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# Objectives

Definition of Asthma

- Epidemiology and risk factors of Asthma
- Pathophysiology of Asthma
- Diagnostics test of Asthma
- Management of Asthma

### Definition of Asthma

- The word "asthma" is derived from the ancient Greek word for "panting"
- The earliest feature described was the labored, rapid breathing typical of asthmatic attacks

Measurement of maximal expiratory flow led to recognition of reversible airflow obstruction as a characteristic feature that is often reversible either spontaneously or with treatment

#### Definition of Asthma

- Chronic inflammatory disorder of the airways in which many cells and cellular elements play a role (mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells)
- In susceptible individuals, inflammation causes episodes of wheezing, breathlessness, chest tightness and coughing
- The inflammation also causes an increase in **bronchial hyperresponsiveness** to a variety of stimuli

#### Definition of Asthma

- National Institute of Health (NIH)
  - In 1991: Chronic inflammatory disorder of the airways in which many cells and cellular elements are involved, with an associated increase in airway hyperresponsiveness that leads to recurrent wheezing, breathlessness, chest tightness and cough, particularly at night and early morning
  - 2007: Updated guidelines emphasize the role of inflammation in Asthma and focus on evidence that the patterns and degrees of inflammation are variable, resulting in phenotypic differences that have important influences on response to therapy



- Prevalence of Asthma has been increasing worldwide over the past several decades
- Etiology is likely multifactorial
  - Obesity
  - exposure to allergens ( house dust mites, mold and tobacco smoke )
  - Atopy and allergic rhinitis ( exposure to allergens at an early age likely contribute to increased incidence of asthma )



 NIH-2006 estimated 16.1 million adults (7.3%) and 6.8 million childrens (9.4%) of the population in the US had a diagnosis of Asthma

The prevalence of Asthma in the US increased from 3.1 % in 1980 to 7.7% in 2005



- There are important racial differences in the prevalence and morbidity of asthma
  - 2005: Puerto Ricans had an asthma prevalence rate 125% higher than non-hispanics whites and 80% higher than nonhispanics blacks
- Females had a 40% higher prevalence rate than males
- Boys under 18 years old had a higher prevalence than girls



- Asthma related deaths steadily increased in the USA and worldwide between 1980 and the mid-1990s
- Although recent death rates have been declining asthma-related morbidity and mortality continue to be a significant problem
- World-wide approximately 180,000 deaths are attributable to asthma each year
- 4000 deaths/yr in the USA are attributed to asthma



- Females had a 45% higher risk of dying from asthma than males
- Puerto Ricans were the most likely to die of asthma ( death rate 3.6 times higher than non-hispanics whites )
- Non-hispanics blacks had an asthma death rate twice as high as non-hispanics whites

#### Risk Factors of Asthma

- Hygiene Hypothesis
- Infections
- Atopy
- Obesity
- Genetics
- Tobacco use and environmental exposure

#### Risk Factors of Asthma

- "Hygiene Hypothesis"
  - Infections early in life results in the development of a predominately T-helper (Th1)-mediated immune response and down regulation of the Th2-mediated response (increased allergic rhinitis and atopy)



Presence of older siblings Early exposure to day care

Tuberculosis, measles, or hepatitis A infection

Rural environment

#### Factors favoring the Th2 phenotype

Widespread use of antibiotics Western lifestyle Urban environment Diet Sensitization to house-dust mites and cockroaches



Protective immunity

Cy tokine balance Allergic diseases including asthma

### Risk Factors of Asthma

- Infections
  - Exposure to microbes early in life may be protective
  - The relationship between infections and development of atopy and asthma is complex and highly dependent on the type of infection
  - RSV is the most common cause of bronchiolitis and is associated with an increase risk of developing subsequent asthma
  - Rhinovirus is also a very important predictor of asthma if the infection occurs early in life



- Infections
  - Atypical bacterial pathogens are implicated in triggering acute asthma and propagating chronic asthma
  - Chlamydophylia pneumonia and mycoplasma pneumonia are present in the airways of chronic asthmatics



- Atopy
  - Maternal or paternal atopy and the occurrence of asthma in children is controversial
  - Several studies show that a family history of atopy is an important risk factor for atopy in children
- Obesity ( BMI > 30% )
  - Almost without exception more than 30 cross-sectional and casecontrol studies of the relationship between obesity and asthma since the 1990's report an increase prevalence of asthma



- Genetics
  - Advances in genomics have led to the discovery of several polymorphism that are important in the development of asthma and the response to therapy

#### Risk Factors of Asthma

- Tobacco use / environmental exposure
  - There is increased evidence that both in utero and childhood exposure to tobacco results in detrimental effects on respiratory health ( increased risk of abnormal lung function and wheezing/ asthma in childhood )
  - Tobacco use is also associated with increase risk of developing asthma
  - Environmental exposure in adults results in increased morbidity and poorer asthma control

# Pathophysiology of Asthma

- **Inflammation** is the cornerstone of the disease and is thought to result from inappropriate immune response to a variety of antigens in genetically susceptible individuals
- It involves many different cells (e.g. neutrophils, basophils, eosinophils, mast cells, macrophages) and mediators (e.g. cytokines, chemokines, histamine, leukotrienes and thromboxanes )



# Pathophysiology of Asthma

- Airway remodeling is a pathologic feature of chronic asthma (structural alteration of the airway with characteristics changes in the nature, content and distribution of airway elements )
- The degree of airway remodeling is a function of disease severity over time





- During asthma exacerbation there is a diffuse narrowing of the airways thought to occur disproportionally in the small airways although recent studies suggest a prominent role for large and medium airways.
- As a result lung function test are abnormal, with an increase in airway resistance and a decline in maximal expiratory flow

- The work of breathing increases due to the decreased lung and chest wall compliance at higher thoracic lung volumes and greater effort required to overcome the resistance of the narrowed airways
- Acute severe asthma
  - Arterial O2 tension (PaO2) < 70 mm Hg and arterial CO2 tension (PaCO2) initially falls as alveolar ventilation increases, follow up by normalization or elevated PaCO2 as muscle fatigue, a sign of impending respiratory failure

#### Pulmonary Function Test: (PFT)

- PEF ( peak expiratory flow )measurement
- Spirometry
- Lung volumes
- Diffusing capacity
- Provocative Challenges and airway

hyperresponsiveness test

#### • PEF ( peak expiratory flow) measurement

- recommended for daily monitoring of ambulatory patients and values should be compared to patient baseline measurement
- PEF % predicted is on average 10% higher than FEV1 with a great variability between measurements, greater predictive value for asthma exacerbations than the absolute PEF



#### Spirometry:

- FEV1: The best and most standardized test of airflow obstruction
- Improvement in FEV1 > 12% and 200 ml after bronchodilator treatment indicate a reversible airflow obstruction and is suggestive, but not diagnostic of asthma
- Need to stop LABA x at least 12 hr and SABA x at least 6 hr

#### • Spirometry ( cont ):

- FEV1 may be normal between asthma flares
- **FEV1/FVC ratio** usually < 70%
- An alternative method for assessing airflow obstruction is to evaluate the mid expiratory flow (FEF 25-75%), more sensitive for identification of obstruction in small airways.





- Lung volumes
  - As a result of dynamic hyperinflation and consequent air trapping
    - RV (residual volume), FRC (functional residual capacity) and TLC (total lung capacity) may be elevated
- Diffusing Capacity
  - DLCO is a marker of CO gas transfer in the lungs and is reduced in most chronic lung disease
  - In asthma DLCO is normal or elevated if airflow obstruction not severe

- Provocative Challenges/ Airway Hyperresponsiveness
  - Patients suspected of having asthma despite normal lung function test usually develop bronchoconstriction in response to a provocative stimulus
  - Nebulized Methacholine, delivered in doubling concentrations until FEV1 falls by more than 20%, (PC20 < 16 mg/ml is consistent with mild AHR, <4 mg/ml moderate < 1 mg/ml severe )

- Newer guidelines emphasize maintaining long-term control of symptoms through attention to environmental and social components of asthma and using treatments regimens tailored to the severity of each patient's symptoms
  - Evaluation of severity
  - Assessment of control
  - Appropriate pharmacology therapy
  - Identification and control of environmental factors that worsen symptoms or trigger exacerbations
  - Creation of partnership between the patient and health care professional

	COMPONENTS OF CONTROL	Classification of asthma control (youth ≥ 12 years of age and adults)		
		Well-controlled	Not-well controlled	Very poorly controlled
I m pair m e n t	Symptoms	≤ 2 days/week	> 2 days/week	Throughout day
	Nighttime awakenings	≤ 2x/month	1-3x/week	≥ 4x/week
	Interference with normal activity	None	Some Limitation	Extremely limited
	SABA use for symptom control (not prevention of EIB)	≤2days/week	>2days/week	Several times per day
	FEV1 or peak flow	>80% predicted/ personal best	60-80 % predicted/ personal best	< 60 predicted/ personal best
	Validated Questionnaires			
	ATAQ	0	1-2	3-4
	ACQ	≤0.75	≥1.5	N/A
	ACT	>20	16-19	≤15
Risk	Exacerbations	0-1/year	≥2/year	
	Progressive Loss of lung function	Evaluation requires long term follow-up care		
	Treatment related side effects	Medication side effects can vary intensity from none to very troublesome. The level of intensity does not correlate to specific levels of control but should be considered in the		
		overall assessment of risk.		



- Pharmacologic therapy is subdivided into acute, short term "reliever" medications and chronic " controller" medications
- Therapy should be adjusted in a stepwise fashion to reduce daily symptoms and risk of exacerbations, while minimizing the use of medications
- Prominent role for controller medications

- Bronchodilators
- Inhaled Corticosteroids
- Leukotriene modifiers
- Phosphodiesterase 4 inhibitors (Theophylline)
- Anti-Immunoglobulin E
- Non pharmacologic therapy
- Additional management strategies

#### Bronchodilators

- B2-Agonist:
  - Short (SABA) and long acting (LABA) agonist
  - SABA should be used to treat symptoms not adequately controlled on a regimen of long acting agents
  - Increase frequency of SABA use is a sign of inadequate control of symptoms or overreliance on rescue medication
  - LABA can be added to an inhaled corticosteroid in patients with inadequately controlled asthma
  - LABA's has been shown to improve lung function, reduce symptoms and reduce the frequency of exacerbations

#### Bronchodilators

- B2-Agonist
  - Adverse events include; tachycardia, arrhythmias, tremors and hypokalemia
  - SMART trial, salmeterol multicenter asthma research trial, patient randomized to salmeterol or placebo plus usual care, there was no significant difference in risk of death in either group but subgroup analysis identified a small increase of death in African American subjects in the salmeterol arm

#### Bronchodilators (cont)

- Anticholinergics
  - Act as bronchodilators via competition with acetylcholine at neuromuscular junctions, blocking transmission of bronchoconstrictor reflexes
  - Second line therapy however specific asthma phenotypes might be more likely to respond, including patients with fixed airway obstruction, advanced age or longer duration of disease
  - Acceptable alternative for patients who do not tolerate B2-Agonist
  - <u>What is the role of tiotropium in asthma, Chest 2015</u>: non inferior to salmeterol and superior to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/salmeterol. Major benefit was an increase in lung function.

#### Inhaled corticosteroids (ICS)

- Reduction in airway inflammation, for long term control of symptoms
- Compared to oral steroids, ICS minimize systemic toxicity
- Improves lung function
- Reduce asthma exacerbations
- Reduce hospitalizations
- Reduce risk of death

#### • Leukotriene modifiers (LTM)

- LT have a modest bronchodilator effect and may improve asthma symptom and exacerbations rates
- Patients with aspirin-sensitive asthma may derive great benefit
- Data also suggest that LTM are adequate as single agents in mild persistent asthma
- Less efficacious than low dose ICS
- Primary role as adjuvant to ICS and its addition typically leads to a reduction in the corticosteroid dose or an improvement in asthma control
- Zileuton can cause hepatotoxicity, need to monitor LFTs

#### Phosphodiesterase 4 Inhibitors (Theophylline)

- Mild anti-inflammatory properties
- Not longer a first line therapy due to its narrow therapeutic index
- Can be used in low dose as adjuvant treatment for asthma that is difficult to control with steroids alone
- Improves markers of control (rescue inhalers use, lung function) to a greater extent than LTMs.
- Side effects include anorexia, palpitations, dysrhythmias and seizure

#### **Anti-Immunoglobulin** E

- **Omalizumab:** monoclonal antibody to Ig E
- Adjuvant to ICS in poorly controlled allergic asthmatics, associated with improved asthma control and fewer exacerbations
- High cost, requirement for monitoring during treatment and the need to carefully select patients likely to benefit have limited its use

#### • Non pharmacologic treatment

- Bronchial thermoplasty
  - Thermal energy is delivered to the airway wall, resulting in reduction of airway smooth muscle mass ( characteristic feature of asthma )
  - Treatment leads to improvement in symptoms and quality of life and reduction in the use of rescue medication in patients with moderate or severe asthma
  - Series of three bronchoscopies, exposing patients to the concomitant procedural risk and long term data outcome lacking

#### Additional management strategies

- Control of triggers
  - Cigarette smoking decreases asthma control and reduces efficacy of corticosteroids
  - Comorbid conditions, e.g. GERD and rhinosinusitis may worsen asthma symptoms and severity
  - Reduction of allergen exposure (most common dust mites and cat dander) and provision of allergen immunotherapy





- Asthma is an important cause of disability, death and economic cost
- Asthma is increasing in developed countries
- Asthma is a disease of misdirected immunity, influenced by many genes and probably also by airway infections, especially viruses in the first few years of life
- The approach to the diagnosis, assessment and treatment of asthma has changed in response to the recognition of asthma as a chronic inflammatory disease punctuated by intermittent exacerbations



- The therapies available are effective in controlling asthma, but their efficacy depends on fully engaging the patient
- More information is needed about the interplay between individuals genotypes and environmental stimuli that are responsible for the disease
- The combined use of anti-inflammatory and bronchodilators therapies, couple with measures to reduce environmental exposure can reduce the consequences and cost for the health care system

# Thank you