Reproducibility of protected brush catheter specimen cultures in critically ill patients with suspected nosocomial pneumonia

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Reproducibility of protected brush catheter specimen cultures in critically ill patients with suspected nosocomial pneumonia. *Can Respir J* 1995;2(3):173-178.

OBJECTIVE: To determine the reproducibility of two protected brush catheter (PBC) specimens obtained during the same bronchoscopy in critically ill patients with suspected ventilator associated pneumonia.

DESIGN: Prospective, observational study.

SETTING: Two university-affiliated multidisciplinary intensive care units with a combined total of 50 beds.

PATIENTS: A total of 75 (50 male, 25 female) patients with 84 episodes of suspected ventilator associated pneumonia were studied between January 1, 1991 and June 30, 1992. Age was 60.7 ± 1.9 (mean $\pm$ SEM) years, and mean APACHE II score was 22.4 ± 2.0 . Twenty-four patients were admitted from various medical services, 19 from surgical services including the operating room, 16 with central nervous system disease and 16 following multiple trauma. Twenty patients were transferred directly to the intensive care unit from peripheral hospitals.

INTERVENTIONS: All patients had lower respiratory tract secretions obtained for culture by both aspiration through the endotracheal tube (tracheal aspirates) and flexible bronchoscopy, with separate samples obtained by two PBCs (PBC-A and PBC-B).

MAIN RESULTS: The overall proportion of agreement between the results of the two PBC specimens was 0.928, with

a calculated kappa statistic (κ) = 0.853 ($P < 0.01$ versus $\kappa = 0.4$, 95% CL 0.692, 1.014) indicating excellent agreement between the two specimens. Both PBC specimens had significant (ie, more than 10^3 colony-forming units/mL) growth (positive/positive) in 33 cases, nonsignificant growth in 45 cases (negative/negative) and discordant results in six (positive/negative, $n=3$ or negative/positive, $n=3$). There was a significant relationship ($P < 0.05$) between the concurrent use of antibiotics and a negative PBC result. However, after exclusion of patients on antibiotics, the overall proportion of agreement between the two PBCs was 0.94 with $\kappa = 0.875$ ($P < 0.01$ versus $\kappa = 0.4$, 95% CL 0.721, 1.029), which also indicates excellent agreement between the two tests.

CONCLUSIONS: Although discordant results were observed in 7.2% cases, the overall reproducibility of the PBC results appears to be high. The significant relationship between concurrent antibiotic use and a negative PBC result is of concern clinically since many patients are being treated with antibiotics at the time of bronchoscopy. Therefore, when the diagnosis of nosocomial pneumonia in critically ill patients is established, the PBC result should be considered only in association with all the other clinical data, particularly in patients receiving concurrent antibiotics. (*Pour le résumé, voir page 174*)

Key Words: Kappa statistic, Mechanical ventilation, Nosocomial pneumonia, Protected brush catheter, Ventilator associated pneumonia

Reproductibilité des cultures de spécimens obtenus par brossage protégé chez des patients des soins intensifs avec une pneumonie nosocomiale suspectée

OBJECTIF : Déterminer la reproductibilité de la culture de deux spécimens obtenus par brossage protégé (BP) au cours d'une même bronchoscopie chez des patients des soins intensifs chez qui l'on suspecte une pneumonie associée à la ventilation mécanique.

MODÈLE : Étude d'observation, prospective.

CONTEXTE : Deux unités de soins intensifs multidisciplinaires affiliées à une université représentant un total de 50 lits.

PATIENTS : Un total de 75 (50 hommes, 25 femmes) patients avec 84 épisodes de pneumonie suspectée associée au respirateur ont été étudiés entre le 1^{er} janvier 1991 et le 30 juin 1992. L'âge de ces patients était de $60,7 \pm 1,9$ (moyenne $\pm$ erreur type de la moyenne) ans et le score moyen APACHE II était de $22,4 \pm 2,0$. Vingt-quatre patients provenaient de services médicaux variés, 19 du service de chirurgie y compris la salle d'opération, 16 souffraient de pathologies du système nerveux central et 16 avaient été admis à la suite de traumatismes multiples. Vingt patients avaient été directement transférés des hôpitaux périphériques vers l'unité de soins intensifs.

INTERVENTIONS : Chez tous les patients, on a prélevé des sécrétions bronchiques pour les mettre en culture, par la sonde endotrachéale (aspirations trachéales) et par bronchoscopie souple, avec deux échantillons distincts obtenus par brossages protégés (BP-A et BP-B).

PRINCIPAUX RÉSULTATS : La proportion globale de concordance des résultats des deux spécimens obtenus par BP était de 0,928 avec une statistique kappa calculée (κ)=0,853 ($P < 0,01$ par rapport à $\kappa=0,4$, intervalle de confiance à 95 % 0,692-1,014) démontrant une concordance excellente entre les deux spécimens. Les deux spécimens obtenus par BP ont révélé une croissance significative (plus de 10^3 unités formant colonies/ml) dans 33 cas (positif-positif), une croissance non significative (négative-négative) dans 45 cas et des résultats discordants dans six cas (positif-négatif, $n = 3$ ou négatif-positif, $n = 3$). On a observé une relation significative ($P < 0,05$) entre l'utilisation concomitante d'antibiotiques et un résultat négatif du BP. Cependant, après avoir exclu de l'étude les patients sous antibiotiques, la proportion globale de concordance entre les deux spécimens obtenus par BP était de 0,94 avec $\kappa=0,875$ ($P < 0,01$ par rapport à $\kappa=0,4$, intervalle de confiance à 95 % 0,721-1,029), ce qui indique également une concordance excellente entre les deux tests.

CONCLUSIONS : Bien que des résultats discordants aient été observés dans 7,2 % des cas, la reproductibilité globale des résultats du BP semble élevée. La relation significative entre l'utilisation concomitante d'antibiotiques et un résultat du BP négatif semble importante cliniquement puisque de nombreux patients sont sous antibiotiques au moment de la bronchoscopie. Donc, lorsque le diagnostic de pneumonie nosocomiale a été posé chez des patients des soins intensifs, le résultat du BP devrait seulement être interprété en fonction de toutes les autres données cliniques, surtout chez les patients qui sont déjà sous traitement antibiotique.

ESTABLISHING THE CLINICAL DIAGNOSIS OF PNEUMONIA in mechanically ventilated patients is both inaccurate and often difficult. Oropharyngeal and endotracheal tube colonization with pathogenic bacteria occurs within 24 h of intubation and decreases the reliability of expectorated or aspirated tracheal secretions (1). Furthermore, critically ill patients often have pulmonary infiltrates, fever and leukocytosis due to other conditions (pulmonary embolism, atelectasis, pulmonary edema, etc), which complicates the diagnosis of pneumonia.

Fibreoptic bronchoscopy has been used extensively in intubated patients with suspected pneumonia to obtain samples of lower respiratory tract secretions for bacterial culture (2-4). The development of the protected brush catheter (PBC) has further enhanced the usefulness of bronchoscopy in the diagnosis of nosocomial pneumonia (5-9). In addition, many investigators (10-12) believe that the PBC used in conjunction with quantitative bacterial culture techniques improves the accuracy of the diagnosis of ventilator associated pneumonia.

The reliability or precision of a diagnostic test depends on how close repeated measurements of a stable phenomenon are to each other (13). To date, the reliability of the PBC technique remains uncertain in the clinical setting. There has been limited experience with collecting multiple PBC specimens from the same individual to determine the repro-

ducibility of this technique (14-16). Marquette et al (15) demonstrated excellent qualitative reproducibility of the PBC technique; however, quantitative cultures varied by more than 1 log₁₀ in over half the patients studied, and the presence or absence of pneumonia (based on the critical 'cutoff' of greater than 10^3 colony-forming units [CFU]/mL) differed in about 14% of patients. Similarly, Timsit et al (16) observed discordant results between two PBC specimens in about 17% of patients with suspected ventilator acquired pneumonia. We previously collected two PBC specimens during bronchoscopy in 48 critically ill patients with 53 episodes of suspected ventilator acquired pneumonia (14) and noted a discrepancy between the two brush specimens in 7.5% of cases. In the present paper, we describe the completed data of this study on 75 patients with 84 episodes of suspected ventilator acquired pneumonia in which we collected two sequential PBC specimens at bronchoscopy.

PATIENTS AND METHODS

The study protocol was approved by the human investigation committee at the University of Western Ontario.

Patient selection: Data were collected during 84 episodes of suspected nosocomial pneumonia occurring in 75 critically ill patients between January 1, 1991 and June 30, 1992. Patients were enrolled from two multidisciplinary intensive care units at the University of Western Ontario with a com-

bined total of 50 beds and approximately 2200 annual admissions. The clinical diagnosis of nosocomial pneumonia was suspected in patients receiving mechanical ventilation for more than 48 h if they developed a new pulmonary infiltrate that persisted longer than 24 h, developed macroscopically purulent tracheal secretions, and either leukocytosis (white blood cell count greater than $11,000/\text{mm}^3$) or elevated temperature (greater than 38.3°C). Patients were excluded if they met any of the following criteria: clinical condition that did not permit flexible bronchoscopy; diagnosis of pneumonia upon admission to the intensive care unit; immunocompromised condition (organ transplant, hematological malignancy, humoral or cellular immune deficiency and patients receiving more than 0.5 mg/kg/day of prednisone or its equivalent); or age less than 18 years.

All patients were ventilated with a Bird (Bird Products Corporation, California), Veolar (Hamilton Medical, Nevada) or a Puritan-Bennett 7200 (Puritan-Bennett Corporation, California) ventilator through an orotracheal, nasotracheal or tracheostomy tube. The ventilator tubing (Marquest Medical Products, Colorado) was changed every 48 h according to routine protocol. Tracheobronchial suctioning, chest physiotherapy and drainage of condensate from the ventilator tubing were performed every 3 h or more frequently if it was deemed necessary by the attending staff.

Experimental protocol: On entry into the study, the patient's hospital chart was reviewed and the following variables recorded: age, sex, underlying medical illnesses, date of hospital and intensive care unit admission, date of intubation, APACHE II score (17) and antibiotics used within 48 h before bronchoscopy. Specific physiological variables (ie, Acute Physiologic Score) (17,18) and a radiographic assessment (radiographic score) (19,20) were recorded on the day of bronchoscopy.

All potentially eligible patients were reviewed on a daily basis for the signs and symptoms of pneumonia described above. Once these signs developed and persisted more than 24 h, the patient (if awake) or the next of kin were approached for possible enrolment into the study. After informed consent was given, lower respiratory tract secretions were obtained for culture from all patients within 12 h of inclusion into the study and within 36 h after the diagnosis of pneumonia was suspected. Bacteriological samples were collected by both aspiration through the endotracheal tube (tracheal aspirates) and flexible bronchoscopy, with separate samples obtained by two PBCs (PBC-A and PBC-B). Tracheal aspirates were obtained immediately before bronchoscopy from all cases by an aseptic technique using deep suctioning via the endotracheal tube and collected in a sterile suction trap.

In preparation for bronchoscopy, all patients were premedicated with intravenous diazepam (5 to 10 mg) or midazolam (2.5 to 5 mg) with or without fentanyl (50 to 100 µg). Topical xylocaine (1 to 2%) was used minimally for local anesthesia only when patients continued to cough despite intravenous sedation. Arterial oxygen saturation and cardiac rhythm were continuously monitored throughout the procedure with a pulse oximeter (SpaceLabs, Washington; Hewlett

TABLE 1
Demographic data of patients with suspected ventilator associated pneumonia

	+/+ (n=33)	-/- (n=45)	+/- (n=6)
Age (years)	53.7 ± 3.6	66.6 ± 1.8	60.8 ± 9.6
APACHE II score	21.0 ± 1.3	22.9 ± 0.9	26.2 ± 3.4
Intubation-bronchoscopy interval (days)	11.5 ± 2.4	17.9 ± 3.3	6.2 ± 2.0
Antibiotics within 48 h of bronchoscopy	11 (33.3 %)	30 (66.7 %)	5 (83.3 %)
Underlying illness			
Medical	11	16	1
Surgical	6	12	2
CNS	7	8	2
Trauma	9	9	1

+/+ Both protected brush catheter (PBC) specimens $>10^3$ colony-forming units (CFU)/mL; -/- Both PBC specimens $<10^3$ CFU/mL; +/- one PBC specimen $>10^3$ CFU/mL, one specimen $<10^3$ CFU/mL. Data are mean ± SEM

Packard, Massachusetts) and cardiac monitor (SpaceLabs; Hewlett Packard). With the fraction of inspired oxygen adjusted to 1.0, the flexible fiberoptic bronchoscope (Pentax model FB19H) was introduced into the endotracheal tube through a special adapter (Rusch-Kernen, Germany) allowing simultaneous mechanical ventilation and the maintenance of positive airway pressure. The bronchoscope was advanced into the bronchial orifice of the involved pulmonary segment that had been identified radiographically. Telescoping PBCs (Mill-Rose; Instrumed) with distal plugs were inserted through the inner suction channel of the bronchoscope. Once in the involved bronchopulmonary segment, the dissolvable cellulose plug was dislodged and the brush advanced under visual guidance into the area of suspected pneumonia. After the involved segment was brushed, the brush (PBC-A) was withdrawn into the protective sheath and the entire catheter was removed from the bronchoscope (19). In each patient, a second protected brush specimen (PBC-B) was immediately obtained from the same bronchopulmonary segment by an identical technique.

To minimize potential contamination of the bronchoscope, suctioning was kept to a minimum throughout the procedure. After withdrawal, the outer catheter was immediately cleansed with an alcohol swab and severed with sterile scissors. The distal portion of the inner telescoping catheter was advanced, cleansed and cut in a similar manner. The brush wire was then advanced and cut with sterile scissors into a sterile glass vial containing 1.0 mL of lactated sterile saline solution.

Between cases the bronchoscope was cleaned according to routine protocol. Briefly, the bronchoscope is dismantled and cleaned with a brush and soap and water, then soaked in Cidex (Johnson and Johnson) for 30 mins before being rinsed with sterile water.

Bacteriological assessment: After collection, specimens were immediately transported to the microbiology department, where tracheal aspirates were Gram stained and cul-

TABLE 2
Clinical features of patients with suspected ventilator associated pneumonia

	+/(n=33)	-/(n=45)	+/(n=6)
Temperature (°C)	38.1±0.19	38.0±0.33	38.1±0.21
Purulent sputum	33	45	6
White blood cells/mm ³	14.0±1.1	16.7±1.6	15.1±1.5
Chest x-ray score	5.1±0.4	5.2±0.3	6.1±1.2

+/- Both protected brush catheter (PBC) specimens >10³ colony-forming units (CFU)/mL; -/- Both PBC specimens <10³ CFU/mL; +/- one PBC specimen >10³ CFU/mL, one specimen <10³ CFU/mL. Data are mean ± SEM

tured on MacConkey agar, 5% horse blood agar and chocolate agar. Identification of pathogenic bacteria and antibiotic sensitivities were determined according to routine laboratory protocol.

Specimen vials containing the protected brush tips were placed in a vortex mixer for 60 s to suspend all material from the brush. After Gram staining, two serial 100-fold dilutions were performed and 0.1 mL of each dilution was plated on MacConkey agar, 5% horse blood agar and chocolate agar for quantitative culture. Cultures were considered positive if more than 10³ CFU/mL of one or more potentially pathogenic bacteria were isolated.

Statistical analysis: All data are presented as mean ± SEM. Qualitative comparisons were performed with $\chi^2=0.05$ statistical analysis. Agreement between the first (PBC-A) and second (PBC-B) culture results was assessed by calculating the kappa statistic (κ) (21).

RESULTS

Eighty-four episodes of clinically suspected pneumonia were identified in 75 patients. The demographic characteristics of these patients are presented in Table 1. There were 50 males and 25 females with a mean age of 60.7±1.9 years. Twenty-four patients were admitted from various medical services, 19 from surgical services including the operating room, 16 with central nervous system disease and 16 following multiple trauma. Twenty patients were transferred directly to the intensive care unit from peripheral hospitals. The mean APACHE II score at the time of intensive care unit admission was 22.4±0.8. Patients were ventilated for an average of 14.5±2.0 days before the development of clinical pneumonia.

No specific clinical features could be identified that would differentiate patients with pneumonia (based on significant PBC specimen culture) from those without pneumonia (non-significant PBC specimen culture). Specifically, there were no differences in temperature, white blood cell count, sputum purulence or radiographic infiltrates among the three groups (Table 2).

Bacteriological results: In all patients, semiquantitative cultures of tracheal aspirates were positive (Table 3). In nine of the 84 cases, the tracheal aspirate specimens grew multiple organisms. The bacteriological criterion of more than 10³ CFU/mL of potentially pathogenic bacteria was used to iden-

TABLE 3
Bacteriology of tracheal aspirate (TA) and significant protected brush catheter (PBC) cultures

Microorganism	TA	PBC
<i>Streptococcus pneumoniae</i>	11	12
<i>Staphylococcus aureus</i>	14	16
<i>Neisseria mucosa</i>	1	2
<i>Haemophilus influenzae</i>	14	18
<i>Pseudomonas aeruginosa</i>	20	18
<i>Escherichia coli</i>	9	7
<i>Klebsiella pneumoniae</i>	7	7
<i>Proteus mirabilis</i>	3	2
<i>Enterobacter cloacae</i>	7	2
<i>Xanthomona maltophilia</i>	4	
<i>Serratia marcescens</i>	2	
<i>Acinetobacter</i> species	1	
Total	93	84

PBC specimens were significant if cultures grew more than 10³ colony-forming units/mL

tify a significant bacterial growth in lower respiratory tract secretions obtained with the PBC. Of the 168 PBC specimens, 72 (42.9%) demonstrated significant bacterial growth, while 96 (57.1%) were considered nonsignificant. In 33 cases, both PBC specimens had significant growth (positive/positive), in 45 cases, both had nonsignificant growth (negative/negative), and culture results were discordant in six (positive/negative, n=3 or negative/positive, n=3).

Quantitative culture of the PBC specimen grew Gram-positive cocci in 13, Gram-negative bacilli in 25 and Gram-negative diplococci in one (Table 3).

Of six patients with discordant results, both PBC-A and PBC-B grew the same organism in four. The quantitative cultures in these four cases differed by 1 log₁₀ above and below the critical cutoff of greater than 10³ CFU/mL. In the remaining two cases, the first PBC specimen was significant (ie, greater than 10³ CFU/mL), while the second specimen was sterile (Table 4). The overall proportion of agreement between the two PBC specimens was 0.928 (Table 5) with a calculated kappa statistic of $\kappa=0.853$ ($P<0.01$ versus $\kappa=0.4$, 95% CL 0.692, 1.014) indicating excellent agreement between the tests.

In 46 (54.7%) cases of pneumonia, antibiotics had been administered within 48 h before bronchoscopy. The use of antibiotics was significantly ($P<0.05$) associated with a non-significant PBC result (Table 1). Of the 33 patients with positive/positive PBC results, only 11 had received antibiotics, whereas 35 of the 51 patients with either negative/negative, positive/negative or negative/positive PBC results had been on antibiotics before bronchoscopy. Of these 46 cases receiving antibiotics, 11 were positive/positive, 30 were negative/negative and four were positive/negative. The overall proportion of agreement (0.94) and the kappa statistic were recalculated using the 38 cases that did not receive antibiotics (Table 5). Thus, excluding prior antibiotics, $\kappa=0.875$ ($P<0.01$ versus $\kappa=0.4$, 95% CL 0.721, 1.029) also indicates excellent agreement between the two tests.

TABLE 4
Bacteriology of six patients with discordant protected brush catheter (PBC) results

Patient	PBC A		PBC B	
	CFU/mL	Organism	CFU/mL	Organism
1	2.3×10^2	<i>Pseudomonas aeruginosa</i>	2.0×10^3	<i>P aeruginosa</i>
2*	4.0×10^2	<i>Staphylococcus aureus</i>	3.0×10^3	<i>S aureus</i>
3	1.1×10^3	<i>Haemophilus influenzae</i>	0	
4	2.3×10^3	<i>P aeruginosa</i>	0	
5	4.0×10^2	<i>P aeruginosa</i>	1.3×10^3	<i>P aeruginosa</i>
6	6.2×10^2	<i>P aeruginosa</i>	1.4×10^3	<i>P aeruginosa</i>

*Did not receive antibiotics before bronchoscopy. CFU Colony-forming units

DISCUSSION

Nosocomial pneumonia continues to be a significant problem in the critically ill patient. As a result of inaccurate clinical features and limited acceptance of invasive diagnostic procedures (22) the diagnosis of pneumonia in mechanically ventilated patients is a common problem (11,23,24). Our data concur with existing literature (11,19,24-27) and demonstrate that, based on clinical features alone, the diagnosis of ventilator associated pneumonia is unreliable compared with the PBC as the 'gold standard'. We have also shown that the PBC used to obtain lower respiratory tract secretions at the time of bronchoscopy is associated with a high degree of reproducibility and interobserver agreement. However, the concurrent use of antibiotics before bronchoscopy may decrease the reliability of the PBC in the clinical setting.

If PBC is assumed to be the gold standard for diagnosing nosocomial pneumonia in critically ill ventilated patients, we would have overdiagnosed ventilator associated pneumonia in the majority of our study patients on the basis of tracheal aspirates and clinical features. Similarly, Fagon et al (19) obtained PBC specimens in 162 cases of suspected ventilator associated pneumonia and obtained significant bacteriological results in only 35%. In our study, significant PBC cultures were obtained in only 72 of 168 (42.9%) specimens. When we examined the two groups separately, we could not identify any distinguishing clinical features between them. These results reinforce the diagnostic dilemma faced by clinicians in the critical care setting when they try to establish the diagnosis of ventilator associated pneumonia. This is particularly important where inappropriate antibiotic therapy in patients without pneumonia may lead to added morbidity and health care costs.

Since the role of the PBC in clinical practice is to guide antibiotic therapy in patients with nosocomial pneumonia, irreproducible or unreliable results may have a detrimental impact on patient outcome. This is the largest series to date examining the reproducibility of PBC results in patients with suspected ventilator acquired pneumonia. We observed an overall proportion of agreement between the two PBC speci-

TABLE 5
Reliability of protected brush catheter (PBC) results

A. All patients

PBC-B		PBC-A		
		Positive	Negative	
Positive	Positive	33	3	36
	Negative	3	45	48
		36	48	84

B. Patients not receiving antibiotics

PBC-B		PBC-A		
		Positive	Negative	
Positive	Positive	22	1	23
	Negative	1	15	16
		23	16	39

mens of 0.928 for all specimens and 0.94 for specimens in patients not treated with antibiotics (Table 5). The kappa statistic for interobserver agreement indicates excellent agreement between the two PBC specimens. Our results are in contrast to those of others (16,28) in that we only observed discordant results in six (7.2%) cases. We believe, however, that the kappa statistic for interobserver agreement is a much more rigorous statistical test (21) than simply measuring the rates of discordance (15,16), because the kappa statistic determines the amount of agreement observed in relation to that expected on the basis of chance alone.

The observed discrepancy between the two brushes in our study may be the result of either sampling error or biological variation in the bacterial population (13). Potential sources of sampling error may be secondary to technical factors (ie, catheter placement, suctioning of tracheal secretions through the bronchoscope, the use of topical anesthetics) or observer variation (ie, laboratory personnel). In an effort to circumvent these potential errors all bronchoscopic procedures were performed by three individuals. The PBC sample was obtained only when endobronchial pus was seen and the same technique was used for both specimens. Furthermore, topical anesthetics were used sparingly and suctioning was minimized throughout the procedure. Biological variation may be due to the concurrent use of antibiotics, presence or absence of comorbid disease and the presence of bacterial colonization. Furthermore, bacteriological counts may vary within the local milieu of the lower respiratory tract (29,30).

We observed a significant ($P < 0.05$) and disproportionately high frequency of antibiotic use in patients with negative/negative, positive/negative or negative/positive PBC results (Table 1). Forty-six of 84 patients had received antibiotics within 48 h of bronchoscopy, of whom 35 had a nonsignificant PBC result and 11 had significant PBC results (positive/positive). Although not conclusive, these data raise the possibility that prior or concurrent antibiotic therapy may be associated with nonsignificant PBC results. Unfortunately, in this study we were unable to determine whether this represents a true false-negative result since tissue samples (the ultimate gold standard) were not collected.

CONCLUSIONS

Even though we observed discordant results in 7.2% of our patients the overall reproducibility of the PBC results appears to be high with excellent agreement between the two tests. More important, however, we noted a significant relationship between the concurrent use of antibiotics and non-significant PBC results. Therefore, although we believe that the PBC is a useful test, we emphasize that when ventilator associated pneumonia is diagnosed, the PBC results should be considered along with other clinical information, particularly in patients receiving antibiotics. In addition, these data add to the recent debate over the use of invasive versus noninvasive diagnostic procedures in this setting, and should stimulate future research on the effects of concurrent antibiotic use and the reliability of PBC specimens.

ACKNOWLEDGEMENTS: The authors acknowledge the contribution of the attending intensive care unit staff and nurses as well as the microbiology laboratories at both Victoria and University Hospitals, London, Ontario.

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