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ARTICLE

Bronchoscopy in neonates with severe bronchopulmonary dysplasia in the NICU

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Abstract

Objectives To describe the findings, resulting changes in management, and safety profile of flexible bronchoscopy in the neonates with severe bronchopulmonary dysplasia.

Study design This was a retrospective case series of twenty-seven neonates with severe bronchopulmonary dysplasia who underwent flexible bronchoscopy in the neonatal intensive care unit.

Results Flexible bronchoscopy revealed airway pathology in 20/27 (74%) patients. Tracheomalacia 13/27 (48%), bronchomalacia 11/27 (40.7%), and airway edema 13/27 (48%) were the most common findings. Bronchoalveolar lavage (BAL) was performed in 17 patients. BAL culture revealed a microorganism in 12/17 (70.5%) cases. Findings from bronchoscopy resulted in change in clinical management in 17/27 (63%) patients. Common interventions included initiation of antibiotics (37%) and treatment of tracheobronchomalacia with bethanechol (22.2%), atrovent (18.5%), and PEEP titration (18.5%). Bronchoscopy was performed without significant complication in 26/27 (97%) patients.

Conclusion Flexible bronchoscopy can be a safe and useful tool for the management of neonates with severe bronchopulmonary dysplasia.

Background

Flexible bronchoscopy is a well-established tool for the evaluation of airway anomalies and secretions in pediatric patients and has been consistently demonstrated to have a favorable safety profile in both the ambulatory and intensive care setting [1]. Infants with severe bronchopulmonary dysplasia (sBPD) may require prolonged periods of invasive mechanical ventilation and undergo multiple intubation/extubation attempts during the initial hospitalization [2, 3]. These infants are at high risk for airway abnormalities such as subglottic stenosis and tracheobronchomalacia and respiratory infections [2, 4]. In one study describing airway evaluations in children with BPD, less than 5% had normal airways [5]. Thus, there is potential diagnostic benefit of performing a flexible bronchoscopy in neonates with sBPD.

However, lung function is impaired in patients with BPD. Multiple studies have identified decreased functional residual capacity, decreased respiratory system compliance, diffusion impairment, and increased airway resistance in children with BPD [6–8]. Approximately 20% of these patients will also have comorbid pulmonary hypertension [9]. Consequently, the risks and benefits of performing flexible bronchoscopy in neonates with sBPD must be carefully considered. Currently, there is a paucity of literature describing outcomes and safety profile of flexible bronchoscopy in neonates with sBPD, particularly in the neonatal intensive care unit (NICU).

The primary objective of this study was to evaluate the safety of flexible bronchoscopy performed in neonates with sBPD in the NICU and to describe the diagnostic findings and resultant changes in clinical management.

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Methods

This was a retrospective review of infants with sBPD at the Children's Hospital of Philadelphia (CHOP) who underwent flexible bronchoscopy from July 1, 2011 through June 1, 2016. This study was approved by the institution review board at CHOP. Only bronchoscopies performed during the initial hospitalization were included for the purpose of this analysis. A diagnosis of sBPD was based on modified guidelines from the National Heart, Lung, and Blood Institute Guidelines [10]. Subjects born prior to 32 weeks postmenstrual age (PMA) with sBPD received supplemental oxygen for ≥28 days and ≥30% supplemental oxygen or positive pressure ventilation at 36 weeks PMA. Subjects born after 32 weeks gestational age and prior to 37 weeks gestational age with sBPD received supplemental oxygen for ≥28 days and ≥30% supplemental oxygen or positive pressure ventilation at 56 days of life. As the use high flow nasal cannula was not specified, neonates born prior to 32 weeks PMA or born after 32 weeks but prior to 37 weeks PMA were defined as having sBPD if on >2 LPM with any fraction of inspired oxygen at 36 weeks PMA or 56 days of life respectively. This definition was based on the consensus of the Children's Hospital Neonatal Consortium.

Bronchoscopies were performed at the bedside in the NICU. Prior to the procedure, intravenous access was secured. Sedation was performed by the attending neonatologist, typically using an opiod with or without benzodiazepine. Medications were given as boluses and doses were titrated to achieve moderate sedation (spontaneous breathing intact, responsive to stimuli). Deep sedation or paralysis were used infrequently and only when needed to ensure patient safety and physiologic stability during the procedure. Inhaled oxygen concentration was increased to 100% at the beginning of the procedure and remained on 100% for the duration of the procedure. Vital signs were carefully monitored and the ventilator settings were adjusted as needed per the attending neonatologist.

Once adequate initial sedation was achieved, a flexible bronchoscopy was performed by an attending pulmonologist and senior pulmonary fellow with the aid of a respiratory therapist. Bronchoscopies were performed with an Olympus BFXP160F bronchoscope, which has an outer diameter of 2.8 mm with a 1.2 mm suction channel and can easily pass through a 3.5 mm endotracheal tube. The Olympus BFN20, which has an outer diameter of 2.2 mm but no suction channel and can pass through a 2.5 mm endotracheal tube, was used for one procedure. The carina was anesthetized using 0.5 ml of 1% topical lidocaine injected via the suction channel of the bronchoscope. If performed via a transnasal approach, the vocal cords were also anesthetized with 0.5 ml of 1% topical lidocaine. Bronchoalveol lavage (BAL) was performed using up to 3 ml/kg of normal saline divided into two aliquots. BAL was performed in a segmental bronchus based on radiographic findings or findings at the time of the bronchoscopy. Following the bronchoscopy, the patient remained in the NICU to recover.

BAL fluid was immediately sent for cytology. An adequate BAL specimen was defined based on the presence of alveolar macrophages without excessive epithelial cells, mucopurulent exudate, or cellular degeneration; identification of a pathologic process was also considered an adequate specimen per previously published guidelines [11]. BAL was also analyzed for lipid-laden and hemosiderin-laden macrophages. A patient was defined as having elevated lipid-laden or hemosiderin-laden macrophages if present in more than 10% of macrophages. Lavage fluid was sent for quantitative bacterial and fungal cultures. CMV titers were assessed in one child.

Patient characteristics including gestational age at birth, birth weight, race, sex, and weight and age on the day of the procedure were abstracted from the electronic medical record. The gross characteristics of the airway and complications of the procedures were abstracted from the bronchoscopy report. Microscopic characteristics were abstracted from the cytology and microbiology cultures of BAL. Culture results from tracheal aspirates performed within one week of BAL were also abstracted from the electronic medical record.

Categorical variables are reported as frequency and percentage, and continuous variables are reported with median and interquartile range. Culture results from BAL and tracheal aspirates were compared using the kappa statistic. All data analyses were performed using Stata 13.1. A p-value of less than 0.05 was considered statistically significant.

Results

We identified 27 infants with sBPD who underwent flexible bronchoscopy in the NICU during their initial hospitalization. The mean gestational age at birth was 27 weeks; however bronchoscopy was not performed until a median of 42.7 weeks PMA. The most common indication for flexible bronchoscopy was failure to wean positive pressure ventilation (Table 1).

Bronchoscopic evaluations revealed at least one abnormality in 20/27 (74.1%) infants (Table 2). Airway edema was the most common abnormality, identified in nearly 50% of all evaluations. Central airway collapse, either tracheomalacia or bronchomalacia, was also frequently present (48 and 41% respectively). Central airway collapse was often severe with near complete occlusion of the airway lumen during quiet exhalation. Other airway abnormalities were less common (Table 2).

Table 1 Characteristics of Neonates with severe BPD undergoing bronchoscopy ($n = 27$)

Gestational age at birth in weeks[a]	26.4 (24.4, 28.6)
PMA at bronchoscopy in weeks[a]	42.7 (40.7, 47.7)
Chronological age at bronchoscopy in weeks[a]	15.9 (13.6, 21.4)
Male	11 (40.7)
Race	
Caucasian	12 (44.4)
Black	4 (14.8)
Other	11 (40.7)
Endotracheal tube	24 (88.9)
Indications[b]	
Failure to wean positive pressure	14 (51.9)
Atelectasis	8 (29.6)
Suspected interstitial lung disease	6 (22.2)
Suspected central airway collapse	4 (14.8)
Failed extubation	4 (14.8)
Hyperinflation	4 (14.8)
Suspected aspiration	2 (7.4)
Pneumonia	1 (3.7)
Bronchiectasis	1 (3.7)
Possible PAP	1 (3.7)
Noisy breathing	1 (3.7)
Abnormal trachea on chest radiograph	1 (3.7)

Data are presented as *N* (%) unless otherwise specified

PMA postmenstrual age, *PAP* pulmonary alveolar proteinosis

[a]Data are presented as median (interquartile range)

[b]20/27 (74.1%) had more than 1 indication for flexible airway endoscopy

Table 2 Gross bronchoscopic findings

Airway edema	13 (48.2)
Tracheomalacia	13 (48.2)
Bronchomalacia	11 (40.7)
Granulation tissue	4 (14.8)
Vascular compression	3 (11.1)
Subglottic stenosis	2 (7.4)
Tracheal bronchus	1 (3.7)
Tracheal stenosis	1 (3.7)
Normal	7 (25.9)

Data are presented as *N* (%)

BAL was performed in 17 of the 27 neonates with sBPD; however, cytology was available in 15 instances (Table 3). Adequate sample was obtained in all cases. The median neutrophil count was 34% (IQR = 7–86%), and only four (27%) patients had a normal neutrophil count. Two patients (13%) had an elevated hemosiderin-laiden macrophage count, and four (26.7%) and an elevated lipid laiden macrophage count (Table 3).

Table 3 Microscopic BAL Findings

Cytology ($n = 15$)	
Percent neutrophils[a]	34 (7, 86)
Percent macrophages[a]	29 (9, 66)
Percent lymphocytes[a]	6 (3, 11)
Elevated hemosiderin-laden macrophages	2 (13.3)
Elevated lipid-laden macrophages	4 (26.7)
BAL culture ($N = 17$)[b,c]	
Klebsiella	4 (23.5)
Pseudomonas	5 (29.4)
Enterobacter	3 (17.6)
Candida	2 (11.8)
Methicillin sensitive staph aureus	1 (5.9)
Methicillin resistant staph aureus	1 (5.9)
Stenotrophomonas	1 (5.9)
Delftia acidovorans	1 (5.9)
Citrobacter	1 (5.9)
Acenetobacter	1 (5.9)
Serratia	1 (5.9)
Achromobacter	1 (5.9)
Cytomegalovirus	1 (5.9)
Negative	5 (29.4)

Data are presented as *N* (%) unless otherwise specified

BAL bronchoalveolar lavage

[a]Data are present as median (interquartile range)

[b]All isolates grew with >10,000 colony forming units

[c]Six patients grew more than one isolate

BAL cultures were available in 17 patients and grew at least one bacterial isolate at >10,000 colony forming units in 12 (70.5%) patients, with more than one organism cultured in 7 (41.1%) patients. Only 5 (29.4%) infants had a negative BAL culture (Table 3). There were eight infants who had bacterial culture performed on tracheal aspirate samples within seven days prior to collection of the BAL. The culture results of BAL and endotracheal aspirate were in agreement in only two patients, $\kappa = -0.55$ (Table 4). Six patients grew organisms > 10,000 CFUs on BAL that were not identified by culture from the tracheal aspirate. The remaining two patients had sterile BAL culture, but normal flora grew from the tracheal aspirate.

Changes in clinical management following bronchoscopy occurred in 17 (63.0%) of neonates who underwent bronchoscopy. Antibiotics were initiated in 10 (37.0%) patients who had a constellation of positive BAL culture, airway edema, and elevated neutrophil counts. Strategies to treat dynamic central airway collapse including bethanechol, atrovent, and PEEP titration were also commonly implemented following flexible bronchoscopy (Table 5).

Table 4 Comparison of tracheal aspirates and bronchoalveolar lavage in neonates with sBPD

Patient	TA culture	TA WBC count	BAL culture	BAL neutrophil count (%)	Days between TA and BAL
1	No Growth	Few	*K. oxytoca*	23	4
2	Normal Flora	None	*K. pneumoniae*	71	5
3	Normal Flora	Many	*D. acidovorans*	86	3
4	Normal Flora	Rare	*No Growth*	3	2
5	Normal Flora	Few	*Methicillin sensitive S. aureus*	91	2
6	*P. aeruginosa*	Moderate	*C. koseri, P. aeruginosa*	Not Available	7
7	Normal Flora	Many	*No Growth*	88	1
8	Normal Flora	Few	*A. baumannii, S. Marcescens, A. xylosoxidans*	34	3

TA Tracheal aspirate, *BAL* bronchoalveolar lavage

Table 5 Change in clinical management

Any change in management	17 (63.0)
Antibiotics	10 (37.0)
Bethanechol	6 (22.2)
Atrovent	5 (18.5)
PEEP Titration	5 (18.5)
Endotracheal/Tracheostomy positioning	4 (14.8)
Systemic steroids	0 (0.0)

Data are presents as *N* (%)

Table 6 Complications attributable to bronchoscopy

No Complications	21 (77.8)
Mild hypoxemia	5 (18.5)
Significant hypoxemia	1 (3.7)
Bradycardia	1 (3.7)
Bleeding	0 (0.0)
Pneumothorax	0 (0.0)
Death	0 (0.0)

Data are presented as *N* (%)

The infants tolerated bronchoscopy well with 21/27 (77.8%) having no complications related to the procedure. Mild hypoxemia, defined as SpO2 < 90% but > 80%, during the bronchoscopy was the most common complication, though one child had more severe hypoxemia (approximately 50%) and bradycardia during the bronchoscopy. The patient was allowed to recover and the bronchoscopy was successfully completed. The patient quickly returned to his baseline respiratory support following the procedure (Table 6).

Discussion

In this retrospective case series of neonates with sBPD, we found that flexible bronchoscopy can be safely performed in the NICU setting and often identifies airway pathology leading to changes in medical management. These results suggest that bronchoscopy can be a useful tool in the treatment of neonates with sBPD and chronic respiratory failure.

While this report highlights the findings of flexible bronchoscopy in neonates with sBPD, flexible bronchoscopy can be performed in conjunction with rigid bronchoscopy. The indications for both procedures are similar; however, the findings are often complementary. Flexible bronchoscopy is ideal for evaluating airway dynamics and more distal airways such as the lobar and segmental bronchi as well as sampling airway secretions. Rigid bronchoscopy provides excellent detail of the airway anatomy, particularly the posterior glottis and subglottis, and is better suited for interventions such as balloon dilation [12, 13]. Although performing a combined procedure provides a more comprehensive assessment, this may not be necessary depending on the clinical question and typically requires transfer to the operating room, which can be challenging in unstable patients.

There are no specific criteria to assess the proficiency of pediatric flexible bronchoscopist [13]; however, we suggest that only experienced bronchoscopists perform airway evaluations in neonates with sBPD. When performed by an experienced bronchosopist, the majority of neonates with sBPD experienced no complications or mild, self-limited complications related to bronchoscopy performed in the NICU. One infant experienced severe hypoxemia and bradycardia; however, the indication for bronchoscopy in this patient was frequent and recurrent episodes of severe hypoxemia and bradycardia with agitation. Previous studies have demonstrated a favorable safety profile of flexible bronchoscopy performed throughout childhood in children with BPD [5]. Similarly, flexible bronchoscopy is safe when performed in the NICU in premature and non-premature neonates [14–16]. To the best of our knowledge, this is the

first report assessing the safety of flexible bronchoscopy performed in the NICU in infants with sBPD.

More than 1/3rd of the patients were started on antibiotic therapy based on results of bacterial culture from BAL fluid, BAL neutrophilia, and airway edema. BAL culture results were often different from those of tracheal aspirate samples obtained within one week prior to bronchoscopy and suggest that the microbial communities present in the endotracheal tube and central airways in infants with severe BPD may be distinct from that of the more distal airways and alveoli. While our study is not able to assess the impact of treatment, it will be important to determine if treatment of positive BAL cultures results in improved outcomes in neonates with established sBPD.

In addition to neutrophilia, BAL also identified elevated lipid-laden macrophages in many patients with sBPD. While the presence of lipid-laden macrophages could be suggestive of aspiration; lipid-laden macrophages are not a specific marker of aspiration. Children with chronic lung disease can have elevated lipid-laden macrophages in the absence of aspiration. Parental nutrition can also increase lipid content in lavage fluid [13, 17, 18]. Consequently, it is difficult to interpret the clinical significant of elevated lipid-laden macrophages in this patient population.

Dynamic airway collapse such as tracheomalacia and bronchomalacia was identified in nearly half of the neonates undergoing bronchoscopy. Flexible bronchoscopy was performed via an artificial airway in the majority of our patients, which can generate auto-PEEP by preventing complete exhalation. This could mask tracheobronchomalacia [19, 20]. Thus, the true prevalence of tracheomalacia and bronchomalacia in neonates with sBPD undergoing bronchoscopy may be higher than we estimate. Prior reports have demonstrated that tracheomalacia and/or bronchomalacia affects 10–50% of neonates with BPD [2, 4, 5]. We have previously demonstrated the increased morbidity associated with tracheobronchomalacia in neonates with BPD throughout the newborn period [2]. Masters et al. also found increased respiratory morbidity throughout childhood in children with tracheobronchomalacia [21]. Bethanechol and PEEP can improve respiratory mechanics in children with tracheomalacia [22, 23] and were commonly used to treat tracheobronchomalacia in this study. Future investigations will need to evaluate the efficacy of these treatments in neonates with severe BPD.

In conclusion, flexible bronchoscopy can be a safe and effective tool for the identification of airway anomalies and infection in infants with sBPD and can assist in the management of neonates with sBPD in the NICU setting.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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