 14 patients (217 samples) the samples were obtained within 30 minutes after death, in five within 60 minutes (62 samples), and in six within 90 minutes (96 samples). Of those 14 patients in whom samples were obtained within 30 minutes of death, eight were organ donors and the period between brain death and sample extraction was less than 12–24 hours. In one organ donor the specimen was taken 30–60 minutes after death.

The average size of the lung biopsy specimens was 2 × 2 × 2 cm. They were always obtained from peripheral zones of the lung. Each fragment was halved lengthwise with one specimen examined histologically and the other submitted for quantitative microbiological culture. All lung tissue specimens were embedded in paraffin and stained with haematoxylin/eosin, periodic acid Schiff, May–Grünwald Giemsa, and Gram stains. The pathologists were blinded to the microbiological results and clinical information. Guided and blind lung biopsy specimens were not analysed separately.
Clinical diagnosis of ventilator associated pneumonia

Microbiological Processing
TBA and PSB specimens and protected BAL fluid were processed as described elsewhere. Biopsy samples were homogenised. Serial dilutions (10¹, 10², 10⁻³) of each sample were prepared in sterile normal saline and 0.1 ml of each dilution was inoculated into different culture media (5% sheep blood, chocolate, CDC agar, and saboraud dextrosa). The cultures were incubated at 37°C under aerobic and anaerobic conditions and in a CO₂ enriched atmosphere. All microorganisms isolated were identified by standard laboratory methods. Non-pathogenic microorganisms (Neisseria spp, Corynebacterium spp, Streptococcus other than S pneumoniae and Candida albicans) were excluded from the analysis.

Definitions
Histological pneumonia: accumulation of polymorphonuclear leucocytes in the capillaries and adjacent alveolar spaces in at least one sample.

Microbiologically active pneumonia: presence of both histological pneumonia and positive lung tissue cultures (as defined by a bacterial burden of >10⁶ cfu/g lung tissue) in the corresponding halves of at least one sample.

Clinical suspicion of pneumonia according to the criteria of Johanson et al: clinical suspicion of pneumonia with an infiltrate on the chest radiograph and at least one of the following clinical criteria: leucocytosis >12 x 10⁹/ml, fever >38.3°C, or the presence of purulent tracheobronchial secretions.

Clinical pulmonary infection score (CPIS): clinical suspicion of pneumonia in the presence of a positive score at different cut offs (0-12 points) which include the following variables: (1) body temperature; (2) blood leucocyte count and number of band forms; (3) character of tracheobronchial secretions (purulent or not) and quantity of tracheobronchial aspirates; (4) microscopic examination (Gram stain) and semiquantitative culture of bronchial secretions; (5) arterial oxygen tension/inspiratory fraction of oxygen (PaO₂/FIO₂); and (6) chest radiograph.

Diffuse alveolar damage: presence of interstitial or alveolar oedema, fibrin deposition, and initial development of hyaline membranes; or the presence of fibroblast proliferation within the interstitium and alveolar lining cell hyperplasia.

Cut off points for sampling techniques: TBA specimens were considered positive in the presence of >10³ cfu/ml, PSB specimens >10⁵ cfu/ml, and protected BAL and BAL specimens >10⁷ cfu/ml.

Statistical Analysis
Results are expressed as mean (SD). The Student’s t test was used to compare means. The accuracy of clinical diagnostic criteria for pneumonia was calculated using microbiologically active pneumonia as a reference test. Operative characteristics were calculated according to standard methods. The level of significance was set at 5%.

Results
HISTOLOGY
The incidence of histological pneumonia in at least one sample was 92% (23 of 25 patients). Two subjects had no histological evidence of pneumonia, three had unilateral pneumonia, 17 others (68%) had bilateral pneumonia and the remaining three patients, in whom the study was restricted to one lung, also had pneumonia.

Other additional histological diagnoses in patients with pulmonary infiltrates were: alveolar haemorrhage (n = 2), diffuse alveolar damage (DAD) (n = 7), interstitial fibrosis (n = 2), DAD plus interstitial fibrosis (n = 3), aspiration pneumonitis (n = 1), pulmonary hypertension (n = 2), bronchiolitis obliterans (n = 3), and pulmonary thromboembolism (n = 1). DAD always coexisted with histological pneumonia.

Microbiology
Cultures of lung tissue revealed growth of 23 pathogenic microorganisms above the threshold in 14 patients (56%). These included Gram positive pathogens in seven (Streptococcus pneumoniae (n = 1), Staphylococcus aureus (n = 2), methicillin-resistant Staphylococcus aureus (MRSA) (n = 4)), Gram negative pathogens in 15 (Proteus mirabilis (n = 1), Serratia marcescens (n = 1), Pseudomonas aeruginosa (n = 9), Stenotrophomonas maltophilia (n = 3), Acinetobacter anitratus (n = 1)), and Candida krusei in one (the latter also confirmed histologically).

Microbiologically Active Pneumonia
The number of patients with both histological pneumonia and positive lung tissue cultures in the corresponding halves of at least one sample (and therefore conforming to the definition of microbiologically active pneumonia used as a reference test in the study) was 13 (52%).

Diagnostic Accuracy of Clinical Parameters
Chest radiography
A total of 47 lungs were evaluated for radiographic infiltrates (three lungs could not be sampled due to technical problems during the procedure). Considering both lungs together, 13 patients (52%) had localised and seven (28%) had diffuse infiltrates. Sensitivity was high (92%) but specificity was low (33%). The diagnostic accuracy of infiltrates of the left lung was considerably higher than that of the right lung (table 2).

Leucocytosis, fever, purulent secretions
Leucocytosis was present in 15 patients (60%), fever in 13 (52%), and purulent secretions in 16 (64%). The diagnostic accuracy of each of these three parameters was generally poor, the sensitivities ranging between 46% and 77% and the specificities between 42% and 58%.

Clinical criteria according to Johanson et al
Two out of three clinical criteria in addition to the presence of infiltrates on the chest radiograph improved the diagnosis, with specificity increasing to 75% and sensitivity to 69%. Sensitivity was not superior in the
absence of antibiotic treatment (67%). The presence of all three criteria increased the specificity to 92% at the cost of a high beta error (sensitivity 23%).

Clinical pulmonary infection score (CPIS)
The use of a Pugin score of ≥6 as recommended by Pugin et al. resulted in a sensitivity of 77% and a specificity of 42%.

DIAGNOSTIC ACCURACY OF NON-INVASIVE AND INVASIVE SAMPLING TECHNIQUES
The accuracies of TBA, PSB, BAL fluid, and protected BAL fluid specimens for the presence of pneumonia with microbiologically active pneumonia as the reference test are given in Table 3. BAL fluid had the highest sensitivity (77%) whereas protected BAL fluid had the highest specificity (100%). TBA specimens had the highest diagnostic accuracy (20/25, 80%) and balanced sensitivity (69%) and specificity (92%). The combined use of all invasive diagnostic techniques (PSB, BAL fluid and protected BAL fluid) increased the sensitivity to 85% but at the cost of a beta error of 50%. These figures were identical when TBA was added as a non-invasive tool.

Sensitivity and specificity did not change substantially when stratified according to antibiotic treatment. This was especially true when comparing the combined invasive as well as invasive and non-invasive techniques (table 4).

IMPACT OF MICROBIOLOGICAL DIAGNOSIS ON THE ACCURACY OF DIAGNOSTIC EVALUATION FOR THE PRESENCE OF PNEUMONIA
In four cases with a clinically false negative diagnosis non-invasive and invasive sampling methods would correctly have established pneumonia in three (75%). Conversely, in three cases with a clinically false positive diagnosis TBA would have correctly identified the absence of pneumonia in all three and invasive sampling methods in one (33%).

On the other hand, an inadequate diagnosis would have been established by TBA in three cases (33%) of nine correctly diagnosed clinically as having pneumonia and invasive sampling methods in one (11%), while in another nine cases correctly classified as not having pneumonia an inadequate diagnosis would have been provided by TBA in one case (11%) and invasive sampling methods in four (44%). These numbers would have been three (75%) and two (67%), and one (11%) and five (55%), respectively, if both non-invasive and invasive techniques were used together. Thus, adequate diagnoses from microbiological investigation were achieved in five cases and inadequate diagnoses in six (table 5).

Discussion
This study offers the following three important findings: (1) the accuracy of clinical criteria (infiltrates on the chest radiograph and two of the following: leucocytosis, fever, purulent secretions) for the diagnosis of pneumonia was reasonable (sensitivity 69%, specificity 75%) and the CPIS was not more accurate; (2) non-

Table 3 Accuracy of non-invasive and invasive diagnostic techniques for ventilator associated pneumonia

<table>
<thead>
<tr>
<th>Diagnostic technique</th>
<th>Sensitivity % (n)</th>
<th>Specificity % (n)</th>
<th>Positive predictive value % (n)</th>
<th>Negative predictive value % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBA</td>
<td>69 (9/13)</td>
<td>92 (11/12)</td>
<td>90 (9/10)</td>
<td>73 (11/15)</td>
</tr>
<tr>
<td>Protected BAL</td>
<td>39 (5/6)</td>
<td>100 (12/12)</td>
<td>100 (6/6)</td>
<td>60 (12/20)</td>
</tr>
<tr>
<td>BAL</td>
<td>77 (10/13)</td>
<td>58 (7/12)</td>
<td>67 (10/15)</td>
<td>70 (7/10)</td>
</tr>
<tr>
<td>PSB</td>
<td>62 (8/13)</td>
<td>75 (9/12)</td>
<td>73 (8/11)</td>
<td>64 (9/14)</td>
</tr>
<tr>
<td>Any invasive diagnostic technique</td>
<td>85 (11/13)</td>
<td>50 (6/12)</td>
<td>65 (11/17)</td>
<td>75 (6/8)</td>
</tr>
<tr>
<td>Any non-invasive or invasive diagnostic technique</td>
<td>85 (11/13)</td>
<td>50 (6/12)</td>
<td>65 (11/17)</td>
<td>75 (6/8)</td>
</tr>
</tbody>
</table>

For definition of terms see footnote to table 2.

Table 4 Accuracy of clinical criteria and non-invasive and invasive diagnostic techniques for ventilator associated pneumonia stratified according to whether or not antibiotics were given during the last 48 hours before death

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>Without antibiotics (n = 8)</th>
<th>With antibiotics (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical*</td>
<td>Sensitivity % (n)</td>
<td>Specificity % (n)</td>
</tr>
<tr>
<td>TBA</td>
<td>67 (4/6)</td>
<td>0 (0/2)</td>
</tr>
<tr>
<td>Protected BAL</td>
<td>83 (5/6)</td>
<td>100 (2/2)</td>
</tr>
<tr>
<td>BAL</td>
<td>17 (1/6)</td>
<td>100 (2/2)</td>
</tr>
<tr>
<td>PSB</td>
<td>83 (5/6)</td>
<td>100 (2/2)</td>
</tr>
<tr>
<td>Any invasive</td>
<td>83 (5/6)</td>
<td>50 (1/2)</td>
</tr>
<tr>
<td>Any non-invasive</td>
<td>83 (5/6)</td>
<td>50 (2/2)</td>
</tr>
</tbody>
</table>

*Chest radiograph infiltrates plus two of the following: leucocytosis, purulent secretions, fever. TBA = tracheobronchial aspirates; BAL = bronchoalveolar lavage; PSB = protected specimen brush.

Table 5 Association of clinical and microbiological diagnoses for ventilator associated pneumonia

<table>
<thead>
<tr>
<th>Histology + lung tissue culture</th>
<th>Clinical diagnosis (chest radiograph + two of three clinical criteria)</th>
<th>Non-invasive microbiological diagnosis (TBA)</th>
<th>Invasive microbiological diagnosis (PSB, BAL, protected BAL)</th>
<th>Both non-invasive and invasive microbiological diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>False negative (n = 4)</td>
<td>Adequate</td>
<td>3/4 (75%)</td>
<td>Adequate</td>
</tr>
<tr>
<td>Negative</td>
<td>False positive (n = 3)</td>
<td>Adequate</td>
<td>3/4 (75%)</td>
<td>Adequate</td>
</tr>
<tr>
<td>Positive</td>
<td>Correct positive (n = 9)</td>
<td>Inadequate</td>
<td>1/3 (33%)</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Negative</td>
<td>Correct negative (n = 9)</td>
<td>Inadequate</td>
<td>1/9 (11%)</td>
<td>Inadequate</td>
</tr>
<tr>
<td></td>
<td>Adequate (n = 2)</td>
<td>Adequate</td>
<td>1/9 (11%)</td>
<td>Inadequate</td>
</tr>
<tr>
<td></td>
<td>Adequate (n = 5)</td>
<td>Adequate</td>
<td>2/3 (67%)</td>
<td>Inadequate</td>
</tr>
</tbody>
</table>

Diagnostic techniques (non-invasive, invasive; or both) are stratified according to the impact which its results would have had on clinical decisions. Adequate = antibiotic treatment would have been administered or withheld adequately in the presence of a false negative or positive clinical diagnosis, respectively; inadequate = antibiotic treatment would have been administered or withheld inadequately in the presence of a correct positive or negative clinical diagnosis, respectively. TBA = tracheobronchial aspirates; BAL = bronchoalveolar lavage; PSB = protected specimen brush.

Discussion
This study offers the following three important findings: (1) the accuracy of clinical criteria (infiltrates on the chest radiograph and two of the following: leucocytosis, fever, purulent secretions) for the diagnosis of pneumonia was reasonable (sensitivity 69%, specificity 75%) and the CPIS was not more accurate; (2) non-

Table 2 Accuracy of clinical and radiographic variables as defined by Johanson et al. for the diagnosis of VAP

<table>
<thead>
<tr>
<th>Variable or combination of variables</th>
<th>Sensitivity % (n)</th>
<th>Specificity % (n)</th>
<th>Positive predictive value % (n)</th>
<th>Negative predictive value % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiograph (right or left)</td>
<td>92 (12/13)</td>
<td>33 (4/12)</td>
<td>60 (12/20)</td>
<td>80 (4/5)</td>
</tr>
<tr>
<td>Chest radiograph (right)</td>
<td>73 (8/11)</td>
<td>33 (4/12)</td>
<td>50 (8/16)</td>
<td>97 (4/7)</td>
</tr>
<tr>
<td>Chest radiograph (left)</td>
<td>92 (11/12)</td>
<td>75 (9/12)</td>
<td>79 (11/14)</td>
<td>90 (9/10)</td>
</tr>
<tr>
<td>Leucocytosis</td>
<td>77 (10/13)</td>
<td>58 (7/12)</td>
<td>67 (10/15)</td>
<td>70 (7/10)</td>
</tr>
<tr>
<td>Fever</td>
<td>46 (6/13)</td>
<td>42 (5/12)</td>
<td>66 (16/31)</td>
<td>42 (5/12)</td>
</tr>
<tr>
<td>Purulent secretions</td>
<td>69 (9/13)</td>
<td>42 (5/12)</td>
<td>56 (9/16)</td>
<td>56 (5/9)</td>
</tr>
<tr>
<td>Chest radiograph + one of three criteria</td>
<td>85 (11/13)</td>
<td>33 (4/12)</td>
<td>58 (11/19)</td>
<td>67 (4/6)</td>
</tr>
<tr>
<td>Chest radiograph + two of three criteria</td>
<td>69 (9/13)</td>
<td>75 (9/12)</td>
<td>75 (9/12)</td>
<td>69 (9/13)</td>
</tr>
<tr>
<td>Chest radiograph + all three criteria</td>
<td>23 (3/13)</td>
<td>92 (11/12)</td>
<td>75 (3/4)</td>
<td>52 (1/12)</td>
</tr>
</tbody>
</table>

Sensitivity = rate of correctly classified patients with VAP and total number of patients with VAP; specificity = rate of correctly classified patients without VAP and total number of patients without VAP; positive predictive value = rate of correctly classified patients with VAP and total number of patients classified as having VAP (correctly positive plus false positive); negative predictive value = rate of correctly classified patients without VAP and total number of patients classified as not having VAP (correctly negative plus false negative).
invasive (TBA) and invasive (PSB, BAL, protected BAL) sampling techniques were not superior to these clinical criteria; and (3) when microbiological results were added to clinical criteria, adequate diagnoses originating from the microbiological investigation which might have corrected false positive and false negative clinical judgements were countered by a similar proportion of inadequate diagnoses.

Three crucial methodological issues must be borne in mind before interpreting these results. Firstly, it must be recognised that there is no irrefutable reference test for the validation of diagnostic criteria and techniques. Specific limitations of the post-mortem lung biopsy approach include the selection of a population not necessarily representative of all mechanically ventilated patients, the risk of an overestimate of lung injuries in histological samples inherent in the study of severely ill patients, and sampling errors due to the multifocal nature of VAP. To minimise these potential pitfalls we used a combination of the histological presence of pneumonia with positive quantitative cultures of lung tissue samples as the reference test. We thought that this approach would allow us to distinguish between foci of residual pneumonia and active and clinically symptomatic pneumonia. It would also represent a rigorous criterion to protect against confounding colonisation with pneumonia.

Secondly, the clinical parameters were calculated on the day of death, a fact that does not necessarily correspond with the evolution of pneumonia, creating a timing discrepancy between both events. The criterion of a new infiltrate on the chest radiograph originally required by Johanson et al could not be met in the majority of patients because of the study design. It should therefore be recognised that our approach does not exactly apply to the majority of patients because of the study design. It should therefore be recognised that our approach does not exactly apply to the initial phases of pneumonia not detected on the plain chest radiograph. In a previous study we found that the initial phases of pneumonia represented 11% of the total histological patterns of pneumonia. The technical limitations of portable chest radiography may hinder interpretation of radiographs. Interestingly, the diagnostic accuracy of the left chest radiograph was considerably higher than that of the right. A possible explanation for this may be the higher incidence of atelectasis on the right side.

Leucocytosis and purulent secretions had a remarkable sensitivity but only poor specificity. Few authors have addressed leucocytosis alone as a clinical parameter for diagnosing VAP and compared it with histological examination. Andrews and colleagues found that bronchiolitis without pneumonia was not an infrequent finding in mechanically ventilated patients. In contrast, false negative results may be due to foci of pneumonia located at the periphery which impair the body temperature response to infection. The prevalence of fever may be explained by mechanisms other than pneumo-
nia. Meduri and coworkers\textsuperscript{20} found that only 42\% of patients with fever and infiltrates on the chest radiograph had pneumonia; most had fewer due to infectious foci other than pneumonia. They also suggested that the fibroproliferative phase of ARDS may frequently occur with fever, thus mimicking pneumonia.\textsuperscript{17}

The combination of infiltrates on the chest radiograph with two of three clinical criteria had a reasonable diagnostic accuracy. Similarly, clinical criteria yielded a sensitivity of 62\% and a specificity of 84\% in a study using microbiological criteria for VAP.\textsuperscript{27} Two necropsy studies have also shown similar results (sensitivity 60\% and specificity 80\%) when evaluating clinical criteria.\textsuperscript{27} Conversely, a previous study from our group\textsuperscript{19} and a more recent one by Kirtland et al\textsuperscript{10} found that clinical criteria predicted the presence of histological pneumonia only poorly. In our view these results reflect limitations inherent in reference tests based on a single biopsy specimen and histological examination, without confirmation of microbiological activity.

The CPIS was not found to be superior to the clinical criteria recommended by Johanson \textit{et al.}\textsuperscript{11} It achieved a sensitivity of 77\% but the rate of false positives was 58\%. Factors responsible for the high rate of false positive results may have been the number of leukocyte band forms, the quantity of tracheobronchial secretions, Gram stains, and the PaO\textsubscript{2}/FiO\textsubscript{2}. The modified CPIS score has been clinically validated by Garrard \textit{et al}\textsuperscript{28} in a unique population who had not received any previous antibiotic treatment. They found that serial determinations of the CPIS followed a similar pattern to quantitative cultures of non-directed bronchoalveolar lavage in both patients who responded to antibiotics and those who did not. In a post-mortem study using combined histology and lung microbiology vs the reference test, Papazian and colleagues found a sensitivity of 72\% and a specificity of 85\% for the CPIS.\textsuperscript{29} These results do not indicate a superiority of the CPIS to Johanson’s criteria and, given that the CPIS is more time consuming to calculate, there is no evidence to recommend this score in routine clinical practice.

The diagnostic accuracy of non-invasive and invasive sampling techniques was comparable to that found in previous post-mortem lung biopsy studies.\textsuperscript{23,25-27} The application of all invasive (or all invasive and non-invasive) techniques together increased the sensitivity but also the beta error. They were not superior to the diagnostic accuracy of clinical criteria. This was true irrespective of previous antibiotic treatment. However, from a clinical point of view a more important consideration is the impact of the microbiological data on correcting false positive results from clinical judgement, thereby avoiding overuse of antibiotics, and the cost of introducing new false negative results. In this regard, sampling techniques proved to be of limited value since TBA, but not invasive techniques, correctly diagnosed the absence of pneumonia in all cases. On the other hand, in those patients correctly diagnosed as having pneumonia by clinical criteria, non-invasive and invasive sampling techniques failed to yield positive results in some cases. These patients would not have received antibiotics and, as a consequence, would have been at high risk of death due to misdiagnosis. Conversely, if patients were screened for infection without clinical suspicion, a considerable number of patients would have been adequately treated at the cost of a similar number of patients with false positive microbiological results who would have been overtreated. Thus, our results suggest that it may be hazardous to base decisions on antibiotic treatment exclusively on the results of sampling techniques. The risk of death in patients with VAP not receiving antibiotic treatment is probably higher than the corresponding risk of overuse of antibiotics. Negative microbiological results in the presence of clinically suspected VAP must not therefore be a reason for withholding antibiotics unless an alternative diagnosis is clearly established.

In summary, our results confirm that clinical parameters are reasonably accurate in the diagnosis of VAP and are still the principal criteria in establishing a diagnosis. We believe that the key point is not to look for a balance between the information provided by clinical judgement and the microbiology of the lower airways, and not to withhold antibiotics if VAP is clinically suspected.

Dr Santiago Ewig was a 1998 research fellow from the Medizinische Universitätsklinik and Poliklinik Bonn, Bonn, Germany; Dr Torsten Bauer was a 1998 research fellow from the Berufsgenossenschaftliche Kliniken Bergmannsheil-Universitätsklinik, Ruhr-Universitätsklinik Bochum, Bochum, Germany; and Dr Hernan Cabellos was a 1996 research fellow from the Hospital Clínico de la Universidad de Chile, Santiago de Chile, Chile. This study was supported in part by the following grants: Commissionat per a Universitats i Recerca de la Generalitat de Catalunya 1997 SGR (00086, Fundació Clinic/CIRIT, IDIBAPS Hospital Clinic Barcelona, FIB (Fondo de Investigacion Sanitaria) 94/0583, and 14D 96/0024.

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