PULMONOLOGY & RESPIRATORY MEDICINE REFERENCE

Asthma

Airway Pathophysiology, Inflammatory Endotypes, Diagnostic Testing, and Stepwise Management

Asthma is a chronic, heterogeneous inflammatory disorder of the conducting airways characterized by variable expiratory airflow limitation and bronchial hyperresponsiveness. Clinically, it manifests with recurrent episodes of wheezing, shortness of breath (dyspnea), chest tightness, and cough that fluctuate over time and in intensity, often worsening at night, upon waking, or following trigger exposure.

> **Modern Treatment Standard:** Because underlying airway inflammation is present even in mild or intermittent asthma, Global Initiative for Asthma (GINA) guidelines no longer recommend short-acting beta-agonist (SABA)-only therapy. All adolescents and adults with asthma should receive inhaled corticosteroid (ICS)-containing treatment—either as needed via ICS–formoterol or daily—to reduce the risk of severe exacerbations.

1. Pathophysiology & Airway Mechanics

Airflow obstruction in asthma is driven by three interrelated structural and functional processes within the bronchial tree, ranging from central bronchi down to small peripheral airways:

- **Chronic Airway Inflammation:** Infiltration of the airway mucosa by activated mast cells, eosinophils, T-helper 2 (Th2) lymphocytes, type 2 innate lymphoid cells (ILC2), and neutrophils, releasing histamine, cysteinyl leukotrienes, prostaglandins, and pro-inflammatory cytokines (IL-4, IL-5, IL-13).
- **Bronchial Hyperresponsiveness & Smooth Muscle Contraction:** Exaggerated bronchoconstriction in response to otherwise benign stimuli (cold air, exercise, allergens, viral infections, pollutants). Histologically, smooth muscle hypertrophy and hyperplasia amplify luminal narrowing.
- **Mucus Hypersecretion & Airway Remodeling:** Goblet cell hyperplasia and submucosal gland enlargement produce thick, tenacious mucus plugs. Over time, persistent inflammation can cause permanent structural remodeling, including subepithelial basement membrane fibrosis, angiogenesis, and fixed airflow obstruction.

2. Major Clinical Phenotypes & Endotypes

Asthma is broadly stratified into **Type 2 (T2-high)** and **Non-Type 2 (T2-low)** inflammatory endotypes, which guide targeted biologic therapy in severe disease.

Phenotype / Endotype	Biomarkers & Mechanism	Clinical Features & Triggers
Allergic Asthma (T2-High)	Elevated serum IgE, allergen-specific IgE, blood/sputum eosinophils, elevated FeNO	Most common phenotype; typically begins in childhood alongside personal or family history of atopy (allergic rhinitis, eczema, food allergies). Responds well to inhaled corticosteroids.
Non-Allergic Eosinophilic Asthma (T2-High)	Marked blood/sputum eosinophilia, elevated FeNO (driven by ILC2 and IL-5)	Often adult-onset, severe, and relatively refractory to standard-dose ICS. Frequently associated with chronic rhinosinusitis with nasal polyposis (CRSwNP) and Aspirin-Exacerbated Respiratory Disease (AERD).
Non-Type 2 / Neutrophilic Asthma (T2-Low)	Normal eosinophils and FeNO; neutrophilic or paucigranulocytic sputum	Associated with adult onset, obesity, smoking, occupational exposures, and recurrent respiratory infections. Less responsive to corticosteroids; benefits from weight management and macrolides.
Exercise-Induced Bronchoconstriction (EIB)	Osmotic/thermal airway drying triggers mast cell mediator release	Transient airway narrowing occurring 5–15 minutes after vigorous exertion, particularly in cold, dry air. Prevented by pre-exercise ICS–formoterol or SABA.

3. Diagnostic Evaluation & Objective Testing

A definitive diagnosis requires both a compatible symptom history and objective demonstration of variable expiratory airflow limitation before initiating long-term controller therapy whenever possible.

- **Spirometry with Bronchodilator Reversibility:** The primary diagnostic test. Airflow obstruction is indicated by a reduced FEV_1/FVC ratio (typically <0.75–0.80 in adults, <0.90 in children). A positive bronchodilator response is confirmed by an increase in FEV_1 of **>12% and >200 mL** from baseline 10–15 minutes after inhaling a rapid-acting bronchodilator (e.g., albuterol).
- **Peak Expiratory Flow (PEF) Monitoring:** Twice-daily serial PEF measurements over 2 weeks showing an average daily diurnal variability **>10%** in adults (>13% in children) supports the diagnosis when spirometry is unavailable.
- **Bronchoprovocation Challenge Testing:** Used when baseline spirometry is normal despite high clinical suspicion. Inhaled methacholine, histamine, mannitol, or standardized exercise challenge confirms bronchial hyperresponsiveness (e.g., ≥20% drop in FEV_1 with methacholine).
- **Adjunctive Biomarkers:** Fractional exhaled nitric oxide (FeNO ≥25–50 ppb), peripheral blood eosinophil count (≥150–300 cells/μL), and allergy skin-prick or specific IgE testing help characterize T2 inflammation and guide biologic selection.

4. Stepwise Management & Acute Exacerbations

Long-term management balances symptom control with risk reduction through a continuous cycle of assessment, treatment adjustment, and review of inhaler technique and trigger avoidance.

Stepwise Maintenance & Reliever Therapy (GINA Track 1 Preferred)

- **Steps 1–2 (Mild / Infrequent Symptoms):** As-needed low-dose **ICS–formoterol** (e.g., budesonide–formoterol) taken solely for symptom relief and prior to exercise, reducing severe exacerbation risk by over 60% compared to SABA alone.
- **Step 3 (Daily Symptoms or Nocturnal Awakening):** Low-dose maintenance and reliever therapy (**MART**) using daily low-dose ICS–formoterol plus additional as-needed doses for relief.
- **Step 4 (Uncontrolled on Low-Dose MART):** Medium-dose maintenance ICS–formoterol plus as-needed ICS–formoterol reliever (or medium/high-dose ICS–LABA plus add-on long-acting muscarinic antagonist [LAMA] such as tiotropium or leukotriene receptor antagonist [LTRA] like montelukast).
- **Step 5 (Severe Uncontrolled Asthma):** High-dose ICS–LABA + LAMA, specialist phenotyping, and targeted monoclonal antibody biologics—anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL-4Rα (dupilumab), or anti-TSLP (tezepelumab)—prior to considering low-dose oral corticosteroids.

Acute Asthma Exacerbation Management

- **Severity Assessment:** Evaluate speech (phrases vs. single words), respiratory rate (>30/min), heart rate (>120 bpm), accessory muscle use, oxygen saturation (SpO_2 <90–92%), and PEF (<50% predicted indicates severe exacerbation). Warning signs of impending respiratory arrest include drowsiness, confusion, or a "silent chest" on auscultation.
- **First-Line Emergency Interventions:** Controlled supplemental oxygen (targeting SpO_2 93–95% in adults, 94–98% in children), repeated inhaled short-acting beta-2 agonists (albuterol) via MDI with spacer or nebulizer, inhaled ipratropium bromide for moderate-to-severe flares, and early systemic corticosteroids (oral prednisone 40–50 mg or IV methylprednisolone).
- **Refractory Severe Exacerbations:** Intravenous magnesium sulfate (2 g over 20 minutes) for severe non-responding bronchospasm, high-flow nasal oxygen, or non-invasive/invasive mechanical ventilation with permissive hypercapnia strategies if respiratory failure ensues.