# 5 The Differential Diagnosis of Asthma in Childhood

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## Contents



## Key Points

- Growth, development, and psychosocial ambiance add to the complexity when evaluating respiratory problems from the neonatal period to late adolescence.
- Cough and wheezing are among the most common health care complaints in childhood. Asthma is, by far, the most common source of wheezing in this age group.
- The suspicion of an alternative diagnosis beyond asthma is heightened in the wheezing infant less than six months of age.
- The incidence of wheezing induced by allergically mediated disease increases progressively after age 2 years.
- Allergic rhinitis, sinusitis, and sinobronchitis are the most frequently missed diagnoses in wheezing children who are historically unresponsive or poorly responsive to bronchodilator and antiinflammatory therapy.
- Exercise induced asthma is primarily a disease of adolescence. Its existence outside of this time period suggests an alternative or concurrent diagnosis influencing the asthmatic expression.

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- In a wheezing child, the correct diagnosis is usually made through the history and by observing the child's breathing pattern during the interview. Physical findings typically substantiate that diagnosis.
- Wheezing which reproducibly responds to bronchodilator therapy suggests a diagnosis of asthma but does not rule out additional aggravating medical problems. All precipitating sources must be identified before the diagnosis of asthma is complete.
- Every child with wheezing, regardless of the age of onset, frequency, or perceived precipitin, should have a minimum of one chest x-ray on record; the results of which are available to the examiner for review.
- A sweat chloride test should be performed in all children under the age of one year with recurrent wheezing and all children with persistent wheezing.
- Adolescents and young adults hyperventilate.
- Gastroesophageal reflux as a source of wheezing or wheezing exacerbation in all age groups has been under-diagnosed in the past and should now be increasingly recognized and appreciated.

## Introduction

Health care providers are commonly faced with wheezing children. Cough and wheezing are among the most common respiratory complaints in the childhood years. Ten–15% of all children under the age of 1 yr experience a wheezing episode. By the age of 5 yr, 1/4 children will have wheezed *(1)*. By far, the most common cause of wheezing in infancy and early childhood is asthma that is typically-infection induced. Infection-induced childhood asthma should always be a primary diagnostic possibility, regardless of the age of onset, disease frequency, or evidence of ancillary atopic disease *(2)*. Nevertheless, asthma can be confused with other respiratory disorders that may be associated with similar signs and symptoms, particularly wheezing in the infant less than 6 mo of age, in whom the suspicion of an alternative diagnosis should be heightened. Still, one half of all asthma starts in the first year of life *(3)*.

## Differential Diagnosis

The differential diagnosis of asthma in infancy and childhood is presented in Tables 1 and 2. The methodology for arriving at the proper diagnostic conclusion follows the time-honored standards of clinical medicine, which include taking a careful clinical history and performing a physical examination, choosing appropriate laboratory investigations, and assessing response to directed medical treatment.

- The key to the differentiation of asthma from other childhood respiratory disorders is commonly found in the history, and by simply observing the child at play during the interview with the caregiver.
- The differential diagnosis of asthma in childhood may be approached based on the probability of occurrence (*see* Table 1) and on age of presentation (*see* Table 2).
- Diagnostic possibilities, other than asthma, should be vigorously sought in any child who wheezes and is under age 6 mo.

Table 1
Differential Diagnosis of Asthma in Infancy and Childhood

| Frequent | Occasional | Infrequent |
|---|---|---|
| Asthma | Bronchopulmonary dysplasia | Congestive heart failure |
| Specific infections | Aspiration | Congenital vascular anomalies |
| Bronchiolitis | Foreign body | |
| Viral bronchitis | Gastroesophageal reflux disease | Mediastinal masses |
| Pneumonia (viral, bacterial) | Fistula | |
| Sinobronchitis | Neurogenic | Immune deficiency diseases |
| Laryngotracheobronchitis | | |
| | Specific infections | Bronchiolitis obliterans |
| | Pertussis syndromes | |
| | Tuberculosis | Specific infections |
| | Fungal pneumonia | Chlamydia trachomatis |
| | | Legionnaire's disease |
| | Cystic fibrosis | |
| | | Vocal cord dysfunction |
| | Epiglottitis | and hyperventilation |
| | | Familial dysautonomia |
| | | Systemic diseases with a |
| | | prominent pulmonary component |
| | | Letterer-Siwe disease |
| | | Hand-Schüller-Christian disease |
| | | Histiocytosis |
| | | Parasitic diseases |
| | | Ciliary dyskinesias |
| | | Pulmonary infiltrates with eosinophilia |

Table 2
The Differential Diagnosis of Asthma as Influenced by Age

| Infancy (0–6 mo) | Toddler (to age 2–3 yr) | Childhood to adolescence |
|---|---|---|
| Structural anomalies | Bronchiolitis | Cystic fibrosis |
| Aspiration syndromes | Foreign body | Foreign body |
| Congestive heart failure | Cystic fibrosis | Sinobronchitis |
| Bronchopulmonary dysplasia | Bronchiolitis obliterans | Allergic rhinitis with postnasal drainage |
| Mediastinal masses | Specific infections | |
| | Pertussis syndromes | Tuberculosis |
| Pulmonary masses | Tuberculosis | |
| | Epiglottitis | Hyperventilation |
| | Immune deficiencies | Vocal cord dysfunction |
| | | Sighing dyspnea |
| | | Aspiration with neurologic disorder |
| | | Gastroesophageal reflux disease |
| | | α-1 antitrypsin deficiency |
| | | Autoimmune disorders |
| | | Immune/ciliary defects |
| | | Cardiac disease |
| | | Tumors |
| | | Hypersensitivity bronchopulmonary diseases |
| | | Familial dysautonomia[a] |

[a]A syndrome of European Jewish ancestry characterized by deficient lacrimation, excessive perspiration, drooling, relative indifference to pain, cough, wheeze, and recurrent respiratory infections, typically from aspiration.

## Clinical History

Although most wheezing episodes after 6 mo of age are attributable to asthma, many other problems may coexist or present in a similar fashion. The differentiation requires a thorough history, physical examination, and selected laboratory tests. Suspicion of an alternative or additional diagnosis should be entertained when the history is atypical or the response to good medical management is suboptimal. In general, the younger the child, the greater the possibility of encountering one of the diagnostic possibilities noted in Tables 1 and 2 *(4)*. This point is especially true in the neonatal period when an underlying structural abnormality should be strongly suspected.

Most congenital malformations or genetic deficiencies present initially in the newborn and infancy time periods. Exceptions are tracheobronchomegaly, bronchomalacia, pulmonary A-V fistula, α-1 antitrypsin deficiency and some instances of immune deficiencies, cystic fibrosis (CF), hiatal hernia, and esophageal stenosis *(5)*. Hints from the history may lead the examiner to the appropriate alternative diagnosis. For example, a history of previous ventilator use in infancy would suggest the possibility of tracheal stenosis from granulation tissue. Very low birth weight or

prematurity in the wheezing infant would suggest the possibility of bronchopulmonary dysplasia, Wilson-Mikity syndrome, or other forms of chronic pulmonary diseases of prematurity. Table 3 lists a differential approach to the diagnostic evaluation of the wheezing infant and child according to this organizational scheme and indicates the relative likelihood of encountering the different entities considered. Repetitive respiratory difficulties accompanying feeding suggest an aspiration syndrome. Most cases of pulmonary edema accompanying congenital cardiovascular malformations occur after the first week of life. By then, either the ductus arteriosis has closed sufficiently in left-sided cardiac disorders to allow significant shunting or pulmonary vascular resistance has fallen sufficiently to aggravate a large left-to-right shunt.

- After 6-12 mo of age, the diagnosis of infection-induced asthma clearly overcomes the likelihood of an alternative source of respiratory distress in childhood.
- A history of viral-like infections and wheezing, with or without accompanying sinusitis or otitis media, which resolves successfully upon resolution of the infection, suggests infection induced asthma.
- Wheezing that predictably responds to bronchodilator therapy suggests a diagnosis of asthma in any age group. However, the diagnosis of asthma by itself is insufficient until all the precipitating sources have been identified.
- If the child is 18–24 mo of age, and the first episode of wheezing occurred in the winter or early spring, the diagnosis of viral bronchiolitis should be entertained.

The approach to any child with cough or wheezing should begin with a historical overview from birth to present. The key questions to ask during this interview are:

1. Was the child full-term or premature?
2. Were there any neonatal respiratory complications such as respiratory distress syndrome, meconium aspiration, and so on?
3. Was the child breast- or bottle-fed? Is there anything unusual about the feeding history in the neonatal and infancy period? Particular emphasis should be placed on any history of colic, frequent vomiting or spitting, or food intolerances, which would suggest aspiration syndromes or atopy.
4. Are there any known congenital anomalies?
5. Are growth and developmental parameters for the child intact?
6. Are immunizations up-to-date, with no adverse affects?
7. Is there any family history of allergy, asthma, atopic dermatitis, immunodeficiency, tuberculosis or CF?
8. Does a constant runny nose or frequent otitis media accompany the wheezing? If so, this would suggest atopic sources or, less likely, immunodeficiencies.
9. Is there any history of recurrent infections, especially pneumonia, otitis media with tympanic membrane perforation, or chronic and/or acute suppurative lymphadenitis, to suggest immunodeficiency?
10. Is this the first wheezing episode or one of many? If the latter is true, are all the wheezing events the same?
11. Finally, obtain a careful history of the events surrounding the wheezing episode at hand. Was the onset sudden and acute with no prodromal symptoms to suggest a foreign body aspiration? Has any bronchodilator treatment been given, and, if so, what was the response?

Table 3
Distinguishing Clinical Features in Tthe Differential Diagnosis of Childhood Asthma

| Diagnosis | Clinical Features |
|---|---|
| Asthma | Wheezing responsive to bronchodilators |
| | Definable triggers, such as environment or infections |
| | Repeated episodes extending into school age |
| Congenital anomaly | Respiratory difficulties since early childhood |
| | Failure to thrive |
| Chronic pulmonary diseases of prematurity (e.g., bronchopulmonary dysplasia) | Prematurity<br>Respiratory distress syndrome<br>Mechanical ventilation |
| Inhalation syndromes | Respiratory difficulties accompanying or following feedings<br>Recurrent pneumonia<br>Spitting and/or vomiting frequently<br>Failure to thrive<br>Swallowing dysfunction<br>Fatigue |
| Cardiovascular disease | Tachypnea<br>Cyanosis<br>Failure to thrive<br>Organomegally |
| Bronchiolitis | Winter to early spring<br>Community epidemic<br>Coryza, transient fever |
| Foreign body aspiration | Sudden onset<br>Choking history<br>Unilateral pulmonary findings common |
| Laryngotracheobronchitis (croup) | Antecedent mild illness<br>Barking cough, hoarseness, and inspiratory stridor<br>Peaks at 3–4 d, worse at night |
| Cystic fibrosis | Failure to thrive common<br>Steatorrhea<br>History of meconium ileus |
| Tuberculosis/pertussis | Family history of respiratory illness<br>Endemic in community |
| Bronchiolitis obliterans | Follows a case (usually severe) of bronchiolitis |
| Immunodeficiencies | History of repeated sinusitis and pneumonia |
| Ciliary dyskinesia | History of repeated otitis media, often with perforation of TM<br>Failure to thrive, if severe |
| Sinobronchitis | Fetor oralis<br>Mucopurulent nasal discharge<br>Poor bronchodilator response by history<br>Good antibiotic response by history |

## Physical Examination

A complete physical examination of any child with cough or wheezing should always be performed, because the differential diagnosis is so extensive *(6)*. Physical findings to emphasize include vital signs and a general inspection of the child for evidence of chronic illness. Examine the extremities for clubbing, cyanosis, and edema. Inspection of the ears, nose, throat, and lymph glands for signs of infection is important, because upper respiratory infectious diseases will precipitate wheezing in most of the differential problems listed in Table 2. Look carefully for other signs of atopic diseases such, as chronic dermatitis, keratosis pilaris, nasal crease, or Dennie's line, which would suggest that the wheezing is asthmatic. Finding generalized lymphadenopathy and/or hepatosplenomegaly, or clubbing of the extremities, would suggest an alternative disorder.

Emphasis should always be placed on examining the upper airways, as well as the cardiopulmonary system, in any child with wheezing or cough. Unfortunately, examination of the chest is not always helpful. Nevertheless, there are some unique features attributable to the physical examination of the wheezing child that should be emphasized.

- Ancillary physical findings are often of critical importance in arriving at the proper diagnosis in a wheezing child.
- The physical examination of any child with cough or wheezing should focus on signs of atopic predisposition. The presence of atopic dermatitis or pruritic rhinoconjunctivitis should strengthen the likelihood of asthma being the source of pulmonary symptoms.
- Wheezing of asthma is a fine, diffuse, musical sound most prominent, or exclusively heard, during the expiratory phase of respiration.
- Focal abnormal breath sounds, especially in the febrile child, is usually not exclusively asthma.

A difficult area of physical examination for some is distinguishing lower airway sounds from upper airway sounds transmitted to the chest. Physicians and midlevel practitioners are well-versed in distinguishing inspiratory stridor from expiratory wheezing. Sometimes it becomes difficult, however, to distinguish lower airway sounds, such as rhonchi, from sounds generated by upper airway mucus. This is especially true in the very young child. In general, the younger the child, the more the upper airway sounds transmit to the chest on auscultation. Transmitted upper airway sounds tend to be coarse, monophonic or polyphonic, symmetrical, present on both inspiration and expiration, and disappear or significantly diminish after vigorous coughing. They contrast with the wheezing of asthma, which is commonly more fine, high-pitched, polyphonic, symmetrical, and prominent on expiration. Such distinctions serve only as generalizations. It is not uncommon to see a child with airway obstruction so severe that very little air is moving and the chest is too tight to demonstrate wheezing, rhonchi, or transmitted upper airway sounds. Parents who complain of "rattling" in their child's chest usually are noticing the transmission of upper airway sounds to the chest.

The cough of upper airway drainage, pneumonia, and foreign body obstruction all have their unique auscultory findings. The cough from postnasal drip and/or sinusitis can be difficult to distinguish from the cough of asthma. On auscultation, the examiner usually hears coarse rhonchi, either from mucus in the large airways of the pulmonary tract or transmitted from the upper airway. Making it more difficult is the fact that wheezing can also be heard with sinusitis. Sinusitis with sinobronchitis is a common precipitin of childhood asthma. In contrast to the diffusely fine abnormal breath sounds of asthma, focally coarse or crepitant rales in an ill child suggests a pneumonic process, especially if the child appears acutely ill. Diffuse crepitant rales may represent bilateral pneumonia or, less commonly, cardiac failure. Unilaterally, absent breath sounds suggest airway obstruction, which, in children, is typically from a foreign body aspiration. Respiratory distress accompanied by any abnormal breath sounds on auscultation, which resolve or significantly improves after bronchodilator treatment, suggests, but does not prove, a diagnosis of asthma.

## Laboratory Investigation

Every child with wheezing, regardless of the age of onset, should have a chest X-ray on record as a screen for congenital anomalies and infrequently encountered chronic pulmonary disorders. However, not all physicians order chest films on first-time wheezers. The utility of a chest X-ray is significantly enhanced by the presence, in a wheezing child, of fever, absence of a family history of asthma, and localized wheezing or rales on auscultation *(7)*. If the respiratory distress is occurring in infancy, the X-ray examination should include a barium swallow, followed by an EKG and/or echocardiogram. Two diagnostic procedures often overlooked in children with recurrent respiratory symptoms are a sweat chloride and a tuberculin skin test. Wheezing may be the first presenting sign of both CF *(8)* and tuberculosis *(9)*.

- The minimal laboratory test required in any child with his or her first wheezing episode is a chest X-ray.
- The minimal laboratory tests required for recurrent childhood wheezing episodes are a sweat chloride test, tuberculosis skin test, and, if technically able, a pulmonary function test.

As long as there are no conflicting structural, respiratory, cardiac, or systemic diseases, pulmonary function testing demonstrating reversible airway obstruction, confirms the diagnosis of asthma. Methods for measuring pulmonary function have been refined so that even infants can be measured. For example, rapid chest compression, using a facemask and pneumotachometer and an inflatable thoracoabdominal jacket, can be used to generate a flow–volume curve in infants. Pre- and post- bronchodilator assessment, demonstrating reversibility, is the key diagnostic feature of asthma in all age groups. However, a lack of significant airflow reversibility during an acute wheezing event does not rule out asthma. This is especially true in the very young child, in whom airway mucosal edema and

inspissated secretions from asthma are more likely to produce poorly reversible airway obstruction. Normal pulmonary function tests in the face of recurrent wheezing and cough, suggests a diagnosis other than asthma, especially if the wheezing is historically unresponsive or poorly responsive to bronchodilators. Many of the parents of these children will relate that antibiotics work best. The missed diagnosis here is typically sinusitis with sinobronchitis, rather than asthma, as the source of cough or wheeze.

Children with persistent or recurrent wheezing, pulmonary infiltrates, atelectasis, or hemoptysis of unknown etiology may benefit from fiberoptic or rigid bronchoscopy. Flexible instruments are now available for children of all ages. Because gastroesophageal reflux with aspiration can be silent children, bronchoscopy can often establish the diagnosis by visually demonstrating the reflux, or by detecting lipid-laden macrophages in the bronchial secretions.

Rare forms of systemic and pulmonary disorders, such as hemosiderosis and hypersensitivity lung diseases, can be defined through examination of pulmonary lavage and biopsy specimens obtained through the bronchoscope. Pulmonary hemosiderosis presents with recurrent respiratory symptoms associated with pulmonary infiltrates and chronic iron deficiency anemia. Acute bleeds in this disorder may be associated with cough, dyspnea, and crackling rales and wheezes on chest auscultation. Characteristic bronchial biopsy findings and evidence of hemosiderin-laden macrophages in bronchial secretions can establish the diagnosis. Various forms of hypersensitivity lung diseases, such as alveolitis and hypersensitive extrinsic or idiopathic, and various forms of autoimmune diseases, can be seen in children, and present with respiratory distress and wheezing. Pulmonary infiltrates in these disorders can be characteristic although they sometimes, quite fleetingly, make the diagnosis elusive. Examination of bronchial washings and biopsy specimens, in conjunction with hematologic studies, will typically establish the diagnosis.

## Specific Problems

### *Structural Abnormalities that Could Present as Wheezing and Respiratory Distress*

- Congenital absence of ribs*
- Congenital absence of bronchial cartilage (Williams-Campbell syndrome)
- Congenital diaphragmatic hernia of Bochdalek*
- Chylothorax
- Tracheal agenesis and stenosis*
- Vascular ring
- Tracheoesophageal fistula without esophageal atresia
- Esophageal atresia*
- Congenital bronchial stenosis
- Foregut cysts
- Pulmonary agenesis, aplasia, and hypoplasia*
- Congenital pulmonary cysts
- Lobar emphysema

- Cystic adenomatoid malformation of the lung*
- Congenital pulmonary lymphangiectasia*
- Congenital cardiac conditions with a large left-to-right shunt
- Mediastinal masses-tumor: lymphadenopathy, or angiomatous lesions

*Indicates presentation usually at birth.

Most congenital anomalies, especially those presenting clinically at birth, are associated with tachypnea and dyspnea with or without cyanosis, rather than with overt wheezing. Those not marked by an asterisk (*) typically present after the neonatal period, but within the first year of life. Most congenital anomalies are accompanied by noisy respirations best described as harsh brassy cough, apneic spells, inspiratory and expiratory coarse rhonchi accompanied by intercostal retractions, dyspnea, and tachypnea. The most common congenital disorders presenting with respiratory distress in infancy are structural cardiovascular disorders, aspiration syndromes, and compliance problems. Stridor and cyanosis with crying suggest a cardiovascular disorder, such as a vascular ring. Noisy respirations after liquid feedings, which clear before the next feeding, suggest a tracheoesophageal fistula without esophageal atresia. Inspiratory stridor is more characteristic of compliance problems.

### *Congenital Cardiovascular Anomalies*

Diagnostic Tests

- Chest posteroanterior (PA) and lateral
- Barium swallow
- EKG
- Echocardiogram
- High resolution chest CT or MRI
- Angiography
- Doppler and color-flow imaging
- Ultrasound

Infants with cyanotic congenital heart disease caused by uncomplicated pulmonary atresia or transposition of the great vessels, commonly have "deep breathing" rather than wheezing, unless heart failure develops. Left-sided cardiac lesions, such as mitral atresia, severe aortic stenosis, preductal coarctation, and aortic arch interruption, may present with cardiac asthma after the first week of life, when the ductus arteriosis closes. Similarly, infants with a ventricular septal defect, complicated by atrioventricular canal, double-outlet right ventricle, truncus arteriosus, and aorticopulmonary transposition, present with pulmonary edema and possibly wheezing, after the first week of life. This usually occurs when pulmonary resistance has fallen sufficiently to allow severe shunting.

### *Tracheoesophageal Fistula with or Without Esophageal Atresia*

Diagnostic Tests

- Chest X-ray
- Endoscopy
- Cinefluoroscopy with contrast-medium swallowing

The tracheoesophageal fistula can present with confusing features because of similarities to laryngeal cleft, neuromuscular pharyngolaryngeal dysfunction, and various respiratory disorders *(10)*. The child usually presents with paroxysmal coughing, choking, or cyanosis with feedings, especially with liquids, abdominal distention from air passing through the fistula, and recurrent pneumonia. Esophageal stenosis may coexist with and cause further diagnostic confusion. The most common form of tracheoesophageal fistula with esophageal atresia consists of esophageal atresia with a proximal blind pouch and a fistula of the distal esophageal segment to the lower trachea.

When faced with an infant with respiratory distress associated with feeding, look carefully for other congenital anomalies. There are distinct patterns of congenital anomalies associated with tracheoesophageal fistula. For example, the VATER complex (vertebral, anal, tracheoesophageal, renal, and radial anomalies) and the VACTEL complex (anal, renal tracheal, intestinal, cardiac, limb, and esophageal ± vertebral anomalies).

Although most cases of tracheoesophageal fistula present in infancy and very early childhood, some forms of H-type fistula may be mild enough to delay the diagnosis until adulthood. Still, respiratory symptoms can be traced back to early childhood. The diagnosis of tracheoesophageal fistula should always be carefully investigated in any age group when respiratory distress is associated with feeding.

### *Pulmonary Compliance Abnormalities*

Diagnostic Tests
- Chest X-ray
- Barium swallow
- Tracheobronchoscopy

Abnormal compliance of the tracheobronchial tree, such as seen in tracheomalacia, bronchomalacia, and congenital lobar emphysema, usually presents with cough, dyspnea, stridor, and recurrent pneumonia on chest radiograph. These problems can also be associated with wheezing in infancy. A diagnosis of tracheomalacia or bronchomalacia should only be made after external compression and localized constrictive disorders of airway obstruction has been excluded. A chest X-ray, barium swallow, and tracheobronchoscopy are all necessary procedures to confirm abnormal compliance problems. Bronchoscopy should not be performed if lobar emphysema is suspected, because anesthesia may cause further air trapping in the affected lobe, exacerbating pulmonary compromise.

### *Mediastinal Masses (Tumor, Lymphadenopathy, Angiomatous Lesions)*

Diagnostic Tests
- Computerized tomography
- Ultrasound
- Probably magnetic resonance imaging
- Possibly tuberculosis skin test
- Possibly 24-h urine or Vanillymandelic acid (VMA)

Children with tracheal and bronchial tumors often present with symptoms similar to asthma. They will manifest cough, wheeze, and inspiratory stridor, and experience frequent pneumonitis with, on occasion, hemoptysis, depending on the character of the tumor and its location. If a mass is suspected, computerized tomography will help distinguish a solid from a cystic lesion. Ultrasound will help define if the mass is pulsatile. Magnetic resonance imaging will define the mass in relation to other anatomic structures. If the mass is lymphadenopathy, tuberculosis testing and diagnostic tests for neurogenic (e.g., urinary VMA) tumors should be pursued *(11)*.

### *Bronchiolitis and Other Virally Induced Wheezing Diseases*

Diagnostic Tests
- Chest P-A and lateral essential, but not diagnostic
- Immunologic viral identification helpful

Bronchiolitis is one of the major causes of hospitalization of children under the age of 1 yr. The airway caliber in infancy and very early childhood is small and easily obstructed by mucosal edema resulting from a viral infection. In very young children, respiratory synstitial virus (RSV), and coronavirus are most frequently isolated during epidemics of bronchiolitis. Influenza A and adenovirus tend to cause wheezing in all ages. Viral bronchiolitis and asthma are probably independent causes of wheezing in early childhood. Still, about 15% of children with bronchiolitis will eventually have asthma *(12)*.

The clinical distinction between bronchiolitis and infection-induced asthma is a difficult one. Even in children with documented RSV bronchiolitis, repeated episodes of milder attacks of wheezing will occur in some 38% of infants over the following few years. The incidence of true asthma developing in later childhood in these children is not significantly increased. However, many of these children are left with increased bronchial hyperreactivity, and may ultimately develop asthma in adulthood *(13)*. It is suspected that those children who develop asthma after RSV bronchiolitis also produce increasing levels of immunoglobulin E (IgE) because of a genetic predisposition. The viral infection in this circumstance may unmask latent forms of asthma-to-be. Most investigators believe that, in those children without an atopic genetic predisposition, RSV-induced wheezing will more likely become quiescent over time.

### *Foreign Body Aspiration*

Diagnostic Test
- Chest P-A and lateral
- Tracheobronchoscopy
- High resolution chest CT

The sudden onset of cough and wheezing in an otherwise normal child, with no previous history of similar respiratory symptoms, suggests a foreign body has been aspirated or ingested *(14)*. A foreign body need to be aspirated in a child to induce wheezing. If ingested and lodged in the esophagus, enough compression of a malleable trachea can induce a wheeze and cough. Usually a history reveals an incident suspicious of ingestion or aspiration of a foreign body. A high level of

Table 4
Tumors of the Chest

| Benign | Malignant |
|---|---|
| Lung parenchyma | |
| Hamartomas | Ewing's-type sarcoma |
| Langerhans cell histiocytosis | Bronchogenic carcinoma |
| Neurofibromas | Lymphoma |
| AV malformations | Metastatic soft tissue sarcoma |
| Hemangiomas/lymphangiomas | |
| Mediastinal | |
| Thymoma | Lymphomas |
| Teratoma | Leukemia |
| Sarcoidosis | Neuroblastoma |
| Neurogenic tumors | |
| Hemangioma/lymphangioma | |
| Chest wall/diaphragm/pleura | |
| Hemangioma/lymphangioma | Ewing's-type sarcoma |
| | Rhabdomyosarcoma |
| | Metastatic disease |

suspicion should be kept when sudden and severe symptoms are encountered, even if the aspiration or ingestion was not witnessed. One-third of patients aspirating foreign bodies are unobserved by a caretaker. The overwhelming majority of aspirated foreign bodies are foods, such as peanuts and sunflower seeds. The chest X-ray findings should never be used as the sole basis of diagnosis or to determine intervention *(15)*. Radiographs may be normal early on, or show air-trapping, atelectasis, or consolidation.

A pitfall in the diagnosis of foreign body aspiration or ingestion is that children often have acute symptoms followed by a quiescent period, which may lead to a delayed diagnosis. A high index of suspicion must be kept, since early intervention is the key to a successful outcome.

### *Cystic Fibrosis*

Diagnostic Test
- Sweat chloride
- Immunoreactive trypsin assay newborn screening

Twenty-five percent of children with CF will present to a medical care provider with recurrent or persistent wheezing by 1 yr of age, secondary to diffuse airway disease. Those who wheeze tend to have a poor pulmonary function as they enter adolescence. Fifty percent of wheezing CF patients will stop wheezing by age 2 yr and 75% by age 4 yr. On this basis, the physicial may be lulled into believing the child has outgrown the wheezing tendency, and the diagnosis will be missed. As with all cases of CF, early recognition and intervention significantly influence quality-of-life factors and survival.

Table 5
Differentiating Bronchiolitis from Asthma

| Bronchiolitis | Asthma (Usually Infection Induced) |
|---|---|
| <2 Yr old, commonly <6 mo | Typically >6–12 mo old |
| Family history unimportant | Atopic family history[a] |
| Normal childhood illnesses | History of atopy[a] or atopy-like [b] illnesses |
| Viral prodrome increased if RSV | |
| Unresponsive to asthma meds including steroids | Viral prodrome |
| | Elevated Immunoglobulin E |
| Wheezing Resolves[c] | Responsive to asthma meds[d] |
| | Wheezing recurs with infection |

[a]Atopic dermatitis, allergic rhinitis, asthma.
[b]Infantile colic, adverse food reactions, recurrent otitis media, recurrent sinusitisia.
[c]Unless bronchiolitis obliterans develops.
[d]Often poor and slow in children under the age of 2 yr.

### *Chronic Lung Disease of Prematurity; Bronchopulmonary Dysplasia, Congenital Cystic Adenomatoid Malformation, and Wilson-Mikity Syndrome*

Diagnostic Test
- Chest X-ray
- Clinical history

Chronic lung disease of prematurity is a common disorder of preterm infants who were ventilated or required supplemental oxygen. Although the exact pathophysiology remains unclear, increased oxidative stress, giving rise to chronic airway inflammation, appears to be the source *(16)*. In bronchopulmonary dysplasia, infants are usually less than 32 wk gestation, and are exposed to oxygen and mechanical ventilation for their hyaline membrane disease. The trauma of mechanical ventilation and increased inspired oxygen is suspected to be the source of the pulmonary injury. Some very low birth weight infants, who have experienced very little, if any, oxygen after delivery, still develop a chronic pattern of lung disease called "neonatal pulmonary emphysema" or Wilson-Mikity syndrome. The pathophysiology of each different spectra of chronic lung disease of prematurity has yet to be explained, but probably rests on different timing, and on insults to the premature lung, with resultant differing degrees of inflammation and repair.

### *Gastoesophageal Reflux (GER) and Asthma (Gastric Asthma)*

Diagnostic Tests
- Significant improvement following reflux therapy
- Esophagram and upper gastrointestinal series
- Esophagogastroscopy
- 24-h esophageal pH probe

Advances in neuroanatomy and neurophysiology of the respiratory and upper gastrointestinal tract have led to a better understanding and appreciation of gastric

asthma. The relationship between GER and asthma has been carefully studied and documented *(17)*. It is clear that, in predisposed individuals, GER can worsen or trigger bronchial asthma. In some circumstances, GER is the sole source of the respiratory complaints. The diagnosis is is important because asthma itself, and many of the drugs used to treat asthma, may aggravate GER. The diagnosis of gastric asthma is particularly difficult, because GER may be silent with no single test being diagnostic *(18)*. Often the best test is a strong suspicion of this disease in difficult-to-control asthmatics, and the demonstration of significant improvement in asthma symptomatology with appropriate GER treatment.

### *Vocal Cord Dysfunction*

Diagnostic Tests
- Clinical history
- Direct laryngoscopy during an episode

Vocal cord dysfunction (VCD) is a condition in which the apposition of the vocal cords is sufficient to cause respiratory distress, wheezing, and cough. This condition has been reported in all age groups, including children as young as 3 yr. Most often, the condition occurs between the second and fourth decades. Among children and adolescents, vocal cord dysfunction has a strong link to participation in competitive sports and to personal and family pressure toward high achievement. The wheezing and respiratory distress in this disorder is characterized by its sudden and episodic nature. Typically, the child has a history of asthma that has proven very difficult to control. The prevalence of inspiratory symptoms confuses this diagnosis with angioedema, at times. Valuable clues are a history of hoarseness, dysphonia, and throat tightness. Unlike asthma, patients suffering from VCD rarely are awakened by their episodes. The diagnosis should be suspected under these clinical circumstances, and when arterial blood gases reveal an increase in $p(A–a)O_2$ gradient. The diagnosis is secured by direct laryngoscopy during an acute attack, which reveals absence of gagging or coughing during laryngoscopy, adduction of vocal cords during inspiration or during both inspiration and expiration, and, presence of adduction of the anterior two-thirds of the vocal cords, with posterior chinking that creates a diamond shape (open glottic chink) *(19)*.

### *Hyperventilation Syndrome*

Diagnostic Tests
- Appropriate history and age group
- Normal auscultation (if asthma is not concurrently present)
- Normal spirometry when the patient is dyspneic

Hyperventilation syndrome is a condition mostly observed in adolescence, and is infrequently seen in childhood *(20)*. It may be mistaken for asthma or may coexist with it. The typical presentation is an anxious patient who complains more of dyspnea and an inability to take a deep breath, rather than overt wheezing. Often there is minimal or no cough. On questioning, hyperventilating patients often admit to headaches and tingling sensations of the distal extremities, and occasionally

around the mouth, along with a feeling of light-headedness. Careful auscultation reveals an absence of true wheezing. If laboratory tests are pursued, they should be limited to spirometry, which is typically normal. It is helpful to perform spirometry during a symptomatic period, just to demonstrate normalcy to the patient. Ancillary tests, such as a chest X-ray, EKG, and echocardiogram, are sometimes needed for reassurance to the parents.

## Conclusion

The key points in differentiating asthma in childhood from alternative clinical conditions that may be associated with wheezing are:

1. Consider an expanded differential diagnosis if this is the first wheezing episode for a child.
2. If the child presenting with wheezing for the first time is unfamiliar to you, always take a careful history from birth, along with the usual history of present illness. Often the key to a differential diagnostic possibility lies within this information.
3. Wheezing in any child less than 6–12 mo of age demands careful scrutiny for possible structural anomalies.
4. If a patient presents with recurrent wheezing that has been poorly responsive or nonresponsive to bronchodilators and anti-inflammatory treatment in the past, the primary diagnosis may have been missed. Do not keep making the same mistake. Allergic sources and/or sinusitis with sinobronchitis are the most frequently missed diagnosos in the ambulatory care setting in children over the age of 2 yr.
5. The incidence of allergy induced sources of wheezing increases progressively from age 2 yr. It is uncommon (but not impossible) for school age children to exclusively have virally induced asthma (e.g., wheezy bronchitis).
6. Every child with wheezing, regardless of the age of onset, frequency, or perceived precipitin, should have a minimum of one chest X-ray in their record, to document, with reasonable accuracy, the absence of a structural anomaly that may contribute, complicate, or cause the symptomatology at hand.
7. A sweat chloride test should be performed in all children under the age of 1 yr with recurrent wheezing, and in all children with persistent wheezing, whether or not symptoms of malabsorption are present.
8. Preadolescent children presenting with exercise-induced asthma usually have another concurrent diagnosis, such as evolving atopic disease (inhalant allergy).
9. Failure to thrive is rare in asthma. Always consider an alternative systemic illness in such circumstances.
10. GER reflux is an increasingly recognized source of difficult-to-control wheezing, and may be silent. Look for a history of frequent spitting or vomiting in infancy, or vomiting in early childhood.
11. Tracheoesophageal fistula has been diagnosed in all age groups, despite the fact that symptoms can always be traced back to infancy. Keep a high index of

suspicion for this disorder when a history is elicited of respiratory difficulties associated with feeding, especially if accompanied by recurrent pneumonias.

12. Adolescents hyperventilate.

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