Asthma

- Elham mohammadhosseini
- Pulmonologist

Objectives

Upon completion, the participant will be able to:

1. Identify statistics related to incidence/prevalence of asthma
2. Discuss the signs and symptoms of asthma
3. Discuss treatment options for asthma

Asthma

Asthma is...

- Derived from the Greek word for panting or breathlessness
- Recurrent airflow obstruction caused by chronic airway inflammation with a superimposed bronchospasm
- Leads to… wheezing, breathlessness and a cough

Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. NIH, NHLBI. June 2002. *NIH publication no. 02-5075.*

Prevalence of Asthma

- Impacts approximately 21 million individuals in the United States
- Most common chronic disease of childhood affecting 6 million children
- Before adolescence, 2 times more common in boys
- Increasing incidence of this disease
  - 76% increase in the prevalence of asthma within the past decade

Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. NIH, NHLBI. June 2002. *NIH publication no. 02-5075.*

Impact of Asthma

- Most frequent cause for hospitalization in children (470,000 each year)
  - Emergency room visits and hospitalizations are increasing
- Most frequent cause of childhood death, particularly amongst certain groups (children, african americans)
  - 4000 - 5,000 people die yearly from asthma

Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for asthma-United States, 1980-1999. *MMWR Surveill Summ*. 2002;51:1-13.

Why Is the Death Rate Increasing?

- Multifactorial
  - Asthma is increasing
  - Asthma is more severe
  - Poor management of the disease
  - Poor patient compliance
  - Inadequate patient and provider response to signs of worsening trouble

Misconceptions and Facts

- Asthma symptoms can begin at any age
- Most often misdiagnosed or underdiagnosed in the elderly
  - Fail to report symptoms because it is thought to be normal
  - Attribute the symptoms to comorbid diseases

Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for asthma-United States, 1980-1999. *MMWR Surveill Summ*. 2002;51:1-13.

Misconceptions

- Most people think that children will outgrow asthma…
  - Children who suffer from intermittent wheezes have a 50% chance or better of outgrowing this disease
  - Children with persistent wheezing have only a 5% chance of outgrowing this disease

Fuerra S, Wright AL, Morgan WJ, et al. Persistence of asthma symptoms: role of obesity and onset of puberty. *Am J Respir Crit Care Med*. 2004;170:78-85.

Pathophysiology of Asthma

- Genetic predisposition
  - Chromosome: 5Q31-Q33
- Results from repeated exposure to allergens in the individual already equipped with the genetic predisposition
- Upon exposure to an allergen, there is a release of IgE antibodies
- IgE antibody binds with the antigen

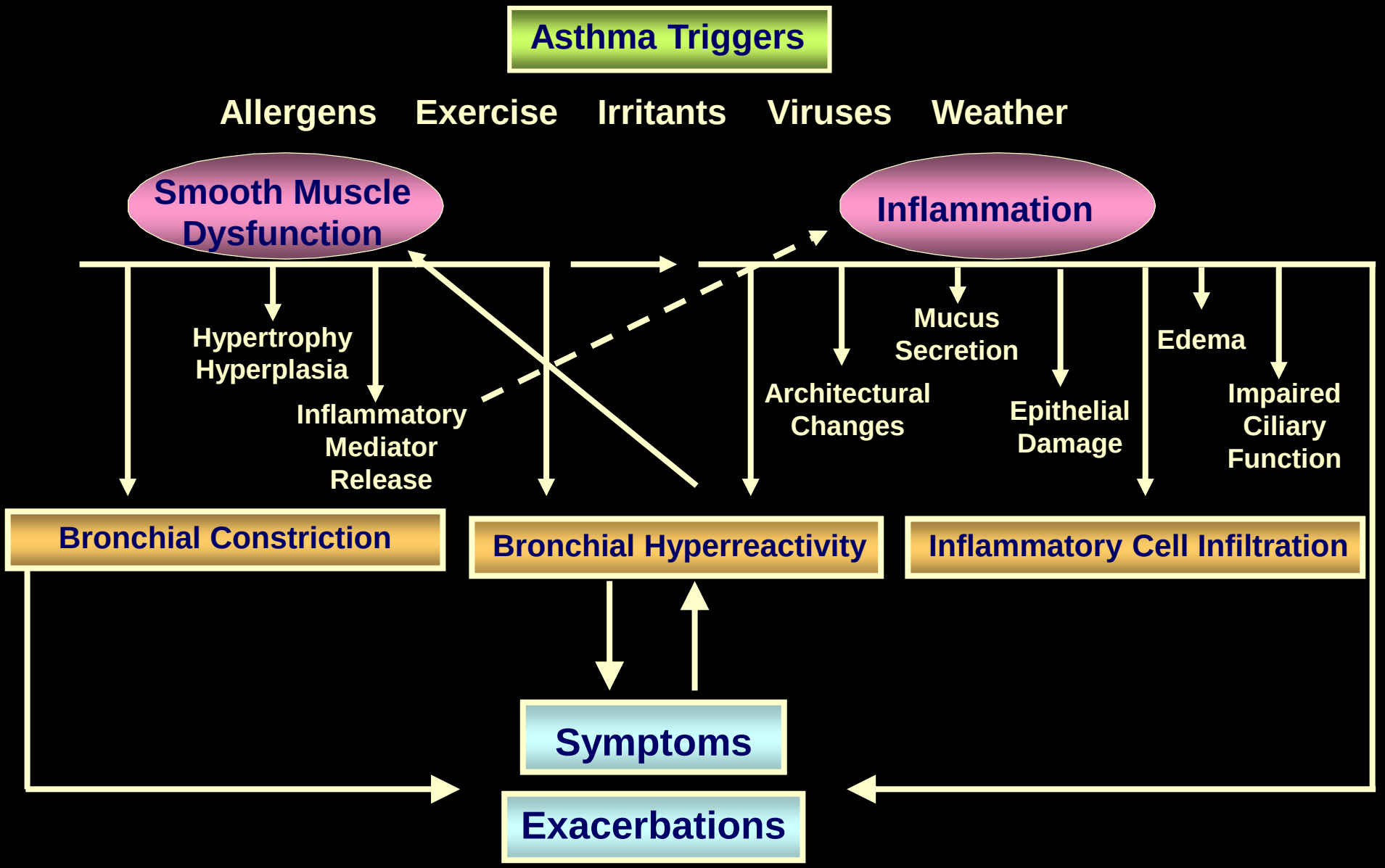
Pathophysiology of Asthma

- IgE/allergen complex - then attaches itself to the mast cells on the nasal and bronchial mucosa
- Release of numerous chemical mediators

Histamine

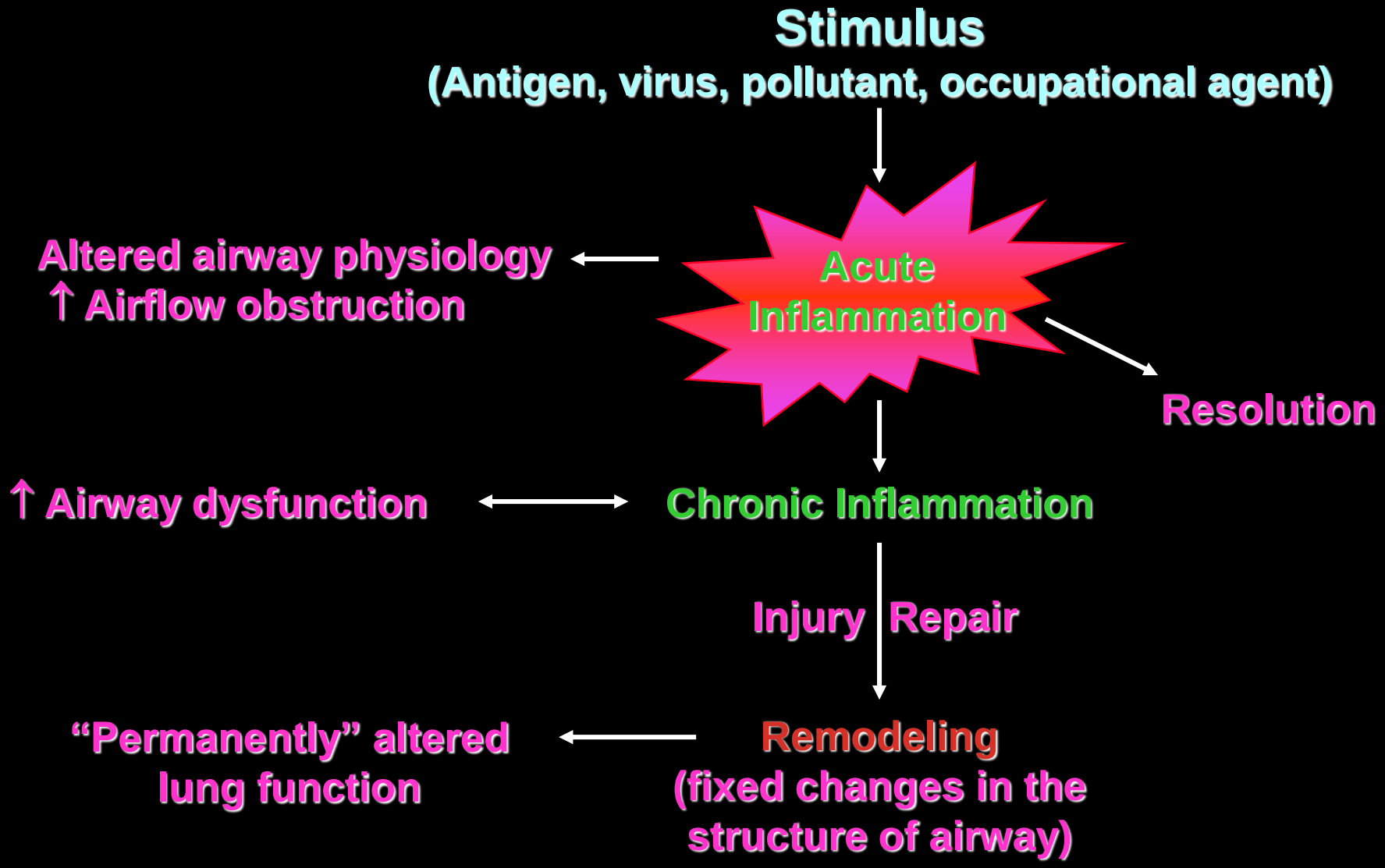
- Histamine is stored mainly in the mast cell
  - Circulated in the blood via the basophil
- Causes an increase in blood flow to the affected area.
  - Responsible for the increased nasal discharge, edematous mucous membranes, sneezing, itchy nose and eyes, and hives
  - Also associated with airway inflammation and bronchoconstriction

Components of Asthma

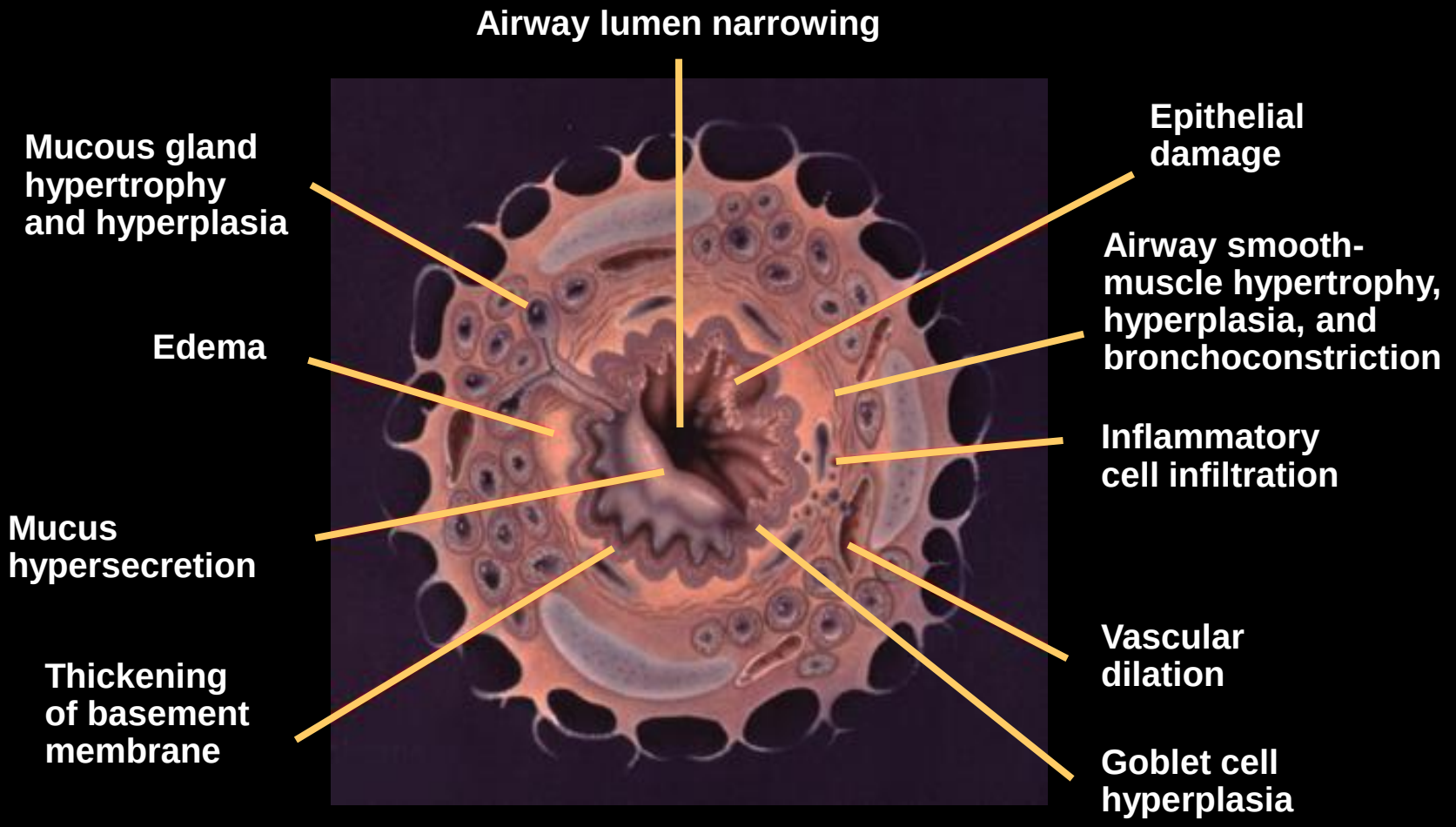


Adapted from Creticos. Adv Stud Med. 2002;2(14):499-503.

Consequences of Inflammation in Asthma

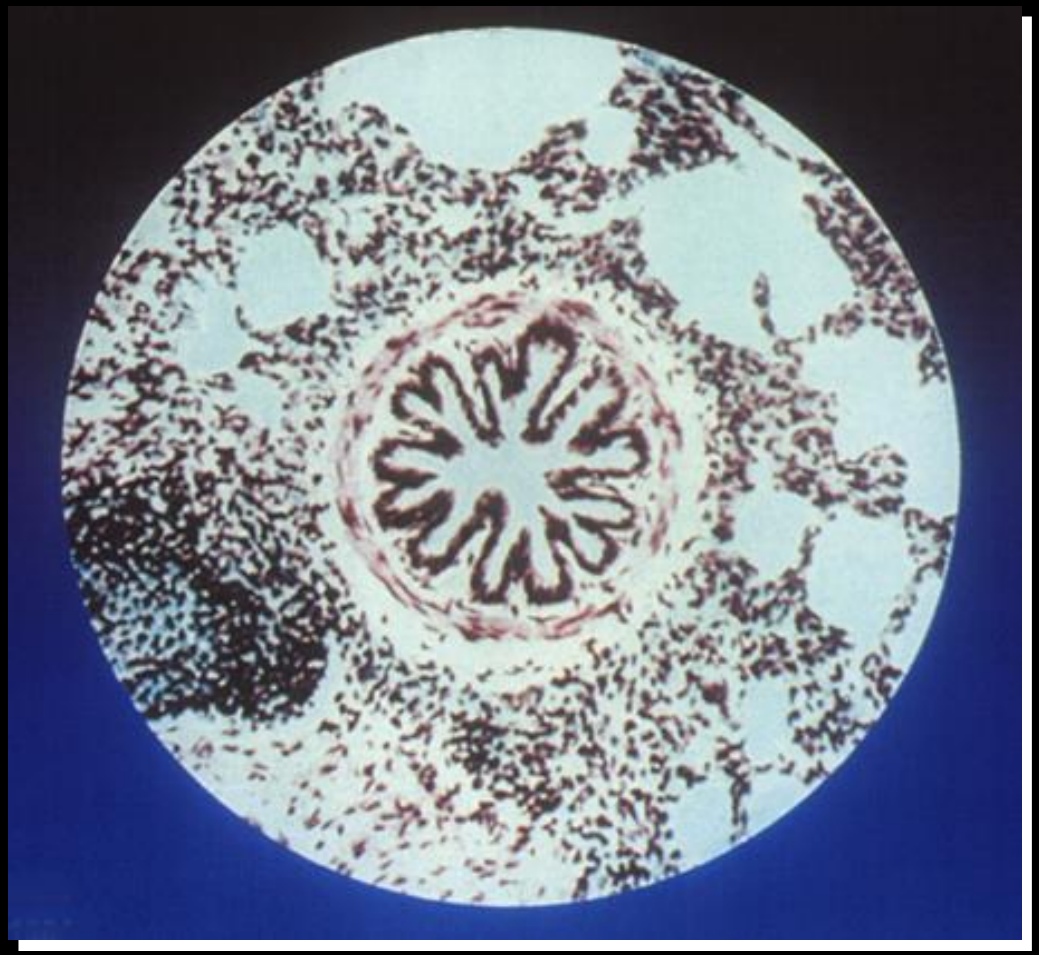


Asthma: Pathophysiologic Features and Changes in Airway Morphology



Adapted from Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma. NIH, NHLBI. 1991. NIH publication 91-3042.

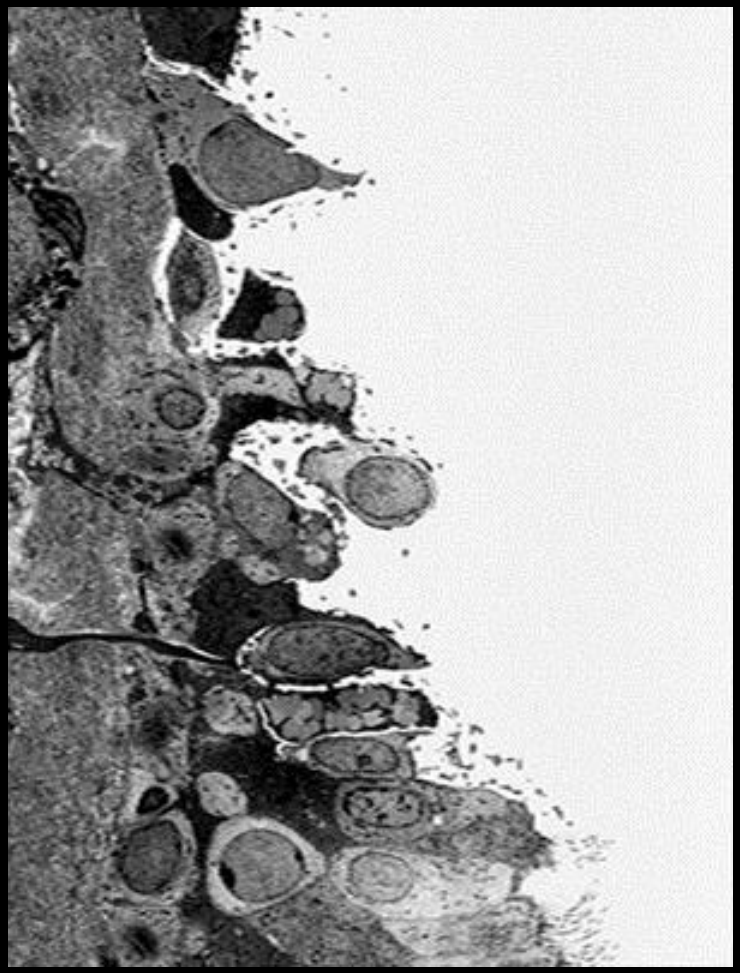
Cross Section of Bronchiole Showing Bronchospasm



Color Atlas of Respiratory Disease. Volume 2, 1995.

Epithelial Damage in Asthma

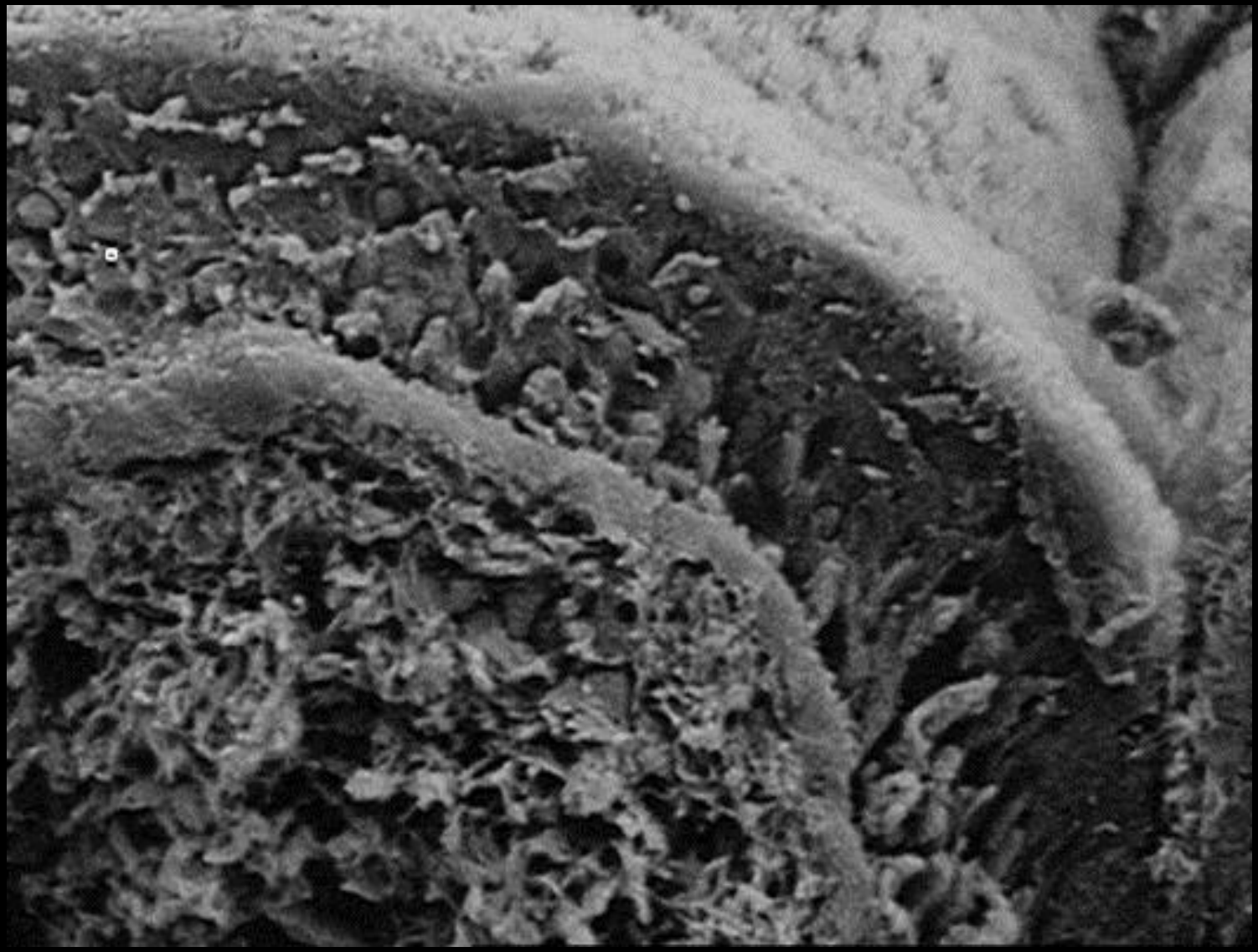
Normal



Asthmatic

Jeffery P. In: Asthma, Academic Press 1998.

Basement Membrane Thickening



Jeffery P. In: Asthma, Academic Press 1998.

Triggers

- Inhalant allergens are the most common triggers for both asthma
  - House dust
  - Pollens
  - Mold spores
  - Animal and insect emanations
    - Cockroach feces

Triggers

- Chemicals
- Perfumes
- Foods
  - Sulfites (wine), shrimp, dried fruit, processed potatoes, beer
- Viruses or infections
- Cold air

Triggers

- Tobacco smoke
- Pollution
  - Work exposures
- Exercise

Gastroesophageal Reflux - A Significant Factor in Children

- 84 healthy infants and children referred for an evaluation of daily wheezing
  - All evaluated for reflux
  - 64% had positive evaluations for reflux
  - After 3 months on anti-reflux treatment, 64.8% of the infants/children were able to discontinue all daily asthma medications (including nebulized flunisolide)

Sheikh S. et. Al. Pediatric Pulmonology. 1999 Sep; 28(3): 181-6

Asthma is…

- A disease of:
  - Inflammation
    - Primary Process
  - Hyperresponsiveness
  - Airway bronchoconstriction
  - Excessive mucous production

Diagnosis of Asthma

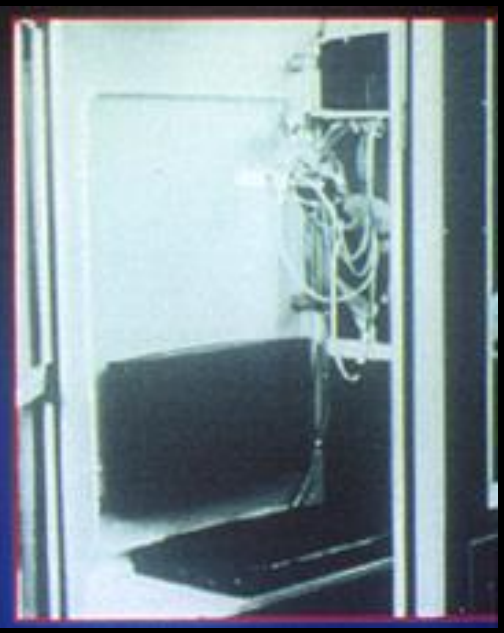
Diagnosis of Asthma

- History and Physical Examination
- Spirometry is needed to make diagnosis
- Monitoring:
  - Peak Flow Meters

Symptoms and Signs of Asthma in Children and Adults

- Coughing, particularly at night or after exercise
- Wheezing
- Chest tightness
- SOB
- Cold that lingers x months

Methods for Measuring Airway Caliber



Maximum PEFR airflow achieved

Home

FVC, FEV_1 $FEF_{25\%-75\%}$

Office/Clinic

Airway Resistance

Clinic/Laboratory

FIGURE 3–4c. CLASSIFYING ASTHMA SEVERITY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

- **Classifying severity for patients who are not currently taking long-term control medications.**

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

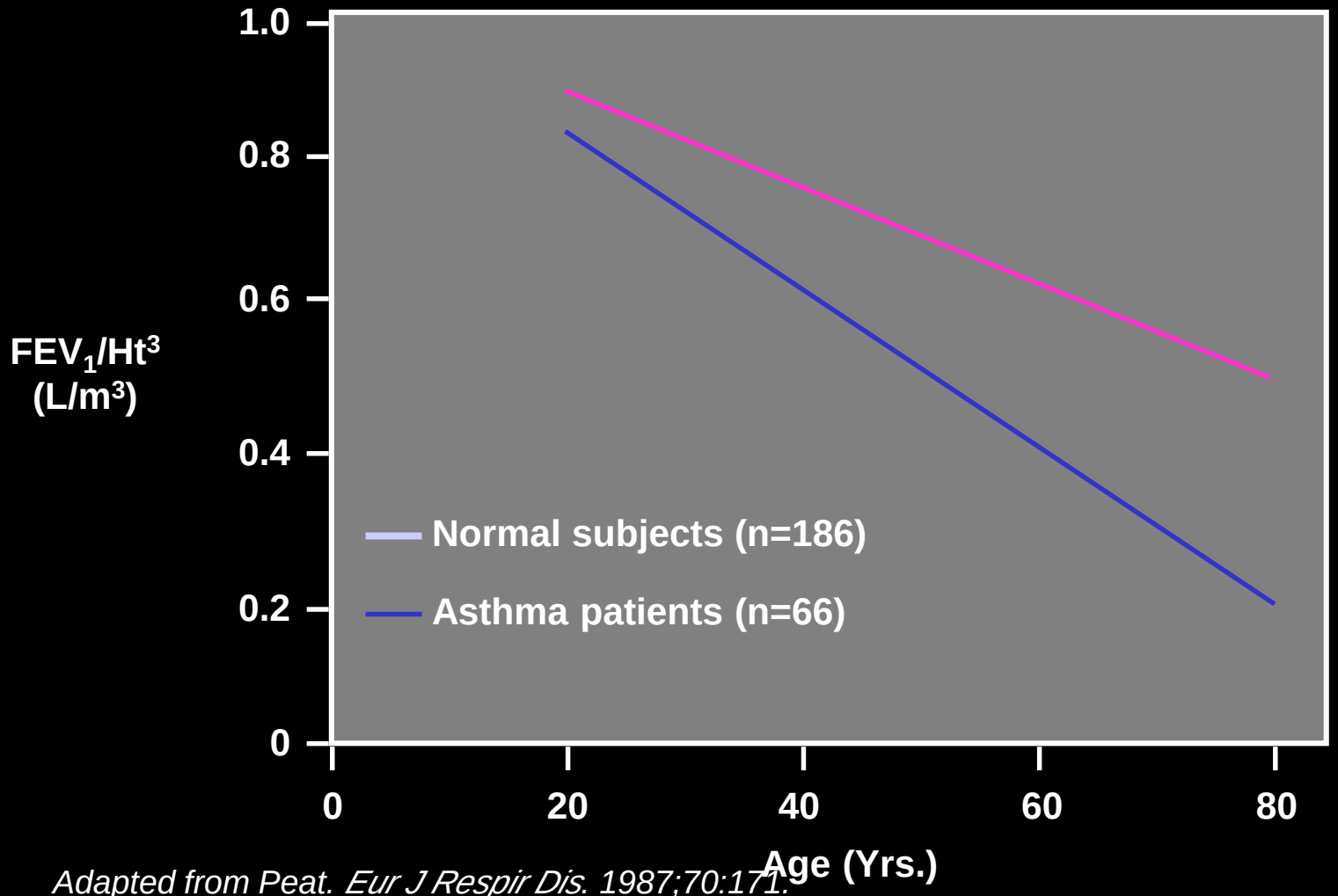
- **Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.**
- **At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.**

Asthma Findings

- Typically, reversibility of 12% or greater after administration of a bronchodilator aerosol is consistent with asthma.

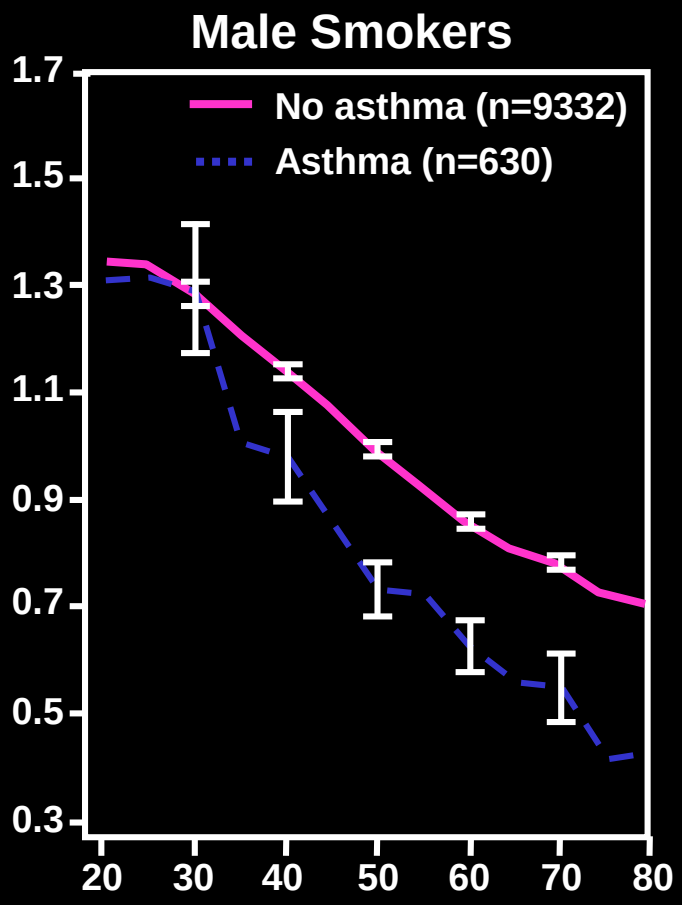
Conboy-Ellis, Kathleen. Asthma: Pathogenesis and Management. *The Nurse Practitioner*: November 2006; Vol.31, No. 11. 24 – 39.

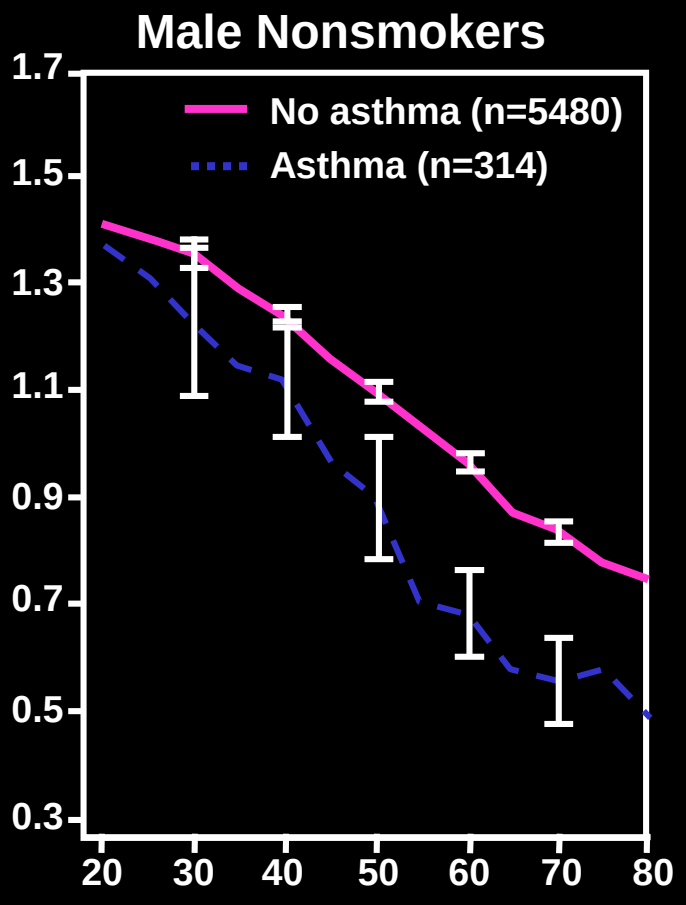
Rate of Decline in FEV_1



Adapted from Peat. Eur J Respir Dis. 1987;70:171.

Changes With Age in FEV_1 According to Smoking and Asthma Status



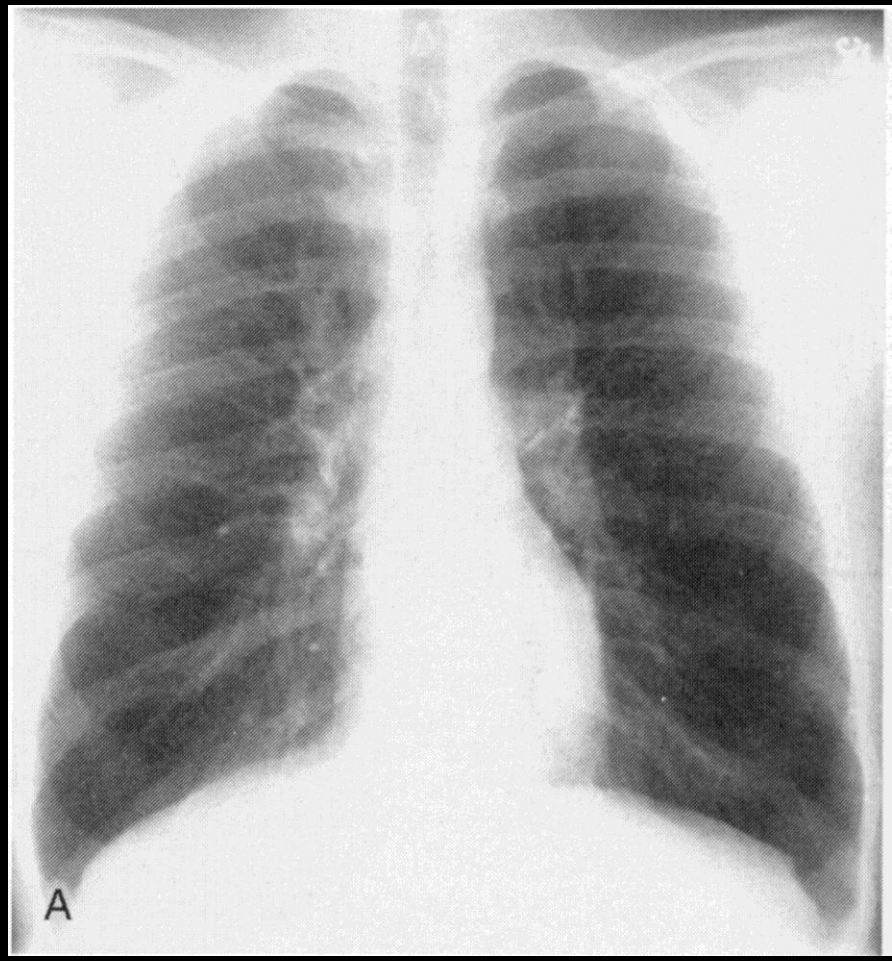


The Biggest Predictor of Sudden Death from Asthma

- History of hospitalization with or without intubation
- These individuals are at a significant risk for a serious exacerbation again

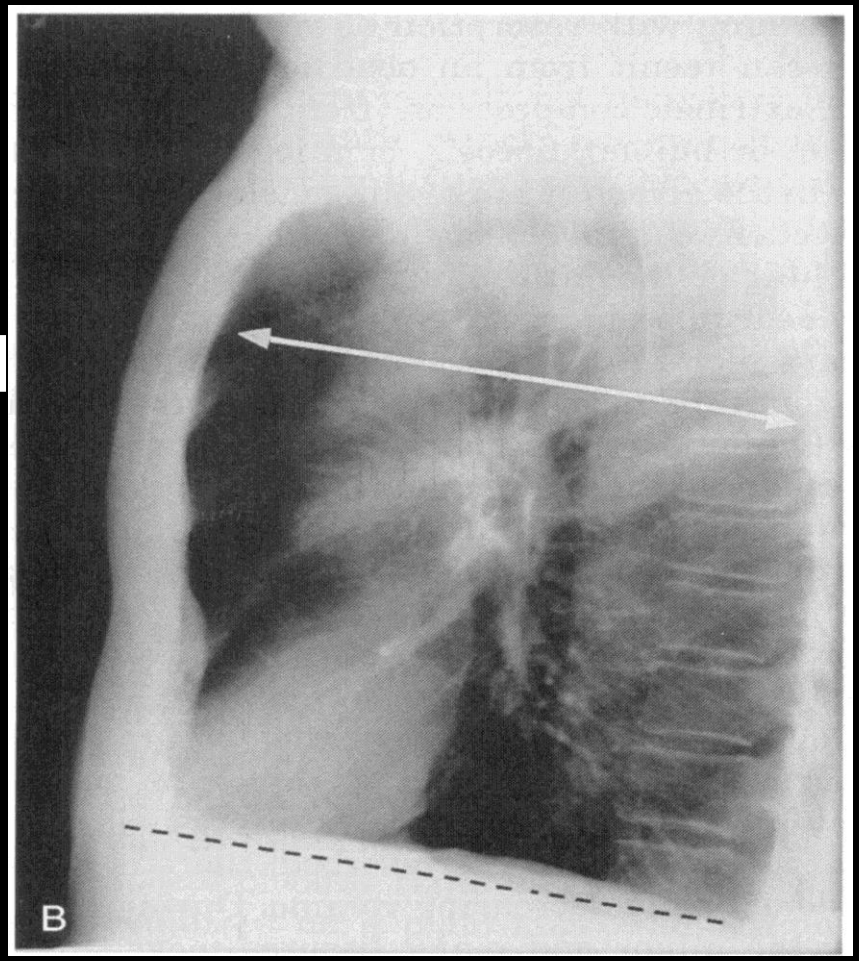
Asthma

- Hyperinflation
- Diaphragm is down to the 11th ribs
- Most patients with asthma have normal x-rays



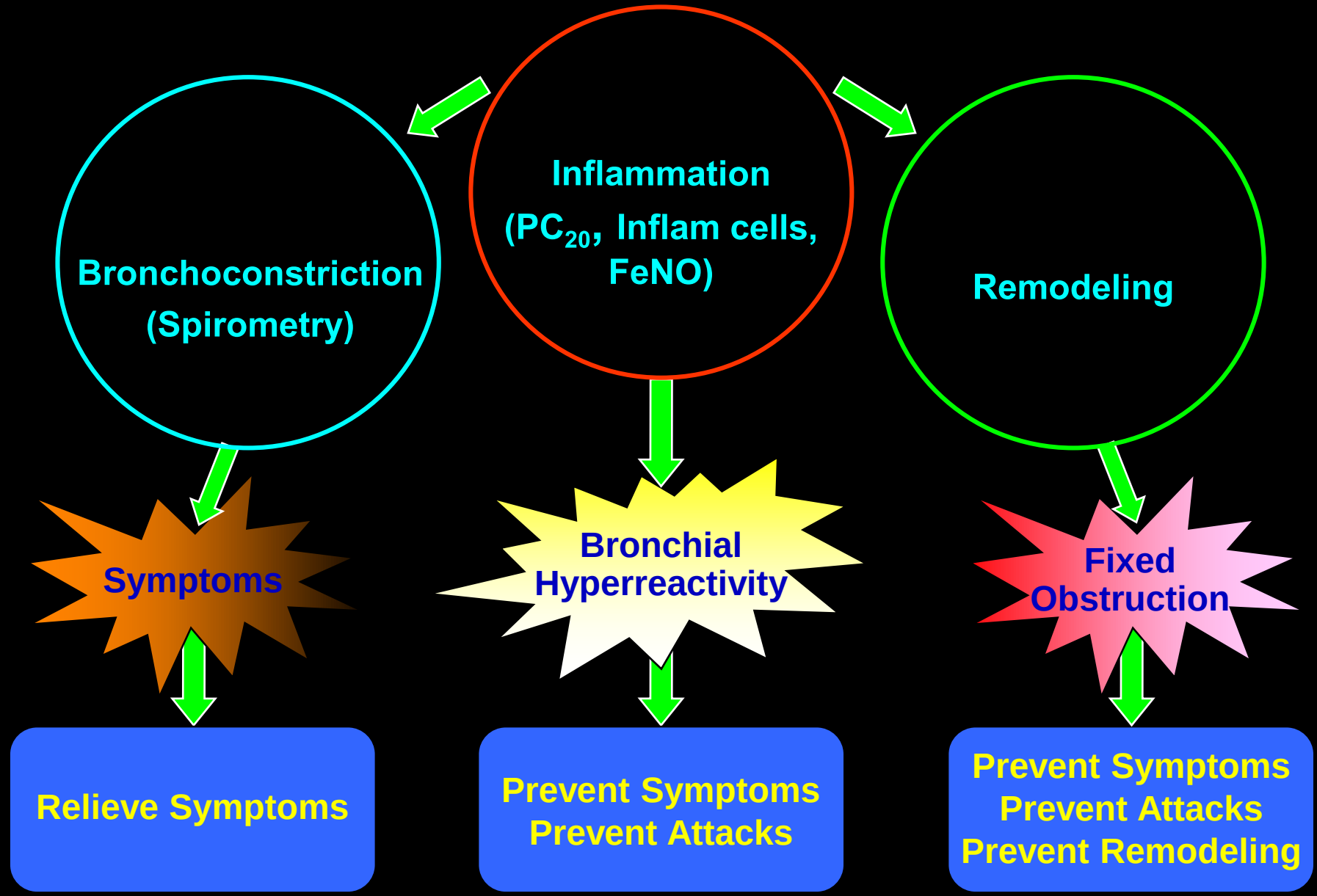
Chronic Asthma Changes

- Increased AP Lateral diameter
- The way you know that AP/Lat diameter is increased is by this clear space between the sternum and the ascending aorta
- Flat diaphragms



Treatment of Asthma

Evolution of Asthma Paradigms



Environmental Control: A Useful but Often Ignored Step

- Dust Mite Avoidance
  - Bed linens must be laundered 1-2 times/week
  - Maintain humidity at <50%
  - Encase pillows and mattresses
  - Frequent vacuuming
    - Remember: 30 minutes after vacuuming: increased dust mite emanations in the air
    - Individuals with significant asthma should avoid vacuuming or avoid the room for 30 minutes after vacuuming

Environmental Control: A Useful but Often Ignored Step

- Pollen Avoidance
  - Air-conditioning
  - Minimize outdoor exposures during times of highest pollen counts
  - Keep bedroom windows closed
  - Air filters

Environmental Control

- Animal Avoidance
  - Keep animals out of the bedroom
  - If the family has a cat, weekly washing of the cat significantly reduces the allergen load
  - May have to remove animals from home
  - Dry clean upholstery and carpets
  - Cover with an air filter any ducts leading into the bedroom

Environmental Control

- Mold Avoidance
  - Children/adolescents with allergic rhinitis and/or asthma should not be sleeping in a damp basement
  - Clean moldy surfaces
  - Avoid houseplants
  - Avoid chores that involve damp grass, leaves

Environmental Control

- Avoidance of Non-allergic Triggers
  - Strong emotions
  - Smoke: No smoking in house or car
  - Pollution
  - Cold air
  - Odors
  - Exercise

Childhood Asthma Control Can Predict Adult Lung Status

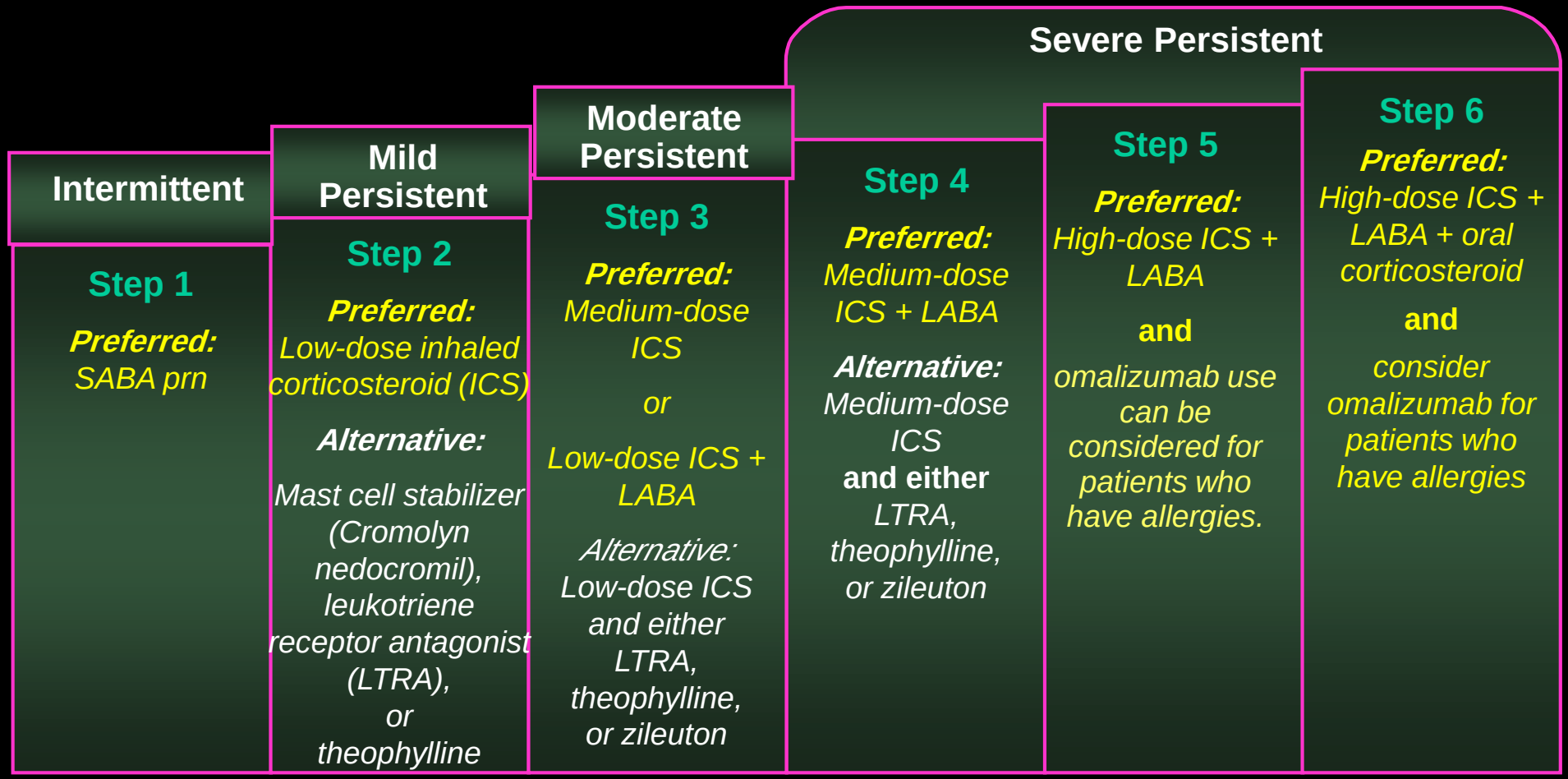
- Study of 119 asthmatic children during 1966 and 1969
- Ages: 5-14 were evaluated using FEV1
- Follow-up performed 17-18 years later and 27-28 years later
- Children who were well controlled during childhood had the smallest decline in total lung volume during adulthood

How Are We Doing With Treatment?

- Study looking at treatment of children over 10 year period showed an increase in the number of prescriptions for beta agonists
  - 4.0% up to 8.1%
- However, despite the significant increase in beta agonist prescriptions, there was only a slight increase in anti-inflammatory medications prescribed (even amongst children using 2+ rescue inhalers/month)
  - 0.4% up to 2.4%

Goodman, DC et. Al. Pediatrics 1999 Aug; 104(2) 187-94

Stepwise Approach for Managing Asthma in Patients Aged ≥12 Years: NAEPP EPR-3 Guidelines



Step Approach to Therapy

- If control is not achieved with therapy, step up the therapy
- Once control is sustained for a minimum of 3 months, can consider stepping down the therapy
- Regardless, therapy should be reviewed q 6 months

Major Focus in EPR-3

- Controlling asthma is a major focus of the EPR-3 guidelines

FIGURE 3–5c. ASSESSING ASTHMA CONTROL IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control		Classification of Asthma Control (Youths ≥12 years of age and adults)		
		Well-Controlled	Not Well-Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakening	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated Questionnaires ATAQ ACQ ACT	 0 ≤0.75* ≥20	 1–2 ≥1.5 16–19	 3–4 N/A ≤15
Risk	Exacerbations	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second. See figure 3–8 for full name and source of ATAQ, ACQ, ACT.

National Heart, Lung and Blood Institute; National Asthma Education and Prevention Program; Expert Panel Report 3: Guidelines for Diagnosis and Management of Asthma, Full Report 2007.

Monitoring Control in Clinical Practice: Asthma Control Test™ for Patients Aged ≥12 Years[1]

1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time	
○	○	○	○	○	☐

2. During the past **4 weeks**, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all	
○	○	○	○	○	☐

3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a weeky	2 or 3 nights a week	Once a week	Once or twice	Not at all	
○	○	○	○	○	☐

4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all	
○	○	○	○	○	☐

5. How would you rate your **asthma** control during the **past 4 weeks**?

Not controlled at all	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled	
○	○	○	○	○	☐

Level of Control Based on Composite Score[2]

≥20 = Controlled

16-19 = Not Well Controlled

≤15 = Very Poorly Controlled

Regardless of patient's self assessment of control in Question 5

1. Asthma Control Test™ copyright, QualityMetric Incorporated *2002, 2004. All rights reserved.*
2. *Available at: http://www.nhlbi.nih.gov/guidelines/asthma/epr3/resource.pdf. Accessed February 5, 2007.*

Short Acting Inhaled Beta 2 Agonists

- Albuterol (Proventil HFA)
  - 90mcg/puff, 200 puffs
  - 2 puffs q 4-6 hours or 2 puffs 15 minutes before exercise
  - Onset: 5 minutes

Short Acting Beta-2 Agonist

- Levalbuterol (Xopenex HFA)
  - 1 – 2 inhalations every 4 – 6 hours prn

Short-Acting Beta-2 Agonists

- Usage of these medications more than 2 times/week is indicative of poor control
- Regular, scheduled use of these medications is usually not recommended

Long-Acting Controller Medications

Maintenance or Prevention is the Key

- Good management is the key to preventing exacerbations and hospitalizations
- As with any disease, preventing the problem is always better than treating it

Corticosteroids

- Most potent and effective anti-inflammatory medication currently available

Inhaled Corticosteroids

- Examples
  - Beclomethasone (Beclovent, Vanceril)
  - Budesonide (Pulmicort turbuhaler)
  - Flunisolide (Aerobid)
  - Fluticasone (Flovent)
  - Triamcinolone Acetonide (Azmacort)
  - Mometasone (Asmanex)

Inhaled Corticosteroids

- Side effects
  - Pharyngitis
  - Dysphonia
  - Oral Candidiasis
- Precautions
  - High dosages: Increased systemic absorption leading to HPA axis suppression
  - Not indicated for an acute exacerbation

To Reduce Side Effects of Inhaled Corticosteroids

- Administer with spacers or holding chambers
- Rinse mouth after inhalation
- Use lowest possible dose to maintain control
- Children - monitor growth

Schenkel, E. et. al

- 98 patients randomized to either placebo or mometasone furoate aqueous nasal spray
- Ages: 3 - 9 years
- After 1 year, there was no suppression of height in the children using the nasal corticosteroid when compared with the child using placebo

Pediatrics Vol 105 No. 2 February 2000, p. 22

Remember...

- Poorly controlled asthma often delays growth
- In general, children with asthma tend to have longer periods of reduced growth rates prior to puberty

Mast Cell Stabilizers

- Cromolyn Sodium (Intal)
- Indications
  - Asthma prophylaxis
  - Prevention of bronchoconstriction before exposure to suspected allergen
- Best for mild-moderate disease
- May be the initial choice for children

Mast Cell Stabilizers

- Mechanism of Action
  - Reduces the production of histamine and prevents the release from the mast cell
- MDI or Nebulizer Solution
  - MDI: ≥ 5 years: 2 puffs po qid
  - Nebulizer Solution: ≥2 years: 1 ampule qid
  - Begin to work within 15 minutes of inhalation but can take up to 2 weeks to become effective

Mast Cell Stabilizer

- Side effects
  - Generally well tolerated
    - Side effects occur in 1:10,000
  - Cough
  - Wheezing
  - Rash
  - Nausea
- Category B

Non-steroidal Inhaled Antiinflammatory Medication

- Nedocromil Sodium (Tilade)
  - Best for mild - moderate disease
  - Works by reducing the production of histamine and by preventing the release from the mast cells
  - MDI: ≥6 years: 2 sprays qid
  - Nebulizer: ≥2 years
    - 0.5% solution; 1 ampule qid

Nedocromil Sodium (Tilade)

- Side effects
  - Unpleasant taste
- Precautions
  - Not for an acute exacerbation
- Category B

Leukotriene Receptor Antagonists

- Cysteinyl leukotriene production in the body has been associated with airway edema, smooth muscle constriction and the inflammatory process
- These medications block the leukotriene receptors which in turn is able to prevent inflammation and bronchoconstriction

Leukotriene Receptor Antagonists

- (Zafirlukast) Accolate
  - 10mg bid for ages 5-11
  - 20mg bid for 12 and older
  - Studied in children as young as 5
  - Avoid food 1 hour before and 2 hours after taking: Food decreases the bioavailability of Accolate
  - Metabolism: Metabolized through the CY P450 2C9 and 3A4 pathways
    - Major pathways in the body
    - Numerous other medications use this same pathway

Zafirlukast (Accolate)

- Drug/Drug Interactions
  - Aspirin: Increased zafirlukast levels by 40%
  - Erythromycin: 40% decrease in zafirlukast
  - Theophylline: Postmarketing reports of increased theophylline levels
  - Coumadin: 35% increase in PT/INR

Zafirlukast (Accolate)

- Side effects
  - Headache (12.9%)
  - Dizziness
  - Nausea
  - Churg Strauss syndrome
- Pregnancy: B
- Precautions
  - Not for an acute exacerbation

Montelukast (Singulair)

- (Montelukast) Singulair
  - 4 mg Granules once daily: 12 – 23 months
  - 4 mg tablet for children 2 - 5 years of age
  - 5mg qhs for ages 6-14
  - 10mg qhs for ages 15 and older

Montelukast (Singulair)

- Drug Interactions
  - Metabolized through CYP2A6 (minor pathway)
  - Phenobarbital: decreases montelukast but no dosage adjustment is required
- Side effects: headache, fatigue, dizziness, Churg-Strauss
- Precautions
  - Not for an acute exacerbation
- Category: B

Methylxanthines

- Theophylline
  - Theo-24, Theo-Dur, Uni-Dur, Slo-Bid
  - Bronchodilates and increases the force with which the diaphragm contracts
  - 6 years and older
  - Difficult to manage and as a result has not really gained wide spread acceptance
  - Indicated for individuals with moderate to severe asthma
  - Numerous drug interactions

Theophylline

- Numerous medications, foods and chemicals interact with theophylline
  - All of the following decrease theophylline levels
    - Smoking (cigarettes and marijuana)
    - High protein/low carbohydrate diet
    - Phenytoin
    - Phenobarbital
    - Carbamazepine
    - Ketoconazole
    - Diuretics

Theophylline

- Theophylline levels (normal 6-15mcg/dL)
  - 15-25: GI upset, N/V, diarrhea, abdominal pain
  - 25-35: Tachycardia, occasional PVC's
  - >35: Ventricular tachycardia, seizures
- Category: C

Long Acting Inhaled Beta 2 Agonist

- Salmeterol (Serevent)
  - Diskus
    - ≥4 years of age-1 puff po q 12 hours
  - No role for acute exacerbations
  - Seems to help children affected by the nocturnal cough and wheezing
  - Good for prevention of exercise induced asthma

Long Acting Inhaled Beta 2 Agonist

- Foradil Aerolizer
  - ≥ 5 years of age: 1 inhalation every 12 hours
  - Also may be used for prevention of EIB

Omalizumab (Xolair)

- Indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen
- And…whose symptoms are inadequately controlled with inhaled corticosteroids
- SC injection

Omalizumab (Xolair)

- Recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to human immunoglobulin E (IgE).
- Inhibits the binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils
- Limits the degree of release of mediators of the allergic response.

Last….

- Don’t forget to treat the nose
- 85% of individuals with asthma have concomitant allergic rhinitis

Acute Asthma Exacerbation Management

Acute Asthma Exacerbation

- Measure FEV1
- Inhaled short acting beta 2 agonist: Up to three treatments of 2-4 puffs by MDI at 20 minute intervals OR a single nebulizer
- Can repeat x 1 – 2 provided patient tolerates
- Prednisone
  - What dose and schedule??

Management of Moderate Exacerbations: Response from ED Treatment

- Good Response
  - Symptom relief sustained x 1hr; FEV1 or PEF ≥ 70%
  - D/C home
  - Continue SABA & oral corticosteroid
  - Consider inhaled corticosteroid (ICS)
  - Patient education / asthma action plan

Management of Moderate Exacerbations: Response from ED Treatment

- Incomplete Response
  - Mild-moderate symptoms, FEV1 or PEF 40-69%
  - SABA, oxygen, oral or IV corticosteroids
  - Can D/C home
- Poor Response
  - Marked symptoms, PEF <40%
  - Repeat SABA immediately
  - ED / 911; oral corticosteroid

Key Differences in the EPR-3 Report

- Point of discharge
  - FEV1 or PEF ≥ 70% predicted
  - Response sustained 60 minutes after last treatment
  - Normal physical exam
- Continued ED treatment needed
  - FEV1 or PEF 40-69% predicted
- Consider adjunct therapies
  - FEV1 or PEF <40% predicted