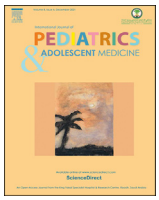
International Journal of Pediatrics and Adolescent Medicine 8 (2021) 203–211

HOSTED BY

Contents lists available at ScienceDirect

International Journal of Pediatrics and Adolescent Medicine

journal homepage: http://www.elsevier.com/locate/ijpam



When is asthma not guilty?

Abdullah Al Shamrani, FRCPCH *, Ayshah AlShammari, MD, Halima AlAlkami, MD, Jawaher AlShanwani, MD, Adel S. Alharbi, FCCP

Department of Pediatrics, Prince Sultan Military Medical City, Saudi Arabia

ARTICLE INFO

Article history:
Received 15 June 2020
Received in revised form
12 September 2020
Accepted 18 October 2020
Available online 20 October 2020

Keywords:
Asthma
Asthma mimickers
Cough
Wheeze
MDI
Nebulizer

ABSTRACT

Asthma is a common childhood condition. Its prevalence in Saudi Arabia is high, increasing, and could exceed 20% at the current trajectory. Asthma is a syndrome with different clinical presentations and phenotypes. Many conditions are often misdiagnosed as asthma because they share the same symptoms, particularly coughing and shortness of breath; physical findings, such as wheezing; radiological findings, such as hyperinflation on chest X-ray; or even responses to asthma therapies, as in some patients with bronchiolitis. When treating the younger age group (>5 years old), there should be a high degree of suspicion of alternative causes when evaluating patients presenting with clinical features suggestive of asthma or patients who do not respond well to asthma therapies. This study will highlight common conditions that may mimic asthma and, as a result of incorrect treatment, unnecessarily expose patients to steroids and other therapies for extended periods. Furthermore, we seek to alert healthcare providers to common symptoms and signs that suggest a cause other than asthma and suggest when to refer the patient to subspecialists.

1. Introduction

Asthma is a common childhood condition. Its prevalence has increased in the last 15 years from 8% to 23% [1,2]. In Saudi Arabia, the highest prevalence is reported in Hafoof (33%) and the lowest in Abha (7%) [3]. Furthermore, the majority of asthma cases are uncontrolled, as shown by the ACT study performed by Dr. Jahdali et al. [4] .Another study by Dr. Aslan et al. showed that 50% of the asthma cases were uncontrolled in a tertiary center in Riyadh [5]. Asthma is a syndrome often with heterogeneous clinical presentation, severity of exacerbation, natural history, and response to asthma therapies [6]. Asthma phenotypes have been divided into two subtypes: intrinsic asthma and extrinsic asthma. There are also clinical, physiological, trigger-defined, and inflammatory phenotypes. Multiple studies of individual asthma phenotypes have improved the understanding of immunologic and pathologic characteristics and have advanced the diagnostic and therapeutic fields. Many conditions are often misdiagnosed as asthma because they share the same symptoms, particularly coughing and shortness of breathing; physical findings such as wheezing; radiological findings such as hyperinflation on chest X-ray; and even response to asthma therapy in a few cases [6]. With regard to the younger age group (less than 5 years of age), there must be a high degree of suspicion of an alternative cause when evaluating patients presenting with clinical features suggestive of asthma or patients presenting with an atypical profile, such as when the patient has not responded well to standard asthma therapies.

2. Objectives of this paper

To highlight common diseases that are misdiagnosed as asthma, to improve the degree of suspicion of alternative causes, and to determine when to refer patients to sub-specialty clinics.

3. Asthma

3.1. Asthma in older age group (>5 years)

A clinical diagnosis of asthma is often made when a child presents with intermittent cough, shortness of breath, chest tightness,

* Corresponding author.
E-mail addresses: dr.alshamrani@psmmc.med.sa (A. Al Shamrani), dr.a.alshammari@hotmail.com (A. AlShammari), dr.halima95@gmail.com (H. AlAlkami), Jalshanwani@psmmc.med.sa (J. AlShanwani), adel.alharbi@psmmc.med.sa (A.S. Alharbi).

Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

https://doi.org/10.1016/j.ijpam.2020.10.002

and wheezing that respond readily to asthma therapy. Chest X-rays should be limited to specific situations such as severe asthma exacerbations that do not respond to the standard asthma therapies, suspected bronchopneumonia, or the presence of an air leak. During exacerbations, the radiological findings are usually marked hyperinflation with peribronchial wall thickening. Asthma in this group can be confirmed by standard spirometry with a 12% or greater increase in the forced expiratory volume in 1 s (FEV1) after inhaled bronchodilator or a more than 30% increase in the forced expiratory flow between 25% and 75% of vital capacity (FEF25-75) allergy skin tests are usually positive in atopic children in this age group if indicated [7,8]. A family history of atopic dermatitis, allergies, or asthma is common.

3.2. Asthma in the younger age group (<5 years)

It is more challenging for clinicians to diagnose asthma in this age group because the presentations are different due to different asthma phenotypes. The symptoms are as follows:

- a residual cough after a viral respiratory illness;
- coughing late at night or early in the morning, which can be the only presentation of asthma;
- recurrent or persistent wheezing;
- bronchopneumonia, which is rare; and
- a cough that is worse with emotional changes, during exercise, and after exposure to triggers [9].

As many diseases might share the same symptoms, clinicians should be alert to the possibility of other diagnoses, and limited investigations might be indicated to provide guidance regarding certain diagnoses. Table 1 summarizes different types of cough and highlights other alternative diagnoses. Preschool pulmonary function tests could be helpful if available, and chest X-rays are helpful for determining lung pathologies or malformations. In this category of patients, the application of the modified asthma predictive index is strongly recommended. Currently, the majority of asthma cases globally are still uncontrolled, even in Saudi Arabia, according to a different report. Fortunately, there has been some improvement according to recent publications [10–12]. The usual causes of uncontrolled asthma are as follows.

a- Inadequate doses or lack of prescription of inhaled corticosteroids (ICS): Inhaled steroids can control asthma and reduce hospital admission rates by 80%. Asthma is globally undertreated, and one study in Saudi Arabia reported that only 5% of asthma cases among patients seen at tertiary care hospitals were controlled. Furthermore, 56.4% of asthma patients do not receive education about asthma, and 60.3% have inadequately controlled asthma, compared to 50% of patients with uncontrolled asthma in the USA [13]. Asthma is a common cause of emergency room visits and hospital admissions [14].

b- Poor technique: The improper use of inhalation devices is a common cause of uncontrolled asthma [15–18].

c- Poor compliance: Dr. Mohsen reported that an alarming 44% of asthma patients who visited the emergency room did not use inhaled corticosteroids, while 56% reported improper use of medications.

d- Comorbidity or presence of risk factors: Nasal allergies and gastroesophageal reflux disease (GERD) are frequent risk factors for uncontrolled asthma, obesity, and vocal cord dysfunction. Vitamin D deficiency is an important factor, especially in older patients. Winter season, tobacco smoke exposure, pet exposure, rain, and day care attendance are common risk factors [19,20].

e- Wrong diagnosis: Asthma can be over-diagnosed in adults, according to a study published in JAMA in which the researcher found that the diagnosis was incorrect in 30–35% of patients diagnosed with asthma, and that these patients were able to stop taking medication. In this study, the authors highlighted the importance of education regarding the diagnosis and importance of ordering spirometry in such cases [21]. Pediatric asthma has historically been underdiagnosed, but clinicians have recently moved in the opposite direction [22–24]. Table 2 summarizes clue for alternative diagnoses.

4. Clinical scenarios when asthma is not the disease

4.1. Case 1

A 6-year-old girl presented to the clinic with intermittent cough for a duration of three months. The cough did not respond to cough syrups, montelukast, or nebulizer treatment. There was a strong family history of atopy; however, the patient did not show a positive response to bronchodilators. On examination, she appeared well and was in no distress. She coughed frequently in the clinic, her throat exam was benign, and chest auscultation revealed normal vesicular breath sounds with no additional sounds. Her father brought several bronchodilators to the clinic and expressed his unhappiness about the number of medications trialed without benefit. Her teacher asked her father to keep the child away from school as she was distracting the other children in the class by her continuous coughing. Her father claimed that the child was able to sleep comfortably without any coughing and that her cough started after having influenza. The family was stable without any social concerns, and the patient was a top student in her class without any previous illnesses. This patient was diagnosed with somatic cough syndrome and managed with psychosocial support and positive rewards; she experienced a marked improvement and was discharged from the clinic in good health. Unfortunately, pulmonary function test was not performed despite it possibly being very helpful in such a case.

Table 1
Summary of the types of cough and related conditions.

Types of cough	Suggested condition
Wet cough	Suggests the complaint is not asthma unless it occurs as a result of asthma exacerbation
Persistent cough	Cystic fibrosis, aspiration, immune disorder, primary ciliary dyskinesia, protracted bacterial bronchitis
Paroxysmal cough	Pertussis or tracheomalacia
Barky cough	Tracheomalacia or croup
Cough that occurs early in the evening	Sinus infection
Cough that disappears when sleeping	Somatic cough syndrome/psychogenic cough
Cough related to eating	Gastroesophageal reflux disease, swallowing incoordination
Cough that does not respond to bronchodilators	Sinus infection, bronchopneumonia
Nasal discharge	**Clear** nasal discharge suggests allergic rhinitis **Purulent** nasal discharge is consistent with chronic sinusitis

Table 2
Clinical clues leading to diagnoses other than asthma.

Clinical clue	Suggested diagnosis
Since birth, term prematurity	Genetic conditions (CF, PCD, immunodeficiency), chronic lung disease, or bronchopulmonary dysplasia
Signs and symptoms	
Wet cough	PBB, CF
Recurrent vomiting	GERD
Dysphagia	Swallowing incoordination
Inspiratory stridor	Malacia (larygomalacia, tracheomalacia)
Voice changes	Laryngeal cause
Focal signs	Foreign body inhalation or congenital anomalies
Symptoms disappear during sleep	Somatic cough syndrome
Finger clubbing	CF, PCD, immunodeficiency
Failure to thrive	CF, immunodeficiency
Post-viral syndrome	BO, rhinosinusitis

CF: cystic fibrosis, PBB: protracted bacterial bronchitis, GERD: gastroesophageal reflux disease, BO: bronchiolitis obliterans, PCD: Primary ciliary dyskinesia.

4.2. Case 2

A 4-month-old girl, who was one of twins delivered by caesarian section, had a birth weight of 2.3 kg and had no issues during the neonatal period apart from mild jaundice requiring one day of phototherapy. When she was 4 months old, tachypnea was observed and worsened during the time required for referral to the tertiary center. On examination, the child appeared well but had a respiratory rate of 52 breaths/minute, a heart rate of 157 beats/minute, and an oxygen saturation level (SaO2) of 97% on room air. Her weight was 4.2 kg (in the 5th percentile but normal considering her initial low birth weight). Chest auscultation revealed a prominent wheeze and decreased breath sounds, both on the left side. The remainder of the physical examination was within normal limits. Her chest X-ray (Fig. 1) showed marked asymmetrical hyperinflation mainly on the left side. Her chest CT scan results (Fig. 2) were consistent with a subcarinal swelling of 1 × 1.2 cm in size and rounded in shape. The swelling compressed the airway, especially of the left main bronchus, leading to attenuation of the blood vessels on the left side. Bronchoscopy confirmed the narrowing of both bronchial orifices, especially the entrance of the left main bronchus. The carina was dome-shaped rather than forming the usual sharp angle, which is consistent with a subcarinal compression that was predominantly on the left side. The patient was diagnosed with a bronchogenic cyst and treated surgically with the complete resolution of symptoms.

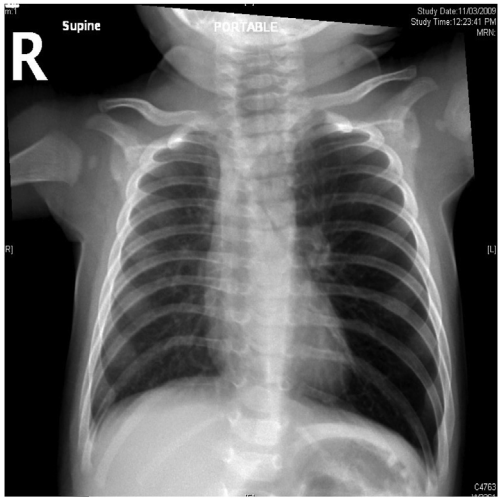


Fig. 1. Chest X-ray, AP view: Marked hyperinflation, diaphragm at the 11th rib posteriorly, with a slight shift of the mediastinum to right side at two levels (trachea and heart) and marked attenuation of the blood vessels and compression of the hemidiaphragm on the left side.

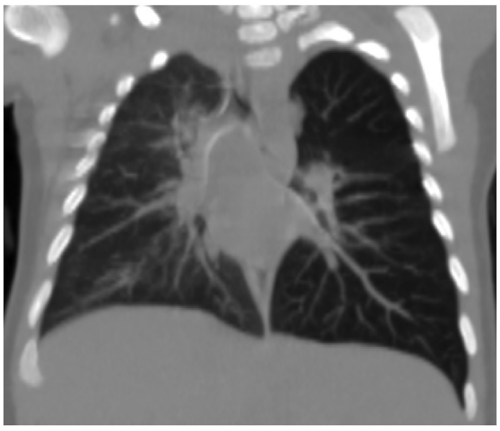


Fig. 2. Chest CT scan, coronal view: Subcarinal swelling that was 1x 1.2 cm in size and rounded in shape was compressing the airway, especially the left side, and there was attenuation of the blood vessels on the left side due to hyperinflation.

4.3. Case 3

A 21-month-old girl had been diagnosed with congenital heart disease (moderate-sized patent arterial duct) at an early age and was also diagnosed with moderately severe asthma. Her PDA was closed using an Amplatzer duct occluder at the age of 16 months. Although she had a small aortopulmonary collateral vessel, she was embolized using a coil. The procedure went smoothly without complications, and chest radiography prior to discharge confirmed the appropriate position of the implanted device. Three months post catheterization, the patient presented with fever, cough, shortness of breath, and wheezy chest which was diagnosed as asthma exacerbation and chest infection. She was treated with the usual asthma therapy including bronchodilators and systemic steroids, and antibiotics were added to cover potential bronchopneumonia. There was minimal response to medical therapy. Due to the persistence of her symptoms, a repeat chest X-ray was requested and suggested the migration of the PAD device due to the significant volume loss in the left lung. The patient was referred to a pediatric cardiologist, and echocardiography confirmed the PDA device to be in the appropriate position, with no residual ductal shunt. Lung perfusion scintigraphy demonstrated minimal perfusion of the left lung. A pediatric pulmonologist was consulted, and the possibility of foreign body inhalation was suggested despite a negative history of choking. This diagnosis was confirmed by

flexible bronchoscopy, which revealed an aspirated watermelon seed (Fig. 3) obstructing the left main bronchus. Under general anesthesia, a 2.8-mm flexible bronchoscope (Olympus) was easily passed through an endotracheal tube, confirming the position of the watermelon seed in the left main stem bronchus with diffuse erythematous airway lumen. Increased exudative secretion distal to the seed was confirmed. Then, the seed was extracted by rigid bronchoscopy with extracting forceps without complications. The patient thereafter made a complete recovery. At follow-up several weeks after discharge, the child remained well, the chest X-ray showed a normal left-sided lung, and the Amplatzer device was in a correct position [25].

5. Common asthma mimickers

5.1. Rhinosinusitis

Allergic rhinitis and sinusitis are common causes of nocturnal coughing and are often misdiagnosed as asthma. The same disease entities can also trigger rhinitis and asthma. Specific triggers include allergens, irritants, infections (viral and bacterial), aspirin and, more rarely, other cyclooxygenase 1 (COX-1)-inhibiting non-steroidal anti-inflammatory drugs (NSAIDs).

Types of allergic rhinitis**:** Type 1 (sneezers and runners): type 1 is the predominant type, wherein the child presents with nasal discharge, nasal itch, and sneezing. Type 2 (blockers): type 2 is the less common type, wherein the child presents with a blocked nose and signs of nasal obstruction. Allergic rhinitis is a clinical diagnosis and should be suspected when there is a history of wet cough in the absence of wheezing and a history of cough that is more common early in the night when the child lays down in the supine position, or in the morning after the child wakes up. It should also be suspected if it is associated with other clinical features of allergic rhinitis such as sneezing, nasal blockage, allergic salute, or allergic shiners or if the response to asthma medications is poor. Commonly used medications include intranasal corticosteroids and oral antihistamines [26]. Intranasal antihistamines may occasionally be necessary to improve the treatment of non-allergic rhinitis with eosinophilia (NARES) or vasomotor rhinitis [27,28]. Longitudinal studies have confirmed that both allergic rhinitis and positive allergic skin tests are risk factors for asthma [29,30].

Sinusitis in children is usually characterized by the following cardinal symptoms: purulent nasal discharge, wet cough, nasal congestion, and halitosis. Several other symptoms are reported by patients, including sleep disturbance (snoring, witnessed apnea, mouth breathing), fatigue, malaise, ear pain or pressure, dizziness, dental pain, dysphonia, and nasal or throat irritation [31]. Rhinitis is an important risk factor for the development of asthma and is a known trigger of asthma exacerbations [32]. Chronic rhinosinusitis with and without nasal polyps may aggravate some symptoms, particularly coughing, which may be attributed to severe asthma [33].

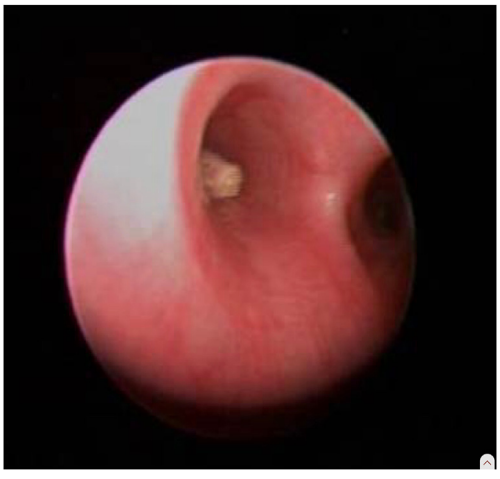


Fig. 3. Bronchoscopic picture of the foreign body (watermelon seed) impacted in the left main bronchus.

5.2. Bronchiolitis

Bronchiolitis is the most common disease and the leading cause of hospital admission in children younger than two years of age [34,35]. It is a seasonal disease, and the peak of admissions for bronchiolitis occurs in the winter season [36]. Acute bronchiolitis is a clinical diagnosis defined by the American Academy of Pediatrics as a constellation of clinical symptoms and signs including a viral respiratory prodrome followed by increased lower respiratory effort, variable hypoxemia, and wheezing in infants <2 years of age [37]. Globally, respiratory syncytial virus is the predominant cause of bronchiolitis, accounting for approximately 70% of cases, while in Saudi Arabia, it accounts for 25–88% of cases [38]. Bronchiolitis may also be caused by other organisms, such as rhinovirus, parainfluenza, human metapneumovirus, adenovirus, and even *Mycoplasma* pneumonia [39]. The Saudi initiative of bronchiolitis diagnosis, management, and prevention (SIBRO) stresses the importance of bronchiolitis in vulnerable infants with comorbidities, which includes infants younger than 3 months, premature infants, children with immunodeficiencies, children with congenital heart disease, and children with underlying cardiopulmonary or neuromuscular disease [40]. This high-risk group includes infants prone to apnea and severe respiratory distress and children. Treatment is usually supportive, and the goal of therapy is to maintain adequate oxygenation and hydration [41]. The use of hypertonic saline of 3–5% and high-flow oxygen supplementation by nasal cannula is becoming common for children with severe bronchiolitis [42]. Bronchiolitis often presents as wheezing, which could be easily confused with an asthma exacerbation. Conversely, there is a relationship between bronchiolitis in early childhood and the later development of asthma. Infants hospitalized with bronchiolitis caused by respiratory syncytial virus and rhinovirus have an up to 30% increased risk of recurrent wheezing during the first 10 years of life. Some studies have also noted an increased risk of asthma following an episode of bronchiolitis [43–45].

5.3. Bronchiolitis obliterans

Bronchiolitis obliterans (BO) is a chronic inflammatory condition with persistent and irreversible obstructive airflow limitation secondary to an insult to the terminal airway and its surroundings [46]. The respiratory symptoms include dyspnea and progressive respiratory failure [40]. Uncomplicated bronchiolitis is a self-limited condition in healthy infants with fever, dry cough, dyspnea, and wheezing. In BO, dry cough is present in 60–100% and dyspnea in 50–70% of cases. Chronic symptoms develop in 20% of cases, while 20% of patients with BO are asymptomatic at the time of diagnosis despite abnormal pulmonary function test results. Wheezing may be detected in as many as 88% of patients [47–49]. Wheezing due to BO is persistent rather than paroxysmal, although it can worsen with viral infections [50]. In children, the most common presentation of BO is the post infectious variant, which typically occurs after a severe viral infection in the first three years of life. A variety of organisms that can trigger asthma can also cause severe lung injury, including those that cause respiratory infections

(e.g., adenovirus, influenza, respiratory syncytial virus (RSV), cytomegalovirus, measles, and varicella). Other important causes are inhalation of toxic substances, use of certain drugs, and specific diseases or treatments (organ transplant, rheumatic diseases); a substantial number of cases are of unknown origin and are labeled idiopathic BO [51]. Furthermore, the increase of lung and bone marrow transplant recipients has been followed by an increase in post-transplant BO. Post-transplant BO is progressive, while post-infectious BO does not seem to be, but both forms share some common pathways that result in a characteristic histopathology of bronchiolar obstruction. BO should be suspected when the following characteristics are observed: chronic dispense with or without over wheezing without response to bronchodilator or steroid therapy in the context of hyperinflation on chest x-ray and mosaic attenuation on chest CT [46]. The treatment includes supportive therapies with oxygen supplementation, airway hydration, intermittent antibiotics, and pulse therapy with intravenous steroids, especially in the younger age group, with a short interval after initial presentation. Severe cases can eventually require lung transplantation [51–53]. Features of BO are summarized in Table 3.

5.4. Bronchogenic cyst

Bronchogenic cysts are rare anomalies of the ventral foregut endoderm and are the most common cystic lesion of the mediastinum [54]. They often exist as single cysts. They generally contain clear fluid or, less commonly, hemorrhagic secretions or air [55]. Tachypnea and cough are the usual initial manifestations in more than 50% of the cases, and wheezing is the predominant finding on auscultation, as in our case, which can easily lead to a misdiagnosis of asthma. A diagnosis can be easily made by chest x-ray in 80% of the patients, but it can be mislabeled as round pneumonia. A CT scan of the chest can be used to confirm the diagnosis. Most bronchogenic cysts originate in the mediastinum. These cysts may lead to life-threatening events such as compression of a major airway, commonly in the subcarinal area, as in our case, leading to persistent tachypnea and wheezing in younger patients, with a lack of improvement after treatment with bronchodilators. Furthermore, in the absence of atopy, all symptoms suggest a diagnosis other than asthma. Complications are more common in patients with symptomatic airway compression and recurrent chest infection, and an increased risk of aspiration and fistula are the usual complications. Furthermore, wheezing with central airway obstructions is more typically low-pitched and monophonic while wheezing in asthma is polyphonic and higher pitched. Other conditions that should be considered in the differential diagnosis are congenital pulmonary airway malformation type 1 and esophageal duplication cysts. Treatment is usually surgery, with an excellent prognosis [56].

5.5. Protracted bacterial bronchitis (PBB)

PBB is a common asthma mimicker, leading to the overuse of bronchodilators and corticosteroids that do not help the condition [57]. It usually presents in preschool-aged children as a wet cough with or without wheezing [58,59]. PBB may be a precursor to bronchiectasis in children [60]. The pediatrician may suspect PBB in a child with asthma if he/she has a chronic wet cough and does not respond well to salbutamol and inhaled steroids. PBB is a clinical diagnosis, meaning it is based on a detailed history and appropriate physical examination with careful questioning to rule out other potential asthma mimickers. PBB can be diagnosed when all three of the following criteria are fulfilled: 1) the presence of a wet cough for more than 4 weeks; 2) the absence of indications of an alternative diagnosis; and 3) a cough that resolves following a 2–4-week course of an appropriate oral antibiotic. A chest X-ray may be performed to exclude lung malformation, foreign body inhalation, or pneumonia or other unusual causes, but often there is no specific visible sign for PBB. If the child is old enough (more than 6 years), he/she should undergo a pulmonary function test, where a pattern of obstructive airflow limitation may be noted. Induced sputum culture is recommended to recover a bacterial sample, which might help in the selection of the appropriate antibiotics. Bronchoscopy and lavage can demonstrate lower airway infection as evidenced by a concentration of respiratory bacterial pathogens $>10^4$ colony forming units/ml. Positive culture from lavage might be added as a criterion for PBB. A course of antibiotics for PBB is suggested when the criteria are fully met, and the course should usually be 2–6 weeks in duration [61–63]. *Hemophilus influenzae*, *streptococcus pneumoniae*, and *Moraxella catarrhalis* are the most common organisms that respond to amoxicillin-clavulanic acid, and second-generation cephalosporins or macrolides are commonly used. Adenovirus is the most common respiratory virus, and bronchiectasis has been reported as a potential complication [64,65].

5.6. Gastroesophageal reflux disease

Asthma and GERD are common conditions in pediatric patients and may exist

together [66]. “Silent” reflux is more common in asthmatic patients than in the normal population. Nocturnal cough in the absence of other features of asthma may suggest reflux, especially during infancy. GERD can cause recurrent cough and wheezing, which are often misdiagnosed as asthma, but reflux can be a comorbid condition in asthmatic patients. Guidelines often recommend anti-reflux therapy when asthma is uncontrolled [67]. GERD should be suspected in any infant with recurrent cough and wheezing that worsens after eating, lacks diurnal variation, occurs when the infant eats in a supine position, is not accompanied by

Table 3
Features of bronchiolitis obliterans (46).

Feature	Bronchiolitis obliterans
Onset	After first year
Clinical feature	Insidious cough, wheeze, and shortness of breath
Chest x-ray	Hyperinflation
Pulmonary function test	Fixed airflow limitation and reduced diffusion capacity
CAT scan	Air trapping, mosaic pattern, reticular infiltrate, bronchiectasis with bronchial wall thickening
Lavage	Neutrophil predominant
Biopsy	Inflammation and scaring sparing the alveoli and alveolar duct
Treatment	Supportive therapies with oxygen supplementation, airway hydration, antibiotics (macrolide) and steroid therapy

atopy, and fails to respond to asthma therapies. To confirm GERD, gastroenterologists often have to perform pH studies, impedance, or endoscopy, and the usual therapy includes proton pump inhibitors and domperidone with lifestyle changes to reduce reflux [68]. Occasionally, in recalcitrant cases, Nissen fundoplication may be needed [69].

5.7. Foreign body aspiration

Foreign body aspiration (FBA) is a common condition and needs to be carefully considered when there is an abrupt onset of wheezing. Children are prone to aspirating foreign bodies when they start crawling and start to discover their surroundings. Children tend to put anything they can reach in their mouth, and in children younger than 4 years old in whom the molars have not yet developed, this may end in premature swallowing and choking. It is easy to diagnose FBA if it is witnessed, but that is the case only 50% of the time [70]. The most common manifestations of FBA are coughing and wheezing with or without respiratory distress; the cough is often dry and paroxysmal, and the wheezing is usually unilateral [71]. FBA can be lethal and may cause complete obstruction and cardiac arrest, especially in the subglottic region. Such severe obstruction is rare but lethal [72]. If the foreign body passes the subglottis, it usually becomes lodged in either the right main bronchus or left main bronchus in approximately 85% of the cases. Impaction in the right side is predominant. Peanuts are the most common foreign body aspirated, followed by watermelon seeds. Chest X-ray might be helpful for diagnosing FBA, but a normal chest X-ray does not rule out aspiration. The foreign body may work as a check valve, with hyperinflation at the affected site, but it may also act as a stop valve, leading to distal atelectasis, and a normal X-ray cannot role aspiration [73,74]. FBA should be suspected when the following characteristics are observed.

1. a clear history of choking;
2. abrupt onset of coughing and wheezing;
3. unilateral wheezing;
4. unilateral hyperinflated or collapsed lung; and
5. a lack of response to asthma therapy.

When FBA is suspected, bronchoscopy is indicated. Flexible bronchoscopy can be used to diagnose FBA, while rigid bronchoscopy is usually needed for removal of the foreign body.

5.8. Cystic fibrosis

Unlike asthma, which is characterized by a dry cough, cystic fibrosis (CF) patients have a productive cough. The symptoms occur early in life and may be associated with recurrent wheezing and chest infections that progress to bronchiectasis and chronic lung disease [75]. A detailed history may reveal a history of antenatal polyhydramnios, delayed passage of meconium, or prolonged jaundice in the neonatal period. Meconium ileus can be the first presentation of CF. Later, during infancy, many patients present with recurrent wheezing that does not respond to either salbutamol or steroid therapy. As many as 90% of CF patients will show symptoms and signs of malabsorption (persistent, offensive odor and oily stool), associated with failure to gain weight, unlike asthmatic patients, who have normal growth [76]. The practitioner should suspect CF if there is clinical evidence of malnutrition or failure to thrive with a persistent wet cough, recurrent chest infections, clubbing, and sinusitis [77,78]. Recurrent vomiting is a common feature of CF in the Kingdom of Saudi Arabia [79]. Clinical features suggesting CF:

1. delayed passage of meconium, meconium ileus, or neonatal jaundice;
2. recurrent wheezy chest or chest infection;
3. chronic diarrhea;
4. failure to thrive;
5. recurrent vomiting with pseudo-Bartter features;
6. chronic sinusitis;
7. infertility in adult males.

The first choice for tests is the sweat chloride test, followed by genetic analysis [80]. Low elastase levels in the stool, which indicates pancreatic insufficiency, is a predominant finding, and in the Kingdom of Saudi Arabia, 75% of CF patients may show evidence of pseudo-Bartter syndrome (metabolic alkalosis and hypokalemia, hypernatremia, and hypochloremia). Treatment regimens are complex and tailored to each patient. These patients should be referred to a tertiary center prepared to treat such cases; treatment includes active respiratory therapy to improve mucociliary clearance, the judicious use of antibiotics, and nutritional support [81].

5.9. Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a common asthma mimic in children. A detailed history may reveal tachypnea in the neonatal period that resolved in a few days. Children with PCD usually present with recurrent otitis media and speech delay due to chronic middle ear effusions [82]. Recurrent sinusitis with purulent discharge with or without nasal obstruction is predominant in preschool-aged children with PCD. Cough is commonly chronic and wet, is exacerbated by viral infections, and may be associated with wheezing, leading to the misdiagnosis of asthma. Recurrent chest infections are a characteristic feature in school-aged children with PCD, and they may lead to bronchiectasis. PCD is a clinical diagnosis and can be suspected under the following conditions [83,84].

1 transient tachypnea or pneumonia in the neonatal period;
2 recalcitrant chronic otitis media;
3 chronic sinusitis;
4 chronic wet cough with recurrent chest infections
5 clubbed fingers;
6 dextrocardia or situs inversus in 50% of the cases (Kartagener syndrome); and
7 a history of infertility in the family.

Nasal nitric oxide (nNO) concentrations are low in patients with PCD, and nNO concentrations can serve as a noninvasive screening test. Diagnostic techniques include high-speed video microscopy to assess the function and transmission electron microscopy to assess the ciliary ultrastructure. Genetic analysis is currently the gold standard diagnostic tool [85].

5.10. Psychogenic cough/somatic cough syndrome

Somatic cough syndrome, a term introduced by the American College of Chest and Physician 2015, is a common asthma mimicker; it often describes a cough with no obvious etiology that is usually refractory to medical therapies [86]. It may follow an upper respiratory tract infection, and the predominant age at onset is school age [87]. The usual manifestation of somatic cough syndrome is a honking, brassy cough that is usually absent during sleep or distraction and may remain for several weeks to months. Another key point is that clinicians may observe an increase in the intensity of cough when the child enters the clinic with parents during the interview and that the physical examination is otherwise normal. Such patients are often treated for asthma without

responding. Somatic cough syndrome may be associated with background asthma or psychiatric illness, and the diagnosis often needs a high degree of suspicion. No investigation is required. The syndrome's management consists of reassurance and simple behavioral approaches such as a positive reward system, stopping asthma therapies, and enlisting a psychologist's support [88].

5.11. Tracheobronchomalacia

Tracheomalacia is a condition characterized by a weakness and/or malformation of the cartilage supporting the trachea, leading to a collapsed tracheal lumen during respiration. The condition is often observed in infants and children of preschool age [89].

5.12. Types

Primary (rare): This type is characterized by the congenital absence or abnormal compliance of the tracheal-supporting cartilage.

Secondary (common): This type is due to tracheoesophageal fistula, cardiac or mediastinal compression, or prolonged intubation [90]. In mild cases, children might be asymptomatic or have a mild barky cough, while in moderately severe cases, children will present with persistent wheezing and a barky cough that does not respond to asthma therapy. In addition, the cough may worsen after the use of a bronchodilator or a viral respiratory illness. Severe cases manifest episodic paroxysmal cough, cyanotic episodes leading to the loss of consciousness, apnea, and even cardiac arrest. The initial assessment depends on the severity and the potential underlying cause [91,92]. Bronchomalacia is very rare and can also present with wheezing that can be easily heard when the child is active or playing [93]. The diagnosis is often difficult, although it can be confirmed by flexible bronchoscopy with minimal sedation, and treatment depends on the severity. The majority of mild cases resolve spontaneously with time [86,90]. The others require supportive therapy, such as chest physiotherapy, a lower threshold for the administration of antibiotics, potential CPAP therapy during exacerbation, and, in severe cases, aortopexy [94,95].

6. Referral

A referral to a subspecialist is recommended under the following conditions:

1. uncertain diagnosis;
2. persistent wet cough;
3. persistent vomiting;
4. failure to thrive;
5. presence of finger clubbing;
6. unusual findings, such as stridor, dysphagia, or hypoxia; culture of unusual organisms, such as *Pseudomonas aeruginosa*; and anxious parents.

7. Conclusion

Asthma mimickers are common. Clinicians must strongly suspect diseases that mimic asthma, particularly in children younger than 5 years of age and in those who do not respond well to standard asthma therapy. A detailed history and meticulous examination are warranted. Referrals should be made to experts, and the asthma index can be utilized when asthma is suspected. Investigations should be limited to certain diagnoses or to rule out congenital malformations.

The authors have no conflicts of interest to disclose.

Declaration of competing interest

There are no conflicts of interest to declare by all authors.

Abbreviations

PBB	Protracted bacterial bronchitis
CF	Cystic fibrosis
PCD	Primary ciliary dyskinesia
BPD	Bronchopulmonary dysplasia
CLD	Chronic lung disease
GERD	Gastroesophageal reflux disease
CROUP	Acute laryngotracheobronchitis
PDA	Patent ductus arteriosus
FEV1	Forced expiratory volume in the first second
MEF	Mid-expiratory air flow
ACT	Asthma control test
CT scan	computerized tomography scan

References

[1] Al Frayh AR, Shakoor Z, ElRab MG, Hasnain SM. Increased prevalence of asthma in Saudi Arabia. Ann Allergy Asthma Immunol 2001 Mar 1;86(3):292–6.
[2] Al Frayh AR, al Nahdi M, Bener AR, Jawadi TQ. Epidemiology of asthma and allergic rhinitis in two coastal regions of Saudi Arabia. Allerg Immunol (Paris) 1989;21:389–93.
[3] Alahmadi TS, Alharbi AS. The prevalence of childhood asthma in Saudi Arabia. The Int J Paed Adol Med 2019;7(2):74–7.
[4] Al-Jahdali HH, Al-Hajjaj MS, Alanezi MO, Zeitoni MO, Al-Tasan TH. Asthma Control assessment using asthma control test among patients attending 5 tertiary Care hospitals in Saudi Arabia. Saudi Med J 2008;29(5):714–7.
[5] Alsahn B, Alshamrani A, Alzahrani A, Alsahmi O, Alqudhybi A. Asthma control assessment using asthma control test among pediatric patients attending a tertiary care hospital in Saudi Arabia. Egypt. J Hosp Med 2017;68(2):1215–23.
[6] Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 2019 Apr 15;56(2):219–33.
[7] Al-Moamary MS, Alhaider SA, Alangari AA, Al Ghobain MO, Zeitouni MO, Idrees MM, et al. The Saudi Initiative for Asthma-2019 Update: guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med 2019 Jan;14(1):3–48.
[8] Liu AH, Zeiger RS, Sorkness CA, Ostrom NK, Chipps BE, Rosa K, et al. The childhood asthma control test: retrospective determination and clinical validation of a cut point to identify children with very poorly controlled asthma. J Allergy Clin Immunol 2010;126:267–73.
[9] Zeiger RS, Mellon M, Chipps B, Murphy KR, Schatz M, Kosinski M, et al. Test for respiratory and asthma control in kids (TRACK): clinically meaningful changes in score. J Allergy Clin Immunol 2011;128:983–8.
[10] Al-Jahdali H, Ahmed A, Al-Harbi A, Khan M, Baharoon S, Bin Salih S, et al. Improper inhaler technique is associated with poor asthma control and frequent emergency department visits. Allergy Asthma Clin Immunol 2013;9(1):8.
[11] Hamdan AJ, Wali S, Salem G, Al-Hameed F, Almotair A, Zeitouni M, et al. Asthma control and predictive factors among adults in Saudi Arabia: results from the epidemiological study on the management of asthma in asthmatic Middle East adult population study. Ann Thorac Med 2019 Apr;14(2):148.
[12] Al-Muhsen S, Horanieh N, Dulgom S, Al Aseri Z, Vazquez-Tello A, Halwani R, et al. Poor asthma education and medication compliance are associated with increased emergency department visits by asthmatic children. Ann Thorac Med 2015 Apr;10(2):123–33.
[13] Uncontrolled Asthma among Children. Centers for disease control and preventions. https://www.cdc.gov/asthma/asthma_stats/uncontrolled-asthma-children.htm; 2012–2014.
[14] Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. Thorax 2000;55(7):566–73.
[15] Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011;105(6):930–8.
[16] Molimard M, Le Gros V. Impact of patient-related factors on asthma control. J Asthma 2008;45(2):109–13.
[17] Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. Eur Respir J 2002;19(2):246–51.
[18] Looijmans-Van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. Br J Gen Pract 2016 Mar 1;66(644):e152–7.
[19] Ramratnam SK, Bacharier LB, Guilbert TW. Severe asthma in children. J Allergy Clin Immunol: In Pract 2017 Jul 1;5(4):889–98.

[20] Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med 2017 Feb 1;195(3):302–13.
[21] Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. Jama 2017 Jan 17;317(3):269–79.
[22] Aaron SD, Boulet LP, Reddel HK, Gershon AS. Underdiagnosis and overdiagnosis of asthma. Am J Respir Crit Care Med 2018 Oct 15;198(8):1012–20.
[23] Bush A, Fleming L. Is asthma overdiagnosed? Arch Dis Child 2016 Aug 1;101(8):688–9.
[24] Vasilopoulou I, Papakonstantopoulou I, Salavoura K, Laliotou N, Kaditis A, Gemou-Engesaeth V. Underdiagnosis and undertreatment of asthma in children: a tertiary hospital's experience. Clin Transl Allergy 2015 Dec 1;5(S2): P19.
[25] Elhoury ME, Almoukirish AS, Alshamrani AS, Galal MO. Abnormal orientation of Amplatzer PDA device on a chest radiogram masking foreign body aspiration. Int J Pediatr Otorhinolaryngol 2008 Oct 1;72(10):1559–62.
[26] Yu L, Xu X, Lv H, Qiu Z. Advances in upper airway cough syndrome. Kaohsiung J Med Sci 2015;31(5):223–8. May.
[27] Greiwe JC, Bernstein JA. Combination therapy in allergic rhinitis: what works and what does not work. Am J Rhinol Allergy 2016;30(6):391–6.
[28] Bernstein JA. MP29-02: a breakthrough for the treatment of allergic rhinitis. Expet Opin Pharmacother 2013 Oct 1;14(15):2101–13.
[29] Martinez FD, Wright AL, Taussig LM, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133–8.
[30] Oswald H, Phelan PD, Lanigan A, Hibbert M, Bowes G, Olinsky A. Out^{co}me of childhood asthma in mid-adult life. BMJ 1994;309(6947):95–6.
[31] Shapiro G, Rachelefsky GS. Introduction and definition of sinusitis. J Allergy Clin Immunol 1992;90(3):417–8.
[32] Giuseppe Di Cara, Carelli Alessia, Latini Arianna, Panfili Elisa, Bizzarri Ilaria, Ciprandi Giorgio, et al. Severity of allergic rhinitis and asthma development in children. WORLD ALLERGY ORGAN 2015;8:13.
[33] Shapiro G, Boulay ME. Asthma-related comorbidities. Expet Rev Respir Med 2011;5:377–93.
[34] Bronchiolitis Guideline Team. Cincinnati Children's Hospital Medical Center: evidence based clinical practice guideline for medical management of bronchiolitis in infants 1 year of age or less presenting with a first time episode. Available from, http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/bronchiolitis.htm; 2005. 1-13.
[35] Nicolai A, Ferrara M, Schiavariello C, Gentile F, Grande ME, Alessandroni C, et al. Viral bronchiolitis in children: a common condition with few therapeutic options. Early Hum Dev 2013;89(3):7–11.
[36] Al-Hajjar S, Akhter J, al Jumaah S, Hussain Qadri SM. Respiratory viruses in children attending a major referral center in Saudi Arabia. Ann Trop Paediatr 1998;18(2):87–92.
[37] American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. Pediatrics 2006;118(4):1774–93.
[38] Bakir TM, Halawani M, Ramia S. Viral aetiology and epidemiology of acute respiratory infections in hospitalized Saudi children. J Trop Pediatr 1998;44(2):100–3.
[39] Al-Muhsen SZ. Clinical profile of respiratory syncytial virus (RSV) bronchiolitis in the intensive care unit at a tertiary care hospital. Curr Pediatr Res 2010;14(2):75–80.
[40] Alharbi Adel S, Alqwaiee Mansour, Al-Hindi Mohammed Y, Mosalli Rafat, Al-Shamrani Abdullah, et al. Bronchiolitis in children, the Saudi initiative of bronchiolitis diagnosis, management and prevention (SIBRO). Ann Thorac Med July 18, 2018;13:127–43.
[41] Zorc JJ, Hall CB. Bronchiolitis: recent evidence on diagnosis and management. Pediatrics 2010;125(2):342–9.
[42] Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics 2014;134(5):474–502.
[43] Saglani Sejal. Viral infections and the development of asthma in children. Ther Adv Infect Dis 2013 Aug;1(4):139–50.
[44] Martinez FD. The connection between early life wheezing and subsequent asthma: the viral march. Allergol Immunopathol (Madr) 2009;37(5):249–51.
[45] Piedra Pedro A, Edwards Morven S, Torchia Mary M. Bronchiolitis in infants and children: clinical features and diagnosis. Datenjournal Oct 26, 2017. https://somepomed.org/articulos/contents/mobipreview.htm?24/35/25137.
[46] Li Ya-Nan, Liu Li, Qiao Hong-Mei, Cheng Hang, Cheng Huan-Ji. Post-infectious bronchiolitis obliterans in children: a review of 42 cases. BMC Pediatr 2014;14:238.
[47] Lino Carolina Arcanjo, M Batista Allyne Kelly, D Soares Maria Aparecida, H de Freitas Angela Elizabeth, Calheiros Gomes Larissa, M Filho José Holanda, et al. Bronchiolitis obliterans: clinical and radiological profile of children followed-up in a reference outpatient clinic. Rev Paul Pediatr 2013;31(1):10–6.
[48] Curtis DJ, Smale A, Thien F, Schwarer AP, Szer J. Chronic airflow obstruction in long-term survivors of allogeneic bone marrow transplantation. Bone Marrow Transplant 1995;16(1):169–73.
[49] Chan CK, Hyland RH, Hutcheon MA, Minden MD, Alexander MA, Kossakowska AE, et al. Small-airways disease in recipients of allogeneic bone marrow transplants. An analysis of 11 cases and a review of the literature. Med (Balt) 1987;66(5):327–40.
[50] Fischer GB, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. Paediatr Respir Rev 2010;11(4): 233–9.
[51] Gherasim Alina, Ahn Dao, Bernstein Jonathan A. Confounders of severe asthma: diagnoses to consider when asthma symptoms persist despite optimal therapy. WORLD ALLERGY ORGAN 2018;11(1):29. https://doi.org/10.1186/s40413-018-0207-2.
[52] Yoon HM, Lee JS, Hwang J-Y, Cho YA, Yoon H-K, Hong S-J, et al. Post infectious bronchiolitis obliterans in children: CT features that predict responsiveness to pulse methylprednisolone. The Br J Radiol. May 2015;88(1049):20140478.
[53] Afessa B, Litzow MR, Feffri A. Bronchiolitis obliterans and other late onset non-infections pulmonary complications in hematopoietic stem cells transplantation. Bone Marrow Transplant 2001;28(5):425–34.
[54] Reichelt O, Grieser T, Wunderlich H, Moller A, Schuber J. Bronchogenic cyst. A rare differential diagnosis of retroperitoneal tumors. Urol Int 2000;64(4): 216–9.
[55] Limaien F, Ayadi-Kaddor A, Djilani H, Kilani T, El Menzi F. Pulmonary and mediastinal bronchogenic cysts: a clinicopathologic study of 33 cases. Lung 2008 Jan –Feb;186(1):55–61.
[56] Sarper A, Ayten A, Golbasi I, Demircan A, Isin E. Bronchogenic cyst. Texas Heart Institute Journal 2003;30(2):105–8.
[57] Donnelly DE, Critchlow A, Everard ML. Outcomes in children treated for persistent bacterial bronchitis. Thorax 2007;62(1):80–4.
[58] Craven V, Everard MLPPP. Reinventing an old disease. Arch Dis Child 2013;98(1):72–6.
[59] Narang R, Bakewell K, Peach J, Clayton S, Samuels M, Alexander J, et al. Bacterial distribution in the lungs of children with protracted bacterial bronchitis. PloS One 2014 Sep 26;9(9):e108523.
[60] Chang AB, Marchant JM. Protracted bacterial bronchitis is a precursor for bronchiectasis in children: myth or maxim? Breathe 2019;15(3):167–71.
[61] Chang AB, Redding GJ, Everard ML. State of the Art - chronic wet cough: protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatr Pulmonol 2008;43(6):519–31.
[62] Kantar A, Chang AB, Shields MD, Marchant JM, Grimwood K, Grigg J, et al. ERS statement on protracted bacterial bronchitis in children. Eur Respir J 2017 Aug 1;50(2).
[63] Di Filippo P, Scaparrotta A, Petrosino MI, Attanasi M, Di Pillo S, Chiarelli F, et al. An underestimated cause of chronic cough: the protracted bacterial bronchitis. Ann Thorac Med 2018 Jan;13(1):7–13.
[64] Wurzel DF, Mackay IM, Marchant JM, Wang CY, Yerkovich ST, Upham JW, et al. Adenovirus species C is associated with chronic suppurative lung diseases in children. Clin Infect Dis 2014;59(1):34–40.
[65] Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, et al. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. The Lancet Respiratory Medicine 2013 Oct 1;1(8):610–20.
[66] Blake K, Teague WG. Gastroesophageal reflux disease and childhood asthma. Curr Opin Pulm Med 2013 Jan;19(1):24–9.
[67] Parsons JP, Mastronarde JG. Gastroesophageal reflux disease and asthma. Curr Opin Pulm Med 2010 Jan;16(1):60–3.
[68] Ramamurthy MB. Asthma mimickers: approach to differential diagnosis. Indian J Pediatr 2018 Aug 1;85(8):667–72.
[69] Jancelewicz Tim, Lopez Monica E, Downard Cynthia D, Islam Saleem, Baird Robert, Range Shawn J, et al. Surgical management of gastroesophageal reflux disease (GERD) in children: a systematic review. J Pediatr Surg 2017;52(8):1228–38.
[70] Tang LF, Xu YC, Wang YS, Wang CF, Zhu GH, Bao XE, et al. Airway foreign body removal by flexible bronchoscopy: experience with 1027 children during 2000–2008. World Journal of Pediatrics 2009 Aug 1;5(3):191–5.
[71] Tomaske M, Gerber AC, Stocker S, Weiss M. Tracheobronchial foreign body aspiration in children—diagnostic value of symptoms and signs. Swiss Med Wkly 2006;136(33–34):533–8.
[72] George TR. Foreign body aspiration in a child with cardiac arrest. JAAPA 2020 Feb;33(2):29–31.
[73] Mu LC, Sun DQ, He P. Radiological diagnosis of aspirated foreign bodies in children: review of 343 cases. J Laryngol Otol 1990 Oct;104(10):778–82.
[74] Heyer CM, Bollmeier ME, Rossler L, Nuesslein TG, Stephan V, Bauer TT, et al. Evaluation of clinical, radiologic, and laboratory prebronchoscopy findings in children with suspected foreign body aspiration. J Pediatr Surg 2006;41(11): 1882–8.
[75] Bhagirath AY, Li Y, Somayajula D, Dadashi M, Badr S, Duan K. Cystic fibrosis lung environment and Pseudomonas aeruginosa infection. BMC Pulm Med 2016;16(1):174.
[76] Li L, Somerset S. Digestive system dysfunction in cystic fibrosis: challenges for nutrition therapy. Digestive and liver disease. Dig Liver Dis 2014;46(10): 865–74.
[77] Solomon M, Bozic M, Mascarenhas MR. Nutritional issues in cystic fibrosis. Clin Chest Med 2016;37(1):97–107.
[78] Goyal V, Grimwood K, Marchant JM, Masters IB, Chang AB. Does failed chronic wet cough response to antibiotics predict bronchiectasis? Arch Dis Child 2014;99(6):522–5.
[79] Al-Mobaireek KF, Abdullah AM. Cystic fibrosis in Saudi Arabia: common and rare presentations. Ann Trop Paediatr 1995 Dec;15(4):269–72.
[80] Mogayzel Jr PJ, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB,

et al. Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2013 Apr 1;187(7):680–9.
[81] Ramsey BW, Downey GP, Goss CH. Update in cystic fibrosis 2018. Am J Respir Crit Care Med 2019 May 15;199(10):1188–94.
[82] Mirra V, Werner C, Santamaria F. Primary ciliary dyskinesia: an update on clinical aspects, genetics, diagnosis, and future treatment strategies. Front Pediatr 2017;5:135.
[83] Campbell RG, Birman CS, Morgan L. Management of otitis media with effusion in children with primary ciliary dyskinesia: a literature review. Int J Pediatr Otorhinolaryngol 2009;73(12):1630–8.
[84] Kennedy MP, Omari H, Leigh MW, Dell S, Morgan L, Molina PL, et al. Congenital Heart Disease and other heterotaxic defects in a large cohort of patients with primary ciliary dyskinesia. Circulation 2007;115(22):2814–21.
[85] Barbato A, Frischer T, Kuehni CE, Snijders D, Azevedo I, Baktai G, et al. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. Eur Respir J 2009 Dec 1;34(6):1264–76.
[86] Vertigan AE, Murad MH, Pringsheim T, Feinstein A, Chang AB, Newcombe PA, Rubin BK, McGarvey LP, Weir K, Altman KW, Weinberger M. Somatic cough syndrome (previously referred to as psychogenic cough) and tic cough (previously referred to as habit cough) in adults and children. Chest 2015 Jul 1;148(1):24–31.
[87] Vertigan AE. Somatic cough syndrome or psychogenic cough—what is the difference? J Thorac Dis 2017;9(3):831–8.
[88] Haydour Q, Alahdab F, Farah M, Barrionuevo P, Vertigan AE, Newcombe PAet al. Management and diagnosis of psychogenic cough, habit cough, and tic cough: a systematic review. Chest 2014 Aug 1;146(2):355–72.
[89] McNamara VM, Crabbe DCG. Tracheomalacia. Paediatr Respir Rev 2004;5(2):147–54.
[90] Wallis C, Alexopoulou E, Antón-Pacheco JL, Bhatt JM, Bush A, Chang AB, et al. ERS statement on tracheomalacia and bronchomalacia in children. Eur Respir J 2019 Sep 1;54(3).
[91] Vicencio AG, Parikh S, Adam HM. Laryngomalacia and tracheomalacia: common dynamic airway lesions. Pediatr Rev 2006 Apr 1;27(4):e33–5.
[92] Fraga JC, Jennings RW, Kim PC. Pediatric tracheomalacia. InSeminars in pediatric surgery, vol. 25; 2016 Jun 1. p. 156–64. No. 3.
[93] Hysinger EB, Panitch HB. Paediatric tracheomalacia. Paediatr Respir Rev 2016 Jan 1;17:9–15.
[94] Weber TR, Keller MS, Fiore A. Aortic suspension (aortopexy) for severe tracheomalacia in infants and children. Am J Surg 2002;184(6):573–7.
[95] Van der Zee DC, Straver M. Thoracoscopic aortopexy for tracheomalacia. World J Surg 2015;39:158–64.