Immunological Lung Diseases
Asthma

Selected topics in Clinical Immunology
March, 28, 2019

Dr. med. Sabina A. Guler, MD MHSc
Oberärztin Universitätsklinik für Pneumologie
Inselspital, Bern
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

Chronic Airway Inflammation

Exspiratory Airflow Obstruction

Respiratory Symptoms
Epidemiology

- More than 300 million people worldwide are 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
Bronchoconstriction

Normal

Asthma

Bronchial Mucosa

Bronchial wall (smooth muscle, connective tissue)

Bronchial wall oedema
Mucus production
Muscle contraction
Allergens, Viruses, Inhalational Toxins
Environmental factors
Genetics

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

Inflammation

Airway narrowing

Symptoms

Airway Hyperresponsiveness

Trigger
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

Variable Airflow Limitation

ASTHMA

 ✓ > 1 symptom
 ✓ worse at night
 ✓ variability
 ✓ triggers

Immunological Lung Diseases_S.Guler
Lung function testing - Spirometry

Volume

Flow

FEV₁

Time (seconds)

Flow

Volume

Normal

Asthma (after BD)

Asthma (before BD)

Normal

Asthma (after BD)

Asthma (before BD)
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

---

Immunological Lung Diseases_S.Guler
Phentotypes

**$T_H^2$-Asthma:**
- Allergic eosinophilic → early onset
- Non allergic eosinophilic → late onset
- Aspirin exacerbated
- Exercise induced

**Non-$T_H^2$-Asthma:**
- Late onset
- Obesity related
- Neutrophilic
- Paucigranulocytic

Wenzel et al., NatMed 2012
Immunological Lung Diseases_S.Guler
Endotypes

Eosinophilic Asthma

Allergic eosinophilic inflammation

Non-allergic eosinophilic inflammation

Mixed granulocytic asthma

Health

Airway smooth muscle

Reticular Basement Membrane

Epithelium

Allergens

Pollutants, oxidative stress

Pollutants, microbes

Dendritic cell

T1/T17 neutrophilic inflammation

Pauci-granulocytic asthma

Non-Eosinophilic Asthma

Eosinophilic Asthma

Brusselle et al., NatMed 2013

Immunological Lung Diseases_S.Guler
Clinical Biomarkers in Allergic Asthma


Immunological Lung Diseases_S.Guler
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

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

Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors

GINA 2018

Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function

REVIEW RESPONSE

ADJUST TREATMENT
**Stepwise approach to control asthma symptoms & reduce risk**

<table>
<thead>
<tr>
<th>CONTROLLER MEDICATION</th>
<th>RELIEVER MEDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 1</strong></td>
<td>ICS</td>
</tr>
<tr>
<td>Low dose ICS</td>
<td>inhaled corticosteroids</td>
</tr>
<tr>
<td>Consider low dose ICS</td>
<td>OCS</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists (LTRA)</td>
<td>oral corticosteroids</td>
</tr>
<tr>
<td>Low dose theophylline*</td>
<td>LABA</td>
</tr>
<tr>
<td></td>
<td>long-acting β2 agonist</td>
</tr>
<tr>
<td><strong>STEP 2</strong></td>
<td></td>
</tr>
<tr>
<td>Low dose ICS</td>
<td></td>
</tr>
<tr>
<td>Leukotriene receptor antagonists (LTRA)</td>
<td></td>
</tr>
<tr>
<td>Low dose theophylline*</td>
<td></td>
</tr>
<tr>
<td>As-needed short-acting beta2-agonist (SABA)</td>
<td></td>
</tr>
<tr>
<td><strong>STEP 3</strong></td>
<td></td>
</tr>
<tr>
<td>Low dose ICS/LABA**</td>
<td></td>
</tr>
<tr>
<td>Med/high dose ICS</td>
<td></td>
</tr>
<tr>
<td>Med/high dose ICS + LTRA (or + theoph*)</td>
<td></td>
</tr>
<tr>
<td>Add tiotropium**</td>
<td></td>
</tr>
<tr>
<td>Add low dose OCS</td>
<td></td>
</tr>
<tr>
<td><strong>STEP 4</strong></td>
<td></td>
</tr>
<tr>
<td>Med/high dose ICS</td>
<td></td>
</tr>
<tr>
<td>Med/high dose ICS + LTRA (or + theoph*)</td>
<td></td>
</tr>
<tr>
<td>Add tiotropium**</td>
<td></td>
</tr>
<tr>
<td>Add low dose OCS</td>
<td></td>
</tr>
<tr>
<td><strong>STEP 5</strong></td>
<td></td>
</tr>
<tr>
<td>Refer for add-on treatment e.g. tiotropium,<strong>†</strong> anti-IgE, anti-IL5*</td>
<td></td>
</tr>
</tbody>
</table>

Modified from GINA 2018

*Immunological Lung Diseases_S.Guler*
Non-pharmacological interventions & management of co-factors

• Patient education
  • Self-monitoring skill, 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 inhale.

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 well 10 to 15 times for the medication to be easy to work. When using a new inhaler, 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: An spacer helps more of the medicine get 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 make a direct path for the medicine to reach the airways.

7. Tongue or teeth in the way of spacer/inhaler opening
   FIX IT: For the mouthpiece of the spacer/inhaler is 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: Breathe slowly. A whole mouth inhaler when using a spacer means the inhalation is too fast.

https://www.nationaljewish.org

Immunological Lung Diseases_S.Guler
Phenotype-directed Asthma Therapy

Inflammation

Eosinophilic
Allergic
High-dose ICS
LTRA
OCS
Biologics
Immunotherapy

Neutrophilic
Non-allergic
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
Asthma therapy has come a long way

Anti-eosinophil drugs for asthma

- Cortisone 1949
- ICS 1973
- omalizumab 2003
- mepolizumab 2015
- reslizumab 2016
- benralizumab 2017
- dupilumab
- tralokinumab
- fevipiprant
- Anti-alarmins

Bel et al., CHEST 2017

Immunological Lung Diseases_S.Guler
Biologics in Eosinophilic Asthma

- Anti IgE: Omalizumab
- Anti IL-5: Mepolizumab
- Anti IL-5R: Reslizumab
- Anti IL-13: Benralizumab
- Anti IL-4R: Lebrikizumab
- Anti IL-4R: Tralokinumab
- Anti TSLP: Dupilumab
- Anti Alarmine: Tezelepumab
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

Immunological Lung Diseases_S.Guler
Mepolizumab: Humanized IgG1 monoclonal anti IL-5 antibody

- Reduction of annual exacerbation rate by >30%
- Incremental 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%
- Incremental 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% BR

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)
Asthma biologics: Indications and limitations

<table>
<thead>
<tr>
<th></th>
<th>Exacerbations (prev. year)</th>
<th>Blood eosinophils</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab (Nucala®)</td>
<td>≥ 2 &amp; GINA Step 5</td>
<td>≥ 0.4G/L</td>
<td>1409 CHF/month</td>
</tr>
<tr>
<td></td>
<td>≥ 2 &amp; OCS ≥ 6 months/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 4 &amp; GINA Step 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reslizumab (Cinqaero®)</td>
<td></td>
<td></td>
<td>Ca. 1300 CHF/month</td>
</tr>
<tr>
<td></td>
<td>≥ 4 &amp; GINA Step 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benralizumab (Fasenra®)</td>
<td></td>
<td>1429 CHF/month</td>
<td></td>
</tr>
<tr>
<td>Omalizumab (Xolair®)</td>
<td>Severe, allergic Asthma. Management by pulmonologist or allergologist.</td>
<td></td>
<td>1000-2000 CHF/month</td>
</tr>
</tbody>
</table>

www.swissmedic.ch
http://www.spezialitätenliste.ch/
Take away

- Asthma is 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.