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Diagnosis of ventilator-associated pneumonia: agreement between quantitative cultures of endotracheal aspiration and plugged telescoping catheter

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Abstract *Objective:* To evaluate the diagnostic agreement between quantitative cultures of samples obtained with endotracheal aspiration (ETA) and plugged telescoping catheter (PTC). *Design:* Prospective study. *Setting:* Medical ICU. *Patients:* Hundred thirty-eight episodes of suspected ventilator-associated pneumonia studied in 100 consecutive patients. *Interventions:* For each suspected episode of ventilator-associated pneumonia, ETA and PTC were performed consecutively. The agreement between microbiological results obtained from the two techniques was evaluated (kappa statistic test). Pneumonia was diagnosed on a positive culture result of telescoping catheter with the threshold set at 10^3 cfu/ml or more. The cut-off points evaluated for ETA ranged from 10^2 to 10^6 cfu/ml. *Results:* Micro-organisms retrieved by aspiration and telescoping catheter were similar and bacterial counts obtained by the two pro-

cedures were well correlated ($r=0.71$ $p<0.001$). There was good agreement between positive and negative ETA and PTC specimens (kappa: 0.78) with a diagnostic threshold for ETA of 10^4 cfu/ml. The sensitivity and specificity of ETA for the diagnosis of PTC-confirmed pneumonia were 92% and 85%, respectively. Kappa decreased to 0.48 when the diagnostic threshold was increased to 10^6 cfu/ml. *Conclusions:* Quantitative cultures of ETA and PTC tallied for both micro-organisms and counts. The simpler ETA appears adequate for determining the presence of pathogenic organisms in significant concentration in the lower respiratory tract.

Keywords Diagnostic procedures · Ventilator-associated pneumonia · Endotracheal aspiration · Plugged telescoping catheter · Diagnostic agreement

Introduction

The accurate diagnosis of ventilator-associated pneumonia (VAP) remains a challenge for clinicians in the ICU setting. A diagnosis of VAP is usually based on a combination of clinical, radiological and microbiological criteria. Quantitative cultures of samples obtained by bronchoscopic techniques such as protected specimen brush sampling (PSB) and bronchoalveolar lavage (BAL) are currently viewed as the tests offering the best combination of sensitivity and specificity [1, 2]. However, routine use

of these techniques is limited by the requirement of fiberoptic bronchoscopy, which may not be available on a 24-h basis in many intensive care units, and its interference with intrathoracic pressure, minute ventilation and blood oxygenation [3, 4].

Blind sampling of tracheobronchial specimens with plugged telescoping catheter (PTC) has been suggested as an alternative to more invasive tests, to increase the availability of protected specimens with quantitative culture and reduce the costs of the procedure [5, 6]. The accuracy of these diagnostic techniques accrue from au-

tosy studies showing that pneumonia often spreads to several pulmonary lobes and particularly to posterior portions of the lower lobes [7, 8]. Yet, among all the techniques used to retrieve bronchial secretions processed by quantitative procedures, tracheal aspiration remains the simplest method in mechanically ventilated patients. When only qualitative results are considered, endotracheal aspiration (ETA) has a good sensitivity but a low specificity [9, 10]. However, its specificity is improved when the tracheal aspirate culture is processed quantitatively. Marquette et al. [11] reported a fair correlation between PSB and ETA at a diagnostic threshold of 10^6 cfu/ml for the latter; in this study, ETA had a sensitivity of 82% and a specificity of 83%. Similar results were reported with a cut-off of 10^5 cfu/ml for ETA [12].

The purpose of this prospective study was to evaluate the diagnostic agreement of quantitative culture of samples obtained with ETA and PTC in ventilator-associated pneumonia.

Patients and methods

Patients

Over a 30-month period (from July 1997 to December 1999) a total of 138 clinically suspected VAP episodes were studied in 100 consecutive patients who had been intubated and mechanically ventilated for more than 48 h prior to the onset of clinical manifestations of VAP. Clinical suspicion of bacterial pneumonia was based on the occurrence of new pulmonary infiltrates on chest radiographs and at least two of the following criteria: fever ($\geq 38.5^\circ\text{C}$) or hypothermia ($< 36.5^\circ\text{C}$), the presence of purulent tracheobronchial secretions, leukocytosis ($> 10.10^9/\text{l}$) or leukopenia ($< 3.10^9/\text{l}$). The following information was obtained from the patients' medical records: age, gender, main cause of ICU admission; the disease severity evaluated at admission and at the onset of VAP was assessed by the SAPS II scoring system [13]. In addition, for each episode studied, the following information was recorded: temperature, blood leukocyte count, $\text{PaO}_2/\text{FIO}_2$, radiological manifestation, the duration of prior mechanical ventilation and time between clinical suspicion of VAP and ICU admission.

Specimen collection

Endotracheal aspiration was always performed before PTC. The two procedures were undertaken consecutively and within a 15-min period of time.

Endotracheal aspirates were obtained by sterile suction using a mucus collector (Mucus extractor, ref 534.16, Vygon, Ecouen, France). PTC sampling procedures were conducted as described by Pham et al. [5]. After careful

endotracheal suctioning, the PTC (Combicath, 5828.20 Plastimed lab, Saint Leu, France) was advanced blindly into the bronchus until it could not be advanced further. Then, it was retracted a few centimetres. The inner catheter was then advanced 2 or 3 cm beyond the tip of the outer catheter, extruding the plug. Three brief aspirations were then applied to the inner catheter with a 10-ml syringe connected to its proximal port. The catheter and the entire unit were removed from the patient. The distal portion of the outer catheter was wiped with a sterile pad. The inner catheter was then advanced and 1 ml of sterile saline was flushed through its proximal port and collected in a sterile vial. The distal segment of the inner catheter was transected with sterile scissors and collected in the same vial [5].

Bacteriological processing

The samples were transported to the microbiology laboratory within 15 min. Specimens were processed as soon as they were obtained. The samples were centrifuged and then aliquots of 0.01 and 0.1 ml were evaluated for growth 24 and 48 h later. The results were expressed as colony-forming units per millilitre (cfu/ml) of the original 1 ml dilution.

Data analysis

Cultures of potentially pathogenic micro-organisms were classified according to positive or negative. A previously established quantitative threshold ($\geq 10^3$ cfu/ml) for positive culture results of PTC was used and considered as the reference test for diagnosing nosocomial pneumonia. The cut-off points analysed to establish a positive result for ETA were 10^2 , 10^3 , 10^4 , 10^5 and 10^6 cfu/ml.

The agreement between the microbiological results obtained from the two techniques was assessed using the kappa statistic test according to the method proposed by Landis and Koch [14, 15]: K less than 0.00, poor agreement; K = 0.00–0.2, slight agreement; K = 0.21–0.4, fair agreement; K = 0.41–0.6, moderate agreement; K = 0.61–0.81, substantial agreement; K = 0.8–1, almost perfect. Sensitivity, specificity and predictive values were calculated according to standard formulae, taking into account the individual micro-organism species. Graphic representations of diagnostic parameters were performed, plotting true-positive against false-positive percentages to obtain a receiver operator characteristic (ROC) curve. The other results are expressed as means \pm standard deviation or as percentages of total values.

Table 1 Characteristics of patients

	Patients (n=100)
Age (years)	56±19
Gender (men/women)	66/34
MacCabe (%)	
1	27.5
2	55.1
3	17.4
Episodes of VAP	138
SAPS II at admission	36±13
SAPS II on the day of VAP	35±13
Elapsed time between VAP and admission (days)	9.9±13.8
Elapsed time between VAP and MV (days)	9.6±13.7
Prior antibiotic therapy, n (%)	104(75)
Leukocyte count (10 ⁶ /mm ³)	12.8±7.1
PaO ₂ /FIO ₂ (mmHg)	204±98
Duration of MV (days)	22±24
Mortality, n (%)	51 (51)

MV mechanical ventilation, VAP ventilator-acquired pneumonia

Table 2 Species recovered from plugged telescoping catheter-diagnosed episodes of ventilator-acquired pneumonia

Species	%
Gram-negative bacteria	
<i>Enterobacteriaceae</i>	32
<i>Pseudomonas aeruginosa</i>	20
<i>Acinetobacter baumannii</i>	18
Gram-positive bacteria	
<i>Streptococcus sp</i>	12
<i>Staphylococcus aureus</i>	4
Others	14

Results

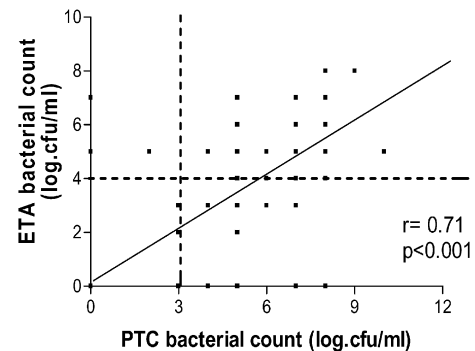
During the study period, a total of 138 episodes of VAP were suspected in 100 patients mechanically ventilated for more than 48 h (66 men and 34 women). The patients had a mean age of 56±19 years and mean SAPS II on admission of 36±13. Patients were admitted to the intensive care unit and required ventilator assistance because of respiratory failure (51), cerebrovascular disease (12), infectious disease (9), heart failure (18), drug overdose (2) or miscellaneous conditions (8).

The patients had received mechanical ventilation for 9.5±7 days prior to the suspicion of VAP. One hundred and four evaluations (75%) were made while the patients were receiving systemic antibiotics that had not been changed during the 72 h prior to sampling; the other patients were not on antibiotics. None of these antibiotic courses was a part of a selective digestive decontamination, which is not currently used in our ICU. No sampling procedure caused a significant complication. The characteristics of the patients are shown in Table 1.

The micro-organisms associated with pneumonia (identified by PTC sampling) are shown in Table 2. In 22 episodes, two or more micro-organisms were recovered

Table 3 Number of micro-organisms recovered per sample

	ETA	PTC				Total
		0	1	2	>2	
	0	34	2	0	0	36
	1	9	64	0	0	73
	2	2	5	18	0	25
	>2	0	0	2	2	4
	Total	45	71	20	2	138

**Fig. 1** Correlation between bacterial count from paired PTC and ETA procedures of all identified micro-organisms

and the diagnosis of polymicrobial pneumonia was made (Table 3). Gram-negative bacilli were the predominant organisms isolated (70%), represented mainly by *Pseudomonas* and *Acinetobacter* (38%) or *Enterobacteriaceae* (32%).

Thirty-four paired cultures were sterile. Eleven ETA yielded one or more micro-organisms while the PTC samples were sterile (Table 3). There was a significant correlation between the bacterial counts obtained by the two procedures ($r=0.71$, $p<0.001$; Fig. 1). Agreement between quantitative cultures of ETA and PTC was calculated over a range of cut-off values (from 10² to 10⁶ cfu/ml) for ETA (Table 4). Using 10⁴ cfu/ml as a diagnostic threshold for ETA, there was 92% and 85% agreement between positive and negative ETA and PTC specimens, respectively (kappa: 0.78). Increasing the diagnostic threshold for ETA to 10⁵ cfu/ml or 10⁶ cfu/ml was not associated with better agreement and the kappa statistic was lowered from 0.78 to 0.48.

The diagnostic value of ETA according to different thresholds of quantitative cultures is shown in Table 5. Depending on the threshold value of ETA, only three to eight episodes could be considered positive by ETA while negative by PTC. The best sensitivity/specificity ratio (92/85) was obtained using 10⁴ cfu/ml. With the same threshold, the negative predictive value was 88%. The ROC curve for ETA is shown in Fig. 2.

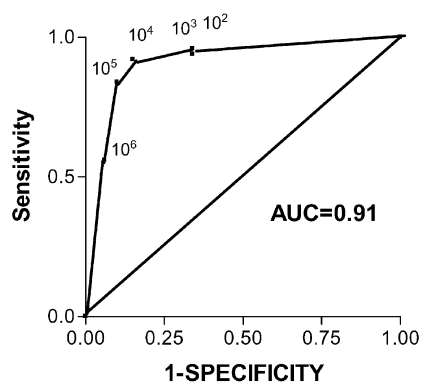
Table 4 Agreement between bacterial counts at the cut-offs analysed

	PTC $\geq 10^3$ cfu/ml (n=85)	PTC $< 10^3$ cfu/ml (n=53)	Kappa
ETA $\geq 10^2$ cfu/ml (n=100)	82	18	0.67
ETA $< 10^2$ cfu/ml (n=38)	3	35	
Agreement (%)	96	66	
ETA $\geq 10^3$ cfu/ml (n=99)	81	18	0.66
ETA $< 10^3$ cfu/ml (n=39)	4	35	
Agreement (%)	95	66	
ETA $\geq 10^4$ cfu/ml (n=87)	79	8	0.78
ETA $< 10^4$ cfu/ml (n=51)	6	45	
Agreement (%)	93	85	
ETA $\geq 10^5$ cfu/ml (n=77)	72	5	0.73
ETA $< 10^5$ cfu/ml (n=61)	13	48	
Agreement (%)	85	91	
ETA $\geq 10^6$ cfu/ml (n=40)	37	3	0.48
ETA $< 10^6$ cfu/ml (n=98)	48	50	
Agreement (%)	44	94	

Table 5 Operating characteristics of endotracheal aspiration for the diagnosis of ventilator-associated pneumonia

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
$\geq 10^2$	96.5	66	82	92
$\geq 10^3$	94	66	81	87.5
$\geq 10^4$	92	85	90	88
$\geq 10^5$	84	90	93	78.6
$\geq 10^6$	44	94	92	51

PPV positive predictive value, NPV negative predictive value

**Fig. 2** Receiver operator characteristic curve of endotracheal aspiration for the diagnosis of ventilator-associated pneumonia

Discussion

In this study designed to evaluate the diagnostic yield of two non-bronchoscopic sampling techniques in VAP, we observed good agreement between ETA and PTC in terms of micro-organisms retrieved. A threshold of 10^4 cfu/ml for ETA resulted in a 92% agreement between the two techniques with a sensitivity and specificity of 92% and 85%, respectively, for the diagnosis of VAP. Increasing

the threshold to 10^5 cfu/ml or 10^6 cfu/ml for ETA resulted in a reduction in the agreement of these techniques.

The presence of prior antimicrobial treatment in up to 75% patients might be regarded as a limitation to accurate diagnosis of VAP, because it may lead to a high number of false-negative results. However, Timsit et al. have shown that the diagnostic yield of some of the procedures used to diagnose VAP (PSB and BAL) is not altered by the administration of long courses of antibiotics (>72 h) to treat earlier septic episodes [16]. Moreover, respiratory secretions usually carry a substantial number of bacteria when a super-infection occurs with a resistant micro-organism to antibiotics currently administered [17]. In addition, since ETA usually preceded PTC in our study, any modification of low respiratory tract flora would have played the same role with both samples.

The clinical diagnosis of VAP is difficult because clinical, biological and radiological signs are neither sensitive nor specific, especially in patients with pre-existing lung disease [18]. In addition, colonisation of the airways by potentially pathogenic micro-organisms is widespread in patients receiving mechanical ventilation. Hence, various techniques have been developed to obtain uncontaminated secretions from the lower airways. These methods include bronchoscopic or blind PSB, bronchoscopic or blind BAL and blind single-sheathed plugged telescoping catheter (PTC). Obviously, in the setting of left-sided pneumonia, bronchoscopic-guided collection of bronchial specimens should minimise the risk of false-negative results. Quantitative cultures of samples obtained by invasive bronchoscopic techniques (PSB and BAL) are currently regarded as the mainstay for the diagnosis of pneumonia. Moreover, Fagon et al. [19] have shown that the combination of quantitative culture and rapid direct examination of bronchoscopic PSB samples or BAL samples in an invasive strategy of management of suspected VAP reduced both mortality and antibiotic use through an early antibiotic cessation in almost 50% of

cases. However, this study did not use quantitative cultures of ETA specimens in the control arm. In addition, the routine use of bronchoscopy is limited by its reduced availability in many intensive care units.

Plugged telescoping catheter with quantitative cultures, a technique that is widely used in France, is actually a safer procedure than the other invasive techniques using bronchoscopy [5]. In spite of its technical pitfalls (mainly the blind positioning of the distal tip), PTC has been established as a reliable and accurate procedure for the diagnosis of VAP [5, 20]. It has been validated in mechanically ventilated patients with bacterial infections, where both sensitivity and specificity of quantitative cultures of PTC have ranged between 60 and 100% [5, 21, 22]. The conventional technique of respiratory tract secretion sampling by ETA, however, remains the easiest and most widely used means to obtain bronchial secretions in mechanically ventilated patients. Despite the lack of specificity of non-quantitative cultures of ETA, it has recently gained renewed attention [23, 24, 25, 26]. Indeed, recent studies suggest that ETA associated with quantitative cultures might have an acceptable overall diagnostic accuracy, similar to that of more invasive techniques [11, 12, 26].

In a study by Marquette et al. [11] the operating characteristics of ETA associated with quantitative cultures compared favourably with those of PSB culture, with a slightly higher sensitivity and a lower specificity. Similarly, El Ebiary et al. [12] found, in 54 patients with suspected VAP, that this technique was relatively sensitive (70%) and specific (72%) for the diagnosis of pneumonia. In a study of 57 consecutive episodes of suspected lung infection, Jourdain et al. reported that the area under the ROC curve of ETA was 0.76 and the threshold of 10^6 cfu/ml appeared to be the most accurate, with a sensitivity of 68% and a specificity of 84% [27]. In addition, studies using histology as a “gold standard”

found that microbial species that grew at a level higher than 10^7 cfu/ml in ETA samples were also found in lung tissue. Torres et al. [2] observed that the lowest rate of false-positive results was obtained using thresholds of 10^6 for ETA, 10^5 for PSB and 10^6 for BAL [2]. The authors reported a specificity of 85% for ETA at 10^6 cfu/ml, 85% for PSB at 10^4 cfu/ml and 78% for BAL at 10^6 cfu/ml.

More recently, two prospective studies using post mortem histological examination of the lung as the “gold standard” assessed the accuracy of cultures obtained using ETA, PSB and BAL [20, 28]. In the first one Marquette et al. [20] found similar sensitivity and specificity of quantitative cultures of samples retrieved by ETA, PSB and BAL. When the diagnostic threshold of ETA was reduced from 10^6 to 10^5 cfu/ml, the sensitivity increased and specificity decreased. Papazian et al. [28] reported an area under the ROC curve significantly greater for ETA than for PSB. The authors concluded that, given that the non-invasive ETA was more sensitive, it should be preferred to PSB for the diagnosis of VAP.

To the best of our knowledge, only one study has previously compared the accuracy of ETA and PTC in the diagnosis of VAP [29]. Forty-six bronchial samplings were obtained from 31 patients with suspected VAP. In this study, the authors observed a lower agreement (76%) than that observed in our study. The sensitivity (89.5%) and the specificity (66.7%) of ETA were also below the levels we recorded. We cannot readily account for these differences, particularly since the design of the study by Fangio et al. [29] systematically excluded VAP that developed in the left lung, which would tend to increase the sensitivity of the sampling method under evaluation.

In conclusion, our study shows that quantitative cultures of ETA and PTC were in agreement for both microorganisms and bacterial counts. Thus, the simpler ETA appears adequate for routine diagnosis of VAP, provided quantitative cultures are obtained.

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