

ASTHMA

Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. This chronic inflammation heightens the twitchiness of the airways—airways hyperresponsiveness (AHR)—to provocative exposures. Asthma management is aimed at reducing airways inflammation by minimizing proinflammatory environmental exposures, using daily controller anti-inflammatory medications, and controlling co-morbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, with fewer exacerbations and decreased need for quick-reliever asthma medications. Nevertheless, exacerbations can still occur. Early intervention with systemic corticosteroids greatly reduces the severity of such episodes. Advances in asthma management and, especially, pharmacotherapy enable all but the uncommon child with severe asthma to live normally.

Etiology

Although the cause of childhood asthma has not been determined, contemporary research implicates a combination of environmental exposures and inherent biologic and genetic vulnerabilities. Respiratory exposures in this causal environment include inhaled allergens, respiratory viral infections, and chemical and biologic air pollutants such as environmental tobacco smoke. In the predisposed host, immune responses to these common exposures can be a stimulus for prolonged, pathogenic inflammation and aberrant repair of injured airways tissues. Lung dysfunction (i.e., AHR and reduced airflow) develops. These pathogenic processes in the growing lung during early life adversely affect airways growth and differentiation, leading to altered airways at mature ages. Once asthma has developed, ongoing exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.

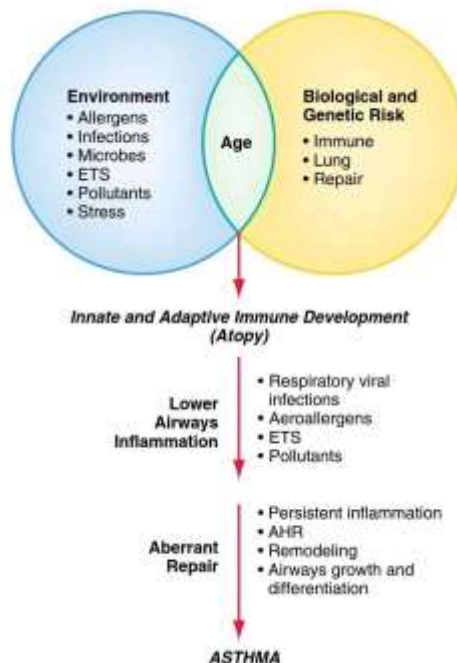
Genetics

More than 100 genetic loci have been linked to asthma. Although the genetic linkages to asthma have sometimes differed between cohorts, asthma has been consistently linked with loci containing proallergic, proinflammatory genes (the interleukin [IL]-4 gene cluster on chromosome 5). Genetic variation in receptors for different asthma medications is associated with variation in biologic response to these medications (polymorphisms in the β 2-adrenergic receptor). Other

candidate genes include ADAM-33 (member of the metalloproteinase family), the gene for the prostanoid DP receptor, and genes located on chromosome 5q31 (possibly IL-12)

Environment

Recurrent wheezing episodes in early childhood are associated with common respiratory viruses, including respiratory syncytial virus, rhinovirus, influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus. This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in early childhood. Furthermore, injurious viral infections of the airways that manifest as pneumonia or bronchiolitis requiring hospitalization are risk factors for persistent asthma in childhood. Other airways exposures can also exacerbate ongoing airways inflammation, increase disease severity, and drive asthma persistence. Indoor and home allergen exposures in sensitized individuals can initiate airways inflammation and hypersensitivity to other irritant exposures, and are strongly linked to disease severity and persistence. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms and can sometimes “cure” asthma. Environmental tobacco smoke and air pollutants (ozone, sulfur dioxide) aggravate airways inflammation and increase asthma severity. Cold dry air and strong odors can trigger bronchoconstriction when airways are irritated but do not worsen airways inflammation or hyper responsiveness.



Epidemiology

Asthma is a common chronic disease, causing considerable morbidity. Nearly 60% of those with current asthma, had experienced at least one asthma attack in the prior year. Boys (14% vs 10% girls) and children in poor families (16% vs 10% not poor) are more likely to have asthma.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. Worldwide, childhood asthma appears to be increasing in prevalence, the prevalence of current wheeze, 0.8-37.6%.

Approximately 80% of all asthmatic patients report disease onset prior to 6 yr of age. However, of all young children who experience recurrent wheezing, only a minority goes on to have persistent asthma in later childhood. Prediction of asthma includes major (parent asthma, eczema, inhalant allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, $\geq 4\%$ eosinophil, food allergen sensitization) risk factors. Allergy in young children has emerged as a major risk factor for the persistence of childhood asthma.

CHILDHOOD RISK FACTORS FOR PERSISTENT ASTHMA

Parental asthma

Allergy:

Atopic dermatitis (eczema)

Allergic rhinitis

Food allergy

Inhalant allergen sensitization

Food allergen sensitization

Severe lower respiratory tract infection:

Pneumonia

Bronchiolitis requiring hospitalization

Wheezing apart from colds

Male gender

Low birth weight

Environmental tobacco smoke exposure

Possible use of acetaminophen (paracetamol)

Exposure to chlorinated swimming pools:

Reduced lung function at birth

Table 169.1

Early Childhood Risk Factors for Persistent Asthma

Parental asthma*

Allergy:

- Atopic dermatitis (eczema)*
- Allergic rhinitis
- Food allergy
- Inhalant allergen sensitization*
- Food allergen sensitization

Severe lower respiratory tract infection:

- Pneumonia
- Bronchiolitis requiring hospitalization

Wheezing apart from colds

Male gender

Low birthweight

Environmental tobacco smoke exposure

Reduced lung function at birth

Formula feeding rather than breastfeeding

*Major risk factors.

Types of Childhood Asthma

There are 2 main types of childhood asthma:

(1) Recurrent wheezing in early childhood, primarily triggered by common viral infections of the respiratory tract.

(2) Chronic asthma associated with allergy that persists into later childhood and often adulthood. A 3rd type of childhood asthma typically emerges in females who experience obesity and early-onset puberty (by 11 yrs. of age).

Pathogenesis

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airways lumens; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airways lumen. Helper T lymphocytes and other immune cells that produce proallergic, proinflammatory cytokines (IL-4, IL-5, IL-13), and chemokine's (exotoxins) mediate this inflammatory process. Pathogenic immune responses and inflammation may also result from a breach in normal immune regulatory processes (such as regulatory T lymphocytes that produce IL-10 and transforming growth factor [TGF]- β) that dampen effector immunity and inflammation when they are no longer needed. Hypersensitivity or susceptibility to a variety of provocative exposures or triggers can lead to airways inflammation, **AHR, edema, basement membrane thickening, sub epithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucous hypersecretion**—all processes that contribute to airflow obstruction .

ASTHMA TRIGGERS

Common viral infections of the respiratory tract

Aeroallergens in sensitized asthmatic patients :

- Animal dander

- Indoor allergens

- Dust mites

- Cockroaches

- Molds

Seasonal aeroallergens :

- Pollens (trees, grasses, weeds)

- Seasonal molds

Environmental tobacco smoke

Air pollutants :

- Ozone
- Sulfur dioxide
- Particulate matter
- Wood- or coal-burning smoke
- Endotoxin, mycotoxins
- Dust

Strong or noxious odors or fumes :

- Perfumes, hairsprays
- Cleaning agents

Occupational exposures :

- Farm and barn exposures
- Formaldehydes, cedar, paint fumes

Cold air, dry air

Exercise

Crying, laughter, hyperventilation

Co-morbid conditions :

- Rhinitis
- Sinusitis
- Gastro esophageal reflux

Clinical Manifestations

Intermittent dry coughing and expiratory wheezing are the most common chronic symptoms of asthma. Older children and adults report associated shortness of breath and chest tightness; younger children are more likely to report intermittent, non-focal chest pain. Respiratory symptoms can be worse at night, especially during prolonged exacerbations triggered by respiratory infections or inhalant allergens. Daytime symptoms, often linked with physical activities or play, are reported with greatest frequency in children. Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue (possibly due to sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (bronchodilators) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms can be triggered by numerous common events or exposures

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergies), parental asthma, and/or symptoms apart from colds, supports the diagnosis of asthma. During routine clinic visits, children with asthma commonly present without abnormal signs, emphasizing the importance of the medical history in diagnosing asthma. Some may exhibit a dry, persistent cough. The chest findings are often normal. Deeper breaths can sometimes elicit otherwise undetectable wheezing. In clinic, quick resolution (within 10 min) or convincing improvement in symptoms and signs of asthma with administration of a short-acting inhaled β -agonist (SABA; e.g., albuterol) is supportive of the diagnosis of asthma.

During asthma exacerbations, expiratory wheezing and a prolonged expiratory phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior lobe, are consistent with regional hypoventilation owing to airways obstruction. Crackles (or rales) and rhonchi can sometimes be heard, resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate acute asthma management. In severe exacerbations, the greater extent of airways obstruction causes labored breathing and respiratory distress, which manifests as inspiratory and expiratory wheezing, increased prolongation of exhalation, poor air entry, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In extremis, airflow may be so limited that wheezing cannot be heard.

Differential Diagnosis

Many childhood respiratory conditions can present with symptoms and signs similar to those of asthma.

Besides asthma, other common causes of chronic, intermittent coughing include gastroesophageal reflux (GER) and rhino sinusitis. Both GER and chronic sinusitis can be challenging to diagnose in children. Often, GER is clinically silent in children, and children with chronic sinusitis do not report sinusitis-specific symptoms, such as localized sinus pressure and tenderness. In addition, both GER and rhino sinusitis are often co-morbid with childhood asthma and, if not specifically treated, may make asthma difficult to manage.

Table 169.5 Differential Diagnosis of Childhood Asthma**UPPER RESPIRATORY TRACT CONDITIONS**

Allergic rhinitis*
 Chronic rhinitis*
 Sinusitis*
 Adenoidal or tonsillar hypertrophy
 Nasal foreign body

MIDDLE RESPIRATORY TRACT CONDITIONS

Laryngotracheobronchomalacia*
 Laryngotracheobronchitis (e.g., pertussis)*
 Laryngeal web, cyst, or stenosis
 Exercise-induced laryngeal obstruction
 Vocal cord dysfunction*
 Vocal cord paralysis
 Tracheoesophageal fistula
 Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
 Endobronchial tumor
 Foreign body aspiration*
 Chronic bronchitis from environmental tobacco smoke exposure*
 Repaired tracheoesophageal fistula
 Toxic inhalations

LOWER RESPIRATORY TRACT CONDITIONS

Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
 Viral bronchiolitis*
 Gastroesophageal reflux*
 Causes of bronchiectasis:
 • Cystic fibrosis
 • Immunodeficiency
 • Allergic bronchopulmonary mycoses (e.g., aspergillosis)
 • Chronic aspiration
 Primary ciliary dyskinesia, immotile cilia syndrome
 Bronchiolitis obliterans
 Interstitial lung diseases
 Hypersensitivity pneumonitis
 Eosinophilic granulomatosis with angiitis
 Eosinophilic pneumonia
 Pulmonary hemosiderosis
 Tuberculosis
 Pneumonia
 Pulmonary edema (e.g., congestive heart failure)
 Vasculitis
 Sarcoidosis
 Medications associated with chronic cough:
 • Acetylcholinesterase inhibitors
 • β -Adrenergic antagonists
 • Angiotensin-converting enzyme inhibitors

*More common asthma masqueraders.

DIFFERENTIAL DIAGNOSIS OF CHILDHOOD ASTHMA

UPPER RESPIRATORY TRACT CONDITIONS

Allergic rhinitis
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Laryngotracheobronchomalacia
 Laryngotracheobronchitis (e.g., pertussis)
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LOWER RESPIRATORY TRACT CONDITIONS

Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
 Viral bronchiolitis
 Gastro esophageal reflux

Causes of bronchiectasis:

Cystic fibrosis

Immune deficiency

Allergic bronchopulmonary mycoses (e.g., aspergillosis)

Chronic aspiration

Immotile cilia syndrome, primary ciliary dyskinesia

Bronchiolitis obliterans

Interstitial lung diseases

Hypersensitivity pneumonitis

Pulmonary eosinophilia, Churg-Strauss vasculitis

Pulmonary hemosiderosis

Tuberculosis

Pneumonia

Pulmonary edema (e.g., congestive heart failure)

Medications associated with chronic cough:

Acetyl cholinesterase inhibitors

B-Adrenergic antagonists

Angiotensin-converting enzyme inhibitors

Table 169.3 Asthma Triggers

COMMON VIRAL INFECTIONS OF RESPIRATORY TRACT

AEROALLERGENS IN SENSITIZED ASTHMATIC PATIENTS

Indoor Allergens

- Animal dander
- Dust mites
- Cockroaches
- Molds

Seasonal Aeroallergens

- Pollens (trees, grasses, weeds)
- Seasonal molds

AIR POLLUTANTS

- Environmental tobacco smoke
- Ozone
- Nitrogen dioxide
- Sulfur dioxide
- Particulate matter
- Wood- or coal-burning smoke
- Mycotoxins
- Endotoxin
- Dust

STRONG OR NOXIOUS ODORS OR FUMES

- Perfumes, hairsprays
- Cleaning agents

OCCUPATIONAL EXPOSURES

- Farm and barn exposures
- Formaldehydes, cedar, paint fumes

COLD DRY AIR

EXERCISE

CRYING, LAUGHTER, HYPERVENTILATION

COMORBID CONDITIONS

- Rhinitis
- Sinusitis
- Gastroesophageal reflux

DRUGS

- Aspirin and other nonsteroidal antiinflammatory drugs
- β -Blocking agents

Diagnosis

The diagnosis depends on the clinical presentations + laboratory findings.

Lung functions tests

Measuring of the expiratory air flow is helpful in the diagnosis, monitoring & assessing the efficacy of treatment.

a) Spirometer (usually for children >6 yrs.): It measures FEV₁ (forced expiratory volume in 1 second) & FVC (forced vital capacity). It also assesses the "bronchodilator response" using inhaled B-agonist, the "exercise challenge", & the "bronchoprovocation challenges" using methacholine, histamine, or cold & dry air which is rarely used.

b) Peak expiratory flow (PEF) monitoring : It is a simple & inexpensive home used tool to measure the peak expiratory flow (PEF).

Lung functions abnormality in asthma

Spirometer

1. Air flow limitation (\downarrow FEV₁, FEV₁ / FVC ratio < 0.8)
2. Bronchodilator response \rightarrow improvement in FEV₁ \geq 12%
3. Exercise response \rightarrow worsening in FEV₁ \geq 15%

PEF morning to afternoon variability \geq 20%

Table 169.6

Lung Function Abnormalities in Asthma and Assessment of Airway Inflammation

Spirometry (in clinic)^{††}:

Airflow limitation:

- Low FEV₁ (relative to percentage of predicted norms)
- FEV₁/FVC ratio <0.80

Bronchodilator response (to inhaled β -agonist) assesses reversibility of airflow limitation.

Reversibility is determined by an increase in either FEV₁ >12% or predicted FEV₁ >10% after inhalation of a short-acting β -agonist (SABA)*

Exercise challenge:

- Worsening in FEV₁ \geq 15%*

Daily peak expiratory flow (PEF)[‡] or FEV₁ monitoring: day-to-day and/or AM-to-PM variation \geq 20%*

Exhaled nitric oxide (FeNO)

- A value of >20 ppb supports the clinical diagnosis of asthma in children
- FeNO can be used to predict response to ICS therapy:
 - <20 ppb: Unlikely to respond to ICS because eosinophilic inflammation unlikely
 - 20-35 ppb: Intermediate, may respond to ICS
 - >35 ppb: Likely to respond to ICS because eosinophilic inflammation is likely

*Main criteria consistent with asthma.

[†]Of note, >50% of children with mild to moderate asthma will have a normal FEV₁ and will not have a significant bronchodilator response.

[‡]PEF variability is insensitive, while being highly specific for asthma.

FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroid; ppb, parts per billion.

Radiology

CXR may be normal apart from the hyperinflation. Subtle and nonspecific findings of hyperinflation (flattening of the diaphragms) and per bronchial thickening. There may be a features of complications & sometimes CT-scan can be used (e.g. bronchiectasis).

Others

As allergy testing & IgE level may help in the management & prognosis.

In severe exacerbation: blood gas analysis, blood PH.

Classification of asthma severity

1. **Acute exacerbation:** It is classified into 3 grades : mild, moderate, & severe acute attack (exacerbation) according to the following parameters : PEFr, PR, Alertness, Dyspnea, Pulsus paradoxus, Accessory muscle use, Color, Auscultation, O₂ saturation, & PCO₂.

Table 185.4 Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting ^a				
	MILD	MODERATE	SEVERE	SUBSET: RESPIRATORY ARREST IMMINENT
SYMPTOMS				
Breathlessness	While walking	While at rest (infant: softer, shorter cry, difficulty feeding)	While at rest (infant: stops feeding)	Extreme dyspnea Anxiety
Talks in...	Can lie down	Prefers sitting	Sits upright	Upright, leaning forward
Alertness	Sentences	Phrases	Words	Unable to talk
	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
SIGNS				
Respiratory rate ^b	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min) ^c	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
FUNCTIONAL ASSESSMENT				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40-69% or response lasts <2 hr	<40%	<25% ^d
PaO ₂ (breathing air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or Pco ₂	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
SaO ₂ (breathing air) at sea level	>95% (test not usually necessary)	90-95% (test not usually necessary)	<90%	Hypoxia despite oxygen therapy
Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.				

***Notes:**

- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other; thus they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

^bNormal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.

^cNormal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.

^dPeak expiratory flow testing may not be needed in very severe attacks.

Adapted from National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3). Guideline for the Diagnosis and Management of Asthma, NIH Pub No 07-4051, Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program; 2007. <https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report>

2. **Chronic asthma:** It is classified into 4 grades : Mild intermittent asthma, Mild persistent asthma, Moderate persistent asthma, & Severe persistent asthma according to the following variables : Daytime symptoms, Nocturnal symptoms, Exacerbations, Lung functions, & B-agonists use.

Table 169.7 Assessing Asthma Severity and Initiating Treatment for Patients Who Are Not Currently Taking Long-Term Control Medications*

CLASSIFICATION OF ASTHMA SEVERITY				
	INTERMITTENT	Mild	Moderate	Severe
COMPONENTS OF SEVERITY				
Impairment				
Daytime symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings:				
Age 0-4 yr	0	1-2x/mo	3-4x/mo	>1x/wk
Age ≥5 yr	≤2x/mo	3-4x/mo	>1x/wk but not nightly	Often 7x/wk
Short-acting β ₂ -agonist use for symptoms (not for EIB prevention)	≤2 days/wk	>2 days/wk but not daily, and not more than 1x on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function:				
FEV ₁ % predicted, age ≥5 yr	Normal FEV ₁ between exacerbations	≥80% predicted	60-80% predicted	<60% predicted
FEV ₁ /FVC ratio [†] :				
Age 5-11 yr	>85%	>80%	75-80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
Risk				
Exacerbations requiring systemic corticosteroids:				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic CS		
		or		
		≥4 wheezing episodes/yr lasting >1 day and risk factors for persistent asthma		
Age ≥5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
Consider severity and interval since last exacerbation.				
Frequency and severity may fluctuate over time for patients in any severity category.				
Relative annual risk of exacerbations may be related to FEV ₁ .				
RECOMMENDED STEP FOR INITIATING THERAPY				
(See Table 169.11 for treatment steps.)				
The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.				
All ages	Step 1	Step 2		
Age 0-4 yr			Step 3 and consider a short course of systemic CS	Step 3 and consider a short course of systemic CS
Age 5-11 yr			Step 3: medium-dose ICS option and consider a short course of systemic CS	Step 3: medium-dose ICS option or Step 4 and consider a short course of CS
			In 2-6 wk, depending on severity, evaluate level of asthma control that is achieved.	
			• Children 0-4 yr old: If no clear benefit is observed in 4-6 wk, stop treatment and consider alternative diagnoses or adjusting therapy accordingly.	
			• Children 5-11 yr old: Adjust therapy accordingly.	

*Notes:

- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.

- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 mo, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma, may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

[†]Normal FEV₁/FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV₁, Forced expiratory volume in 1 sec; FVC, forced vital capacity; CS, corticosteroid; ICS, inhaled corticosteroid; EIB, exercise-induced bronchospasm.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma—summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94-S138, 2007.

Asthma medications

1. Quick-relief medications (relievers)

- ✓ Short-acting inhaled B-agonists: as albuterol (ventolin) & terbutaline.
- ✓ Inhaled anticholinergic: as ipratropium bromide & atropine.
- ✓ Short course systemic glucocorticoids: as prednisone & methylprednisolone.

2. Long term-control medications (controllers)

- ✓ NSAI agents: as cromolyn & nedocromil.
- ✓ Inhaled glucocorticoids : as beclomethasone & budesonide.
- ✓ Sustained-release theophylline.
- ✓ Long-acting inhaled B-agonists (LABA S): as salmetrol.
- ✓ Leukotriene modifiers: as monteleukast & zafirleukast.
- ✓ Oral glucocorticoids: as prednisone & methylprednisolone.

Table 169.12 Usual Dosages for Long-Term Control Medications

MEDICATION	AGE		
	0-4 yr	5-11 yr	≥12 yr
INHALED CORTICOSTEROIDS (see Table 169.13)			
Methylprednisolone: 2, 4, 8, 16, 32 mg tablets	0.25-2 mg/kg daily in single dose in AM or qod as needed for control	0.25-2 mg/kg daily in single dose in AM or qod as needed for control	7.5-60 mg daily in a single dose in AM or qod as needed for control
Prednisolone: 5 mg tablets; 5 mg/5 mL, 15 mg/5 mL			
Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/mL, 5 mg/5 mL	Short-course "burst": 1-2 mg/kg/day; maximum 30 mg/day for 3-10 days	Short-course "burst": 1-2 mg/kg/day; maximum 60 mg/day for 3-10 days	Short-course "burst" to achieve control: 40-60 mg/day as single or 2 divided doses for 3-10 days
Fluticasone/salmeterol (Advair): DPI: 100, 250, or 500 µg/50 µg	N/A	1 inhalation bid; dose depends on level of severity or control (the 100/50 dosage is indicated in children ≥4 yr)	1 inhalation bid; dose depends on level of severity or control
HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg			2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol (Symbicort): HFA: 80 µg/4.5 µg, 160 µg/4.5 µg	N/A		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol (Dulera): HFA: 100 µg/5 µg, 200 µg/5 µg			2 inhalations bid; dose depends on level of severity or control
Leukotriene receptor antagonists: Montelukast (Singulair): 4 or 5 mg chewable tablet 4 mg granule packets 10 mg tablet	4 mg qhs (1-5 yr of age)	5 mg qhs (6-14 yr)	10 mg qhs (indicated in children ≥15 yr)
Zafirlukast (Accolate): 10 or 20 mg tablet	N/A	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)
5-Lipoxygenase inhibitor: (Zileuton CR): 600 mg tablet	N/A	N/A	1,200 mg bid (give 2 tablets bid)
Immunomodulators: Omalizumab (anti-IgE; Xolair): SC injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection	N/A	N/A	150-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level
Mepolizumab (anti-IL-5; Nucala): SC injection, 100 mg after reconstitution with 1.2 mL sterile water for injection	N/A	N/A	100 mg SC q 4 wk

bid, 2 times daily; DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; q, every; qhs, every night; qid, 4 times daily; qod, every other day; SC, subcutaneous(ly).

Management

Management of the acute attack (exacerbation)

- ✓ Mild attack can be treated at home.
- ✓ Indications of hospital admission
 1. Moderate-severe attack which does not improve within 1-2 hrs of initial treatment.
 2. Prolonged symptoms before admission.
 3. Inadequate access to the medical care & medications.
 4. Difficult psychological conditions.
 5. Difficulty in obtaining transportation to the hospital in event of further deterioration.

Home management

- ✓ Immediate inhaled short acting B-agonist (up to 3 times / 1 hr.).
- ✓ Good response is characterized by: resolution of symptoms in 1 hr., no further symptoms over the next 4 hrs. & improvement of PEF of 80% predicted or personal best.
- ✓ If the child has incomplete response to B-agonist (i.e. persistent symptoms &/or PEF of 60-80% of predicted or personal best) → short course of oral glucocorticoids (e.g. prednisone 1-2 mg/kg/day for 4 days) in addition to inhaled B-agonist.

Hospital management

- ✓ O2 administration.
- ✓ Close monitoring of the clinical status.
- ✓ Inhaled short acting B-agonist (every 20 min. for 1 hr.).
- ✓ If necessary, systemic glucocorticoids (prednisolone 2 mg/kg/day oral or IV). [NAEPP recommends the use of methylprednisolone at 1 mg/kg/dose every 6 hrs. for 2 days then ↓ dose to 1-2 mg/kg/day in 2 divided doses until PEF reaches 70% of predicted or personal best. This is especially useful in the very severe attacks of asthma].
- ✓ Inhaled ipratropium bromide may be added to B-agonist if no significant response is seen with 1st inhaled B-agonist.
- ✓ Subcutaneous epinephrine may be given in severe cases.
- ✓ IV fluid may be given in persistent severe dyspnea (slightly below maintenance due to ↑ ADH).

In status asthmatics , the following options may be added

1. Intubation & mechanical ventilation.
2. IV B-agonist, IV theophylline.
3. Inhaled Heliox (Helium & O2).
4. IV Mg sulfate (smooth muscle relaxant).

Table 185.17 Management of Asthma Exacerbation (Status Asthmaticus)**RISK ASSESSMENT ON ADMISSION**

Focused history	Onset of current exacerbation Frequency and severity of daytime and nighttime symptoms and activity limitation Frequency of rescue bronchodilator use Current medications and allergies Potential triggers History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes
Clinical assessment	Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status Pulse oximetry Lung function (defer in patients with moderate to severe distress or history of labile disease)
Risk factors for asthma morbidity and death	See Table 185.18

TREATMENT

DRUG AND TRADE NAME	MECHANISMS OF ACTION AND DOSING	CAUTIONS AND ADVERSE EFFECTS
Oxygen (mask or nasal cannula)	Treats hypoxia	Monitor pulse oximetry to maintain O ₂ saturation >92% Cardiorespiratory monitoring
Inhaled short-acting β-agonists	Bronchodilator	During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, V/Q mismatch, and hypoxemia Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume.
Albuterol MDI (90 μ g/puff)	2–8 puffs up to every 20 min for 3 doses as needed, then every 1–4 hr as needed	For MDI: use spacer/holding chamber
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum 1.25 mg) every 20 min for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects
Systemic corticosteroids	Antiinflammatory	If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis For daily dosing, 8 AM administration minimizes adrenal suppression Children may benefit from dosage tapering if course exceeds 7 days Adverse effects monitoring: frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 615); see Table 185.14 for adverse effects screening recommendations
Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution Depo-Medrol (IM); Solu-Medrol (IV)	Short course oral “burst” for exacerbation: 1–2 mg/kg/day divided qd or bid for 3–7 days (maximum 40 mg/day)	
Dexamethasone: 0.5, 0.75, 1, 1.5, 2, 4, 6 mg tablets; 0.5 mg/5 mL, 1 mg/mL Intensol solution	0.5–1 mg/kg every 6–12 hr for 48 hr, then 1–2 mg/kg/day qd or bid Short course oral “burst” for exacerbation: 0.6 mg/kg, maximum 16 mg; can be repeated next day	
Anticholinergics	Mucolytic/bronchodilator	Should not be used as first-line therapy; added to β_2 -agonist therapy
Ipratropium Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 μ g/inhalation)	Nebulizer: 0.5 mg q6–8h (tid–qid) as needed MDI: 2 puffs qid	
Ipratropium with albuterol DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	1 vial by nebulizer qid	Nebulizer: may mix ipratropium with albuterol
Injectable sympathomimetic epinephrine	Bronchodilator	For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)

Continued

Table 185.17 Management of Asthma Exacerbation (Status Asthmaticus)—cont'd		
Adrenalin 1 mg/mL (1:1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min	
Terbutaline	Terbutaline is β -agonist-selective relative to epinephrine Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia	
Brethine 1 mg/mL	Continuous IV infusion (terbutaline only): 2-10 μ g/kg loading dose, followed by 0.1-0.4 μ g/kg/min Titrate in 0.1-0.2 μ g/kg/min increments every 30 min, depending on clinical response.	
Other medications		
Magnesium sulfate	25-75 mg/kg over 20 min Max 2 gm	Flushing, headache, hypotension (rare)
RISK ASSESSMENT FOR DISCHARGE		
Medical stability	Discharge home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air	
Home supervision	Capability to administer intervention and to observe and respond appropriately to clinical deterioration	
Asthma education	See Table 185.10	

IM, Intramuscular; IV, intravenous; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β -agonist; V/Q, ventilation/perfusion; bid, 2 times daily; tid, 3 times daily; qid, 4 times daily; qd, every day.

Patient may be discharged home if there are

1. Sustained improvement in symptoms.
2. Normal physical findings.
3. PEF > 70% of predicted or personal best.
4. O₂ saturation > 92% on room air for 4 hrs.

Discharge therapy includes inhaled B-agonist (up to ever 3-4 hrs.) + glucocorticoids (3-7 days course of prednisolone).

Management of chronic asthma

1. Mild intermittent asthma

There is no continuous daily treatment but inhaled short acting B-agonist can be used when there are symptoms or as prophylactic therapy for exercises.

- ✓ Daily treatment with a "controller" drug is recommended for all 3 types of persistent asthma :

2. Mild persistent asthma

- ✓ Low-dose inhaled glucocorticoid
- ✓ Inhaled cromolyn
- ✓ Leukotriene modifier

- ✓ [Sustained-release theophylline (as alternative)].
- 3. Moderate persistent asthma
 - ✓ Medium-dose inhaled glucocorticoid
 - ✓ Low-dose inhaled glucocorticoid + either LABA inhaler or leukotrien modifier, or [Sustained-release theophylline or LABA tab.(as alternative)].
- 4. Severe persistent asthma
 - ✓ High-dose inhaled glucocorticoid + either LABA inhaler or leukotrien modifier, or [sustained-release theophylline or LABA tab. (as alternative)] +
 - ✓ Oral glucocorticoid (if needed).

Table 169.11 Stepwise Approach for Managing Asthma in Children*

AGE	THERAPY [†]	INTERMITTENT ASTHMA	PERSISTENT ASTHMA: DAILY MEDICATION				
<div>STEP DOWN if possible (and asthma is well controlled at least 3 months)</div> <div>ASSESS CONTROL</div> <div>STEP UP if needed (first check inhaler technique, adherence, environmental control, and comorbid condition)</div>							
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
0-4 yr	Preferred	SABA prn	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + either LABA or LTRA	High-dose ICS + either LABA or LTRA	High-dose ICS + either LABA or LTRA and OCS
	Alternative		Cromolyn or montelukast				
5-11 yr	Preferred	SABA prn	Low-dose ICS	Either low-dose ICS ± LABA, LTRA, or theophylline or Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA and OCS
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline		Medium-dose ICS + either LTRA or Theophylline	High-dose ICS + either LTRA or Theophylline	High-dose ICS + either LTRA or Theophylline and OCS
≥12 yr	Preferred	SABA prn	Low-dose ICS	Low-dose ICS + LABA or Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA and Consider omalizumab for patients with allergies	High-dose ICS + LABA + OCS and Consider mepolizumab for patients with eosinophilic asthma Consider omalizumab for patients with allergies
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS + LTRA, theophylline, or zileuton	Medium-dose ICS + LTRA, theophylline, or zileuton		
<p>Each step: Patient education, environmental control, and management of comorbidities.</p> <p>Age ≥5 yr: Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.</p> <p>QUICK-RELIEF MEDICATION FOR ALL PATIENTS</p> <p>SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.</p> <p>Caution: Use of SABA >2 days/wk for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment.</p> <p>For ages 0-4 yr: With viral respiratory infection: SABA q4-6h up to 24 hr (longer with physician consult). Consider short course of systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.</p>							

*Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
 - If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
 - If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
 - Studies on children age 0-4 yr are limited.
 - Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
 - Theophylline is a less desirable alternative because of the need to monitor serum concentration levels. The 2016 GINA guidelines do not recommend the use of theophylline as a controller medication and in IV forms to treat status asthmaticus due to its severe adverse effects profile.
 - Zileuton is less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function.
 - †Alphabetical order is used when more than 1 treatment option is listed within either preferred or alternative therapy.
- ICS, Inhaled corticosteroid; LABA, Inhaled long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; prn, as needed; SABA, inhaled short-acting β_2 -agonist.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma—summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94-S138, 2007.

Table 169.8 Assessing Asthma Control and Adjusting Therapy in Children*

	CLASSIFICATION OF ASTHMA CONTROL		
	Well-Controlled	Not Well-Controlled	Very Poorly Controlled
COMPONENTS OF CONTROL			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1x/mo	>1x/mo	>1x/wk
Age 5-11 yr	≤1x/mo	≥2x/mo	≥2x/wk
Age ≥12 yr	≤2x/mo	1-3x/wk	≥4x/wk
Short-acting β ₂ -agonist use for symptoms (not for EIB pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV ₁ (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
FEV ₁ /FVC:	>80%	75-80%	<75%
Age ≥12 yr:			
FEV ₁ (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
Validated questionnaires ¹ :			
Age ≥12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15
Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Reduction in lung growth or progressive loss of lung function	Evaluation requires long-term follow-up care.		
RECOMMENDED ACTION FOR TREATMENT			
	Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well controlled for at least 3 mo.	Step up ² (1 step) and reevaluate in 2-6 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.	Consider short course of oral corticosteroids. Step up ³ (1-2 steps) and reevaluate in 2 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.

*Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

¹Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:

- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0.
- ACQ, Asthma Control Questionnaire; MID = 0.5.
- ACT, Asthma Control Test; MID not determined.

²ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

³Before step-up therapy: (a) review adherence to medications, inhaler technique, and environmental control; (b) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FEV₁, Forced expiratory volume in 1 sec; FVC, forced vital capacity; EIB, exercise-induced bronchospasm; N/A, not available.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94-S138, 2007.

Prognosis

Recurrent coughing and wheezing occurs in 35% of preschool-aged children. Of these, approximately one third continue to have persistent asthma into later childhood, and approximately two thirds improve on their own through their teen years. Asthma severity by the ages of 7-10 yrs. of age is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years); however, complete remission for 5 yrs. in childhood is uncommon.

Prevention

Several non pharmacotherapeutic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 mo.), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Immunizations are currently not considered to increase the likelihood of development of asthma; therefore, all standard childhood immunizations are recommended for children with asthma, including varicella and annual influenza vaccines.