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Usefulness of a strategy based on bronchoscopy with direct examination of bronchoalveolar lavage fluid in the initial antibiotic therapy of suspected ventilator-associated pneumonia

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Abstract *Objectives:* To evaluate (a) the routine accuracy of bronchoalveolar lavage by direct examination (BAL-D) in diagnosing ventilator-associated pneumonia (VAP), and (b) the impact of a diagnostic strategy including clinical judgment, bronchoscopy, and BAL-D on the initial diagnosis and appropriateness of treatment when VAP is suspected.
Design and setting: Prospective cohort study in two academic ICUs in Paris, France.
Patients and participants: Mechanically ventilated patients with suspected VAP underwent bronchoscopy with BAL and protected specimen brush (PSB). BAL-D results were available within 2 h, BAL on culture and PSB results after 24 h, and antibiotic susceptibility after 48 h. At each step in the strategy the senior and the resident in charge of the patient were asked their diagnosis and their therapeutic plan on the basis of presently available data. Definite diagnosis of suspected VAP was based on histology, appearance of cavitation, positive pleural fluid culture, results of PSB and BAL culture, and follow-up.
Measurement and results: A total of 110 episodes of suspected VAP were studied; 94 definite diagnoses were made (47 VAP, 47 no VAP). Using a threshold 1 % of infected cells, BAL-D discriminated well between patients with and those without VAP (sensitivity 93.6 %, specificity 91.5 %, area under the receiver-operating characteristic curve 0.953). The senior clinical judgment was correct in 71 % cases. It was correct in 78 % and 94 % of cases after airway visualization and BAL-D findings, respectively. After BAL-D the positive and negative predictive values in diagnosing VAP were 90 % and 98 %, respectively. However, the therapeutic plan was correct in only 65 % using clinical judgment (15 untreated patients, 3 ineffective treatment, 15 useless treatment), 66 % using airway visualization (14 untreated VAP, 4 ineffective treatment, 14 useless treatment), and 88 % using BAL-D results (1 untreated patients, 6 ineffective, 4 useless), according to definite diagnosis and final antibiotic susceptibility testings.
Conclusions: A strategy based on bronchoscopy and BAL-D generally leads to a rapid and appropriate treatment of nosocomial pneumonia in ventilated patients.

Key words Nosocomial pneumonia · Antimicrobials · Treatment · Bronchoalveolar lavage · Protected specimen brush

Introduction

There is considerable controversy about the proper means for diagnosing and managing nosocomial pneumonia in ventilated patients [1, 2]. There are two principal strategies that may be pursued when ventilator-associated pneumonia (VAP) is suspected. The first is to treat every patient with clinical evidence of nosocomial pneumonia and to adapt treatment to the micro-organisms recovered on qualitative culture of tracheal aspirates. The second is to use bronchoscopy with distal sampling before starting any new antibiotic therapy when pneumonia is clinically suspected.

The purpose of this study was to evaluate prospectively the respective contribution of a routine diagnostic strategy based on bronchoscopy and direct examination on bronchoalveolar lavage fluid (BAL-D) in the initial management of patients suspected of VAP.

Material and methods

Background

The clinical definition of VAP is the combination of new and persistent abnormality on chest radiography and purulent tracheobronchial aspirates, or fever or hypothermia or abnormality of blood leukocyte count and a tracheal aspirate Gram stain showing more than 25 leukocytes and fewer than 10 squamous epithelial cells per low-power field with recovery of a potential pathogen. Mechanically ventilated patients, however, frequently develop other conditions that either obscure these findings or give rise to a similar clinical picture, and only 30–50% of those suspected of having VAP do in fact have it [3]. Diagnoses based on clinical criteria may overestimate the disease and thus expose patients to the overuse of extended-spectrum antimicrobials and further increase antibiotic resistance.

Our routine policy for diagnosing VAP is based on bronchoscopy with BAL-D, BAL on culture (BAL-C), and protected specimen brush (PSB). When VAP is suspected, the management protocol is based on preliminary findings: (a) The accuracy of clinical findings in predicting VAP is poor as only two-thirds of clinical predictions are correct [3]. (b) Schematically all the distal samples are safe and accurate, giving a 0.85–0.95 area under the receiver-operating characteristic curve. The accepted thresholds for these examinations are 10^3 cfu/ml for PSB and 10^4 cfu/ml BAL-C, respectively. (c) None of these examinations has a 100% accuracy [4, 5]. BAL-D is available 2 h after bronchoscopy. Using a 5% threshold, BAL-D is very specific (90–100%) but less sensitive (60–80%). The sensitivity is 80–90% with a threshold at 2%, and this does not substantially decrease specificity [4, 5, 6]. BAL-D is also able to recover extracellular organisms. (d) The accuracy of these procedures is dramatically decreased when new extended-spectrum antimicrobials are introduced immediately before bronchoscopy [7].

Patients

During the study period ten patients were excluded because of contraindication to bronchoscopy and/or BAL (PaO_2/FIO_2 ratio < 100 mmHg in six, unstable angina in one) or technical reasons (three). A total of 110 patients were included. The duration of mechanical ventilation was at least 7 days in 74 of these. Sixteen patients in whom no definite diagnosis was available were excluded. BAL-D recovered of 0% infected cells in nine cases, 1% in one case, 2–5% in two cases, and 22% in one case. PSB (10^3 cfu/ml) and BAL-C (10^4 cfu/ml) were positive in two and ten cases, respectively. In 9 of these 16 patients antimicrobial therapy was instituted to treat possible pulmonary infection. Ninety-four patients were retained for analysis (47 VAP, 47 noVAP). Their main characteristics are presented in Table 1. Eighty-five episodes occurred after the fifth day of hospital stay.

Table 1 Patients characteristics; values are reported as mean ± SD for quantitative value and number (%) for qualitative value (*SAPS II* Simplified Acute Physiology Score, *MOFS* Multisystem Organ Failure Score)

	VAP (n = 47)	No VAP (n = 47)	p[a]
SAPS II at admission	48 (16)	43 (17)	0.08
Duration of mechanical ventilation (days)	11 (8)	12.3 (10)	0.67
Temperature (°C)	39 (1.4)	38.5 (1.2)	0.15
Purulent tracheal aspirates (%)	46 (97)	43 (90)	0.10
Leukocytes (/mm^3)	15,500 (7,000)	15,555 (6,000)	0.75
PaO_2/FIO_2 ratio (mmHg)	225 (110)	213 (102)	0.76
Decrease in $PaO_2 2/FIO_2$ ratio > 50 mmHg	36 (76)	20 (42)	0.004
MOFS at diagnosis	2 (0.8)	1.7 (0.9)	0.15
Duration of ICU stay (days)	49 (58)	48 (63)	0.9
Observed mortality	21 (45)	15 (32)	0.29
Expected mortality[b]	42.6 (17)	33.7 (18)	0.4
Standardized mortality ratio	1.05	0.95	–
Diagnostic criteria[c]			
Abscess or positive pleural fluid	8	–	–
Histology	2	4	–
BAL-C ≥10^4 and PSB ≥10^3 cfu/ml	38	–	–
Spontaneous recovery	–	20	–
Sterile PSB and BAL-C < 100 cfu/ml	–	28	–

[a] Mann-Whitney or Fisher test as appropriate
[b] As predicted by SAPS II
[c] See the text for complete definitions (more than one diagnostic criterion per patient)

Initial therapeutic strategy

The initial therapeutic strategy was decided on the BAL-D findings by the medical staff. This depended on the level of hypoxemia and the number of organs showing dysfunction. Every patient with more than 5 % infected cells was treated. Most of the patients with 2–5 % infected cells were treated except when clinical symptoms resolved spontaneously.

Antimicrobial therapy was started in patients with recent organ system failures and in those with severe hypoxemia ($PaO_2/FIO_2 < 200$ mmHg) except when no intra- or extracellular microorganisms were recovered from BAL-D examination, and alternate diagnosis was confirmed (other diagnoses on BAL include: intra-alveolar hemorrhage, hypersensitivity pneumonia, and other noninfectious processes such as cardiogenic pulmonary edema diagnosed simultaneously). In the less severely affected patients (i.e., $FIO_2 \leq 0.4$, no decrease in the PaO_2/FIO_2 ratio in the preceding 48 h, no other organ dysfunctions) when no intracellular organisms were recovered, no treatment was instituted before the culture results. The choice of antimicrobials was determined according to risk factors [8], duration of mechanical ventilation, background of previous known patients, and unit colonization and previous antibiotic therapy and Gram stain of BAL-D [9, 10].

When BAL-C recovers no more than 100 cfu/ml, the negative predictive value is near 100 % [4]. In such cases, if probabilistic antimicrobial therapy has been initiated, it was stopped at the receiving of culture results. When the three examinations yielded discordant results (approximately 20 % cases), no definite diagnosis could be made except in patients recovering without antimicrobials for clinical and radiological signs. These patients were generally treated.

Definitions

Definite diagnosis

VAP was diagnosed in the following cases: (a) positive pleural fluid culture or rapid cavitation of the lung infiltrate associated with the resolution of the clinical and radiological signs after adapted antimicrobial therapy; (b) histopathological diagnosis (i.e., the presence of consolidation with intense polymorphonuclear leukocyte accumulation in bronchioles and adjacent alveoli involving several adjacent microscopic fields) in autopsies performed within 3 days of bronchoscopy; (c) PSB culture 10^3 cfu/ml or higher and BAL-C 10^4 cfu/ml or higher, and absence of recovery without antibiotic treatment. The diagnosis of absence of VAP was accepted in the following cases: (a) full recovery without antimicrobial therapy plus the diagnosis of another disease of the chest accounting for the chest radiographic abnormality; (b) absence of bacterial pneumonia at autopsy performed within 3 days; (c) sterile PSB and BAL culture less than 100 cfu/ml [5].

Appropriateness of treatment

The following definitions were used in judging the appropriateness of treatment: *effective treatment*, the administration of at least one antimicrobial that is effective over all the recovered strains at significant concentration in PSB and/or BAL-C; *ineffective treatment*, the recovery of strains not susceptible to the prescribed antimicrobials; *partially effective treatment*, the presence of multimicrobial pneumonia in which at least one recovered strain was not appropriately treated; *useless treatment*, the administration of new antimicrobials after bronchoscopy in patients without VAP; *incorrect treatment,* patients receiving no, partial, ineffective, or useless treatment. When the diagnosis of VAP was based only on distal culture results, treatment was considered incorrect in the case of persistence of clinical signs of sepsis after 3 days. When the diagnosis of no VAP was based only on distal culture results, treatment was considered incorrect when new antibiotic therapy was given to the patient within 3 days because of a persistent suspicion of VAP. *ATS guideline treatment* referred to the initial treatment of severe nosocomial pneumonia using American Thoracic Society (ATS) recommendations [8] and considering that methicillin-resistant *Staphylococcus aureus* (MRSA) is possible. The first-choice antimicrobial therapy was taken to be imipenem plus amikacin plus vancomycin or imipenem plus ciprofloxacin plus vancomycin for every VAP occurring after 5 days of hospital stay and cefotaxime for early-onset VAP.

Methods

The study was conducted in two intensive care units (the 10-bed medical-surgical unit of Hôpital Saint Joseph and the 18-bed unit of La clinique de réanimation des maladies infectieuses, Hôpital Bichat-Claude Bernard) in Paris, France. Between March 1995 and February 1997 each mechanically ventilated patient suspected of having VAP was prospectively included. Patients in whom PSB or BAL was not performed and patients in whom antimicrobials were modified in the 48 h before suspicion of VAP were not included. Bronchoscopy with BAL and PSB was performed according to previously published methods [4, 5, 6, 7]. Patients were sedated and paralyzed, FIO_2 was 100 % during and 2 h after the procedure.

At each step of the strategy used the attending physician and the resident in charge of the patient were asked, blindly, on real time, to complete a form. The questions were: Is a pulmonary infection present? Which micro-organisms are suspected? What is your immediate treatment assuming that further diagnostic steps are unavailable? Finally, the medical team determined the initial antibiotic treatment after 2 h with the BAL-D results. The results of the diagnostic and therapeutic prediction were compared to the definite diagnosis and the treatment of all micro-organisms recovered at significant concentration in PSB and/or BAL.

Statistical analysis

Groups were compared statistically using nonparametric tests. Diagnostic accuracy at each step of the procedure was evaluated using the Wilcoxon test for paired data. We also assessed the accuracy of BAL-D using the area under the receiver-operating characteristic curve [11]. Finally, we performed a sensitivity analysis by successively introducing as VAP or absence of VAP those patients with no definite diagnosis. The BMDP 7.0 statistical softwares package (BMDP Statistical Software, Los Angeles, Calif., USA) and the MedCalc (MedCalc Software, Mariakerke, Belgium) statistical software were used.

Results

No clinical or biological variable was able to differentiate between patients with and those without VAP except changes in PaO_2/FIO_2. The tolerance of bronchoscopy was excellent. Measured oxygen saturation was 100 % in all patients. No instance of barotrauma or bronchial hemorrhage was reported. The definite diagnosis of VAP was based only on positive culture of both BAL-C

Table 2 Micro-organisms recovered according to definite diagnosis (at significant concentration in PSB or BAL-C)

	VAP	No VAP
Staphylococcus aureus (meticillin sensitive)	2	0
Staphylococcus aureus (meticillin resistant)	8	0
Coagulase-negative *staphylococci*	4	2
Other Gram-positive	14	2
Pseudomonas aeruginosa	21	5
Klebsiella spp.	6	0
Proteus spp.	3	0
Enterobacter spp.	3	0
Escherichia coli	5	2
Serratia spp.	2	0
Acinetobacter spp.	4	0
Hemophilus spp.	5	0
Stenotrophomonas maltophilia	3	0
Citrobacter spp.	0	0
Fungi	2	1
Total	82	12

Table 3 Results of Gram stain examination of BAL fluid (at significant concentration or PSB and/or BAL-C)

Gram stain	Culture results		
	Gram-negative bacili	Gram-positive cocci	Mixed
Gram-negative. bacili	18	0	2
Gram positive cocci	0	5	2
Mixed	4	1	14
Negative	0	0	1

and PSB in 37 cases. In all but one of the cases with VAP, at least one of the culture results was positive (and greater than conventional threshold). In patients without VAP, BAL-C was at least 10^4 cfu/ml in seven cases, and PSB was at least 10^3 cfu/ml in two. The radiological infiltrates were considered due to an alternate diagnosis in all 47 cases. No new antimicrobials were given to 35 patients, and 20 were discharged alive. Four antimicrobial therapies were started upon receiving the BAL-D results and stopped upon receiving the BAL-C and PSB results. In the 8 remaining patients the cause of sepsis and pulmonary infiltrates was mesenteric infarction in two, acute pancreatitis in two, acalculous cholecystitis in one, catheter-related bloodstream infection in one, and multisystem organ failure of unknown origin in two. These received broad-spectrum antimicrobials. VAP was excluded by histology in four.

Before suspicion of VAP 27 of the 94 patients were known to be carriers of multiresistant bacterias (MRSA, $n = 13$; *Acinetobacter baumannii*, $n = 5$; extended-broad spectrum β-lactamases Enterobacteriaceae $n = 2$; *Stenotrophomonas maltophilia*, $n = 3$; *Pseudomonas aeruginosa* resistant to ceftazidime and/or imipenem, $n = 6$).

From the 47 patients with VAP significant concentrations of 82 micro-organisms were recovered from BAL-C or PSB (Table 2). In patients without VAP significant concentrations of 12 micro-organisms were recovered in one of the distal samplings.

Prediction of the diagnosis of VAP

The results of the diagnostic prediction of physicians according to their experience and to the step in the diagnostic strategy are shown in Fig. 1. The clinical judgment was poor in predicting nosocomial pneumonia, with 60–70 % positive and negative predictive values. The clinical judgment was correct by 59 % of residents and 71 % of senior physicians. Clinical judgment was more accurate among senior physicians (sensitivity 0.77 ± 0.12; specificity 0.66 ± 0.14) than among residents (sensitivity 0.69 ± 0.15; specificity 0.5 ± 0.16; $p = 0.03$)

Bronchoscopic findings partially improved the accuracy of prediction, yielding a correct clinical judgment of 74 % by residents and 78 % by senior physicians. The prediction by physicians improved dramatically ($p < 10^{-4}$) after the results of BAL-D became available (Fig. 1). For example, the prediction of senior physicians was correct in 88 of the 94 patients (94 %). At this step the sensitivity among senior physicians was 0.98 ± 0.04 and specificity 0.89 ± 0.09 in diagnosing VAP. The accuracy of the diagnosis did not differ between residents and senior physicians.

Diagnostic value of the direct examination of BAL fluid

The area under the receiver-operating characteristic curve of BAL-D was 0.953 (95 % confidence interval 0.888–0.986). Using the threshold of 1 % infected cells, sensitivity was 93.6 % and specificity 91.5 %. Sensitivity and specificity of BAL-D remained unchanged when restricting the analysis to patients with diagnosis based on cavitation, histology, pleural fluid, or spontaneous recovery. The very good discrimination of BAL-D in diagnosing VAP persisted even when introducing the 16 patients with no definite diagnosis as VAP (area under the curve 0.888, sensitivity: 82 %, specificity 91.5 %) or no VAP (area under the curve 0.928, sensitivity 91.5 %, specificity 86.9 %). The Gram stain of BAL-D corresponded to the PSB and BAL-C findings in 37 of 47 cases (Table 3).

Adequacy of the initial treatment

The therapeutic plans of senior physicians before bronchoscopy were incorrect in 33 of the 94 cases (35 %; Fig. 2). In patients without VAP vancomycin was used

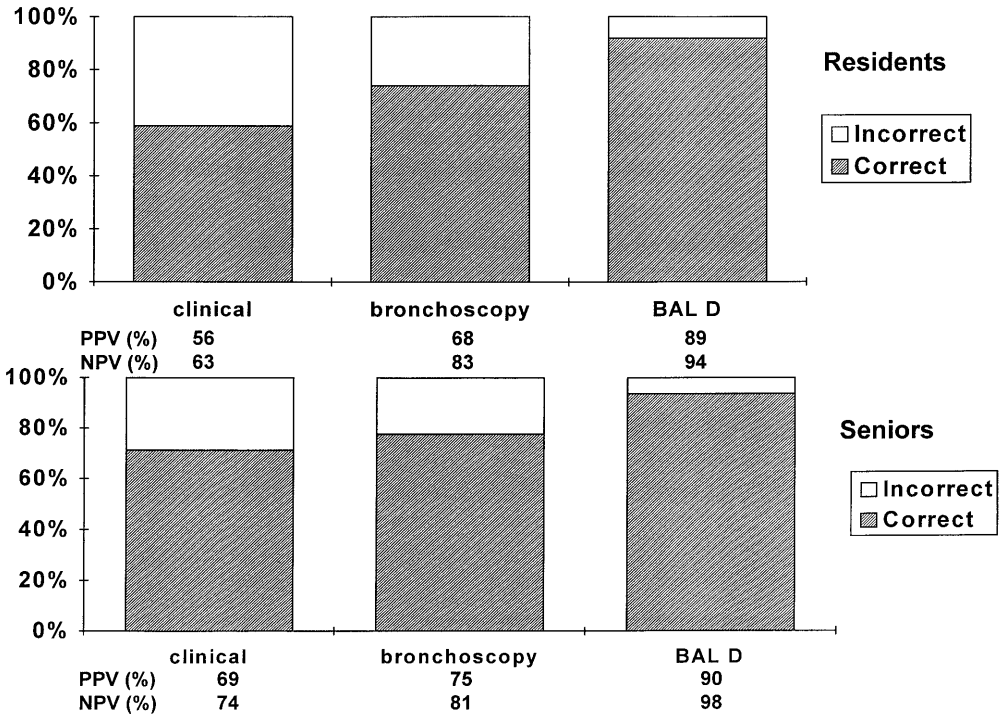

Fig. 1 Positive *(PPV)* and negative predictive values *(NPV)* at each step of a diagnostic strategy based on bronchoscopy, direct examination of BAL fluid *(BAL D)* and BAL and PSB culture *Above* Residents; *below* senior physicians

inappropriately in 7 cases, imipenem in 9, ceftazidime in 2, and amikacin in 8. Overall, the probabilistic treatment would have led to prescription of 40 inappropriate antimicrobials in 18 patients without VAP.

After the results of BAL-D became available, the treatment proved incorrect in 11 of 94 episodes (12%). The antimicrobials effectively prescribed consisted of tritherapy in 10 cases, bitherapy in 33, and monotherapy in 7 (glycopeptides, $n = 12$; imipenem, $n = 13$; ceftazidime, $n = 10$; other cephalosporins, $n = 14$; piperacillin/tazobactam, $n = 5$; aminoglycosides, $n = 35$; ciprofloxacin, $n = 4$; other antimicrobials, $n = 10$). In patients without VAP vancomycin, imipenem, and amikacin were used inappropriately in one case each.

BAL-D findings confirmed the diagnosis of VAP and avoided unnecessary treatment in 11 cases. It also reduced the number of patients who were inappropriately not treated ($n = 10$; Fig. 2). In these 10, after receiving the BAL-D results, 7 were treated effectively and 3 not (*S. maltophilia,* $n = 1$; *P. aeruginosa*, $n = 2$).

In patients with VAP in whom treatment had been determined before bronchoscopy ($n = 36$), the chosen antibiotic combination was effective in 29. In 7 the treatment was ineffective against at least one micro-organism (MRSA, $n = 2$; *P. aeruginosa*, $n = 2$; *S. maltophilia*,: $n = 1$; *A. baumannii*, $n = 1$; methicillin-resistant coagulase negative staphylococci, $n = 1$; *Enterococcus faecium*, $n = 1$). In this subgroup of patients the Gram stain of BAL-D led to an effective change in treatment in 5 patients, i.e., MRSA ($n = 1$, adjunction of vancomycin because of Gram-positive cocci on Gram stain), *A. baumannii* (switch from ceftazidime to imipenem because of Gram-negative cocco-bacilli), *P. aeruginosa* (switch between cefotaxime and ciprofloxacin to ceftazidime plus amikacin in an episode of early onset pneumonia because of Gram-negative bacilli on Gram stain) and *Enterococcus* (adjunction of vancomycin because of mixed flora on Gram stain). On the other hand, in one case of MRSA VAP the effective clinically determined treatment (imipenem + vancomycin + gentamicin) was switched to an ineffective treatment (imipenem + gentamicin) because of the absence of Gram-positive cocci on Gram stain. Finally, the antimicrobial prescription was ineffective or only partially effective in 6 of 47 cases (13%).

A systematic treatment based on ATS guidelines (imipenem + amikacin + vancomycin for suspected late-onset cases and cefotaxime for early-onset ones) would have led to 6 ineffective or partially effective antimicrobial therapy and 47 useless treatments [8]. The use of ciprofloxacin instead of amikacin would have led to 8 ineffective or only partially effective treatments.

Of the 47 patients with VAP 21 died. Death was not related to the inadequacy of the initial treatment (incorrect treatment, 2/6 deaths, 33%; correct treatment, 19/41 deaths, 46%; $p = 0.43$). However, the Sequential Organ Failure Assessment score [12] on the day on which VAP was suspected was slightly higher in the group receiving correct treatment (7 ± 4 vs. 5 ± 5, $p = 0.2$).

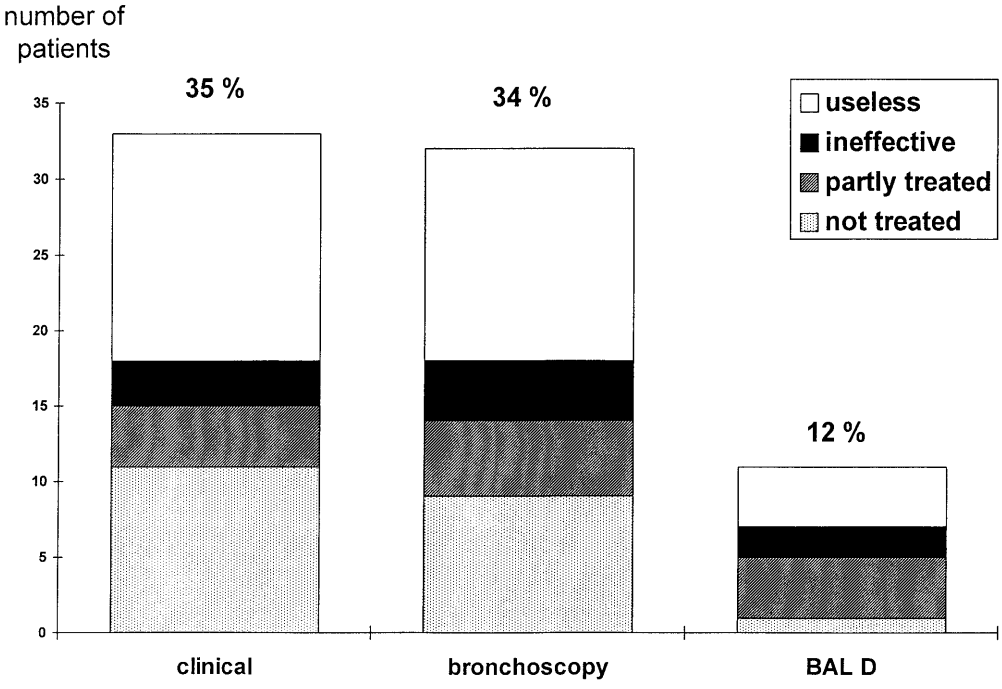

Fig. 2 Treatment was evaluated at each step of the distal strategy according to culture results and antibiotic susceptibility testing. See the text for definition of useless treatment, ineffective treatment, and partly treated patients

Discussion

These findings confirm that clinical judgment is poor in diagnosing VAP. Clinical judgment was confirmed by distal samplings and follow-up in two-thirds of the cases, in agreement with the findings of other studies [3, 13]. The correctness of the initial diagnosis was unrelated to the physician's experience when using the BAL-D results. BAL-D fluid discriminated between patients with and those without VAP with a sensitivity and a specificity greater than 90 % when using a 1 % threshold value. This confirms that a threshold of 1–2 % infected cells is probably more accurate than a 5 % threshold in discriminating between patients with and those without VAP [4, 5, 6, 7].

Gram's stain examination of BAL-D was in agreement with BAL-C in 79 % of VAP cases. This figure is much higher than that in previously published reports [6] and is probably due to the experience of the microbiological teams in the two hospitals. Whether similar results could have been obtained by Gram-stain of tracheal aspirates remains to be determined.

The probabilistic treatment chosen by the senior physician before bronchoscopy would have been effective in 29 of 47 (62 %) of the patients with VAP. Inappropriate antibiotic therapy was chosen by physicians in 15 of 47 patients (32 %) without VAP. Although the clinical strategy was simulated and not effectively used, the proportion of patients in whom antimicrobials would have been effective was quite similar to that observed in other studies (33–66 % [3, 13, 14]) which used an effective clinical strategy.

Our strategy led to effective treatment of 87 % of VAP cases. The appropriateness of treatment was very similar to that obtained using the current ATS guidelines [8]. This strategy avoided the overuse of extended-spectrum antibiotics in patients suspected of having VAP and who ultimately were found not to have VAP. It thus helped to reduce the risk of multiresistant bacteria emerging [15].

Surprisingly, the appropriateness of the initial treatment was unrelated to patient outcome [16]. Inappropriateness or absence of treatment of nosocomial pneumonia is considered a major prognostic factor [17, 18, 19]. This finding in our study is probably due to two major factors. The increased risk of death related to the inappropriateness of initial treatment is probably too low to reveal differences. Moreover, as suggested by the Sequential Organ Failure Assessment score on the day of VAP, the more severely affected patients received empirically broad-spectrum antibiotic combinations even without cells containing bacteria on BAL-D.

The superiority of invasive method in managing patients with suspected VAP is still under debate. Fabregas et al. [20] found the accuracy of clinical diagnosis in 25 patients to be similar to that based on microbiological results of invasive and noninvasive samplings, comparing to the results of postmortem pulmonary biopsies (histology and culture). However, this study addressed a very particular population (i.e., deceased patients, with or without clinical suspicion of VAP), and therefore the results may not be compared to those in the routine management of patients suspected of having

VAP. Moreover, two-thirds of these patients received antibiotics until the day of death, and in the eight patients without antimicrobials the accuracy of clinical signs (sensitivity 67%, specificity 0%) was far lower than that obtained by PSB (sensitivity 83%, specificity 100%).

Sanchez-Nieto et al. [21] reported significantly more modifications in the initial antimicrobial therapy among patients managed by an invasive strategy than those managed by a clinical strategy. Unfortunately, this study lacked a coherent management of patients in the invasive strategy group. In particular, the initiation of antimicrobial treatment was based only on clinical evaluation and not Gram stain, and the administration of antibiotics was continued in all patients despite negative culture results. Similarly, two recent randomized studies found clinical strategy to be associated with the same amount of effective initial antibiotic therapy [22, 23]. However, the use of distal sampling more frequently led to a change in antibiotics, with a narrower spectrum antibiotic being preferred [23].

On the other hand, Fagon et al. [24] randomly compared patients managed by a clinical strategy to those managed by an invasive strategy very close to ours. They found that only 1% (vs. 24% in the clinical management group) of patients with suspected VAP and positive PSB or BAL-C findings (or tracheal aspirate culture in the clinical management group) received antimicrobials to which at least one culture isolate was resistant in vitro.

The effect of clinical or invasive distal strategy on prognosis is also controversial. Invasive strategy significantly improved ICU outcome in the study by Fagon et al. [24]. On the other hand, ICU mortality was increased, although nonsignificantly, in the Sanchez-Nieto et al. study [20] and was unchanged in the studies by Sole Violan et al. [23] and Ruiz et al. [24]. Our cohort study shows that a strategy based on bronchoscopy and BAL-D performed in routine practice leads to the rapid and correct treatment of most patients. As there was no control group of patients effectively managed using a clinical strategy, our findings do not contribute to resolving this controversial issue.

Some shortcomings in the design of this prospective cohort study must be noted. First, we used the results of PSB and BAL-C to define the presence or absence of VAP. PSB is considered by most authors to be very specific in patients suspected of having VAP [5] even in studies favoring proximal blind bronchial samplings [25]. Moreover, our definitions for the absence and presence of VAP may be questioned. Combining the results of two distal examinations in the final diagnosis has been postulated to provide high diagnostic accuracy [5]. Our microbiological criteria for the absence of VAP may also be considered. However, the sensitivity of BAL-C in diagnosing VAP is 92% [25] and 100% [26] when using a threshold of 10^2 cfu/ml. Finally, the findings remained unchanged when limiting the analysis to patients in whom the diagnosis was not based on distal samplings culture results.

Another concern in diagnosing VAP is patients who already are receiving antibiotics. However, previous antibiotic therapy used for other infections, prior to the first symptom consistent with VAP, did not modify the diagnostic yield of PSB and BAL-C [7, 10]. On the contrary, recent changes in antimicrobials have decreased dramatically the accuracy of these examinations [7, 26]. This is why we excluded from the study patients in whom antimicrobials were modified or introduced in the last 48 h. Second, bronchoscopy and distal samplings as well as BAL-D were available at any time. It is thus possible that our results cannot be extrapolated to other teams who are not familiar with distal samplings 24 h a day. Finally, most of the episodes of suspected VAP occurred after mechanical ventilation lasting more than 7 days, and a substantial proportion of our patients were at a high risk of multiresistant bacteria colonization [10]. It is possible that our results are much more related to late-onset suspicion of pneumonia than to early-onset suspicion.

However, today, in an era in which minimizing costs and restricting the spread of multiresistant bacteria, the limited use of antimicrobials is highly recommended. The use of empirical broad-spectrum antibiotics in patients without infection is potentially harmful, facilitating colonization and superinfection with multiresistant bacterias [27] and has been shown to be correlated with increased length of hospital stay and increased hospital costs [28].

We conclude that distal strategy using BAL-D is safe and as effective as empirical very high dose triple-antibiotic therapy in treating patients suspected of having VAP.

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