

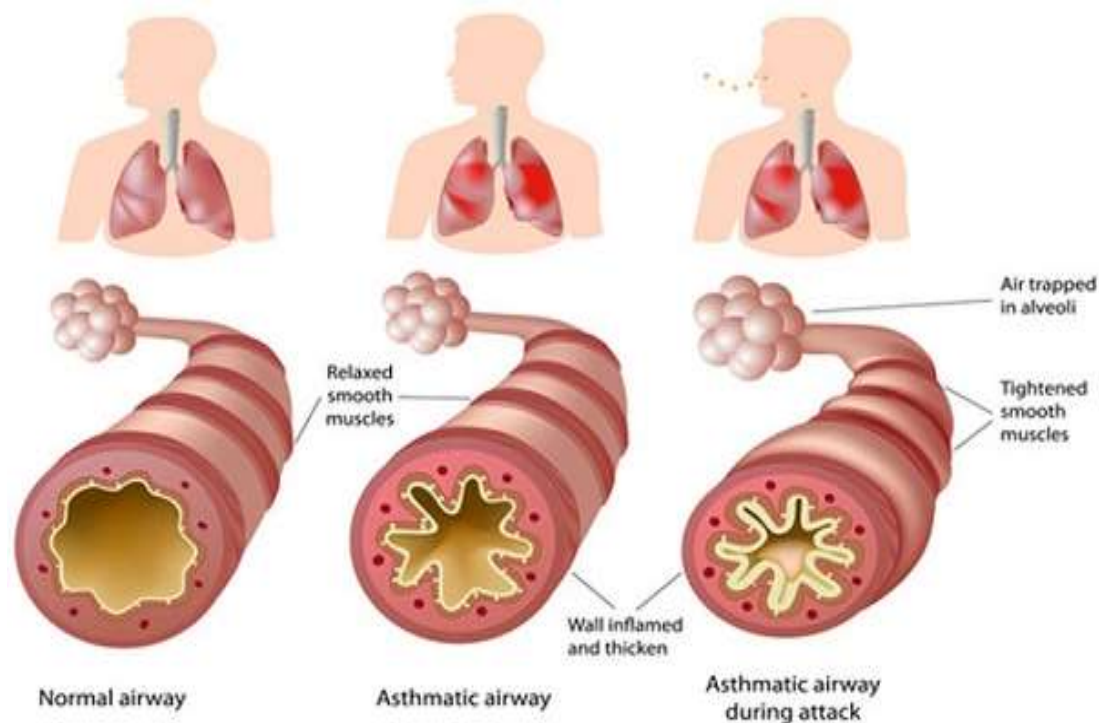
Supportive module 3 "Basics of diagnosis, treatment and prevention
of major pulmonary diseases "

Bronchial Asthma

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

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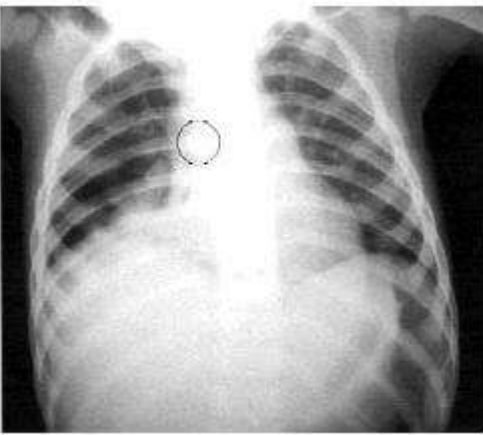
Plan of the Lecture



- Definition
- Epidemiology
- Risk Factors and Etiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

Definition

(Bronchial) Asthma is defined as a chronic inflammatory disorder of the airways which characterized by bronchial hyper-responsiveness and variable airflow obstruction, that is often reversible either spontaneously or with treatment, and manifests itself as recurrent episodes of wheezing, breathlessness, chest tightness and cough, that may occur a few times a day or a few times per week and depending on the person may become worse at night or with exercise.



USMLE TEST

A child accidentally aspirates a small pebble that lodges in the lower portion of the right inferior lobe. A radiograph is shown in Figure A. What changes are expected to occur in the arterial blood supply for this portion of the lung?

1. Increased, secondary to arterial vasodilation
2. Increased, secondary to active hyperemia
3. No change, due to autoregulation
4. Decreased, secondary to arterial vasoconstriction
5. Decreased, secondary to a decrease in surfactant synthesis

USMLE TEST

The correct answer is 4: The clinical presentation is consistent for an aspirated object. As a result arterial blood supply for this portion of the lung will decrease due to arterial vasoconstriction.

Incorrect answers:

1: As described above, local alveolar hypoxia causes vasoconstriction, not vasodilation in the lung, 2: Active hyperemia refers to an increase in blood flow secondary to the accumulation of metabolic byproducts. Active hyperemia is not a response that alters blood flow in the lung, 3: Unlike the kidney, heart, and brain, autoregulation does not influence the flow of blood in the lung, 5: Surfactant, synthesized by type II pneumocytes, reduces surface tension in the lung and is not a major factor in blood flow regulation.

Global Initiative for Asthma (GINA)

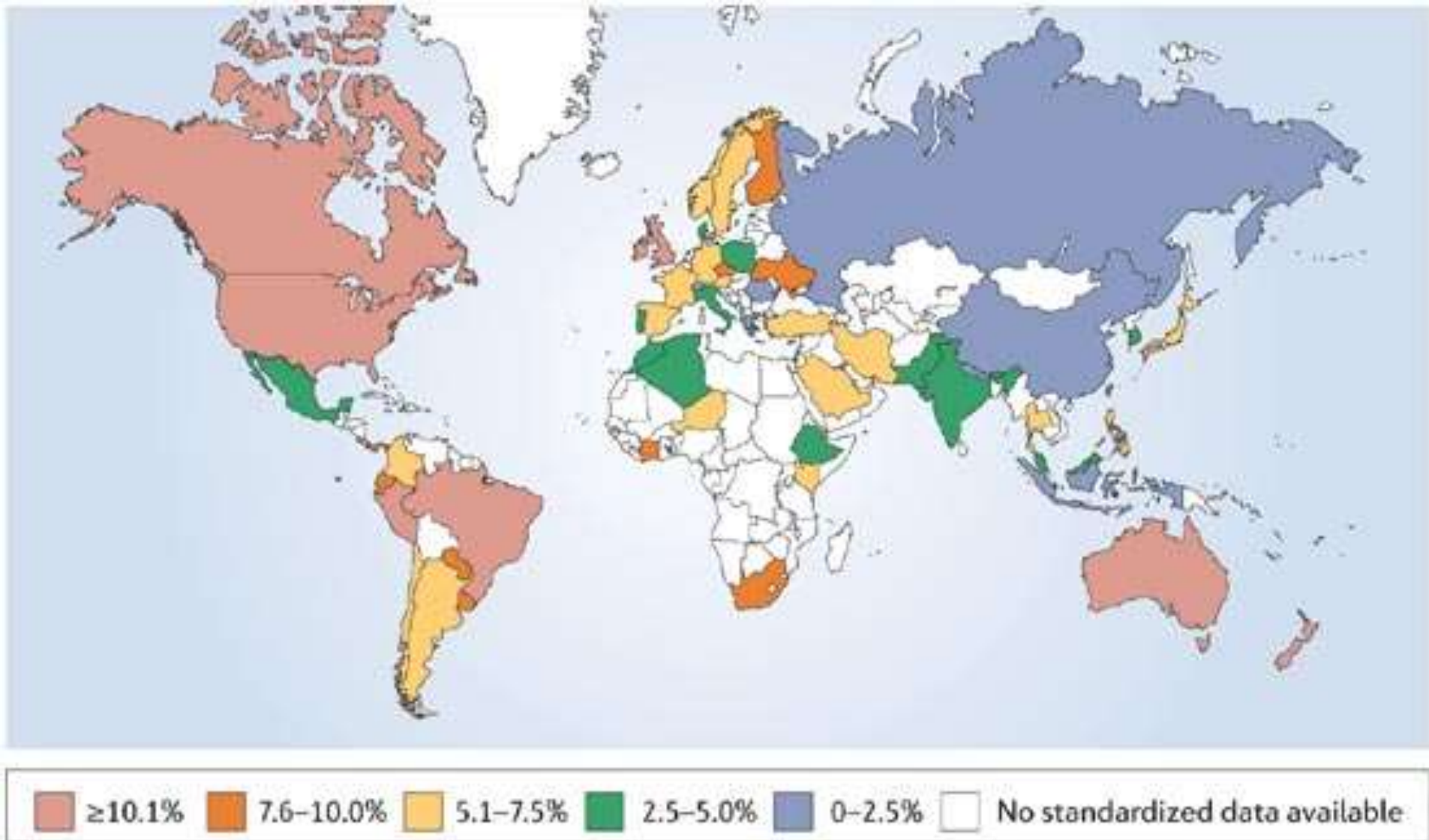
In 1992, WHO and the US-based National Heart, Lung and Blood Institute jointly formed GINA to cut deaths and disability by developing and implementing an optimal strategy for asthma management and prevention.

GINA's goal is to build an active network with multiple organizations concerned with asthma to ensure better patient care world-wide.

Epidemiology

- There are about 315 million people estimated to be suffering from asthma worldwide
- The global prevalence of asthma, using a definition of clinical asthma or treated asthma, is estimated to be about 4.5%
- Using a less rigorous definition for diagnosis of asthma, the global prevalence is approximately 8.6%

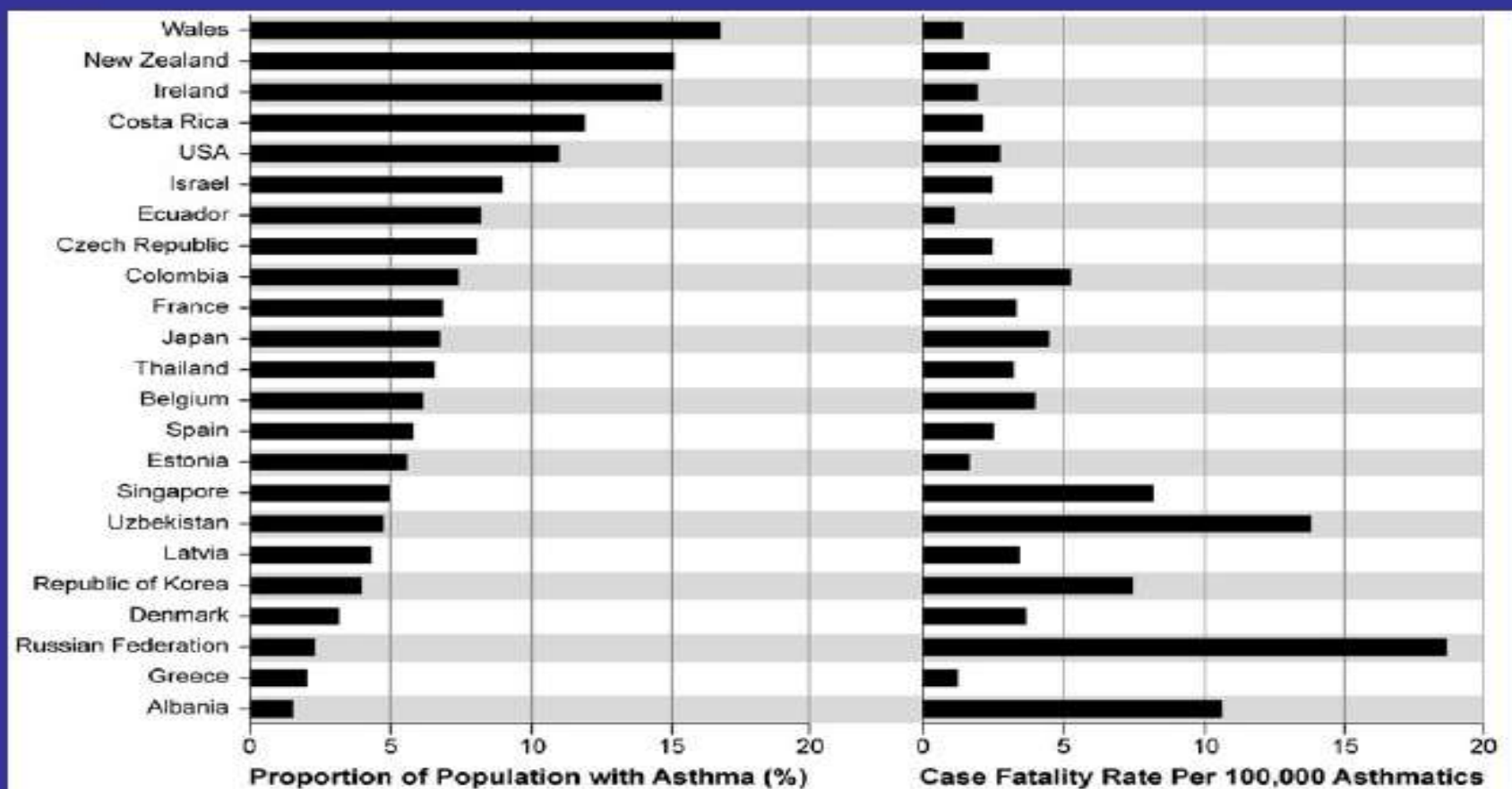
Epidemiology



Epidemiology



Asthma Prevalence and Mortality



Source: Masoli M et al. Allergy 2004

Risk Factors and Etiology

- Asthma is caused by a combination of complex and incompletely understood environmental and genetic interactions
- These factors influence both asthma severity and asthma responsiveness to treatment
- Onset before age 12 is more likely due to genetic influence, while onset after 12 is more likely due to environmental influence.

Risk Factors and Etiology

Environmental

- Smoking during pregnancy and after delivery
- Low air quality
- Exposure to indoor volatile organic compounds (formaldehyde, phthalates, etc.)
- There is an association between paracetamol use and asthma
- Exposure to indoor allergens (dust mites, cockroaches, animal dander, and mold.)
- Certain viral respiratory infections (respiratory syncytial virus and rhinovirus)
- Certain other infections, however, may decrease the risk.

Risk Factors and Etiology

Hygiene Hypothesis

- The increased rates of asthma is a direct and unintended result of reduced exposure, during childhood, to non-pathogenic bacteria and viruses
- Exposure to bacterial endotoxin in early childhood may prevent the development of asthma
- Use of antibiotics in early life has been linked to the development of asthma
- Delivery via caesarean section is associated with an increased risk (estimated at 20–80%) of asthma.

Risk Factors and Etiology

Genetic

- Family history is a risk factor for asthma, with many different genes being implicated
- If one identical twin is affected, the probability of the other having the disease is approximately 25%
- By the end of 2005, 25 genes had been associated with asthma in six or more separate populations, including GSTM1, IL10, CTLA-4, SPINK5, LTC4S, IL4R and ADAM33, among others
- Some genetic variants may cause asthma when are combined with specific environmental exposures.

Risk Factors and Etiology

Medical Conditions

- A triad of atopic eczema, allergic rhinitis and asthma is called atopy
- Asthma has been associated with an autoimmune disease, vasculitis and urticaria
- There is a correlation between obesity and the risk of asthma
- Medications that can cause problems in asthmatics are beta blockers, angiotensin-converting enzyme inhibitors, aspirin, and NSAIDs.

Risk Factors and Etiology

Exacerbation

- Some individuals will have stable asthma for weeks or months and then suddenly develop an episode of acute asthma
- Most individuals can develop severe exacerbation from a number of triggering agents (dust, cat and dog hair, perfumes, etc.)
- Viral and bacterial infections of the upper respiratory tract can worsen the disease
- Psychological stress may worsen symptoms.

Risk Factors and Etiology

Triggers

inflammatory factors



respiratory
infections

allergens

work

medication

irritants



temperature
change

exercise

cold air

stress and emotions

strong odors

others



tobacco

gastric
reflux

pollutants

food
additives

Mechanism

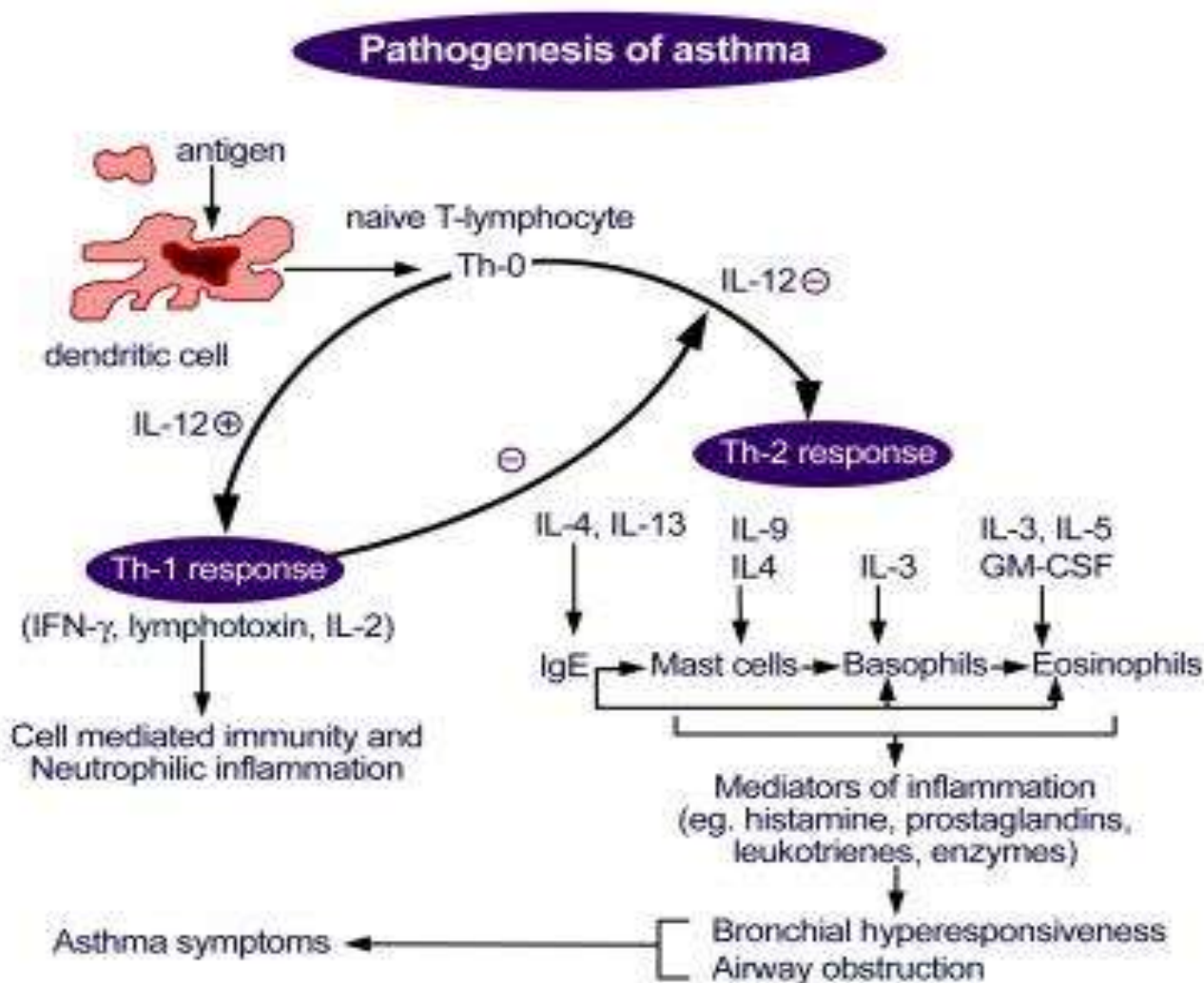
- The mechanism involves airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness
- Mononuclear cell and eosinophil infiltration, mucus hypersecretion, desquamation of the epithelium, smooth muscle hyperplasia, and airway remodeling are present
- Airway hyperresponsiveness or bronchial hyperreactivity is an exaggerated response to numerous stimuli
- The mechanisms include direct stimulation of airway smooth muscle and indirect stimulation by pharmacologically active substances from mediator-secreting cells (mast cells, nonmyelinated sensory neurons).

Mechanism

Airway Inflammation

- Inflammation may be acute, subacute, or chronic, and the presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity
- Cells in airway inflammation include mast cells, eosinophils, epithelial cells, macrophages, activated T lymphocytes, fibroblasts, endothelial cells, etc.
- Adhesion molecules and cytokine imbalance (e.g., selectins, integrin's) are critical in directing the inflammatory in the airway
- The degree of airway hyperresponsiveness correlates with the clinical severity of asthma.

Mechanism



Mechanism of asthma. Antigen presentation by the dendritic cell with the lymphocyte and cytokine response leading to airway inflammation and asthma symptoms.

Mechanism

Airflow Obstruction

- Airflow obstruction can be caused by acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling
- Acute bronchoconstriction is the consequence of immunoglobulin E-dependent mediator release upon exposure to aeroallergens and is the primary component of the early asthmatic response
- Chronic mucous plug formation consists of an exudate of serum proteins and cell debris
- Airway obstruction causes increased resistance to airflow and decreased expiratory flow rates.

Mechanism

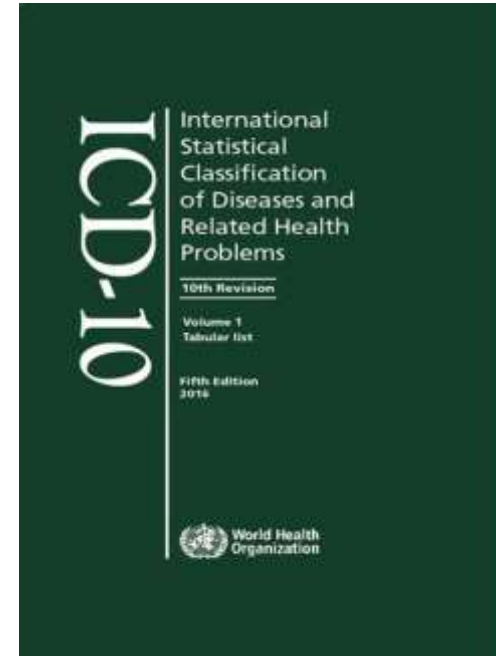
Bronchial Hyperresponsiveness

- Uneven changes in airflow resistance and vasoconstriction due to alveolar hypoxia lead to ventilation-perfusion mismatch
- Hyperventilation triggered by the hypoxic drive causes a decrease in PaCO_2
- With worsening obstruction and increasing ventilation-perfusion mismatch, carbon dioxide retention occurs
- Later, the increased work of breathing, increased oxygen consumption, and increased cardiac output result in metabolic acidosis
- Respiratory failure leads to respiratory acidosis.

Classification

International Classification of Diseases

- X Diseases of the respiratory system
- J45 Asthma
- J45.0 Predominantly allergic asthma
- J45.1 Nonallergic asthma
- J45.8 Mixed asthma
- J45.9 Asthma, unspecified
- J46 Status asthmaticus



Classification

Clinical

Severity	Symptom frequency	Night time symptoms	%FEV ₁ of predicted	FEV ₁ Variability	SABA use
Intermittent	≤2/week	≤2/month	≥80%	<20%	≤2 days/week
Mild persistent	>2/week	3–4/month	≥80%	20–30%	>2 days/week
Moderate persistent	Daily	>1/week	60–80%	>30%	daily
Severe persistent	Continuousl y	Frequent (7×/week)	<60%	>30%	≥twice/day

Symptoms and Signs

- Asthma is characterized by recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing
- Sputum may be produced from the lung by coughing but is often hard to bring up
- During recovery from an attack, it may appear pus-like due to high levels of white blood cells called eosinophils
- Symptoms are usually worse at night and in the early morning or in response to exercise or cold air
- Some people with asthma rarely experience symptoms, usually in response to triggers, whereas others may have marked and persistent symptoms.

Clinical Manifestations

Intermittent Asthma

- Symptoms (difficulty breathing, wheezing, chest tightness, and coughing):
 - Occur on fewer than 2 days a week
 - Do not interfere with normal activities
- Nighttime symptoms occur on fewer than 2 days a month
- Lung function tests (spirometry and peak expiratory flow[PEF]) are normal when the person is not having an asthma attack (the results of these tests are 80% or more of the expected value and vary little (PEF varies less than 20%) from morning to afternoon).

Clinical Manifestations

Mild persistent Asthma

- Symptoms occur on more than 2 days a week but do not occur every day
- Attacks interfere with daily activities
- Nighttime symptoms occur 3 to 4 times a month
- Lung function tests are normal when the person is not having an asthma attack (the results of these tests are 80% or more of the expected value and may vary a small amount (PEF varies 20% to 30%) from morning to afternoon).

Clinical Manifestations

Moderate persistent Asthma

- Symptoms occur daily, inhaled short-acting asthma medication is used every day
- Symptoms interfere with daily activities
- Nighttime symptoms occur more than 1 time a week, but do not happen every day
- Lung function tests are abnormal (more than 60% to less than 80% of the expected value), and PEF varies more than 30% from morning to afternoon.

Clinical Manifestations

Severe persistent Asthma

- Symptoms:
 - Occur throughout each day
 - Severely limit daily physical activities
- Nighttime symptoms occur often, sometimes every night
- Lung function tests are abnormal (60% or less of expected value), and PEF varies more than 30% from morning to afternoon.

Clinical Manifestations

History

- Whether symptoms are attributable to asthma
- Asthma severity
- Possible precipitating factors
- Family history (asthma, allergy, sinusitis, rhinitis, eczema, nasal polyps)
- The social history (home and workplace, smoking, education, employment, social support, etc)
- The patient's exacerbation history
- The patient's perception of asthma.

Clinical Manifestations

an Acute Episode

- Mild episode: patients may be breathless after physical activity, can talk in sentences and lie down, RR is increased, accessory muscles of respiration are not used; HR < 100 bpm; end-expiratory wheezing; oxyhemoglobin saturation (OS) is >95%
- Moderately severe episode: RR is increased; accessory muscles of respiration are used; HR is 100-120 bpm; loud expiratory wheezing; OS is 91-95%
- Severe episode: patients are breathless during rest, sit upright, talk in words rather than sentences, are agitated; RR >30 1/m; accessory muscles of respiration are used, HR is >120 bpm; expiratory and inspiratory wheezing; OS <91%.

Complications

- Status asthmaticus if obstruction remains for days and weeks and fails to respond to treatment
- Pneumonia or infection in the lungs by bacteria or viruses
- Atelectasis or collapse of a section of the lung can happen if there is excessive mucosal blockage in a smaller airway
- Respiratory failure, where the levels of oxygen in the blood become dangerously low, or the levels of carbon dioxide become dangerously high
- Absenteeism from workplace
- Anxiety, Depression.

Diagnosis

- The classical symptoms (wheezing, breathlessness, cough, and chest tightness) tend to be variable, seasonal, recurrent and/or nocturnal
- Presence of atopy, family history of asthma in a first degree relative, and/or symptomatic worsening after exposure to non-specific triggers support a diagnosis of asthma
- The presence of expiratory polyphonic wheeze is a typical finding, and hyperinflated chest may suggest long-standing disease
- Tachycardia, tachypnea, use of accessory muscles of respiration suggest an asthma exacerbation.

Diagnosis

Recommendations

- A clinical diagnosis of asthma should be suspected in the presence of recurrent/episodic wheezing, breathlessness, cough, and/or chest tightness with no alternative explanation for these symptoms
- None of the symptoms and signs are specific for asthma
- Absence of signs and symptoms at the time of presentation does not rule out the presence of asthma.

Diagnosis

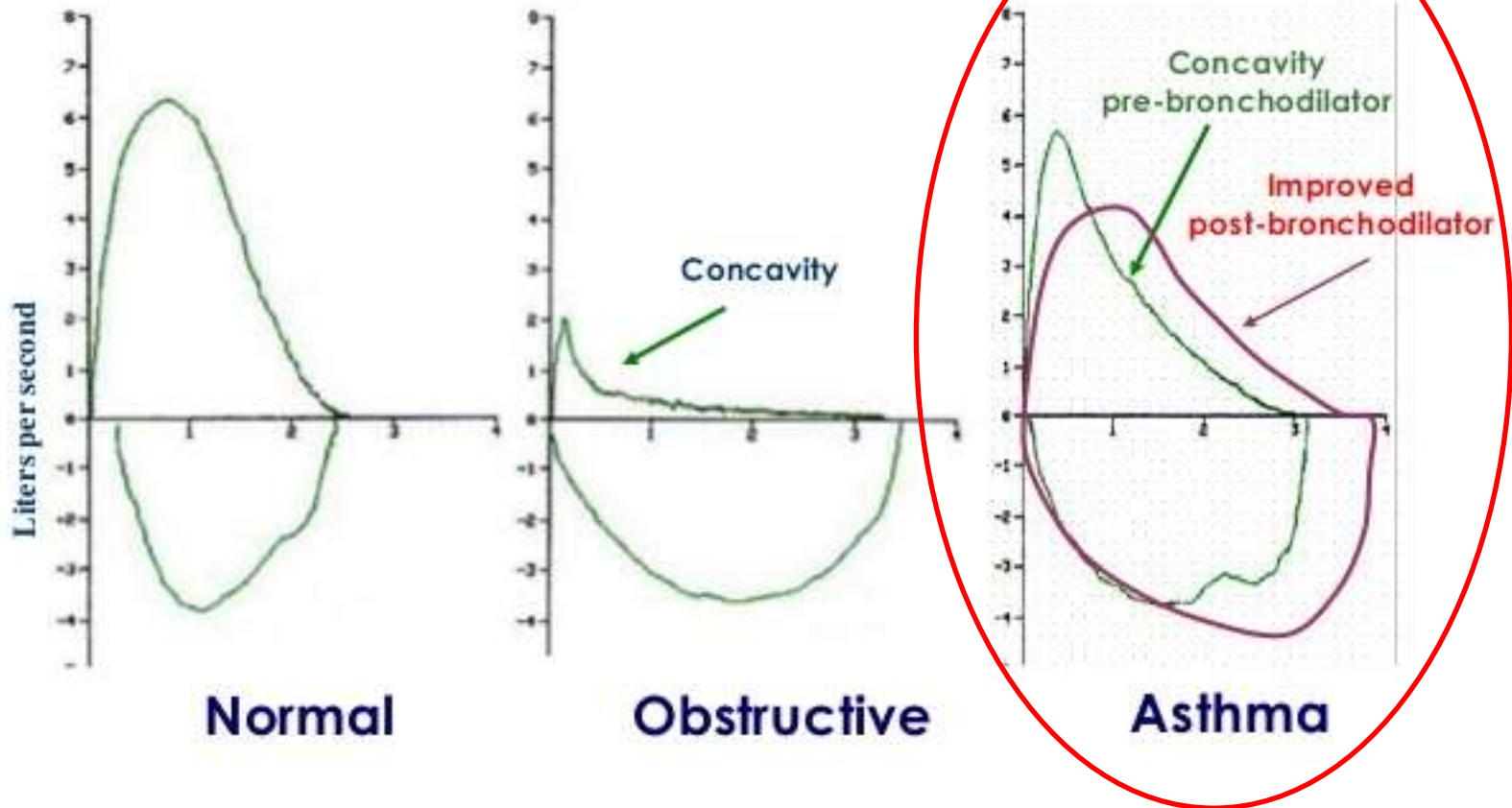
Spirometry

- If the FEV1 improves $>12\%$ following administration of a bronchodilator, this is supportive of the diagnosis
- It however may be normal in those with a history of mild asthma, not currently acting up
- As caffeine is a bronchodilator in people with asthma, the use of caffeine before a lung function test may interfere with the results
- Single-breath diffusing capacity can help differentiate asthma from COPD
- It is reasonable to perform spirometry every one or two years to follow how well a person's asthma is controlled.

Diagnosis

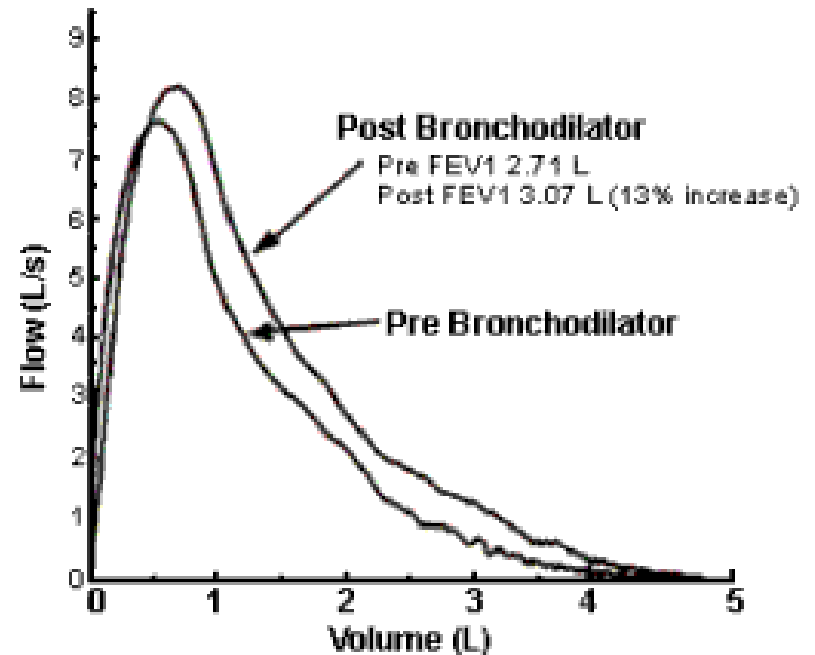
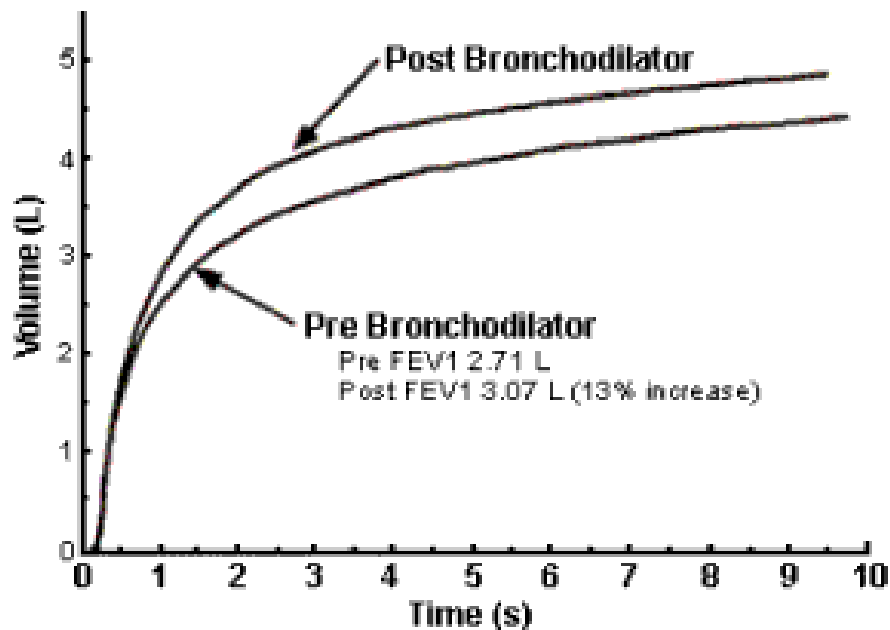
Spirometry

Types of Flow Volume Curves



Diagnosis

Spirometry



Diagnosis

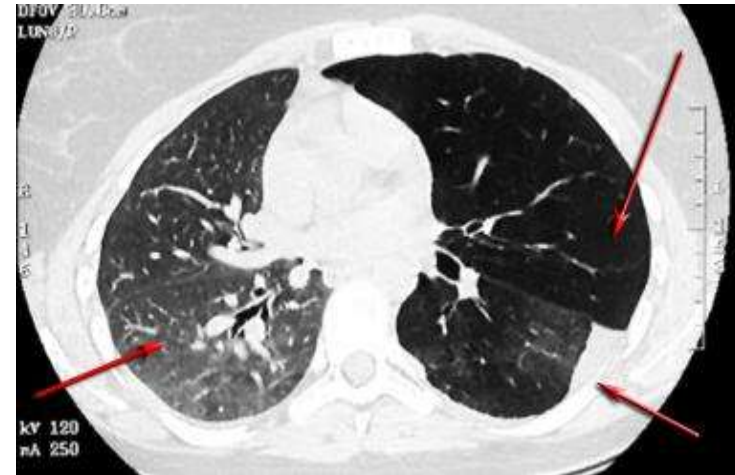
Chest Radiography

- A chest radiograph may be warranted when additional complications like allergic bronchopulmonary aspergillosis, or an alternative diagnosis like tuberculosis, are under consideration
- Presence of increased bronchovascular markings and low diaphragm are few features noted in asthmatics more commonly than normal individuals; however, these do not differentiate asthma from other pulmonary disorders.

Diagnosis

Imaging Studies

- CT, single-photon emission computerized tomography and positron emission tomography are being investigated to understand the pathophysiologic and anatomic abnormalities in asthmatics
- They have no role in the routine diagnosis of asthma.



Asthma. Recurrent left lower lobe pneumonia.
Mucoepidermoid carcinoma.

Diagnosis

Differentiation

- Alpha1-Antitrypsin Deficiency
- Aspergillosis
- Bronchiectasis
- Bronchiolitis
- COPD
- Chronic Sinusitis
- Eosinophilic Granulomatosis with Polyangiitis
- Cystic Fibrosis
- Foreign Body Aspiration
- Gastroesophageal Reflux Disease
- Heart Failure
- Pediatric Airway Foreign Body
- Pediatric Tracheomalacia
- Pulmonary Embolism
- Pulmonary Eosinophilia
- Sarcoidosis
- Upper Respiratory Tract Infection
- Vocal Cord Dysfunction

USMLE TEST

In which of the following pathological states would the oxygen content of the trachea resemble the oxygen content in the affected alveoli?

1. Emphysema
2. Pulmonary fibrosis
3. Pulmonary embolism
4. Foreign body obstruction distal to the trachea
5. Exercise.

USMLE TEST

The correct answer is 3: Pulmonary embolism (PE) effectively results in a blockage of flow in a vessel to its corresponding alveoli. As a result, there is no extraction of oxygen or ventilation in this region (i.e. dead space physiology) and the alveoli have a gas composition similar to the trachea ($PAO_2=150$, $PACO_2=0$).

Incorrect answers: 1: Emphysema is a diffuse process and does not change the oxygen content of an affected alveoli, 2: Pulmonary fibrosis reduces the number of functioning alveoli, 4: An airway foreign body would reduce the oxygen content of the affected alveoli, and would result in shunt physiology of the alveoli distal to the obstruction, 5: Exercise does not significantly change the oxygen content of the alveoli.

Management

Approach Considerations

- Treatment of acute asthmatic episodes and control of chronic symptoms
- Pharmacologic management: inhaled corticosteroids, long-acting bronchodilators, theophylline, leukotriene modifiers, anti-immunoglobulin E (IgE) antibodies (omalizumab) and anti-IL-5 antibodies in selected patients
- Relief medications (bronchodilators, systemic corticosteroids, and ipratropium)
- The ultimate goal is to prevent symptoms, minimize morbidity from acute episodes, and prevent functional and psychological morbidity to provide a healthy (or near healthy) lifestyle.

Management

The Stepwise Approach to Asthma Therapy

<p>STEP 1</p> <p>Intermittent</p> <p>Adults and children >5 years of age No daily medication needed</p> <p>Infants and young children ≤5 years of age No daily medication needed</p>	<p>STEP 2</p> <p>Mild Persistent</p> <p>Adults and children >5 years of age Low-dose inhaled corticosteroids</p> <p>Infants and young children ≤5 years of age Low-dose inhaled corticosteroids (with nebulizer or MDI with holding chamber with or without face mask or DPI)</p> <p>Alternative treatments Leukotriene modifier Cromolyn Theophylline</p>	<p>STEP 3</p> <p>Moderate Persistent</p> <p>Adults and children >5 years of age Low-to-medium dose inhaled corticosteroids and long-acting inhaled beta2-agonists</p> <p>Infants and young children ≤5 years of age Low-dose inhaled corticosteroids and long-acting inhaled beta2-agonists OR medium-dose inhaled corticosteroids</p> <p>Alternative treatments Low-dose inhaled corticosteroid and either leukotriene modifier or theophylline or oral beta2-agonists</p>	<p>STEP 4</p> <p>Severe Persistent</p> <p>Adults and children >5 years of age High-dose inhaled corticosteroids AND long-acting inhaled beta2-agonists</p> <p>Infants and young children ≤5 years of age High-dose inhaled corticosteroids AND long-acting inhaled beta2-agonists</p> <p>Alternative treatments No alternative recommendations</p>
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MDI indicates metered-dose inhaler; DPI, dry powder inhaler.

Source: Reference 6.

Management

Environmental Control

- Efforts should focus on the home, patients should clean and dust their homes regularly
- If a patient cannot avoid vacuuming, he or she should use a face mask or a double-bagged vacuum with a high-efficiency particulate air filter
- If possible, consideration can be given to moving to a higher floor in the house or different neighborhood
- Active smoking and exposure to passive smoke must be avoided
- Air pollution caused by traffic may increase the risk of asthma and wheezing.

Management

Allergen Immunotherapy

- Immunotherapy be considered if a relationship is clear between symptoms and exposure to an unavoidable allergen to which the patient is sensitive; symptoms occur all year or during a major portion of the year; symptoms are difficult to control with pharmacologic management because the medication is ineffective, multiple medications are required, or the patient is not accepting of medication.

Management

Monoclonal Antibody Therapy

- Omalizumab (a humanized murine IgG antibody against the Fc component of the IgE antibody) was approved in 2003 for patients ≥ 12 y with moderate-to-severe persistent
- Mepolizumab (a humanized IgG1 kappa monoclonal antibody specific for interleukin 5) is indicated for add-on maintenance treatment of patients ≥ 12 y with severe asthma with an eosinophilic phenotype
- Reslizumab (an IgG kappa monoclonal antibody that inhibits IL-5) is indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype. It is administered as an intravenous infusion every 4 weeks.

Management

Fast-acting Medications

- Short-acting beta₂-adrenoceptor agonists (SABA), such as salbutamol are the first line treatment for asthma
- Anticholinergic medications, such as ipratropium bromide, provide additional benefit when used in combination with SABA in those with moderate or severe symptoms; they can also be used if a person cannot tolerate a SABA
- Older, less selective adrenergic agonists, such as inhaled epinephrine, have similar efficacy to SABAs; they are however not recommended due to concerns regarding excessive cardiac stimulation.

Management

Long-term Control

- Corticosteroids are the most effective treatment
- Inhaled forms are usually used except in the case of severe persistent disease
- Inhaled corticosteroids carries a minor risk of adverse effects (cataracts, a mild regression in stature)
- Long-acting beta-adrenoceptor agonists (LABA) can improve asthma control, at least in adults
- Leukotriene receptor antagonists (montelukast and zafirlukast) may be used in addition to inhaled corticosteroids, typically also in conjunction with a LABA
- 5-LOX inhibitors may be used as an alternative in the chronic treatment of mild to moderate asthma.

Management

Nebulizers and Spacers



Nebulizer Dry powder inhaler

Spacer

Medications are typically provided as metered-dose inhalers (MDIs) in combination with an asthma spacer or as a dry powder inhaler. A nebulizer may also be used. Nebulizers and spacers are equally effective in those with mild to moderate symptoms.

Management

Emergency Management

- Oxygen to alleviate hypoxia if saturations fall below 92%
- Corticosteroid by mouth are recommended with five days of prednisone being the same 2 days of dexamethasone
- Magnesium sulfate intravenous treatment increases bronchodilation in moderate severe acute asthma attacks
- Heliox, a mixture of helium and oxygen, may also be considered in severe unresponsive cases
- The dissociative anesthetic ketamine is theoretically useful if intubation and mechanical ventilation is needed in people who are approaching respiratory arrest; however, there is no evidence from clinical trials to support this.

Management

Patient Education

- All members of the healthcare team, including nurses, pharmacists, and respiratory therapists, should provide education
- Clinicians should teach patients asthma self-management based on basic asthma facts, self-monitoring techniques, the role of medications, inhaler use, and environmental control measures
- Treatment goals should be developed for the patient and family
- A written, individualized, daily self-management plan should be developed.

Prognosis

- International asthma mortality is reported as high as 0.86 deaths per 100,000 persons in some countries
- Mortality is primarily related to lung function, but it has also been linked with asthma management failure
- The estimate of lost work and school time from asthma is approximately 100 million days of restricted activity
- Approximately 500,000 annual hospitalizations (40.6% in individuals aged 18 y or younger) are due to asthma
- Patients with poorly controlled asthma develop long-term changes over time (i.e., with airway remodeling).

Prophylaxis

- Cover bedding with allergy-proof casings
- Remove carpets from bedrooms and vacuum regularly
- Use unscented detergents and cleaning materials
- Keep humidity levels low and fix leaks to reduce the growth of organisms such as mold
- Keep the house clean and keep food in containers
- If someone is allergic to an animal that cannot be removed from the home, the animal should be kept out of the bedroom
- Eliminate tobacco smoke from the home
- Avoid air pollution, industrial dust, and irritating fumes as much as possible.

Abbreviations

COPD - Chronic Obstructive Pulmonary Disease

EF - peak expiratory flow

FEV₁ - forced expiratory volume in 1 second

ILO - inducible laryngeal obstruction

HR - heart rate

LABA - long-acting beta-adrenoceptor agonists

OS - oxyhemoglobin saturation

RR - respiratory rate

SABA - short-acting beta₂-adrenoceptor agonists.

Diagnostic and treatment guidelines

[Global Initiative for Asthma - Global Initiative for Asthma - GINA](#)

[Asthma Treatment & Management](#)

[Guidelines for diagnosis and management of bronchial asthma: Joint ICS/NCCP \(I\) recommendations](#)

[International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma](#)

[BTS/SIGN British guideline on the management of asthma](#)

[Asthma](#)