**Asthma**

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In the past year, Dr. Israel has been a Consultant or has performed Clinical Research for the following companies:

- Aerovance
- Amgen
- Astra-Zeneca
- Biota
- Cowen & Co.
- Gilead Sciences
- Johnson & Johnson
- Merck / Schering & Co.
- NKT Therapeutics
- Ono Pharma, USA
- Teva Specialty Pharmaceuticals

**Asthma**

- Effect of Asthma
- Pathobiology and classification of severity
- Therapy including new rx and controversies
- Subcategories eg Exercise, Aspirin-induced
- Difficult to control asthma
- Asthma Exacerbations

**Definition of Asthma**

Chronic inflammatory disorder of the airways
Characterized by:
- Airflow limitation,
  - reversible either spontaneously or with treatment
- Airway inflammation
- Increased hyperresponsiveness to a variety of stimuli

**One Year in the USA with Asthma**

- Over 30 million people had a diagnosis of asthma
- 20 million people said they currently had asthma
- 60% of them had an asthma attack in a year
- In one year almost 2 million had to be cared for in an emergency room
- Half a million required hospitalization
- Almost 5,000 died from their asthma
- In 2001 the estimated economic cost was 13 billion dollars

**The Burden of Asthma in the U.S.**

- prevalence increasing at 5% per year
  - 500,000 new cases every year
- #1 cause for hospitalizations in children
- #1 cause for days lost from school
Asthma

- Reversible airway obstruction
- Airway hyperreactivity
- Airway inflammation

Inflammatory Changes in Chronic Asthma

- Mucus secretion
- Inflammatory cell infiltration
- Edema
- Smooth muscle constriction & hypertrophy
- BM thickening and subepithelial collagen

Inflammation in Asthma

Normal
Asthma

Diagnosis

- Compatible history of wheezing, shortness of breath, or cough
- Reversible airway obstruction
  - FEV1 improved at least 12% post-bronchodilator
  OR
- Airway reactivity – methacholine, mannitol, exercise, hypertonic saline
- Exclusion of other causes of symptoms

Essential Concepts for Successful Asthma Management

- 3 concepts essential for successful asthma management
  - Severity
  - Control
  - Responsiveness
- Concepts of severity and control include the domains of current impairment and future risk

Severity and Control

- Severity
  - Intrinsic intensity of the disease process
  - Guides clinical decisions during initial evaluation and before the start of controller therapy
  - Most easily measured when not on long-term therapy
- Control
  - Degree to which symptoms, impairment, and risk of exacerbations are minimized and the goals of therapy are met
  - Used to guide whether to maintain or adjust therapy

Asthma Severity and Control: Impairment Domain
Impairment = Frequency and Intensity of Symptoms and Functional Limitations

Symptoms
- Nighttime awakenings
- Need for short-acting β₂-agonists (SABAs) for quick relief of symptoms
- Work/school days missed
- Ability to engage in normal daily activities or desired activities
- Quality-of-life assessments

Lung Function
- Spirometry
- Peak flow

Goal of Asthma Therapy: Achieve Control
Reduce Impairment
- Prevent chronic and troublesome symptoms
- Require infrequent use of inhaled SABA (2 days/week)
- Maintain normal activity levels
- Meet patients’ expectations of, and satisfaction with, asthma care

Reduce Risk
- Prevent recurrent exacerbations
- Minimize need for emergency department visits or hospitalizations
- Prevent progressive loss of lung function
- Provide optimal pharmacotherapy, with minimal or no adverse effects

Classifying Asthma Severity & Initiating Treatment in Youths ≥12 Years & Adults

Components of Severity

<table>
<thead>
<tr>
<th>Classification of Asthma Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td>FEV1 &gt;80%</td>
<td>FEV1 60-80%</td>
<td>FEV1 &lt;60%</td>
</tr>
<tr>
<td>Symptom frequency</td>
<td>&lt;2 days/week</td>
<td>2-7 days/week</td>
<td>≥8 days/week</td>
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<tr>
<td>Nighttime awakenings</td>
<td>None</td>
<td>&lt;2/week</td>
<td>≥2/week</td>
</tr>
<tr>
<td>Work/school days missed</td>
<td>None</td>
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<tr>
<td>Risk</td>
<td>None</td>
<td>&lt;2/week</td>
<td>≥2/week</td>
</tr>
</tbody>
</table>

Recommended Step for Initiating Therapy
1. Assess
2. PREFER
3. Step 1
4. Step 2
5. Step 3
6. Step 4
7. Step 5
8. Step 6

Stepwise Approach for Managing Asthma in Patients >12 Years of Age

Step 1: Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required. Consider consultation in step 2.

Step 2: Additional Medication
Step 3: Additional Medication
Step 4: Persistent Asthma: Daily Medication
Step 5: Persistent Asthma: Daily Medication

Patient Education and Environmental Control at Each Step

Rule of 2’s for Severity and Control

- Mild Persistent or Lack of Control
  - Nighttime awakenings >2/mo
  - SABA use for sxs (not pre-exercise) >2/wk
  - Sx >2 wk
  - ACT / ACO >20 / >1.5
  - Lung function Reduced by >20%
  - Exacerbations >2/yr
- Moderate
  - Daily or weekly as appropriate
  - FEV1 >40% reduction

Asthma Severity and Control: Risk Domain

- Likelihood of asthma exacerbations, progressive decline in lung function, or risk of adverse effects from medications
- Assessment
  - Frequency and severity of exacerbations
  - Oral corticosteroid use
  - Urgent-care visits

Step up if patients report symptoms, and asthma is not controlled adequately
Asthma Control Test™ (ACT)

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?
2. During the past 4 weeks, how often have you had shortness of breath?
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. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?
5. How would you rate your asthma control during the past 4 weeks?

Control on ACT or ACQ

- ACT
  - 20 or more
- ACQ
  - ≤ 1.0
  - A 0.5 change is felt to be enough to make a change in therapy
    - Therefore 1.5 is inadequately controlled

Short-Acting Beta₂-Agonists

- Most effective medication for relief of acute bronchospasm
- More than 2 times a week (other than pre-exercise) suggests inadequate asthma control
- Regularly scheduled use is not generally recommended
  - May lower effectiveness
  - May increase airway hyperresponsiveness
  - May be particularly problematic for those who are Arg/Arg at the 16th amino-acid position

Albuterol-HFA

- MDI inhalers contain propellants, traditionally CFCs.
- New, environmentally-friendly propellants (HFAs) have replaced CFCs.
- For albuterol, these are:
  - ProAir-HFA, Proventil-HFA, and Ventolin-HFA (as of yet, no generic albuterol-HFA)

Three Things to Know about Albuterol-HFA Inhalers

1. They are equally effective as albuterol-CFC.
2. They have a different feel; a less forceful, less cold “plume” of medication.
3. The plastic holder needs to be cleaned weekly to prevent plugging of medication.

Long-Acting Beta₂-Agonists

- Not a substitute for anti-inflammatory therapy
- Not appropriate for monotherapy
- Not for acute symptoms or exacerbations
- May be beneficial when added to inhaled corticosteroids to allow lower ICS dose
- BLACK BOX WARNING based on data that suggest that their use (particularly without ICS, but possibly even with them) can increase the risk of severe asthma exacerbations and deaths especially in Blacks.
- Due to the above, the FDA has suggested that patients controlled on combination therapy undergo an attempt to have their LABA eliminated after they achieve control.
ICS

- Most effective controller medications
- Use with a spacer reduces local side-effects such as thrush and dysphonia
- Long-term high doses are associated with small increases in
  - Osteoporosis
  - Glaucoma
  - Cataracts
  - Dermal thinning esp elderly
- Prn use with symptoms has been shown to be as effective as regular use in patients with mild-persistent asthma in adults and children
- Prn use in combination with LABA, when combined with regular bid use, appears to produce good symptom control but is NOT APPROVED IN THE USA and actively discouraged by the FDA.

Exacerbation Rates
(symptoms triggering course of inhaled or oral cs)

Exacerbations of Wheezing and Respiratory Tract Illness in Children <5yo.

66% decrease in ICS dose

Rescue ICS therapy in Trexa
(1 yr in children > 5yo)

1.1 cm reduction in height in continuous groups

Martinez et al, Lancet, 2011

ICS/LABA
Three Currently Approved

- salmeterol/fluticasone (Advair)
- formoterol/budesonide (Symbicort)
- formoterol/mometasone (Dulera)

Leukotriene Modifiers

- Indications
  - Aspirin-exacerbated respiratory disease
  - Exercise-induced asthma
    - Equal or better long term protection than long acting beta-agonists
  - Alternative in guidelines to additional ICS or LABA
  - Add-on therapy in severe asthma
- Caveats
  - Watch for CSS with steroid tapers
Anti-IgE

- For poor control on high dose ICS/LABA or equivalent Step 5 therapy
- Qualifications – IgE 30 to 700 and a positive skin test or RAST
- Efficacy – reduces exacerbations by \( \frac{1}{4} \) to \( \frac{1}{2} \)
  - FEV1 increases 4%
  - Not all patients respond
- Toxicity – rare anaphylaxis
  - Questionable increases in cancers

Managing Exercise-Induced Bronchospasm (EIB)

- Management Strategies
  - Short-acting inhaled beta-agonists used shortly before exercise last 2 to 3 hours
  - Salmeterol may prevent EIB for 10 to 12 hours
    - 50% or greater tachyphylaxis occurs if used regularly
  - LT modifiers provide long acting inhibition
  - Cromolyn and nedocromil are also acceptable
  - A lengthy warmup period before exercise may preclude medications for patients who can tolerate it
  - Long-term-control therapy, if appropriate

Aspirin-Exacerbated Respiratory Disease (AERD)

- Characterized by leukotriene overproduction in response drugs that block COX-1
  - Appears to be related to downregulation of PGE2 which “brakes” leukotriene production
- Most common in patients with rhinosinusitis
  - Usually occurs in adulthood
- Prevalence 5-25% with increased prevalence in those with more severe asthma

AERD (Rx)

- Use LT modifiers as part of treatment regimen since they affect leukotriene mediated effects
- Treat rhinosinusitis aggressively
- Specific COX-2 inhibitors are generally safe in moderate doses
- Acetaminophen safe in most patients although some may have reactions to high doses

Examining Factors Contributing to Asthma Severity

- Poor adherence/technique
- Rhinitis/sinusitis
- Gastroesophageal reflux (only in those that have symptomatic reflux)
- Drugs (NSAIDs, beta-blockers)
- Environmental allergens
- Occupational exposures
- Sulfite sensitivity

Recommendations Regarding Allergen Immunotherapy

- Consider allergen immunotherapy for asthma patients when:
  - Clear relationship exists between symptoms and unavoidable exposure
  - Symptoms are seasonal
  - Strong rhinitis component
Differential Dx of Persistent Wheezing Poorly Responsive to Therapy

- VCD
  - Flattening of the FV loop
  - Chinking of the vocal cords on fiberoptic exam
  - Frequently in depressed patients
  - Almost always in setting of some degree of airway hyperresponsiveness
- Central airway obstruction

Differential Dx of Persistent Wheezing Poorly Responsive to Therapy

- Aspirated foreign body
- Constrictive bronchiolitis
  - Rheumatoid Arthritis, Ulcerative Colitis
- Bronchiectasis
- CHF

New Therapies

- Anti-IL5 (blocks eosinophils)
  - Decreases exacerbations in patients who have persistent sputum eosinophils
  - Does not improve lung function
- Bronchial Thermoplasty
  - Reduces symptoms and reduces asthma exacerbations counted after bronchoscopy
  - Significant up-front morbidity

Effect of Lebrikizumab (Anti-IL13) on FEV1

Corren et al, NEJM, 2001

Tiotropium as Add on Therapy

Peters & ACRN, NEJM, 2010

EXACERBATIONS
Treatment

- Increased beta-agonists up to every 20 minutes
- 40-60 mg of prednisone for 5-10 days

Consider Referral to ED

- Beta-agonist effects not lasting more than an hour
- Unable to complete sentences
- Lower threshold for high-risk patients

Definition of “High-Risk”

- Newly diagnosed asthma
- On daily prednisone prior to admission
- ≥2 E.D. visits in last 6 months
- ≥1 prior hosp’ns in last 12 months
- Ever intubated for asthma
- Severe psychosocial problems
- Drug addiction
- Lower socio-economic status

Antibiotics for Acute, Severe Asthma

- Purulent-appearing sputum often contains eosinophils rather than neutrophils
- During attacks, transtracheal aspirates reveal no greater prevalence of bacterial pathogens than among controls without respiratory disease
- Empiric antibiotics of no proven benefit in hospitalized patients with acute attacks

Achieving Asthma Control

The Five-Point Plan:
A. Making the correct diagnosis
B. Modifying environmental inciters
C. Medications to control asthma
D. Plan for dealing with asthmatic attacks
E. Specialist consultation

Indications for Specialist Consultation

- Uncertainty regarding diagnosis;
- Failure to achieve good asthma control;
- Frequent need for systemic steroids;
- Frequent ED visits or hospitalizations;
- Unacceptable medication side-effects.
Points to Remember

• Rules of two’s for severity and step up
• Steps 1-6
• Aggravating factors
• Differential Diagnosis

Question #1

Which of the following is NOT indicative of poor asthma control?

A. As needed reliever medication 3x/wk
B. Reliever medication use pre-exercise 4x/week
C. Night-time awakening 3x/mo
D. Three exacerbations/yr

Question #2

Which of the following is NOT required for consideration for anti-IgE therapy?

A. IgE > 30
B. Allergic rhinitis
C. A positive skin test or RAST
D. Poor response to level 5 therapy

Short List of References


