Immunological Lung Diseases

Asthma

Selected topics in Clinical Immunology
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Outline

• What is asthma?
• From epidemiology to pathophysiology
• From symptoms to diagnosis
• From endotypes to phenotypes
  o Eosinophilic asthma
• Asthma exacerbation
• From assessment to treatment
  o Non-pharmacological management
  o Generic pharmacological management
  o Phenotype directed treatment
  o Biologics in eosinophilic asthma
Asthma

Heterogeneous chronic airway disease

Chronic Airway Inflammation

↓

Expiratory Airflow Limitation

↓

Respiratory Symptoms
Epidemiology

- 300-400 million people worldwide affected
- Prevalence increasing
- High burden on health care system
- Major cause of school and work absence
- Early diagnosis, prevention, and treatment is cost-effective

Teresa et al. BMC Public Health, 2012
Impaired Airway Inflammatory Response → Bronchoconstriction

Normal

Bronchial Mucosa

Asthma

Bronchial wall oedema
Mucus hypersecretion
Muscle contraction

Bronchial wall
(smooth muscle, connective tissue)
Allergens, Viruses, Inhalational Toxins
Environmental factors
Genetics

Dysregulated epithelial barrier

Airway Remodeling
- Epithelial damage
- Cilial dysfunction
- Goblet cell hyperplasia
- Increased vascularity
- Proliferation of myofibroblasts and fibrocytes

Inflammation

Airway Hyperresponsiveness

Airway narrowing

Symptoms

Trigger
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Symptoms

Variable in 1) occurrence, 2) frequency, 3) intensity

• **Shortness of breath**
  • Acute – chronic – at rest – at night! - at or after exercise
• **Wheezing**
• **Chest tightness**
• **Cough**

• **Triggers**
Diagnosis

Typical Symptoms
- > 1 symptom
- worse at night
- variability
- triggers

Variable Airflow Limitation
- Office pulmonary function test
- Home peak-flow measurement

ASTHMA
Measurement of airflow limitation

Airflow limitation & variability:
- At follow-up (spontaneous, changing triggers)
- Improvement after inhalation with bronchodilator (e.g. Salbutamol)
- Worsening after bronchoprovocation (e.g. Methacholine)

National Heart Lung and Blood Insitute (NIH)
Spirometry

Time (seconds)

Volume

FEV₁

Asthma (after BD)

Asthma (before BD)

Normal

Flow

Volume
**Example**

Forced Vital Capacity in 1s

Forced Vital Capacity

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<th>Testdatum</th>
<th>Soll</th>
<th>Best</th>
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<th>Nach</th>
<th>% Nach</th>
<th>%Änd...</th>
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<td>3.39</td>
<td>45</td>
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<td>PEF</td>
<td>L/s</td>
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Asthma Endotype - Phenotype

Asthma Syndrome
Symptoms
Variable airflow limitation
Bronchial hyperreactivity
Airway inflammation

Endotypes
Links molecular pathways and clinical characteristics

Phenotypes
Clinical presentation
Treatment response

Wenzel et al., NatMed 2012
Phenotypes

**$T_{H2}$-Asthma:**
- Allergic eosinophilic → early onset
- Non allergic eosinophilic → late onset
- Aspirin exacerbated
- Exercise induced

**Non-$T_{H2}$-Asthma:**
- Late onset
- Obesity related
- Smoking related
- Elderly (Immunosenescence)
- Neutrophilic
- Paucigranulocytic

Wenzel et al., NatMed 2012

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Endotypes

**Eosinophilic Asthma**
- Allergic eosinophilic inflammation
- Non-allergic eosinophilic inflammation

**Non-Eosinophilic Asthma**
- Pauci-granulocytic asthma
- T1/T17 neutrophilic inflammation

**Mixed granulocytic asthma**


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Eosinophilic Asthma

Brusselle et al., NatMed 2013

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Asthma Exacerbation

• ‘Flare-up’, ‘Attack’
• Acute or sub-acute worsening of symptoms and lung function compared with the patient’s usual status
• Triggers: Viral respiratory infection, respiratory allergens, medications (β-blockers, aspirin, NSAIDs)
Asthma Exacerbation

Severity determines management

1) Self-management with a written asthma action plan

2) Management in primary care

3) Management in the emergency department/hospital
Asthma Treatment: Goals

1) **Minimise symptom burden**
   - Day-to-day symptoms
     - Need no/little reliever medication
   - Disturbed sleep
   - Activity limitation

2) **Minimise the risk of adverse asthma outcomes**
   - Exacerbations
   - Persistent airflow limitation
     - Goal: normal/near normal lung function
   - Medication side-effects

Compliance/Adherence to treatment
Inhalation technique
Comorbidities/Co-factors

Shared decision making
From Assessment to Treatment

Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function

Diagnosis
Symptom control & risk factors (including lung function)
Inhaler technique & adherence
Patient preference

Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors

GINA 2019
Stepwise approach to control asthma symptoms & reduce risk

**CONTROLLER MEDICATION**

**STEP 1**
As-needed low dose ICS-formoterol

**STEP 2**
Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol

**STEP 3**
Low dose ICS-LABA

**STEP 4**
Medium dose ICS-LABA

**STEP 5**
High dose ICS-LABA

Phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

**RELIEVER MEDICATION**

- As-needed short-acting β2-agonist (SABA)
- As-needed low dose ICS-formoterol
- Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA is taken
- Medium dose ICS, or low dose ICS+LTRA
- High dose ICS, add-on tiotropium, or add-on LTRA
- Add low dose OCS, but consider side-effects

**Genotype assessment**
Type 2 targeted biologic therapies

ICS: inhaled corticosteroids
OCS: oral corticosteroids
LABA: long-acting β2 agonist

Modified from GINA 2019

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Non-pharmacological interventions & management of co-factors

- Patient education
  - Self-monitoring skills, peak flow measurement, written asthma action plan
- Smoking cessation
- Assess and manage work-related asthma
- Encourage Physical activity
  - Exercise-induced bronchoconstriction
- Allergen avoidance
  - House dust mite eradication
  - Pets…
  - Sublingual immunotherapy (SLIT)
  - Availability of injectable epinephrine for anaphylaxis
- Potential intolerance to NSAIDs or beta-blockers
Assess asthma control & act accordingly

If you feel …
Then do …
Asthma inhalation therapy

TOP 10 INHALER MISTAKES
Inhaled asthma medicine needs to reach the airways to work. Here are 10 common mistakes made when using a metered-dose inhaler (MDI) and how to correct them.

1. Slouching
   FIX IT: Sitting up straight or standing allows the lungs to fully inhale and provides more power to exhale.

2. Using an empty inhaler
   FIX IT: Request a refill when the inhaler has 30 puffs or doses left.

3. Not shaking or priming the inhaler
   FIX IT: Shake the inhaler several times before each use. Prime it by releasing three to four test sprays. Prime again if not used for several weeks.

4. Using an MDI inhaler without a spacer
   FIX IT: A spacer helps get more medicine to the airways. Insert the inhaler into the spacer. Spray one puff of medicine and inhale slowly. Hold your breath for a count of 10 and exhale slowly.

5. Spraying several puffs of inhaler into spacer
   FIX IT: Spray only one puff of the inhaler into the spacer for each breath. Breathe out before inhaling. Inhale and hold your breath for a count of 10. Then exhale. Repeat for the number of puffs the doctor prescribed.

6. Holding the head too far forward or backward
   FIX IT: The head needs to be in a normal position, not too far back or too far forward, to help move the medicine to reach the airways.

7. Tongue or teeth in the way of spacer/inhaler opening
   FIX IT: Put the mouthpiece of the spacer/inhaler in the mouth above the tongue, under the top teeth.

8. Mouth not tight enough around spacer/inhaler
   FIX IT: Close the lips around the mouthpiece of the spacer or inhaler so air does not escape.

9. Directing spacer/inhaler at tongue or roof of mouth
   FIX IT: Aim the spacer/inhaler at the back of the throat, so the medicine reaches the lungs.

10. Inhaling medicine too fast
    FIX IT: Inhale slowly. A whoosh sound means when using a spacer means the inhalation is too fast.

https://www.nationaljewish.org
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Phenotype-directed Therapy in severe Asthma

Inflammation

- Eosinophilic
  - Allergic
    - High-dose ICS
    - LTRA
    - OCS
    - Biologics
  - Non-allergic
- Neutrophilic
  - Low-dose macrolide antibiotic
- Pauci-granulocytic
  - Weight loss in female obese asthma
- Fixed Obstruction*
  - Bronchial thermoplasty?

*Smooth muscle bronchial hyperplasia

Adapted from Rothe T et al. Schweiz Med Forum 2015
Asthma therapy is effective

Papi et al. Lancet 2018

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Asthma therapy has come a long way

**Anti-eosinophil drugs for asthma**

- IgE
- IL-4Rα
- IL-5Rα
- IL-5
- IL-13
- CRTH2
- IL-25, IL-33, TSLP

**Timeline:**
- 1950: Cortisone (1949)
- 1960: ICS (1973)
- 2010: benralizumab (2017)
- 2020: dupilumab
- 2020: tralokinumab
- 2020: fevipiprant

Bel et al., CHEST 2017

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Intersection of biology and therapeutics: Type 2 targeted therapeutics

Peters & Wenzel, The Lancet 2020
## Biologics in Eosinophilic Asthma

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Description</th>
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<tbody>
<tr>
<td>Anti IgE</td>
<td>Omalizumab</td>
</tr>
<tr>
<td>Anti IL-5</td>
<td>Mepolizumab</td>
</tr>
<tr>
<td></td>
<td>Reslizumab</td>
</tr>
<tr>
<td>Anti IL-5R</td>
<td>Benralizumab</td>
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<td>Anti IL-13</td>
<td>Lebrikizumab</td>
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<tr>
<td>Anti IL-4R</td>
<td>Dupilumab</td>
</tr>
<tr>
<td>Anti TSLP</td>
<td>Tezelepumab</td>
</tr>
<tr>
<td>Anti Alarmine</td>
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</table>

Diagram illustrating immune cells and cytokines involved in eosinophilic airway inflammation.
Omalizumab: anti IgE monoclonal antibody

Reduction in Exacerbations

Reduction in Hospitalisations

Meta-analysis including 10 studies and >3200 participants
Follow-up 4-15 months.

Normansell et al. Cochrane Database of Systematic Reviews 2014
Mepolizumab: Humanized IgG1 monoclonal anti IL-5 antibody

- Reduction of annual exacerbation rate by >30%
- Improvement of lung function (FEV1) by 100ml
- Improved quality of life
Mepolizumab: Humanized IgG1 monoclonal anti IL-5 antibody

- Reduction of annual exacerbation rate by >30%
- Improvement of lung function (FEV1) by 100ml
- Improved quality of life
- Improved asthma control
- Reduction in need for oral glucocorticoids (-50%)

Benralizumab: Humanized monoclonal antibody against IL-5R

Reduction in Oral Glucocorticoid Dose
Placebo: -25%
Benralizumab: -75%

Longer time to the first exacerbation with benralizumab:
HR 0.39 (95%CI 0.22-0.66)
HR 0.32 (95%CI 0.17-0.57)

Nair et al., NEJM 2017
Dupilumab:
Humanized monoclonal antibody against IL-4R
Inhibits IL-4 and IL-13 signalling

C/D: Eosinophilic (≥300 cells/mcl); E/F: Non-eosinophilic (<300 cells/mcl)
Primary endpoint: Improvement in FEV1 after 12 weeks for both groups met
Larger effect size in eosinophilic group.

Wenzel et al., Lancet 2017
Dupilumab: Humanized monoclonal antibody against IL-4R
Inhibits IL-4 and IL-13 signalling

Severe exacerbations event rates/year
B: Eosinophilic (≥300 cells/mcl)
C: Non-eosinophilic (<300 cells/mcl)

- Significant reduction in frequency of severe exacerbations.
- Better effect in patients with high eosinophil blood count

Wenzel et al., Lancet 2017
Treatment effect of type 2 biologic agents in patients with eosinophilic asthma

Peters & Wenzel, The Lancet 2020
## Asthma biologics: Indications and limitations

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Indications</th>
<th>Exacerbations (prev. year)</th>
<th>Blood eosinophils</th>
<th>Price</th>
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</thead>
<tbody>
<tr>
<td>Mepolizumab (Nucala®)</td>
<td>≥ 2 &amp; GINA Step 5, ≥ 2 &amp; OCS ≥ 6 months/year</td>
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<td>≥ 0.4G/L</td>
<td>1409 CHF/month</td>
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<tr>
<td>Reslizumab (Cinqaero®)</td>
<td>≥ 4 &amp; GINA Step 4</td>
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<td>Ca. 1300 CHF/month</td>
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<tr>
<td>Benralizumab (Fasenra®)</td>
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<td></td>
<td></td>
<td>1429 CHF/month</td>
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<tr>
<td>Omalizumab (Xolair®)</td>
<td>Severe, allergic Asthma. Management by pulmonologist or allergologist.</td>
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<td></td>
<td>1000-2000 CHF/month</td>
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<tr>
<td>Dupilumab (Dupixent®)</td>
<td>Severe atopic dermatitis (not approved for asthma yet)</td>
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<td>3033 CHF/month</td>
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</table>
Biomarkers for asthma diagnosis & treatment response

Emerging therapies for non-eosinophilic (Th2 low) asthma

Tezepelumab:
- Human monoclonal antibody for thymic stromal lymphopoietin (TSLP)
- Phase 2 study (Corren et al. NEJM 2017)
- Lower rates asthma exacerbations (-62 to -71%) and higher FEV1 independent of baseline blood eosinophil counts

IL-33 Inhibitors:
- Involved in ILC2 activation: Little clinical effect in Phase 2

Other potential pathways:
- Targeting systemic (IL-6 high) inflammation in obesity and age-associated asthma
- Treatment to restore inflammation resolution
- Treatment of microbial dysbiosis
Take away

- Asthma is a common and potentially severe chronic disease with variable degree of airway inflammation and obstruction.
- Pathophysiology is based on complex gene–environment & host-environment interactions.
- Respiratory symptoms include shortness of breath, cough, wheezing and chest tightness.
- Presentation is heterogeneous as there are several different phenotypes and underlying endotypes of asthma.
- Therapy includes non-pharmacological, generic pharmacological, and phenotype directed medication in severe asthma.
- Asthma can be controlled – not cured.