Bronchial asthma: the nature of the disease, pathogenesis, risk factors, epidemiology, and diagnosis

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The learning resources


What is asthma?

- Asthma is a heterogeneous disease, an "asthma syndrome", that is characterized by chronic airway inflammation.
- Heterogeneity: variability between and within patients.
- Asthma is defined by the history (or presence) of symptoms:
  - Wheeze
  - Cough
  - Shortness of breath
  - Chest tightness
- The symptoms vary over time and in intensity due to variable expiratory airflow limitation.
- Typically, the airflow limitation is variable and/or reversible.
Definition of bronchial asthma (hereinafter asthma) *(Global Initiative for Asthma 2016→)*

- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation
- It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation

www.ginasthma.com
The nature of asthma by the definition (I)

• Asthmatic respiratory tract inflammation causes chronically recurrent airflow limitation that in turn results in symptoms that may resolve spontaneously or in response to medication, and may sometimes be absent for days, weeks, or months

• Asthma symptoms are classically more frequent at night or early in the morning

• Episodic “flare-ups” (exacerbations) of asthma occur; these may be life-threatening

This defines asthma clinically and is called as ”the history of asthma”

GINA 2011-2017 www.ginasthma.com
The nature of asthma by the definition (II)

- The variable airflow obstruction and asthma symptoms are often triggered by factors like:
  - Physical exercise/activity
  - Exposure to allergens
  - Exposure to non-allergic irritants
  - Viral respiratory infections (*Rhinovirus* etc.)
  - Even changes in weather

*Global Initiative for Asthma 2015-2016* [www.ginasthma.com](http://www.ginasthma.com)
The nature of asthma by the definition (III)

- Asthma is usually associated with airway hyperresponsiveness (AHR) to direct or indirect stimuli and with chronic airway inflammation.
- AHR and inflammation usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment.

Global Initiative for Asthma 2017 www.ginasthma.com
Asthmatic bronchoconstriction: the basis for the symptoms

Normal Asthma

Jeffery P., 2003
Inflammation as the main component of the pathogenesis of asthma

Asthmatic airway inflammation as a classical immune-inflammation cascade mechanism

Inflammation:
• Almost always present, albeit symptoms and their severity are varying
• Present in all airways: upper and lower
• Although the clinical spectrum asthma is highly heterogeneous with different underlying disease processes, inflammation is basically present in all phenotypes of asthma (is not necessarily eosinophilic or neutrophilic)
Pathogenesis of asthma

Asthmatic airway inflammation as a classical immune-inflammation cascade mechanism

- Different inflammatory cells participate: mast cells, eosinophils, T-lymphocytes; dendritic cells macrophages, and neutrophils
- Both the inflammatory cell and the structural cells of the respiratory tract are activated, they release mediators (>100 different ones):
  - Mediators responsible for regulation and maintenance of the inflammation
  - Growth factors
  - Effector mediators that directly cause symptoms

GINA, 2011; Akbari et al., 2006
Endotypes and phenotypes

• **Endotype**: subtype of a disease defined by a certain distinct pathophysiological mechanism: links clinical characteristics with corresponding pathobiological mechanism.

• **Phenotypes** are based on observable (mainly clinical or immunological) characteristics: subtypes of a disease, defined by one or more properties, that is connected to clinically meaningful outcome measures: response to (certain) therapy/therapies and prognosis (but also symptoms, clinical presentation, triggers, exacerbations, progression rate, mortality etc.).

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Asthma phenotypes in clinical practice

- 1. Allergic asthma
- 2. Eosinophilic non-allergic asthma
- 3. Non-eosinophilic asthma

Phenotypic analysis of observable clinical or biological characteristics can facilitate patient management.
- Particularly important in severe refractory asthma
- Personalized medicine
- Costly therapies

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Lambrecht & Hammad, Nature Immunol 2015
1. Allergic asthma

- The most classical phenotype of asthma
- The most intensely studied and modelled
- The most common (most childhood asthma, ~50% of adult asthma)
- IgE-mediated: typical pathogenesis (allergic sensibilization, IgE synthesis)
- Typically, begins in (early) childhood
- Is connected to a history (or a family history) of food allergy, drug allergies, allergic eczema and/or allergic rhinitis (so-called „allergic march“)
- Peripheral eosinophilia (>0.3×10⁹/L)
- Eosinophilia in sputum or in induced sputum (>1.01%)

Therapy:
- Responds well to inhaled (ICS) and oral glucocorticosteroids
- Anti-IgE pharmacotherapy can be considered

GINA, 2015; Lambrecht & Hammad, Nature Immunol 2015
Enhanced eosinopoesis, chemotaxis and kinesis, increased survival, activation, and priming of eosinophils
Differentiation of T-lymphocytes into Th2 subtype: an important step in the pathogenesis of allergic asthma
The role of lymphocytes in the pathogenesis of asthma

- Allergen
- Dendritic cell
- Mast cell
- Th1
- Th2
- B-lymphocyte
- Eosinophil

Decrease in Treg cells
Th17 cells

IL-2, IL-12, IL-18
IFN-γ
IL-2, IFN-γ
IL-4, IL-13

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Allergic asthma: IgE and eosinophilia

Increased content of IgE in serum:
• The main sign of allergic asthma
• IgE isotype switch in lymphocytes is caused by IL-4
• One of the main indicators of the Th2-mediated acquired immune response
• Based on the expression of IL-13-inducible genes, is divided Th2-high and Th2-low subendotypes (Th2-high results in more severe asthma)

Eosinophilia in the lung and the respiratory tract
• Peripheral eosinophilia (>0.3×10⁹/L) ± sputum eosinophilia (>1-3%)
• Mainly due to the effect of IL-5
• Related to risk of severe exacerbations (Berry et al. 2007)
• Provides the basis of novel biological treatment with commercial anti-IL-5 monoclonal antibodies (mepolizumab, reslizumab, benralizumab etc.)
Release of effector mediators in the pathogenesis of asthma

• Following the binding of allergen-specific IgE to the FcεRI on mast cells (FcεRII on eosinophils and macrophages), these cells activate and release effector mediators that directly cause bronchoconstriction → ... and symptoms

• Deposited mediators:
  • Histamine, kinins, tryptase, chymase, heparin etc.

• De novo synthesized mediators:
  • Cysteinyl leukotrienes (CysLT): LTC₄, LTD₄, LTE₄
  • Prostaglandins: PGD₂, Pgf₂α
  • PAF, TX
  • Adenosine

• Rapidly develops “early asthmatic reaction” ("EAR")
Early asthmatic reaction: rapid release of effector mediators

- The major effects of the effector mediators in the bronchi and bronchioli (3) in the order of significance:
  - Mucosal edema (due to increased vasopermeability)
  - Glandular (mucus) hypersecretion
  - Contraction of smooth muscle

- These are the main mechanisms that are responsible for airway obstruction and thereby asthma symptoms
- Cysteinyl leukotrienes (CysLT) are major mediators causing bronchoconstriction and symptoms
- Tissue injury: proteinases (tryptase, chymase etc.) from mast cells and cationic proteins (ECP, MBP, EPO, EDN) from eosinophils
Cysteinyl leukotrienes (CysLT) as major effector mediators

CysLT: essential effector mediators in asthma and most allergic diseases of the respiratory tract

- Directly responsible for symptoms due to causing changes leading to bronchoconstriction
- CysLT are not simply effector mediators: they also support inflammation
- Increased secretion of mucus
- Increased vasopermeability
- Contraction of airway smooth muscle

- 100-10 000 × more potent than histamine
  - Delayed onset, more durable effect
  - By strength: LTD₄>LTC₄>>LTE₄
  - By durability: LTC₄<LTD₄<LTE₄

Bronchoconstriction
Remodeling
Asthmatic bronchoconstriction

Normal

Bone’s Atlas of Pulmonary Medicine, 2005

Asthma
How does the asthmatic inflammation turn to permanent

• 4-6 hours after the early asthmatic reaction → occurs s.c. “late asthmatic reaction” (”LAR”)
• Release of the pro-inflammatory cytokines and chemokines by the inflammatory cells participating in the EAR: stimulating, chemotactic, and chemokinetic effect to the secondary inflammatory cells
• Chemotactic effect of the effector mediators on the inflammatory cells
• Expression of the adhesion molecules (ICAM-1…-3, VCAM-1 etc.)
Summary of allergic asthma

• Th2-determined inflammation
• Participation of the acquired immunity
• Early onset of asthma (<18 years of age)
• Allergic symptoms in response to exposure to allergens
• Allergic concomitant illnesses
• Allergy tests are usually positive
• FeNO usually increased and respond to treatment
• Responds well to glucocorticosteroids
2. Eosinophilic non-allergic asthma

- Ca 40% of adult asthma
- Is not IgE-mediated (atopic) and is not overall allergic
- Peripheral eosinophilia (>0.3×10^9/L) ± sputum eosinophilia (>1-3%)
- Eosinophilia is an independent risk factor of both severe asthma and severe exacerbations (Berry et al. 2007; Walsh et al. 2016)
- Acquired immunity (Th2) does not play a major role
- Innate immunity is central:
  - Bronchial epithelium (IL-25, IL-33, TSLP)
  - ILC2 cells (formerly, natural helper cells):
    - Release similar to that of Th2 cytokine repertoire (IL-13, IL-5, IL-9) → eosinophilia
    - But not significantly IL-4 (Klein Wolterink et al. 2012) → no particularly increased synthesis of IgE
Pathogenesis of allergic and non-allergic eosinophilic asthma

Allergic (eosinophilic) asthma

- Allergens
- Goblet cells
- TH2 cells
- IL-4, IL-13
- IL-9
- IL-5
- Eosinophils
- Bronchial hyperresponsiveness

Non-allergic eosinophilic asthma

- CRTH2
- IL-33R
- IL-25R
- IL-9R
- Lipoxin A4
- PGD2
- Smooth muscle

Modified from: Lambrecht & Hammad, Nature Immunol 2015
Eosinophilic non-allergic asthma: the summary

- Participation of the innate immune system
- Late-onset asthma (>18 years of age)
- Many symptoms, frequent exacerbations
- Clinically relevant allergy is absent (allergy tests are negative)
- Peripheral eosinophilia (>0.3×10⁹/L) ± sputum eosinophilia
  - In the blood: ≥0.3×10⁹ /L (≥0.15×10⁹ /L if on oral glucocorticosteroids)
- FeNO usually increased (>50 ppb)
- Nasal polyps, disturbed sense of smell and taste
- So-called aspirin intolerant asthma belongs here
- Sensitive to viral respiratory infections
- Responds relatively well to inhaled and oral glucocorticosteroids
- Responds also to antileukotrienes

Allergic (Th2-driven) and eosinophilic non-allergic (ILC2-driven) asthma together

- So-called. „High Type2 asthma“ (Th2 and ILC2)
- Altogether 90% (50% + 40%) of adult asthma
- Eosinophilic, increased FeNO
- New biomarkers: periostin (≥50 ng/mL) etc.

- Responds relatively well to glucocorticosteroids and antileukotrienes
- In cases on non-responsiveness: phenotype-based therapy, biologicals etc.
Periostin as a novel biomarker for „high Type2 asthma“

- An ECM protein induced by IL-4 and IL-13 in airway epithelial cells and fibroblasts
- A biomarker of Th2-driven inflammation, eosinophilia, and treatment response

Parulekar et al. 2014; Brightling et al. 2015
3. Non-eosinophilic asthma

- About 10% of adult asthma
- Is not IgE-mediated (atopic) and is neither allergic nor eosinophilic at all
- Neutrophilic (Th17-driven asthma) (>61% neutrophils in sputum) or paucicellular asthma
- Elevated levels of IL-17 and IL-8
- Relatively resistant to anti-inflammatory therapy (glucocorticosteroids, antileukotrienes)
- Mainly late-onset, severe asthma
- Often characterized by significant remodeling
- Often in overweight people: both the cause and the result
- Therapy with high-dose and continuous systemic (oral) glucocorticosteroids (OCS)
- A major role for long-acting bronchodilators (LABA + LAMA)
- Macrolides, PDE4i, CXCR2, P38 MAPK antagonists
Immune inflammatory pathways of neutrophilic asthma

Earl et al. 2015; Agache 2015
A mixed Th17/Th2 endotype of asthma

- IL-17 ↔ IL-4/IL-13 feedback
- Most severe airway obstruction and AHR
- Steroid resistance

Agache 2015; Irvin et al. 2014
Summary of the asthma phenotypes with some therapeutic insights

- **Non-allergic asthma**
  - Anti-IL-5
  - Anti-IgE (off-label)

- **Allergic asthma with eosinophilia**
  - Anti-IgE
  - Anti-IL-5

- **Non-Type 2-asthma (non-allergic, non-eosinophilic)**
  - Macrolides (?)
  - PDE4I etc.(?)

- **Allergic asthma**
  - Anti-IgE

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Lambrecht & Hammad, Nature Immunol 2015, GINA, 2015
The multiplicity of asthma andotypes and phenotypes

Gauthier et al. AJRCCM 2015; 192: 660-8
Main mechanisms of the reversible obstruction in asthma

• These mechanisms are directly responsible for symptoms due to causing changes leading to bronchoconstriction

• Increased secretion of mucus
• Increased vasopermeability
• Contraction of airway smooth muscle
Cysteinyl leukotrienes (CysLT) as major effector mediators

CysLT: essential effector mediators in asthma and most allergic diseases of the respiratory tract

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Mucus hypersecretion
Mucosal edema
Contraction of smooth muscle
Bronchoconstriction
Remodeling

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Mechanisms of airway hyperresponsiveness

• Hypertrophy of the airway smooth muscle, hyperplasia of the smooth muscle cells, and increased contractility: the role of mast cells
• Inflammation dissociates the contraction of the respiratory tract smooth muscle independent on the neural regulation of the tone: direct responsiveness to mediators released by inflammatory cells
• Thickening of the wall of the conducting airways: due to edema (reversible) and remodeling (irreversible)
• Involvement of sensory nerve endings
Asthmatic airway inflammation as a result of continuous balance between pro-inflammatory and anti-inflammatory mechanisms

Mild intermittent asthma (also s.c. “pre-asthma”): the balance returns to very low grade inflammation

Natural endogenous anti-inflammatory mechanisms
Moderately severe asthma: the balance returns to moderate inflammation

- Natural endogenous anti-inflammatory mechanisms
- Controller therapy
Severe asthma: high-grade inflammation almost always

Asthmatic airway inflammation as a result of continuous balance between proinflammatory and anti-inflammatory mechanisms

The level of inflammation

Severe asthma: high-grade inflammation almost always

Time - years

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Asthmatic inflammation as a chronic condition

- Permanent stimulation of both inflammatory cells and airway structural cells (auto- and paracrine)
- Moving of new inflammatory cells into the airway tissues
- Increased survival of the inflammatory cells (inhibition of apoptosis)
- Neurogenic inflammation
- In certain phenotypes of asthma: neutrophilic inflammation in neutrophilic asthma
- Activation and participation of NK cells

- Structural remodeling of the airway tissues resulting from the effects of growth factors
Airway structural cells in asthma

• **Epithelium**: activates first, synthesizes a very broad spectrum of mediators; epithelial-mesenchymal transition (EMT)
• **Airway smooth muscle cells**: wide repertoire of mediators
• **Endothelium**: Expression of adhesion molecules, adhesion of inflammatory cells
• **Fibroblasts and myofibroblasts**: synthesis of collagens etc. components of the extracellular matrix → remodeling
• **Nerve fibers**: cholinergic (regulation of the muscle tone and secretion by the glands), sensory (cough, chest tightness, inflammation, release of neuropeptides)
Functional relationships between inflammatory cells in the pathogenesis of asthma: Auto- and paracrine stimulation
The balance between proinflammatory and anti-inflammatory mechanisms in asthma is unstable

- Different specific and non-specific factors
- Natural endogenous anti-inflammatory mechanisms
- Controller therapies

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Auto- and paracrine stimulation causes avalanche-like inflammatory reaction

- Inflammatory cells: auto- and paracrine stimulation, chemotaxis, effector mediators, growth factors
Asthmatic inflammation, airway obstruction, and respiratory symptoms

Inflammation: almost always present, although symptoms are varying

Obstruction: $\text{FEV}_1$, PEF ↓

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Development of asthma in an individual

- Important in the development of asthma, its severity, and phenotype

- Genetic
- Epigenetic

- Genes
- Gene expression

- Transcriptome
- Proteome
- Metabolome
- Immunity
- Inflammation
- Microbiome

- Airway inflammation
- Obstruction
- BHR
- Remodeling

- Symptoms
- Severity
- Quality of life
- Concomitant diseases
- Phenotype
- Response to therapy

Immune inflammatory and cellular mechanisms in the pathogenesis of the phenotypes of asthma

Allergens, smokes and gases; pathogens, physical factors, cells, and metabolic factors

Morphological changes in the airways in asthma: airway remodeling

• Changes present in the bronchial epithelium:
  • Shedding and desquamation
  • Decreased ciliated-to-goblet-cell ratio
  • Squamous cell metaplasia
  • Thickening and altered composition of the subepithelial basement membrane: “subepithelial fibrosis”
  • Infiltration of the epithelium and the whole mucosa by activated inflammatory cells

• Subepithelial fibrosis
• Airway smooth muscle (ASM) hypertrophy with muscle cell hyperplasia
• Increased density of the mucosal vasculature
• Glandular hyperplasia
• Mucus plugging of the conducting airways (fatal)
Epithelial shedding in asthma

Normal

In untreated asthma

Edema of the bronchial mucosa in asthma

Mucosal edema, thickening of the subepithelial basement membrane, and lymphocytic infiltration of the mucosa in a 16-year-old boy

Thickening of the subepithelial basement membrane in asthma

Bronchial mucosal infiltration with inflammatory cells in asthma

Before and after 3-month therapy with budesonide 600 µg b.i.d.

Eosinophils in bronchial mucosa of an asthmatic patient

Inflammation in the bronchial mucosa in newly diagnosed asthma (symptoms for just 2 weeks)

Healthy person

Newly diagnosed asthma

Laitinen et al., Am Rev Respir Dis 1985
Bronchial mucosal biopsy from a 10-year-old boy with glucocorticosteroid-dependent asthma for 15-months

Tissue remodeling

Changes in the size, amount, or mass of the structural components of tissues that occur due to inflammation or injury, or during development (P. Jeffery)
Remodeling of the respiratory tract

“Targeted or reasonable”
- Developmental changes,
- Responses to e.g. wound healing

“Non-reasonable” or deleterious
- The inflammatory reaction is permanent, self-stimulating (“chronic wound scenario”) resulting from the effect of growth factors

In asthma
- Permanent decline in lung function
- Disappearance of the reversibility of airflow obstruction (reversibility is otherwise typical of asthma)
Hyperplasia of the bronchial smooth muscle

Structure of the bronchial subepithelial basement membrane (BM)

- Epithelium
- Lamina rara
- Lamina densa
- Lamina fibroreticularis
- Lamina propria of the mucosa

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Changes in the bronchial subepithelial basement membrane (BM) in asthma

Epithelium

Lamina rara

Lamina densa

Lamina fibroreticularis

Lamina propria of the mucosa

• Novel constituents
• Thickening
• Novel constituents (tenascin, collagens III, IV, V, VII etc.)
Subepithelial collagen deposition is present already in mild asthma

Bronchial lumen

Epithelium

Subepithelial deposition of collagens etc. proteins

Holloway et al. Asthma and Rhinitis 1995
Thickening of the wall of small airways in asthma

Severe chronic

Fatal attack

Normal

Source: Hong Wei Chu, M.D.
Bronchial epithelium in inflammation and remodeling

Genes and environmental factors

Injured / activated epithelium

Chronic inflammation

Growth factors and cytokines

Differentiation of fibroblasts to myofibroblasts

Remodeling

- BHR
- Broncho-constriction
- Asthma symptoms

- ICS
- LTRA

- Anti-IgE
- IT
- PDE4I
- Anti-histamines
- LABA + ICS

Folli et al., 2008
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Chronic (inflammatory) epithelial injury and activation of the subepithelial mesenchymal cells create the “chronic wound scenario”

Environmental factors and inflammatory cell products

Stress

Structural injury

Epithelial injury

Intensive eosinophil recruitment and activation

Activation of myofibroblasts

TGF-β

FGF

PDGF
Epithelial-driven remodeling of the airways

- Chronic injury or stimulation by profibrotic cytokines (TGF-β, IL-11, IL-13) causes secondary release of TGF-β
- Bronchial epithelial cells synthesize:
  - EGF, HB-EGF
  - Amphiregulin
  - FGF-1, FGF-2
  - PDGF
  - IGF
  - Neurotrophins (e.g. NGF)
  - VEGF
- Result: proliferation of fibroblasts and/or differentiation to myofibroblasts → synthesis of ECM
Epithelial-mesenchymal trophic unit (EMTU)

• Similarity with organ morphogenesis and especially, wound healing / “chronic wound” / remodeling → a novel concept of chronic inflammation
• Mutual stimulation by the structural components: EMTU
• Mutual interactions between the immune inflammatory and structural cells
• Mutual interdependence between structure and inflammation that involves epithelia, fibroblasts, myofibroblasts, and airway smooth muscle cells and matrix synthesized by these cells explains:
  • Why the inflammation persists in the more severe and chronic spectrum of asthma
  • Why the response to anti-inflammatory treatment is often incomplete
Epithelial-mesenchymal trophic unit (EMTU)

Th2 and Th1 cytokines

- Dendritic cell
- Th-2 cell
- IL-9, IL-3, IL-4
- Mast cell
- TNF-α
- Eosinophils
- Neutrophil

Environmental factors
Inflammatory cell products

Mucus

Augmentation
(Proliferation
Blood vessels

EMTU

Chemoattractants (IL-8) etc.
Inflammation mediators

Bousquet, 2000
Pathogenesis of allergic asthma with airway remodeling

1. Inhaled allergens activate dendritic cells to secrete TSLP.
2. TSLP promotes the differentiation of Th2-lymphocytes, which secrete IL-4, IL-13, and IL-18.
3. IL-4, IL-13, and IL-18 stimulate the synthesis of IgE.
4. Epithelial cells secrete cytokines, chemokines, and growth factors.
5. IL-4, IL-13, and TGF-β promote airway smooth muscle proliferation.
6. Fibroblasts secrete TGF-β, leading to thickening of the basement membrane.
8. FcεRI activation leads to chronic inflammation and irreversible obstruction.

Chronic inflammation
Cytokines, Chemokines, Growth factors
Irreversible obstruction
Practical consequences of the airway remodeling in asthma

Remission → During exacerbations

Normal airway → Bronchoconstriction

Remodeled airway → Severe bronchoconstriction
”The paradigm of remodeling of the cavitary organs”

All (factors and mechanisms) that in short-term perspective cause reversible contraction (reversible constriction of the lumen), cause remodeling of the walls of the organ resulting in irreversible constriction of the lumen, when the influence is durable

- Parallel: obstructive remodeling of the pulmonary arteries in pulmonary arterial hypertension (PAH) (endothelin-1)
- Smooth muscle hypertrophy, muscle cells hyperplasia, deposition of the extracellular matrix (ECM) proteins (collagens, elastin, fibronectins, tenascins etc.) (Cowan et al., 2000)

- Effector mediators
- Regulatory mediators
- Growth factors or mediators with growth factor domains/properties
For comparison: pulmonary vasoconstriction and remodeling in PAH

**Vasoconstriction**

Relatively early process in PAH (Humbert et al., 2002)
- Endothelial dysfunction (Budhiraja et al., 2004)
- Abnormal functioning of the K⁺ channels and/or dysfunction of the vascular smooth muscle cells (Yuan et al., 1998)
- “Imbalance of the vascular effectors” (Farber & Loscalzo, 2004)

- Obstructive remodeling of the pulmonary arteries
- Chronically insufficient production of vasodilator mediators (NO, PG1₂, VIP)
- Overproduction of vasoconstrictors (ET-1, TxA₂, serotonin)
- Mutations in the genes of receptors for growth factors
Development of airflow obstruction in asthma during the lifespan

The average decline in FEV₁ in healthy persons is 15-20 mL/year (Kohansal et al. 2009)

The component of permanent obstruction

Remodeling
Development of airflow obstruction in asthma during the lifespan: why is the remodeling important?

The component of permanent obstruction

Disability

Remodeling: mainly smooth muscle changes

Exacerbation

Exacerbation

Exacerbation

Exacerbation

Time (years)
The significance of addition of the irreversible component of the obstruction in asthma

In chronic asthma:
• The ventilation function of the lung (spirometric “lung function”: FEV₁, PEF etc.) may not increase up to the normal limits even at the level of clinically best asthma control
• This is due to the developing irreversible obstruction or permanent loss of lung function: the effect for the host is similar to that observed in chronic obstructive pulmonary disease (COPD) (ventilation insufficiency, disabling in severe cases) → is though not by far COPD

• Therefore, for assessment of the response to treatment and the level of asthma control, “personal best” is used for reference (instead of the physiological limits of normality)
Asthma phenotypes in the literature

- The spectrum of clinical types of asthma is extremely broad and heterogeneous: certain phenotypes and subphenotypes have been identified (Bel, 2004; Wenzel, 2012, 2013)
- The phenotypes connect steady subtypes of asthma of similar clinical manifestations and response to treatment
- In practice, the phenotypes are used for planning personalized therapy and describe:
  - Clinical (observable and meaningful) and morphological characteristics of asthma
  - Response to treatment and prognosis
Phenotypes of asthma by the GINA

- **Allergic asthma**: mainly eosinophilic inflammation (eosinophils in sputum and blood), often starts in childhood, is associated with a history of allergic diseases, responds well to treatment with inhaled glucocorticosteroids (ICS)
- **Non-allergic asthma**: eosinophilic and non-eosinophilic (neutrophilic, mixed granulocytic, or paucigranulocytic) inflammation; typically responds less well to ICS
- **Late-onset asthma**: appears first in adulthood (>16-18 years of age), is typically non-allergic, occurs often in women, is difficult-to-treat (may require higher doses of ICS or is relatively refractory to glucocorticosteroids)
- **Asthma with fixed airflow limitation**: due to long-standing asthma, often improperly treated during childhood; develops on the basis of airway wall remodeling
- **Asthma with obesity**: in obese individuals, prominent respiratory symptoms and little eosinophilic airway inflammation
Epidemiology of asthma I

Prevalence
• 1-18% of the population in different countries (highest in Great Britain, New Zealand, Australia, Ireland, USA; lowest in Balkan countries, Russia, Indonesia)
• Worldwide, an estimated >370,000,000 people have asthma; estimated to increase to 400 million by 2025
• Mortality: 0.4-0.6 / 10^5; 250 000 deaths per year, mortality correlates inversely with prevalence
• ~250,000 people die annually prematurely due to asthma (WHO)
Epidemiology of asthma II

• In countries with developed economy (North-America, Western-Europe): the prevalence of asthma symptoms is slightly decreasing
• In developing countries and in countries with earlier lower prevalence: a tendency towards increase
• Asthma is:
  • More frequent in developed than in developing countries
  • In rich countries, more frequent among less affluent people; in poorer countries, more frequent among affluent people;
  • More frequent in urban children than in rural children: a reference to the role of lifestyle (access to health care resources, exposures to allergens, hygiene hypothesis etc.)
Asthma prevalence and mortality

- Mortality correlates inversely with prevalence

Masoli et al., 2004; GINA, 2011
What do the asthma-related costs depend on?

• In developed countries, 1-2% health care resources are spent to asthma care
• In developing countries, the expenditures will rise
• The costs depend on the level of asthma control and the frequency of exacerbations
• Emergency care is always more expensive than ordinary/planned therapy
• Non-medicament costs are huge (hospitalizations, emergency care visits)
• Guideline-based therapy is always cheaper
• Expenditures on asthma have an influence on economical well-being of families
Asthma-related costs depend on asthma severity

- Patients with severe asthma represent 3-10% of the asthma population
- But their healthcare costs account for ~50% of the overall costs associated with asthma (Peters et al. 2006)

A major unmet need in asthma is associated with severe asthma:
- Patients with symptoms or exacerbations despite use of medium-to-high dose inhaled glucocorticosteroids and other controller therapy, or long-term oral glucocorticosteroids

Peters SP et al. RespMed 2006;100:1139-1151;
Pawankar R. World Allergy Organ J 2014
Risk factors of asthma

There are:
• Risk factors for asthma to develop in an individual
• Risk factors for worsening of the pre-existing asthma (emerging or persistent symptoms, asthma attack)

Risk factors may be:
• Related to the host organism: genetic, related to the “asthmatic constitution”
• Environmental: increase the risk of development of asthma in persons with an appropriate predisposition
Risk factors of asthma related to the host I

- Genetic predisposition: inherited component is multifactorial
  - Connected to genetic control of IgE secretion (atopy), as well as all types of asthma-related immune response and release of proinflammatory cytokines, chemokines, and growth factors
  - Connection of atopic asthma with other atopic diseases (allergic rhinitis, atopic dermatitis, and other atopies (chromosome 5q: IgE, BHR)
  - More frequent incidence of individuals with „asthmatic constitution“ among pedigrees
  - In practice: the family history as the support to the diagnosis of asthma
Risk factors of asthma related to the host II: the obesity

- **Overweight: BMI >30 kg/m²**
  - In obese individuals, asthma is more frequent, more severe, and more complicated to control
  - Obesity: the airway mucosa is thicker and more soft: the inflammatory edema is much worse
  - More obstructive even outside the asthma attack!
  - Respiratory mechanics: decrease in the expiratory reserve volume (ERV), reduced plasticity of the airway smooth muscle
  - Proinflammatory mediator release from adipocytes:
    - Leptins (Beuther *et al.*, 2006)
    - IL-6
    - TNF-α
    - Eotaxins
    - Decreased release of anti-inflammatory adipokines
Risk factors of asthma related to the host III

- Gender issues (size of the lungs and airway diameter)
  - Asthma is more frequent and more severe on average in boys than in girls (up to $2\times$ before 14 years of age)
  - From puberty, the prevalence equals and later, asthma is more frequent and more severe on average in women than in men
Environmental risk factors of asthma

- **Allergens**: well-known causes of asthma exacerbations, but the role in the development of asthma in an individual is contradictory
  - Indoor allergens (house dust mites (sublingual immunotherapy is effective!), animal epidermis, cockroaches, molds etc. fungi)
  - Outdoor allergens (pollens, fungi etc.)
  - Occupational sensitizers
- **Infections**: viral in early childhood may trigger “asthmatic constitution“ (RSV, parainfluenza)
- **“Hygiene hypothesis”**: (the changes in the immune system that accompany the western lifestyle/nutrition: the result of missing the „normal“ contact with environmental bacteria in childhood

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GINA, 2011
Hygiene hypothesis: the theory

Kumar & Bhatia, 2013
Environmental risk factors of asthma II

• **Occupational asthma:** >400 occupational sensitizers (10% of asthma in people at working age)
• **Tobacco smoke:** (even during intrauterine age): more rapid decline of lung function with age, asthma worsening and addition of COPD, emergence of treatment-resistance
• **Outdoor and indoor air pollution:** the role in getting ill with asthma is contradictory
• **The diet:**
  • Artificial nutrition during early childhood
  • Later, lack of antioxidants, imbalance of polyunsaturated fatty acids (low contents of ω3- and high contents of ω6-polyunsaturated fatty acids: fast food etc.)
Pathogenesis of occupational asthma: sensibilizer- and irritant-induced

Tarlo & Lemiere, NEJM 2013
Factors that contribute to exacerbations of asthma and/or persistence of symptoms

- Indoor and outdoor air allergens
- Indoor and outdoor air pollution
- Respiratory tract infections
- Physical activity and hyperventilation
- Irritant gases and particles (SO₂)
- Tobacco smoke (active and passive smoking)
- Other irritants in the air (housekeeping aerosols, paints, solvents etc.)
- Food, food additives
- Drugs (NSAID, β-blockers, contrast media, nitrofurantoin, cocaine, propellents etc.)
- Extreme emotions (hyperventilation, hypocapnia)
- Changes of the weather
- Concomitant diseases (gastroesophageal reflux)
The course of asthma throughout the human lifespan

- Asthma can manifest at all ages
- As a rule, it manifests before 6th year of age
- Infantile or childhood asthma may „disappear“ in puberty (30-50% of cases, especially in boys), but re-emerges again later
- In about 2/3 of children, asthma persists throughout the rest of the life
- Even in cases of clinical “disappearance” of asthma, the lung function (FEV₁, FEV₁/FVC) remain lower; the bronchial hyperresponsiveness and cough may persist
- **Childhood asthma does not “grow out”:** mild childhood asthma has a good prognosis, moderate-to-severe asthma retains its severity
- Children with persistent asthma may have reduced growth in lung function and a risk of accelerated decline in lung function in early adult life (McGeachie, NEJM 2016)
The reasons for hypodiagnostics and undertreatment in asthma

A worldwide problem:

• Symptoms are intermittent or reversible (except severe asthma), therefore, uneducated patients may voluntarily interrupt treatment
• Symptoms are non-specific by nature, that may foster working on alternative diagnoses
• Patients tolerate well milder symptoms (do not seek for care or turn for the first time with an exacerbation of asthma
• Historically, even the physicians have not been willing to make the diagnosis of asthma (instead, e.g. “wheezy bronchitis”)
Typical history of bronchial asthma

In addition to the history of having asthma symptoms ("the history of asthma"):

- Episodic or periodical symptoms (wheeze, but also cough, dyspnea, and chest tightness)
- The symptoms emerge or worsen rapidly: with hours or within some days
- The symptoms abate or improve either spontaneously or as a result of therapy
- Commencement of symptoms in childhood, a history of allergic rhinitis or eczema, or a family history of asthma or allergy, increases the probability that the respiratory symptoms are due to asthma
- Not seen in all phenotypes of asthma, however
- Patients with allergic rhinitis or atopic dermatitis should be asked specifically about asthma symptoms
Physical examination in bronchial asthma

• Due to variable course, physical examination in asthma is often normal (except in severe asthma)
• Most frequently: expiratory wheeze (or rhonchi) on auscultation (may be absent or only heard on forced expiration only; or during severe exacerbations due to reduced airflow (“silent chest”))
• Breathlessness (expiratory dyspnea)
• Cough (usually dry cough; mucous sputum in severe cases and after exacerbations)
• Chest hyperinflation (use of accessory respiratory muscles, avoidance of supine position)
• Interrupted speech, anxiousness, fear
• Nose, eyes: inspection may reveal signs of allergic rhinitis or nasal polyposis
Symptoms of bronchial asthma

Asthma symptoms are:
- Wheeze
- Cough
- Shortness of breath
- Chest tightness

- The symptoms vary over time and in intensity due to variable expiratory airflow limitation
- Typically, the airflow limitation is variable and/or reversible
An approach to the diagnosis of asthma in adults and children >6-11 years

1. ”A history of asthma”: episodic symptoms (wheeze, but also cough, dyspnea, and chest tightness)
   - Typically, >1 asthma symptom should be present (in adults, isolated cough can be, though is rarely a sign of asthma)
   - Symptoms are variable for occurrence and intensity
   - Symptoms are more severe at night/early in the morning
   - Symptoms are triggered by exercise, emotions, allergens, cold air etc.
   - Symptoms appear/get more severe during viral respiratory infections

2. Confirmation of reversible/variable airflow obstruction should follow
Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years: From the definition of asthma

• By definition, asthma is a heterogeneous disease, usually characterized by chronic airway inflammation

• Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, along with variable airflow limitation
Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years:
1. History of variable respiratory symptoms

• Wheeze, shortness of breath, chest tightness, cough:

• Generally, >1 type of respiratory symptom (in adults, isolated cough is seldom due to asthma)
• Symptoms:
• Occur variably over time and vary in intensity
• Are often worse at night or on waking
• Are often triggered by exercise, laughter, allergens, cold air
• Appear often or worsen with viral infections
Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years:
2. Confirmation of the variable expiratory airflow limitation

• Documented airflow limitation
  AND
• Documented excessive variability in lung function (one or more of the tests discussed further)

• Defining an obstruction: at least once during the diagnostic process, when FEV₁ is low, confirm that FEV₁/FVC is reduced (normally, the ratio is >0.75–0.80 in adults, >0.90 in children)
• The greater the variations or the more occasions excess variation is seen, the more confident is the diagnosis
• The tests can be repeated during symptoms or early in the morning

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GINA, 2016-2017
Forced flow-volume spirometry in obstruction (volume-to-time curve)

Volume (L)

Time (s)

Normal

Obstruction

FEV₁

A. Altraja ©2017
2. Confirmation of the variable expiratory airflow limitation

• Positive bronchodilator (BD) reversibility test (known as the “bronchodilator test”) with spirometry (more likely to be positive if bronchodilators are withheld before test: SABA ≥4 hours, LABA ≥15 hours)

• Adults: increase in FEV$_1$ of >12% and >200 mL from baseline, 10-15 min. after 200-400 µg albuterol or equivalent (greater confidence if the increase is “major” (>15% and >400 mL)).
• Children: increase in FEV$_1$ of >12% predicted
Bronchodilator test in forced spirometry

- For the main parameters, FEV₁ and FVC, the highest value out of at least 3 technically successful attempts are registered (the variability of FEV₁ and FVC cannot exceed 5% or 100 mL between the measurements.

- The ratio FEV₁/FVC is calculated from the attempt, where the sum of FEV₁ and FVC is highest.

- For the bronchodilator test: 400 μg rapidly-acting β₂-agonist or up to 160 μg short-acting anticholinergic drug, or their combination is used (Pellegrino et al., 2005).

- Repeated measurement occurs 10-15 min. after the administration of the rapidly-acting bronchodilator or 30-45 min. after the administration of the combination.

- The bronchodilator test is positive, if FEV₁ increases by >12% and >200 mL (Pellegrino et al., 2005) (”major” or significant increase, if by >15% and >400 mL).
Confirmation of asthma by spirometry

Forced flow-volume spirometry:

Before bronchodilator

After bronchodilator

• The criterion of reversibility (a “positive bronchodilator test”) is an increase in FEV₁ by >12% and >200 mL

*With 400 μg rapidly-acting β₂-agonist or up to 160 μg short-acting anticholinergic drug

*Pellegrino et al., 2005
Forced flow-volume spirometry in asthma

Major advantages of spirometry:
• Exactness, repeatability of the measurements
• Good correlation with measures of inflammation in the respiratory tract
• Very informative in the diagnostic process of obstructive lung diseases, assessment of severity, course of the disease, and effect of treatment

Relative disadvantages of spirometry:
• Needs effort and perfect cooperation on behalf of the patient
• Needs careful supervision and experienced/educated to achieve reliable results
• Reliability decreases, if FEV$_1$ <1 L
• Relatively more expensive devices; accessibility is still problematic for many reasons
2. Confirmation of the variable expiratory airflow limitation II

• Significant increase in lung function after 4 weeks of anti-inflammatory treatment

• Adults: increase in FEV₁ by >12% and >200 mL (or peak expiratory flow (PEF) by >20%*) from baseline after 4 weeks of treatment, outside respiratory infections

*For PEF, use the same meter each time, as PEF may vary by up to 20% between different meters; BD reversibility may be “naturally” lost during severe exacerbations or viral infections
Solving the problems with bronchodilator testing

- If bronchodilator reversibility is not present at initial presentation, but a history (and hence, a suspicion) of asthma persists:
  - Significant mucosal edema and/or mucus plugging of the airways not reversible by a rapidly-acting bronchodilator (that works on relaxation of the airway smooth muscle only) serves as the reason
  - The next step depends on the availability of other tests and the urgency of the need for treatment

- If the patient with a history (and hence, a suspicion) of asthma presents with normal lung function (absence of an airflow obstruction):
  - The occurrence of an airflow obstruction can be expected (supporting on the former history of the particular patient) OR
  - Provoked, if this is considered harmless to the patient
2. Confirmation of the variable expiratory airflow limitation III

• **Excessive variability in twice-daily PEF over 2 weeks**

• Adults: average daily diurnal PEF variability >10%
• Children: average daily diurnal PEF variability >13%

**Daily diurnal PEF variability is calculated from twice daily PEF as ([day’s highest minus day’s lowest] / mean of day’s highest and lowest), and averaged over one week**

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Registration of the diurnal variability of PEF (DvarPEF)

By the patient, during at least in the morning (H) and in the evening (Õ) before (blue) and after (red) bronchodilator (optional) (the highest PEF value of at least 3 valid attempts per measurement is registered)

- Healthy person, DvarPEF <10%
- Asthmatic person: DvarPEF >10% or bronchodilator response >20%

Asthma, DvarPEF:
- Adults: average daily diurnal PEF variability >10%
- Children: average daily diurnal PEF variability >13%

Is calculated from twice daily PEF as ([(day’s highest minus day’s lowest) / mean of day’s highest and lowest], and averaged over one week

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PEF-meters

- PEF-meters are simple, easily accessible, and inexpensive
- Models of various shape, always with the same working principle
- A light piston, located within a cylinder, connected to a scale, and kept at zero with a weak and elastic spring
- In sitting position of the patient, during forced expiration through the PEF-meter, the piston moves away from zero with the airflow and registers the peak value of the airflow
- Per measurement, the highest value of 3 valid attempts is registered

Mini-Wright Peak Flow Meter for adults (Clement Clarke International Ltd., Great Britain
- Measuring limit: 900 L/min

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Circadian rhythm of the bronchomotor tone

- Decrease in the adrenergic tone and increase in the cholinergic tone at night
- Decreases content of glucocorticosteroids (resp. Anti-inflammatory potential) at night

Figure: Bone’s Atlas of Pulmonary Medicine, 2005
Measurement of PEF in asthma

Advantages of PEF follow-up:
• Simple, easily accessible, inexpensive
• Useful in primary care
• Useful for asthmatics for long-term self-monitoring and for detection of eventual exacerbation (a fall in PEF may occur before the symptoms appear or worsen)

Disadvantages of PEF follow-up:
• Inexactness, inaccurateness
• Low repeatability of the measurement results
• Bad correlation of the measurement results with other parameters of lung function (FEV₁ etc.) and with bronchial hyperresponsiveness
• PEF measurement does not replace forced flow-volume spirometry
2. Confirmation of the variable expiratory airflow limitation IV

- **Excessive variation in lung function between visits** (less reliable method)
- **Adults:** variation in FEV$_1$ of >12% and >200 mL between visits, outside of respiratory infections
- **Children:** variation in FEV$_1$ of >12% in FEV$_1$ or >15% in PEF between visits (may include respiratory infections)
2. Confirmation of the variable expiratory airflow limitation V

• **Positive exercise challenge test**

• Adults: fall in \( FEV_1 \) of >10% and >200 mL from baseline

• Children: fall in \( FEV_1 \) of >12% predicted, or a fall in \( PEF \) >15%
2. Confirmation of the variable expiratory airflow limitation VI

- **Positive bronchial challenge test (usually performed in adults only)**
  - Fall in FEV₁ from baseline of ≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline, or mannitol challenge
  - The provocation tests are sensitive, but non-specific of asthma, though they have high negative predictive value (negative result excludes asthma with high probability) (O’Byrne et al., 2000; Boulet, 2003)
  - Endobronchial provocations with allergens exist (specific, e.g. to diagnose occupational asthma, though require experience, special conditions, safety measures)
Measurement of bronchial responsiveness; defining bronchial hyperresponsiveness (BHR)

- What provocative concentration of histamine, methacholine etc. causes a significant fall in FEV<sub>1</sub> (e.g. 20%) (PC20FEV<sub>1</sub>)
- Similarly, what provocative cumulative dose causes the same (PD15FEV<sub>1</sub> or PD20FEV<sub>1</sub>)

After achieving the fall in FEV<sub>1</sub>; a bronchodilator is administered (bronchodilator test)
Provoking obstruction with standardized eucapnic voluntary hyperventilation (EHV) or with mannitol

- **EHV:**
  - Preferred in suspicion of asthma in persons in a very good physical shape (sportsmen)
  - Or when exercise testing, mannitol, and hypertonic saline are not able to provoke asthmatic obstruction
  - Recommended by the IOC (Rundell & Slee, 2008)
  - Methacholine test is non-specific (can provoke measurable obstruction in infections, cystic fibrosis, allergic rhinitis, bronchopulmonary dysplasia, and COPD): the risk of false-positivity for asthma

- **Mannitol test:**
  - Comfortable to use: spirometer + ready-to-use kits of dry-powder inhalers (0, 5, 10, 20, 40, 80, 160, 160, and 160 mg)
  - Spirometry after each dose
Diagnostic flowchart for asthma for clinical practice (GINA, 2016)

Respiratory symptoms: are they typical of asthma?

- Yes
  - Detailed history/examination for asthma: does it support asthma diagnosis?
    - Yes
      - Spirometry/(PEF) with reversibility test: Do the results support the diagnosis of asthma
        - Yes
          - Empiric therapy with ICS and prn. SABA, if other diagnoses improbable: review response; new testing in 1-3 months
            - Yes
              - Treat for asthma
            - No
              - Trial to treat other disease or other tests
                - Yes
                  - Treat for other diagnosis
                - No
                  - Repeat on another occasion: confirms asthma?
                    - Yes
                      - Treat for other diagnosis
                    - No
                      - Further history and tests for alternative diagnoses: other diagnosis confirmed?
                        - Yes
                          - Treat for other diagnosis
                        - No
                          - Yes
                            - Treat for asthma
                          - No
                            - No
                              - Yes
                                - Empiric therapy with ICS and prn. SABA, if other diagnoses improbable: review response; new testing in 1-3 months
                                  - Yes
                                    - Treat for asthma
                                  - No
                                    - Repeat on another occasion: confirms asthma?
                                      - Yes
                                        - Treat for other diagnosis
                                      - No
                                        - Yes
                                          - Treat for asthma
                                      - No
                                        - No
                                          - No
                                            - No
Reversibility of airflow obstruction is specific of asthma

- Characteristic of basically only asthma
- Corresponds to the reversibility of the (activity of) the airway inflammation
  - Airway smooth muscle contraction resolves in minutes (short perspective)
  - Longer time (days, weeks) is required for resolving the mucosal edema and evacuation of the secretions
- For the same reasons, unfortunately, asthmatics have the potential for rapid constriction of the airways (inflammation, use of β-blockers etc.)
- **Reversibility**: rapid and significant bronchodilation as a result of a bronchodilating agent (as shown during the bronchodilator test) or slower resolution of the obstruction by the controller therapy (in days or weeks)
- **Variability**: more spontaneous two-way movements in airway obstruction and symptoms with time due to the variable nature of the asthma(tic inflammation)
A standard questionnaire to the patient

• Whether the patient has experienced episodic or periodic wheeze?
• Whether the patient has had troublesome cough, especially during night-time?
• Whether the patient has had cough or wheeze after physical exercise?
• Whether the patient has had cough, wheeze, or chest tightness after contact with air-borne allergens or pollutants?
• Whether “the common cold goes in deep” or the recovery from a common cold takes more time than it occurs commonly (>10 days)?
• Whether the patient has used asthma medications and benefitted from them?

A positive answer to any of these questions makes asthma very probable
Other, supportive measures in the diagnosis of asthma

- **Allergy testing**
  - Allergic concomitant diseases (rhinitis etc.) lends support to the diagnosis of asthma, but does not confirm it
  - **Skin prick testing with common environmental allergens**
  - **Measurement of specific IgE in serum**
  - **Provocation tests with allergens (demanding)**
  - Positive tests do not mean that the allergen is causative of asthma (or symptoms)

- **Non-invasive assessment of the airway inflammation**
  - To diagnose the phenotype (and to decide on specific treatments):
    - Eosinophils and/or neutrophils in the sputum/induced sputum
    - Peripheral blood eosinophils and serum IgE
    - Exhaled air nitric monoxide (FeNO) (Kharitonov et al., 1997) and CO (Horvath & Barnes, 1999) (is not asthma-specific, but are in use to monitor the level of asthma control)
Diagnostic difficulties asthma: children

- Asthma in children <5 years: → the diagnosis is based on symptoms and clinical assessment by the clinician:
  - Symptom patterns (wheeze, cough, breathlessness (typically manifested by activity limitation), and nocturnal symptoms or awakenings)
  - Prolonged cough in infancy, and cough without cold symptoms, are associated with later asthma (Oren, 2015)
  - Presence of risk factors for development of asthma
  - Therapeutic response to controller treatment

- Other measures:
  - Fractional concentration of exhaled nitric oxide (FeNO)
  - Lung function testing after 4-5 years of age
  - Tests for atopy (skin prick testing or allergen-specific IgE)
  - Chest X-ray for differential diagnosis
  - Risk profiles: The Asthma Predictive Index (API) for frequent wheezers (≥4 episodes a year)
Differential diagnosis of wheeze in younger children

- Chronic rhinosinusitis
- Gastroesophageal reflux disease (GERD)
- Recurrent viral infections
- Cystic fibrosis
- Bronchopulmonary dysplasia, tracheomalacia
- Tuberculosis
- Congenital constrictive malformations of the intrathoracic airways
- Foreign body aspiration
- Primary ciliary dyskinesia
- Immune deficiency syndromes
- Congenital heart disease
Differential diagnosis of wheeze in adults

- Dysfunctional (hyper)ventilation syndrome and panic attack
- Upper airway obstruction and foreign body aspiration
- Vocal cord dysfunction ("pseudoasthma")
- Other obstructive lung diseases (chronic obstructive pulmonary disease)
- Diffuse parenchymal lung diseases (DPLH)
- Symptoms form non-respiratory reasons and sources (cardiovascular disease or left ventricular failure, pulmonary hypertension)
Diagnostic difficulties asthma: the elderly

- Asthma is often undiagnosed in the elderly: due to poor perception of airflow limitation; acceptance of dyspnea as being “normal”; lack of fitness
- Differentiation from conditions with wheezing, breathlessness and cough:
  - Chronic obstructive pulmonary disease (COPD); diffuse parenchymal lung diseases
  - Asthma-COPD overlap syndrome (ACOS)
  - Cardiovascular disease or left ventricular failure
  - Side effects of therapies (β-blockers, ACE inhibitors, medications for glaucoma etc.)
  - Churg-Strauss syndrome
  - Allergic bronchopulmonary aspergillosis

- Increase in FEV₁ by >12% with a bronchodilator or 2-week therapy ("steroid test") refers to asthma (as a concomitant or alternative diagnosis!)
Asthma in obese people

• Represents a separate phenotype of asthma
• Asthma is more common and more severe in obese than non-obese people
• Respiratory symptoms associated with obesity can mimic asthma (e.g. breathlessness on exertion due to overweight and deconditioning); overdiagnosis of asthma (around 30%) is not uncommon in obese patients
• Important to confirm asthma with objective measurement of variable airflow limitation
Diagnostic difficulties in asthma: smokers and ex-smokers

- Asthma and COPD: difficult to distinguish, particularly in older patients and smokers and ex-smokers,
- These conditions may overlap (asthma-COPD overlap (syndrome), ACO(S))
- Low diffusion capacity is more common in COPD (emphysema-type) than asthma
- The history (incl. risk factors) and pattern of symptoms and past records can assist to distinguish patients with COPD from those with long-standing asthma, who have developed fixed airflow limitation
- Uncertainty in the diagnosis should prompt early referral for specialized investigation and treatment, as ACOS conveys worse prognosis than does asthma or COPD alone

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## Diagnosis of asthma in people already on treatment (GINA, 2014-2016)

<table>
<thead>
<tr>
<th>Situation</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable symptoms and variable obstruction</td>
<td>• Diagnosis of asthma is confirmed</td>
</tr>
</tbody>
</table>
| Variable symptoms, but no variable obstruction | • Repeat BD reversibility test again after withholding BD; if normal, consider alternative diagnoses  
• If FEV₁ is >70% predicted: consider a bronchial provocation test; If negative, consider stepping down controller treatment  
• If FEV₁ is <70% predicted: consider stepping up controller treatment for 3 months, then reassess; if no response, resume previous treatment and refer patient for diagnosis and investigations |
| Few symptoms, normal lung function, and no variable airflow obstruction | • Repeat BD reversibility test again after withholding BD; if normal, consider alternative diagnoses  
• Consider stepping down controller treatment:  
• If symptoms emerge and lung function falls: asthma  
• If no change at lowest controller step: consider ceasing controller, and monitor for at least 12 months |
| Persistent shortness of breath and fixed airflow limitation | • Consider stepping up controller treatment for 3 months;  
• If no response, resume previous treatment and refer patient for diagnosis and investigation  
• Consider asthma-COPD overlap syndrome |
Certain variants of asthma I: occupational asthma

• Important to distinguish between occupational asthma and work-aggravated asthma
• Occupational asthma: appears at workplace and is due to the factors present on the workplace
• 5-20% in adult-onset asthma
• Inhaled 1) allergens or 2) irritants (>400 ”asthmagens”)
• Occupational rhinitis may precede asthma by ≤1 year
• Careful and complex history: a systematic inquiry about work history and exposures, including hobbies; asking whether the symptoms improve when they are away from work (weekends or vacation) is essential for screening
• Detailed measurements of lung function (FEV₁, PEF) and bronchial responsiveness at work and away
• Early diagnosis and cessation of the exposures are essential, as persistent exposure is associated with worse outcomes (permanent loss of lung function)
Certain variants of asthma II: cough variant asthma
• Chronic cough as the principal, if not only, symptom, associated with airway hyperresponsiveness
• Often more problematic at night
• More common in children
• Lung function may be normal

Diagnosis:
• Documentation of the variability in lung function
• Measurement of bronchial reactivity, sputum eosinophils etc.

Differential diagnosis:
• Eosinophilic bronchitis: cough and sputum eosinophils but normal spirometry and airway responsiveness
• Other variants for differential diagnosis [ACE inhibitors, GERD, chronic upper airway cough syndrome (“postnasal drip”), chronic sinusitis, vocal cord dysfunction etc.]
Certain variants of asthma III: seasonal asthma

• Symptoms overall or more severe symptoms during <2 months per years during certain season
• Allergic: outdoor allergens
• Possible intermittent therapy with inhaled glucocorticosteroids is indicated (with coverage of the allergen season + 4 weeks after that, with a prn. bronchodilator)
Exercise-induced bronchoconstriction (EIB) and exercise-induced asthma (EIA)

- In the majority of asthma patients, physical exercise is a symptom-provoking factor, in a minority, it is the only factor (exercise provocation for the diagnosis, e.g. 8-min. running protocol, Anderson, 2002)
- Typically, the asthma symptoms due to EIB (wheeze, dyspnea, cough etc.) commence 5-10 min. after the end of the exercising (rarely during the exercise)
- Running is the most potent among the exercise triggers
- The symptoms typically resolve in 30-45 minutes
- More prominent in dry cold weather/climate
- Reasons and mechanisms (2):
  - Evaporation of water from the airway surfaces in heightened ventilation volumes → relative increase in the concentrations of mediators and irritants
  - Cooling of the respiratory mucosal surfaces of the respiratory tract → vasoconstriction, followed by reperfusion edema after the end of the exercise (after the „cooling“)
  - Rapid effect of inhaled β₂-agononists or prevention by β₂-agonists before the panned exercise
## Differential diagnosis of asthma: children 6-11 years (GINA, 2016)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic upper airway cough syndrome</td>
<td>Sneezing, itching, blocked nose, throat-clearing</td>
</tr>
<tr>
<td>• Inhaled foreign body</td>
<td>Sudden onset of symptoms, unilateral wheeze</td>
</tr>
<tr>
<td>• Bronchiectasis</td>
<td>Recurrent infections, productive cough</td>
</tr>
<tr>
<td>• Primary ciliary dyskinesia</td>
<td>Recurrent infections, productive cough, sinusitis</td>
</tr>
<tr>
<td>• Congenital heart disease</td>
<td>Cardiac murmurs, other signs of LHD</td>
</tr>
<tr>
<td>• Bronchopulmonary dysplasia</td>
<td>Pre-term delivery, symptoms since birth</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
<td>Excessive cough and mucus production, gastrointestinal symptoms</td>
</tr>
</tbody>
</table>

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## Differential diagnosis of asthma: people 12-39 years (GINA, 2016)

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<tr>
<td>• Vocal cord dysfunction (&quot;pseudoasthma&quot;)</td>
<td>Dyspnea, inspiratory wheezing (stridor)</td>
</tr>
<tr>
<td>• Hyperventilation, dysfunctional breathing</td>
<td>Dizziness, paresthesia, sighing</td>
</tr>
<tr>
<td>• Bronchiectasis</td>
<td>Productive cough, recurrent infections</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
<td>Excessive cough and mucus production</td>
</tr>
<tr>
<td>• Congenital heart disease</td>
<td>Cardiac murmurs, other signs of LHD</td>
</tr>
<tr>
<td>• Alpha1-antitrypsin deficiency</td>
<td>Shortness of breath, family history of early emphysema</td>
</tr>
<tr>
<td>• Inhaled foreign body</td>
<td>Sudden onset of symptoms</td>
</tr>
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<td>Cough, sputum, dyspnea on exertion, smoking or noxious exposure</td>
</tr>
<tr>
<td>Cardiac failure (&quot;cardiac asthma&quot;)</td>
<td>Dyspnea with exertion, nocturnal symptoms</td>
</tr>
<tr>
<td>Medication-related cough</td>
<td>Treatment with angiotensin converting enzyme (ACE) inhibitor</td>
</tr>
<tr>
<td>Parenchymal lung disease</td>
<td>Dyspnea with exertion, non-productive cough, finger clubbing</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Sudden onset of dyspnea, chest pain</td>
</tr>
<tr>
<td>Central airway obstruction</td>
<td>Dyspnea, unresponsive to bronchodilators</td>
</tr>
</tbody>
</table>
Vocal cord dysfunction („pseudoasthma“)

- Flow-volume curves of forced spirometry: classical curve shapes of a patient with vocal cord dysfunction caused by injury of the recurrent laryngeal nerve during thyroid resection due to nodular struma
- The patient has neither history nor signs of asthma
- The black dots indicate the expected normal curves (by gender, age and body length)
### Differences between asthma and COPD

<table>
<thead>
<tr>
<th></th>
<th><strong>Asthma</strong></th>
<th><strong>COPD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of the patient</strong></td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td><strong>Smoking (history)</strong></td>
<td>May be</td>
<td>Almost always</td>
</tr>
<tr>
<td><strong>Allergy</strong></td>
<td>Often</td>
<td>Rarely</td>
</tr>
<tr>
<td><strong>Peripheral eosinophilia</strong></td>
<td>Often</td>
<td>Rarely</td>
</tr>
<tr>
<td><strong>Eosinophils in sputum</strong></td>
<td>Often</td>
<td>Rarely</td>
</tr>
<tr>
<td><strong>Onset of the disease</strong></td>
<td>Relatively abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td><strong>Breathlessness, shortness of breath</strong></td>
<td>An early problem</td>
<td>Relatively late complaint</td>
</tr>
<tr>
<td><strong>Asymptomatic periods</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Nocturnal symptoms</strong></td>
<td>Frequent</td>
<td>Not in the beginning</td>
</tr>
<tr>
<td><strong>Normal pulmonary function</strong></td>
<td>Often, sometimes</td>
<td>Never</td>
</tr>
<tr>
<td><strong>Diffusing capacity of the lung</strong></td>
<td>Normal</td>
<td>Decreased in emphysema</td>
</tr>
<tr>
<td><strong>PEF diurnal variability</strong></td>
<td>Usually &gt;20%</td>
<td>Usually &lt;20%</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; response to β&lt;sub&gt;2&lt;/sub&gt;-agonists</strong></td>
<td>Good (&gt;15%)</td>
<td>Low (&lt;10%)</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; response to oral steroids</strong></td>
<td>Usually good (&gt;15%)</td>
<td>Low (&lt;10%)</td>
</tr>
<tr>
<td><strong>Late complications</strong></td>
<td>No emphysema</td>
<td>Emphysema, cor pulmonale</td>
</tr>
<tr>
<td><strong>T-lymphocytes</strong></td>
<td>CD4+</td>
<td>CD8+</td>
</tr>
<tr>
<td><strong>BM thickening</strong></td>
<td>Characteristic</td>
<td>Not characteristic</td>
</tr>
<tr>
<td><strong>Bronchial epithelium</strong></td>
<td>Destroyed</td>
<td>Usually not destroyed</td>
</tr>
<tr>
<td><strong>Course of the disease</strong></td>
<td>Intermittent</td>
<td>Progressive</td>
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A. Altraja ©2017
Distinguishing between COPD and asthma: the effect of oral glucocorticosteroids (an example)

**COPD**
- Prednisolone 30 mg/day, for 2 weeks

**Asthma**
- Prednisolone 30 mg/day, for 2 weeks
Distinguishing between COPD and asthma

Forced flow-volume spirometry

Obstruction is present

Bronchodilator test

- FEV<sub>1</sub> ↑ ≥12%
- FEV<sub>1</sub> ↑ <12%

Asthma

Steroid test:
- 30-40 mg prednisolone ×1: 2 weeks
- FEV<sub>1</sub> ↑ ≥12%
- FEV<sub>1</sub> ↑ <12%

Asthma

COPD

Obstruction is absent

Repeat test or provocation:
- Physical exercise
- Methacholine, histamine, mannitol, hypertonic saline, hyperventilation

- FEV<sub>1</sub> ↓<15(20)%
- FEV<sub>1</sub> ↓ ≥15(20)%

Healthy

Asthma

Asthma suspicion

- New spirometry, when obstruction is more probable
- Cough variant asthma etc.

FEV<sub>1</sub> ↑ ≥12% after bronchodilator
### Asthma and COPD: alone or together, mild or severe, clear or not clear

<table>
<thead>
<tr>
<th></th>
<th>Asthma history</th>
<th>COPD risk factors</th>
<th>Positive bronchodilator response</th>
<th>Obstruction remains after bronchodilator</th>
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<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
<th>Newly-diagnosed asthma</th>
<th>Asthma and COPD (overlap)</th>
<th>COPD and (probable) COPD manifested asthma</th>
<th>Chronic asthma with airway inflammation (therapeutic trial or steroid test)</th>
<th>Chronic asthma, probably in remission</th>
<th>Mild asthma (PEF-follow-up or provocation)</th>
<th>Newly-diagnosed chronic asthma (consider also other causes of obstruction)</th>
<th>Consider other causes of obstruction</th>
</tr>
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Other differential diagnostic variants in asthma I

- Local obstruction of the respiratory tract (neoplasm, foreign body, stenosis, compression by the superior vena cava, retrosternal struma): there is local, unilateral, intrapulmonary stridor (bronchoscopy is indicated for the diagnosis)
- Panic disorder
- Anemia
Other options for the differential diagnosis of asthma II

- Gastroesophageal reflux disease (precipitates causes cough, may release asthma symptoms)
- Viral bronchitis and bronchiolitis
- Eosinophilic pneumonia and eosinophilic bronchitis
- Systemic vasculitis (eosinophilic granulomatosis with polyangiitis, formerly Churg-Strauss syndrome): real asthma as a component
- Carcinoid syndrome
- Allergic bronchopulmonary aspergillosis (ABPA): real asthma as a component
General differential diagnosis of the obstructive status of the airways

• “Conducting airway-type symptoms”:
  • Cough, wheeze, dyspnea, breathlessness (with airflow resistance in the airways) and obstruction on spirometry or PEF measurement)

• Always the need to decide: is the obstruction local or generalized (involves all conducting airways bilaterally)
• Always to clarify: is the finding on auscultation not unilateral: local obstruction
General differential diagnosis of the obstructive status of the airways

- Central obstruction (stridor during inspirium > that in expirium, decreased PIF on spirometry etc.)
  - In the lumen: tumor, foreign body
  - In the wall: tumor, stenosis, granulation tissue, paresis of \textit{n. laryngeus recurrens}, vocal cord dysfunction
  - Outside the wall: enlarged lymph nodes, neoplasms

- Obstruction in the medium-sized or small airways
  - In the lumen: mucus, pus, mycetoma, tumor
    - In the wall: mucus, glandular hypertrophy, edema, bronchospasm
  - Outside the airways: peribronchial inflammation, emphysema
„Severe asthma“

WHO classification:
• Untreated asthma
• Improperly treated asthma
• Difficult-to-treat asthma
  • Bad compliance
  • Persistent exacerbating factors or important concomitant diseases
• 10% true, severe, treatment-refractory asthma
Severe asthma: ERS/ATS definition (for patients ≥6 years)

• **Severe asthma:** asthma, which requires treatment with guideline-suggested medications for GINA steps 4-5:
  • High dose ICS and LABA or leukotriene modifier/theophylline) for the previous year
  • Or systemic CS for ≥50% of the previous year to prevent it from becoming “uncontrolled”
  • Or which remains “uncontrolled” despite this therapy

• **Uncontrolled asthma:** defined as at least one of the following:
  1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or “not well controlled” by NAEPP/GINA guidelines)
  2) Frequent severe exacerbations: ≥2 bursts of systemic CS (>3 days each) in the previous year
  3) Serious exacerbations: at least one hospitalization, ICU stay, or mechanical ventilation in the previous year
  4) Airflow limitation: after appropriate bronchodilator withhold FEV₁ <80% predicted

• Controlled asthma that worsens on tapering of the high doses of ICS or systemic CS (or additional biologics)
Investigations in severe asthma

- Confidence in the diagnosis: COPD, ACOS, (recurrent) infections
- Investigations directed to concomitant diseases: sinusitis, obesity, GERD, obstructive sleep apnea, psychosocial and psychiatric conditions
- Inhalation techniques and control of compliance (barriers to that)
- Control and analyses for threats: exposures, permanent exacerbators, incl. allergens and irritants

GINA, 2015-2017
Phenotypes of severe asthma (ERS/ATS)

- **Severe allergic asthma**
  - Eosinophils in blood and sputum, high S-IgE, high FeNO
  - Treatment: anti-IL-4/IL-13, anti-IgE, anti-IL-4 receptor

- **Eosinophilic asthma**
  - Eosinophils in blood and sputum, recurrent exacerbations, high FeNO
  - Treatment: anti-IL-5, anti-IL-4/IL-13, anti-IL-4 receptor

- **Neutrophilic (non-eosinophilic) asthma**
  - Glucocorticosteroid resistance, bacterial infections
  - Treatment: anti-IL-8, CXCR2 antagonists, anti-LTB₄, macrolides

- **Chronic airflow obstruction**
  - Airway wall remodeling as increased airway wall thickness
    - Treatment: anti-IL-13, bronchial thermoplasty

- **Recurrent exacerbations**
  - Eosinophils in sputum, glucocorticosteroid resistance (ICS, SCS)
    - Treatment: anti-IL5, anti-IgE

- **Glucocorticosteroid resistance**
  - Increased sputum neutrophilia
    - Treatment suggestions: p38 MAPK inhibitors, theophylline, macrolides