Pharmacotherapy of Asthma: Part 1

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Learning Objectives

As a result of attending the asthma lectures, the participant should be able to:

1. Describe the definition, epidemiology, and diagnosis of asthma.
2. Outline the assessment of asthma across the ages.
3. Outline GINA asthma management cycle to minimize risk & control symptoms
4. Identify medications, regimens, and strategies for asthma risk reduction and symptom control.
5. Discuss NAEPP & GINA guideline asthma recommendations, and medication selections based on efficacy & safety, as well as age groups

Learning Objectives (Cont'd)

6. Describe the risks and benefits of asthma controller therapies.
7. Articulate the FDA's decision and rationale for label precautions on ICS and LABAs in asthma.
8. Contrast the marketed ICS in regards to pharmacokinetic/ pharmacodynamic/potency differences.
9. Discuss the role of combination and biologic therapies for persistent asthma.

References*

- Focused Updates to the Asthma Management Guidelines (EPR4)
  - J Allergy Clin Immunol 2020;146:1217-70
- Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention, updated 2020
  - www.ginasthma.org
- National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma - Summary Report 2007.
  - *J Allergy Clin Immunol* 2007; 120(5)supplement: S94-S138.

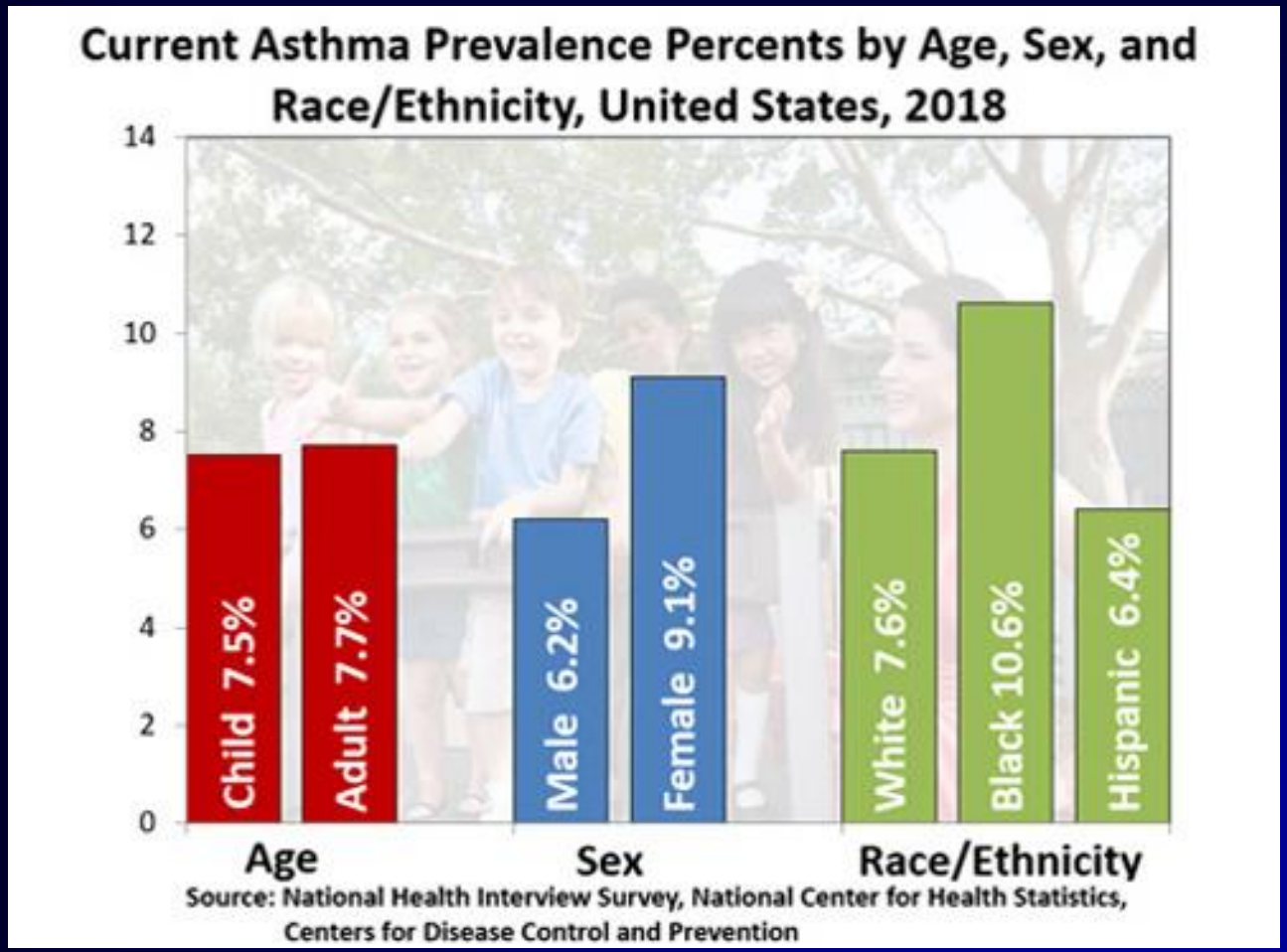
(https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines)*

*For details, clarifications, and review of tables/figures in readable fashion

Burden of Asthma

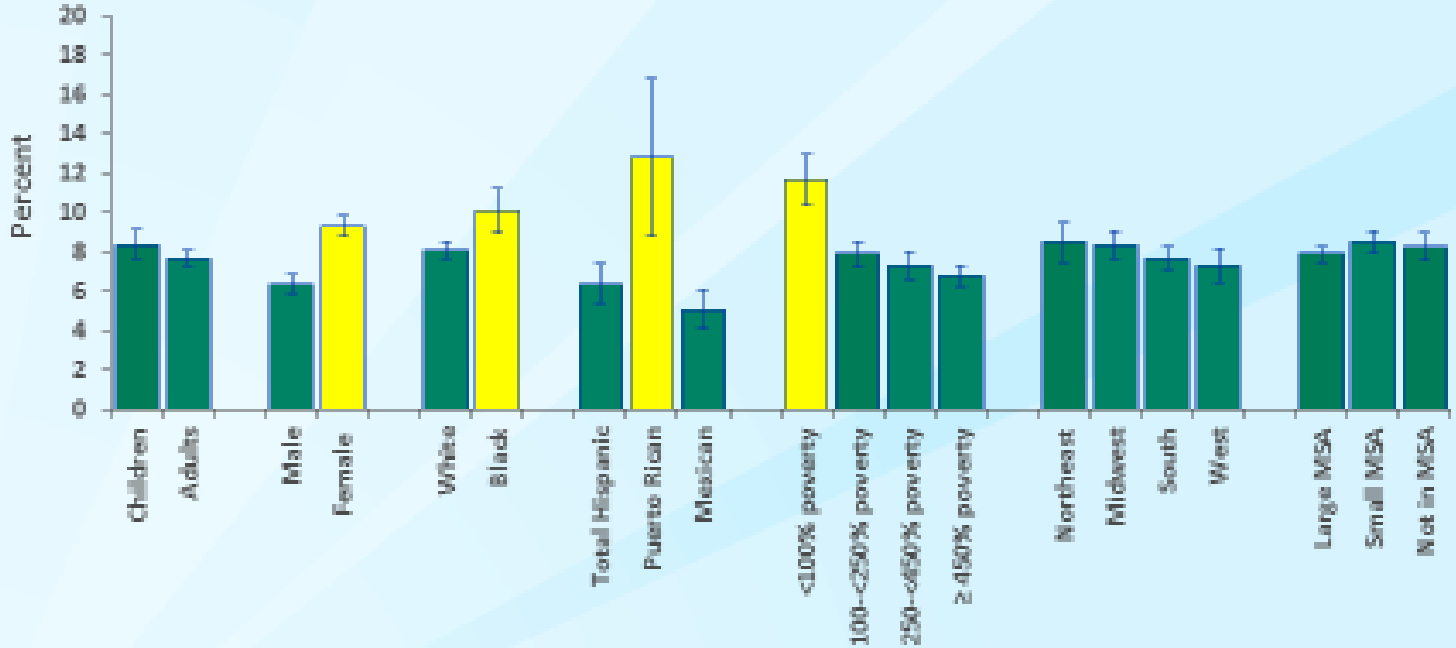
- One of the most common chronic diseases worldwide; estimated 300 million patients
- Prevalence increasing in many developing countries, especially in children
- Major cause of school and work absence
- Health care expenditures very high
- Substantial burden on patients, their families, and their community

Prevalence of Current Asthma, 2018



https://www.cdc.gov/asthma/national-surveillance-data/default.htm

Current Asthma Prevalence by Age Group, Sex, Race and Ethnicity, Poverty Status, Geographic Region, and Place of Residence: United States, 2017



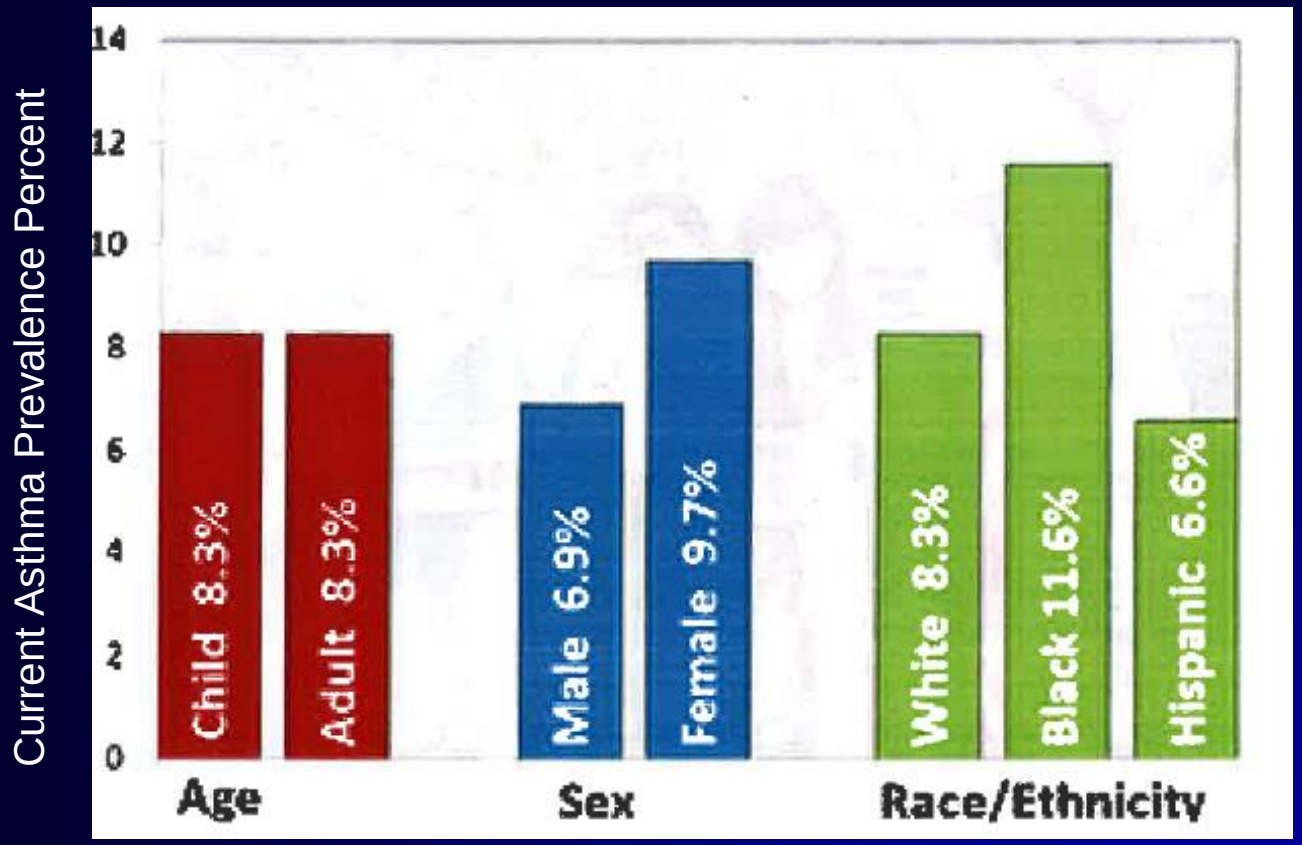
Females, blacks, and Puerto Ricans are more likely to have asthma.

People with lower annual household income were more likely to have asthma.

Asthma did not differ by age group, region, or Metropolitan Statistical Area (MSA).

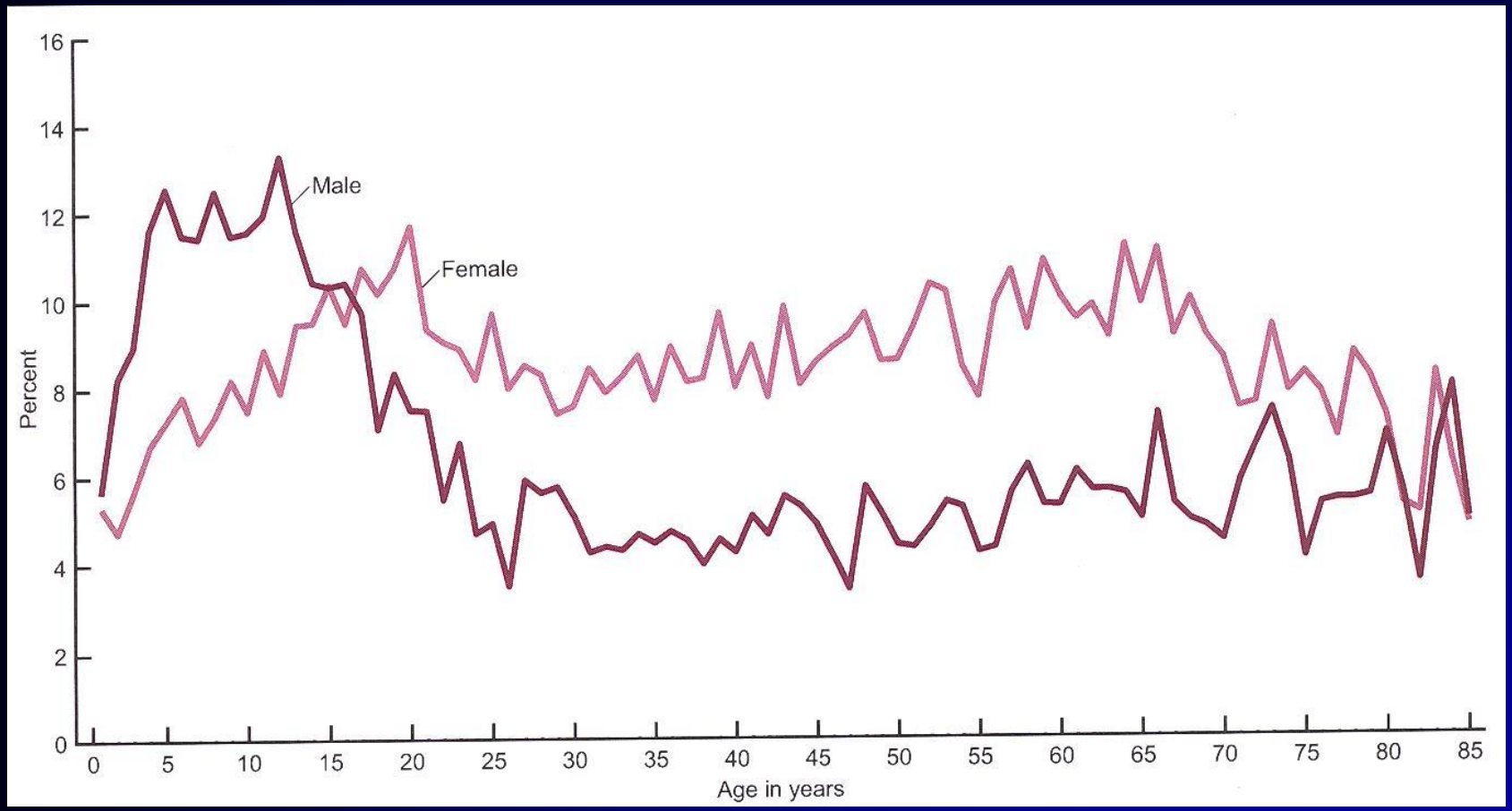
https://www.cdc.gov/asthma/national-surveillance-data/default.htm

Current Asthma Prevalence Percent by Age, Sex, and Race/Ethnicity, United States, 2016



Source: National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention

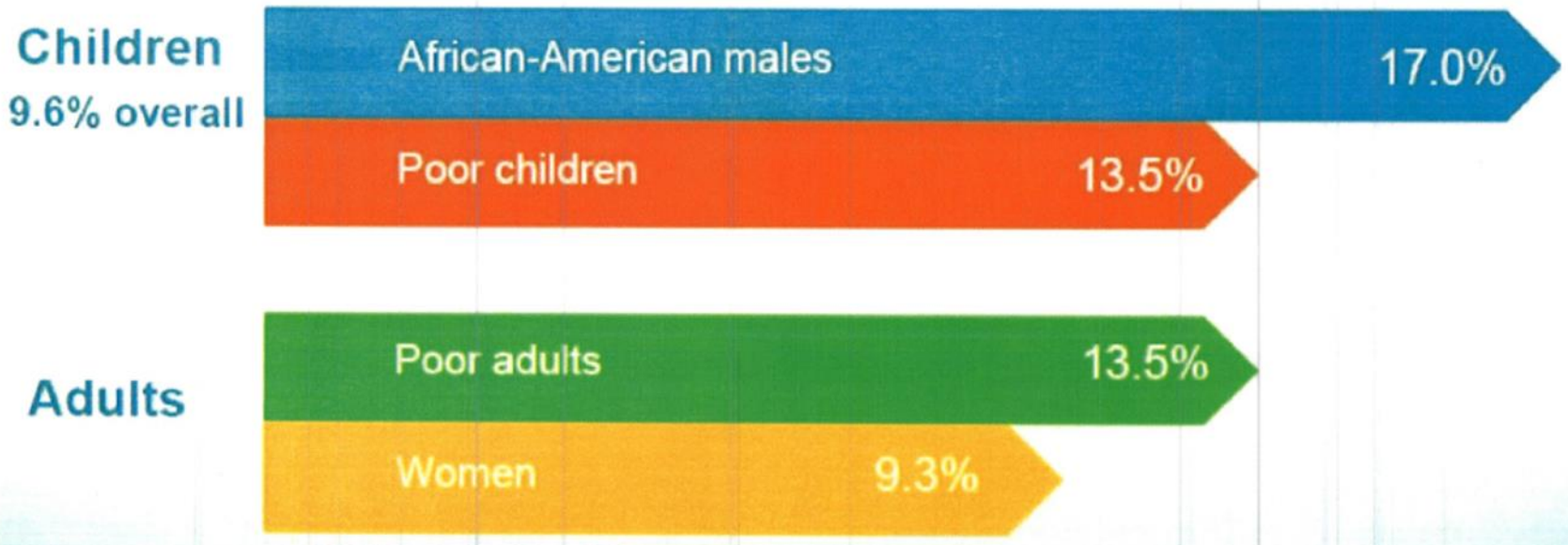
Current Asthma, Ages 1-85 years, 2001-2009



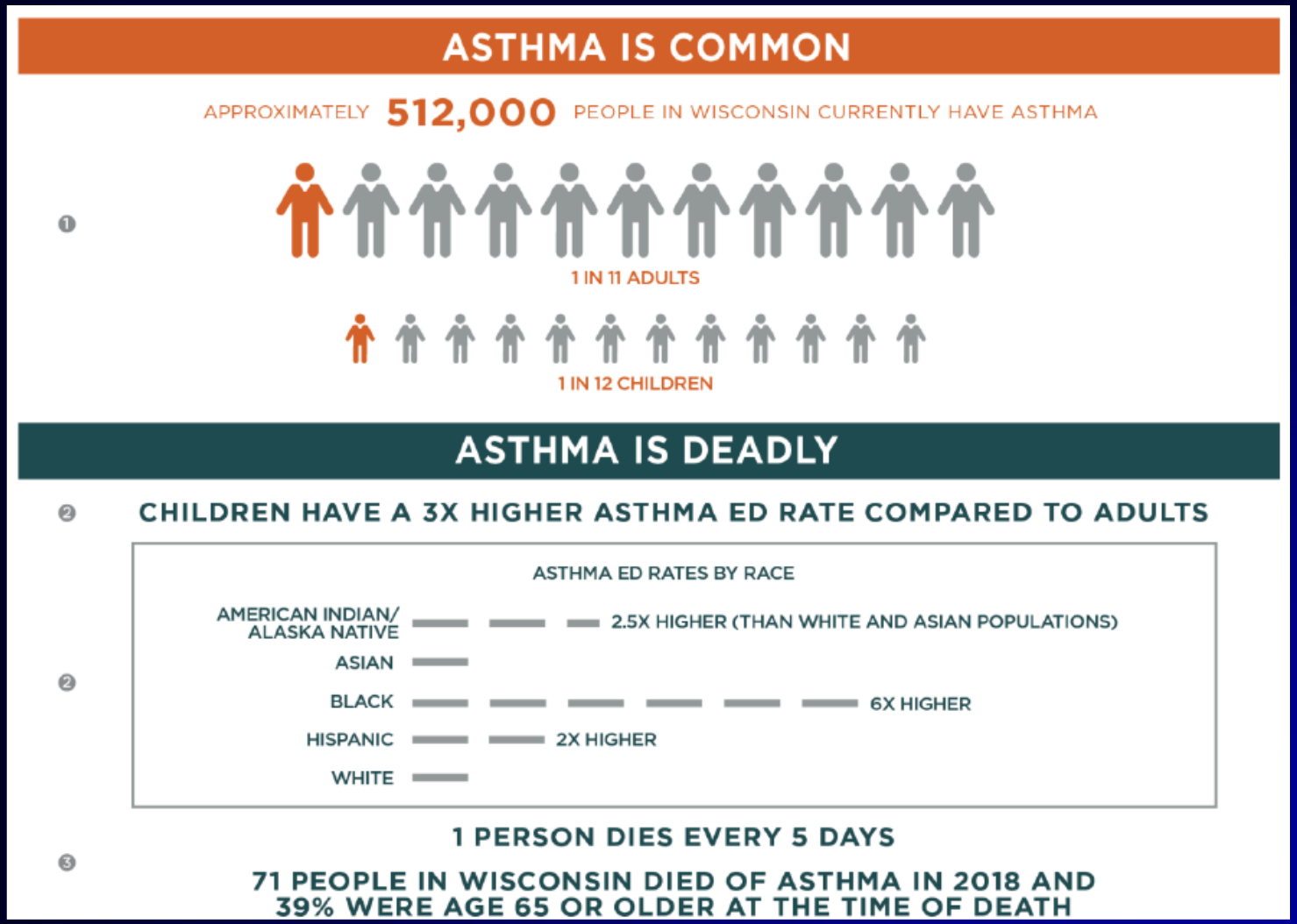
The Face of Asthma, 21st Century

Since 2000, asthma prevalence has grown 12.3%!

8.2% of the population has asthma, most notably in:



Asthma in Wisconsin



www.chawisconsin.org Wisconsin Asthma Plan 2021-2025

Definition of Asthma

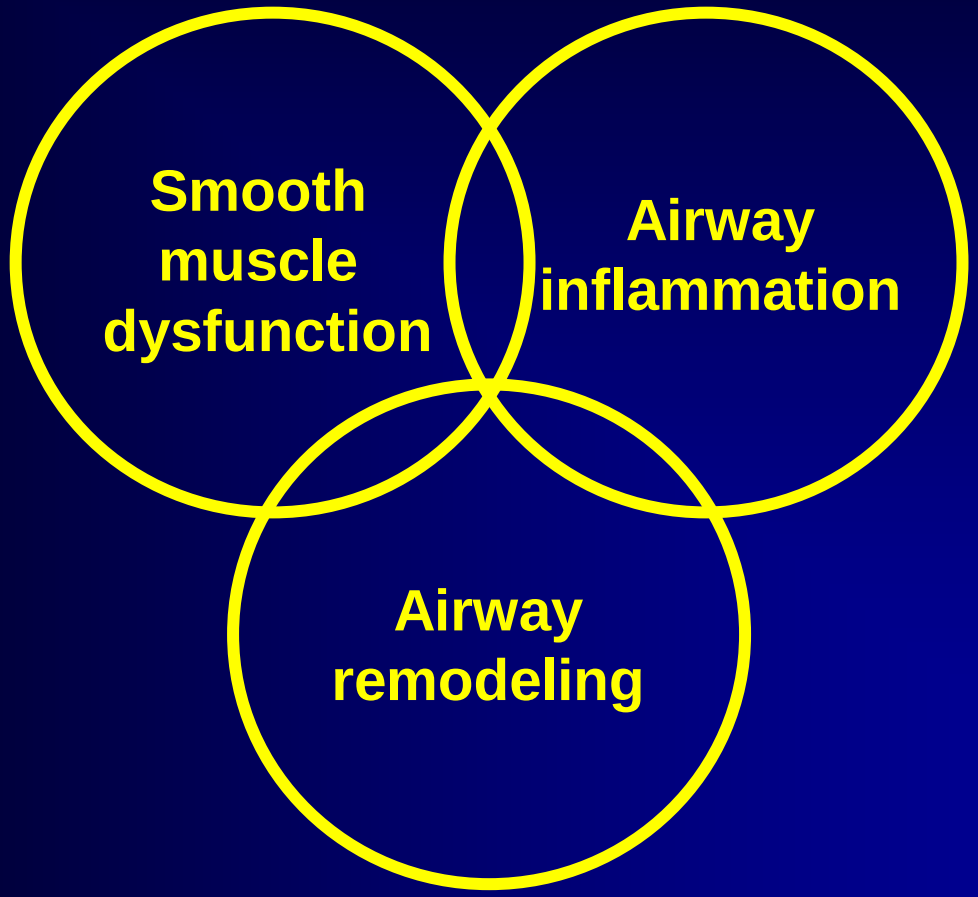
- A heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.
- Triggers
  - Exercise
  - Allergens at home or work
  - Occupational exposures
  - Irritant exposure e.g. tobacco smoke
  - Change in weather
  - Viral respiratory infections
  - Medications e.g. beta blockers, ASA/NSAIDS (in some)

www.ginasthma.org

Key Asthma Pathophysiologic Features

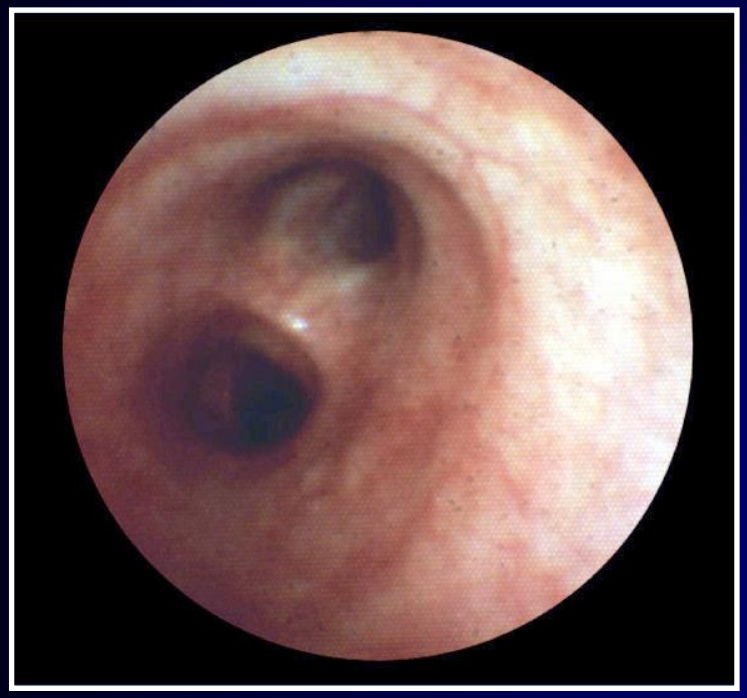
- Inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night and in the early morning.
- Symptoms are associated with obstruction, often reversible either spontaneously or with treatment.
- Obstruction is caused by bronchoconstriction, airway edema, chronic mucus plug formation, and airway remodeling.
- Inflammation causes increased bronchial hyperresponsiveness (BHR) to stimuli; these stimuli or “triggers” result in airflow obstruction and symptoms.

Asthma Pathophysiology



Adapted from Bousquet et al. Am J Respir Crit Care Med. 2000;161:1720-1745.

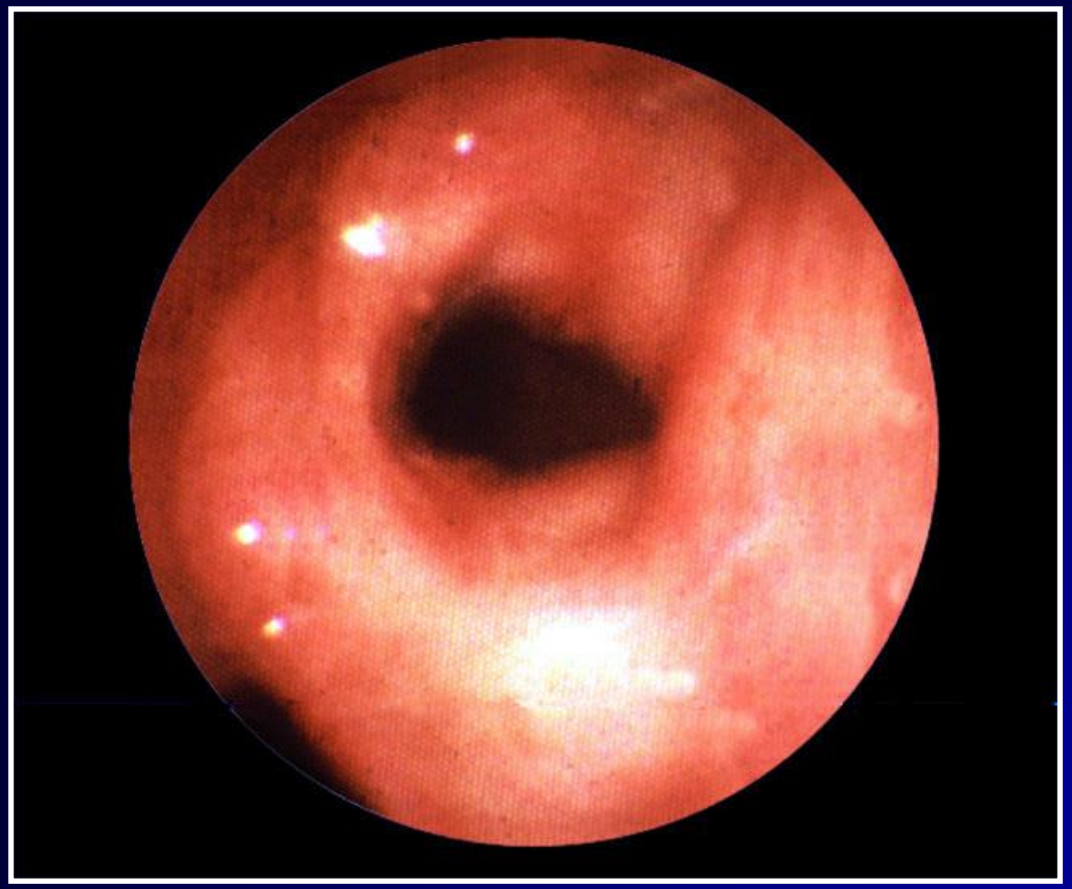
Bronchoconstriction



Before

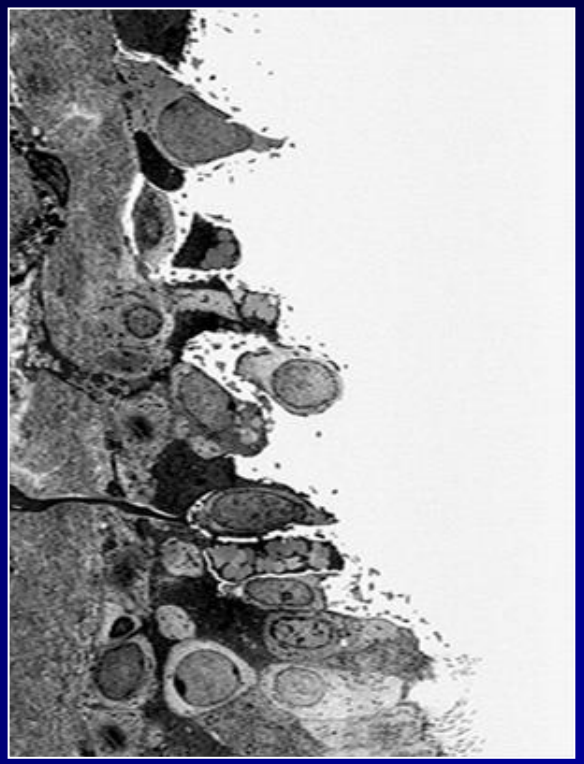
10 Minutes After
Allergen Challenge

Airway Mucosal Edema



Epithelial Damage

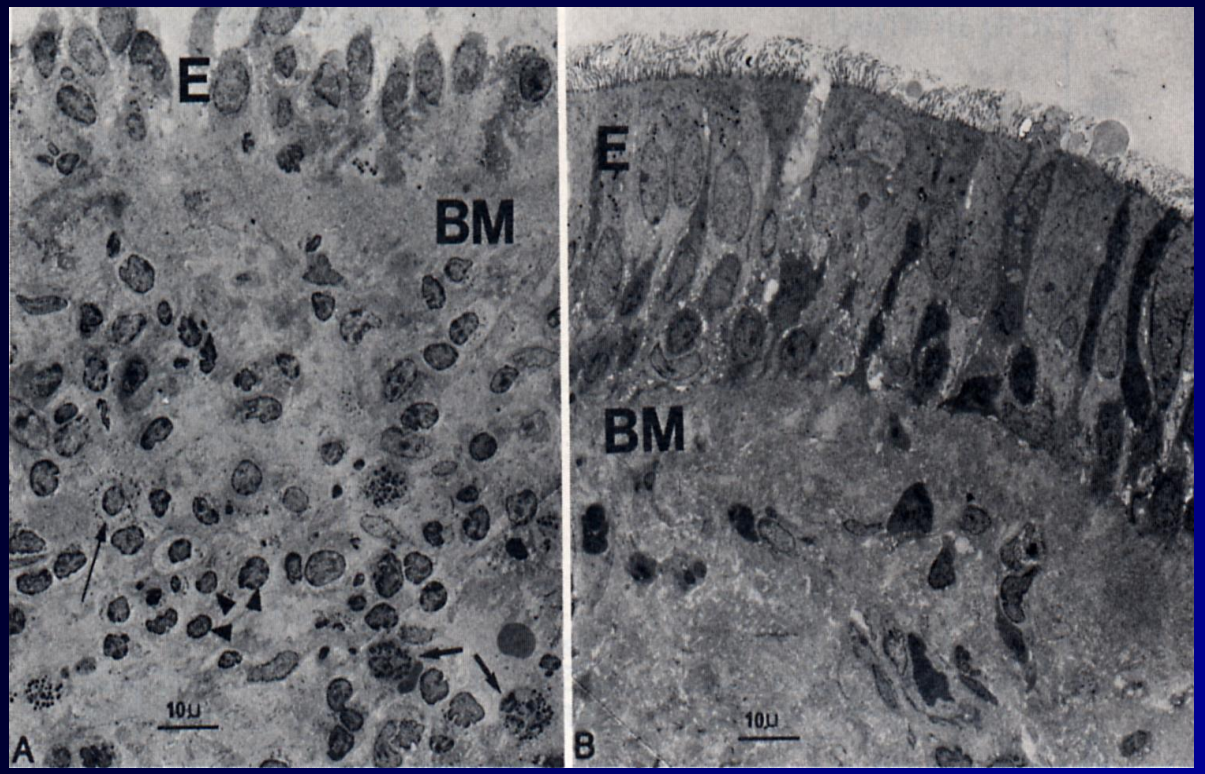
Normal



Asthmatic

Jeffery P. In: Asthma. New York, NY: Academic Press; 1998.

Effects of Inhaled Corticosteroids on Inflammation



Pre- and post-3–month treatment with BUD 600 µg b.i.d.

Laitinen. *JACI.* 1992;90:32-42.

Making the Initial Diagnosis of Asthma

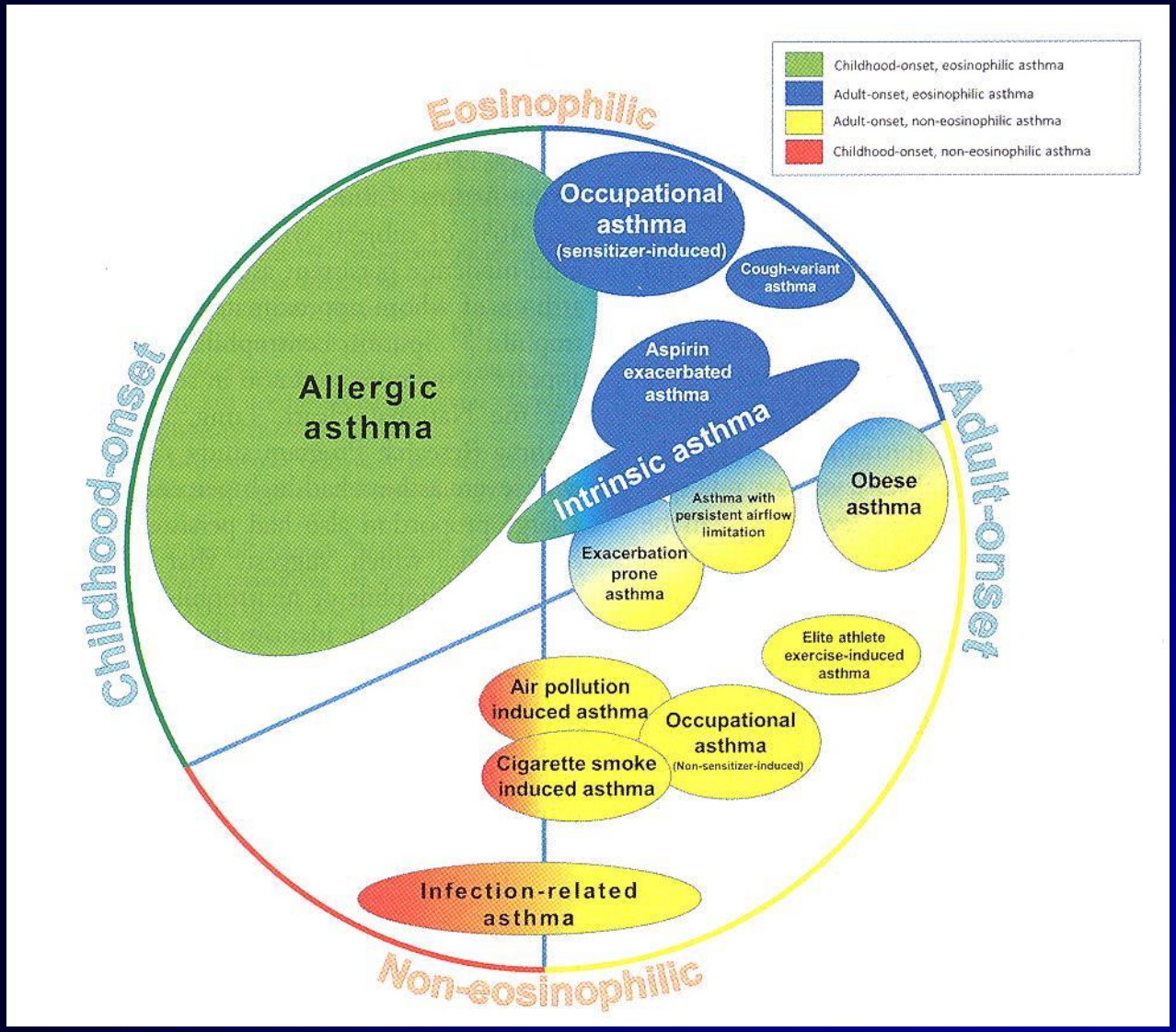
- History (personal and family)
- Physical exam
- Lung function testing to confirm variable expiratory airflow limitations (FEV_1 or PEF)
- Other tests
  - Bronchoprovocation (methacholine, exercise)
  - Allergy testing (skin prick testing or specific IgE in serum)
  - Exhaled Nitric Oxide
- Tests to ID co-morbidities
  - CXR, sinus X-ray
  - GE reflux assessment
  - Sleep disorder assessment
- Tests to exclude other diagnoses in children and adults
- Emerging biomarkers eg. serum eosinophilia

Asthma Phenotypes

- Phenotypes = recognizable clusters of demographic, clinical, and/or pathophysiological characteristics
- Common phenotypes
  - Allergic asthma
  - Non-allergic asthma
  - Adult-onset (Late-onset) asthma
  - Asthma with persistent airflow limitation
  - Asthma with obesity
- Wheezing phenotypes
- Refractory or severe asthma

www.ginasthma.org

Asthma Phenotypes



Childhood Asthma – Predictive Phenotype

- Wheezing phenotypes (Tucson Children's Resp. Study)
  - Never wheezers (healthy children w/o wheezing)
  - Early, transient wheezers (onset before age 3 and resolution by age 6)
  - Persistent wheezers (onset before age 3 and sustained at age 6)
  - Late-onset wheezers (onset between ages 3-6)
- Asthma predictive risk models

Guilbert TW et al. J Allergy Clin Immunol Pract 2014; 2:664-70

Childhood Asthma – Predictive Phenotype (Cont'd)

- Key characteristics
  - Male sex
  - Hx freq. wheezing with respiratory tract infections often 6-8x/year (esp. rhinovirus) & other triggers
  - Hx parental asthma
  - Hx atopic dermatitis
  - Blood eosinophilia ≥ 4%
  - Early sensitization to food or aeroallergens
  - Lower lung function in early life
- Positive Asthma Predictive Index (API) →4-10x greater chance of asthma at age 6-13

Guilbert TW et al. J Allergy Clin Immunol Pract 2014; 2:664-70

Pediatric Asthma Risk Score (PARS) Scoring Sheet

	Possible Scores		
	No	Yes	Child's Score
1. Parental Asthma	0	2	
2. Eczema before age 3 years	0	2	
3. Wheezing apart from colds	0	3	
4. Wheezing before age 3 years	0	3	
5. African-American Race	0	2	
6. SPT positive to ≥ 2 aero and/or food allergens	0	2	
Child's PARS (add lines 1-6 above):			

Patient Score Interpretation

Score	Risk of Asthma by age 7 years	Interpretation	
0	3%	LOW RISK	Children with these scores have a 1 in 33 [score of 0] to a 1 in 9 [score of 4] risk of developing asthma by age 7 years
2	6%		
3	8%		
4	11%		
5	15%	MODERATE RISK	Children with these scores have a 1 in 7 risk [Score of 5] to a 1 in 3 [Score of 8] risk of developing asthma by age 7 years
6	19%		
7	25%		
8	32%		
9	40%	HIGH RISK	Children with these scores have a 2 in 5 [Score of 9] to a 4 in 5 [Score of 14] risk of developing asthma by age 7 years
10	49%		
11	58%		
12	66%		
14	79%		

Sherenian MG, et al. *Expert Rev Clin Immunol*, 2019

Asthma Severity

Asthma Control

2 Domains:

Impairment

Risk

www.nhlbi.nih.gov/guidelines/asthma

Goals of Therapy: Addressing the Domains of Impairment and Risk

- Reducing Impairment or Discomfort
  - Prevent chronic troublesome symptoms
  - Require infrequent use of SABA (≤ 2 days a week)
  - Maintain (near) "normal" pulmonary function
  - Maintain normal physical activity
  - Enable quality of life unimpaired by asthma
- Reducing Risk
  - Preventing recurrent exacerbations of asthma and minimizing the need for ED visits or hospitalizations
  - Preventing disease progression
    - progression of irreversible airflow obstruction (development of more severe asthma)
  - Avoiding toxicities of treatment

www.nhlbi.nih.gov/guidelines/asthma

GINA Assessment of Asthma in Adults, and Children Older than 5 years

- Assess asthma control = symptom control and risk factors
  - Assess symptom control over the last 4 weeks
  - ID other risk factors for poor outcomes
  - Measure lung function at diagnosis/start of treatment, 3-6 months later, then at least yearly in most patients
- Assess co-morbidities
- Assess treatment issues
  - Document current treatment step (1-5); query side effects
  - Watch inhaler technique; assess adherence
  - Check on written asthma action plan
  - Ask about patient's attitudes/goals for asthma

www.ginasthma.org (Box 3)

Level of Asthma Symptom Control in Adults and Children Older than 5 years

In the past 4 weeks, has the patient had:

- Daytime Sx > 2x/week?
  Yes □ No □
- Any night waking due to asthma?
  Yes □ No □
- Reliever needed for Sx* > 2x/week? Yes □ No □
- Any activity limitation due to asthma? Yes □ No □

LEVEL OF ASTHMA Sx CONTROL		
WELL CONTROLLED	PARTLY CONTROLLED	UNCONTROLLED
NONE OF THESE	1-2 OF THESE	3-4 OF THESE

*Excludes reliever eg albuterol, taken before exercise

www.ginasthma.org (Box 4)

Risk Factors for Poor Asthma Outcomes

- Potentially modifiable independent risk factors for exacerbations
  - Uncontrolled asthma Sx (as above)
  - ICS not prescribed; poor ICS adherence; incorrect device technique
  - High SABA use (↑ mortality if > 1 x 200-dose canister/month)
  - Low FEV_1 (esp < 60% predicted)
  - Major psychological or SE problems
  - Exposures (smoking, allergens, air polution)
  - Comorbidities
  - Sputum or blood eosinophilia; elevated FENO
  - Pregnancy

www.ginasthma.org (Box 4)

Risk Factors for Poor Asthma Outcomes (cont)

- Others
  - Ever intubated or in intensive care for asthma
  - ≥ 1 severe exacerbation in last 12 months
- Risks for Medication side effects
  - Systemic: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors
  - Local: high-dose or potent ICS; poor inhaler technique

www.ginasthma.org (Box 4)

Asthma Symptom Control Tools

- Patient-centered measurements of asthma control
- Preferred
  - Asthma Control Test (ACT)
  - Childhood Asthma Control Test (CACT)
  - Asthma Control Questionnaire – 5 (ACQ-5)
  - Asthma Control Questionnaire - 6 (ACQ-6)
  - Asthma Control Questionnaire – 7 (ACQ-7)
- Also Available
  - Asthma Therapy Assessment Questionnaire (ATAQ)
  - Composite Asthma Severity Index (CASI)
  - Global Evaluation of Treatment Effectiveness (GETE)
  - Test for Respiratory and Asthma Control in Kids (TRACK)

Validated Asthma Control Tools

- Asthma Control Questionnaire (ACQ®) for ≥12 years
  - Score calculated as the average of 5, 6, or 7 items; all versions have 5 symptom questions
  - ACQ – 6 includes reliever use
  - ACQ – 7 includes score for pre-bronchodilator FEV_1 which is averaged with symptom and reliever items
  - MID = 0.5
  - Scores range 0-6 (higher is worse)

    0.0 – 0.7 well controlled

    0.75-1.5 "grey zone"

    > 1.5 poorly controlled

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Validated Asthma Control Tools

- Asthma Control Test (ACT®) for ages ≥ 12 years
  - 5 total questions (4 symptom/reliever questions plus a patient self-assessed level of control)
  - MID = 3
  - Scores range 5-25 (higher is better)

    20-25 well-controlled

    16-19 not well-controlled

    5-15 very poorly controlled
- Childhood ACT® for ages 6-11 years of age
  - Separate sections for parent and child to complete

www.ginasthma.org

Monitoring Pulmonary Function Spirometry

- Frequency recommendations
  - Initial assessment
  - After Tx is initiated and symptoms and peak flow have stabilized, to document attainment of (near) “normal” airway function
  - During a period of progressive or prolonged loss of asthma control
  - At least every 1-2 years to assess maintenance of airway function
- Consideration
  - Yearly check on accuracy of PF meter
  - When more precision is desired eg step-down Tx
  - When PF results are unreliable
- Severity: FEV_1 > 80% = mild, 60-80% = moderate, <60% = severe

Ref. EPR3 guidelines

Peak Flow (PF) Monitoring

- Consider long-term PF monitoring for
  - Moderate-severe persistent asthma
  - Hx severe exacerbations
  - Poor perceivers
  - Patients who prefer this
- Consider home PF monitoring during exacerbations for
  - Hx severe exacerbations
  - Hx severe persistent asthma
  - Poor perception of worsening asthma
- Use personal best PF (from twice daily readings reached on average within 2 weeks) as reference value in action plan
- PF vs Sx-Based Action Plan: equally effective IF taught and followed correctly.

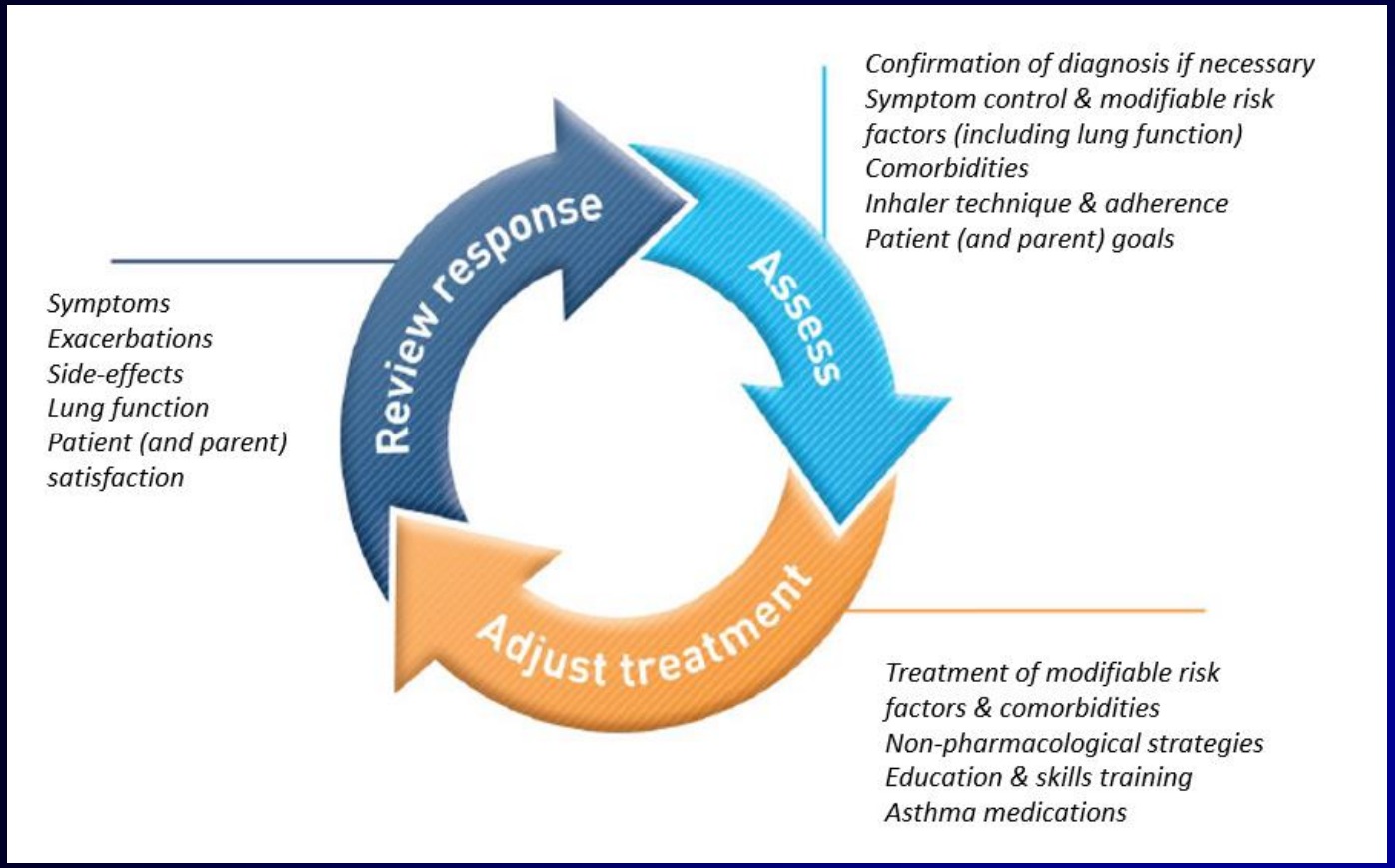
Ref. EPR3 guidelines

Exhaled Nitric Oxide (FeNO)

- Adjunct to the evaluation process in patients ≥ 5 years where diagnosis is uncertain and spirometry cannot be performed
- Part of the monitoring and management strategies when there is uncertainty in choosing or adjusting anti-inflammatory therapy for patients ≥ 5 years

J Allergy Clin Immunol 2020;146:1217-70

Providing Treatment and Assessment



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Box 6

Population-Level Treatment Recommendations

- “Preferred” medication at each step is the best treatment for most patients, based on:
  - Efficacy
  - Effectiveness
  - Safety
  - Availability and cost at the population level e.g. national/system formularies, health care organizations formularies and guidelines

Patient-Level Treatment Decisions*

- Preferred Tx for risk reduction and Sx control
- Patient characteristics or phenotypes
  - Patient features that predict differences in future risk or Tx response (allergy Hx, past exacerbations, blood eosinophilia, smoker)
  - Modifiable risk factors or comorbidities (obesity, sinusitis)
- Patient/family preference
- Practical issues
  - Device technique
  - Adherence
  - Cost

***Shared decision-making with patient/parent/care giver**

Categories of Asthma Medications

- Reliever (rescue) medications
  - For all patients prn relief of breakthrough Sx, including ↑ asthma or exacerbations
  - Rec. for short-term prevention EIB
  - Goal: ↓ or eliminate need for reliever (a measure of success)
  - Examples: albuterol, levalbuterol, ipratropium
  - Inhaled route preferred
- Controller medications
  - Regular maintenance Tx
  - Reduce inflammation, control Sx, reduce future risks such as exacerbations and decline in lung function.

Asthma Controller Medications

- Inhaled corticosteroids (ICS)
- Oral corticosteroids (OCS)
- Antileukotrienes/Leukotriene Receptor Antagonists (LTRA)
- Long-acting Beta-Agonists (LABA)
- Long-acting Muscarinic Antagonists (LAMA)
- Biologic therapies
  - Anti-immunoglobin E (anti-IgE) – omalizumab (Xolair®)
  - Anti-IL5-Mepolizumab (Nucala®)
  - Anti-IL5-Reslizumab (Cinqair®)
  - Anti-IL5-Benralizumab (Fasenra®)
  - Anti IL-4Rα / IL-13Rα 1 (Dupixent®)
  - Allergen immunotherapy (SCIT, SLIT)