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Safety and benefits of bronchoalveolar lavage and lung biopsy in the management of pulmonary infiltrates in children with leukemia

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Abstract

Background—Children with leukemia are at risk of developing life threatening opportunistic pulmonary infections. The role of bronchoalveolar lavage (BAL) and lung biopsy (BX) in the management of these patients is controversial. In this study, we evaluate the yield and safety of BAL and BX in children with leukemia.

Procedure—We reviewed the records of all children with leukemia who underwent either BAL or BX between 1997 and 2007 at the St Jude Children's Research Hospital.

Results—A total of 64 patients were included, of whom 35 (55%) had BX and 29 (45%) had BAL. Positive results were obtained in 69% of BAL cohort and in 46% of BX cohort. Both procedures resulted in change in antimicrobial coverage (77% in lung biopsy, 83% in BAL). Pulmonary hemorrhage occurred in 2 patients, and transient hypoxia was the most frequent complication. All resolved without negatively impacting the clinical course.

Conclusion—Both BAL and BX are safe and useful in the management of children with leukemia and pulmonary disease.

Keywords

Cancer; Leukemia; Bronchoalveolar lavage; Lung biopsy; Safety; Pediatrics

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Conflict of interest

The authors declare no conflict of interest.

Introduction

While advances in supportive care have significantly contributed to the improved survival and cure of children with leukemia, pulmonary infiltrates remain a leading cause of morbidity and mortality in these immune-compromised patients. The management of these cases is particularly challenging when the microbiology work up with nasal wash, sputum, and blood is not informative. More invasive diagnostic approaches like bronchoalveolar lavage (BAL) and lung biopsy (BX) are frequently performed in children who are hospitalized with pulmonary disease not responding to broad empiric antimicrobial coverage. Both procedures could help in the identification of micro-organisms, and sometimes in tailoring antimicrobial therapy, even if cultures are negative. In this study, we evaluate the benefit and safety of BAL and BX in children with leukemia hospitalized with pulmonary disease. In addition, we evaluate factors that may impact the microbiologic yield of both procedures.

Materials and Methods

Patients

Patients in this study were admitted to St. Jude Children's Research Hospital, a tertiary-care pediatric oncology center between January 1, 1997 and December 31, 2007. Patients were included if they had an oncologic diagnosis of leukemia, were younger than 18 years of age, had abnormal radiologic findings of the lungs suggestive of respiratory illness, and had either bronchoscopy with BAL, or BX. Patients were excluded if the procedure was done for the purpose of oncologic disease evaluation or if they had received hematopoietic stem cell transplantation. If a patient had multiple procedures, only the first one was included in the data analysis. BAL was done either in the intensive care unit or in the operating room by a pulmonologist. BX was done either under computed tomography (CT) guided or ultrasound (U/S) guided biopsy by an interventional radiologist, or as surgical lung biopsy by a surgeon in the operating room.

Data collection

After approval by the St. Jude institutional review board, which waived the need for informed consent, the following data were extracted from patient medical records: demographic variables, oncologic diagnosis, absolute neutrophil count (ANC) at time of procedure, use of steroids at the time of the procedure, and antimicrobial coverage prior and after the procedure. Any change in antimicrobial coverage was noted whether it was addition, removal, or change in the dose of any antimicrobial agent. Radiologic findings including chest x-ray (CXR) and chest CT prior to the procedures were recorded and classified into three categories: no abnormal findings, unilateral lung disease, or bilateral lung disease. Antimicrobial coverage was documented in each patient for up to seven days post procedure with a detailed review of daily physician and nursing notes indicating patient response.

In our patient population, complications were defined as the presence of any of the following during the procedure and up to 48 hours post-procedure: new or increased oxygen

requirement; new intubation; hemoptysis or blood from endotracheal tube if patient was intubated; new or increased need for vasopressors or inotropes; stridor; and pneumothorax or hemothorax.

Statistical analysis

The yield and safety of BAL versus BX in children with leukemia were compared with Fishers exact or exact chi-square test. The same statistical approaches were also applied to investigate the relationship between clinical features such as disease diagnosis, gender, age, complication type, and frequency of positive yield within each diagnostic tool separately. All statistical analyses were performed with SAS release 9.2 software (Cary, NC). Results were considered statistically significant if P value was <0.05.

Results

Baseline characteristics

A total of 76 procedures were performed in 64 children with leukemia over the ten year study period. After excluding multiple procedures in the same patient, 35 BX and 29 BAL were included as the first diagnostic approach used. BX performed were U/S guided in 4 patients, CT guided in 27, and surgical lung biopsies in 4 (2 thorascopies and 2 thoracotomies). About two thirds of BAL were performed in patients with acute lymphoblastic leukemia (ALL), whereas two thirds of BX were done in patients with acute myelogenous leukemia (AML) (Table 1). In the BAL cohort, symptoms before procedure were fever (86%), cough (45%), and tachypnea (55 %). In the BX cohort, fever was noted in 66%, cough in 20%, and tachypnea in 23%. Of the 29 patients receiving BAL, 62% had an ANC below 500/mm³ and 24% were on steroids; compared to 60% and 20% respectively in the BX group. Patients were more likely to get a BX rather than a BAL if they had AML (66% versus 34% respectively, p=0.01) and unilateral pulmonary disease finding on radiologic imaging (51% versus 21%, p=0.02) (Table 1). The majority of patients in both cohorts were on antibiotics before the procedure. However, more patients were on antifungals in the BX cohort compared to the BAL cohort (91% versus 69% respectively, p=0.03). CT scan of chest was performed in all patients prior to BX and in 66% prior to BAL. Pulmonary nodules were detected in 21 patients in BX cohort versus 3 patients in BAL cohort.

Microbiologic Yield

There was a trend towards higher microbiologic yield with BAL compared to BX (69% versus 46% respectively; p=0.08). In the BAL cohort, 17 bacterial, 7 fungal, and 3 viral organisms were isolated in 20 patients (Table 2). In the BX cohort, infectious etiology was identified in 16 patients. The most common microorganisms identified were fungal (11), bacterial (4), and less commonly viral (1). Multiorganisms were isolated in 6 patients in the BAL cohort and in 2 patients in the biopsy cohort.

Factors associated with yield

Children with leukemia had a BAL yield of 80% if they were males, non-neutropenic, or if they had unilateral lung disease on CXR (Table 3). Chest CT findings didn't predict better

yield in the BX cohort; children with bilateral lung disease had 56% positive yield compared to 37% in children with unilateral lung disease ($p=0.32$). Use of steroids before BX was significantly associated with higher yield (85% compared to 35% in patients who didn't receive steroids, $p=0.03$).

Change in management

Both procedures, BAL and BX, resulted in change in antimicrobial management. Changes in antimicrobial coverage occurred in 83% of patients after BAL and in 77% after BX. Both procedures lead to changes in antimicrobial coverage even when yield is negative. There was a change in antimicrobials in 86% of children with positive yield compared to 71% in those with negative yield. The majority of patients were on antibiotics and antifungals before procedures, and only ~ 20% of patients were on antivirals. In the BAL cohort, 97% of patients were on antibiotics at the time of the procedure, and 76% had a change in antibiotic coverage subsequent to the procedure (Figure 1). In addition, 69% of the BAL cohort was on antifungal agents, with alterations in antifungal treatment in 52%. In the BX cohort, the majority were on both antibiotics and antifungals with 17% on antivirals at the time of biopsy. Again, the most common change was in antibiotics (66% followed by antifungal antimicrobials (51%) (Figure2). In the BAL cohort, yield confirmed 2 positive blood culture and 2 tracheal cultures in 3 patients. In the biopsy cohort, one patient had positive blood culture with the positive yield from the biopsy.

Complications

In general, both procedures were well tolerated with minimal complications (Table 4). Hypoxia occurred more commonly in the BAL cohort during procedure (38%), however, only 17% had evidence of persistent increased oxygen requirements at 48 hours post procedure. Hypoxia occurred in 17% of the cohort of BX and was still present in 14% at 48 hours after the procedure. Two patients developed pulmonary hemorrhage: one intubated patient in the BAL cohort had blood tinged secretion through his endotracheal tube but no change in his oxygen requirements, and 1 patient in the BX cohort was coughing blood tinged secretions but didn't require any intervention. All patients survived beyond 72 hours after the procedure. One patient developed pneumothorax after CT-guided biopsy that resolved spontaneously without chest tube insertion.

Discussion

Children with leukemia are at increased risk of developing life threatening pulmonary infections due to their immune-compromised status. Radiologic imaging and contemporary microbiologic testing on nasal wash and blood allow establishment of a diagnosis in some patients and tailoring of antimicrobial coverage accordingly. Many patients improve with broad spectrum empirical coverage which then gets tapered gradually. However, when there is no adequate response to treatment or when respiratory status worsens, timely diagnosis using more invasive approaches is essential to ensure adequate coverage and avoid organ toxicity from unnecessary empirical antimicrobials in these already compromised patients. BAL or BX is performed to establish a more definitive diagnosis in such patients. BAL is regarded to be less invasive compared to BX, but it is perceived by some to have a lower

yield compared with BX. Our results in a cohort of 64 children with leukemia indicate that BAL may surpass lung biopsy in establishing a microbiologic etiology. BAL had positive microbiologic yield of 69% compared to 46% in BX. Our BAL yield is similar to that reported previously in 2 pediatric cohorts with leukemia and hematologic malignancies. BAL microbiologic yield was 63.6% and 54% in Furuya et al cohort of 31 children with leukemia and Rao et al cohort of 33 children with hematological malignancy respectively [1,2]. In a recent metanalysis that examined 53 previously published studies of BAL in patients (both adults and children with cancer or post-HSCT), infectious etiology was identified in 53% [3]. BAL resulted in 65% positive infectious yield in an adult cohort of patients with hematologic malignancies [4].

One earlier report by Armenian et al has indicated that open lung biopsy is superior to BAL in establishing diagnosis. They compared 3 pediatric oncology cohorts: BAL, CT guided biopsy, and open lung biopsy [5]. Diagnostic yield was 61% in surgical lung biopsy versus 36% in BAL and 24% in CT guided biopsy. In our study, the BAL yield is similar to that reported for open lung biopsy in Armenian et al cohort, and of 4 children who underwent open lung, 3 had a positive yield. Naiditch et al reported a 50% positive histopathologic or microbiologic yield in 50 immunocompromised children who underwent surgical lung biopsy [6]. Similar to our cohort, the most common diagnosis was that of fungal infection (22% in Naiditch cohort versus 31% in our cohort). In another cohort of 14 children who underwent percutaneous lung biopsy, 14% had positive microbiologic yield [7]. While it seems that surgical lung biopsy has better yield compared to CT or U/S guided biopsy, it is not clear if this is due to the superiority of procedure used, or to other factors (eg, location, bulk, etc.) contributing to choice of specific procedure.

Neutropenic patients may pose more challenge because clinicians are more concerned about complications or the utility of these procedures in these children. In fact, immunocompromised patients with neutropenia tend to have lower yield with BAL compared to non-neutropenic patients [8, 9]. In a cohort of 26 adults with hematological disorders and febrile neutropenia, the diagnostic yield for BAL was 23% [8]. In another adult immunocompromised cohort, there was a trend towards higher yield in non-neutropenic patients versus those who were neutropenic (79% versus 57%) [9]. In our cohort, BAL yield was 81% in non-neutropenic children compared to 61% in children with neutropenia although the difference wasn't statistically significant. In the BX cohort on the other hand, microbiologic yield was higher in neutropenic versus non-neutropenic children (57% versus 28% respectively). In our cohort, lung biopsy was done more frequently in children with AML and who were on antifungals. This is not surprising because clinicians often tend to achieve more definitive diagnosis of suspected fungal infection with lung biopsy. In addition, children with AML are more prone to fungal infection and that may explain why these children were more likely to get a lung biopsy. Pulmonary nodules were detected on chest CT in 60% of the BX cohort.

Use of immunosuppressive therapy like steroids has been reported to reduce the yield from BAL [10]. In our BAL cohort, the yield was not significantly lower in patients who were receiving steroids at the time of the procedure. Steroid use was actually associated with a significantly higher yield in BX cohort.

In our 2 cohorts, the most common infectious agent was bacteria. Both procedures resulted in change in antimicrobial coverage in the majority of patients (83% in BAL cohort, and 77% in lung biopsy cohort). The most common change was in antibiotic coverage (mainly removing an antibiotic and then adding a new antibiotic). Both positive and negative yield guided further antimicrobial coverage. This is consistent with Rao et al. who reported a change in management in 83.3% of patients with positive yield and in 80% with negative yield in a pediatric oncology cohort [2]. However, in another cohort of adult patients with acute leukemia, BAL results contributed to treatment change in only 40% of patients [11].

The most common complication secondary to these procedures in our cohorts was hypoxia that was transient in children post bronchoscopy. Mild pulmonary hemorrhage occurred in 2 patients, with no increase in their oxygen requirement or need for further intervention. Thus, it is prudent to correct coagulopathy that may increase risk of bleeding before embarking on these procedures.

To our knowledge, this is the first study to compare BAL and biopsy in a pure cohort of children with leukemia. These procedures aid in diagnosis as well as management even when no infectious organisms are identified as unnecessary and potentially toxic antimicrobial coverage can be removed.

To conclude, our data support the use of BAL in the evaluation of pulmonary infiltrates in children with leukemia, as it resulted in high yield especially in non-neutropenic children with ALL. It is unclear whether surgical lung biopsy is superior to CT guided biopsy from our study because the number of patients who underwent surgical lung biopsy was small. Both procedures were helpful in therapeutic management, many times in discontinuing unnecessary antimicrobial coverage.

Acknowledgments

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Figure 1.

Changes in antimicrobial coverage after Bronchoscopy and the change that was made (either added, removed, or changed dose of antimicrobial agent)

Figure 2.

Changes in antimicrobial coverage after Bronchoscopy and the change that was made (either added, removed, or changed dose of antimicrobial agent)

Table 1

Characteristics of BAL and Lung Biopsy Cohorts

	BAL (29)	Biopsy (35)	P value
Mean Age (years)	11	11	
Gender			
Female	12 (41%)	17 (49 %)	0.62
Male	17 (59%)	18 (51 %)	
Diagnosis			
ALL	20 (69 %)	12 (34 %)	0.01
AML	9 (31%)	23 (66%)	
Neutropenia [†]	18 (62 %)	21 (60%)	1.00
Intubated	14 (48 %)	3 (9 %)	<0.001
Steroids	7 (24 %)	7 (20 %)	0.77
Antibiotics	28 (97%)	32 (91%)	0.62
Antifungals	20 (69%)	32 (91%)	0.03
Antivirals	6 (21%)	6 (17%)	0.76
Radiologic findings			
Unilateral disease	6 (21%)	18 (51%)	0.02
Bilateral disease	23 (79%)	17 (49%)	

[†]Neutropenia defined as absolute neutrophil count (ANC) <500/mm³

BAL, Bronchoalveolar Lavage; ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia

Table 2

Microbiologic yield

	BAL (29)	Biopsy (35)
Positive microbiologic yield 20 (69%)		16 (46%)
Bacterial	17	4
Coagulase negative Staph	5	
Alpha hemolytic Strep	4	1
MRSA	2	
Staphylococcus aureus	1	
Lactobacillus rhamnosus	1	
Corynebacterium species	1	
Staph epidermidis	1	
Mycoplasma	1	
Pneumocystis jiroveci or PCP	1	
Actinomyces		1
Prevotella melanogenica		1
G + cocci		1
Viral	3	1
CMV	2	
Parainfluenza	1	
RSV		1
Fungal	7	11
Candida albicans	2	
Cryptococcus neoformans	1	
Aspergillus	1	4
Budding yeast	1	
Histoplasma capsulatum	1	
Fungal elements	1	
Fungal hyphae		5
Mucor		2

Table 3

Factors associated with positive BAL Yield

N=29	Yield	P value
Gender		
Female (12)	5 (42%)	0.014
Male (17)	15(88%)	
Diagnosis		
ALL (20)	16 (80%)	0.088
AML (9)	4 (44%)	
Neutropenia [†]		
Y (18)	11 (61%)	0.42
N (11)	9 (81%)	
Intubated		
Y (14)	9(64%)	0.70
N (15)	11 (64%)	
Steroids		
Y (7)	3 (42%)	0.16
N (22)	17(77%)	
CXR Findings		
Unilateral disease (6)	6 (100%)	0.15
Bilateral disease (20)	13 (65%)	

[†]Neutropenia defined as absolute neutrophil count (ANC) <500/mm³

BAL, Bronchoalveolar Lavage; CXR, Chest X Ray; ALL, Acute Lymphocytic Leukemia; AML, Acute Myeloid Leukemia; Y, Yes; N, No

Table 4**Complications**

	BAL	BX
Complications during procedure		
New need for oxygen	2	4
Increased oxygen need	8	1
Intubation	1	1
Bleeding	0	0
Increase in vasopressor/inotrope	0	0
New vasopressor/inotrope	0	0
Stridor	0	1
Hemothorax/Pneumothorax	0	1
Complications at 48 hours		
New need for oxygen	1	3
Increased oxygen need	4	2
Intubation	0	0
Bleeding	1	1
Increase in vasopressor/inotrope	4	0
New vasopressor/inotrope	3	0
Stridor	0	0
Hemothorax/Pneumothorax	0	0

BAL, Bronchoalveolar Lavage; BX, Biopsy