Asthma Pathophysiology and Treatment

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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)
  - 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

Epidemiology of Asthma

- 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)

Epidemiology of Asthma

- During the period from 1982 to 1992, the overall annual age-adjusted prevalence rate of self-reported asthma increased by 42 percent, from 34.7 to 49.4 per 1000.
- During the years 2001 through 2009, the age-adjusted prevalence of asthma increased from 73 to 82 per thousand
- Data from the CDC have shown that the prevalence of asthma increased in the United States from the early 1980s to the mid 1990s. During the years 2001 through 2009, the prevalence of asthma increased more gradually, and then remained stable in the years 2009 to 2012 with a decline in 2013

Epidemiology of Asthma

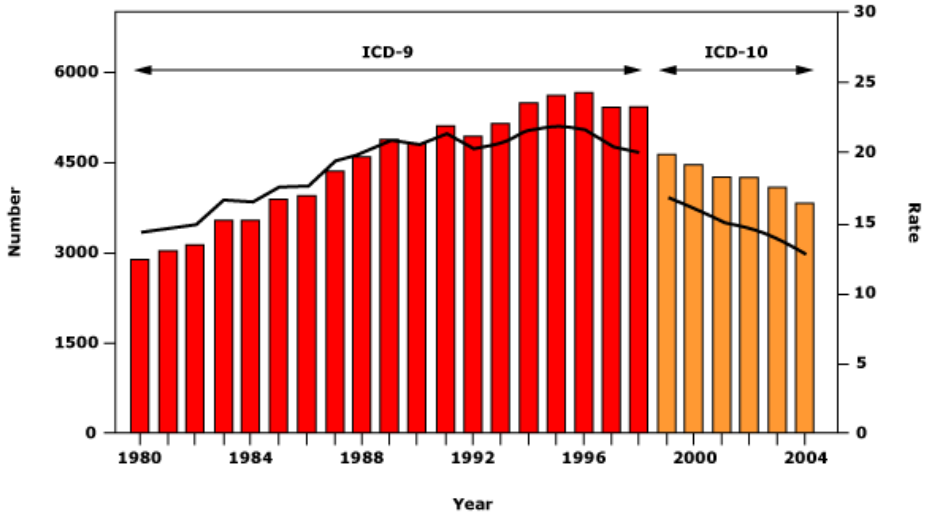
- The reasons for the plateau and potential decrease in prevalence of asthma in some countries remain unclear.
- It has been hypothesized that the rapidly changing exposures and lifestyles led to asthma developing in susceptible individuals in the latter half of the past century, but the proportion of the population that is susceptible to developing asthma is now reaching capacity

Epidemiology of Asthma

- There are important racial differences in the prevalence and morbidity of asthma
- National Health Interview Survey (NHIS)2011 Females had a higher prevalence rate than males
- Boys under 18 years old had a higher prevalence than girls

Epidemiology of Asthma

- Asthma related deaths steadily increased in the USA and world-wide 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



Moorman JE, Rudd RA, Johnson CA, et al. National surveillance for asthma-United States, 1980-2004. MMWR Surveill Summ 2007; 56:1.

Epidemiology of Asthma

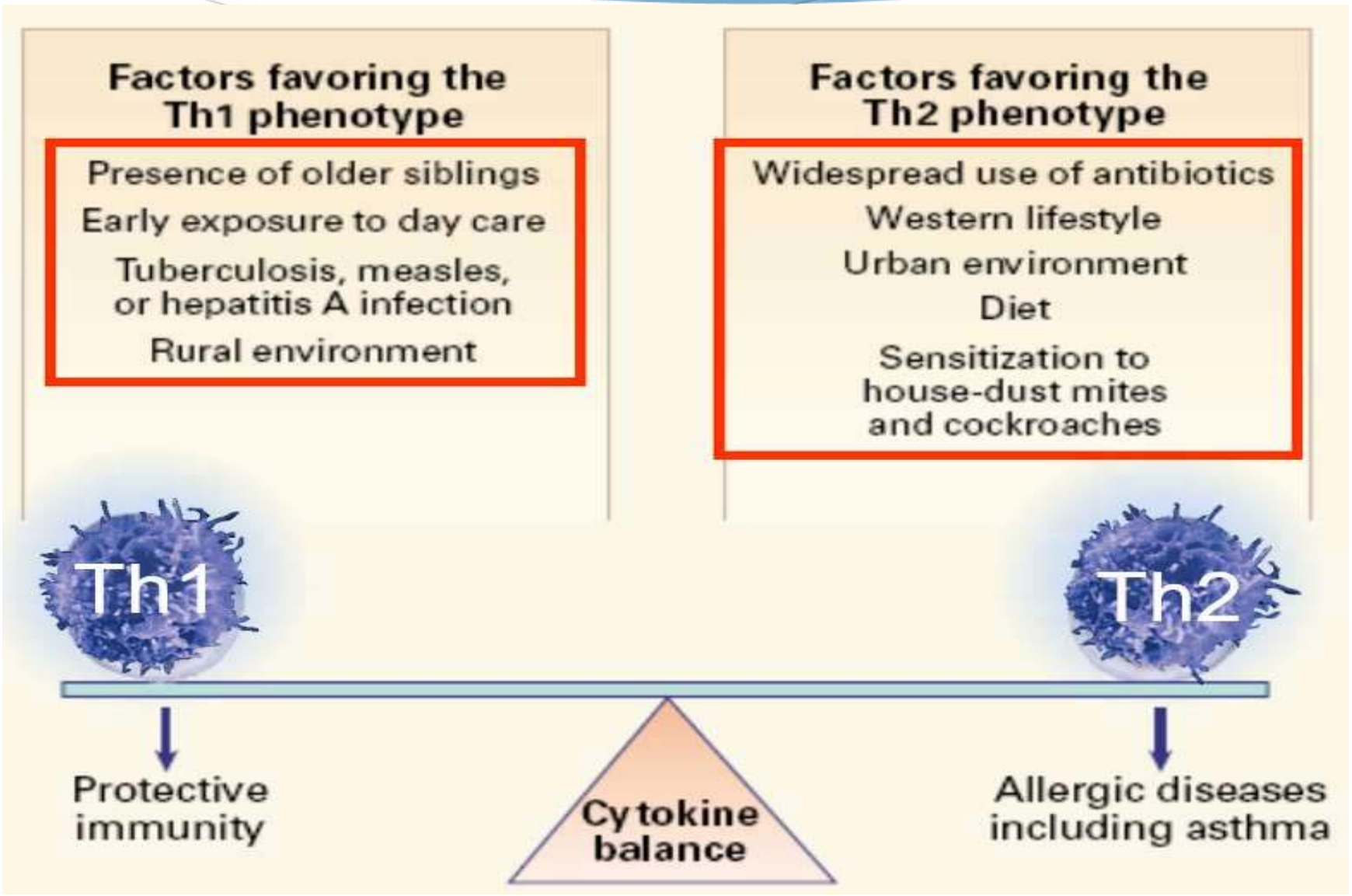
- Females had a 45% higher risk of dying from asthma than males
- Puerto Ricans were the most likely to die of asthma (death rate 3.6 times higher than non-hispanics whites)
- Non-hispanics blacks had an asthma death rate twice as high as non-hispanics whites

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)


Factors favoring the Th1 phenotype
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
Th1
Th2
Protective immunity
Cytokine 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

Risk Factors of Asthma

- 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

Risk Factors of Asthma

- 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 case-control studies of the relationship between obesity and asthma since the 1990's report an increase prevalence of asthma

Risk Factors 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)

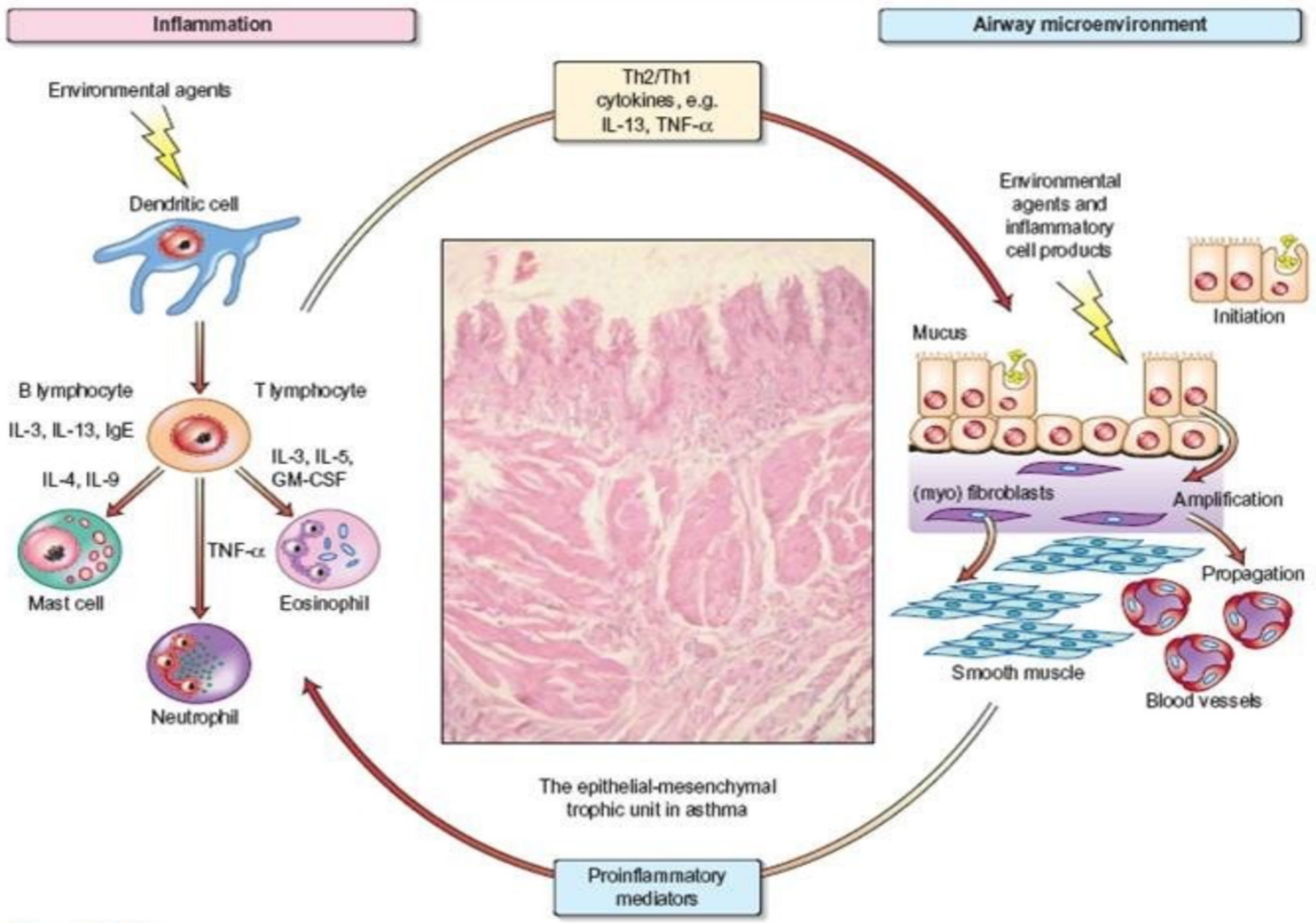
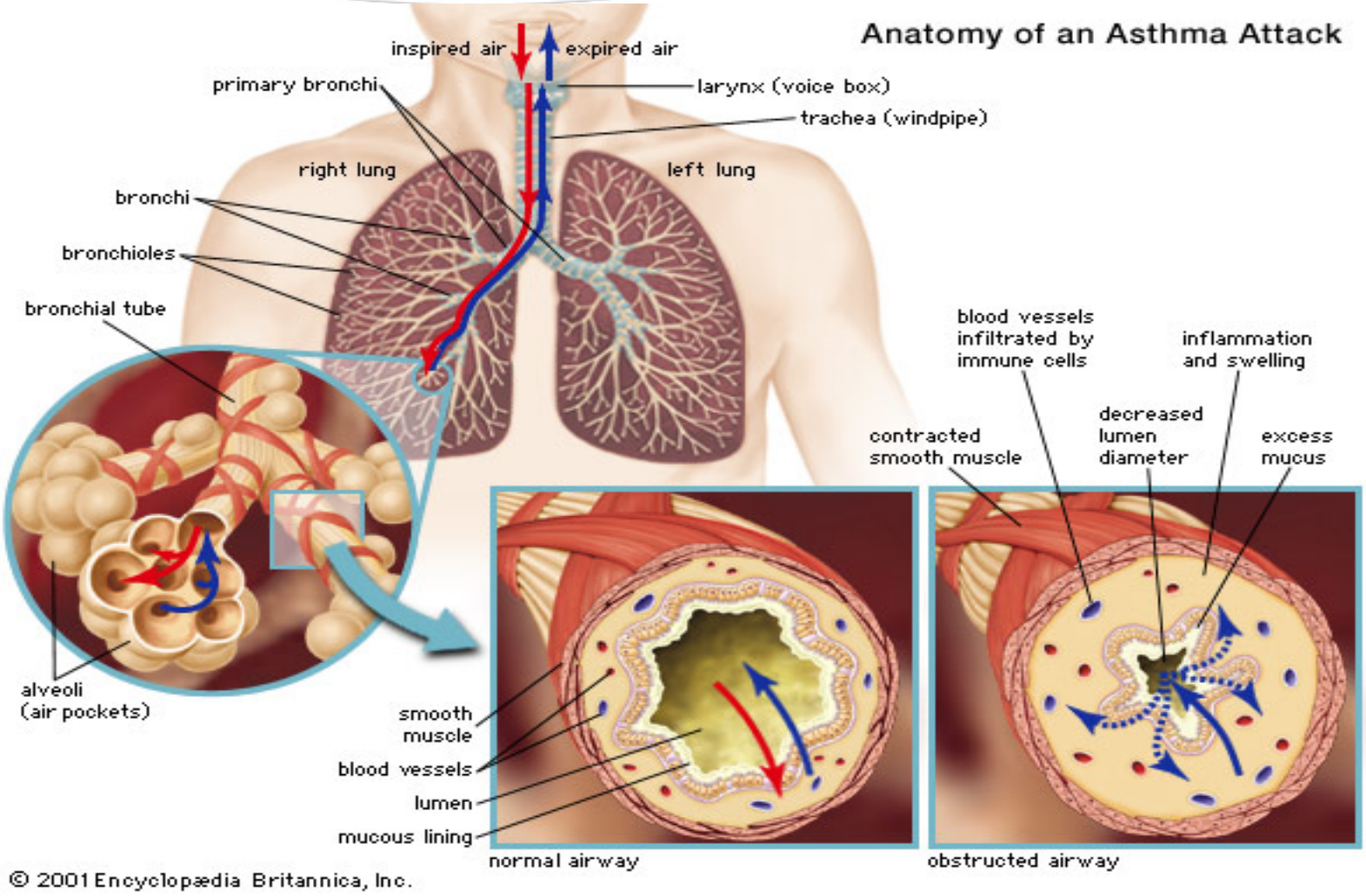


Fig. 14.34 **Inflammatory and remodelling responses in asthma with activation of the epithelial mesenchymal trophic unit.** Epithelial damage alters the set point for communication between bronchial epithelium and underlying mesenchymal cells, leading to myofibroblast activation, an increase in mesenchymal volume, and induction of structural changes throughout airway wall. Adapted from Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet* 2006; 368: 780–793 with permission from Elsevier.

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


Anatomy of an Asthma Attack
inspired air
expired air
primary bronchi
larynx (voice box)
trachea (windpipe)
right lung
left lung
bronchi
bronchioles
bronchial tube
alveoli
(air pockets)
blood vessels
infiltrated by
immune cells
inflammation
and swelling
contracted
smooth muscle
decreased
lumen
diameter
excess
mucus
smooth
muscle
blood vessels
lumen
mucous lining
normal airway
obstructed airway
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Physiology of Asthma

- 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**

Physiology of Asthma

- 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

Physiology of Asthma

- Pulmonary Function Test: (PFT)
  - PEF (peak expiratory flow)measurement
  - Spirometry
  - Lung volumes
  - Diffusing capacity
  - Provocative Challenges and airway hyperresponsiveness test

Physiology of Asthma

- **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

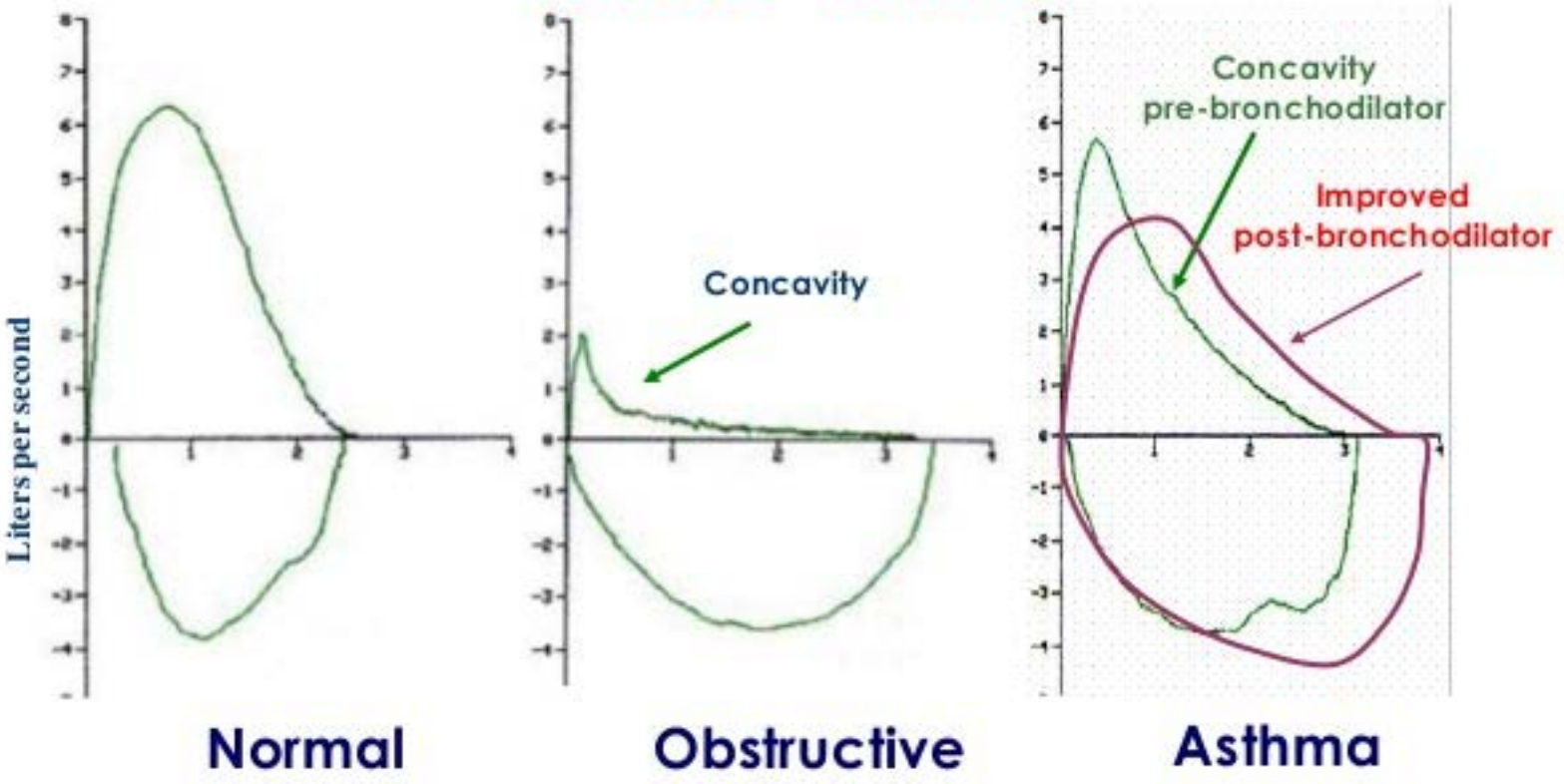
Physiology of Asthma

- **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

Physiology of Asthma

- **Spirometry (cont):**
  - FEV1 may be normal between asthma flares
  - **FEV1/FVC ratio** can be normal**, unless patient is having a flare or patient has developed chronic airflow obstruction.**
  - **FEF 25-75%, is not a well validated tool to diagnose or monitor asthma in adult population**

Types of Flow Volume Curves



Physiology of Asthma

- 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

Physiology of Asthma

- 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)

Management of Asthma

- 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
Impairment	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.		

Management of Asthma

- 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

Management of Asthma

- Bronchodilators
- Inhaled Corticosteroids
- Leukotriene modifiers
- Phosphodiesterase 4 inhibitors (Theophylline)
- Biologic agents
- Non pharmacologic therapy
- Additional management strategies

Management of Asthma

- **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

Management of Asthma

- **Bronchodilators**
  - B2-Agonist
    - Adverse events include; tachycardia, arrhythmias, tremors and hypokalemia, lactic acidosis
    - 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

Management of Asthma

- **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
    - ***What is the role of tiotropium in asthma,*** *Chest 2015*: 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.

Management of Asthma

- **Inhaled corticosteroids (ICS)**
  - Reduction in airway inflammation, for long term control of symptoms
  - **Centerpiece in any severity other than intermittent**
  - Compared to oral steroids, ICS minimize systemic toxicity
  - Improves lung function
  - Reduce asthma exacerbations
  - Reduce hospitalizations
  - Reduce risk of death

Management of Asthma

- **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

Management of Asthma

- **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 but **has fallen out of favor: side effect profile and greater availability of other options**
  - Improves markers of control (rescue inhalers use, lung function) to a greater extent than LTMs.
  - Side effects include anorexia, palpitations, dysrhythmias and seizure

Management of Asthma

- **Biologic Agents**
  - **Omalizumab:** monoclonal antibody to Ig E
  - Mepolizumab: Interleukin-5 Receptor Antagonist
  - **Reslizumab:** Interleukin-5 Receptor Antagonist
  - **Benralizumab:** Interleukin-5 Receptor Antagonist
  - Dupulilumab: Interleukin-4 Receptor Antagonist

Anti IgE Therapy

For patients with elevated IgE and sensitivity to perennial allergens

Agent and target	FDA-approved age	Patient selection	Route	Dose	Dosing interval	Adverse effects
For patients with elevated IgE and sensitivity to perennial allergens[¶]						
Omalizumab (anti-IgE)	≥6 years	IgE 30 to 700 IU/mL in United States; 30 to 1500 IU/mL in Europe	SC	Based on weight and IgE Doses ≥225 mg need to be divided over >1 injection site Maximal dose: 375 mg every 2 weeks in United States; 600 mg every 2 weeks in Europe	2 to 4 weeks depending on IgE level and body weight	•Local injection site reaction (severe 12%), usually within 1 hour •Thromboembolic disease ≤3% •Anaphylaxis, immediate or delayed <1% •Antibody development (<1%)

Anti- Eosinophilic

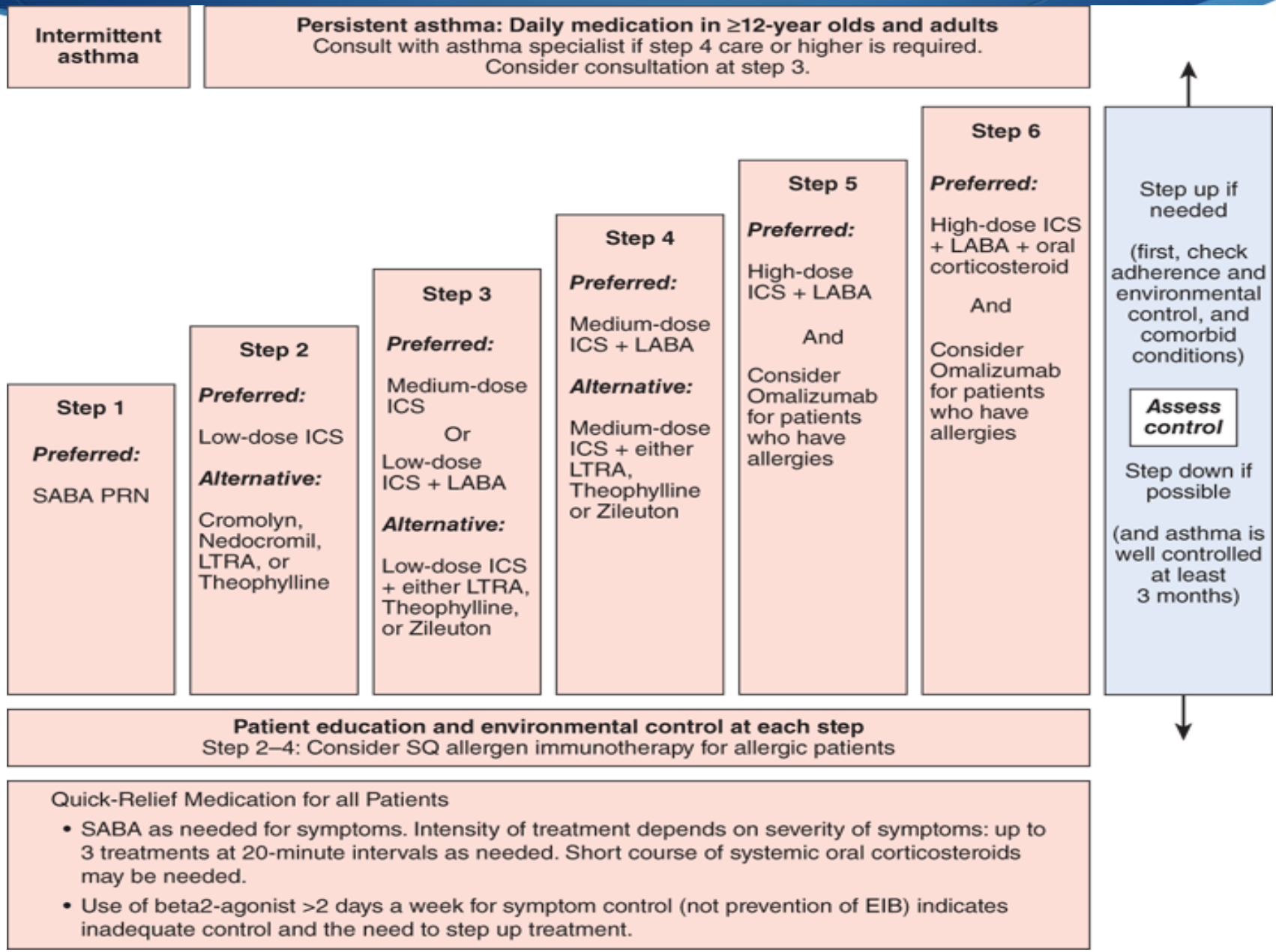
Agent and target	FDA-approved age	Patient selection	Route	Dose	Dosing interval	Adverse effects
Mepolizumab (anti-IL-5)	≥12 years	Peripheral blood eosinophils ≥150/microL	SC	100 mg	4 weeks	•Local injection site reaction (8 to 15%) •Anaphylaxis: immediate or delayed <1% •Human anti-human neutralizing antibody (<1%) •Herpes zoster (<1%): Administration of zoster vaccine is suggested prior to initiation
Benralizumab (anti-IL-5 receptor alpha)	≥12 years	Peripheral blood eosinophils ≥300/microL	SC	30 mg	4 weeks for first 3 doses, then 8 weeks	•Human anti-human antibody development (13%; neutralizing 12%) •Headache 8% •Fever 3% •Hypersensitivity (anaphylaxis, angioedema, urticaria) (3%): typically within hours of injection but can be delayed (3%)
Dupilumab (anti-IL-4 receptor subunit alpha)[◊]	≥12 years	Peripheral blood eosinophils ≥150/microL	SC[Δ]	First week, 2 doses of 200 mg (total 440 mg), then 200 mg every 2 weeks	2 weeks	•Human anti-human antibody development in patients receiving the 300 mg dose every 2 weeks for 52 weeks (6%; 2% neutralizing antibodies) and in patients taking 200 mg dose every 2 weeks for 52 weeks (9%; 4% neutralizing antibodies) •Transient eosinophilia (4%); over 3000 cells/mL (1.2%) •Anaphylaxis and other hypersensitivity reactions (<1%) •Injection site reactions, conjunctivitis, keratitis, oral and other herpes simplex viral infections
				First week, 2 doses of 300 mg (total 600 mg), then 300 mg every 2 weeks[◊]	2 weeks	
Reslizumab (anti-IL-5)	≥18 years	Peripheral blood eosinophils ≥400/microL	IV	3 mg/kg	4 weeks	•Human anti-human antibody development (5%) •Anaphylaxis 0.3% during infusion or within 30 minutes after infusion; may occur as early as second dose or can be delayed •Transient increase in creatine phosphokinase (20%)

Management of Asthma

- **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 though modality can work well in carefully selected patients.

Management of Asthma

- **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


Intermittent asthma
Persistent asthma: Daily medication in ≥12-year olds and adults
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.
Step 1
Preferred:
SABA PRN
Step 2
Preferred:
Low-dose ICS
Alternative:
Cromolyn, Nedocromil, LTRA, or Theophylline
Step 3
Preferred:
Medium-dose ICS
Or
Low-dose ICS + LABA
Alternative:
Low-dose ICS + either LTRA, Theophylline, or Zileuton
Step 4
Preferred:
Medium-dose ICS + LABA
Alternative:
Medium-dose ICS + either LTRA, Theophylline or Zileuton
Step 5
Preferred:
High-dose ICS + LABA
And
Consider Omalizumab for patients who have allergies
Step 6
Preferred:
High-dose ICS + LABA + oral corticosteroid
And
Consider Omalizumab for patients who have allergies
Step up if needed
(first, check adherence and environmental control, and comorbid conditions)
Assess control
Step down if possible
(and asthma is well controlled at least 3 months)
Patient education and environmental control at each step
Step 2–4: Consider SQ allergen immunotherapy for allergic patients
Quick-Relief Medication for all Patients
• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
• Use of beta2-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.

Key points

- 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

Key Points

- 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

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