Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2022.21315

The Importance of Flexible Bronchoscopy in Difficult-to-treat Asthma from a Pediatric Pulmonology Perspective

Halime Nayir Büyükşahin, Nagehan Emiralioğlu, Dilber Ademhan Tural, Beste Özsezen, Birce Sunman, İsmail Güzelkaş, Ebru Yalçın, Deniz Doğru, Uğur Özçelik, Nural Kiper

Department of Pediatric Pulmonology, Hacettepe University, School of Medicine, İhsan Doğramacı Children's Hospital, Ankara, Turkey

What is already known on this topic?

- *Asthma is the most common chronic lung disease in childhood. In the differential diagnosis of patients with difficult-to-treat asthma, flexible fiberoptic bronchoscopy is recommended to exclude other lung diseases.*
- *Persistent bacterial bronchitis, congenital-structural problems, foreign body aspiration, and gastroesophageal reflux should be excluded in patients with difficult-to-treat asthma.*

What this study adds on this topic?

- *Persistent bacterial bronchitis, airway malacia, gastroesophageal reflux, and other anatomic anomalies were successfully diagnosed using flexible fiberoptic bronchoscopy and treated without any complications Suggesting that flexible fiberoptic bronchoscopy is an important diagnostic tool with a low complication rate in children with difficult-to-treat asthma.*

Corresponding author:
Halime Nayir Büyükşahin
✉hnayirbuyuksahin@gmail.com
Received: November 1, 2021
Accepted: December 22, 2021

ABSTRACT

Objective: Asthma is the most common chronic lung disease in childhood. Difficult-to-treat asthma is defined as the continuation of symptoms or attacks of patients despite step 4 or 5 of Global Initiative for Asthma therapy. In the differential diagnosis of these patients, flexible fiberoptic bronchoscopy is recommended to exclude other lung diseases. In this study, we aimed to examine the clinical and radiologic features and flexible fiberoptic bronchoscopy findings of patients referred to our pediatric pulmonology department due to difficult-to-treat asthma and determine the effects of flexible fiberoptic bronchoscopy on the differential diagnosis and treatment.

Materials and Methods: The demographic characteristics and flexible fiberoptic bronchoscopy results of 62 patients who were diagnosed as having difficult-to-treat asthma in our pediatric pulmonology department between January 2015 and June 2020 were evaluated retrospectively. The symptoms, history, medications, physical examination findings, pulmonary function tests, and radiologic findings of patients who underwent flexible fiberoptic bronchoscopy were evaluated.

Results: The median age of the patients was 69 (interquartile range: 42–108 months). The most common reasons for the referral of these patients were chronic cough, recurrent pulmonary infections, and persistent wheezing. All patients had chest radiography and 37 (59.7%) had chest computed tomography at their first admission; 14 (37.8%) patients had abnormal findings on chest computed tomography. There was no significant difference in terms of age, physical examination findings, pulmonary function test results, and radiologic examinations between patients with and without pathologic bronchoscopy findings. None of the patients had complications during and after flexible fiberoptic bronchoscopy. The most common diagnoses of patients based on flexible fiberoptic bronchoscopy were persistent bacterial bronchitis in 19 (30.6%) patients, tracheomalacia and/or bronchomalacia in 12 (19.4%), and anatomic anomalies in 3 (4.8%) patients (separation of lingula into 3, separation of right upper lobe bronchus into 4, and tracheal dyskinesia). *Mycobacterium tuberculosis* growth was observed in the tuberculosis culture of 1 patient. According to the flexible fiberoptic bronchoscopy and bronchoalveolar lavage results, antituberculosis treatment was initiated in 1 patient and polypoid mass excision was performed in 1 patient. A proton pump inhibitor was started in 9 (15.5%) patients, physiotherapy in 5 (8.0%), antibiotics in 14 (22.5%), and ipratropium bromide in 7 (11.2%) patients. All patients were followed up with the diagnosis of asthma except for 2 patients.

Conclusion: To date, there is no prospective study evaluating the importance of flexible fiberoptic bronchoscopy in difficult-to-treat asthma in childhood. In our small cohort, persistent bacterial bronchitis, airway tracheomalacia and/or bronchomalacia, gastroesophageal reflux, and other anatomic anomalies were successfully diagnosed using flexible fiberoptic bronchoscopy and treated without any complications, suggesting that flexible fiberoptic bronchoscopy is an important diagnostic tool with a low complication rate in children with difficult-to-treat asthma.

Keywords: Difficult-to-treat asthma, flexible fiberoptic bronchoscopy, persistent bacterial bronchitis, gastroesophageal reflux

Cite this article as: Büyükşahin HN, Emiralioğlu N, Tural DA, et al. The importance of flexible bronchoscopy in difficult-to-treat asthma from a pediatric pulmonology perspective. *Turk Arch Pediatr.* 2022;57(3):310–315.

INTRODUCTION

Asthma is the most common chronic disease of childhood. Difficult-to-treat asthma is defined as the continuation of symptoms or attacks of patients despite step 4 or 5 of Global Initiative for Asthma (GINA) therapy.[1] In the differential diagnosis of these patients, flexible fiberoptic bronchoscopy (FFB) is recommended to exclude other lung diseases.[2]

Persistent bacterial bronchitis (PBB), congenital-structural problems, foreign body aspiration, GER, bronchiolitis obliterans, vascular rings, and H-type fistules should be excluded in patients with a diagnosis of difficult-to-treat asthma.[3-6] Persistent bacterial bronchitis is characterized by a wet cough lasting more than 4 weeks, isolation of bacteria in the bronchoalveolar lavage (BAL) culture, and good response of the symptoms to 2-week antibiotic treatment.[7] Due to the difficulties in collecting sputum samples from children, it is difficult to prove PBB microbiologically; therefore, the gold standard in diagnosis is obtaining BAL samples via bronchoscopy.[8] Flexible bronchoscopy often reveals signs of bronchitis characterized by purulent secretion, airway edema, and inflammation.[9-10] Tracheomalacia is defined as at least a 50% collapse of the tracheal lumen on expiration.[11] There is no gold standard for the detection of tracheobronchomalacia (TBM), but FFB is preferred by pediatric pulmonologists in children who breathe spontaneously.[12-15] Gastroesophageal reflux (GER) has been shown to be associated with chronic upper and lower airway symptoms, including reactive airway disease, recurrent stridor, chronic cough, and recurrent pneumonia in patients who do not respond to asthma treatment.[16] Although the gold standard for the diagnosis of GER is a 24-hour pH meter measurement, studies are showing that this is not superior to the detection of lipid-loaded macrophages in the cytology of BAL fluid.[17]

In this study, we aimed to evaluate the clinical characteristics, radiologic features, and FFB findings of patients who were referred to our pediatric pulmonology department due to difficult-to-treat asthma. Our second aim was to determine the effects of FFB on diagnosis, symptoms, and treatment in patients with difficult-to-treat asthma.

MATERIALS AND METHODS

Study Design

In this retrospective cross-sectional study, the demographic characteristics and FFB results of 62 patients who were diagnosed as having difficult-to-treat asthma among 582 patients who underwent FFB in the pediatric pulmonology department of our hospital between January 2015 and June 2020 were evaluated. Patients who were diagnosed as having difficult-to-treat asthma based on GINA criteria and referred to our pediatric pulmonology department due to their prolonged symptoms were included in the study.[1] Patients without primary lung disease comorbidity were not excluded.

Before the FFB procedure, the consent of the patient's relatives was obtained for the procedure. The study was approved by the ethics committee of Hacettepe University Institutional Ethics Committee (No:20/1085)

Data Collection and Definitions

The symptoms, previous history, medications, physical examination findings, respiratory function tests, and radiologic findings of patients who underwent FFB were evaluated. The FFB images of the patients and microbiologic and cytologic analyses of the BAL samples obtained during the procedure were examined. Tracheomalacia was considered as at least a 50% collapse of the tracheal lumen on expiration and was evaluated under mild sedation to minimize the effect of anesthesia on airway dynamics.[11]

Physiotherapy was recommended to patients with atelectasis and abnormal mucus secretions. Ipratropium bromide was used for patients diagnosed with tracheomalacia and/or bronchomalacia and severe wheezing.[11]

Although normal pulmonary function tests do not exclude the diagnosis of asthma, it is recommended to use the Forced expiratory volume in one second (FEV1)/Forced vital capacity (FVC) ratio as the most appropriate test to diagnose airflow limitation, since the FEV1 value may be found to be low in many diseases. Values below the 90% limit indicate obstruction.[18]

Bronchoscopy Procedure

Our bronchoscopy team consists of the following: physician, assistant for procedures, nurse, anesthesiologist, and sedation nurse. We obtained consent from the family before the procedure. The procedure was conducted with an Olympus® flexible bronchoscope that included 2.2 mm, 3.6 mm, 4.2 mm, and 5.0 mm external diameter options. Either laryngeal masks (LMA) or the nasal cavity route was utilized for entry. Bronchoalveolar lavage was performed through the injection of a pre-warmed sterile saline solution. Bronchoalveolar lavage samples were taken from the most affected lung segment; the right middle lobe of the lung was preferred for patients in whom the most affected lung segment could not be identified. Microbiological cultures and cytology are studied from BAL in all patients. Viral tests are also running from the BAL of immunocompromised patients. Detection of bacteria above 10^4 cfu/mL in BAL was considered significant and defined as clinically important lower airway infection.[19]

Statistical Analysis

Data analyses were performed usingthe Statistical Package for Social Sciences, version 22.0 software (SPSS Inc.; Chicago,IL, USA).. Continuous variables were tested for normality using the Shapiro–Wilk test. Values are presented as mean ± standard deviation for variables with normal distribution or in the case of nonnormally distributed variables, as median and range. Comparisons of percentages between different groups of patients were performed using the Chi-square (χ^2) test if indicated or Fisher's exact test. For data without normal distribution, comparisons were made using the Mann–Whitney *U*-test (for 2 groups). In all analyses, $P < .05$ was taken to indicate statistical significance.

RESULTS

Patient Characteristics

The median age at asthma diagnosis was 36 months (interquartile range (IQR): 18-60) in the study population (n = 62). At first visit to the pediatric pulmonology department, 19 (30%)

patients had comorbidity. Those were congenital heart diseases, myasthenia gravis, common variable immune deficiency, selective immunoglobulin (Ig)-A deficiency, Morgagni hernia, and atopic dermatitis.

The median age of the patients at the first admission to the pediatric pulmonology department was 69 (range: 42-108) months. The most common reasons for referral to the pediatric pulmonology department were prolonged cough in 29 patients (46.8%), recurrent pulmonary infection in 14 patients (22.6%), and persistent wheezing in 10 patients (16.1%). Ten patients had a history of atopy. Three of those with comorbidities had a history of atopy. Ten patients had a family history of asthma and 4 had smoking exposure. Except for 1 (1.6%) patient with antibiotic allergy, there was no history of drug allergy. During the first evaluation of these patients at our pediatric pulmonology department, 75.8% had no pathologic findings in the respiratory system physical examination. Clubbing was not observed in any patients. Thirty-four (54.8%) patients had pulmonary function tests. Seven patients had an FEV1/FVC ratio of less than 90%. None of the patients were using high-dose inhaled steroids and long-acting beta-agonists. Characteristics of the patients at the time of first visit are given in Table 1. All patients had chest radiography and 37 (59.7%) had chest computed tomography (CT) in their first admission to the pediatric pulmonology department (Table 2).

Bronchoscopy and Bronchoalveolar Lavage

In the bronchoscopy procedure, the access route of 2 patients was nasal, and the bronchoscopic examination of all other patients was performed through an LMA. There were no complications during any procedures. The bronchoscopic diagnosis of 24 (38.8%) patients was normal. Persistent bacterial bronchitis was diagnosed using FFB in 19 (30.6%) patients, tracheomalacia and/or bronchomalacia in 12 (19.4%), anatomic anomalies in 3 (4.8%) (separation of the lingula into 3, separation of right upper lobe bronchus into 4, and tracheal dyskinesia), polypoid mass in the trachea in 1 patient, splitting in the right upper lobe into 2 segments in a patient with PBB, accessory bronchi in the right main bronchus in a patient with malacia, and malacia with PBB in 1 patient.

Table 1. Clinical Characteristics of the Patients at the Time of First Visit

Gender	
Female:male (n)	27:35
Asthma diagnosis age (months), (median, IQR)	36 (18-60)
BMI (median, IQR)	16.9 (15-20)
SPO_2 (median, IQR)	97.0 (96-98)
Initial symptoms, n (%)	
Wheezing	10 (16.1%)
Cough	29 (46.8%)
Wheezing and cough	5 (8.1%)
Recurrent lung infection	14 (22.6%)
Shortness of breath	4 (6.4%)
Atopy history, n (%)	10 (16.1%)
Initial physical examination findings, n (%)	
Crackle	3 (4.8%)
Ronchus	6 (9.6%)
Crackle and ronchus	6 (9.6%)
Treatments used, n (%)	
Inhaled corticosteroid	60 (96.7%)
Leukotriene receptor antagonist	31 (50%)

BMI, body mass index; IQR, interquartile range.

The cell type in the BAL was examined but not given as a percentage. Neutrophil predominance was present. Eosinophils were not predominant in any sample. Bronchoalveolar lavage aerobic culture revealed microorganism growth in 14 (22.5%) patients, 5 were *Streptococcus pneumonia*, 4 were *Moraxella catarrhalis*, 3 were *Haemophilus influenza*, and 2 were *Klebsiella pneumonia*, and these patients were diagnosed as having PBB. *Mycobacterium tuberculosis* growth was observed in the tuberculosis culture of 1 patient. There were no patients with fungal growth. The cytomegalovirus polymerase chain reaction result was positive in 1 patient, but it was not significant due to the low viral load. Human rhinovirus was positive in only 1 patient who was sent for a viral respiratory tract panel. Lipid-loaded macrophages were detected in the BAL cytology of 9 patients. Treatment recommendations were planned according to the results and diagnosis of bronchoscopy, BAL culture, and cytopathology. Antituberculosis treatment was initiated in 1 patient, excision of a polypoid mass was performed in 1 patient, 9 (15.5%) patients received proton pump inhibitors (PPI), 5 (8.0%) were recommended for physiotherapy, 14 (22.5%) were prescribed antibiotics, and 7 (11.2%) received ipratropium bromide treatment.

After the bronchoscopy procedure, 27 (43.5%) patients were lost to follow-up and the final diagnosis changed (tuberculosis and inflammatory myofibroblastic tumor in the trachea) in 2 (3.2%) patients. Thirty-one (50%) patients' symptoms disappeared after the FFB; however, the symptoms of 2 (3.2%) patients were similar compared with the period before FFB. Inhaled steroid dosage was increased by the pediatric allergy department in these 2 patients.

Patients with and without positive bronchoscopy findings were compared and there were no significant differences between their age, physical examination findings, pulmonary function test results, and radiologic examinations (Table 3). Atelectasis, ground-glass appearance, and infiltrations were evaluated as radiologic findings compatible with an infection in the chest CT.

Infection with FFB was detected in 7 (50%) of 14 patients with consistent findings with an infection in chest CT, and 15 (65.2%) of 23 patients who had no signs of infection in CT were found to have an infection with FFB ($P = 0.3$). The median age of the patients with tracheomalacia and/or bronchomalacia during bronchoscopy was 45 (IQR: 9-139) months, and the median age of those without malacia was 72 (IQR: 9-168) months. Patients with malacia had significantly lower age compared with patients without malacia ($P = .04$).

The diagnosis of asthma persisted in all patients except for 2. These 2 patients were diagnosed as having tuberculosis with the growth of *M. tuberculosis* in BAL and a polypoid mass was diagnosed with an inflammatory myofibroblastic mass in the trachea. All patients had persistent symptoms when they were referred to the pediatric pulmonology department, but 94.2% of the 35 patients who came for follow-up visits after the FFB had

Table 2. Pulmonary Function Test, Radiological and Flexible Fiberoptic Bronchoscopy Findings at First Admission to Pediatric Pulmonology Department

Pulmonary function test (n = 34) (median, IQR)	
FEV1%	98 (76-108)
FVC%	95 (83-105)
FEF 25%–75%	87.5(57-120)
FEV1/FVC%	101.5 (90-113)
PEF%	83 (71.2-100)
	n (%)
Chest x-ray (n = 62)	
Normal	36 (58.1)
Peribronchial thickening	5 (8.1)
Atelectasis	7 (11.3)
Bronchiectasis	3 (4.8)
Hyperaeration	5 (8.1)
Pneumonic infiltration	3 (4.8)
Multiple findings*	3 (4.8)
Chest computed tomography (n = 37)	
Normal	9 (24.3)
Peribronchial thickening	2 (5.4)
Atelectasis	6 (16.2)
Ground glass	1 (2.7)
Hyperaeration	1 (2.7)
Pneumonic infiltration	2 (5.4)
Multiple findings*	16 (43.2)
Bronchoscopy diagnoses	
Normal	24 (38.8)
Persistent bacterial bronchitis (PBB)	19 (30.6)
PBB with malacia+	1 (1.6)
PBB with anatomical anomaly	1 (1.6)
Malacia+	12 (19.4)
Malacia+ with anatomical anomaly	1 (1.6)
Anatomical anomaly	3 (4.8)
Polypoid mass	1 (1.6)

*Peribronchial thickening, atelectasis, ground glass, hyperaeration, pneumonic infiltration, +tracheomalacia and/or bronchomalacia.
FEV1, forced expiratory volume in 1 second; PEF, Peak expiratory flow; FEF, Forced mid-expiratory flow.

no symptoms. The follow-up of 17 patients (4 were irregular) in the pediatric pulmonology department and 20 patients (5 were irregular) in the pediatric allergy department continues to date. No patient was diagnosed with severe asthma after the evaluation.

DISCUSSION

Asthma is a common chronic lung disease. It affects 1%-18% of society in different countries.[20] In our country, the prevalence of asthma in children has been reported to vary between 0.7% and 21.2 %.[18] When the treatment response is not sufficient in patients with a diagnosis of difficult-to-treat asthma, further examinations should be performed for the differential diagnosis of other lung diseases. Bronchoscopy is an important method used for the diagnosis and treatment of airway and pulmonary problems in infants and children.[21] In our study, it was found that 62% of the patients referred to the pediatric pulmonology department with a diagnosis of difficult-to-treat asthma had positive FFB findings, the most common findings were PBB and tracheomalacia and/or bronchomalacia. The diagnosis of asthma remained present, except for 2 patients who were diagnosed as having tuberculosis with the growth of *M. tuberculosis* in BAL and who were found to have a polypoid mass with an inflammatory myofibroblastic mass in the trachea. However, when the patients were referred to the pediatric pulmonology department, all of the patients had persistent symptoms, but after FFB, 94.2% of those who presented for follow-up had no symptoms.

To the best of our knowledge, there is no study evaluating the effect of FFB in patients with difficult-to-treat asthma in the pediatric age group. Many adult studies have shown that FFB is safe in patients with difficult-to-treat asthma.[22-24] In our study, no complications were found during or after the procedure.

Fraccia et al[25] found the most common causes of chronic cough were malacia and PBB in their triple endoscopy study performed with 243 children. In our study, 54.9% of our patients had symptoms of cough at their presentation and similarly, the most common bronchoscopic diagnoses were PBB in 33.9% and malacia in 19.3% of the patients. The most common microorganisms grown in BAL cultures in patients diagnosed as having persistent bacterial bronchitis were reported as *S. pneumonia* and *H. influenza*.[9] Similarly, in our study, we found that most of the patients who were diagnosed as having PBB had growth of the same microorganisms.

Table 3. Comparison of the Clinical Characteristics, Pulmonary Function Tests and Chest Radiology of the Patients with Positive and Negative Flexible Bronchoscopy Findings Who Were Referred with Difficult-To-Treat Asthma

	With Positive Findings in FB (n = 40)	Without Finding in FB (n = 22)	*P*
Age, months (median, IQR)	116 (82.5-151)	108.5 (83-141)	.9[a]
Physical examination (n = 62)			
Those with symptoms (n, %)	11 (17.7)	4 (6.4)	.4[b]
Those with no symptoms (n, %)	29 (46.7)	18 (29.0)	
FEV1% (median, IQR)	91 (73-104)	104 (97-126)	.05[a]
Chest radiography (n=62)			
Those with finding (n, %)	16 (25.8)	10 (16.1)	.6[b]
Those with no finding (n, %)	24 (38.7)	12 (19.3)	
Chest CT (n=37)			
Those with finding (n, %)	7 (18.9)	7 (18.9)	.3[b]
Those with no finding (n, %)	15 (40.5)	8 (21.6)	

FEV1, forced expiratory volume in 1 second; FB, flexible bronchoscopy; CT, computed tomography.
[a]Mann–Whitney *U*, [b]Chi-square.

Gastroesophageal reflux is one of the diseases associated with asthma.[26] The sensitivity of lipid-loaded macrophages in the diagnosis of GER is low,[27] but there are also studies supporting that it is as significant as 24-hour pH meters.[16-17] No significant benefit has been demonstrated in patients with asthma or chronic cough using PPIs.[28-29] In our study, with the detection of lipid-loaded macrophages in the BAL cytology of nine patients, PPI treatment was recommended for GER. Their symptoms improved, and they were referred to the gastroenterology department for follow-up. Unlike the literature, although the number of patients is low, we think that our patients who started PPI had a benefit from the treatment, so it can be a guide in the differential diagnosis.

Tuberculosis and airway lesions are diseases that should be kept in mind in the differential diagnosis of asthma.[18] When the diagnosis of asthma is suspected, chest radiography should be performed to exclude structural anomalies and infections. Depending on the patient's clinical findings and response to asthma treatment, further examinations such as chest CT and bronchoscopy may be required. As shown in the literature,[30] even though there were no findings suggestive of tuberculosis in chest radiography in one of our patients, the patient was diagnosed as having tuberculosis due to the growth in BAL. In one of our patients, a biopsy was obtained using rigid bronchoscopy from a polypoid mass detected in the trachea, which was diagnosed as an inflammatory myofibroblastic tumor.

Tracheomalacia and TBM are primary abnormalities of the large airways and may be associated with a wide variety of congenital and acquired conditions.[31] Studies are showing that malacia has been detected in patients who do not respond to asthma treatment.[32] Also, the patients who underwent FFB due to recurrent wheezing were found to have malacia in 60%, and in our study, 24.2% of our patients had wheezing symptoms, and 69% were diagnosed as having malacia. Ipratropium bromide is one of the medical treatments used in malacia according to the European Respiratory Society statement on tracheomalacia and bronchomalacia in children report.[11] Gallagher et al[33] reported that ipratropium bromide treatment in tracheomalacia reduced symptoms. In our study, it was observed that the symptoms improved in all patients who were started on ipratropium bromide. In addition, as shown in the literature,[34] a significant difference was observed between the incidence of malacia and age in our study; the median age of patients with malacia at the time of bronchoscopy was 45 months, and the median age of patients without malacia was 72 months.

Chest CT is not routinely recommended for patients with difficult-to-treat asthma.[18] In our study, 37 of the patients had chest CT. Silva et al[35] found that children with severe asthma showed differences in airway wall thickness and increased ventilation in high-resolution lung tomography compared with healthy controls. In our study, no significant relationship was found between radiologic imaging and FFB findings. These findings show that the exposure of patients to radiation could be prevented and also suggest that in patients with FFB indications for differential diagnosis, history and physical examination findings will be sufficient for the decision of FFB. In addition, the fact that none of our patients developed complications proved once again that the FFB is a safe procedure in tertiary care centers.

There are several limitations of our study. Firstly, some of our patients did not come for follow-up visits, therefore some of the records could not be reached. Secondly, we do not know if the pulmonary function tests were done according to the optimal conditions due to our retrospective design. Thirdly, preferring the LMA in the majority of the patients during the bronchoscopy procedure prevented us from evaluating the upper respiratory tract. Lastly, the study group was heterogeneous.

CONCLUSION

In conclusion, although there is no prospective study evaluating the importance of FFB in difficult-to-treat asthma, our study recommends FFB because of the low complication rate, the benefits in improving the differential diagnosis, quickly starting the appropriate treatment for PBB, airway malacia, GER, and also in excluding anatomic anomalies and persistent infections.

Ethics Committee Approval: This study was approved by Ethics committee of Hacettepe University, (Approval No:20/1085).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.N.B., N.E.; Design – B.Ö., D.A.T.; Supervision – H.N.B., N. E.B.Ö., D.A.T.; Resources – İ.G., B.S.; Data Collection and/or Processing – İ.G., B.S.; Analysis and/or Interpretation – H.N.B., B.Ö.; Literature Search – B.Ö., D.A.T.; Writing Manuscript – H.N.B., N. E. ; Critical Review – E.Y., D.D., U.Ö., N.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Global Initiative For Asthma(GINA); Diffucult-to-Treat&Severe Asthma in Adolescent and Adult Patients, Diagnosis and Management; 2019.
2. Januska MN, Goldman DL, Webley W, et al. Bronchoscopy in severe childhood asthma: irresponsible or irreplaceable? *Pediatr Pulmonol.* 2020;55(3):795-802. [CrossRef]
3. Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J.* 2008;32(4):1096-1110. [CrossRef]
4. Aslan AT, Kiper N, Dogru D, Karagoz AH, Ozcelik U, Yalcin E. Diagnostic value of flexible bronchoscopy in children with persistent and recurrent wheezing. *Allergy Asthma Proc.* 2005;26(6):483-486.
5. Cakir E, Ersu RH, Uyan ZS, al, et al. Flexible bronchoscopy as a valuable tool in the evaluation of persistent wheezing in children. *Int J Pediatr Otorhinolaryngol.* 2009;73(12):1666-1668. [CrossRef]
6. Sovtic A, Grba T, Grahovac D, Minic P. Flexible bronchoscopy in evaluation of persistent wheezing in children-experiences from national pediatric center. *Medicina (Kaunas).* 2020;56(7):329. [CrossRef]
7. Chang AB, Upham JW, Masters IB, et al. Protracted bacterial bronchitis: the last decade and the road ahead. *Pediatr Pulmonol.* 2016;51(3):225-242. [CrossRef]

8. de Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. *Eur Respir J*. 2002;20(5):1271-1276. [CrossRef]
9. Zgherea D, Pagala S, Mendiratta M, Marcus MG, Shelov SP, Kazachkov M. Bronchoscopic findings in children with chronic wet cough. *Pediatrics*. 2012;129(2):e364-e369. [CrossRef]
10. Kompare M, Weinberger M. Protracted bacterial bronchitis in young children: association with airway malacia. *J Pediatr*. 2012;160(1):88-92. [CrossRef]
11. Wallis C, Alexopoulou E, Antón-Pacheco JL, et al. ERS statement on tracheomalacia and bronchomalacia in children. *Eur Respir J*. 2019;54(3). [CrossRef]
12. Su SC, Masters IB, Buntain H, et al. A comparison of virtual bronchoscopy versus flexible bronchoscopy in the diagnosis of tracheobronchomalacia in children. *Pediatr Pulmonol*. 2017;52(4):480-486. [CrossRef]
13. Sanchez MO, Greer MC, Masters IB, Chang AB. A comparison of fluoroscopic airway screening with flexible bronchoscopy for diagnosing tracheomalacia. *Pediatr Pulmonol*. 2012;47(1):63-67. [CrossRef]
14. Lee S, Im SA, Yoon JS. Tracheobronchomalacia in infants: the use of non-breath held 3D CT bronchoscopy. *Pediatr Pulmonol*. 2014;49(10):1028-1035. [CrossRef]
15. Lee EY, Mason KP, Zurakowski D, et al. MDCT assessment of tracheomalacia in symptomatic infants with mediastinal aortic vascular anomalies: preliminary technical experience. *Pediatr Radiol*. 2008;38(1):82-88. [CrossRef]
16. Rosbe KW, Kenna MA, Auerbach AD. Extraesophageal reflux in pediatric patients with upper respiratory symptoms. *Arch Otolaryngol Head Neck Surg*. 2003;129(11):1213-1220. [CrossRef]
17. Özdemir P, Erdinç M, Vardar R, et al. The role of microaspiration in the pathogenesis of gastroesophageal reflux-related chronic cough. *J Neurogastroenterol Motil*. 2017;23(1):41-48. [CrossRef]
18. Çelik G, Soyer Ö, Aydın Ö. Astım Tanı ve Tedavi Rehberi 2020 Güncellemesi. *Türk Toraks Derneği*. 2020;1(1):187-232.
19. De Schutter I, De Wachter E, Crokaert F, et al. Microbiology of bronchoalveolar lavage fluid in children with acute nonresponding or recurrent community-acquired pneumonia: identification of nontypeable Haemophilus influenzae as a major pathogen. *Clin Infect Dis*. 2011;52(12):1437-1444. [CrossRef]
20. Global Initiative for Asthma(GINA); Global Strategy for Asthma Management and Prevention; 2021.
21. Wood RE, Bronchoscopy and Bronchoalveolar Lavage in Pediatric Patients. In: Wilmott R, Deterding R, Li A, Ratjen F, Sly P, Zar H, Bush A, eds. *Kending's; Disorders of the Respiratory Tract in Children*, 9th ed. Philadelphia: Elsevier; 2019:134-146.
22. Moore WC, Evans MD, Bleecker ER, et al. Safety of investigative bronchoscopy in the Severe Asthma Research Program. *J Allergy Clin Immunol*. 2011;128(2):328-336.e3. [CrossRef]
23. Jarjour NN, Peters SP, Djukanović R, Calhoun WJ. Investigative use of bronchoscopy in asthma. *Am J Respir Crit Care Med*. 1998;157(3 Pt 1):692-697. [CrossRef]
24. Elston WJ, Whittaker AJ, Khan LN, et al. Safety of research bronchoscopy, biopsy and bronchoalveolar lavage in asthma. *Eur Respir J*. 2004;24(3):375-377. [CrossRef]
25. Fracchia MS, Diercks G, Cook A, et al. The diagnostic role of triple endoscopy in pediatric patients with chronic Cough. *Int J Pediatr Orl*. 2019;116:58-61. [CrossRef]
26. Boulet L-P, Boulay M-È. Asthma-related comorbidities. *Expert Rev Respir Med*. 2011;5(3):377-393. [CrossRef]
27. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;66(3):516-554. [CrossRef]
28. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev*. 2011;19:CD004823. [CrossRef]
29. Centers HJT, Wise RA, Gold BD, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. Writing Committee for the American Lung Association Asthma Clinical Research. *JAMA*. 2012;25:373-381.
30. de Blic J, Azevedo I, Burren CP, Le Bourgeois M, Lallemand D, Scheinmann P. The value of flexible bronchoscopy in childhood pulmonary tuberculosis. *Chest*. 1991;100(3):688-692. [CrossRef]
31. Masters IB, Chang AB, Patterson L, et al. Series of laryngomalacia, tracheomalacia and bronchomalacia disorders and their associations with other conditions in children. *Pediatr Pulmonol*. 2002;34(3):189-195. [CrossRef]
32. Chung KF. Clinical management of severe therapy-resistant asthma. *Expert Rev Respir Med*. 2017;11(5):395-402. [CrossRef]
33. Gallagher T, Maturo S, Fracchia S, Hartnick C. An analysis of children with tracheomalacia treated with ipratropium bromide (Atrovent). *Laryngoscope*. 2011;121(S4):S211-S211. [CrossRef]
34. Yalçin E, Doğru D, Özçelik U, Kiper N, Aslan AT, Gözaçan A. Tracheomalacia and bronchomalacia in 34 children: clinical and radiologic profiles and associations with other diseases. *Clin Pediatr*. 2005;44(9):777-781. [CrossRef]
35. Silva TKBD, Zanon M, Altmayer S, et al. High-resolution CT pulmonary findings in children with severe asthma. *J Pediatr (Rio J)*. 2021;97(1):37-43. [CrossRef]