Obstructive Lung Disorders
COPD & Asthma

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Afferent Lymphatics
Efferent Lymphatics

Afferent Lymphatics
Draining Lymph Node

Respiratory Tract Homing

Systemic Circulation

DC, dendritic cell
AMDC, airway mucosa DC
LPDC, lung parenchyma DC
AM, alveolar macrophage
Naïve T cell Differentiation

**Cellular Immunity**
e.g. bacteria, viruses

**Humoral Immunity**
e.g. parasites, allergens

**Tolerance auto-antigens**
e.g. cell death

**Autoimmune disease**
e.g. asthma, RA

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**COPD Epidemic**

- Globally approx. 210 Million persons suffer from COPD

- 2005 approx. 3 Million died from COPD (=5% global causes of death)

- in Europe 200.000 – 300.000 die annually from COPD

- if no measures taken to reduce risk factors (tobacco smoking) → number of COPD-related death cases will increase by 30% in the next decade

Adapted from: World Health Organization, 2009, fact sheet Nr. 315
Epidemiology COPD – Mortality

percent change age-corrected mortality rates, USA, 1965-1998

CHD | Stroke | Other Cardiovascular events | COPD | Other causes
---|---|---|---|---
– 59% | – 64% | – 35% | + 163% | – 7%

GOLD (Global Initiative for Chronic Obstructive Lung Disease), Workshop Report, Updated 2003. BIC 2017

COPD Diagnosis too little too late...

Lung function | Symptoms
---|---
1. visit | Therapy

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Mechanisms Underlying Airflow Limitation in COPD

Small Airways Disease
- Airway inflammation
- Airway fibrosis, luminal plugs
- Increased airway resistance

Parenchymal Destruction
- Loss of alveolar attachments
- Decrease of elastic recoil

AIRFLOW LIMITATION

Histopathology in COPD: Causes of inflammation

Normal
- Airway held open by alveolar attachments

Chronic Obstructive Pulmonary Disease
- Mucus hypersecretion (luminal obstruction)
- Disrupted alveolar attachments (emphysema)
- Mucosal and peribronchial inflammation and fibrosis (obliterative bronchiolitis)

Airflow limitation

Barnes P, NEJM 2000;343:269-280

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Risk Factors for COPD

- Genes
- Infections
- Socio-economic status
- Aging Populations

- Cigarette smoke
- Occupational dust and chemicals
- Environmental tobacco smoke (ETS)
- Indoor and outdoor air pollution
Diagnosis of COPD

SYMPTOMS
shortness of breath
chronic cough
sputum

EXPOSURE TO RISK FACTORS
- tobacco
- occupation
- indoor/outdoor pollution

SPIROMETRY: Required to establish diagnosis

Spirometry
Lung function measurement

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COPD Comorbidities

COPD patients at increased risk for:

- Cardiovascular diseases
- Osteoporosis
- Respiratory infections
- Anxiety and Depression
- Diabetes
- Lung cancer

*comorbid conditions may influence mortality and hospitalizations → should be looked for routinely, and treated appropriately.*

Differential Diagnosis: COPD and Asthma

**COPD**
- Onset in mid-life
- Symptoms slowly progressive
- Long smoking history

**ASTHMA**
- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms worse at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma

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Manifestations of asthma

- Dyspnoea
  - acute or chronic
  - at rest or exercise-related
  - sometimes trigger
  - reversible
- Cough usually dry
- sometimes associated with allergies

Airways inflammation in Asthma

**Normal**
- Bronchial Mucosa
- Bronchial wall (smooth muscle, connective tissue)

**Asthma**
- Oedema
- Mucus production
- Muscle contraction
What happens during worsening of Asthma?

- Bronchi - The bronchial tubes are wrapped with muscles.
- Bronchiole - Smaller branches of the bronchial tubes.
- Mucus lines the bronchial tubes.
- Inflamed airway.
- Aired with trapped air.
- Extra mucus.

Factors:
- Allergens
- Viruses
- Inhalational toxins
- Genetics
- Environmental factors

Inflammation leads to:
- Bronchial Hyperreactivity
- Remodelling

Trigger leads to:
- Symptoms
**Asthma Diagnosis**

- History and symptoms
- Examination
- Lung function testing
  - Spirometry
  - Peak expiratory flow (PEFR)
- Bronchial Hyperreactivity
- Allergy testing

**Typical spirometric tracings**

- Normal
- Asthma (before BD)
- Asthma (after BD)

Note: Each FEV₁ represents the highest of three reproducible measurements
Diagnosis of asthma: Flow-Volume Loops

- before bronchodilation
- after bronchodilation
- healthy individual

Expiration

Inspiration

Volume (Litres)

Flowrate (Litres per second)

positive bronchodilation test: Increase FEV₁ by 12% and 200ml

Peakflow Variability

PEFR Variability = \frac{\text{highest value} - \text{lowest value}}{\text{highest value}} \times 100

PEFR

Weeks of inhaled glucocorticosteroid treatment

Inhaled glucocorticosteroids commenced
Measurement of Airways Hyper-reactivity

Histamine (mg/ml) vs Methacholine (mg/ml)

% Fall in FEV

PC_{20}

Normal
Mild AHR
Moderate AHR
Severe AHR

Airways: NO Production

Macrophage
LUMEN
IL-1β+TNF-α

Epithelial cell
INOS

NO
EXHALED

MUCOSA
Bronchodilatation?

Vasodilatation
Plasma leak
Eosinophilic inflammation

NO Online Measurement

Chemiluminescence analyser

$\text{NO} + \text{O}_3 \rightarrow \text{NO}_2^* + \text{O}_2$

$\text{NO}_2^* \rightarrow \text{NO}_2 + \text{O}_2$

LOCALISATION EXHALED NO

<table>
<thead>
<tr>
<th>Location</th>
<th>Healthy</th>
<th>Asthmatic</th>
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<tbody>
<tr>
<td>Mouth</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
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<td>Trachea</td>
<td>p&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Bronchi</td>
<td>p&lt;0.01</td>
<td></td>
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</tbody>
</table>

Kharitonov S et al: AJRCCM 1996
EFFECT OF iNOS INHIBITOR ON EXHALED NO


Stepwise management - pharmacotherapy

For children 0-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
# Tiotropium by soft-mist inhaler is indicated as add-on treatment for adults ≥18 yrs with a history of exacerbations
Asthma Phenotypes & Endotypes

**Asthma Syndrome**
Variable Symptoms, expiratory airflow limitation, Bronchial hyperreactivity, inflammation

**Phenotypes**
Observed characteristics
- Clinical presentation
- Trigger
- Response to therapy

**Endotypes**
Functional or pathophysiologic mechanism (link between clinical characteristics and molecular pathway)

Asthma: Clinical phenotypes

- **Discordant Symptoms**
  - Early symptom predominant
    - Early onset, eosinophilia
    - High symptom expression
  - Obese non-eosinophilic
    - Late onset, late appearance
    - High symptom expression

- **Concordant Symptoms**
  - Early onset, atrial fibrillation
    - Concordant symptom predominant
  - Benign asthma
    - Well-controlled symptoms and inflammation

- **Primary Care Asthma**
- **Secondary Care Asthma**

- **Concordant Disease**
  - Symptom-based approach to dosing treatment may be insufficient.

- **Discordant Inflammation**
  - Erosion level inflammation allows targeted corticosteroids to lower exacerbation frequency.

- **Eosinophilic Inflammation**

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Asthma: TH2 Phenotype


Hygiene Hypothesis

Exposition to microbes during infancy protects against allergies and asthma

Certain bacteria of the intestinal flora are essential for the immune balance

Immune imbalance

Autoimmune disease

Ivanov II et al. Cell Host Microbe 2008;4:337–349
Ivanov II et al. Cell Host Microbe 2008;4:337–349
Atarashi K et al. Science 2011;331:337–341

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Human Microbiome

**Microbiota**
Totality of microbes (bacteria, viruses, fungi) in a niche or region (e.g. lung)

**Microbiome**
Totality of microbiota + genome in its environment of interaction (e.g. human organism)

10x bacterial cells than human cells

100x more bacterial genomic material than human

Little sequencing, Large information

Carl R. Woese (Discovery of Archea by 16S rDNA sequencing): Defined the phylogenetic taxonomy of 16S ribosomal RNA (1977), a technique that revolutionized the discipline of microbiology

Woese, Carl R.; George E. Fox "Phylogenetic structure of the prokaryotic domain: the primary kingdoms, PNAS 1977"
Lower respiratory tract: Sterile?
Classical culture-based studies: lower respiratory tract = sterile


Majority of microbial life resistant to conventional laboratory culture

New technologies: bioinformatics and molecular biology (16S rRNA sequencing, micro-arrays → culture-independent investigation of microbiota


overall view of microbiota, symbiotic and pathogenic bacteria

Lung: 2000 genomes/cm²

Why study pulmonary microbiota?

Identification potentially pathogenic bacteria refractory to conventional culture (e.g. cystic fibrosis)

Pathogenic potential of microbiota containing mix of species can be distinct from that of its individual members
Sibley CD. PLoS Pathog 2008

Composition of airway microbiota reflection of the physicochemical characteristics of airway niches (e.g. tuberculosis in upper lobes)

1. Role of microbiota in health and disease?
2. Cross-talk with host immune system?
Microbiome: Future...

- Constitution of « healthy » microbiome?
- Predominant microbiome: Cause or effect of disease?
- Manipulation microbiota: probiotics, prebiotics, antibiotics → prevention, therapy
- Strategies for the modulation of the microbiota:
  - targetted elimination of bacterial species
  - « transplantation » of healthy microbiota
- Modulation of the host immune system through interaction with microbiota

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