Asthma 2009:
Latest in Diagnostic and Treatment Options

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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

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


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

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

- 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

Asthma Triggers

- Allergens
- Exercise
- Irritants
- Viruses
- Weather

Smooth Muscle Dysfunction

- Hypertrophy
- Hyperplasia

Inflammation

- Inflammatory Mediator Release
- Mucus Secretion
- Edema

Architectural Changes

- Epithelial Damage

Bronchial Constriction

- Bronchial Hyperreactivity

Symptoms

- Exacerbations

Consequences of Inflammation in Asthma

Stimulus

- Antigen, virus, pollutant, occupational agent

Altered airway physiology

↑ Airflow obstruction

Resolution

Chronic Inflammation

- Injury
- Repair

"Permanently" altered lung function

Remodeling (fixed changes in the structure of airway)

Asthma: Pathophysiologic Features and Changes in Airway Morphology

Airway lumen narrowing

- Mucus gland hypertrophy and hyperplasia
- Edema

Epithelial damage

- Airway smooth-muscle hypertrophy, hyperplasia, constriction
- Bronchoconstriction

Inflammatory cell infiltration

- Vascular dilation
- Goblet cell hyperplasia

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)


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
- FVC, FEV, FEF25%-75%
- Airway Resistance
  - Home
  - Office/Clinic
  - Clinic/Laboratory
Asthma Findings

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


Rate of Decline in FEV<sub>1</sub>

Changes With Age in FEV₁ 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

Wright, 2009
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

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

- **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%


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

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

1. Asthma Control Test™ copyright. Quidel Corporation. 2002, 2005. All rights reserved.
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)

- **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.

(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

• 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

Thank you for your time and attention.

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