PAPER

Sensitivity and Specificity of Bronchoalveolar Lavage and Protected Bronchial Brush in the Diagnosis of Pneumonia in Pediatric Burn Patients

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Background: Infection is still one of the leading causes of death in burn patients. The diagnosis of respiratory tract infection in critically ill burn patients is still difficult. The diagnostic technique of choice remains uncertain, especially because of the lack of a criterion standard by which other diagnostic methods can be compared.

Hypothesis: Bronchoalveolar lavage (BAL) and protected bronchial brush (PBB) cultures are not efficacious for the diagnosis of pneumonia in critically ill burn patients.

Design: All pediatric patients with burns who died at Shriners Burns Hospital, Galveston, Tex, in the past 10 years were studied. We compared the clinical diagnosis of pneumonia, BAL quantitative culture results, and PBB culture results with autopsy findings. The diagnosis of pneumonia at autopsy was considered the criterion standard, and it was used to calculate the sensitivity and specificity of BAL and PBB cultures.

Results: Forty-three patients were studied. Pneumonia was present in 19 (44%) of the 43 autopsies. Pneumonia was diagnosed clinically in 12 (28%) of the 43 patients, and 6 (50%) of them had negative autopsy findings. The sensitivity and specificity of BAL were 56% and 28%, respectively; PBB, 55% and 61%, respectively. The same microorganisms were found at autopsy, in BAL cultures, and in PBB cultures in fewer than 10% of the patients.

Conclusions: Bronchoalveolar lavage and protected bronchial brush have a low sensitivity and specificity and cannot be relied on by themselves for the diagnosis of pneumonia in critically ill burn patients. The results of these sampling techniques must be interpreted in the context of the overall clinical picture of each individual patient.

Arch Surg. 1999;134:1243-1247

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INFECTION IS one of the leading causes of mortality in patients with burns. Immunosuppression and the loss of the cutaneous barrier increase the susceptibility of burn patients to infection. Pneumonia, smoke inhalation injury, and respiratory distress syndrome are the leading causes of mortality in burn patients. Respiratory tract infections in these situations are not uncommon, and the combined mortality of inhalation injury and pneumonia is quoted to be as high as 60%. The diagnosis of pneumonia in critically ill burn patients poses a major challenge to the medical team caring for burn patients. Clinical diagnosis is often difficult, and the use of bronchoalveolar lavage (BAL) quantitative cultures and protected bronchial brush (PBB) cultures is still controversial.[1-6]

The present study compares the results of BAL quantitative cultures and PBB cultures with autopsy findings to assess the sensitivity and specificity of these techniques in diagnosing pneumonia in pediatric burn patients.

RESULTS

In the past 10 years, 45 pediatric burn patients died at Shriners Burns Hospital. Forty-three patients had diagnostic BAL quantitative cultures and PBB cultures available for the study. The mean age of the patients was 3.7 ± 0.5 years, the total body surface area burned was 70% ± 4%, and the full-thickness total body surface area burned was 65% ± 5%. Inhalation injury was present in 39 (91%) of the 43 children. The mean time from burn to death was 15.9 ± 4.5 days. The primary causes of death were as follows:

Cause	No. (%) of Patients
Respiratory distress	12 (26)
Respiratory distress and pneumonia	3 (8)
Sepsis	2 (5)
Pneumonia	6 (13)
Anoxic brain injury	10 (24)
Multiple organ dysfunction	9 (21)
Disseminated intravascular coagulation	1 (3)

Tracheobronchitis was present in 29 (69%) of all patients, and 34 (80%) presented with different stages of respiratory distress syndrome. All patients

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PATIENTS AND METHODS

Between January 1988 and January 1998, we studied all burned children admitted to Shriners Burns Hospital, Galveston, Tex, who died of their injuries. We analyzed hospital course, complications, septic episodes, results from PBB and BAL quantitative cultures, cause of death, and clinical and autopsy evidence of respiratory tract infection.

CLINICAL DIAGNOSIS OF LOWER RESPIRATORY TRACT INFECTIONS

Clinical diagnosis of lobar pneumonia or bronchopneumonia was established by the following specific criteria: systemic inflammatory response syndrome, radiographic evidence of a new or progressive infiltrate, and class 3 sputum or better with presence of microorganisms and white blood cells.

DIAGNOSIS OF LOWER RESPIRATORY TRACT INFECTIONS AT AUTOPSY

Autopsy lobar pneumonia and bronchopneumonia were diagnosed when gross and microscopic signs of consolidation with invasion of living tissues and inflammatory infiltration were observed with microscopic identification of microorganisms in the lung with positive postmortem lung culture results.

Autopsy findings of lower respiratory tract infections were assigned to be the criterion standard. A true lobar pneumonia or bronchopneumonia in burn patients was defined in our study as positive autopsy findings with isolation of microorganisms.

TECHNIQUE OF BAL AND PBB

Bronchoalveolar Lavage

Three aliquots of isotonic sodium chloride solution, 0.25 mL/kg, were instilled to the affected area, and the aspirate was sent for quantitative cultures. The bronchoscope was passed through a nasotracheal tube and then aimed to the suspected infected area of the lung. When extensive signs of respiratory distress syndrome were present, a lavage of both lungs was performed, and separate aspirates for cultures were obtained. The positivity for infection was set at greater than 10 000 colonies per milliliter in patients not receiving systemic antibiotics and greater than 1000 colony-forming units per milliliter in those receiving antibiotics.

Protected Bronchial Brush

The bronchoscopy technique was performed as outlined for BAL. When the bronchoscope was in the affected area, a probe was introduced into the bronchoscope and extended beyond the tip of the bronchoscope. At that point, the tip of the internal probe was opened, permitting a brush to come into contact with the terminal bronchi. Afterward, the brush was returned to the probe and withdrawn inside the bronchoscope. This technique allows the tip of the brush to be in contact with the area of interest but not with the rest of the tracheobronchial tree, thus reducing the possibility of contamination of the specimen by upper respiratory tract flora. Positivity was set at greater than 1000 colony-forming units per milliliter of Ringer lactate solution.

CULTURE CORRELATION AND DETERMINATION OF RESULTS

Results of BAL and PBB quantitative cultures were compared with the autopsy findings. Pathogens found in the BAL quantitative cultures and PBB cultures were compared with those found in the lungs at autopsy. Results of BAL quantitative cultures and PBB cultures were correlated with the clinical diagnosis of pneumonia and the autopsy results. Positive results in BAL and PBB cultures were compared with autopsy culture results. Biochemical reactions, biotype, and antibiotic sensitivities were also compared.

Results of BAL or PBB cultures were considered positive and diagnostic only if the same microorganism was isolated at autopsy with the same biotype, biochemical reactions, and antimicrobial sensitivity pattern.

False-positive and false-negative clinical diagnosis, BAL quantitative culture results, and PBB culture results were correlated with the postmortem examination of any given patient to establish the sensitivity and specificity of the techniques.

Data are depicted as mean ± SEM. Statistical analysis was performed with the unpaired t test, the Fisher exact test, and linear regression analysis. Significance was accepted at $P<.05$.

received ventilatory support with nasotracheal intubation.

Pneumonia was present in 19 (44%) of the 43 autopsies, while the clinical diagnosis of pneumonia was made in only 12 (28%) of the 43 patients. In 6 (50%) of these patients, an incorrect clinical diagnosis of pneumonia was made, with no positive autopsy findings. In 13 patients (68%) with true pneumonia (positive autopsy findings), there was no clinical suspicion of lower respiratory tract infection during the hospital course.

Results of PBB cultures were positive in 20 (46%) of the 43 patients, but only half of them (10 of 20 patients) corresponded to patients with positive findings at autopsy.

Microorganisms in BAL quantitative cultures were found in 27 (62%) of the 43 patients, but only 10 of 27 patients had positive autopsy findings. When the positive predictive values of PBB and BAL quantitative cultures were combined, the diagnosis of true pneumonia was accomplished only in 11 (57%) of all 19 patients by these techniques.

When positive findings at autopsy were compared with positive findings in BAL quantitative cultures and PBB cultures and microorganisms isolated were compared also (true positives), only 6% (2/43) of BAL cultures isolated the same microorganisms found at autopsy. Similarly, only 9% (4/43) of PBB cultures with positive results had the same microorganism result as the autopsy cultures. Microorganisms found at autopsy (true pneumonias), BAL quantitative culture results, and PBB culture results are summarized in the **Table**.

The sensitivity and specificity of BAL quantitative cultures were 56% and 28%, respectively; PBB, 55% and 61%, respectively.

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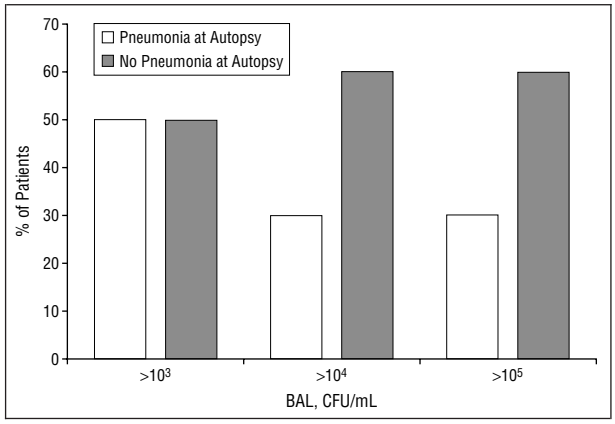
Microorganisms Identified*

Microorganism	Autopsy	Culture BAL	Culture PBB
Pseudomonas aeruginosa	33.3	18.7	21.4
Escherichia coli	11.1	9.3	0
Staphylococcus aureus	5.5	21.8	28.5
Staphyloccocus epidermidis	0	3.1	10.7
Staphylococcus species	16.6	9.3	7.1
Enterococcus faecalis	11.1	9.3	7.1
Proteus mirabilis	0	6.2	3.5
Enterobacter cloacae	5.5	3.1	0
Klebsiella pneumoniae	22.2	12.5	14.2
Streptococcus species	0	6.2	3.5

*Data are given as percentages. BAL indicates bronchoalveolar lavage; PBB, protected bronchial brush.



Correlation of bronchoalveolar lavage (BAL) cultures and pneumonia at autopsy. There was no significant difference between the number of colony-forming units per milliliter (CFU/mL) in BAL quantitative cultures and true pneumonia.

There were no statistically significant differences in sensitivity and specificity of the diagnostic tests when subgroup analysis by age, total body surface area burned, and positive or negative diagnosis of clinical or autopsy pneumonia was performed.

When BAL and PBB culture results were compared in the same patient, a low correlation was found between them by linear regression (adjusted $R^2 = 0.10$, $P = .03$). Results of BAL quantitative cultures tended to be higher when patients survived longer (adjusted $R^2 = 0.44$, $P = .03$).

Interestingly, we did not find a significant relation between the presence of tracheobronchitis and BAL quantitative culture results.

There was no relation between the number of colony-forming units per milliliter in BAL quantitative cultures and true pneumonia (**Figure**). There were no significant differences in sensitivity or specificity of the diagnostic test when different concentrations of colony-forming units per milliliter were considered. Linear regression rendered a low predictive value for BAL (adjusted $R^2 = 0.04$) and PBB (adjusted $R^2 = 0.07$).

COMMENT

Nosocomial pneumonia is one of the leading causes of death in thermally injured patients.[1,2] It has been established that cutaneous burns promote a state of immunosuppression along with a derangement of the cutaneous barrier that predispose the burn patient to the development of infections.[3] Pneumonia can result from hematogenous spread of microbial pathogens in this setting. In addition, smoke inhalation injury, respiratory distress syndrome, and ventilatory support have been related to an increased incidence of respiratory tract infections in these patients.[4,5] Respiratory tract infections had an incidence of 43% in all autopsies performed in our hospital in the past 10 years. As previously stated by other researchers,[1-5] smoke inhalation injury and ventilatory support promote an impaired mucociliary transport and cause an increased risk for descending pulmonary infections. This was also our experience. Nevertheless, diagnosis of these nosocomial infections is still difficult in the intensive care unit setting.

Burn patients undergo a prolonged inflammatory response that resembles a sepsislike syndrome. The large amount of fluids necessary to resuscitate these patients, the presence of smoke inhalation injury, and different stages of respiratory distress syndrome make the clinical diagnosis of pulmonary infections difficult. Most of the time, chest x-ray examination results are abnormal and may reveal diffuse nonspecific changes.[6] In only 18% of all patients with pneumonia found at autopsy was a correct clinical diagnosis made before death. In 31% of patients with positive autopsy findings, there was no clinical suspicion that pneumonia was present. This has also been found to be true in the diagnosis of nosocomial pneumonia in patients in intensive care units for other reasons than burns requiring ventilatory support.[7]

Different techniques have been advocated to improve the diagnosis of pneumonia in critically ill patients and in burn patients. Bronchoalveolar lavage cultures have been advocated as a good technique to diagnose pneumonia in critically ill patients, with a sensitivity and specificity as high as 87% and 91%, respectively.[7-9] However, in a recent review, Ramzy et al[10] showed a lack of correlation of positive BAL culture results with abnormal radiographic chest examination results in burn patients.

All the previously mentioned studies, however, lacked standard criteria for true-positive pneumonia. In the present study, we defined true pneumonia as positive findings of pulmonary infection at autopsy, which has no possible false-positive result. When clinical suspicion and results of BAL and PBB cultures were compared with the true pneumonia findings, the sensitivity and specificity of both techniques were extremely poor. When we combined the results of both techniques to improve the diagnostic efficacy, the results were also poor, which supports the experience of Jolis et al,[8] who advocated that BAL alone had the same predictive value as both techniques together in critically ill patients. Other researchers,[11] however, compared BAL culture results taken 15 minutes after the death of critically ill patients with the autopsy results, and the sensitivity of the technique was 46%—results that are comparable with our results in critically ill burn patients.

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When we compared the microorganisms found in PBB and BAL cultures with those found at autopsy, the same isolates were identified in fewer than 10% of the cases. This finding suggests that there is a strong colonization of the tracheobronchial tree in burn patients. It has been advocated that patients with tracheobronchitis following smoke inhalation injury suffer a colonization of the lower airway following their injury[12] that may lead to an increase in positive BAL quantitative culture results. However, in our recent experience, there was no relation between tracheobronchitis and BAL culture results in concentrations. On the other hand, true pneumonia was present in either patients with or patients without tracheobronchitis and also with a range of BAL quantitative culture counts anywhere from less than 10 to 1 million colony-forming units per milliliter. Because of this strong colonization and lack of similarity of bacterial isolates, it is also tempting to assume that there is cross colonization between the burn wound and the tracheobronchial tree. Nevertheless, recent studies[12] at Shriners Burns Hospital showed a correlation between them in only about half of the cases.

Another reason for the low diagnostic accuracy in burn patients may be prior systemic antimicrobial therapy. It is true that perioperative antibiotics are normally given during surgery for burns, and sometimes, facing the onset of a possible septic episode, empirical systemic antimicrobial regimens are started. It has been postulated that this practice can decrease the accuracy of BAL techniques in immunocompromised hosts,[13] but other studies[14] in critically ill patients receiving short-term systemic antimicrobials have not shown this effect on the accuracy of the techniques. All our patients received perioperative antibiotics, and those in whom respiratory tract infections were suspected received systemic antimicrobial treatment. In these circumstances, we considered positive culture results to be more than 10 000 colony-forming units per milliliter to increase the accuracy of the clinical diagnosis, but these results were also poor. Moreover, when subgroup analysis was performed in patients with or without clinical suspicion of pneumonia and who were or were not receiving systemic antimicrobials, we found no significant differences.

Finally, transbronchial biopsy of suspected affected areas has been advocated as an aid in the diagnosis of pneumonia in immunocompromised hosts and in transplant recipients.[15] Its sensitivity, however, has been shown in this setting as 46.6%, but when combined with BAL cultures, the sensitivity and specificity were 80% and 75%, respectively. The possible reason for this low sensitivity of transbronchial biopsies is, again, the difficulty in assessing clinically the critically ill patient with respiratory complications. Furthermore, transbronchial biopsies are associated with an increased risk of iatrogenic complications, such as pneumothorax.

In conclusion, BAL quantitative cultures and PBB cultures are not reliable, by themselves, for the diagnosis of pneumonia in burn patients. The technique of choice remains uncertain. Since the sensitivity and specificity of all techniques are low in burn patients, and clinical suspicion is wrong in more than half of the patients, the diagnosis of lower respiratory tract infection has to be tailored to the individual burn patient.[16]

Presented at the 19th Annual Meeting of the Surgical Infection Society, Seattle, Wash, April 30, 1999.

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DISCUSSION

William G. Cioffi, MD, Providence, RI: Dr Barret and colleagues have attempted to validate the techniques of bronchoalveolar lavage and protected bronchial brush cultures in a cohort of severely burned children. The strengths of this study are obvious and include the use of autopsy data as a gold standard for the diagnosis of pneumonia. They have compared clinical diagnosis using CDC [Centers for Disease Control and Prevention] criteria with BAL and PBB cultures. The results indicate that clinically pneumonia was suspected in only 28% of the patients, while documented only in 50% of those patients at autopsy. In addition, nearly two thirds of the pneumonias were never clinically suspected. Sensitivity and specificity of BAL and PBB cultures were poor but within the range of previous reports, and finally, premorbid cultures correlated

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with autopsy data only 10% of the time. Although the authors' conclusions fit my personal bias, we need to know a few more things before we discard these techniques in the clinical arena.

First, what was the time interval between BAL and PBB cultures and death? How many patients received antibiotics prior to death? How do you know that none of the patients were successfully treated prior to death or developed pneumonia after their BAL or PBB cultures? This is particularly relevant given that almost 50% of the patients with pneumonia at autopsy had essentially negative BAL cultures. In an effort to improve your BAL specificity, did you look at the presence of intracellular organisms on smears?

Finally, in most series, the clinical diagnosis of pneumonia is overcalled, but in your series, just the opposite occurred. Given your data, what do you now recommend that we do to make the diagnosis of pneumonia in our intensive care unit patients?

Dr Barret: In terms of the time of the BALs and when they were done, the BALs and PBBs were done in most of the patients within 72 hours prior to death. There were 3 patients that had their BAL done too far apart from the diagnostic technique and death of the patients and when the autopsy was available. So these were the 3 patients that were excluded from the persons in the study.

In terms of how many patients had antibiotics, all of the patients at the time of death were taking systemic antibiotics, with broad-spectrum antibiotics. There were 4 patients that at the time of their initial BAL when it was performed were not taking antibiotics, but subsequently they went on antibiotics. We do believe that the patients were really very well treated in terms of what sort of antibiotics were given, since in our institution there is a protocol of bacteria surveillance that is performed in all the patients, and in analyzing all the data that we had from the true pneumonias found at autopsy, all these bacteria were covered by the systemic antibiotics that the patients had on board.

We did not measure the intracellular organisms. And they may improve the efficacy of BAL in this setting, but we think it is still controversial, since there are some studies, like studies by Crawford et al, where they studied intracellular organisms, and they could only recover 28% of microorganism identification with BAL, despite the fact that 80% of the cytology wasn't normal, and also showing that all use 5% intracellular organisms as a measure for the diagnostic technique in BAL, they also found that without antibiotics the efficacy was as high as 70% and with previous antibiotics it fell down to 50%.

And, finally, in terms of what do we recommend to do now in the ICU with severely burned patients, well, in view of the poor results of the clinical judgment and the diagnostic techniques, it is a bit difficult to really say, but probably bacterial surveillance approach for every burn center, that maybe can cover what sort of isolation you may expect when you suspect a clinical infection, and probably more extensive views of PBB in this setting, and of course probably prospective evaluation of BAL and PBB with, as you quoted, intracellular organisms and the correlation with autopsy results to try to improve these techniques.

Jorge L. Rodriguez, MD, Minneapolis, Minn: The proof is really in the outcomes. Since two thirds of the patients with nosocomial pneumonia were not suspected, in your clinical decision making, do you think if you would have treated them for the nosocomial pneumonia that was not suspected that they would have survived?

Dr Barret: Well, I think that probably what is most striking is the fact that they were not suspected but they really died with pneumonia. These patients were treated with systemic antibiotics, as we already said, but clearly, they were not efficacious to treat these pneumonias. So maybe what is more important is to think why these patients had these infections in spite of the treatment that they had on board.

Howard Belzberg, MD, Los Angeles, Calif: You are shedding more light on a problem that sort of is almost like in the Supreme Court: most of us can't define pneumonia but think we know what it is when we see it. I would like to know if you had any radiological correlations, and, in particular, if you have any CAT [computed tomography] scan correlation between actual CAT scan findings and your autopsy data?

Dr Barret: No, we did not analyze in this regard and we don't have CAT scan data.

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