CONSISTENCY BETWEEN BRONCHOALVEOLAR LAVAGE AND ENDOTRACHEAL ASPIRATE IN THE DIAGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA

Kamaran Omer Amin [a], Bnar J. Hama Amin [b], Haval Othman [b], Safeen Othman Mahmood [b], Nsar Jamal Abdalla [b], and Kosar Mohamed Ali [a]

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ABSTRACT

Background

Ventilator-associated pneumonia (VAP) is a common nosocomial lung infection. Quick and accurate identification of the causative pathogen is crucial to improve prognosis. To date, the literature is controversial regarding whether endotracheal aspirate (ETA) can be used as an alternative to bronchoalveolar lavage (BAL) in VAP diagnosis.

Objectives

To evaluate the consistency between the results of BAL and ETA in the diagnosis of early- and late VAP and to determine the microbial profiles of the involved microorganisms and their antimicrobial susceptibility.

Patients and Methods

This is a single-centre prospective study that included 50 VAP-suspected patients conducted at Shar Hospital, Sulaimani, Iraq, from July 2021 to February 2022. The patients were categorised into early VAP and late VAP. For each patient, both ETA and BAL techniques were used to obtain samples for microbiological analysis and antimicrobial susceptibility testing.

Results

Ten (20%) patients developed early VAP, and 40 (80%) developed late VAP. The culture results of samples obtained by BAL showed microbial growth in 45 (90%) of the cases. Meanwhile, ETA resulted in microbial growth in 40 (80%) patients. In 45 (90%) of the samples, both techniques yielded the same results regarding microbial growth in the cultures. Among the 45 samples with the same growth results, 35 (70%) showed the same type of microbes, and 5 (10%) showed no microbial growth, indicating substantial agreement. In both BAL and ETA, *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Acinetobacter baumannii* were the most frequently isolated pathogens. Both early- and late-VAP were associated with a high frequency of multidrug-resistant microorganisms, 6 (75%) and 25 (56.8%), respectively. However, extensively drug-resistant/pan-drug-resistant isolates were much more common in late-VAP patients (12, 27.3%).

Conclusion

ETA can be a reliable, non-invasive alternative to BAL in VAP diagnosis associated with rapid and relatively accurate results.

Keywords: *Ventilator-associated pneumonia; endotracheal aspirate; comparison; bronchoalveolar lavage; antimicrobial susceptibility screening*

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[a] College of Medicine, University of Sulaimani, Kurdistan Region, Iraq.
[b] Shar Teaching Hospital, Sulaimani City, Kurdistan Region, Iraq.
Correspondence: bnarjamaal@gmail.com

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is a very common nosocomial lung infection [1]. It develops after at least 48 hours of mechanical ventilation via endotracheal intubation or tracheostomy [2]. In the intensive care unit (ICU), VAP is the second most common hospital-acquired infection. Meanwhile, it is the most prevalent infection in patients receiving mechanical ventilation, with an incidence of 20% [3,4]. VAP can be categorised into early and late subtypes, with the former occurring between 2-5 days post mechanical ventilation and the latter occurring from the fifth day onwards [5]. Patients with VAP and other related conditions are often immunocompromised, and diagnosing such conditions is challenging due to non-specific signs and symptoms [6]. VAP poses a serious threat to public health, associated with a longer hospitalisation period, increased need for resources, and additional costs [7]. In the ICU, the condition also leads to a significant increase in mortality rate (32.5%) [8]. Early diagnosis of VAP is crucial, as delayed antimicrobial therapy can result in even higher mortality (9). Bacteria are the primary pathologic agents responsible for VAP, including gram-negative bacteria such as *Klebsiella pneumonia*, *Escherichia coli, Pseudomonas aeruginosa*, and Acinetobacter species, and gram-positive bacteria such as *Staphylococcus aureus* [10]. Multidrug-resistant (MDR) bacteria are the main contributors to the high mortality rates observed in VAP patients. Inappropriate use of antibiotics is a significant cause of the emergence of antibiotic resistance. Hence, quick and accurate identification of the causative microbial agent is crucial to improve prognosis [11]. The diagnosis of VAP is challenging due to the absence of a reference standard [9]. The literature is quite controversial regarding the best sampling method for obtaining specimens for microbiological diagnosis [12]. Some studies state that the result of invasive techniques such as bronchoalveolar lavage (BAL) is superior and associated with better prognosis in comparison to non-invasive procedures such as endotracheal aspirate (ETA). Meanwhile, others believe that ETA can be used as an alternative to BAL as there is no significant difference between the results of the two sampling techniques [13].

The current study aimed to evaluate the consistency between the results of BAL and ETA in the diagnosis of early- and late VAP and to determine the microbial profiles of the involved microorganisms and their antimicrobial susceptibility.

MATERIALS AND METHODS

The current single-centre prospective study included 50 suspected VAP patients and was conducted at Shar Hospital, Sulaimani, Iraq, from July 2021 to February 2022. Approval for the research was acquired from the ethical committee of the Kurdistan board for medical specialities. Written and oral informed consent was collected from all the participants enrolled in the study. VAP-suspected patients who were admitted to our ICU and were mechanically ventilated for at least two days were included in this study. Pneumonia was suspected by a C-reactive protein level >17 mg/dL, the presence of purulent airway secretions, a new or evolving infiltrate on chest radiograph, and systemic inflammatory response syndrome, which was characterised by fever (>38 °C), a white blood cell count of > 10,000/µl or < 3,000/µl, elevated respiratory rate (>20 cpm) and heart rate (>90 bpm)—patients suffering from COVID-19 or pneumonia before ventilation were excluded.

Based on the time of pneumonia development since admission, the patients were categorised into early-VAP (2-5 days after entry) and late-VAP (>5 days post admission) (in this case, access equals mechanical ventilation). For each patient, both ETA (via a sterile catheter) and BAL (via a fiberoptic bronchoscope) techniques were performed simultaneously and by the same person to obtain samples later used in further microbiological analysis and antimicrobial susceptibility testing.

The samples were inoculated on blood agar (HiMedia, India) and MacConkey agar (Lab M Ltd., UK) for atmospheric air culture and chocolate agar (Condalab, Spain) for 5% CO_2 incubated overnight at 37 °C.

An examination of the cultured plates was performed to detect visible growth. Semi-automated API system (bioMérieux SA, France) or Vitek-II system (bioMérieux SA, France) was used for isolate identification. Antimicrobial susceptibility testing was performed via either the manual disk diffusion method (Kirby-Bauer method), Vitek-II system, or using BD phoenix M50 (USA), and the results were interpreted by the recommendations of the clinical and laboratory standards institute (CLSI).

Sample rejection was according to the following criteria: (1) insufficient volume, (2) clotted specimens, (3) external contamination, (4) specimens not submitted in an appropriate transport container, or (5) improperly labelled specimens.

Microorganisms were classified into four groups based on susceptibility to the given antimicrobials: a) Susceptible; sensitivity to all the given drugs, b) multidrug-resistance (MDR): acquired resistance to one or more agents in three or more antimicrobial categories, c) extensively drug-resistant (XDR); resistance to one or more agents in all but two or fewer antimicrobial categories, and d) pan drug-resistant (PDR); resistance to all agents in all antimicrobial categories.

Baseline characteristics of the patients were obtained, such as age, gender, and comorbidities. Then, the necessary data were recorded on a Microsoft Excel sheet, and the analysis of the data required was performed using the Statistical Package for the Social Sciences (SPSS) software 25.0.

RESULTS

In this study, 50 VAP-suspected patients who met our inclusion criteria were enrolled. Thirty-four patients were male (68%), and sixteen were female (32%). They had a mean of 50.2 years, ranging from 12 to 87 years. Nearly half of the patients (n = 24, 48%) had no comorbidities, 14 were associated with only one comorbidity, and 12 had two or more comorbidities. The most common comorbidities, with decreasing frequency, were diabetes mellitus (n = 11, 22%), cerebrovascular accident (n = 7, 14%), hypertension (n = 5, 10%), heart failure (n = 5, 10%), chronic obstructive pulmonary disease (n = 3, 6%), asthma (n = 2, 4%), femur fracture (n = 2, 4%), Duchenne muscular dystrophy (n = 1, 2%), motor neuron disease (n = 1, 2%), myasthenia gravis (n=1, 2%), and thyrotoxicosis (n = 1, 2%). Among the patients, 27 (54%) were admitted to the ICU for medical reasons, and 23 (46%) were recognised for surgical reasons. Based on the time of pneumonia development since admission, the patients were categorised into early VAP (2-5 days after entry) and late VAP (> 5 days post admission). Only 10 (20%) of the patients developed early VAP, and 40 (80%) of them developed late VAP, (Table 1).

The culture results of samples obtained by BAL showed microbial growth in 45 (90%) of the cases. Meanwhile, samples obtained by ETA resulted in microbial growth in 40 (80%) of the patients. In 45 (90%) of the samples, both techniques yielded the same results regarding microbial growth in the cultures. Among the 45 samples with the same growth results, 35 (70%) showed the same type of microbes, and 5 (10%) showed no microbial growth. Polymicrobial infection was more frequently observed in the results of ETA (7, 14%) than BAL (3, 6%). Regarding the polymicrobial diseases into account, 48 isolates were obtained through BAL, and 47 isolates were obtained through ETA.

The agreement between BAL and ETA based on Kappa was found to be substantial (P > 0.61), Tables 2 and 3. Gram-negative bacteria were the most commonly isolated from BAL (33, 68.7%) and ETA cultures (29, 61.7%). Pseudomonas aeruginosa was the most frequently obtained isolate from BAL cultures (10, 20.8%), followed by *Staphylococcus aureus* (9, 18.8%), *Acinetobacter baumannii* (8, 16.7%), *Escherichia coli* (6, 12.5%), *Streptococcus pneumoniae* (4, 8.3%), *Klebsiella pneumoniae* (3, 6.3%), unknown gram-negative bacteria (3, 6.3%), *Haemophilus influenza* (2, 4.2%), *Proteus Vulgaris* (1, 2.1%), C*andida albicans* (1, 2.1%), and *Aspergillus fumigatus* (1, 2.1%). Meanwhile, the most common isolates from ETA cultures included *Pseudomonas aeruginosa* (10, 21.3%), *Staphylococcus aureus* (10, 21.3%), *Acinetobacter baumannii* (6, 12.8%), *Escherichia coli* (6, 12.8%), *Candida albicans* (5, 10.6%), *Streptococcus pneumoniae* (2, 4.3%), *Klebsiella pneumoniae* (2, 4.3%), *Haemophilus influenzae* (2, 4.3%), unknown gram-negative bacteria (2, 4.3%), *Proteus Vulgaris* (1, 2.1%), and *Aspergillus fumigatus* (1, 2.1%),(Table 4).

In both early-VAP and late-VAP cultures, there were 52 isolates; 8 in early-VAP and 44 in late-VAP. Antimicrobial screening tests of the isolates showed that among the early-VAP isolates, 1 (12.5%) was fully susceptible to all the antimicrobials, 6 (75%) were MDR, and 1 (12.5%) was XDR. Meanwhile, a higher frequency of XDR and PDR microbes was found in late-VAP isolates. The late-VAP isolates had the following antimicrobial resistance pattern; 7 (15.9%) were susceptible, 25 (56.8%) were MDR, 9 (20.5%) were XDR, and 3 (6.8%) were PDR (see Table 5). *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were high-risk microorganisms as they comprised most of the XDR/PDR isolates; 6 (50%) and 4 (33.3%), respectively.
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Table 1. Baseline characteristics of the participants.

Characteristics	No. patients (%)
Gender	
Male	34 (68%)
Female	16 (32%)
Age (Year)	
Mean	50.2
Minimum	12
Maximum	87
Admission category	
Medical	27 (54%)
Surgical	23 (46%)
VAP (admission duration)	
Early-VAP (2-5 days)	10 (20%)
Late-VAP (>5 days)	40 (80%)
Comorbidity	
Diabetes mellitus	11 (22%)
Cerebrovascular accident	7 (14%)
Hypertension	5 (10%)
Heart failure	5 (10%)
Chronic obstructive pulmonary disease	3 (6%)
Asthma	2 (4%)
Femur fracture	2 (4%)
Duchenne muscular dystrophy	1 (2%)
Motor neuron disease	1 (2%)
Myasthenia gravis	1 (2%)
Thyrotoxicosis	1 (2%)

Table 2. Cultural results of BAL and ETA.

Culture Results	No. Samples (%)
BAL	
Growth	45 (90%)
No Growth	5 (10%)
Polymicrobial	3 (6%)
ETA	
Growth	40 (80%)
No Growth	10 (20%)
Polymicrobial	7 (14%)
The same cultural results	
Types of microbes	35 (70%)
No Growth	5 (10%)

Table 3. Agreement test between BAL and ETA culture.

ETA culture	BAL culture		Kappa	P-value
	Growth	No growth		
Growth	40 (80%)	0 (0%)	0.62	**<0.001**
No growth	5 (10%)	5 (10%)		

Table 4. Type of microorganisms from positive BAL and ETA cultures.

Type of microorganisms	BAL (no. isolates = 48) No. (%)	ETA (no. isolates = 47) No. (%)
Gram-negative bacteria	33 (68.7%)	29 (61.7%)
Unidentified bacteria	3 (6.3%)	2 (4.3%)
Pseudomonas aeruginosa	10 (20.8%)	10 (21.3%)
Acinetobacter baumannii	8 (16.7%)	6 (12.8%)
Escherichia coli	6 (12.5%)	6 (12.8%)
Klebsiella pneumoniae	3 (6.3%)	2 (4.3%)
Haemophilus influenzae	2 (4.2%)	2 (4.3%)
Proteus Vulgaris	1 (2.1%)	1 (2.1%)
Gram-positive bacteria	13 (27.1%)	12 (25.5%)
Staphylococcus aureus	9 (18.8%)	10 (21.3%)
Streptococcus pneumoniae	4 (8.3%)	2 (4.3%)
Fungi	2 (4.2%)	6 (12.8%)
Candida albicans	1 (2.1%)	5 (10.6%)
Aspergillus fumigatus	1 (2.1%)	1 (2.1%)

Table 5. Antimicrobial resistance pattern in early-VAP and late-VAP isolates.

Resistance pattern	Early-VAP (no. isolates = 8)	Late-VAP (no. isolates = 44)
Susceptible	1 (12.5%)	7 (15.9%)
MDR	6 (75%)	25 (56.8%)
XDR	1 (12.5%)	9 (20.5%)
PDR	0 (0%)	3 (6.8%)

DISCUSSION

Ventilator-associated pneumonia VAP is a highly prevalent condition associated with a high mortality rate that depends on the causative microorganisms' severity, comorbidities, age, and characteristics [14]. Multiple risk factors can contribute to the risk of developing VAP, such as underlying lung disease, neurological disease, the duration of mechanical ventilation, sepsis, previous use of antibiotics, and trauma [5]. The diagnosis of VAP is quite challenging, and clinical diagnosis methods yield correct results in only 30 to 50% of the patients, hence are primarily inaccurate and unreliable [15]. Timely use of antimicrobial drugs is necessary for treating these cases, as any delay in initiating antimicrobials can lead to a worse clinical outcome [4]. Additionally, early identification and determination of antimicrobial susceptibility of the causative pathogen are crucial in adequately managing VAP cases [12]. Hence, an optimised, accurate, and rapid diagnostic method is a top priority for the microbiological diagnosis of these cases, mainly due to the continuous increase of MDR microorganisms, which can lead to an increased mortality rate of up to 76% [16,17].

Mechanically ventilated patients may have several colonising microbes in their tracheobronchial tree only hours after intubation. Therefore, the diagnostic technique used in sample acquisition should pass through the airways and prevent contamination [11]. An invasive procedure such as BAL may be used to identify the infective microbial agent accurately. However, it is associated with multiple limitations; it is costly, requires special training to perform, is not universally available,

and provides the result too late to influence survival [4]. As a result, a BAL-based management strategy requires empirical broad-spectrum antimicrobials before microbiological results can be obtained [14]. ETA has been used as a more feasible, readily available, and rapid diagnostic approach for VAP. However, the literature has been conflicting regarding whether or not ETA can be used as an accurate alternative to BAL. In this study, we attempted to test the consistency between the two techniques.

In 2004, Carvalho et al. compared the results of BAL and ETA in suspected VAP patients and found agreement in 88% of the patients [11]. Another study by Shafi and colleagues showed no significant difference between ETA and BAL culture results in 30 suspected VAP patients [18]. In 2019, Asty et al. found that the sensitivity and specificity of ETA cultures compared to BAL were very good at 78.9% and 75%, respectively. Therefore, they suggested that ETA be used as an alternative to diagnose suspected VAP cases [13].

However, others have reported that BAL is a superior diagnostic approach compared to ETA, as ETA has a lower specificity than BAL due to a more favourable diagnosis, and ETA has overdiagnosed ETA (12,19,20). Morris et al., in their study, suggested that ETA is only partially suitable to be used as an alternative to BAL due to the proportion of false results [21]. It has also been reported that reliance on the results of ETA commonly leads to the misclassification of VAP [22,23]. In addition, it has been pointed out that ETA specimens are more likely to yield false positives due to oral and tracheal contamination during the sampling procedure and may not distinguish colonisation from infection [12,24]. The current study found a substantial agreement between BAL and ETA cultures. In 80% of the cases, the same type of microorganism was detected in both BAL and ETA. In the other 8%, ETA detected a polymicrobial infection, one of which was the same as the pathogen detected by BAL.

It has remained debatable whether either of the sampling techniques is associated with a higher mortality rate. Some studies show that invasive techniques (BAL) are associated with lower mortality [25]. However, some studies show no difference in clinical outcomes between the ETA and BAL [4]. Despite BAL being used as a reference for ETA, it has been shown that it also suffers from its limitations as it has been associated with false positive and false negative results. Hence, only histopathological examination can be considered a gold standard for diagnosing VAP [9].

The most frequently isolated microorganisms from suspected VAP patients have been reported to be Pseudomonas aeruginosa, Acinetobacter baumanii, Staphylococcus aureus, Klebsiella pneumonie, and Escherichia coli. These results are consistent across BAL and ETA cultures [5,24]. However, there exists a difference in the proportion of these isolates, likely due to geographic variations [5]. In addition, it has been reported that most VAP infections are monomicrobial, with only a small portion polymicrobial [21]. Similar findings were observed in our study.

Antimicrobial-resistant microorganisms have a high prevalence in VAP patients and make treating VAP much more complex [14]. The most frequent high-risk antimicrobial-resistant microorganisms have been reported to be Pseudomonas aeruginosa and Acinetobacter baumanii [26]; this agrees with our study. Azzab and associates reported that out of 85 isolates, 71 (82.6%) were MDR [27]. Djordjevic et al. reported an MDR prevalence of 85–95% [28]. Lakhal and colleagues reported that 97% of their isolated bacteria were MDR [7]. The isolated microorganisms in this study showed antimicrobial resistance characteristics in 84.6% of the isolates.

Usually, a distinction is made between the microbial profiles of early-VAP patients and those of late-VAP patients. It has been reported that late VAP is generally more severe and is associated with highly infectious microbes with antimicrobial resistance characteristics, such as Pseudomonas aeruginosa, Acinetobacter baumanii, and Klebsiella pneumoniae [11]. Meanwhile, early VAP is thought to be associated with better prognosis and caused by more antimicrobial-sensitive microbes, including methicillin-sensitive Staphylococcus aureus, Streptococcus pneumoniae, or Haemophilus influenzae [6,27]. However, this idea has been questioned in recent years, as in some studies, no significant difference in the microbiological profile has been found between early and late VAP [7]. Our study supported that high-risk pathogens are more commonly found in late-VAP patients.

In conclusion, high-risk pathogens with antimicrobial resistance characteristics are highly prevalent in VAP. Hence, their early and accurate identification is crucial for proper and timely treatment of the condition. In addition, ETA can be a proper rapid, non-invasive technique for diagnosing VAP that substantially agrees with the cultures of BAL. Thus, ETA can be used as a reliable alternative to BAL.

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