

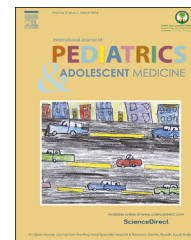
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## ORIGINAL RESEARCH ARTICLE

# Flexible bronchoscopy in children: Utility and complications



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Risk factors

**Abstract** *Background and objectives:* The flexible bronchoscope has become widely used by pediatric pulmonologists as a diagnostic and therapeutic tool. Nevertheless, there are several gaps in our knowledge to help refine its use and reduce its complications. In this study, we aimed to evaluate the utility and complications of pediatric bronchoscopy.

*Design and setting:* We conducted a retrospective review of bronchoscopy cases between March 2006 and April 2015 at a tertiary care medical center (King Fahad Medical City). One-hundred forty nine patients were studied.

*Patients and methods:* We evaluated how bronchoscopy contributed to the patients' diagnosis, assessed the accuracy of bronchoalveolar lavage white blood cell count (BAL WBC) to differentiate between infectious and non-infectious conditions, assessed the ability of clinical factors to predict high risk of desaturation during bronchoscopy, and finally summarized the reported procedural complications.

*Results:* We found pediatric bronchoscopy was a crucial diagnostic (confirming, ruling out, and discovering unexpected diagnosis) and therapeutic tool. The accuracy of BAL WBC counts is poor (AUC (95% CI) = 0.609 (0.497–0.712)); however, using two cutoff values ( $\leq 10$  WBCs (sensitivity = 84.44% and specificity = 29.27%) to rule out, and  $\geq 400$  WBCs (sensitivity = 33.33% and specificity 81.49%) to rule in infection) helped in early differentiation between infectious and non-infectious conditions. From the factors that we test, none we found predictive of desaturation. The most common procedural complication was

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desaturation (pooled incidence (95% CI) = 13 (8–19%)) followed by cough, mild airway bleeding, and spasm.

*Conclusions:* Flexible bronchoscopy is an important and relatively safe diagnostic and therapeutic tool in pediatric medicine, and utilization of this service should be encouraged after a careful consideration of which patient needs this procedure and a rigorous estimate of its pros and cons.

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## 1. Introduction

The flexible fiber optic bronchoscope, a real revolution in the management of respiratory diseases, was first introduced into pediatric care in 1978 [1], long time after Germany first reported the use of a rigid bronchoscope in 1897 to remove a foreign body from an adult [1]. Subsequent to its introduction, the flexible bronchoscope has been widely used as both a diagnostic and therapeutic tool [1,2].

In general, bronchoscopy aids in the visualization of the airway anatomy (e.g., agenesis), the assessment of airway dynamics (e.g., malacia), in the localization and treatment of obstructions (e.g., mucus plugs), obtaining fluid samples (i.e., bronchoalveolar lavage (BAL)), and brushing/biopsy for microbiology and histopathology. Additional therapeutic indications consist of suctioning, re-inflation, therapeutic wash out, administration of medication, and guidance for difficult intubation [1–8].

Bronchoscopy is an invasive procedure that requires anesthesia in children. It carries some risk of complications such as desaturation, airway trauma, and laryngeal spasm [2,5]. Several gaps in our knowledge remain, especially regarding ways to improve diagnostic capabilities and minimize complications [9,10]. Consequently, further studies to reach these objectives are warranted.

In this study, we aimed to: (1) investigate the usefulness of the pediatric flexible bronchoscope in our practice; (2) assess the accuracy, sensitivity, and specificity of white cell count (WBC) in BAL for detecting infectious conditions; (3) determine the rate of complications of this procedure; and (4) delineate the risk factors/predictors for desaturation during the procedure to avoid this serious complication.

## 2. Patients and methods

This is a retrospective review of records of children (under 14 years old) who underwent flexible bronchoscopy by a single pulmonologist (A.A) at King Fahad Medical City, Riyadh, Saudi Arabia, between March 2006 and April 2015.

### 2.1. Anesthesia care and procedure monitoring

Written consents were taken from all families after explaining the pros and cons of the bronchoscopy procedure. The majority of procedures were conducted under general anesthesia with a muscle relaxant, either rocuronium or succinylcholine at the discretion of the attending

anesthesiologist, except for cases of suspected malacia where the patient was consciously sedated initially to facilitate diagnosis. Patients with suspected malacia were typically underwent conscious sedation, mainly with inhalational anesthetics, followed by intubation and general anesthesia as indicated. Once malacia was identified, the procedure was continued under general anesthesia. Anesthesia was maintained with volatile anesthetics (without nitrous oxide) for procedures in the operating theater and with total intravenous anesthesia with propofol, midazolam, and fentanyl for procedures in the pediatric intensive care unit. Routine anesthesia monitoring included pulse oximetry, capnography, temperature, three-lead electrocardiogram, and non-invasive blood pressure monitoring. All patients were instructed to have nil per os (NPO) for at least 6 h before anesthesia while intravenous fluids were given for maintenance.

When lidocaine was used intra-operatively, intravenous fluids were continued after the procedure and patients were kept NPO for 2 h. In this case, vital signs (including oxygen saturation, respiratory rate, and pulse rate) were measured every 5 min and then every 15 min when the patient was awake. If lidocaine was not used, patients were given an oral diet as tolerated.

### 2.2. Medications used and procedure technique

We used normal saline in all lavage cases. Lidocaine (1% or 2% solution, whichever was available, at a dose of 1–2 mg per kg) was used either on the vocal cords or carina to minimize cough and bronchospasm. Hypertonic saline, acetylcysteine, and/or recombinant human deoxyribonuclease (dornase-alfa) were used in collapsed lung lobes to re-channelize airways. Albuterol inhaler and IV dexamethasone were used during prolonged intervention to minimize airway constriction. Epinephrine was also used for a patient with a hemorrhagic airway.

Bronchoalveolar lavage (BAL) was performed in patients with suspected respiratory infection to determine the offending microbe, as well as in cases of suspected hem siderosis, lipoid pneumonia, alveolar proteinosis, and in cases of unclear diagnosis, in addition to therapeutic use to re-channelize airways. The location and extent of BAL depended on the disease. For localized lesions, BAL was performed only in the affected lobe, while with diffuse disease it was performed in the right middle lobe and lingual lobe with or without the anterior/lateral segments of the lower lobes.

BAL was accomplished with the use of normal saline warmed to body temperature. A volume of 3 ml/kg was calculated and administered in three divided doses in children less than 20 Kg. In children weighing more than 20 Kg, 20 ml volumes were injected using a syringe via the suction channel of the bronchoscope. Approximately 40–70% of fluids were recovered by suction using a pressure of 25–100 mmHg as recommended by the European Society for Clinical Respiratory Physiology [11]. BAL fluids were transported to the laboratory in isolated bags containing ice, or at body temperature if processing was performed within 30 min (in emergency settings). All procedures were performed with an Olympus pediatric flexible fiber optic bronchoscope (BF-XP260F; Olympus America; Melville, NY, USA). As in most paediatric bronchoscopy centers, we used two sets of 2.8 mm sized bronchoscopes, which is the smallest size with a suction channel [8]. No biopsies were taken during any of the procedures. An automated counting method for cell counts and differentials was used.

### 2.3. Data extraction and synthesis

With the Institutional Review Board approval, we collected a predetermined data set from children who underwent flexible bronchoscopy at King Fahad Medical City during the above indicated time period. Extracted data included: age, gender, indication (pre-bronchoscopy diagnosis), post-bronchoscopy diagnosis, medications used during the procedure, observed complications associated with the procedure, location of the procedure in the hospital, and the patient's immune status. Complete blood count (CBC) within 24 h before the procedure, BAL WBC counts, bacterial, fungal, and mycobacterium cultures, polymerase chain reaction (PCR) results for detection of viruses were also collected. Histopathology reports were reviewed whenever applicable.

We included tracheoesophageal fistula and tracheomalacia in one category, as the former is a leading cause of tracheomalacia in approximately 75% of patients, and 10–20% will have significant tracheomalacia [12]. In our practice, we use bronchoscopy to evaluate tracheomalacia more often than to diagnose fistulas because fistulas can be diagnosed by other non-invasive tests such as barium studies. Malacia of different levels and etiologies (except malacia secondary to tracheoesophageal fistula) were placed in the same category because many of these patients have diffuse or multiple levels of malacia, and all of them have non-specific clinical manifestations. Therapeutic BAL for each disease was merged with its disease in Table 1.

Post-bronchoscopy diagnosis was based on visualization of the airway in certain conditions. For instance, lower airway infection/inflammation was diagnosed when the airway was noted to be erythematous or swollen or to have dilated vessels or mucopurulent secretions.

To create a comprehensive picture of pediatric bronchoscopy complications, we performed a PubMed search using the following terms (“bronchoscopy” and “pediatrics” and “complications”), without any limitation on the date of publication or language. Two authors (RST and AST) screened the articles and conducted the data extraction independently. Disagreements were resolved by consensus.

### 2.4. Statistical analysis

We first assessed the data for normality using the Shapiro–Wilk test. Normally distributed data are presented as the mean and standard deviation (SD), while non-normally distributed are presented as the median with the first and third interquartile [IQR]. Categorical data are presented as frequency and percentage.

We used the Receiver Operating Characteristics (ROC) curve to detect the accuracy (as area under the curve (AUC)) of WBC count in BAL in differentiating between infectious and non-infectious causes and to select the best cut-off values. AUC values were divided into four ranges; 0.61–0.70, 0.71–0.80, 0.81–0.90, and 0.91–1, indicating poor, fair, good, and excellent levels of accuracy, respectively [13].

We assessed the agreement between the pre- and post-bronchoscopy diagnoses using Kappa statistics. The values of Kappa were divided into three ranges; 0.41–0.60, 0.61–0.80, and 0.81–1, indicating moderate, substantial, and almost perfect agreements, respectively [14]. The agreement value reflects how the bronchoscopy procedure changed the diagnosis.

We looked for possible risk factors that led to desaturation during bronchoscopy using logistic regression [15]. The tested predictors/risk factors were age (continuous and categorical; less than one year, from one to five years, and more than five years), gender, weight, the location of the procedure (e.g., pediatric ICU vs. operating theater), airway access route (e.g., endotracheal tube, tracheostomy tube), BAL performed (yes or no), pre-procedure and post-procedure diagnoses, and the presence of infection. These factors were determined *a priori* based on clinical experience and previous reports [6,16].

Finally, we summarized the incidence of reported complications in different studies using pooled-effect estimates and corresponding 95% confidence intervals that were derived using a random-effects model that incorporates between-study variability [17].

A *P*-value of .05 was considered significant. SPSS software version 21 (SPSS, Chicago, IL) was used for most analyses. MedCalc Statistical Software version 15.2.2 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2015) was used for the ROC and pooled incidence analyses.

## 3. Results

One hundred sixty patients who underwent flexible bronchoscopy were considered for this study. Eleven were excluded due to missing significant data. The remaining one hundred and forty-nine patients were included. Seventy-five (50.3%) were males, and 74 (49.7%) were females. Their median [IQR] age was 27 [9.5,60] months, ranging from 12 days and 14 years. The majority of the bronchoscopy procedures were performed in the operating theaters 74.5% ( $n = 111$ ) followed by the pediatric ICU 24.8% ( $n = 37$ ). Only one procedure was performed in the cardiac catheterization laboratory.

An endotracheal tube was the major airway access device (82%), followed by a face mask (9%), nose (7%), and

**Table 1** Pre- and post- bronchoscopy diagnoses.

Indication (suspected pre-bronchoscopy diagnosis)	Post-bronchoscopy diagnosis	
Suspected lower airway infections (n = 73) 41.2%	<b>61</b>	<b>LAW<sup>a</sup> infection/inflammation</b>
	5	Malacia <sup>b</sup>
	2	Airway H/A, MP or Plastic B. <sup>c</sup>
	2	Normal airway
	1	Foreign body
	1	Pulmonary hemorrhage
	1	Lipoid pneumonia
Chronic stridor/wheezing (n = 44) 24.9%	<b>34</b>	<b>Malacia</b>
	4	LAW infection/inflammation
	2	Normal airway
	1	Airway H/A, MP or Plastic B.
	1	Foreign body
	1	Tracheoesophageal fistula
	1	UA trauma, SS or VCP <sup>d</sup>
Persistent atelectasis/hypoplasia (n = 24) 13.6%	<b>11</b>	<b>Airway H/A, MP or Plastic B.</b>
	8	Malacia
	3	LAW infection/inflammation
	1	Normal airway
	1	UA trauma, SS or VCP
Suspected TEF <sup>e</sup> \ secondary malacia (n = 14) 7.9%	<b>8</b>	<b>Malacia</b>
	2	Normal airway
	2	Tracheoesophageal fistula
	1	LAW infection/inflammation
	1	UA trauma, SS or VCP
Suspected foreign body (n = 8) 4.5%	<b>2</b>	<b>LAW infection/inflammation</b>
	<b>2</b>	<b>Normal airway</b>
	<b>2</b>	<b>Foreign body</b>
	1	Malacia
	1	Airway H/A, MP or Plastic B.
Suspected airway trauma (n = 3) 1.7%	<b>2</b>	<b>Normal airway</b>
	1	LAW infection/inflammation
Suspected P.H. <sup>f</sup> /telangiectasia (n = 3) 1.7%	3	Pulmonary hemorrhage
Suspected lipoid pneumonia (n = 3) 1.7%	3	Lipoid pneumonia
Suspected pulmonary alveolar proteinosis (n = 2) 1.1%	2	Alveolar proteinosis
Suspected pulmonary alveolar microlithiasis (n = 1) 0.6%	1	Pulmonary microlithiasis
Suspected malignancy (n = 1) 0.6%	1	LAW infection/inflammation

Summary of the indications: pre-bronchoscopy suspected diagnosis and post-bronchoscopy diagnosis, arranged from the most common to the least common. For example, we had three patients who were suspected to have airway trauma: two were diagnosed after the procedure to have normal airway, and one had LAW infection/inflammation.

<sup>a</sup> Lower airway.

<sup>b</sup> Tracheomalacia, bronchomalacia, laryngomalacia, and/or any malacia secondary to cardiac compression.

<sup>c</sup> Airway hypoplasia/agenesis, mucus plugs, or plastic bronchitis.

<sup>d</sup> Upper airway trauma, subglottic stenosis, or vocal cord paresis.

<sup>e</sup> Tracheoesophageal fistula.

<sup>f</sup> Pulmonary hemorrhage.

tracheostomy tube (2%). The following medications were used during the procedures: normal saline in 78% of the procedures, lidocaine in 22%, hypertonic saline in 3%, recombinant human deoxyribonuclease in 3%, acetylcysteine solution in 1%, albuterol in 1%, epinephrine in 1%, and dexamethasone in 1%. Eleven percent of the procedures were performed without medication.

The majority of the procedures were without complications 76% (n = 113), while 22% (n = 32) of the subjects experienced desaturation (defined as transient drop in SpO<sub>2</sub> below 90%), making this the most common complication. All

cases of desaturation were transient and were managed by retracting the bronchoscope for a limited time to regain the baseline saturation and then resuming the procedure. These episodes were not accompanied by bradycardia or hypotension. Other rare complications were vomiting (n = 1), laryngeal spasm (n = 1), and apnea (n = 1). The patient who had apnea (for more than 1 min) was a three-month-old infant. He was observed in the intensive care unit for 24 h until he recovered his normal respiration and was transferred back to the ward. We did not encounter any serious adverse effects such as

pneumothorax or surgical emphysema that have been reported in other studies [6,18,19].

The majority of the patients were immune-competent 77% (n = 114), while 23% (n = 35) were immune-compromised, 6% (n = 8) had leukemia, 5% (n = 7) were neutropenic, 3% (n = 4) had lymphoma, 2% (n = 3) cystic fibrosis, 2% (n = 3) h Bare lymphocyte syndrome, 1% (n = 2) chronic granulomatous disease, and the remainder of the patients (1% or n = 1 for each condition) were diagnosed with Chediak-Higashi syndrome, hypogammaglobinaemia, primary ciliary dyskinesia (Kertaginer's syndrome), pancytopenia, severe combined immunodeficiency (SCID), and hemophagocytic-lympho-histiocytosis (HLH).

Table 1 summarizes the indications (suspected pre-bronchoscopy diagnosis) for bronchoscopy, post-bronchoscopy diagnoses, and explains their relationship. The Kappa ( $\pm$ SE) value of the agreement between the pre- and post-bronchoscopy diagnosis was  $0.58 \pm 0.04$  indicating moderate agreement.

BAL was performed in 70.5% (n = 105) of patients. Table 2 [20,21] summarizes the WBC counts and differentials results from blood tests and BAL. We tested the accuracy of the WBC count in the BAL in differentiating between infectious and non-infectious/normal condition, which was poor. The AUC (95% CI) was 0.61 (0.50–0.71) (Fig. 1). Thus, it is impractical to rely on a single cut-off value to differentiate (predict) between infectious and non-infectious/normal conditions. We therefore selected two cut-off values one with high sensitivity (to rule out) and one with high specificity (to rule in) infection. We found that a BAL WBC cut-off value of less than 10 WBCs had a sensitivity of 84% (95% CI 71 to 94) and a specificity of 29% (95% CI 16 to 46), while a value of more than 400 WBCs had a sensitivity of only 33% (95% CI 20 to 49) but a specificity of 81% (95% CI 66 to 91).

One hundred and five BAL samples were processed for culture and PCR. Fifty per cent were positive. Of the positive cultures/PCR, 32% (n = 17) grew multiple organisms, six of which were from immunocompromised patients. A summary of the microbiological identification of the BAL is presented in Table 3.

None of the covariates that were tested as possible risk factors for desaturation in the logistic regression analysis were significant. Tested variables were (age, weight, gender, type of airway access, procedure location, BAL obtained, presence of infection, suspected pre-procedure diagnosis, post-procedure diagnosis).

Finally, to create a more comprehensive picture of potential complications associated with pediatric flexible bronchoscopy, we summarized our findings along with those reported in previously published studies in Table 4 [22–26, 27].

#### 4. Discussion

We tested the importance of the flexible bronchoscope as a diagnostic tool in the pediatric population. We found only moderate agreement ( $0.58 \pm 0.04$ ) between the pre-bronchoscopy suspected diagnoses and the post-bronchoscopy confirmed diagnoses, which arguably

indicates an important role for bronchoscopy in determining medical care in our practice (making the correct diagnosis). Bronchoscopy was particularly helpful in identifying malacia, foreign bodies, fistulas, traumas, and other diseases simply by visualizing the airway. BAL helped in differentiating between infectious and non-infections conditions (mainly by providing samples for culture) and identify the infective microbe in cases of respiratory infection. Thus, adjustments of anti-microbial therapy were possible and tailored according to microbial sensitivity. Targeting the infective organism with narrow spectrum agents minimizes the development of resistant organisms, which is becoming a threatening issue globally [28]. As with BAL, brush samples and biopsies for histopathology helped to identify some uncommon diseases including lipoid pneumonia, alveolar proteinosis, and pulmonary microlithiasis. Bronchoscopy was not only important in confirming or ruling out a suspected diagnosis, but more importantly, it was instrumental in identifying unexpected diagnoses. For instance, two out of four (50%) of the patients with a post-bronchoscopy diagnosis of foreign body aspiration were not suspected of having this diagnosis prior to the procedure (Table 1). Patients who had lipoid pneumonia, alveolar proteinosis, or pulmonary microlithiasis had multiple procedures for therapeutic purposes. Bronchoscopy was also useful not only in reaching diagnoses and treating conditions, but it was instrumental in gauging the severity of some conditions such as malacia secondary to tracheoesophageal fistula or the degree of airway obstruction by a foreign body or mucus plug.

We then tested the accuracy of the WBC count in BAL (a routine test for most practitioners) in differentiating infectious from non-infectious causes, which turned out to be poor if a single cut-off value was used. To overcome this limitation, we proposed two different cut-off values to help the pulmonologist identify an infectious etiology with reasonable confidence while waiting for the results of cultures and histopathological stains that could take days to weeks. About one-half of our study population had a respiratory infection. Therefore, we compared cases of infection with cases without infection in BAL WBC counts using a ROC curve. Two cut-off values were considered, one with a high sensitivity (to rule out) and other with a high specificity (to rule in). The first cut-off value of less than 10 WBCs/ $\mu$ L ruled out the respiratory infection in approximately 84% of cases, and the second cut-off value of more than 400 WBCs/ $\mu$ L ruled in respiratory infection in approximately 82% of cases. Initiating antimicrobial therapy is still a matter of contention when the diagnosis is still not clear. This decision whether to initiate antibiotic therapy or not should be balanced with other factors such as vital signs, general condition, and other laboratory tests (e.g.: serum WBC count and differentials) in addition to the results of BAL WBC count.

We found that the yield of BAL cultures\PCR in our center was 50%. Positive cultures\PCR were distributed evenly between patients regardless of their immune status and despite the fact that most of them received antibiotics prior to bronchoscopy. This high yield of cultures\PCR compared to those reported by other published studies [29] may be explained by the nature of our patient mix, which generally involved complicated cases with prolonged hospitalizations that may have increased their chances of

**Table 2** Summarizes the WBC counts and differential for each diagnosis in blood and bronchoalveolar lavage for patients with a single diagnosis.

Post-bronchoscopy diagnosis	Blood (serum)					Bronchoalveolar lavage					
	Total WBC count <sup>a</sup>	Neutrophils percentage	Lymphocytes percentage	Monocytes percentage	Eosinophils percentage	Total WBC count <sup>b</sup>	Neutrophils percentage	Lymphocytes percentage	Monocytes percentage	Eosinophils percentage	Macrophages percentage
LAW <sup>c</sup> infection/inflammation (n = 70)	9.4 [5.5,14.3]	50.4 [30.6,68]	36.3 [20.9,50]	7.6 [4.3,11.6]	1 [0.4,2.8]	180 [24.5,531]	67 [37.3,87]	12 [5.5,24.5]	6.5 [3,13.8]	2 [1,5.5]	40 [1.5,80]
Bacterial infection (n = 25)	9.8 [7.8,15]	51.2 [38.2,63.6]	37.2 [22.8,49.7]	8.2 [4.6,11.9]	1.6 [0.4,3.6]	343 [64.5,1584]	80 [41.5,90.5]	12 [5,27.5]	3.5 [2,9.3]	2 [2,3]	3 [0,NA]
Mixed infection (n = 6)	10.6 [1.1,20.8]	38.6 [20.7,88.5]	42.4 [6.6,62.5]	7.6 [6.3,22.5]	1.2 [0.1,5.3]	486 [25,3612]	82 [44,97]	8.5 [2,28.8]	4 [1.5,5.5]	NA	NA
Viral infection (n = 5)	10.1 [3.1,21.9]	49.6 [39.1,64]	24.4 [23.7,44.7]	10.3 [7.5,24.9]	0.4 [0.3,2.9]	40 [17,187.5]	50 [34.5,75.5]	10 [4,20]	14 [8,21]	NA	NA
Fungal infection (n = 2)	5.5 [1, NA]	33.8 [0.4, NA]	10 [0.4, NA]	12.2 [11.4, NA]	11.9 [11.9,11.9]	NA	NA	NA	NA	NA	NA
Infection with negative culture/ PCR <sup>d</sup> (n = 32)	8 [2.6,13.8]	50 [22.7,78.4]	36.3 [20,67.8]	6 [3.1,10.4]	0.8 [0.5,2.6]	142 [10,360]	49 [13.5,82.3]	15.5 [8,24.8]	10 [5,19.5]	1 [1,8]	NA
Malacia <sup>e</sup> (n = 29)	10.8 [9.2,13.5]	41.8 [33.8,65.8]	42.2 [28,53.2]	7.8 [4.5,11.4]	0.9 [0.3,2.1]	44 [18,1024]	65.5 [28,83.8]	30 [9,37.8]	16 [2.6,29.3]	5 [3, NA]	NA
Normal airway (n = 16)	10.3 [7.5,16,8]	48.9 [22.5,69.5]	40.8 [23.4,64.6]	8.1 [3.3,10.2]	1.1 [0.2,1.9]	10.5 [4,443]	10 [8, NA]	35.5 [3, NA]	15.5 [1, NA]	NA	NA
Airway hypoplasia/agenesis (n = 6)	8.5 [7,12.7]	24.4 [18.8,36]	62.1 [50.8,71.7]	8.2 [6.2,9.6]	0.5 [0,3.9]	90 [3, NA]	95 [59, NA]	4 [1, NA]	1 [1, NA]	NA	NA
Lipoid pneumonia (n = 4)	12 [7.5,13.7]	47.6 [31.3,69.8]	39.9 [19.8,46.4]	10 [6.3,13.7]	1.8 [0.1,11.4]	369.5 [181,634.5]	35 [11.5,63]	32.5 [12.5,66.8]	8 [5,17]	NA	NA
Alveolar proteinosis (n = 3)	8.4 [5.2, NA]	29.7 [27.7, NA]	50.3 [26.1, NA]	15.7 [8.2, NA]	2.9 [0.4, NA]	725 [450, NA]	NA	NA	NA	NA	NA

Data presented as median and 1st and 3rd [IQR].

<sup>a</sup> Total WBC count in 10<sup>e9</sup>/L.

<sup>b</sup> Total WBC count in cells/ $\mu$ L (micro liter).

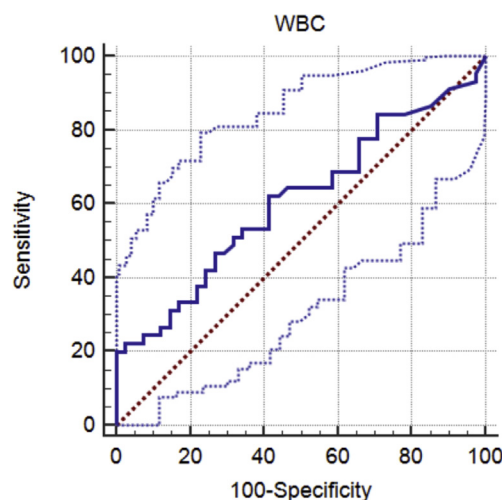
<sup>c</sup> Lower airway.

<sup>d</sup> Negative cultures and polymerase chain reaction in bronchoalveolar fluid.

<sup>e</sup> Tracheomalacia, bronchomalacia, laryngomalacia, and/or malacia secondary to cardiac compression. NA = Cannot be calculated because of small sample size.

colonization and infection (as *Pseudomonas aeruginosa* was the most common pathogen). Contamination of samples is another major issue that may affect laboratory outcomes, even when using the most standardized techniques. As with any other test, there is a risk of false positive/false negative results in BAL cultures/PCR. Currently, however, these are the most accurate tools at our disposal. Nevertheless, clinicians should consider the general condition of the patient and other laboratory tests to obtain an integrated view of the accuracy of any given results.

We tested multiple potential demographic and clinical risk factors to identify patients with a greater risk for desaturation during the procedure. However, none was significant. It would be helpful to know which patients and conditions might carry a greater risk of this common complication to allow for special precautions (e.g., doing the procedure in operating theater with a more specialized pediatric anesthesiologist). Studies by Schnapf's and Peng's found that younger patients are more susceptible to desaturation [6,16]. Schnapf's study reported that patients between six and 12 months are more susceptible to desaturation, while Peng et al mentioned that desaturation occurred more often in small infants without mentioning the age. Finally, though it would be helpful to assess how the skill of the pulmonologist impacts the occurrence of desaturation during bronchoscopy, this was not possible in our study because a single operator performed all procedures. Nonetheless, having the entire cohort managed by



**Figure 1** Receiver operating characteristic (ROC) curve (dark blue line) with its 95% CI (outer dashed blue lines) reflecting the accuracy of the BAL WBC count to differentiate between infectious and non-infectious conditions.

a single operator allowed for control for this potential cofounder while assessing the other possible risk factors.

We found also that recombinant human deoxyribonuclease (*dornase-alfa*) is useful in patients with atelectasis. We used it in four patients with aliquots of 2.5 mg injected

**Table 3** A summary of the microbiological identification from the BAL.

Category	Micro-organisms	Number (n = 53)	Percentage
Bacteria \ 23.5% (n = 35)	<i>Pseudomonas aeruginosa</i>	21	39.6%
	<i>Acinetobacter baumannii</i>	6	11.3%
	<i>Escherichia coli</i>	4	7.5%
	<i>Staphylococcus aureus</i>	4	7.5%
	<i>Enterobacter cloacae</i>	4	7.5%
	<i>Streptococcus pneumoniae</i>	3	5.7%
	<i>Haemophilus influenzae</i>	3	5.7%
	<i>Stenotrophomonas maltophilia</i>	3	5.7%
	<i>Delftia acidovorans</i>	2	3.8%
	<i>Klebsiella pneumoniae</i>	2	3.8%
	<i>Klebsiella oxytoca</i>	1	1.9%
	<i>Streptococcus intermedius</i>	1	1.9%
	<i>Streptococcus salivarius</i>	1	1.9%
	<i>Streptococcus milleri</i>	1	1.9%
	<i>Streptococcus viridans</i>	1	1.9%
	<i>Kluyvera ascorbata</i>	1	1.9%
	<i>Moraxella catarrhalis</i>	1	1.9%
	<i>Mycobacterium</i> species (not <i>m. tuberculosis</i> )	1	1.9%
	<i>Pseudomonas putida</i>	1	1.9%
	Viruses \ 7.4% (n = 11)	Cytomegalovirus (CMV)	7
Epstein–Barr virus (EBV)		3	5.7%
Herpes simplex virus (HSV)		1	1.9%
Fungi \ 4.7% (n = 7)	<i>Candida albicans</i>	3	5.7%
	<i>Aspergillus flavus</i>	3	5.7%
	Yeast, not <i>candida</i>	1	1.9%

Due to the presence of more than one organism that grew from the BAL cultures from the same patient, percentages add up to more than 100%.

**Table 4** Comparison between complications within different studies.

Authors and number of patients	Desaturation	Mild bleeding/epistaxis	Laryngeal/bronchial spasm	Coughing	Hypotension	Apnea	Subglottic Edema	Vomiting
Our study (n = 149) Saudi Arabia; 2015	21.5% (n = 32) <sup>a</sup>	0.7% (n = 1)	0.7% (n = 1)			0.7% (n = 1)		0.7% (n = 1)
Peng et al [6] (n = 725) Taiwan; 2011			0.8% (n = 6)					
Woodhull et al [22] (n = 216) Singapore; 2010	13.4% (n = 29)		1.9% (n = 4)					
Malherbe et al [23] (n = 52) Canada; 2010	19% (n = 10)			27% (n = 14)		21% (n = 11)		
Tang et al [24] (n = 53) China; 2009	20.8% (n = 11) <sup>a</sup>	3.8% (n = 2)	1.9% (n = 1)					
Righini et al [25] (n = 82) France; 2007			2.4% (n = 2)				2.4% (n = 2)	
Manna et al [10] (n = 148) UK; 2006	10.8% (n = 16)				17% (n = 25)			
Rodríguez et al [26] (n = 66) Colombia; 2003	27.3% (n = 18) <sup>b</sup>			6.1% (n = 4)				
Sánchez et al [21] (n = 700) Chile; 2003	2.7% (n = 19)		0.7% (n = 5)					
Nussbaum [5] (n = 2836) USA; 2002	0.7% (n = 21) <sup>c</sup>	4% (113)	0.6% (n = 17)					
De Blic et al [27] (n = 1382) France; 2002	2.6% (n = 36) <sup>d</sup>	0.5% (n = 6)	0.9% (n = 13)	1.9% (n = 26)				
Wong et al [20] (n = 141) Taiwan; 1995	3.5% (n = 5)					0.7% (n = 1)		
De Blic et al [3] (n = 37) France; 1991	70.3% (n = 26) <sup>e</sup>							
Puhakka et al [7] (n = 1032) Finland; 1987	10.8% (n = 77)		2.1% (n = 16)					
Total (n = 7620)	3.9% (n = 300)	1.6% (n = 122)	0.9% (n = 65)	0.6% (n = 44)	0.3% (n = 25)	0.2% (n = 13)	0.03% (n = 2)	0.01% (n = 1)
Pooled incidence (95% CI) per 100 patients <sup>f</sup>	13 (8–19)	2 (0.2–5.4)	1 (0.7–1.4)	9.3 (0.6–26.6)	NA	4.7 (0.04–16.7)	NA	NA

NA = not applicable.

<sup>a</sup> Desaturation defined in our study and in Tang's study as a transient drop in SpO<sub>2</sub> (Hemoglobin Oxygen Saturation) below 90%.<sup>b</sup> Desaturation defined in Rodríguez's study as a drop in SpO<sub>2</sub> below 10% or more from baseline.<sup>c</sup> Desaturation defined in Nussbaum's study as a drop in SpO<sub>2</sub> 65%–80%.<sup>d</sup> Desaturation defined in De Blic's study at 2002 as a drop in SpO<sub>2</sub> below or equal 90%.<sup>e</sup> Desaturation defined in De Blic's study at 1991 as a transient drop in SpO<sub>2</sub> not less than 80%.<sup>f</sup> We used a random-effects model to account for heterogeneity between studies, data represents the incidence (percentage) with (95% CI). There was no significant heterogeneity in cough; however, we still reported the random-effects model result, both random and fixed-effects estimates for cough were almost identical.



directly in the airways of the affected lobe. Marked bronchoscopic, radiological and even clinical improvements were observed. Although we do not have a control group for comparison and cannot be certain that the improvement was due to dornase-alfa and not to simple suctioning or infusion of normal saline, the efficacy of this medication has been reported in couple of case-reports, and we used it on trial basis [30–32].

Bronchoscopy, like all invasive procedures, has its pros and cons. It carries the risk of complications from the inserted bronchoscope, extensive lavage, and anesthetic medications. In our study, 24% of patients developed non-life-threatening complications. The most common was transient desaturation. We summarized the complications associated with pediatric bronchoscopy that have been reported in the literature to determine a global, comprehensive estimation. A good understanding of procedural complications can better prepare for appropriate patient management as well as aid in counseling parents. Consistent with our findings, desaturation was the most common reported complication. Previous authors have used widely variable reductions in SpO<sub>2</sub> to define desaturation leading to significant heterogeneity. For instance, Nussbaum et al [5] defined desaturation as a drop in SpO<sub>2</sub> to 65%–80%, Rodríguez et al [26] defined it as a drop in SpO<sub>2</sub> of 10% or more below the baseline, while still other studies did not define the term at all. We used a random-effects model to overcome this issue. It is important to realize that desaturation in children is particularly dangerous and can rapidly cause bradycardia and even cardiac arrest. Therefore, prompt response and precise coordination and cooperation between the pulmonologist and anesthesiologist are essential.

Contrary to the findings in our study, cough reflex was a significant complication reported by Malherbe et al [23] and Rodríguez et al [26]. The difference is likely because we used a muscle-relaxing agent during the procedures. Malherbe et al [23] suggested that the use of remifentanyl can decrease the incidence of cough during the procedure. Similarly, Nicolai et al [9] suggested that deep sedation/anesthesia can mitigate the cough reflex when muscle relaxation is undesirable.

Airway bleeding during bronchoscopy is another known complication. In this cohort, we encountered only one patient who developed minor bleeding. This patient had a diagnosis of pulmonary hemosiderosis, and epinephrine was used to control bleeding.

Of note, post-bronchoalveolar lavage fever is a reported complication in some studies [6, 11, 33]. While the origin of this fever is unknown, it is transient and more common in children less than two years old [33]. In our cohort, there were no reports of new fevers following bronchoscopy.

Our study has some limitations including the relatively small sample size and the retrospective design. This might affect some of our results, in particularly those related to WBC count accuracy in BAL and the risk factors for desaturation. We, therefore, recommend further studies with a larger number of patients to identify and address these issues more conclusively.

In conclusion, the flexible bronchoscope is a valuable tool in the diagnosis and treatment of airway disorders in children. It has a good safety profile with rarely reported life threatening or longstanding complications. Furthermore, the ability

to perform BAL with this procedure can play a significant role in the early differentiation of conditions due to infection versus those unrelated to infection, and aids in identifying the exact pathology and best treatment. Earlier intervention and utilization of bronchoscopy should be encouraged after a careful consideration of which patients would benefit from this procedure and a rigorous estimate of its pros and cons.

## Conflict of interest

Authors have no conflict of interest to declare.

## Ethical clearance

Our manuscript respected the confidentiality of patients and worked with an ethical base.

## Author contribution

Authors worked voluntarily and for free. They worked in collaboration as a team.

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