Reappraisal of Distal Diagnostic Testing in the Diagnosis of ICU-Acquired Pneumonia

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Reappraisal of Distal Diagnostic Testing in the Diagnosis of ICU-Acquired Pneumonia*

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Background: **The thresholds of the diagnostic procedures performed to diagnose ICU-acquired pneumonia (IAP) are either speculated or incompletely tested.**
Purpose: **To evaluate the best threshold of protected specimen brush (PSB), plugged telescoping catheter (PTC), BAL culture (BAL C), and direct examination of cytocentrifugated lavage fluid (BAL D) to diagnose IAP. Each mechanically ventilated patient with suspected IAP underwent bronchoscopy successively with PSB, PTC, and BAL in the lung segment identified radiographically.**
Population: **One hundred twenty-two episodes of suspected IAP (occurring in 26% of all mechanically ventilated patients) were studied. Forty-five patients had definite IAP, and 58 had no IAP. Diagnosis was uncertain in 19 cases.**
Results: **Using the classic thresholds, sensitivity was 67% for PSB, 54% for PTC, 59% for BAL D, and 77% for BAL C. Specificity was 88% for PSB, 77% for PTC, 98% for BAL D, and 77% for BAL C. We used receiver operating characteristics methods to reappraise thresholds. Decreasing the thresholds to 500 cfu/mL for PSB, 10^2 cfu/mL for PTC, 2% cells containing bacteria for BAL D, 4×10^3 cfu/mL for BAL C increased the sensitivities (plus 14%, 23%, 25%, 10%, respectively) and moderately decreased the specificities (minus 4%, 9%, 2%, 4%, respectively) of the four examinations. The association of PSB with a 500 cfu/mL threshold and BAL D with a 2% threshold recovered all but one episode of pneumonia (SE 96±4%) with a 84±10% specificity. For a similar ICU population, these "best" thresholds increased negative predictive value with a minimal decrease of positive predictive value. They need to be confirmed in multiple ICU settings in prospective fashion.** ***(CHEST 1995; 108:1632-39)***

AUC=area under the ROC curve; BAL C=BAL culture; BAL D=direct examination of BAL fluid; cfu=colony forming unit; FIo_2=fraction of inspiratory oxygen; IAP=ICU=acquired pneumonia; NPV=negative predictive value; PPV=positive predictive value; PSB=protected specimen brush; PTC=plugged telescoping catheter; ROC=receiver operating characteristic

Key words: bronchoalveolar lavage; diagnostic procedures; nosocomial pneumonia; plugged telescoping catheter; protected specimen brush; ROC curves

The diagnosis of ICU-acquired pneumonia (IAP) remains a challenge for clinicians in the ICU setting. Fever, purulent secretions, and lung infiltrates can be associated with IAP or with various other common pathologic processes such as atelectasis, pulmonary edema, intra-alveolar hemorrhage, lung contusion, and drug reactions.

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During the past decade, many diagnostic techniques (protected specimen brush [PSB],[1-3] BAL,[4,5] protected BAL,[6,7] minilavage,[8] plugged telescoping catheter [PTC][9]) performed with or without fiberoptic bronchoscopy have been evaluated. Various and controversial diagnostic values have been described.

Repeated studies have shown that when bacterial infections of the lung manifest clinically, the lung contains at least 10^4 colony forming unit (cfu) per gram of tissue[1,10] and the exudate contains 10^5 or more bacteria per milliliter,[11,12] although the initial concentration of organisms necessary to cause pneumonia varies in relation to the virulence of the bacteria and the competence of host defenses.

Some studies have evaluated the threshold of the diagnostic procedure. The PSB is diluted in 1 mL of holding medium that results in a 100- to 1,000-fold dilution before plating. A growth of 10^3 cfu/mL in the culture plate indicates an initial concentration of 10^5 to

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10^6 bacteria per milliliter in the retrieved secretions.[13] In patients with pneumonia, BAL is estimated to recover at least five to ten times the amount of organisms retrieved by PSB.[14] Nevertheless, BAL culture (BAL C) threshold was 10^3 cfu/mL,[4] 10^4 cfu/mL,[5] or 10^5 cfu/mL[14] in previously reported studies. For direct examination of BAL fluid (BAL D) and PTC, there are no *in vitro* data that allowed an evaluation of the probable threshold. Finally, even if these procedures have been fully investigated considering one estimated (PSB, BAL C) or postulated (BAL D, PTC) threshold, to our knowledge, no study has tried to confirm prospectively, in routine practice, that these thresholds are the most adequate in patients in the ICU.

METHODS

Between March 1990 and December 1992, we performed serially PSB, PTC, BAL D, and BAL C on consecutive patients with suspected IAP and evaluated the diagnostic value of each procedure and its best threshold.

Study Population

Between March 1990 and December 1992, every patient hospitalized and mechanically ventilated for more than 48 h in our eight-bed ICU was prospectively included in the study when IAP was suspected. The clinical suspicion of IAP was based on the appearance of new and persistent infiltrate during the ICU stay on the chest radiograph and at least one of the following clinical criteria:[15] temperature greater than 38.5°C or hypothermia less than 36.5°C, leukocytosis (>10X10^9/L) or neutropenia (<4×10^9/L), and purulent tracheal aspirates.

When IAP was suspected, the following clinical variables were collected on a standardized reporting form: age, simplified acute physiologic score,[16] prior antimicrobial therapy, duration of mechanical ventilation, temperature, change in temperature in the prior 2 days, blood leukocytes, blood polymorphonuclear cells and lymphocytes, PaO_2/FIO_2 ratio, its maximum change in the prior 2 days, and radiologic score using the classification of Fagon and coworkers.[3] No patient received new antimicrobials before bronchoscopy.

BAL was not performed on patients with poor oxygenation (*ie,* PaO_2/FIO_2 <100 mm Hg) or unstable hemodynamic condition (systolic blood pressure <90 mm Hg despite inotropic support) who could suffer from a prolonged bronchoscopic procedure.

The protocol was approved by the ethics committee of the hospital. Informed consent was obtained from closest relatives.

Study Design

Fiberoptic bronchoscopy was performed for each patient within 12 h of the inclusion in the study. Patients were premedicated with phenoperidine, midazolam, and pancuronium bromide. Topical anesthetics were never used. Each patient was monitored with a pulse oximeter and ventilated with an FIO_2 of 1 during the time of broncoscopy and for 2 h after the end of the procedure. Chest radiography was performed after each bronchoscopy. Immediately after endotracheal aspiration via a sterile tube, the bronchoscope was introduced through a special adapter (Bodaï, Suction Safe, Y; Sontek Medical; Lexington, Mass) and advanced, without suction, to the bronchial orifice of the lung segment identified radiographically as containing the new infiltrate. The PSB was then inserted into the inner suction channel and advanced to a 3-cm peripheral position before dislodging. The PSB was then removed and placed on a sterile operative field.

The PTC (Combicath 5828.20; Plastimed Lab; Saint Leu la Forêt, France) was then inserted in the same subsegment as previously described.[8] The bronchoscope was then positioned in the adjacent subsegment and BAL was performed by infusing a total of six 20-mL aliquots of sterile nonbacteriostatic saline solution. The lavage recovered after the first aliquot was discarded and the remaining lavage aliquots were pooled. BAL was considered unavailable when the retrieved lavage fluid was less than 20 mL. When the fiberoptic bronchoscopy was finished, the specimens were separately prepared as follows:

PSB: Using strict aseptic conditions, the distal portions of the outer and inner cannulas were sequentially cleaned with a 70% alcohol sponge, dried with sterile compresses, and discarded with sterile scissors, distal to the brush so that the brush would not come into contact with the possibly contaminated distal portion of the inner cannula. The brush was then advanced and severed with sterile scissors into numbered screw-capped glass vials containing 1.0 mL of sterile Ringer's lactate solution.[2]

PTC: The distal portion of the outer sheath was wiped dry with a sterile pad and transsected with sterile scissors several centimeters distal to the inner catheter; the inner catheter was then advanced and 1 mL of sterile saline solution was flushed through its proximal part and collected into a sterile vial; finally, the distal segment (4 to 5 cm of the catheter) was transsected with sterile scissors and collected into the same vial.[9]

BAL: The pooled lavage fluid was divided into three samples, one for cytologic examination, BAL C, and BAL D. The containers were then sent to the laboratory for immediate processing. Microbiologic procedures were performed by experienced technicians, according to the protocol previously described.[2,3,9]

Diagnostic Categories

Four diagnostic categories were established before initiating the study: certain bacterial pneumonia, excluded bacterial pneumonia, probable bacterial pneumonia, and uncertain pneumonia.

Bacterial pneumonia was considered as certain if patients fulfilled one of the following criteria: positive pleural fluid culture or rapid cavitation of the lung infiltrate associated with the resolution of the clinical and radiologic signs after adapted antimicrobial therapy, or histopathologic proof. A histopathologic diagnosis required the presence of consolidation with intense polymorphonuclear leukocyte accumulation in bronchioles and adjacent alveoli involving several adjacent low-power microscopic fields in autopsies performed within 8 days of bronchoscopy.

Bacterial pneumonia was considered as excluded if at least one of the following criteria was fulfilled: (1) full recovery without antimicrobial therapy plus the diagnosis of another disease of the chest accounting for the chest radiograph abnormality; (2) absence of bacterial pneumonia at autopsy performed within 8 days of the bronchoscopic procedure in patients who had not received prior antibiotics between bronchoscopy and death or within 3 days after bronchoscopy if antibiotic therapy had been initiated. Probable pneumonia was defined as a complete recovery after antimicrobial therapy without treatment of another infectious site and no other disease of the chest diagnosed during the follow-up. When no diagnostic definition was available, according to those definitions, patients were classified as having uncertain pneumonia. The number of organisms recovered from the cultures of the PSB PTC, BAL C specimens was expressed as colony forming units per milliliter. Results of BAL D were expressed as percentage of BAL cells containing bacteria.

Statistical Analysis

Statistical threshold analysis was done considering certain and probable pneumonia as definite pneumonia. Uncertain pneumonia was excluded from the statistical analysis. The determination of the

best threshold of each test was made using receiver operating characteristic (ROC) curves. A ROC curve for each test was constructed by plotting the false-positive rate (1-specificity) on the horizontal axis against the true-positive rate (sensitivity) on the vertical axis for each possible cutoff point. An ideal test would have a high rate of true-positives (sensitivity) and a low rate of false-positives (1-specificity) and should therefore produce a curve running close to the upper left corner of the graph. A test with no predictive value would, at any cutoff point, have an equal number of false- and true-positives and would therefore follow the identity line along the diagonal. The area under the ROC curve (AUC) for each test was calculated. AUC evaluated the diagnostic yield of each procedure independent of any previously chosen threshold. The optimal sample threshold was identified to be the point from the ROC curve with the highest sensitivity and specificity (*ie,* the nearest point to the top left corner of the graph).[17,18]

The calculation of positive predictive values (PPV) and negative predictive values (NPV) is highly dependent on the probability of the occurrence of IAP on the population at risk (prevalence). The prevalence of IAP is unknown. The NPV and PPV were calculated over the range of prevalence using the classic threshold and the best threshold found in our study for PSB, BAL C, BAL D, and PTC. We represented the predictive values whatever the prevalence was. Briefly, for each diagnostic procedure, the curve was constructed by plotting the prevalence on the horizontal axis against the predictive values (PPV and 1—NPV) on the vertical axis. An ideal test produces a curve of PPV running close to the upper left corner and a curve of 1—NPV close to the lower right corner of the graph.[19]

Assessment of Outcome

Therapeutic decisions were left to the discretion of the attending physicians and discussed daily with the medical staff. All patients were monitored until their discharge from the hospital, and changes in the clinical and therapeutic course were recorded. Postmortem histopathologic investigations were performed as often as possible, especially when the diagnostic category remained uncertain.

RESULTS

Patients

During the study period, 663 patients were admitted to the ICU. Four hundred eighteen patients (63%) were mechanically ventilated for more than 2 days. IAP was suspected in 122 patients who were enrolled into the study. Reasons for ICU admission are summarized in Table 1. Patients had been receiving mechanical ventilation for 13.2±10 days prior to suspicion of IAP. Forty-nine (40%) of these patients fulfilled criteria for diagnosis of ARDS and 39 (32%) patients had a history of preexisting COPD. Before the septic signs associated with the clinical suspicion of nosocomial pneumonia, 56 (46%) patients received antibiotics for various reasons (patients with COPD with bronchial superinfection, n=11; community-acquired pneumonia, n=8, including *Pneumocystis carinii* pneumonia, n=2; catheter-related infection, n=3; antibioprophylaxis for digestive surgery, n=3; endocarditis, n=2; mediastinitis, n=4; peritonitis, n=10; septic vascular surgery, n=8; bacteriemia of unknown origin, n=5). In 12 patients, this antibiotic therapy was stopped in the 48 h preceding the bronchoscopic procedure because the initial infectious focus was considered cured. Other patients' clinical characteristics are shown in Table 2.

Table 1—*Reasons for ICU Admission in 122 Study Patients*

Type of Patients	No. of Patients
Surgical	66
Digestive	30
Vascular	20
Cardiac	12
Other	4
Medical	56
COPD	20
Other pulmonary	11
Neurology	12
Cardiology	5
Other medicine	8

Overall ICU mortality was 60% (73 patients). Forty-nine patients had autopsies, 20 on the first 3 days after bronchoscopy, 19 between day 4 and day 8, and 10 after day 8.

Pneumonia was certain in 23 patients (9 by cavitation, 13 by histologic confirmation, 1 positive pleural fluid). The diagnosis was definitely excluded in 58 pa-

Table 2—*Clinical Characteristics of Patients at the Time of Study Entry**

	Pneumonia†		
	Definite n=45	Excluded n=58	Uncertain n=19
Age, yr	67±2	65±2	68±3
SAPS	13.2±0.7	15.7±0.7	12.9±1§
Prior antibiotics, %	25	56	65§
Duration of MV, d	12±2.0	14.4±1.5	13±1.7
Bacteriemia, %	9	12	25
Purulent tracheal aspirates, %	95	74	85§
Temperature, °C	38.4±0.1	38.2±0.2	37.8±0.3
Changes in temperature, °C	0.72±0.1	0.39±0.1	0.31±0.15
PaO_2/FIO_2 ratio, mm Hg	237±15	247±15	231±27
Change in PaO_2/FIO_2 mm Hg	53±11	39±7	14±7§
Leukocytes, $\times 10^9$/L	15.7±1.2	19±1.4	17.2±1.9
Polymorphonuclear cells, $\times 10^9$/L	13.2±1.2	15.5±1.3	15±2.1
Lymphocytes, $\times 10^9$/L	1.7±0.5	1.5±0.2	1.2±0.1
Radiologic score	3.95±0.2	3.84±0.2	4.5±0.4
No. of diagnostic criteria, %‡			
2	100	100	100
3	84	88	85
4	48	35	45

*SAPS=simplified acute physiologic score; MV=mechanical ventilation. The rate of prior purulent tracheal aspirates was significantly different only between definite pneumonia and excluded pneumonia groups (p=0.003; Student *t* test).

†The classification of the status regarding pneumonia has been made during the follow-up (see the text for definitions).

‡Radiologic criteria associated with purulent aspirate criteria and/or leukocyte criteria and/or temperature criteria.

§$p<0.05$ (one-factor analysis of variance).

Table 3—*Results of Procedures on Each Diagnostic Category Using Classic Threshold*

Procedures (Threshold)	IAP, No. Positive/No. Tested			
	Certain	Probable	Excluded	Uncertain Status,* No. Positive/ No. Tested
PSB, 1,000 cfu/mL	12/22	16/21	7/57	1/18
PTC, 1,000 cfu/mL	11/20	11/21	13/56	0/17
BAL C, 10,000 cfu/mL	13/17	15/19	9/39	3/16
BAL D, 5% infected cells	9/17	12/19	1/39	0/16
≥1 positive procedure†	19/23	21/22	21/58	4/19

*The four patients with uncertain pneumonia with one positive sample were considered as false-positive, but were treated after bronchoscopy with antimicrobials directed against another infectious focus but effective on microorganisms recovered from pulmonary distal samples.
†One or more positive procedures, using classic thresholds, for each patient.

Table 4—*Microorganisms Recovered From Episodes of Definite IAP**

Organism	Total No.
Gram-positive bacteria	30
Staphylococcus aureus	16
Other staphylococci	3
Streptococcus sp	9
Corynebacterium sp	2
Gram-negative bacteria	36
Haemophilus sp	10
Pseudomonas sp	7
Acinetobacter baumanii	9
Enterobacter sp	2
Escherichia coli	3
Proteus sp	2
Klebsiella sp	1
Other	2
Total	66

*Refers to recovery of organisms, for all procedures, independent of any previously defined threshold.

tients (histologic examination in 25, regression without antibiotic therapy in 33). The radiologic infiltrates were considered caused by an alternate diagnosis in all 58 patients (atelectasis, n=17; ARDS, n=15; pleural involvement, n=5; cardiac failure, n=8; pulmonary infarction, n=3; intra-alveolar hemorrage, n=2; pulmonary contusion, n=3; bronchioloalveolar carcinoma, n=2; amiodarone pneumonia, n=1; cytomegalovirus pneumonia, n=1; disseminated aspergillosis, n=1). The diagnosis was uncertain in 19 patients because antibiotic therapy was initiated after bronchoscopy to treat an associated extrapulmonary infected site (8 patients), because histologic confirmation was not possible (2 patients), or because death occurred more than 8 days after the clinical suspicion of IAP (9 patients). Only two patients who died in the first days after suspicion of pneumonia were classified in the uncertain category because histologic studies were not done. The distal samples were sterile for one of them. For one patient, however, death could have been related to pneumonia, although it was not the opinion of the medical staff. For the four diagnostic categories, results of each procedure are presented in Table 3.

Among the uncertain group (n=19), the bronchial samples recovered no microorganism in 8 cases. The medical staff considered that bronchopulmonary infection could have played a role in the new infectious episode in only one patient, but this infection was associated with purulent sinusitis and catheter sepsis. The accepted causes of the clinical symptoms for the remaining 18 patients were as follows: uncontrolled abdominal sepsis (n=5); uncontrolled sepsis of a vascular prosthesis (n=2); mesenteric infarction (n=2); thrombophlebitis (n=1); cellulitis (n=1); sinusitis (n=1); cytomegalovirus infection (n=1); multiple organ failure after extracorporeal circulation (n=2) or multiple organ failure of unknown origin (n=2); and cardiac failure (n=1). The accepted causes of infiltrates were then ARDS (n=10), cardiogenic pulmonary edema (n=1), pulmonary infarction (n=2), atelectasis (n=2), and pulmonary edema with cardiac failure and ARDS (n=3). Depending on whether we considered those in the uncertain IAP group as having definite pneumonia or excluded pneumonia, estimated prevalence of definite IAP on the patients suspected of having IAP varied from 36.9% (45/122) to 54% (64/122). If we considered the opinion of the medical staff on the uncertain pneumonia group, the estimated prevalence was 37.7% ([45+1]/122).

Adverse Side Effects

There were no deaths during the bronchoscopic procedures. Follow-up chest radiographs demonstrated no barotrauma. No patient experienced a decrease in oxygen saturation to below 95% during the procedure. There were no episodes of bronchial hemorrhage requiring local or intravenous therapy or making BAL impossible.

Microorganisms Recovered From Samples of Definite Pneumonia

Microorganisms isolated from the different samples on definite pneumonia are plotted on Table 4. Of the 45 episodes of definite IAP, 10 were considered as related to 2 or more different microorganisms. PSB and PTC and BAL C recovered, respectively, 81, 66, and 82% of microorganisms recovered from the definite pneumonia episodes.

Results of Each Procedure

PSB and PTC: In four cases for PSB and eight cases

Table 5—*Sensitivity and Specificity of Each Diagnostic Procedure Using Classic (C) and Best (B) Threshold**

Test	Threshold	Se (CI), %	Sp (CI), %	No. Tested/ No. Evaluable†
PSB				
C	1000 cfu/mL	67 (53-81)	88 (79-97)	118/100
B	500 cfu/mL	81 (69-93)	84 (74-94)	
PTC				
C	1000 cfu/mL	54 (38-70)	77 (66-88)	114/97
B	100 cfu/mL	77 (64-90)	68 (56-80)	
BAL D				
C	5% infected cells	59 (40-78)	98 (94-100)	91/75
B	2% infected cells	74 (57-91)	96 (92-100)	
BAL C				
C	10,000 cfu/mL	77 (62-92)	77 (65-89)	91/75
B	4,000 cfu/mL	87 (75-99)	73 (60-86)	

*Se=sensitivity; Sp=specificity, CI=95% confidence intervals. The best thresholds have been evaluated using ROC curve analysis (see text).
†The definite diagnoses of 19 patients were considered uncertain and were excluded from statistical analysis. Four PSB, 8 PTC, and 31 BAL could not be performed for various reasons (see the text for details).

for PTC, sampling was not possible for technical reasons. Sensitivity and specificity are shown in Table 5 using a 10^3 cfu/mL threshold for each procedure.

BAL: BAL was not performed on 14 patients because of severe hypoxemia. For 17 patients, the retrieved lavage fluid was less than 20 mL and thus inadequate for accurate bacteriologic analysis (histologic examination recovered less than 60,000 cells per milliliter and more than 5% ciliated cells in ten patients). For 91 patients, the retrieved BAL fluid was greater than 20 mL (median, 37 mL; range, 25 to 70 mL). The median number of recovered cells was 285,000/mL (range, 6 to 4×10^6 cells/per milliliter) and the median percentage of neutrophil polymorphonuclear cells was 83.5% (range, 15 to 100%). Contamination by bronchial ciliated cells was less than 5% of the total number of cells recovered by lavage in all cases. In four samples, bronchial epithelial cells ranged between 2 and 5%. Sensitivity and specificity of BAL D (threshold, 5% cells containing bacteria) and BAL C are shown in Table 5.

Among the four procedures, the best sensitivity was obtained with BAL C and the best specificity was obtained with BAL D. The four procedures were performed in 78 patients. Sensitivity (75±17% for PSB, 50±20% for PTC, 75±17% for BAL C, and 67±19% for BAL D) and specificity (93±8% for PSB, 83±12% for PTC, 78±13% for BAL C, and 98±5% for BAL D) were not statistically different among procedures in this subgroup.

ROC Curves and Best Threshold

The AUC and the best threshold of each bronchoscopic bacteriologic procedure are shown in Figure 1. The best AUCs, which represent the diagnostic value independently of any threshold, were obtained from PSB, BAL C, and BAL D. The best thresholds of each procedure were 500 cfu/mL for PSB, 100 cfu/mL for PTC, 4,000 cfu/mL for BAL C, and 2% cells containing bacteria for BAL D (Table 5). The inclusion of the uncertain pneumonia group either in the definite pneumonia group or in the excluded pneumonia group modified sensitivity and specificity of each technique, thus modifying the AUC but not the best thresholds.

Predictive Values

For each of the diagnostic techniques tested, when the thresholds were decreased, the sensitivity was increased and the specificity was moderately decreased (Table 5). This change necessarily decreased PPVs and increased NPVs. The advantage of decreasing thresholds for each test depends on the pretest probability of IAP among the patients suspected of having pneumo-

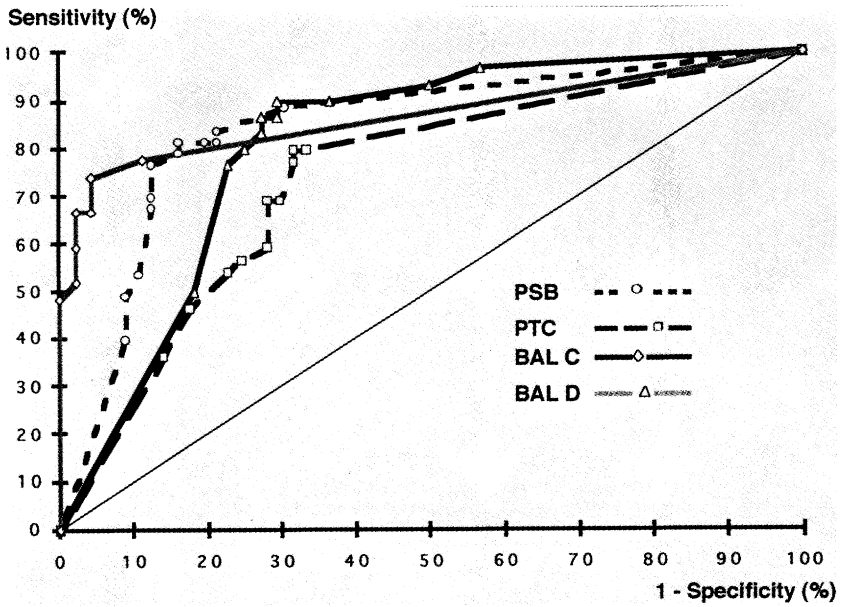

FIGURE 1. ROC curves of each diagnostic procedure. Each point on the curve for a specific test indicates the sensitivity and 1-specificity for a particular threshold ranging from 10 to 10^5 for PSB, PTC, and BAL C and from 1 to 7% for BAL D. AUCs were 0.85 for PSB, 0.73 for PTC, 0.86 for BAL C, and 0.83 for BAL D.

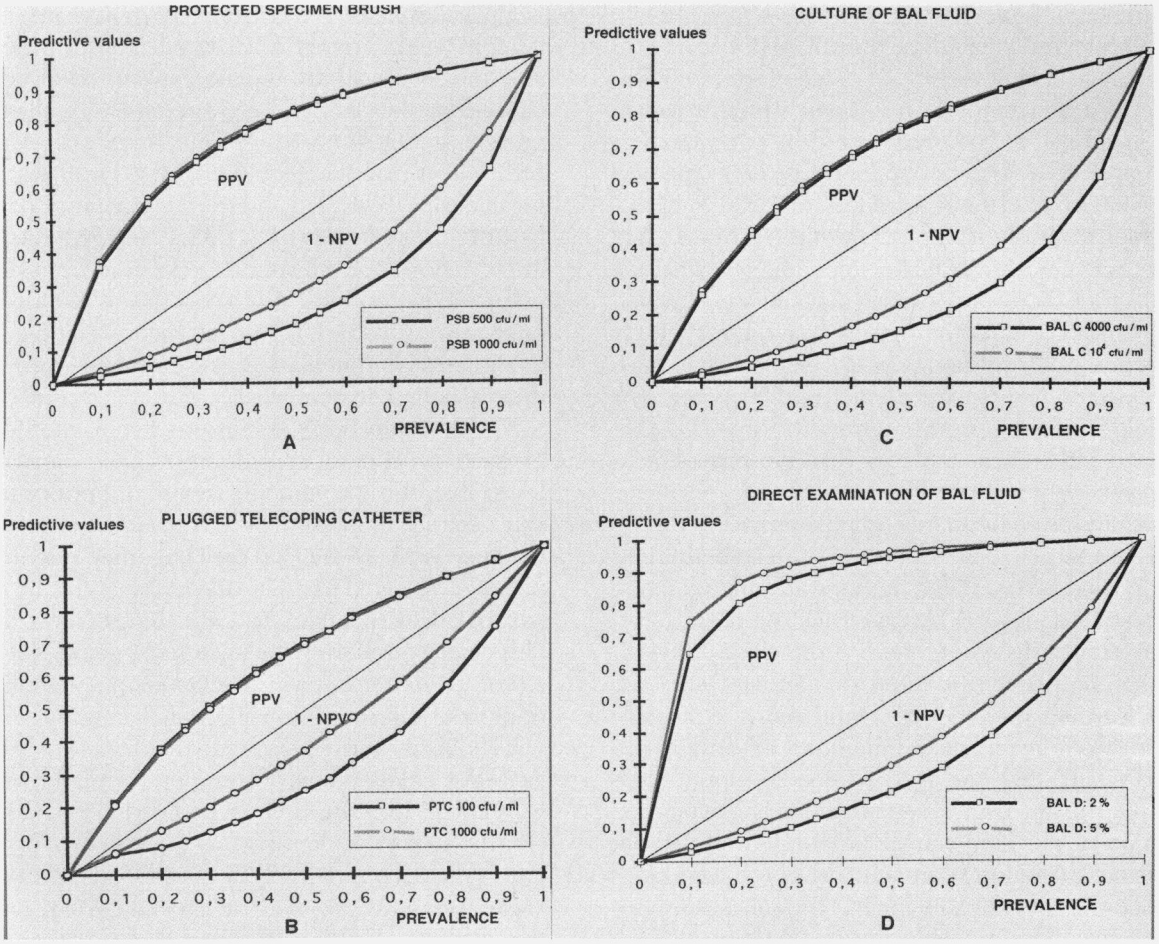

FIGURE 2. Results of the predictive value of each diagnostic procedure expressed as a function of the prevalence. (See the text for explanation.) *Top left:* PSB; *bottom left:* PTC; *top right:* culture of the lavage fluid; *bottom right:* direct examination of the lavage fluid. On the top and the left of each figure are shown PPVs. On the right and the bottom of each figure are shown 1–the negative predictive value (1–NPV). The black line corresponded to the best threshold of each procedure, The gray line corresponded to the classic threshold. An ideal test would have a PPV curve right to the upper left corner and a (1–NPV) curve right to the lower left corner.

nia (prevalence). This probability was unknown. Figure 2 displays the negative and positive values for each diagnostic test of varying the prevalence from 0 to 100%. The PPV for PSB, PTC, and BAL C changed negligibly with use of a lower threshold (Fig 2, top left, bottom left, and top right: the upper curves are very similar). PPV for BAL D decreased with use of a 2% threshold, particularly when prevalence was less than 25%. NPV decreased (NPV increased) for each test with the lower thresholds (Fig 2: the lower curves are shifted to the right). Using the 38% estimated prevalence of the studied population, PPV and NPV were optimized for every diagnostic test.

Association of Two Procedures

PSB and BAL C and BAL D were performed simultaneously in 84 patients. Using classic thresholds, the BAL C and BAL D recovered 21 of 26 episodes of definite pneumonia (sensitivity, 81±15%; specificity, 77±12%). The association PSB and BAL D recovered 21 of 26 episodes (sensitivity, 81±15%) and gave a better specificity (specificity, 89±10%). The association of PSB with a 500 cfu/mL threshold and BAL D with a 2% threshold recovered all but one episodes of pneumonia (sensitivity, 96±4%) with a minimal decrease in specificity (specificity, 84±10%).

DISCUSSION

Our ICU patient population was quite similar to those previously studied.[3,4] The high ratio of patients with COPD,[20] with ARDS,[20-22] and with previous antibiotic therapy during the ICU stay[1,4,23] was presumed to decrease the diagnostic value of bacteriologic samples and partly explains modest sensitivity and specificity results using classic thresholds. However, the diagnostic value of each procedure is similar to those previously reported.[1-3,5,6,9,23,24] The best results were obtained with BAL C for sensitivity and with BAL D

for specificity (Table 5).

This conclusion could be questioned because of methodologic problems. (1) As in many studies on invasive diagnostic methods, results vary from investigator to investigator. This study could be considered as an example of how data obtained from one medical team differ from data obtained by others. (2) Moreover, approximately 15% of all evaluated patients had an uncertain clinical diagnosis. Depending on what the true diagnosis in this population actually was, it would greatly affect the reported sensitivity and specificity of the methods. (3) Although we observed that BAL could become the most accurate method if the best threshold is selected, it is important to emphasize that patients could be unsuitable for BAL because of technical problems or severe hypoxemia.

Criteria used to definitely exclude or accept the diagnosis of IAP are still under question. The definitions were decided before initiating the study and are quite similar to those from Chastre et al.[25] A recent international consensus conference on the clinical investigation of ventilator-associated pneumonia[26] has defined "certain pneumonia" with more restrictive criteria: (1) CT evidence of pulmonary abscess is considered insufficient and positive needle aspirate culture from the abscess is needed, and (2) histologic examination of the lung cannot be considered without positive culture of lung parenchyma. These definitions are, of course, not suitable for ICU population in routine practice. The probable pneumonia group of the present study could also be considered questionable. Resolution after antibiotherapy, even with restrictive clinical patterns, might have been considered as overtreated excluded pneumonia. It would not have been adequate to take into account the results of the procedures to be tested (PSB, PTC, BAL C, BAL D) to classify the targeted population. In fact, it has been noted that for 21 of the 22 patients of the probable pneumonia group, one or more of the diagnostic procedures gave positive results considering classic thresholds (Table 3).

BAL sampling was inadequate in 15% of the patients in whom the small amount of retrieved fluid was considered more as a rinsing of the inner channel of the bronchoscope and the proximal bronchus than as a BAL. This technical problem must be taken into account for the choice of the best diagnostic procedure. It might be appropriate to use aliquots of 30 to 50 mL and a total amount of injected fluid greater than 150 mL to minimize this technical problem. Nevertheless, histologic examination of BAL fluid was useful in diagnosing nonbacterial pulmonary infiltrates (amiodarone pneumonia, one case; cytomegalovirus pneumonia, one case; intra-alveolar hemorrhage, three cases) that might make its utilization favorable in patients suspected of having IAP.

Considering the frequency[3,20] of polymicrobial IAP, it might be important to choose a diagnostic procedure able to recover all the microorganisms involved. In a baboon model, BAL C recovered 74% of all species present in the lung tissue compared with 41% for PSB.[27] This result might be considered as an argument for choosing BAL for a better adaptation of the antibiotic therapy. In our study, BAL C and PSB recovered more than 80% of all species recovered from definite pneumonia episodes. With the same method, the qualitative value of PTC, which recovered 66% of microorganisms, appeared of lesser value, even if the difference is not significant.

The best thresholds, optimizing the diagnostic value of each procedure considering ROC, were always lesser than those commonly reported. Performing the ROC curves, the sensitivity and specificity values were obtained without utilizing the "uncertain pneumonia" patients. To avoid any bias due to the exclusion of this part of our population, we evaluated the best thresholds when considering the uncertain pneumonia group either as "definite" or as "excluded" pneumonia. The optimized threshold remained unchanged.

The AUC, which represents the diagnostic value of each test independent of a chosen threshold, seemed to be better for PSB, BAL D, and BAL C than for PTC (Fig 1). However, the order of the different bacteriologic samples was defined by the study design and was always the same. So the PSB procedure may have influenced the results of PTC and BAL and their AUC. Moreover, the exclusion criteria for performing a BAL may have selected a population for which the diagnostic value of BAL was different. Therefore, statistical comparisons between the AUCs are unavailable, as they do not refer exactly to the same population.

Considering the Bayesian approach, the optimization of the threshold increases NPV without significant decrease of the PPV, especially when the prevalence is intermediate.

The choice of an optimized threshold depends on the cost ratio of the false-positive and the false-negative results (*ie,* the respective consequences of the administration of antimicrobials to patients without pneumonia and of the absence of treatment of patients with pneumonia) which is not actually known. Some authors have shown, using multivariate analyses, that appropriate antibiotic treatment might significantly increase survival of ventilated patients with pneumonia, particularly those without terminal illness.[28,29] However, overtreatment of patients with suspected IAP exposes them to the use of expensive and ineffective antibiotics increasing the risk of colonization with potentially multiresistant microorganisms[30,31] and leading to other unrecognized conditions that mimic pneumonia.[11]

From our study, decreasing the thresholds of diagnostic samples would have moderately increased the

false-positive results and would have necessarily induced a small increase in overtreated patients. However, the use of these new thresholds would decrease the false-negative results and would increase the NPV, minimizing the risk of undertreatment of nosocomial IAP.

The ideal thresholds are probably dependent on the ICU population, the hospital category, and the bacteriologic laboratory. We carefully respected the previously reported sampling procedures for each diagnostic test and the best thresholds could be accepted using the same performing techniques on a similar ICU population.

Independently of the diagnostic value of the procedure and ICU population, the choice of the best technique depends on many factors, such as the cost (favoring PTC[9]), the easiness of the technical procedure (favoring PTC and PSB), adverse side effects (favoring PTC and PSB[3,5,9]), and the swiftness of available results (favoring BAL D). The association of BAL D and PSB appears to be the best available, recovering 80% of the microorganisms for a 96% sensitivity and a 84% specificity.

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