

Biomedical Science

Molecular Genetics



BMS 301 | Fall 2026-2027

Systematic and Cellular Pathology

Obstructive Lung Diseases

جميع الأوراق والمحتويات التابعة للمنصة محمية بموجب حقوق الملكية الفكرية.
يُمنع منعاً باتاً نسخ، أو نشر، أو مشاركة أي محتوى أو مستندات تخص المنصة بأي شكل
دون إذن مسبق. ويُعد أي تجاوز أو مخالفة لهذا القرار خرقاً قانونياً يعرض مرتكبه للمساءلة
والملاحقة القانونية الفورية

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Respiratory System Review

Before we discuss obstructive lung diseases, let us first review the **anatomy, normal histology, and physiology** of the respiratory system.

DRAWING TASK

After watching the video, create a detailed drawing of the respiratory system with special attention to the **internal structures of the lungs**. Your drawing should include and clearly label:

1 · Upper Respiratory Tract

Nasal cavity



Pharynx



Larynx



Trachea

2 · Lower Respiratory Tract

- **Bronchi** – the main branches from the trachea
- **Bronchioles** – smaller branching airways
- **Terminal bronchioles** – the smallest airways without alveoli
- **Respiratory bronchioles** – airways with some alveoli
- **Alveolar ducts** – passages leading to alveolar sacs
- **Alveoli** – tiny air sacs where gas exchange occurs
- **Alveolar sacs** – clusters of alveoli



Obstructive and Restrictive Lung Diseases

Obstructive Lung Diseases

- Characterized by **increased resistance to airflow**, primarily due to partial or complete obstruction at any level of the tracheobronchial tree.
- The hallmark feature is **difficulty with expiratory airflow**, leading to **air trapping** and **hyperinflation** of the lungs.
- **Examples:** Asthma, Chronic Obstructive Pulmonary Disease (COPD): chronic bronchitis, emphysema, bronchiectasis.

Restrictive Lung Diseases

- Characterized by **reduced lung compliance** and **decreased total lung capacity (TLC)**. The primary defect is an **inability of the lungs to expand fully**, which limits the volume of air that can be inhaled.
- May result from parenchymal lung disease (**intrinsic**) or from extrapulmonary causes affecting the chest wall, pleura, or neuromuscular function (**extrinsic**).
- **Examples:** Idiopathic pulmonary fibrosis, obesity, neuromuscular disorders.

01

SIDE-BY-SIDE

Key Differences: Obstructive vs Restrictive

Feature	Obstructive Lung Diseases	Restrictive Lung Diseases
Primary Defect	Increased resistance to airflow (especially during expiration)	Decreased lung compliance and reduced lung expansion
Airflow Pattern	Difficulty exhaling → prolonged expiration, air trapping	Difficulty inhaling → reduced lung volumes
Spirometry Findings	↓ FEV ₁ , ↓ FEV ₁ /FVC ratio (<70%)	↓ TLC, ↓ FVC, normal or ↑ FEV ₁ /FVC ratio
Pathophysiology	Narrowed or obstructed airways	Stiff lungs, chest wall, or weak respiratory muscles
Examples	Asthma, COPD, emphysema	Pulmonary fibrosis, scoliosis, neuromuscular



Chronic Obstructive Pulmonary Disease (COPD)

WHO DEFINITION

"A **common, preventable and treatable disease** that is characterized by **persistent respiratory symptoms and airflow limitation** that is due to airway and/or alveolar abnormalities caused by exposure to noxious particles or gases."

4th

cause of death worldwide, according to the WHO

35–50%

of **heavy cigarette smokers** develop COPD

2

major forms: **emphysema** and **chronic bronchitis**

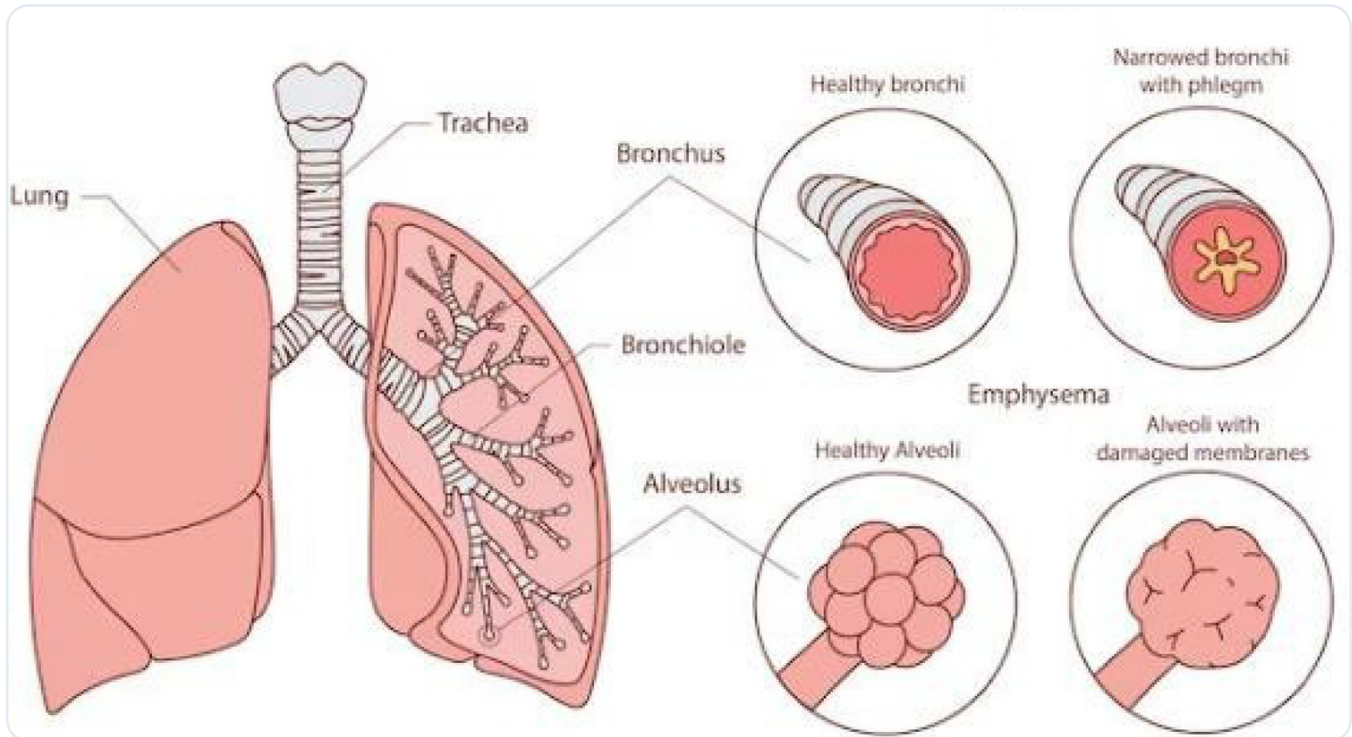
1

shared etiology for both: **tobacco smoking**

02

COPD

Chronic Obstructive Pulmonary Disease



Healthy vs narrowed bronchi with phlegm, and healthy alveoli vs alveoli with damaged membranes (emphysema).

Source: Freepik

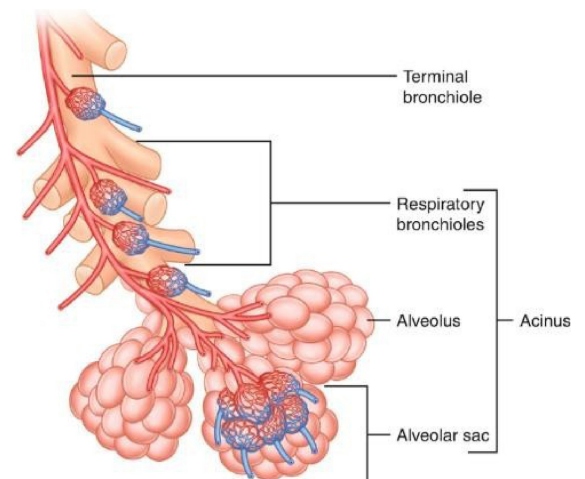


Emphysema

DEFINITION

Irreversible enlargement of the airspaces distal to the terminal bronchioles, accompanied by **destruction of their walls**.

Anatomic site: Lobule / cluster of acini — the terminal respiratory unit.



CLASSIFIED BY THE PART INVOLVED INTO FOUR

a) Centriacinar

b) Panacinar

c) Paraseptal

d) Irregular



Emphysema Classification

a Centriacinar (centrilobular)

95% OF CASES

UPPER LOBES

Most common form; common in **heavy smokers**. The **central or proximal part** of the acini is enlarged and damaged, while the distal part is not affected.

b Panacinar

A1-ANTITRYPSIN DEFICIENCY

LOWER LOBES

Gets worse by smoking. The **whole acinus** is affected (from the respiratory bronchiole to the terminal alveoli).

c Distal acinar (Paraseptal)

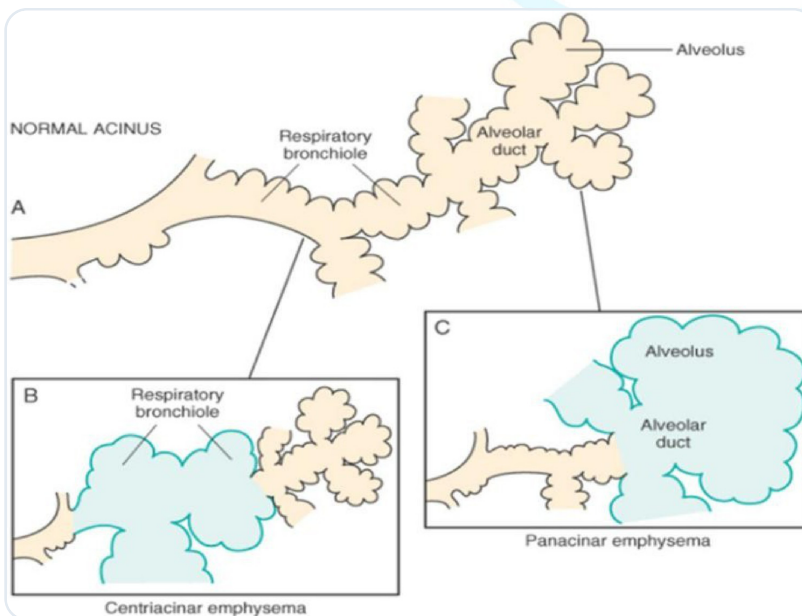
The proximal part of the acini is normal, while the **distal part** is predominantly involved.

d Irregular (air space enlargement with fibrosis)

As the name suggests, the acinus is **irregularly involved**.

MICROSCOPIC FINDINGS

Normal vs Centriacinar vs Panacinar



A) Normal lung · B) Centriacinar · C) Panacinar

Robbins & Cotran, Fig 15-6 (Saunders, 2004) · Medpics – UC San Diego

B) Centriacinar

Dilation affects the **respiratory bronchioles**, while the distal alveoli are initially spared, though severe disease may affect the distal acinus.

C) Panacinar

Acini are **uniformly enlarged** from the respiratory bronchiole to the terminal alveoli.

03

EMPHYSEMA

Etiology & Risk Factors

a) Primary causes

- Cigarette smoking.
- Alpha-1-antitrypsin deficiency (genetic).

b) Contributing factors

- Air pollution.
- Repeated respiratory tract infections.

RISK FACTORS



Occupation exposure



Exposure to "secondhand" smoke



Infection



Air pollution



Genetic abnormalities



Asthma



Severe respiratory infection in childhood



Pathogenicity of Emphysema

1) TOXIC INJURY AND INFLAMMATION

Cigarette smoke & noxious particles



Damage respiratory epithelium



Inflammation



Parenchyma destruction

- Associated with **high levels of inflammatory mediators** at the site of destruction — **tumor necrosis factor (TNF), interleukin 8 (IL-8), leukotriene B** and others — released by the epithelial cells and macrophages.
- Through these mediators, **inflammatory cells are attracted from the blood circulation**, increasing the inflammatory process and changing the structure (growth factors).

04

PATHOGENICITY OF EMPHYSEMA

Imbalance, Oxidants & Infection

2) Protease and Antiprotease Imbalance

Proteases, which can break down connective tissue, are released from epithelial cells and inflammatory cells. Patients who develop emphysema have an **impairment in the mechanism that prevents protease activity (antiprotease)** — this can be related to genetic causes.

3) Oxidative Stress

Tobacco smoke + Alveolar damage + Inflammatory cells → Oxidants

Together they produce oxidants, leading to **tissue damage, endothelial cell dysfunction and inflammation**.

NRF2 gene — a transcription factor that acts as a sensor for the level of oxidants and increases the expression of genes that regulate and protect the cell from oxidant damage (NRF2 is inactivated in some cases).

4) Infection

May lead to **progression** of the condition — either viral or bacterial infection.



Alpha-1-Antitrypsin Deficiency

Normal role

- Some patients with emphysema have a genetic deficiency in **alpha-1-antitrypsin**, the **inhibitor of elastase activity** (proteases).
- Normally available in the serum, tissue fluids, and macrophages.
- Elastase is secreted by the **neutrophil** during the inflammation process.
- When elastase is released, alpha-1-antitrypsin inhibits its activity and **prevents alveolar wall destruction**.

DEFICIENCY LEADS TO

Uncontrolled elastase activity



Excess elastin breakdown



Loss of elastic recoil (elastic fibres in the alveolar wall), which keeps the small airways open



Collapse of respiratory bronchioles during expiration



Emphysema — Clinical Manifestations



Dyspnea (labored breathing)

Difficulty or impaired breathing that requires more effort than usual



Shortness of breath



Decreased exercise capacity



Reduced exhalation velocity & volume

Velocity is the speed of air leaving the body



Hyperinflated lungs



Chronic Bronchitis

DEFINITION

"Clinically **persistent cough with sputum production** for at least **3 months** in at least **2 consecutive years** in the absence of any identifiable cause."

Associated with progressive lung dysfunction.

Pathogenicity starts by exposure to toxic or irritating inhaled substances (**tobacco, dust, cotton, and silica**).

CONTRIBUTORS TO PATHOGENICITY — A) MUCUS HYPERSECRETION

- **Early stage · large airways**
Hypersecretion of mucus with **enlargement of the submucosal glands** in the trachea and bronchi.
Mediators: **histamine and interleukin 13 (IL-13)**.
- **Progression · small airways**
Marked increase in the number of **goblet cells** (which also produce mucus), mainly in the small bronchi and bronchioles.
- **Result**
Obstruction of airways. The mechanism is thought to be a defence mechanism against tobacco smoke and other pollutants.

05

CHRONIC BRONCHITIS

Pathogenicity (continued)

b Acquired CFTR Dysfunction

(Cystic fibrosis transmembrane conductance regulator.) Previous literature indicates that smoking results in **acquired cystic fibrosis**, which results in secretion of **abnormal dehydrated mucus** — consequently increasing the severity of chronic bronchitis.

c Inflammation

Inhalation of toxic material → Cell damage → Acute & chronic inflammation

+ Recruitment of the related inflammatory cells (**neutrophils, lymphocytes and macrophages**). The prolonged inflammation period results in **fibrosis of small airways** (bronchioles and small bronchi).

d Infection

Not responsible for initiating the condition, but **contributes to the progression**.



Chronic Bronchitis — Morphology

Macroscopic

- **Hyperemia** — increased blood flow to the site, appearing as redness, swelling and warmth.
- Swelling.
- Edema of the mucous membranes.
- Excessive secretions in small airways.

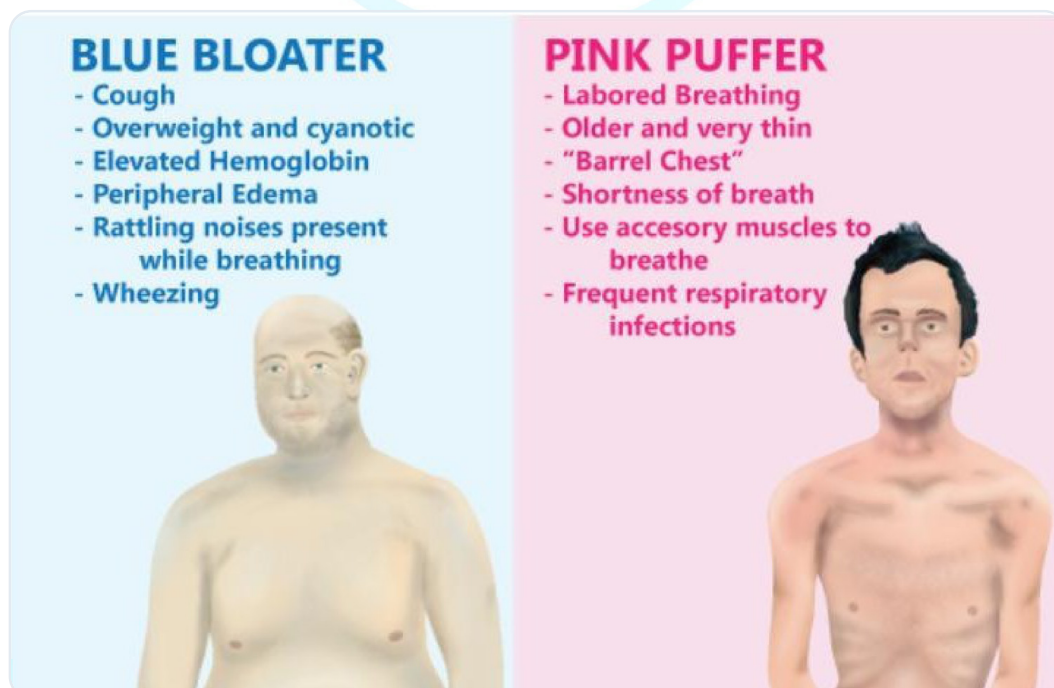
Microscopic

- **Chronic inflammation** — indicated by the presence of lymphocytes and macrophages.
- Thickening of the bronchiolar wall as a result of **smooth muscle hypertrophy**.
- **Goblet cell hyperplasia**.
- Enlargement of mucus-secreting glands.



COPD — Clinical Features

Aspect	Bronchitis	Emphysema
Age / Years of Onset	Usually >40 years	Usually >50 years
Dyspnea (labored breathing)	Mild to moderate; mainly during exertion	Severe and progressive; eventually at rest
Cough	Prominent productive cough; thick, purulent sputum	Minimal or absent cough; little to no sputum
Infections	Frequent respiratory infections	Less frequent infections
Respiratory Insufficiency	Late in disease course	Early and progressive; chronic hypoxemia
Airway Resistance	Markedly increased — due to inflammation and mucus	Normal to mildly increased — mainly due to loss of support (elastic fibres)
Elastic Recoil	Normal or slightly reduced	Severely reduced; loss of elastic fibres
Chest Radiograph	Increased lung markings · thickened bronchial walls · normal heart size	Hyperinflation · flattened diaphragm · enlarged heart shadow
Appearance	Often overweight	Thin, cachectic build · barrel-shaped chest · pursed-lip breathing



Blue Bloater vs Pink Puffer. Source: EdTech Books

06

COPD & ASTHMA

Diagnosis — Spirometry

SPIROMETRY TEST

A common, **non-invasive pulmonary function test** that measures **how much air your lungs can hold and how quickly you can breathe air out.**

HOW

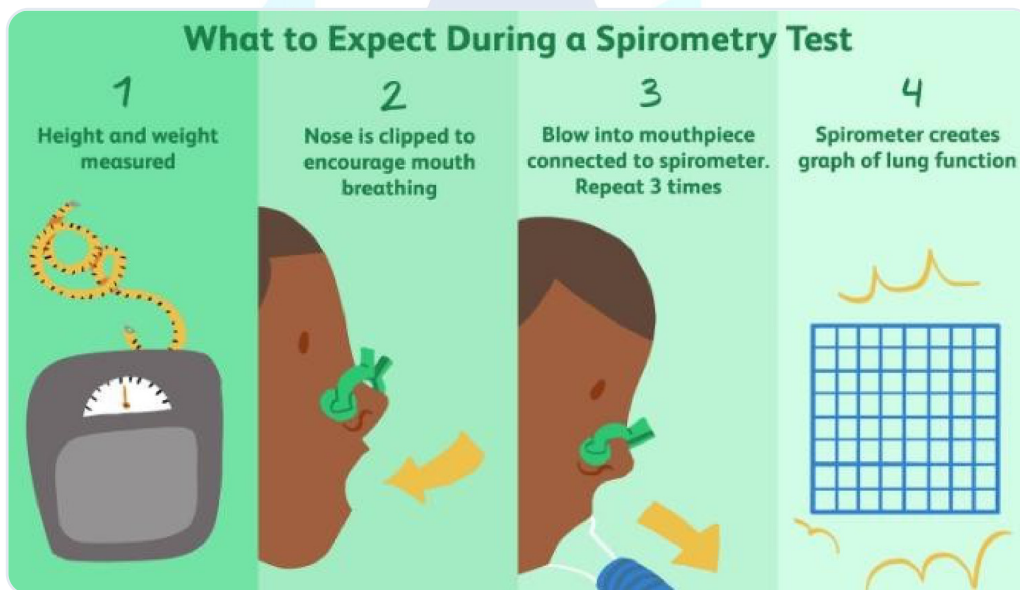
You breathe forcefully into a tube attached to a spirometer, while a nose clip prevents air leaks.

WHY

Helps diagnose lung conditions like **asthma and COPD**, monitor lung disease progression, and check overall lung health.

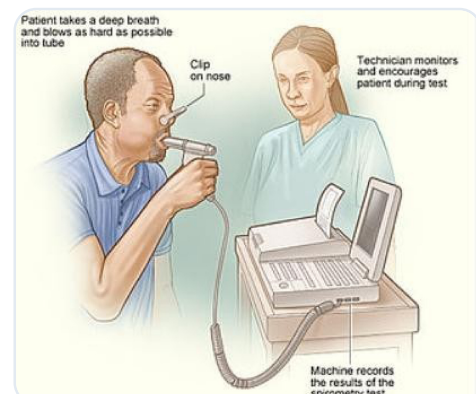
DETECTS

Two distinct categories of abnormal breathing: **obstructive** (airflow impeded) and **restrictive** (lung expansion limited).



What to expect during a spirometry test

Spirometer designs — multiple designs exist, each employing different measurement technologies such as **pressure sensors, ultrasonic detection systems, or water-based gauges.**



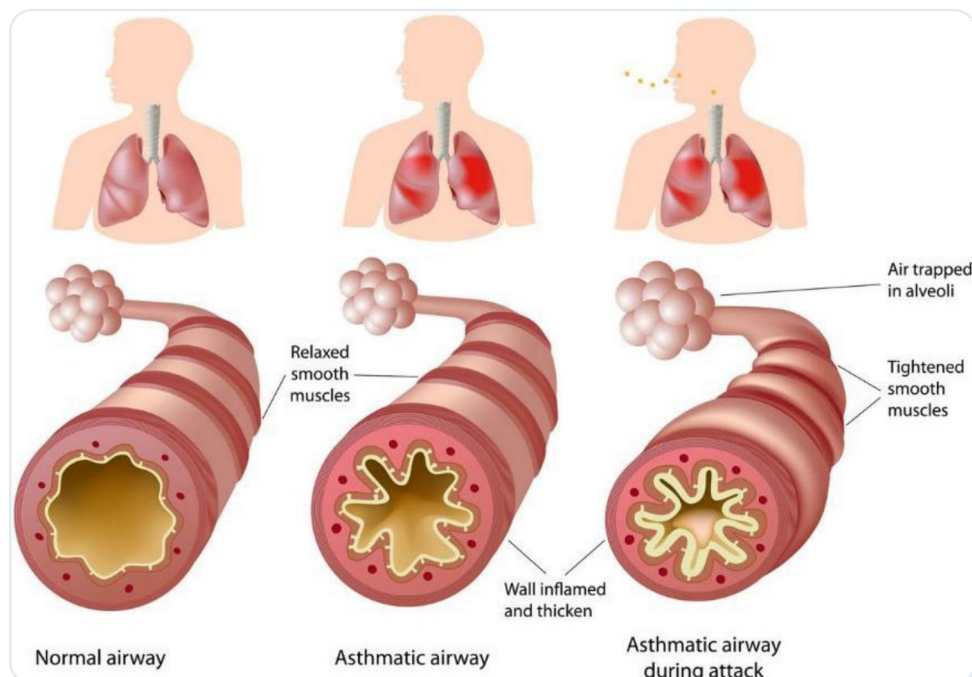
Source: Wikipedia — Spirometer



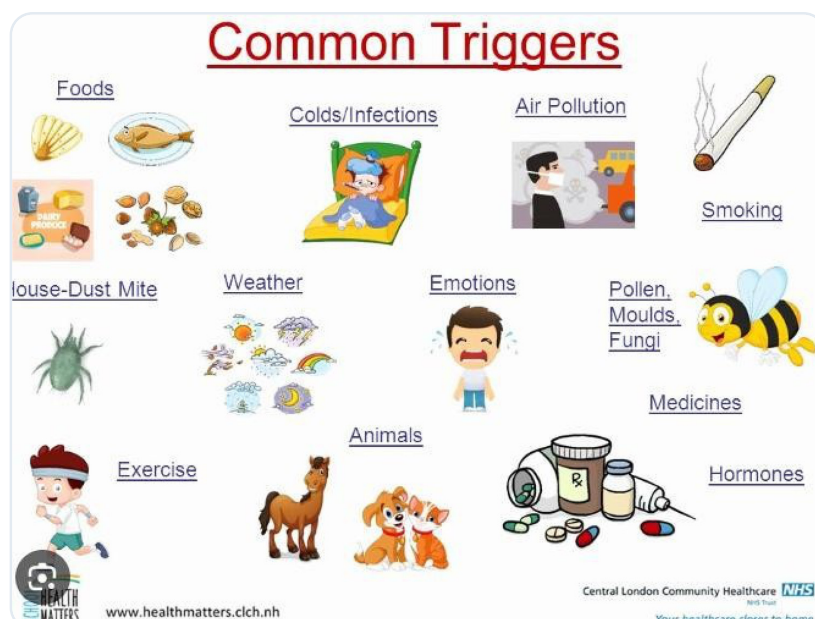
Asthma

DEFINITION

"A **heterogeneous disease**, usually characterized by **chronic airway inflammation** and **variable expiratory airflow obstruction**, that produces symptoms such as wheezing, shortness of breath, chest tightness, and cough, which vary over time and intensity."



Normal airway · asthmatic airway · asthmatic airway during attack. Source: AsthmaMD



Common triggers

07

MAJOR SUBTYPES OF ASTHMA

Atopic & Non-Atopic Asthma

SUBTYPE 1 Atopic Asthma

Classic example of a **hypersensitivity reaction mediated by IgE antibodies.**

- Starts in **childhood**.
- Triggered by environmental factors: food, pollens, dust, cockroach.
- In contribution with other cofactors such as respiratory viral infection (proinflammatory).
- **Positive family history** of asthma.
- Skin test with antigen results in an immediate **wheal and flare** reaction.
- **Diagnosis:** level of serum IgE, or serum radioallergosorbent tests (RASTs).
- **RASTs** assess the presence of IgE antibodies that target a specific allergen.

SUBTYPE 2 Non-Atopic Asthma

- **No evidence** of allergen sensitization.
- Skin test usually **negative**.
- Family history of asthma is less common.
- Respiratory viral infection is common.
- Other contributors to airway inflammation: **tobacco smoke, air pollutants, sulfur dioxide, ozone, nitrogen dioxide.**
- An asthma attack can be triggered by exposure to **cold, and even just exercising.**



Drug-Induced & Occupational Asthma

SUBTYPE 3

Drug-Induced Asthma

- Several medications may provoke asthma.
- Some individuals are sensitive to **aspirin** and non-steroidal anti-inflammatory medications.
- These individuals may experience an asthma attack in addition to **urticaria**.

SUBTYPE 4

Occupational Asthma

May be triggered by:

- Fumes (epoxy resins, plastics).
- Organic and chemical dust (wood, cotton, platinum).
- Gases · Chemicals (formaldehyde).
- Small amounts of these chemicals may induce an attack.

SIDE NOTE · STEROIDAL ANTI-INFLAMMATORY DRUGS

Also known as **corticosteroids** or steroids — medications that reduce inflammation and suppress the immune system.

1

Man-made versions of **cortisol**, a hormone naturally produced by the body.

2

Common examples: **hydrocortisone** and **dexamethasone**.

3

Used to treat inflammatory conditions like asthma and inflammatory bowel disease.

SOME REFERENCES CLASSIFY ASTHMA BY TRIGGER TYPE

Allergic vs Non-Allergic Triggers

Allergic

- **Outdoor allergens**, such as pollens from grass, trees and weeds.
- **Indoor allergens**, such as pet dander, dust mites and mold.

Non-Allergic

- Certain drugs (beta blockers, aspirin) and food additives (sulphites, tartrazine, MSG, aspartame).
- Irritants in the air: smoke, chemical fumes and strong odors.
- Colds, the flu or other illnesses · Stress.
- Exercise (although people with asthma can benefit from some exercise).
- Weather: cold air or extremely dry, wet or windy weather.

Source: Asthma Triggers | AsthmaMD



Pathogenesis — Atopic Asthma

Atopic asthma, the **most common form** of the disease, is caused by a **Th2-mediated IgE response to environmental allergens** in genetically predisposed individuals. Several components contribute to the pathogenicity.

1) IMMUNE COMPONENT

Environmental allergen (harmless) →

Exaggerated response led by Th2 cells →

Cytokines: inflammation + B cells make IgE

IL-4

Production of **IgE** by B cells.

IL-5

Recruits **eosinophils**.

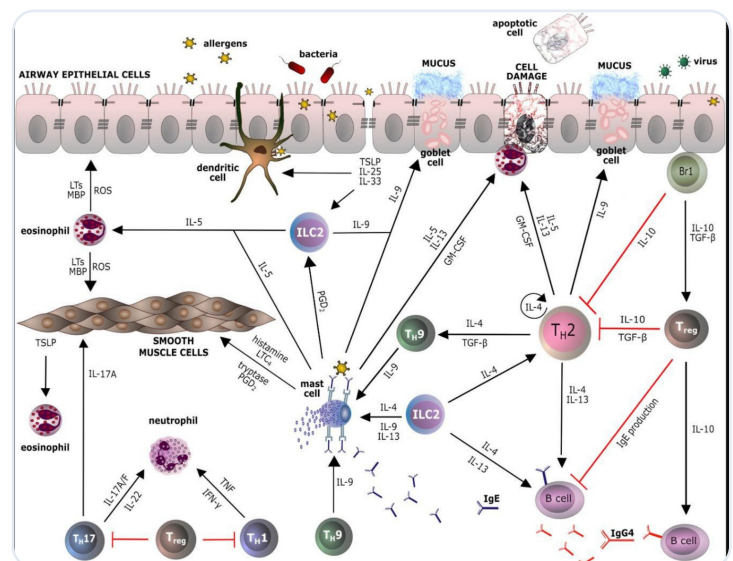
IL-13

Stimulates **mucus secretion** from bronchial submucosal glands + promotes B cells to produce IgE.

BACKGROUND

What Are Interleukins?

- **Interleukins (ILs)** are proteins made by immune cells and other body cells that act as **signaling molecules (cytokines)** to facilitate communication between cells.
- They are critical for a functioning immune system, helping regulate inflammation and immune responses to infections and injuries.
- Diverse functions: promoting the growth and differentiation of immune cells and coordinating immune cell movement.

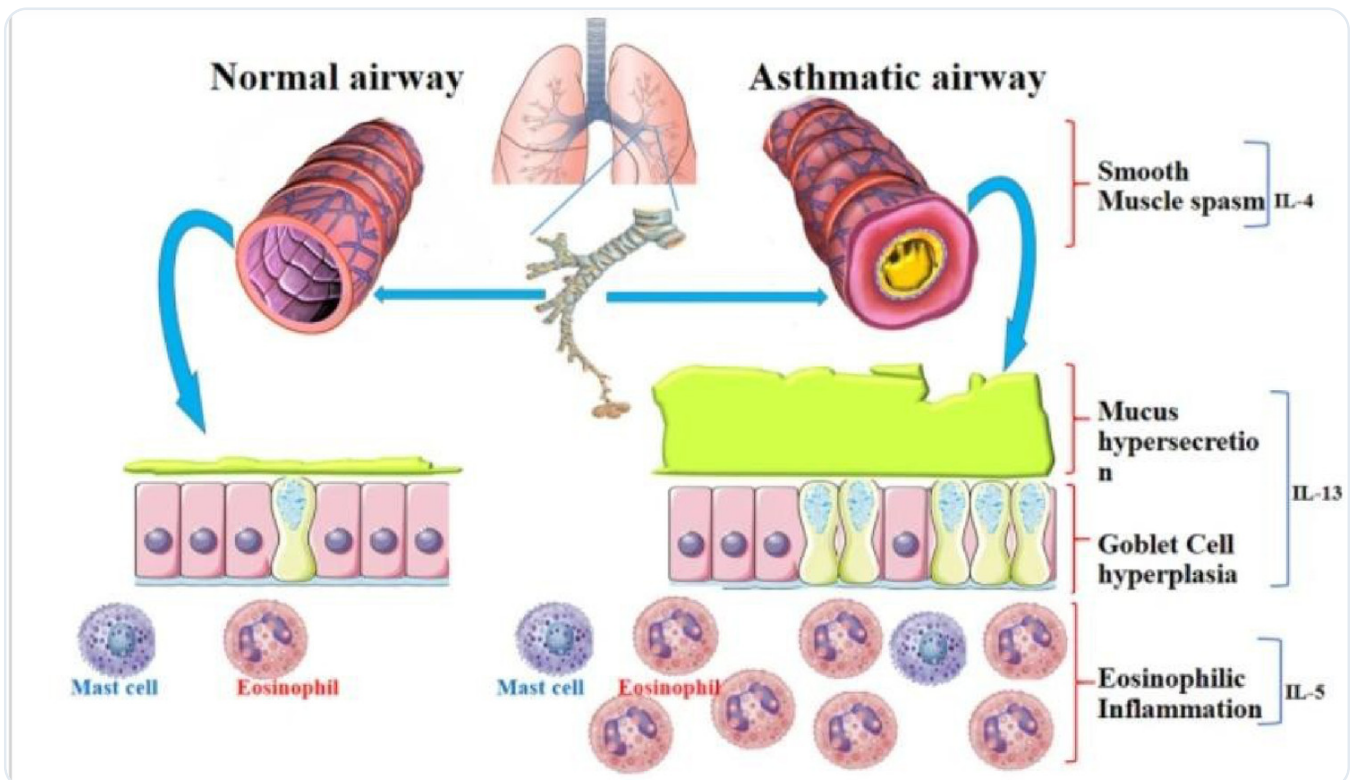


Akdis et al., J Allergy Clin Immunol 138(4):984–1010

08

ATOPIC ASTHMA

Normal vs Asthmatic Airway



Athari, S.S. Targeting cell signaling in allergic asthma. Sig Transduct Target Ther 4, 45 (2019)

Asthma, a chronic inflammatory airway disease, is characterized by **eosinophilic inflammation, mucus hypersecretion, goblet cell hyperplasia, airway hyper-responsiveness, and breathlessness**. Th2 cell immune responses are dominant. **IL-4** has a role in B-cell IgE isotype switching and upregulation of FcεRI on mast cells, which release histamine and other mediators that lead to allergic symptoms and smooth muscle spasm. **IL-5** leads to activation, migration and accumulation of eosinophils to the airway. **IL-13** has a main role in mucus hypersecretion and goblet cell hyperplasia and promotes AHR.

PATHOGENESIS CONTINUES

- 1 The **T cell and the epithelial cell** continue recruiting more T cells and eosinophils to the site, amplifying the reaction.
- 2 **IgE binds to Fc receptors** on the surface of mast cells found in the submucosal layer.
- 3 Upon **repeated exposure** to the allergen, the mast cell releases the content of its granules and other cytokines, which collectively result in the **early phase and late phase reactions**.



Atopic Asthma — Early Phase

CHARACTERIZED BY

- a Bronchoconstriction
- b Increased mucus production
- c Variable vasodilation
- d Increased vascular permeability

- Bronchoconstriction is triggered by **cytokines released by mast cells** and other cells, which directly affect subepithelial vagal receptors.
- Key chemicals: **histamine, leukotrienes, and prostaglandins** — cause airway smooth muscles to contract.
- Contraction leads to **bronchospasm**, a sudden narrowing of the airways.

Early-phase symptoms: coughing, wheezing, shortness of breath, chest tightness.



Atopic Asthma — Late Phase

CHARACTERIZED BY

- **Recruitment of leukocytes**, mainly eosinophils, neutrophils and additional T cells.
- Beside Th2, **Th17 (IL-17)** is present — responsible for recruiting neutrophils.
- The efficacy of pharmacologic interventions reflects the role of the mediators (cytokines) in the pathogenicity of asthma (different mediators contribute).

MEDIATORS CRUCIAL FOR THE BRONCHOSPASM

- a **Leukotrienes C4, D4 and E4** — implicated in bronchoconstriction, vascular permeability and increased mucus secretion.
- b **Acetylcholine** — released by intrapulmonary parasympathetic nerves; results in smooth muscle constriction.
- c **IL-5 antagonists** — effective in treating asthma related to eosinophilia.
- d **Galectin-10 (GAL10)** — released from eosinophils; induces inflammation and mucus production.

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LATE PHASE (CONTINUED)

Minor Mediators & Genetics

Mediators with minor contribution

- a** **Histamine** — bronchoconstrictor.
- b** **Prostaglandin D2** — bronchoconstriction and vasodilation.
- c** **Platelet Activating Factor** — promotes aggregation of platelets and release of serotonin.

Without inhibitors or antagonists

IL-4

IL-13

TNF

... etc.

CONCLUSION

Several mediators are implicated in an asthma attack, and they **vary from individual to individual** or according to the different type of asthma.



2) Genetic Susceptibility

Multigenic

Atopic asthma is multigenic.

Allergy

Usually associated with other allergies (eczema, allergic rhinitis, etc.).

GENETIC VARIANTS ASSOCIATED WITH ASTHMA



Chromosome 5q locus

Close to the gene cluster encoding the cytokines **IL-3, IL-4, IL-5, IL-9, IL-13**, and the IL-4 receptor.



IL-13 polymorphisms

The **most common genetic variation** in asthma and allergic patients.



IL-4 receptor gene variant

Related to serum IgE and asthma.



IL-33 and its receptor ST2

Variants induce the production of Th2 cytokines.



3) Environmental Factors

1 A disease of industrialized countries (cities)

Two hypotheses were proposed:

Airborne pollutants (allergens) are more common in cities.

Limited exposure to microbes during early life results in less protection from allergens later in life.

2 Infections

Both viral and bacterial infections exacerbate the disease — **10–30-fold** increase in the disease becoming persistent or severe.

3 Airway remodeling

Repeated exposure to allergen and immune response results in:

Smooth muscle hypertrophy & hyperplasia

Epithelial damage

Increased vascularity

Mucous gland enlargement

Subepithelial fibrosis



Clinical Features

- An asthma attack lasts up to **several hours**.
- In some patients the cardinal symptoms (**dyspnea, wheezing, coughing**) may be present at a low level constantly.
- In severe forms, the paroxysm may persist for **several days and even weeks**.



Diagnosis

- Demonstration of increased airflow obstruction.
- Difficulty with exhalation (**wheeze**).
- Identification of **eosinophils** in a peripheral blood sample.
- Sputum microscopy: **Curschmann spirals** and **Charcot-Leyden crystals**.

10

ASTHMA DIAGNOSIS

Sputum Microscopy Findings

**Charcot-Leyden Crystals**

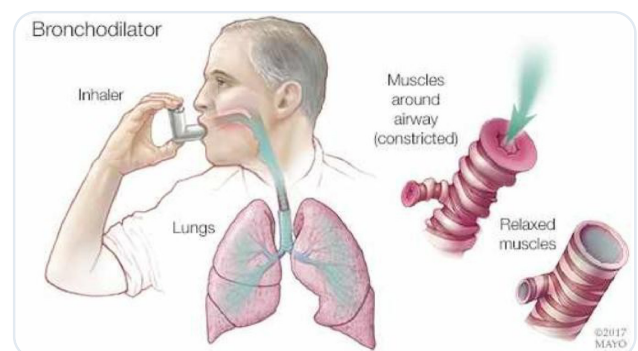
Result from the **breakdown of eosinophils**; may be seen in the sputum of patients with allergic diseases such as asthma. Colorless, slender and pointed; stain **purplish-red in trichrome stain**.

**Curschmann Spirals**

Microscopic finding in the sputum of patients with **bronchial asthma** — **twisted, condensed mucus** several centimeters long.

**Asthma — Treatment**

- 1 Standard therapy: bronchodilators** — relax the smooth muscles around the airways, widening the passages (bronchi and bronchioles) and making it **easier to breathe**.
- 2 Glucocorticoids** — steroid hormones naturally produced by the adrenal glands (like cortisol); reduce inflammation and suppress the immune system. Used for asthma, eczema and rheumatoid arthritis.
- 3 Novel therapies** — targeting inflammatory mediators such as IL-15 using specific antibodies.



Source: Mayo Clinic



To Summarise...

OBSTRUCTIVE <70%

Obstructive vs Restrictive

- Obstructive: ↑ resistance to airflow, difficulty exhaling
- ↓ FEV₁ and ↓ FEV₁/FVC ratio (<70%)
- Restrictive: ↓ compliance, ↓ TLC, normal or ↑ FEV₁/FVC

COPD 4th

Cause of death worldwide (WHO)

- Two forms: emphysema and chronic bronchitis
- 35–50% of heavy smokers develop COPD
- Shared etiology: tobacco smoking

EMPHYSEMA 95%

Centriacinar — most common

- Irreversible enlargement of airspaces distal to terminal bronchioles
- Panacinar: α1-antitrypsin deficiency, lower lobes
- Protease/antiprotease imbalance & oxidative stress

BRONCHITIS 3 mo × 2 yr

Persistent productive cough

- Mucus hypersecretion & goblet cell hyperplasia
- Acquired CFTR dysfunction → dehydrated mucus
- Inflammation → fibrosis of small airways

ASTHMA 4

Major subtypes

- Atopic, non-atopic, drug-induced, occupational
- Atopic: Th2-mediated IgE response to allergens
- IL-4 → IgE · IL-5 → eosinophils · IL-13 → mucus

DIAGNOSIS Spirometry

Diagnosis & treatment

- Eosinophils in peripheral blood
- Curschmann spirals & Charcot-Leyden crystals in sputum
- Bronchodilators, glucocorticoids, anti-mediator antibodies

THE OBSTRUCTIVE HALLMARK

Obstruction of the tracheobronchial tree



Difficulty with expiratory airflow



Air trapping



Hyperinflation