CLINICAL MICROBIOLOGY

Comparison of bronchoalveolar lavage and catheter lavage to confirm ventilator-associated lower respiratory tract infection

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Lower respiratory tract infection (LRTI) is a well recognised complication of artificial ventilation in intensive care units (ICU). Ideally, specimens for microbiological analysis should be obtained during bronchoscopy, but this is not always possible. Therefore, the microbiological diagnosis of lower respiratory tract infection by broncho-alveolar lavage (BAL) obtained during bronchoscopy was compared with catheter lavage (CL) with a balloon-tipped catheter. Adult patients with clinical evidence of lower respiratory tract infection in an adult ICU were randomly assigned to undergo BAL followed by CL or vice versa. Forty ml of normal saline 0.9% were instilled and then aspirated with a flexible bronchoscope to obtain BAL. A similar volume was instilled and aspirated with a 12-gauge Foley balloon-tipped catheter to obtain a CL sample. The number of inflammatory cells, epithelial cells and organisms seen by microscopy were quantified. Culture results were semi-quantified and classified as negative, positive, equivocal or contaminated. Seventy-nine paired specimens were obtained from 66 patients, including specimens from 10 patients taken on two or more occasions. Only 20% of BAL and 16% of CL had one or more epithelial cells and bacteria were seen in 26 BAL and 21 CL specimens, respectively; 35% of BAL and CL specimens were positive and there was a discrepancy in the culture result in only two cases. *Staphylococcus aureus* was the pathogen isolated most frequently and polymicrobial lower respiratory infection was diagnosed on 10 occasions (15%). CL fluid is as reliable as BAL in diagnosing lower respiratory tract infection in ICU. This approach does not require bronchoscopic expertise and utilises convenient laboratory techniques.

Introduction

The increasing use of invasive techniques, tracheal intubation and mechanical ventilation in intensive care units (ICU) contributes to the risk of nosocomial infection, especially ventilator-associated lower respiratory tract infection (LRTI), including pneumonia. The incidence varies from 8 to 55 cases/100 ICU patients, with a median of 27 cases/100 patients [1] and various risk factors have been described [1–3]. This high incidence is accompanied by significant mortality, ranging from 26 to 71% [1,3]. The extra cost attributable in 1992 to ventilator-associated pneumonia in one study was calculated to be >US\$8000/patient [4].

Most cases of LRTI in the ICU are due to gram-negative bacilli such as *Escherichia coli*, other *Enterobacteriaceae* and *Pseudomonas aeruginosa*,

but *Staphylococcus aureus* is also important [5,6]. The usual causes are endogenous bacteria, including those colonising the stomach and oropharynx of the ICU patient [7,8]. Consequently, it is often difficult to distinguish colonising organisms from those causing infection.

A diagnosis of LRTI is usually made on the basis of clinical, radiological and microbiological evidence. The presence of fever, leucocytosis, increasing tracheobronchial secretions and the appearance of new infiltrates on chest radiography are some of the criteria used in diagnosis. However, these are non-specific and may also be present following chest trauma, as part of the adult respiratory distress syndrome (ARDS) and during acute exacerbation of chronic bronchitis [9,10]. In a study of 69 patients, air bronchograms were predictive of pneumonia but radiology identified only 65% of cases of pneumonia diagnosed at autopsy [11]. Tracheal aspirates are commonly used in the diagnosis of pneumonia, but a more critical analysis of their usefulness indicates that they are less helpful and indeed may be

misleading [12]. It is increasingly recommended that specimens such as protected brush specimens (PBS) or bronchoalveolar lavage (BAL) be obtained during bronchoscopy in ICU patients. Organisms recovered from such specimens are more likely to reflect pathology in the lung parenchyma, and quantification differentiates between specimen contamination during the procedure, colonisation of the airways and LRTI [9, 13, 14].

Bronchoscopic diagnosis requires the ready availability of a flexible bronchoscope and considerable expertise. There is a need for easier, more accessible diagnostic approaches and this study compared the microbiological results of specimens obtained by BAL with those obtained by passing a balloon-tipped catheter *via* the endotracheal tube and obtaining catheter lavage (CL) specimens. Semi-quantitative microbiology was done on both specimens to determine how CL compared with BAL in diagnosing LRTI.

Materials and methods

Patients and procedure

The Adult Intensive Care Unit (AICU) at University Hospital has nine beds including one isolation cubicle. Approximately 650 patients are admitted annually, following multiple trauma, for organ support, for ventilation during respiratory infection or for post-operative care after major surgery. All patients are assessed on admission by the APACHE II score [15]. The AICU is staffed by five consultants with four resident junior staff and a consultant medical microbiologist visits the unit daily.

All patients were considered for BAL or CL when lower respiratory tract infection was suspected on the basis of two or more of the following criteria: two temperature spikes $>38.5^{\circ}\text{C}$, white cell count $>12\,000$ or $<2500 \times 10^9/\text{L}$, increased respiratory secretions, new infiltrates on chest X-ray, or an increase of 0.15 in the FiO_2 to maintain arterial oxygen tension. Infection was considered community-acquired if present at or within 48 h of admission to hospital and hospital-acquired if diagnosed after this time [16]. Bronchoalveolar and catheter lavage were each performed on every patient in an order determined by selection of a randomly ordered card in a sealed envelope. During BAL, the flexible bronchoscope (Olympus BFIT20) was wedged in the radiologically affected zone and the midzone or lingula of the unaffected side, and washings of 40 ml of normal saline (0.9%) were instilled and subsequently aspirated. The balloon-tipped catheter was a 12-gauge Foley with the balloon pre-inflated with 10 ml of air, which was then withdrawn. The catheter was then inserted blindly until wedged and the balloon was inflated gently with 2 ml of air. Forty ml of normal saline (0.9%) were instilled and then aspirated. All

specimens were processed within 2 h of being taken or refrigerated. This study was started before the publication of consensus guidelines for bronchoscopy [17] and it was decided not to modify the protocol subsequently.

Microbiological examination

The volume of fluid received and the appearance of the specimen was recorded. Samples were inoculated with a standard loop ($5\,\mu\text{l}$) on to blood agar, chocolate (heated blood) agar, MacConkey agar and for anaerobic bacteria on to neomycin blood agar. Culture for legionellae, mycobacteria, fungi or viral pathogens was performed when clinically indicated, as was antigen detection by direct immunofluorescence for atypical causes of pneumonia such as *Mycoplasma pneumoniae* and *Chlamydia* spp., etc. Bronchoalveolar and catheter fluid was centrifuged for 5 min at 3000 rpm and the sediment was Gram stained. The mean number of inflammatory cells (white cells, mainly polymorphonuclear neutrophils), organisms and epithelial cells seen in 15–20 high power fields (magnification $\times 1000$) was recorded for each specimen. The number of organisms isolated (expressed as cfu/ml of lavage fluid) was semi-quantified and categorised into three groups: $>10^5$ cfu/ml, 10^4 cfu/ml or $<10^4$ cfu/ml, by comparison with standard cultures [18]. The diagnosis of pneumonia and the interpretation of culture results for BAL and CL specimens were as described previously [19]. Briefly, specimens were considered positive if the number of pathogenic organisms was $>10^5$ cfu/ml or 10^4 cfu/ml (pure growth only), negative if sterile or $<10^{4-5}$ cfu/ml, equivocal if there was a pure growth 10^{4-5} cfu/ml with inflammatory cells on microscopy and contaminated if 10^{4-5} cfu/ml without inflammatory cells or $\geq 10^{4-5}$ cfu/ml or greater but with more than one organism isolated and two or more epithelial cells seen per high power field.

Statistical analysis

All data were entered on to a spreadsheet (Quattro Pro, Borland, USA) and kappa, i.e., the proportion of potential agreement beyond chance that was actually achieved, was calculated [20]. Numerical kappa values of 0.6–0.8 show substantial agreement and 0.8–1.0 almost perfect agreement [20]. Further statistical analysis was performed with Minitab for Windows (Minitab Inc.), version 10 and paired non-parametric data were analysed by Wilcoxon with p values <0.05 considered significant.

Results

Patient characteristics

Seventy-nine paired specimens were received from 66 patients. The mean age was 53 years (range 15–87) and

the male:female ratio was 37:29. Table 1 outlines the clinical characteristics of the patients, comparing those for whom BAL was performed first followed by CL and *vice versa*. The most common indication for admission to the AICU was respiratory failure (22 patients) followed by post-operative neurosurgical care (seven patients). There was no significant difference in APACHE II score on admission, duration of ventilation and whether respiratory infection was considered to be hospital- (41 patients) or community- (25 patients) acquired and the outcome was similar (i.e., death or discharge from the AICU) in the two groups whether BAL preceded or followed CL.

BAL and CL microscopy

BAL was obtained first on 35 occasions and followed CL on 41 occasions (for three pairs of specimens, the order was not stated). Patients were receiving antibiotics at the time of the procedure on six occasions (18%) when BAL preceded CL and on 14 occasions (36%) when CL was performed first. Paired specimens were received from 10 patients on two or more occasions. The mean BAL volume received for microbiological processing was 7.4 ml compared with 7.9 ml for CL. Volumes aspirated did not differ significantly according to the order in which the specimen was obtained. Fig. 1 and 2 outline the number of inflammatory and epithelial cells seen on Gram's stain. In only 16 (20%) of BAL and 13 (16%) of CL specimens was one or more epithelial cells seen. There was reasonable agreement between the two techniques in the detection of inflammatory (kappa, 0.44) and epithelial (kappa, 0.62) cells. Bacteria were seen on microscopy in 26 BAL and 21 CL specimens (kappa, 0.64) usually in low numbers, i.e., one-to-three bacteria per high power field (magnification $\times 1000$). Intracellular organisms were seen in four BAL and three CL specimens only.

Culture results

Forty-one (52%) BAL and 44 (56%) CL specimens gave negative culture results; 27 (35%) BAL and 28 (35%) CL specimens gave positive results. Similar numbers of patients were receiving antibiotics in the culture-positive (8 of 28, 29%) and culture negative (17 of 51, 33%) groups. There was good agreement between the interpretation of BAL and CL specimens (kappa, 0.91, Table 2). The organisms isolated, the order of investigation and the outcome of patients with positive results are outlined in Table 3. There was a discrepancy in culture results between CL and BAL specimens in two cases; in one, the positive CL specimen ($>10^5$ cfu/ml, *P. aeruginosa*) was obtained before the negative BAL ($<10^4$ cfu/ml, *P. aeruginosa*); this may be explained by a dilutional effect. In the other, this explanation is less likely as the first specimen gave a negative result (CL, $<10^4$ cfu/ml, *Enterobacter cloacae*) and the BAL, which followed, was positive (10^{4-5} cfu/ml, *E. cloacae*).

Polymicrobial infection was diagnosed on 10 occasions. *S. aureus* was isolated with gram-negative bacilli on six occasions and more than three pathogens were isolated on two occasions. One patient had pulmonary aspergillosis with underlying lymphoma. *Mycobacterium kansasii* was isolated from another patient. He died some weeks after discharge from AICU and post-mortem examination indicated that *M. kansasii* was a probable cause of chronic infection.

Discussion

The diagnosis of ventilator-associated LRTI, especially in the presence of ARDS, is often difficult and requires a combined clinical, radiological and microbiological approach. The combination of fever, an infiltrate on

Table 1. Demographic characteristics of the patients studied

Characteristics	BAL first (29)*†	CL first (34)*†
Mean age (years)	49.6 (19–81)	55.6 (15–77)
Male: female	14:15	19:15
Reason for admission		
Multiple trauma	8	8
Organ support	0	0
Neurosurgical	5	2
Respiratory failure	7	14
Other	9	10
Mean duration of ventilation (d)	11.7	10.9
Interval to procedure (d)	5	4
Mean APACHE II score on admission	12.8 (2–25)	14.1 (3–33)
Hospital-acquired LRTI	18	21
Community-acquired LRTI	11	13
Outcome		
Discharged from AICU	16	24
Death	13	10

*Where a patient was studied on more than one occasion, findings on the first occasion only are included.

†Details of three patients, for whom the order is not known, are excluded.

Fig. 1. Number of epithelial cells seen on microscopy (magnification $\times 1000$) of BAL (□) and CL (■) samples.

Fig. 2. Number of inflammatory cells seen on microscopy (magnification $\times 1000$) of BAL (□) and CL (■) samples.

chest X-ray and increased respiratory secretions may be explained by other causes. In a study of 84 patients suspected of having nosocomial pneumonia because of new pulmonary infiltrates on chest X-ray and purulent sputum, a clinical diagnosis was accurate in 62% of cases and therapy was inappropriate in two-thirds, especially for polymicrobial infection [10]. Bronchoscopic techniques are increasingly recommended to confirm a diagnosis microbiologically. PBS has undergone the most extensive evaluation but doubts remain about its specificity [21, 22]. False negative results may occur in patients on antibiotics [21] but this also

applies to BAL, which is the preferred technique in our hospital. Torres and colleagues compared BAL, bronchial aspirates, percutaneous lung needle aspirates (PLNA) and PBS with immediate histopathology of post-mortem lung biopsies and good correlation was found between PBS and BAL [22]. Because PBS and BAL require bronchoscopy, a fall in arterial O_2 tensions, arrhythmias and fever may follow [21]. These complications, together with the unavailability of flexible bronchoscopes in some units and the requirement for an experienced bronchoscopist, have prompted a search for alternatives.

In this study, the laboratory techniques used were those available in most centres and it was designed to assess whether BAL and CL specimens were equivalent microbiologically in confirming a diagnosis of LRTI. A semi-quantitative technique was used rather than a spiral plater, which is not always available. These results suggest that non-bronchoscopic lavage, i.e., CL, is a useful alternative to BAL. Volumes of fluid aspirated, the numbers of epithelial cells, inflammatory cells and bacteria seen on microscopy were similar and culture results were equivalent. Without histological analysis obtained either from lung biopsy or at autopsy, it is not possible to differentiate pneumonia from airways infection. The relatively small volume of fluid obtained for analysis was similar to that recorded by Meduri and colleagues, who received only 22% of the fluid instilled in ventilated patients by unprotected BAL and who could not distinguish pneumonia from bronchitis [23]. Since the start of this study, consensus guidelines on the techniques used, including sampling, microscopy and diagnostic thresholds, have been published [17]. The use of the May-Grünwald Giemsa stain for the evaluation of alveolar cell populations and discarding the first 20 ml of BAL, both of which were not part of our protocol, are recommended. The detection of intracellular bacteria was not as useful a predictor of pneumonia as previously described [24] except for *S. aureus*, for which intracellular bacteria were seen on three occasions.

Gaussorgues and colleagues compared non-bronchoscopic lavage (NBL) with a cuffed re-usable catheter with open lung biopsy in 13 patients with pulmonary infiltrates who died in ICU [25]. Culture of NBL revealed the same organisms as lung biopsy in eight of nine patients with pneumonia, despite all patients receiving antibiotics for ≥ 4 days beforehand. Another study compared BAL obtained by bronchoscopy with NBL in 40 samples from 28 patients, using a bacterial index to assess significance of the numbers of bacteria isolated [24]. Although BAL and NBL were obtained from all patients, this study differed from the present study in that BAL always preceded NBL. The number of bacteria isolated from specimens as expressed by the bacterial index was similar in both specimens, even where NBL was obtained from radiologically

Table 2. Interpretation of BAL and CL specimens

BAL result	CL result				Total
	contaminated	negative	positive	equivocal	
Contaminated	4	2	0	0	6
Negative	0	40	1	0	41
Positive	0	1	26	0	27
Equivocal	0	1	1	3	5
Total	4	44	28	3	79

kappa, 0.91.

Table 3. Organisms isolated, order of procedure and outcome for culture-positive patients

Organisms	Number of patients	Order of procedure	Outcome
Gram-negative bacilli			
<i>Enterobacter</i> spp.	4	BAL 1st, 1 CL 1st, 2 Not known, 1	Discharged, 3 Died in AICU, 1
<i>Haemophilus influenzae</i>	2	BAL 1st, 1 CL 1st, 1	Discharged, 1 Died in AICU, 1
<i>Escherichia coli</i>	2	BAL 1st, 1 CL 1st, 1	Discharged, 1 Died in AICU, 1
Others	3	BAL 1st, 1 CL 1st, 2	Discharged, 2 Died in AICU, 1
<i>S. aureus</i>	4	BAL 1st, 3 CL 1st, 1	Discharged, 3 Died in AICU, 1
Polymicrobial	10	BAL 1st, 5 CL 1st, 5	Discharged, 7 Died in AICU, 3
Others	3	CL 1st, 3	Discharged, 2 Died in AICU, 1

unaffected lung [24]. Two further studies have assessed the usefulness of quantitative bacterial cultures of endotracheal aspirates (EA) and recorded a lower specificity for EA compared with BAL and PBS [26,27]. A negative EA culture result may exclude pulmonary infection but both studies recommend BAL or PBS unless unavailable [26,27]. NBL has also been used to investigate the flora of distal airways during mechanical ventilation and to diagnose 65 episodes of pneumonia, in 20 of which BAL was also performed [28]. Concordant results between NBL and BAL were obtained in 16 of 20 episodes and the authors concluded that BAL was no better or accurate than NBL. The present study compared semi-quantitative bacterial cultures of BAL and CL and although there were minor differences in the number of squamous epithelial cells, inflammatory cells and organisms seen on microscopy and some differences in culture results, we believe that by taking sequential samples from the same patient, we have validated the use of NBL or CL as an alternative to BAL and confirmed the findings of Pugin and colleagues [24].

S. aureus was the most frequent pathogen isolated from our group of patients. In other studies, aerobic gram-negative bacilli, including *Pseudomonas* spp., have accounted for 40% of cases [1,29]. Staphylococcal pneumonia is described as being more common in neurosurgical patients [30] – a relatively large proportion of admissions to this unit. *Acinetobacter* spp. were responsible for LRTI in two patients and, as in other ICUs, this unit is experiencing increasing numbers of infections with this hospital pathogen. An

epidemic of *Acinetobacter* infection occurred in the ICU during part of this study with over 35 patients becoming either colonised or infected [31].

We disagree with the reasons cited by some for not using either BAL, PBS or an appropriate alternative to diagnose nosocomial LRTI [32,33] and recent reviews on the subject confirm our view [34,35]. Whilst there is some disagreement about the quantitative criteria used to distinguish infection from colonisation, we do not believe that concern about the safety of a cytocentrifuge [32] represents a contra-indication to these diagnostic techniques. In the present study, a simple, cheap and convenient approach to confirming a diagnosis of ventilator-associated LRTI was used. The development and validation of a new catheter for obtaining lavage specimens without the need for bronchoscopy [36] and the application of new guidelines [17] may facilitate accurate diagnosis. When a non-infectious cause of pulmonary infiltrates and fever such as tumour or haemorrhage is considered likely, especially in immunocompromised patients, bronchoscopy is preferred to inspect the bronchial tree with the option of obtaining tissue for histological analysis.

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