Asthma Basics

Chapter 1: Airway Anatomy — Oropharynx to Alveoli

Welcome to Chapter One. In this chapter, we follow the path of air from the oropharynx to the alveoli.

Air enters the oropharynx — a shared passage for air and food — lined with **stratified squamous epithelium** for protection.

It then moves into the laryngopharynx, just above the laryngeal inlet, where air is directed **anteriorly** into the larynx and food is guided **posteriorly** into the esophagus.

Next is the larynx, or *voice box*. Functions: **air conduction**, **airway protection**, and **phonation**. The epiglottis closes during swallowing to prevent aspiration.

Below lies the trachea — supported by C-shaped cartilage rings — ending at the **carina**, where it splits into right and left main bronchi.

The right main bronchus is wider, shorter, and more vertical — the most common site for aspiration. The left is longer and more angled.

Each main bronchus divides into **lobar bronchi** (3 right, 2 left), then **segmental bronchi** supplying bronchopulmonary segments.

Smaller **bronchioles** have **no cartilage** and more smooth muscle; the last conducting portion is the **terminal bronchiole**.

Gas exchange begins in **respiratory bronchioles**, continues through **alveolar ducts**, and culminates in **alveolar sacs** and **alveoli**.

In the alveoli: **Type I pneumocytes** enable gas exchange; **Type II pneumocytes** produce surfactant; **alveolar macrophages** clear debris.

Chapter 2: Asthma Definition and Epidemiology

Asthma is a **heterogeneous** disease with **chronic airway inflammation**, **variable symptoms**, and **reversible airflow obstruction**.

It often starts with epithelial injury and release of **alarmins**: **IL-25**, **IL-33**, and **TSLP** which is **Thymic stromal lymphopoietin**. TSLP is primarily produced by airway epithelial cells in response to environmental triggers including allergens, viruses, bacteria, and air pollutants

Clinically, patients report wheeze, shortness of breath, chest tightness, and cough with these symptoms varying over time. Episodes result due to acute airway narrowing caused by swelling (edema), increased mucus, and bronchial smooth muscle constriction.

In the U.S., prevalence is about **7%**; heritability ranges **35–95%**, with higher risk from maternal history.

Phenotypes include cough-variant, exercise-induced, allergic, eosinophilic (Type 2), pediatric or adult onset, steroid-resistant, aspirin-induced, and obesity-related.

Spirometry demonstrates variable and reversible airflow limitation in asthma where FEV1 increases greater than 12% and and greater than 200 milliliters after bronchodilator

Peak Expiratory Flow is used for monitoring variability.

Bronchoprovocation, or methacholine challenge with a greater than 20% drop in FEV1 at low concentration supports diagnosis of asthma.

Fractional exhaled nitric oxide indicates type 2 (eosinophilic) and is a Direct marker of IL-13

Blood eosinophils greater than 150 to 300 is an indirect marker of airway eosinophilia.

Allergen-specific IgE indicates allergic asthma

COPD differs by being typically **neutrophilic** and **poorly reversible** with bronchodilators.

Chapter 3: Pathophysiology — Type 2 and Non–Type 2

Chronic inflammation leads to **airway remodeling**: subepithelial fibrosis, smooth muscle hypertrophy, mucus gland hyperplasia, and basement membrane thickening. Airway remodeling in asthma refers to structural changes in the airway architecture that develop from chronic inflammation and repeated injury-repair cycles. These changes include subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, goblet cell metaplasia with mucus hypersecretion, basement membrane thickening, and increased vascularity. Remodeling occurs in lower airways and primarily in mucosa and submucosa contributing to narrower airways and increased mucus.

Epithelial alarmins (TSLP, IL-25, IL-33) initiate downstream immune activation.

Type 2 asthma (T2-high): Th2 cells and ILC2s produce **IL-4**, **IL-5**, **IL-13** → eosinophilic inflammation, IgE production, mucus hypersecretion, and airway hyperresponsiveness. named for Type 2 T Helper cell lymphocyte. IgE production leads to allergic sensitization and mast cell degranulation.

These alarmins activate dendritic cells, Th2 cells, and ILC2 cells resulting in the production of IL-4, IL-5, and IL-13

IL-4, IL-5, and IL-13 drive IgE class switching of B cells where B cells switch from producing IgM, IgG, or IgA to producing IgE, and then eosinophil recruitment and activation, mucus hypersecretion, and airway hyperresponsiveness. IL13 is responsible for mucus hyperresponsiveness

Th2 cells are activated, especially in allergic asthma.

ILC2 cells which stands for Innate Lymphoid Cells type 2 are activated in both allergic and non-allergic asthma in type 2 asthma.

The **Key Cytokines Produced are IL-4**, **IL-5** and **IL-13** where IL13 causes Mucus hypersecretion, bronchial hyperresponsiveness, and goblet cell metaplasia

The **Effector Cells in type 2 asthma are Eosinophils**, **Mast cells** which Release histamine, and **B cells** which are responsible for IgE production in allergic asthma.

The **Clinical Manifestations are** Eosinophilic airway inflammation, Mucus hypersecretion, Bronchospasm and Airway hyperresponsiveness.

Type 2 Biomarkers are increased Blood eosinophils, increased Sputum eosinophils, increased Fractional Exhaled Nitric Oxide driven by IL-13, and increased Serum IgE in allergic phenotype.

Diagnosis of Type 2 asthma is seen when Blood eosinophils are greater than 300, fractional exhaled nitric oxide is greater than 25 and elevated total IgE.

Biomarkers: elevated **blood eosinophils**, **FeNO**, and **IgE** in allergic asthma.

Next is **Non–Type 2, or T2-low**: Th1/Th17 pathways with **IFN-γ**, **TNF-α**, **IL-17** → neutrophilic inflammation and often **steroid resistance**.

Non T2 is primarily Neutrophilic inflammation often associated with obesity, infection, pollution and steroid resistance where Poor response to corticosteroids is a hallmark.

In Non T2 asthma you see Increased neutrophils, absence of eosinophilia, low fractional exhaled nitric oxide, and low IgE.

Epithelial alarmins and environmental triggers activate Th1 and Th17 which produce interferon-y, Tumor necrosis factor-a, and IL-17 leading to neutrophilic inflammation. Mast cells and airway smooth muscle also contribute to hyperresponsiveness and remodeling in both pathways.

In non T2 asthma **Th1 cells** produce interferon-y, **Th17 cells** Produce IL-17 and **Type 3 ILCs** Produce IL-17.

The **Key Cytokines in non T2 asthma are IL-17** responsible for Neutrophil recruitment and interferon-y responsible for Neutrophilic inflammation.

The **Effector Cells are predominately Neutrophils** and also **Macrophages.**

Clinical Manifestations of non T2 asthma are Neutrophilic airway inflammation Often associated with infections, cigarette smoke, and pollution and May relate to low lung function, older age, altered airway microbiome, and high-dose ICS use.

The Non-Type 2 Biomarkersare increased Sputum neutrophils, Low to normal eosinophils, Low to normal fractional exhaled nitric oxide and Normal to low IgE.

The COMMON PATHOPHYSIOLOGICAL FEATURES for both T2 and non T2 are that the airway smooth muscle exhibits Hypercontractility, Mast cell infiltration and Airway hyperresponsiveness.

Structural Changes for both T2 and non T2 are Airway remodeling, Subepithelial fibrosis, Smooth muscle hypertrophy and Mucus gland hyperplasia.

Common endpoints across pathways: **hyperresponsiveness**, **smooth-muscle hypercontractility**, and **remodeling**.

Chapter 4: Diagnostics — Spirometry, Variability, Biomarkers

Diagnosis requires evidence of **variable expiratory airflow limitation**.

FEV1 (Forced Expiratory Volume in 1 second) is The volume of air forcefully exhaled in the first second. This is the single most important measurement in asthma. A reduced FEV1 indicates airflow obstruction but can occur in many lung diseases or with poor technique.

FVC (Forced Vital Capacity) is The total volume of air that can be forcefully exhaled after maximal inhalation. This helps distinguish obstructive from restrictive patterns.

FVC helps distinguish obstructive from restrictive patterns by serving as the denominator in the FEV1 to FVC ratio and by its absolute value where a low ratio with normal or high FVC indicates pure obstruction (typical of asthma), while a low FVC with normal ratio suggests restriction, and both abnormalities together indicate a mixed pattern.

Spirometry: **obstruction** if **FEV1 to FVC ratio** is below the lower limit of normal and **Reversibility**is confirmed if **FEV1** increases >12% and >200 mL after bronchodilator.

FVC reflects total exhaled volume; **Peak Expiratory Flow, or PEF** is useful for monitoring but less reliable for diagnosis.

- In **pure obstruction** (asthma, early COPD): FEV1 to FVC is low, but FVC is normal or even elevated
- In **possible restriction**: FEV1 to FVC is normal, but FVC is below the 5th percentile in adults or less than 80% predicted in children
- In **mixed pattern**: Both FEV FVC ratio and FVC are low

Why FVC Behaves Differently

In asthma and other obstructive diseases, **airway narrowing primarily affects flow rates (FEV1) rather than lung volumes (FVC)**. Patients can still inhale and exhale a normal total volume of air—it just takes longer to get out due to increased airway resistance. This is why the FEV_1/FVC ratio drops

FEV1 FVC ratio: The proportion of total lung capacity exhaled in the first second. **A reduced FEV1 FVC ratio compared with the lower limit of normal is the spirometric hallmark of expiratory airflow limitation**, distinguishing obstructive diseases (asthma, COPD) from restrictive patterns. Many modern spirometers include age-specific predicted values for the lower limit of normal.

PEF (Peak Expiratory Flow): The maximum flow rate during forced exhalation. While less reliable than spirometry, PEF is useful when spirometry is unavailable. The same meter must be used for serial measurements, as readings can vary by up to 20% between devices.

Demonstrating Variable Airflow Limitation

The hallmark of asthma is that **expiratory lung function varies over time to a greater extent than in healthy populations**—it may range from completely normal to severely obstructed in the same patient. According to the Global Initiative for Asthma, obtaining evidence of excessive variability is essential for diagnosis.

Bronchodilator responsiveness is a hallmark of asthma. In adults with typical asthma symptoms, an FEV 1 increase of greater than 12% AND greater than 200 mL after inhaling 200 to 400 mcg salbutamol indicates significant reversibility. In children, only the greater than 12% criterion is required. This dual threshold in adults helps distinguish clinically meaningful reversibility from normal variation, though overlap exists between health and disease.

Important caveat is that a **negative bronchodilator test does not rule out asthma**, particularly in patients with normal baseline lung function, since asthma's variability may not be present at every

Bronchoprovocation such as methacholine challenge supports diagnosis with ≥20% fall in FEV1 at low concentration.

Biomarkers: **FeNO** for Type 2 inflammation, **blood eosinophils**, **serum IgE**, and **sputum cell counts**. Tools: **ACT** and **ACQ** for control.

Asthma Control Test, or ACT ranges between 5 to 25 points with greater than or equal to 20 points meaning well controlled asthma.

Asthma Control Questionaire, or ACQ ranges from 0 to 6 points with less than or equal to 0.75 points meaning well controlled asthma

Chapter 5: Pharmacologic Strategy — Relievers, Controllers, Biologics

Medications are divided into **relievers** and **controllers**.

SABA provides rapid relief; **ICS** are foundational for control. **LABA** only with ICS. **LAMA** can be added in moderate to severe disease.

LTRA offers modest anti-inflammatory benefit. **Biologics** target pathways (anti-IgE, anti-IL-5, anti-IL-4Rα, anti-TSLP) for severe, phenotype-guided care.

Systemic steroids for exacerbations; minimize chronic use due to adverse effects.

Short-acting beta-agonists provide rapid bronchodilation for symptom relief and exercise prophylaxis.
Inhaled corticosteroids remain the most effective controllers, improving symptoms, lung function, and exacerbation risk.
LABAs offer prolonged bronchodilation but should **always** be paired with ICS, not used alone.
LAMAs provide M3 blockade and can be added for moderate to severe disease.
Leukotriene receptor antagonists, or LTRAs are oral options with modest anti-inflammatory effect, helpful in mild disease or when an oral route is preferred.
Biologics target defined pathways such as anti-IgE, anti-IL-5, anti-IL-4Rα, anti-TSLP and reserved for **severe, phenotype-guided** disease.
Systemic corticosteroids are for exacerbations and select severe cases; chronic use is limited by adverse effects.

Guideline-aligned care emphasizes a **stepwise, personalized approach**, regular assessment of symptom control and risk, and routine checks of **adherence and inhaler technique** at every visit.

Success requires a **personalized, stepwise** plan, with routine checks of adherence and inhaler technique.

Chapter 6: Inhaler Devices — MDI vs DPI and Formulations

MDIs use propellant; require **hand–breath coordination**. **DPIs** rely on a **rapid, deep inhalation** and less coordination.

Technique matters—up to **70–80%** of patients misuse inhalers; teach and reinforce at every visit.

- **Metered-dose inhalers, or MDIs**, deliver drug using a propellant, so delivery is **independent of the patient's inspiratory effort**, but they require **hand-breath coordination**.
- **Dry powder inhalers, or DPIs**, rely on the patient's **rapid, deep inhalation** to disperse powder from lactose carriers—eliminating hand-breath coordination, but demanding adequate inspiratory flow.

Solution vs Suspension MDI Formulations and Why It Matters

Foundational differences are as follows:

- **Solution MDIs contain drug fully dissolved in an HFA propellant with cosolvents like ethanol, creating a single-phase system; upon actuation, the droplets contain dissolved drug that remains uniformly distributed.** ***Hydrofluoroalkane (HFA) propellants are non-ozone-depleting, chemically stable compounds that replaced chlorofluorocarbon (CFC) propellants in pressurized metered-dose inhalers to comply with the Montreal Protocol on ozone layer protection***
- **Suspension MDIs contain micronized solid drug particles—typically 1 to 5 microns—suspended in propellant with surfactants such as oleic acid to mitigate aggregation. These must be shaken to ensure uniform dosing.**

Aerosol performance and deposition is as follows

- **Solution MDIs tend to generate smaller particle sizes—often around 1 to 2 microns—favoring peripheral lung deposition and maintaining therapeutic delivery despite modest coordination errors or variable inspiratory flow.**
- **Suspension MDIs typically emit larger particles, about 2 to 4 microns, which can increase oropharyngeal deposition and reduce peripheral penetration if technique is suboptimal. Proper shaking and timely actuation-inhalation coordination become critical.**

Clinical implications:

- **In patients with suboptimal technique, solution MDIs can be more forgiving and maintain deposition; studies suggest they can achieve three to four times greater lung deposition than suspension formulations when technique is poor.**
- **Real-world examples reflect these differences: beclomethasone dipropionate solution inhalers, such as Qvar, versus albuterol sulfate suspension inhalers, like Proventil HFA.**

KOL talking point: When a clinician describes a patient who "can't get MDIs right," probe whether the challenge is coordination versus inspiratory flow and whether a solution MDI or a DPI aligns better with that patient's capabilities and preferences. Link the device choice to phenotype, exacerbation risk, and adherence history—then reinforce technique training at every visit.

Solution MDIs: dissolved drug, smaller particles, better peripheral deposition, more forgiving of minor errors.

Suspension MDIs: solid particles; **must be shaken**; larger particles increase oropharyngeal deposition if coordination is off.

Choose device based on inspiratory ability, dexterity, preferences, availability, and environmental factors.

Chapter 7: GINA 2025 Strategy — Key Updates

GINA emphasizes **anti-inflammatory reliever (AIR)** therapy with **ICS–formoterol** over **SABA-only** regimens.

Track 1 (Preferred): ICS–formoterol as both controller and reliever at all steps; lowers severe exacerbations.

Track 2 (Alternative): Daily ICS or ICS–LAMA with SABA reliever when ICS–formoterol is unavailable; ensure adherence to avoid SABA-only use.

Type 2 biomarkers (**blood eosinophils**, **FeNO**) inform risk and biologic selection. Pediatric and environmental guidance updated.

Chapter 8: MSL Key Takeaways

Verify diagnosis and phenotype; optimize adherence, technique, and trigger control first.

Match therapy to risk and phenotype; prefer **ICS–formoterol** strategies when appropriate.

Choose the right device; consider **solution vs suspension** MDI differences.

Escalate thoughtfully to **triple therapy** or **biologics**. Stay aligned with **GINA 2025**.