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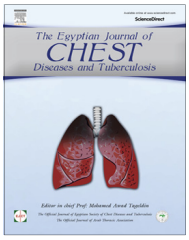

ORIGINAL ARTICLE

Comparison between bronchoscopic BAL and non-bronchoscopic BAL in patients with VAP

Mohammad H. Afify [a], **Enas A. Shaheen** [a], **Samy S. El-Dahdouh** [b], **Hanady M. El-Feky** [a,*]

[a] *Department of Anaesthiology, Intensive Care and Pain Management, Faculty of Medicine, Menoufia University, Abd Elnaser St., Shebein Elkom, Menoufiya, Egypt*
[b] *Department of Chest Diseases and Tuberculosis, Faculty of Medicine, Menoufia University, Egypt*

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KEYWORDS

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Abstract *Background:* The diagnosis of ventilator associated pneumonia (VAP) remains a challenge because the clinical signs and symptoms lack both sensitivity and specificity and the selection of microbiologic diagnostic procedure is still a matter of debate. *Objective*: To compare the diagnostic value of bronchoscopic BAL and non-bronchoscopic protected BAL in patients with VAP. *Materials and methods*: Twenty patients, clinically diagnosed with VAP, were involved in this research; they were evaluated by bronchoscopic and non-bronchoscopic BAL for diagnosis of VAP. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of bronchoscopic and non-bronchoscopic BAL were calculated, taking clinical pulmonary infection score (CPIS) of $\geqslant 6$ as reference standard. *Results*: There was a good microbiologic concordance and strong correlation between bronchoscopic BAL and non bronchoscopic BAL in diagnosis of VAP. There was a high concordance between CPIS score and both procedures' results. Percentage of concordance between CPIS and bronchoscopic BAL was 97.5% and with non bronchoscopic BAL was 95%. Gram negative organisms were the commonest organisms isolated by both techniques. *Conclusion*: Non bronchoscopic BAL is an inexpensive, easy, and useful technique for microbiologic diagnosis of VAP. This finding, if verified, might simplify the approach for the diagnosis of VAP.

Introduction

The diagnosis of ventilator associated pneumonia (VAP) remains a challenge because the clinical signs and symptoms lack both sensitivity and specificity and selection of microbiologic diagnostic procedure is still a matter of debate [1]. Accurate clinical and microbiologic diagnosis of VAP is

* Corresponding author. Tel.: +20 01003274372.
E-mail address: dbasiony@gmail.com (H.M. El-Feky).
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essential not only for selection of appropriate antimicrobials but also to prevent their misuse. The invasive diagnostic methods, including quantitative cultures of distal airway specimens obtained by using bronchoscopic bronchoalveolar lavage (BAL) could improve identification of patients with true VAP and selection of appropriate antibiotics [2,3]. However, bronchoscopy requires technical expertise and adds to the cost of care. In an attempt to overcome these limitations, non-bronchoscopic distal airway sampling methods have emerged, like non-bronchoscopic BAL (NBAL) and non-bronchoscopic PBS [4,5].

Aim of the work

To compare the diagnostic value of bronchoscopic BAL and non-bronchoscopic protected BAL in patients with VAP.

Patient and methods

This prospective comparative study was conducted in intensive care unit (ICU) at Menoufia University Hospitals. Patients older than 17 years who required ventilatory support for more than 48 h or more with clinical and radiological diagnosis of VAP according to CPIS score were enrolled. Patients with diagnosis of community acquired pneumonia or hospital acquired pneumonia before starting of mechanical ventilation and who mechanically ventilated in another hospital for 48 h or more before admission were excluded.

In each patient, Two respiratory samples were collected which include bronchoscopic BAL and NB-BAL. To avoid contamination of the lower airways, the non-bronchoscopic sampling was performed first; before either procedure, the ventilatory settings were adjusted by increasing tidal volume by 100 ml and FiO_2 to 1.0. All the vital signs including heart rate, blood pressure, temperature and oxygen saturation were monitored during the procedure. A special elbow adaptor mounted on the endotracheal tube allows catheter or the flexible bronchoscope to be inserted while the patient is on the mechanical ventilator. The seal on the hole of elbow adaptor was open during the procedure and therefore airway pressure was not maintained during the procedure. Sedation was maintained with boluses of 3–5 mg of intravenous midazolam as required (see Figs. 1 and 2).

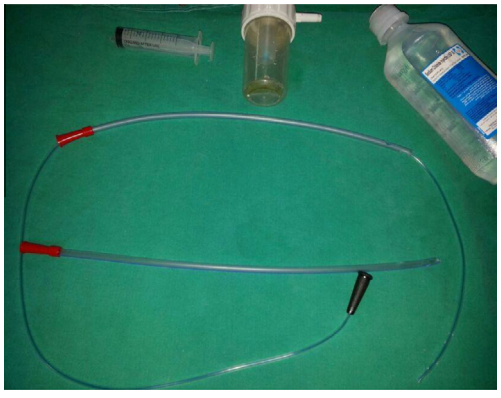

Figure 1 NB-BAL catheters used in the study.

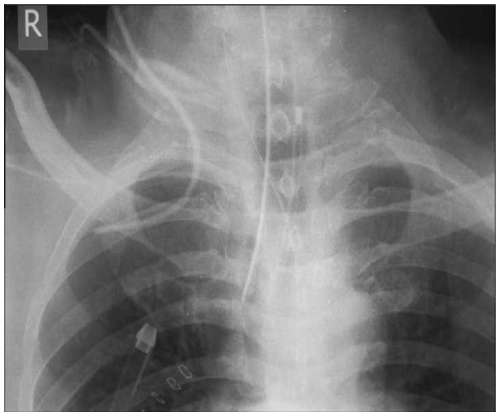

Figure 2 Chest X-ray showing the site of catheter wedge in NB-BAL.

NB-BAL was performed by the double catheter technique. A sterile suction catheter of size 16 Fr was cut 2–3 cm from the distal end to give a final length of about 47–48 cm and inserted through the endotracheal tube and blindly advanced into the distal airways till resistance is felt then the catheter was wedged in that position. A second 50-cm long sterile suction catheter of size 8 Fr was passed through the first catheter and advanced as far as possible and chest X ray was done to confirm that the site of suction tip catheter wedged in the right lung and normal saline (150 ml) was instilled through the inner tube and aspirate was collected in a sterile container by suction.

Then, bronchoscopic BAL, Using (Pentax FB, 18-TV, with internal diameter of 2 mm), any patient having contraindication for fiber-optic bronchoscopy is excluded as; 1 – Severe uncorrected hypoxemia despite the administration of supplemental oxygen. 2 – Unstable cardiovascular or hemodynamic status. 3 – Coagulation defects. The prothrombin concentration should be greater than 70%, and the platelets count greater than 60,000/mm [3].

Once the site had been chosen, the bronchoscope was advanced into a subsegmental bronchus until the tip was wedged. Care must be taken to avoid "over wedging" the bronchoscope, since this can result in additional trauma to the airway and diminish fluid recovery. A good wedge position was confirmed by noting slight airway collapse when gentle suction is applied. A poor wedge position allows leakage of lavage fluid around the bronchoscope. Optimum fluid recovery occurs when the bronchoscope completely occludes the bronchial lumen of a 3rd or 4th bronchial subsegment. Normal saline (commercial 0.9 percent NaCl) was used as the instillate. We used two to three sequential aliquots of 50 mL each. Using tubing with three way stopcock, a saline-filled 50 mL syringe was attached to the side port of the bronchoscope. The first aliquot of saline was instilled slowly and steadily. After the first aliquot of saline was infused, it was recovered immediately into the same syringe by gentle continuous hand suction. Suction should be gentle enough that visible airway collapse should not occur. In patients with marked airway collapse despite gentle suction, the suctioning process was slowed, and discontinuous suction was used to maximize fluid retrieval. When no further fluid could be aspirated, the stopcock was closed and the syringe (but not the tubing) removed. The second saline filled syringe was attached to the tubing

and the procedure repeated. Following these steps, a third lavage was completed, if desired.

Microbiology processing: All the samples were transported to our microbiology laboratory within 1 h of collection. Samples were cultured and were used for quantification of bacterial load. Bacterial identification was done using standard microbiologic techniques and antibiotic sensitivity was estimated as per National Committee for Clinical Laboratory Standard (NCCLS). The growths were expressed as number of colony forming units (CFU)/mL. The thresholds applied to quantitative cultures for the diagnosis of VAP were 10^4 CFU/mL for NB-BAL and B-BAL.

Data management: Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 20.

Two types of statistics were done:

(a) Descriptive statistics e.g. number (No), percent (%) for qualitative data, mean (x^-), standard deviation (SD) and range for quantitative data.
(b) Analytic statistics e.g.
- Chi- squared test (χ^2) was used to study association between qualitative variables.
- Fisher's exact test for 2×2 tables when expected cell count of more than 25% of cases was less than 5.
- Two-by-two tables were used to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of BAL and non BAL in patients of VAP.
- Kappa test is a measure of association (correlation or reliability) between two measurements of the same individual when the measurements are categorical.
- *P*-value of (>0.05) was considered statistically insignificant.
- *P*-value of ($\leqslant 0.05$) was considered statistically significant.
- *P*-value of ($\leqslant 0.001$) was considered statistically highly significant.

Results

We prospectively evaluated 20 patients with high clinical suspicion of VAP, patients' age ranged between 18 and 70 years (mean 47.70 ± 16.29). There was a male preponderance in the study group with a male:female ratio of 2.3:1. Trauma with disturbed conscious level (DCL) was the commonest cause of ICU admission. DM and hypertension were the commonest comorbidities. DCL was the commonest indication for mechanical ventilation followed by COPD exacerbation.

All patients were diagnosed to have late onset VAP except seven patients who had early onset VAP. All patients in the study were on presumptive antibiotic treatment. All patients had CPIS score >6 and there were either diffuse bilateral or right sided infiltrate on chest X ray. Hypoxemia was the commonest complication that occurred during both procedures as shown in Table 1. In NB-BAL, it was detected in four patients and in bronchoscopic BAL, it was detected in ten patients. Other complications include tachyarrhythmia that was detected in NB-BAL with five patients and in BAL with ten patients, hemorrhage was detected in one case, it was mild and mostly as a result of trauma during bronchoscopic BAL.

Table 1 Complications among the studied sample of patients ($n = 20$).

Complications	Studied respiratory samples tech.				Fisher's exact test	*P* value
	NB-BAL ($n = 20$)		B-BAL ($n = 20$)			
	No.	%	No.	%		
Hypoxemia	4	20.0	10	50.0	3.95	0.04 S
Arrhythmia	5	25.0	10	50.0	2.66	0.10 NS
Bleeding	0	0.0	1	5.0	1.03	0.31 NS
Others	0	0.0	4	23.5	2.50	0.11 NS

Microbial cultures were positive in 18 of 20 (90%) samples of Non-bronchoscopic protected BAL and were positive on 19 of 20 (95%) samples on bronchoscopic BAL as shown in Table 2, Most of the sample results were polymicrobial on both procedures except in three cases on NB-BAL and BAL which were unimicrobial, *Klebsiella* was the most common organism isolated (20 of 40 samples) followed by Acinetobacter (17 of 40) and then pseudomonas (11 of 40). Among these pathogens, 60% were extended spectrum beta-lactamase (ESBL) positive and 40% were metallo beta-lactamase (MBL) positive. Perfect qualitative concordance (organisms) among the two techniques was seen in 10 out of 20 cases and there is change on one or two organisms between the two procedures on the remaining samples. Contamination with MRSA was detected on one case in both procedures and with candida on NB-BAL ($n = 1$) and on BAL ($n = 2$). All patients included in this study were diagnosed to have VAP based on CPIS score but there were two samples of NB-BAL and one sample of BAL showing no growth. Organisms isolated in patient with early onset VAP were mainly polymicrobial and mainly gram negative with either ESBL or MBL type as like the late onset VAP and there is no significant change between the two sampling procedures' results in the two types of VAP in our ICU according to the type of microorganisms.

There was a high concordance between CPIS score and both procedures' results as shown in Table 3. Percentage of concordance between CPIS and bronchoscopic BAL was 97.5% and with non bronchoscopic BAL was 95%. The diagnostic utility of the two sampling techniques is shown in Fig. 3: Non-bronchoscopic protected BAL sensitivity, specificity, PPV and NPV were 89%, 75%, 77% and 88% respectively and Bronchoscopic BAL had a sensitivity of 85% and specificity of 77%, PPV and NPV were 74% and 82% respectively.

Discussion

Even though the B-BAL has several advantages, the most important being the ability to direct sampling into the desired lobe, it is important to emphasize its limitations in resources as fiberoptic bronchoscopes and qualified operators are not always readily available thus potentially delaying pathogen-directed treatment with its harmful consequences [6,7]. Kollef et al. mentioned that NB-BAL is a simple procedure which can be performed by resident doctors and paramedics posted at the ICU after a small demonstration which can reduce the cost of management of VAP [8]. Similar benefits should be

Table 2 Organisms isolated in microbiologic cultures among the studied sample of patients (n = 20).

Organisms (CFU)/mL	Studied respiratory samples				Fisher's exact test	P value
	NB-BAL (n = 20)		B-BAL (n = 20)			
	No.	%	No.	%		
No growth	2	10.0	1	5.0	0.36	0.54 NS
Pseudomonas aerugenisa						
ESBL+	2	10.0	2	10.0	0.28	0.59 NS
MBL	4	20.0	3	15.0	0.17	0.68 NS
Klebsiella spp.						
ESBL+	7	35.0	7	35.0	0.00*	1.00 NS
MBL	3	15.0	3	15.0	0.20	0.66 NS
Acinetobacter spp.						
ESBL+	5	25.0	6	30.0	0.13	0.72 NS
MBL	3	15.0	3	15.0	0.20	0.66 NS
E-coli						
ESBL+	2	10.0	2	10.0	0.28	0.59 NS
MBL	1	5.0	2	10.0	0.36	0.54 NS
Proteus						
ESBL+	2	10.0	1	5.0	0.36	0.54 NS
MBL	0	0.0	0	0.0	–	–
Citrobacter						
ESBL+	0	0.0	0	0.0	–	–
MBL	1	5.0	1	5.0	0.53	0.47 NS
MRSA						
True infection	4	20.0	5	25.0	0.14	0.70 NS
Contaminant	1	5.0	1	5.0	0.53	0.47 NS
Candida						
True infection	2	10.0	3	15.0	0.23	0.63 NS
Contaminant	1	5.0	2	10.0	0.36	0.54 NS

Table 3 Concordance among CPIS score and both procedure culture results.

Sampling techniques	Kappa coefficient	% Concordance	P value
NB-BAL vs. CPIS	0.90	95	0.04 S
B-BAL vs. CPIS	0.95	97.5	0.04 S
NB-BAL vs. B-BAL	0.61	82	0.03 S

expected in our setting as the catheters and mucus extractors used in our study have low cost. This study showed that NB-BAL was less invasive with less compromise of oxygenation than B-BAL. Weardon et al., Ruiz et al., Papazian et al., and Violán et al. reported that complications of invasive tests were not serious but the most commonly reported complications were pulmonary hemorrhage (0–14.3%) and pneumothorax (0–8.9%) [9–12]. Pugin et al., Pham et al. and Rouby et al. showed that previous reports of blind invasive procedures had yielded conflicting evidence mostly because of variable methodologies, different thresholds of quantitative studies and reference standards. Blinded invasive procedures that are used to obtain lower respiratory tract samples may be done by different techniques as blind bronchial sampling (BBS), blind protected specimen brush (BPSB) and mini-BAL. [2,13,14]. In some instances, an unprotected catheter can be used instead. In the present study, we used 20 pairs of samples that were isolated from 20 patients requiring mechanical ventilation and diagnosed to have VAP depending on CPIS score (CPIS > 6). We used a double catheter technique in NB-BAL in an attempt to standardize a technique that is simple, widely available and with low risk of complications. The study analyzed the performance of the double catheter technique of NB-BAL with the B-BAL in the same patient by using the same lavage volume and quantitative threshold. Pugin et al. enrolled 28 patients in their study comparing the B-BAL with NB-BAL that was done by mini BAL technique and CPIS score was used as standard reference [2]. Papazian et al. enrolled 38 patients comparing Mini BAL with B-BAL but postmortem cultures were used as reference standard [15]. Leal-Noval et al. enrolled 38 patients using the protected blind brush technique for NB-BAL and comparing it with B-BAL and used CPIS score as standard reference [16]. Minutoli et al. reported the use of a nasogastric tube [17].

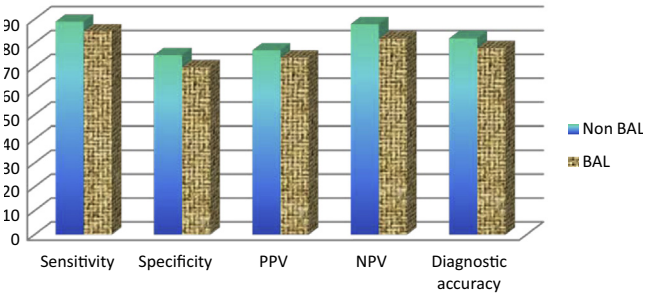

Figure 3 Diagnostic validity of NB-BAL and B-BAL in diagnosis of VAP (n = 20).

Gaussorgues et al. used a balloon-tipped catheter (protected BAL) for BAL [18]. The reference standard in this study was the clinical pulmonary infection score (CPIS) with a total score more than six for the diagnosis of VAP. CPIS was proposed by Pugin et al. and it was compared to quantitative culture of BAL. [2]. This study showed a high concordance between CPIS score and both techniques B-BAL and NB-BAL. Fartoukh et al. found that clinical prediction alone was inaccurate but a modified CPIS score incorporating a Gram stain of respiratory tract secretions improved diagnostic accuracy [19]. Fabregas et al. compared CPIS to pathological diagnosis and found that CPIS had a moderate performance with a sensitivity between 7% and 77% and specificity between 42% and 85% [20]. Pham et al. found that CPIS had a high specificity in diagnosing VAP compared to quantitative BAL fluid culture [21]. Luyt et al. was against the use of CPIS score as reference standard, where they studied 201 mechanically ventilated patients in whom strict bronchoscopic criteria were applied to diagnose or exclude pneumonia and the CPIS did not differ significantly for patients with or without VAP [22]. The use of CPIS to diagnosis VAP was also evaluated in 158 trauma patients and it was found to be not specific in diagnosis of VAP [23]. A major limitation of validating CPIS for diagnosing VAP is that BAL culture is not a true gold standard [15,20,24,25]. In addition, the calculation of CPIS was modified by some authors and different cutoff points were used to diagnose VAP [25,26]. In this study, we used quantitative cultures for both procedures expressed in colony-forming units per milliliter. A cutoff point of (10^4 CFU/mL) was used as an indication of infection and less than this number was considered as contamination. Quantitation of bacteria is important in invasive procedures used to obtain specimens through an airway as it is normally colonized with bacteria and the necessity of an endotracheal tube for mechanical ventilation and colonization of the trachea by oropharyngeal bacterial flora is expected [27]. Torres and El-Ebiary reviewed 23 studies evaluating B-BAL methods and reported that 10^4 CFU/mL was the most frequent cutoff used to differentiate colonization from infection [28]. There was variability in quantitative cultures cutoff point used as a reference standard for B-BAL and NB-BAL. This explains the sensitivity and specificity variability as it inversely varies with cutoff point. Most studies cite 10^4 CFU/mL as a positive result; however, a finding of 10^3–10^5 CFU/mL is also considered positive as showed by Vallés et al. and Torres et al. [29,30]. All patients who were enrolled in this study were receiving antibiotics before and at the time of the procedure. All the cultures are positive except two cases on BAL and three cases on NB-BAL. When patients with pneumonia are receiving antimicrobial agents at the time of sampling, cultures may be negative and concentrations of bacteria may be below the diagnostic threshold. Timsit et al. assessed the impact of antimicrobial therapy on the diagnosis of VAP and he concluded that when patients acquire pneumonia while on antibiotics for infections at extra pulmonary sites, the microorganisms are resistant to these antibiotics and the diagnostic yields of BAL are unaffected [31]. Souweine et al. confirmed and extended the observations of Timsit et al. [32]. These studies suggest that the sensitivity of PSB and BAL for the diagnosis of VAP is unchanged in patients who acquire VAP while on antibiotics for >72 h for treatment of an extra pulmonary infection. Therefore, for such patients, lower respiratory tract secretions should be obtained for quantitative culture and microscopic examination before any changes is made in antimicrobial therapy [31,32].

In performing BAL by both procedures, we used 150 mL of 0.9% saline solution. In a large meta-analysis, there was some controversy over whether amounts lower than 140 mL would influence culture results. Studies in which amounts lower than 140 mL were used presented lower diagnostic accuracy. However, of the 26 studies selected by this meta-analysis, 7 did not mention the amount of volume in use, and only 6 (26%) used amounts higher than 140 mL, which might have biased the data. In addition, there were 6 studies that used amounts of 100 mL [29]. Kollef et al. in their study showed that NB-BAL done by a respiratory physiotherapist had shown good microbiologic agreement (83.3%) with bronchoscopic protected brush. These results signify that blind sampling techniques like NB-BAL are good modalities for microbiologic diagnosis of VAP [2]. The utility of NB-BAL for diagnosis of VAP has been demonstrated by other researchers also, both in clinical as well as autopsy studies. Rouby et al. showed that the sensitivity and specificity of NB-BAL were 70% and 69% respectively, using postmortem histologic and bacteriologic analysis of lung as the gold standard for the diagnosis of VAP [14]. Pugin et al. used CPIS as the diagnostic criteria for VAP and found that sensitivity, specificity, and PPV of NB-BAL were 73%, 96%, and 92%, respectively [2]. The sensitivity of quantitative B-BAL fluid cultures in the literature ranges from 42% to 93%, with a mean of 73%; the variability reflects the characteristics of the study population, prior administration of antibiotics (which reduces sensitivity) and the reference test used [15,31]. The specificity ranges from 45% to 100%, with a mean of 82% in most studies. The sensitivity range of NB-BAL is 63–100% and the specificity ranges are similar to those reported for BAL [6,33]. The present study mean results are comparable to these reports and we hope that this technique would find utility in clinical practice. In the present study, NB-BAL had an excellent concordance with bronchoscopic BAL in diagnosis of VAP which proves the fact that despite it is a blind procedure, samples adequately represent the lower airway secretions and efficiently diagnose VAP in case of diffuse disease involving multiple lobes, and in right lobe pneumonia. We specified the diffuse or right side infiltrate in our study as the NB-BAL is a blind technique and is easily directed to the right side. That was also done by Leal-Noval et al. who enrolled patients with right or bilateral pulmonary infiltrate in their study [16]. The present study has several limitations; an important one is the validity of the exact operating characteristics (sensitivity, specificity, PPV, and NPV) for both techniques, which may be questioned in the absence of the gold standard for the diagnosis of VAP. The diagnostic criteria used for VAP should have a high sensitivity. This approach is based on that the risk for not treating a patient with pneumonia probably outweighs the risk for unnecessary antibiotic administration [36]. For this reason, CPIS was used as the standard and was found to have a high sensitivity for the diagnosis of VAP [8]. However, there are other studies where usefulness of CPIS for the diagnosis of VAP was questioned as shown by Croce et al. and Schurink et al., Rouby et al., Chastre et al. and Torres et al. used the autopsy examination of lung tissue (bacteriologic and histologic) as a gold standard to determine the precise diagnostic yield of similar bronchoscopic and non-bronchoscopic procedures. However, this has a

limitation that it is not useful in clinical decision making. The diagnostic utility of this approach may be further compromised due to histologic sampling errors, the effects of previous antibiotic administration on tissue cultures, and problems related to the timing of postmortem lung examination. Therefore, one should keep this limitation in mind during interpretation of the results of our study [23,26,34,35,30]. Another important limitation is that this is a single center study with a small sample size; its results may not be generalizable to other settings. However, the main objective of the study was to compare the microbiologic findings of the two techniques and the study achieved this objective. Pugin et al., Papazian et al., Kollef et al. and Rouby et al. did larger studies and had shown comparable results to this study. Till date, the optimal strategy for the diagnosis of VAP remains to be defined [2,15,17,14]. The American Thoracic Society guidelines do provide expert opinion supporting quantitative or semi-quantitative cultures of respiratory specimens, although the panel favors invasive quantitative techniques [36].

Conclusion

NBAL is an acceptable alternative to bronchoscopy for the evaluation of suspected VAP as NBAL is an inexpensive, easy, requires lesser expertise and useful technique for microbiologic diagnosis of VAP and has a good microbiologic concordance with bronchoscopic BAL in distal airway sampling.

References

[1] C.P. Andrews, J.J. Coalson, J.G. Smith, et al, Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury, Chest 80 (1981) 254–258.

[2] J. Pugin, R. Auckenthaler, N. Mili, et al, Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid, Am. Rev. Respir. Dis. 143 (5 Pt 1) (1991) 1121–1129.

[3] Torres A., el-Ebiary M. Invasive diagnostic techniques for pneumonia: protected specimen brush, bronchoalveolar lavage, and lung biopsy methods. Infect. Dis. Clin. North Am. 1998;12 (3):701–22.

[4] M.D. Zilberberg, A.F. Shorr, S.T. Micek, et al, Antimicrobial therapy escalation and hospital mortality among patients with health-care-associated pneumonia: a single-center experience, Chest 134 (2008) 963–968.

[5] C. Mietto, R. Pinciroli, N. Patel, et al, Ventilator associated pneumonia: evolving definitions and preventive strategies, Respir. Care 58 (6) (2013 Jun) 990–1007.

[6] J.Y. Fagon, J. Chastre, M. Wolff, Invasive and noninvasive strategies for management for suspected ventilator-associated pneumonia. A randomized trial, Ann. Intern. Med. 132 (2000) 621–630.

[7] P.E. Marik, W.J. Brown, A comparison of bronchoscopic vs. blind protected specimen brush sampling in patients with suspected ventilator-associated pneumonia, Chest 108 (1995) 203–207.

[8] M.H. Kollef, S. Ward, The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia, Chest 113 (1998) 412–420.

[9] P.D. Weardon, A. Chendrasekhar, G.A. Timberlake, Comparison of nonbronchoscopic techniques with bronchoscopic brushing in the diagnosis of ventilator-associated pneumonia, J. Trauma 41 (1996) 703–707.

[10] M. Ruiz, A. Torres, S. Ewig, et al, Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia. Evaluation of outcome, Am. J. Respir. Crit. Care Med. 162 (2000) 119–125.

[11] L. Papazian, C. Martin, B. Meric, et al, A reappraisal of blind bronchial sampling in the microbiologic diagnosis of nosocomial bronchopneumonia. A comparative study in ventilated patients, Chest 103 (1993) 236–242.

[12] J.S. Violán, R. De Castro, J.C. Luna, et al, Comparative efficacy of bronchoalveolar lavage and telescoping plugged catheter in the diagnosis of pneumonia in mechanically ventilated patients, Chest 103 (1993) 386–390.

[13] Pham LH, Brun-Buisson C, Legrand P, et al. Diagnosis of nosocomial pneumonia in mechanically ventilated patients. Comparison of a plugged telescoping catheter with the protected specimen brush. Am. Rev. Respir. Dis. 1991;143(5 Pt 1):1055–61.

[14] J.J. Rouby, M.D. Rossignon, M.H. Nicolas, et al, A prospective study of protected bronchoalveolar lavage in the diagnosis of nosocomial pneumonia, Anesthesiology 71 (1989) 679–685.

[15] L. Papazian, P. Thomas, L. Garbe, et al, Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia, Am. J. Respir. Crit. Care Med. 152 (1995) 1982–1991.

[16] S.R. Leal-Noval, E. Alfaro-Rodriguez, F. Murillo-Cabeza, et al, Diagnostic value of the blind brush in mechanically ventilated patients with nosocomial pneumonia, Intensive Care Med. 18 (1992) 410–414.

[17] R. Minutoli, E. Eden, C. Brachfeld, Bronchoalveolar lavage via a modified stomach tube in intubated patients with the acquired immunodeficiency syndrome and diffuses pneumonia, Thorax 45 (1990) 771–773.

[18] P. Gaussorgues, D. Piperno, P. Bachmann, et al, Comparison of nonbronchoscopic bronchoalveolar lavage to open lung biopsy for the bacteriologic diagnosis of pulmonary infections in mechanically ventilated patients, Intensive Care Med. 15 (1989) 94–98.

[19] M. Fartoukh, B. Maitre, S. Honore, et al, Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited, Am. J. Respir. Crit. Care Med. 168 (2003) 173–179.

[20] N.S. Fabregas, N. Torres, El-Ebiary, Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies, Thorax 54 (1999) 867–873.

[21] T.N. Pham, M.J. Neff, J.M. Simmons, et al, The clinical pulmonary infection score poorly predicts pneumonia in patients with burns, J. Burn. Care Res. 28 (2007) 76–79.

[22] C.E. Luyt, J. Chastre, J.Y. Fagon, Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia, Intensive Care Med. 30 (2004) 844–852.

[23] M.A. Croce, J.M. Swanson, L.J. Magnotti, et al, The futility of the clinical pulmonary infection score in trauma patients, J. Trauma 60 (2006) 523–527.

[24] Torres A, el-Ebiary M, Padró L, et al.: Validation of different techniques for the diagnosis of ventilator-associated pneumonia. Comparison with immediate postmortem pulmonary biopsy. Am. J. Respir. Crit. Care Med. 1994;149:324–31.

[25] C.H. Marquette, M.C. Copin, F. Wallet, et al, Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard, Am. J. Respir. Crit. Care Med. 151 (1995) 1878–1888.

[26] C.A. Schurink, C.A. Van Nieuwenhoven, J.A. Jacobs, et al, Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability, Intensive Care Med. 30 (2004) 217–224.

[27] B. Jourdain, A. Novara, M.L. Joly-Guillou, et al, Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia, Am. J. Respir. Crit. Care Med. 152 (1995) 241–246.
[28] A. Torres, M. El-Ebiary, Bronchoscopic BAL in the diagnosis of ventilator associated pneumonia, Chest 117 (2000) 198S–202S.
[29] J. Vallés, J. Rello, R. Fernández, et al, Role of bronchoalveolar lavage in mechanically ventilated patients with suspected pneumonia, Eur. J. Clin. Microbiol. Infect. Dis. 13 (1994) 549–558.
[30] A. Torres, A. Martos, J. Puig de la Bellacasa, et al, Specificity of endotracheal aspiration, protected specimen brush, and bronchoalveolar lavage in mechanically ventilated patients, Am. Rev. Respir. Dis. 147 (1993) 952–957.
[31] J.-F. Timsit, B. Misset, B. Renaud, et al, Effect of previous antimicrobial therapy on the accuracy of the main procedures used to diagnose nosocomial pneumonia in patients who are using ventilation, Chest 108 (1995) 1036–1040.
[32] B. Souweine, B. Verber, J.P. Bedos, et al, Diagnostic accuracy of protected specimen brush and bronchoalveolar lavage in nosocomial pneumonia: impact of previous antimicrobial treatments, Crit. Care Med. 26 (1998) 236–244.
[33] A.F. Shorr, J.H. Sherner, W.L. Jackson, et al, Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta- analysis, Crit. Care Med. 33 (2005) 46–53.
[34] Rouby J.J., Martin De. Nosocomial bronchopneumonia in the critically ill. Histologic and bacteriologic aspects. Am. Rev. Respir. Dis. 1992;146:1059–66.
[35] J. Chastre, Conference summary: ventilator-associated pneumonia, Respir. Care. 50 (2005) 975–983.
[36] American Thoracic Society, Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am. J. Respir. Crit. Care Med. 2005;171:388–90.