Asthma Update 2013

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Disclosures

- None
Objectives

- Review burden of asthma in 2013
- Discuss current guidelines and outline strategies for assessing control
- Identify current gaps in application of guidelines
- Introduce next steps for moving asthma care beyond the current guidelines
The burden of asthma

- 25 million people in U.S.
  - 7 million children
- #1 cause of school absenteeism in children
  - 13 million missed days annually
- 10 million missed days of work in adults
- Annual cost $18 billion
- ~ 4,000 deaths annually

Asthma pathophysiology

- Smooth muscle dysfunction
- Airway inflammation
- Airway remodeling

Chronic asthma with remodeling

Normal

Asthma
Factors in development & persistence
Historical perspectives

- 1980s
- Reports brought attention to increasing mortality
- Recognized as chronic inflammatory disease
- Management strategies transitioned
  - From predominantly bronchodilator-based (theophylline) to anti-inflammatory-based (inhaled corticosteroid)

Historical perspectives

- 1990s
- **Asthma Guidelines**
  - National Asthma Education & Prevention Program (NAEPP), 1991
  - Global Initiative for Asthma (GINA), 1995
- **Medications**
  - Potent inhaled corticosteroids (ICS)
  - Long-acting β-adrenergic agonists (LABA)
  - LABA/ICS combinations
  - Leukotriene modifiers
  - Omalizumab

Historical perspectives

- Focus of management changed
  - Episodic to ongoing disease state
- Population level surveillance developed
  - Monitor disease related morbidity & mortality
  - Identification of disparities
  - Recognition of gaps in current strategies
- 2000’s
  - Clinical heterogeneity with phenotyping

Asthma prevalence in U.S. 2001-2010

NOTES: Asthma prevalence refers to percentage of people who have ever been diagnosed with asthma and still have asthma. Data are age adjusted to the 2000 U.S. standard population. Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db94_tables.pdf#1.
SOURCE: CDC/NCHS, National Health Interview Survey.
Asthma prevalence by demographics, 2008-2010

- Total
- Child
- Adult
- Male
- Female
- White
- Black
- American Indian or Alaska Native
- Asian
- Multiple race
- Total Hispanic
- Puerto Rican
- Mexican
- Less than 100% poverty
- 100% to less than 200% poverty
- 200% or more of poverty

95% confidence interval.

NOTES: Asthma prevalence refers to percentage of people who have ever been diagnosed with asthma and still have asthma. Access data table for Figure 2 at http://www.cdc.gov/nchs/data/databriefs/db84_tables.pdf#2.

SOURCES: CDC/NCHS, Health Data Interactive and National Health Interview Survey.
Asthma encounters per 100 persons, 2001-2009

Office and outpatient visits per 100 persons with asthma

Emergency department visits per 100 persons with asthma

Hospitalizations per 100 persons with asthma

Deaths per 1,000 persons with asthma

Year

2001 2002 2003 2004 2005 2006 2007 2008 2009

Rate (log scale)

0.21 0.14

NOTE: Access data table for Figure 3 at: http://www.cdc.gov/nchs/data/databriefs/db94_tables.pdf#3.

SOURCES: CDC/NCHS, National Ambulatory Medical Care Survey, National Hospital Ambulatory Medical Care Survey, National Hospital Discharge Survey, National Vital Statistics System, and National Health Interview Survey.
Asthma deaths per 1000 persons, 2007-2009

NOTE: Access data table for Figure 5 at: http://www.cdc.gov/nchs/data/databriefs/db94_tables.pdf#5.
SOURCES: CDC/NCHS, National Vital Statistics System and National Health Interview Survey.
Evolution of the NAEPP guidelines

- 1991
  - State-of-the-Union
  - Treatment recommendations based on consensus

- 1997
  - A decade of new pathophysiology
  - Evidence based treatment recommendations
  - Incorporation of new drugs (LABAs, LTRAs)

- 2002
  - Further clarification of treatment of moderate persistent asthma and treatment of children

- 2007
  - Emphasis on assessment of control
“Control: the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met.”
NAEPP EPR-3 2007 Guidelines

- Asthma *severity*
  - Assessed at time of disease presentation
  - Details a chronic status that represents the patient’s potential impairment & risk

- Asthma *control*
  - Volatile status which is often inconsistent
  - Represents a point in time where impairment & risk can be evaluated & measured
**NAEPP EPR-3 2007 Guidelines**

- Asthma severity and control can be assessed in two domains
  - **Impairment**
    - The *frequency* and *intensity* of symptoms
    - The *functional limitations* patient is experiencing
  - **Risk**
    - Likelihood of either
      - Asthma *exacerbations*
      - Progressive *loss of pulmonary function*
# Classification of Asthma Severity (Youths ≥12 years of age and adults)

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification</th>
<th>Intermittent</th>
<th>Persistent Mild</th>
<th>Persistent Moderate</th>
<th>Persistent Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>&gt; 2 days/week</td>
<td>&gt; 2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
<td></td>
</tr>
<tr>
<td><strong>Nighttime awakenings</strong></td>
<td>≤2x/month</td>
<td>3–4x/month</td>
<td>&gt; 1x/week but not nightly</td>
<td>Often 7x/week</td>
<td></td>
</tr>
<tr>
<td><strong>Beta₂-agonist use</strong></td>
<td>≤2 days/week</td>
<td>&gt; 2 days/week but not &gt; 1x/day</td>
<td>Daily</td>
<td>Several times per day</td>
<td></td>
</tr>
<tr>
<td><strong>Interference with normal activity</strong></td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
<td></td>
</tr>
</tbody>
</table>

| Normal FEV₁/FVC: 8–19 yr 85% | 20–39 yr 80% | 40–59 yr 75% | 60–80 yr 70% |

<table>
<thead>
<tr>
<th>Lung function</th>
<th>Intermittent</th>
<th>Persistent Mild</th>
<th>Persistent Moderate</th>
<th>Persistent Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal FEV₁ between exacerbations</td>
<td>• FEV₁ &gt; 80% predicted</td>
<td>• FEV₁ ≥ 80% predicted</td>
<td>• FEV₁ &gt; 60% but &lt; 80% predicted</td>
<td>• FEV₁ &lt; 60% predicted</td>
</tr>
<tr>
<td>FEV₁/FVC normal</td>
<td>• FEV₁/FVC normal</td>
<td>• FEV₁/FVC reduced 5%</td>
<td>• FEV₁/FVC reduced &gt; 5%</td>
<td></td>
</tr>
</tbody>
</table>

| 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 FEV₁ |

**NAEPP EPR–3 2007. NIH Item No. 08–4051**
<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>3–4x/month</td>
<td>&gt;1x/week but not nightly</td>
<td>Often 7x/week</td>
</tr>
<tr>
<td>Short-acting beta-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not &gt;1x/day</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
</tbody>
</table>

**Normal FEV₁/FVC:**
- 8–19 yr: 85%
- 20–39 yr: 80%
- 40–59 yr: 75%
- 60–80 yr: 70%

**Lung function**
- FEV₁ >80% predicted
- FEV₁/FVC normal
- FEV₁ >80% predicted
- FEV₁/FVC normal
- FEV₁ >60% but <80% predicted
- FEV₁/FVC reduced 5%
- FEV₁ <60% predicted
- FEV₁/FVC reduced >5%

**Risk**

<table>
<thead>
<tr>
<th>Exacerbations (consider frequency and severity)</th>
<th>0–2/year</th>
<th>&gt;2/year</th>
</tr>
</thead>
</table>

- Frequency and severity may fluctuate over time for patients in any severity category
- Relative annual risk of exacerbations may be related to FEV₁

**Recommended Step for Initiating Treatment**

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4 or 5</th>
</tr>
</thead>
</table>

- In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.

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**References**

NAEPP EPR–3 2007. NIH Item No. 08–4051
<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control (Youths ≥ 12 years of age and adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well-Controlled</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/personal best</td>
</tr>
<tr>
<td>Validated Questionnaires</td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>0 ≤0.75*</td>
</tr>
<tr>
<td>ACQ</td>
<td>≥20</td>
</tr>
<tr>
<td>ACT</td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0–1/year</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term followup care</td>
</tr>
<tr>
<td>Risk</td>
<td>Treatment-related adverse effects</td>
</tr>
</tbody>
</table>

NAEPP EPR–3 2007. NIH Item No. 08–4051
How should control be measured?

- Utilization of Healthcare Resources
- Inflammation Direct or Indirect
- Lung Function
- Functional Status
- Daytime Symptoms
- Nighttime Awakenings
- Use of a “Quick Relief” Inhaler and/or Nebulizer
- Missed Work and/or School
- Patient Self-Report of Control

Physicians overestimate control

- Study of 354 primary care physicians
- Evaluated control of 50 consecutive asthma patients
- N = 10,428
- 42% classified as uncontrolled
- 59% classified as uncontrolled when researchers applied consensus guidelines

Patients are poor at assessing control

Patient assessment of control*

*Patients with severe persistent symptoms – past 4 wk: Sx ≥ 3x/day in the daytime; Most nights/every night.

www.asthmainamerica.com
Patients have low expectations for control

<table>
<thead>
<tr>
<th>Asthma characteristic</th>
<th>% patients consider asthma well managed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only 2 unplanned visits to MD/year</td>
<td>67%</td>
</tr>
<tr>
<td>Only 1 ED visit/year</td>
<td>60%</td>
</tr>
<tr>
<td>Bothersome &lt; 50% time with exercise</td>
<td>64%</td>
</tr>
<tr>
<td>Exacerbated 3-4 times/year</td>
<td>63%</td>
</tr>
<tr>
<td>Exacerbations at least 2 months apart</td>
<td>64%</td>
</tr>
<tr>
<td>Rescue inhaler use 3 times/week</td>
<td>46%</td>
</tr>
<tr>
<td>Daily symptoms 3 times/week</td>
<td>46%</td>
</tr>
</tbody>
</table>

Murphy et al. Allergy Asthma Proc 2012; 33:54.
Symptoms correlate poorly with FEV$_1$

Rules of Two®

- Symptoms requiring rescue inhaler > two times a week?
- Awaken at night > two times a month?
- Refill rescue inhaler > two times a year?
- Measure peak flow < 2 times 10 (20%) your best with asthma symptoms?

Adapted from: Rules of Two®, www.baylorhealth.com
Monitoring Asthma Control: Asthma Control Test™

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 week
   - 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
- 20-25 = Controlled
- 14-19 = Suboptimal
- <14 = Poorly Controlled

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

Asthma Therapy Assessment Questionnaire (ATAQ)

1. In the past 4 weeks did you miss any work, school, or normal activities due to your asthma? (1 point for yes)

2. In the past 4 weeks, did you wake up at night because of your asthma? (1 point for yes)

3. Do you believe your asthma was well controlled in the past 4 weeks? (1 point for no)

4. Do you use an inhaler for quick relief of asthma symptoms? If yes, in the past 4 weeks, what was the highest number of puffs you used in one day? (1 point for >12)

**Level of Control Based on Composite Score**
1-2 = not well controlled, 3-4 = very poorly controlled

How should control be assessed?

- Multiple parameters evaluated simultaneously
- Patient self-monitoring
  - Peak flow monitoring with moderate-severe disease or poor perception
  - Symptom diaries or targeted questions regarding impact on activity, sleep, work, school and rescue inhaler use
- Spirometry every 1-2 years
- Validated questionnaires
- ? Fractional exhaled nitric oxide (FeNO)
Do the guidelines work?

- Asthma control is suboptimal in the U.S.
  - 41% of adults surveyed with Asthma Control Test reported asthma not well controlled (n=10,139)\(^1\)
- Uncontrolled asthma associated with increased health care utilization
- Guideline driven treatment
  - Results in adequate control in most patients\(^2\)
  - Improved health-related quality of life\(^3\)
- Guidelines often under-utilized

Asthma Insight & Management (AIM) Survey

- Telephone survey 2500 patients with asthma
- 309 physicians
  - 104 allergists
  - 54 pulmonologists
  - 101 family practitioners
  - 50 internists
- Consistency with NAEPP-EPR 3

Murphy et al. Allergy Asthma Proc 2012; 33:54.
Asthma Insight & Management (AIM) Survey

- Asthma care
  - General practice 29% (n = 713)
  - Family practice 25% (n = 635)
  - Pulmonologists 11% (n = 271)
  - Allergists 11% (n = 268)
  - Internists 8% (n = 208)
  - Pediatricians 8% (n = 193)
  - Ob/Gyn 0.4% (n = 100)
- 96% physicians aware of NAEPP
- 87% follow “always” or “most of the time”

Murphy et al. Allergy Asthma Proc 2012; 33:54.
### Asthma management practices

<table>
<thead>
<tr>
<th></th>
<th>Allergist (n=104)</th>
<th>Pulmonary (n=54)</th>
<th>Family Med (n=101)</th>
<th>Internist (n=50)</th>
<th>Patient report (n=2499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung function testing</td>
<td>98%</td>
<td>96%</td>
<td>57%</td>
<td>58%</td>
<td>74%</td>
</tr>
<tr>
<td>Peak flow</td>
<td>84%</td>
<td>74%</td>
<td>79%</td>
<td>58%</td>
<td>49%</td>
</tr>
<tr>
<td>Action plan</td>
<td>68%</td>
<td>41%</td>
<td>46%</td>
<td>36%</td>
<td>32%</td>
</tr>
<tr>
<td>Asthma control test (ACT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25%</td>
</tr>
</tbody>
</table>

Murphy et al. Allergy Asthma Proc 2012; 33:54.
Guidelines under-utilized

- Survey of 202 inner-city primary care providers
- 30% unaware of NAEPP EPR-3 guidelines
- 46% routinely use for asthma care
- Comfort level with components
  - Prescription of ICS 62%
  - Influenza vaccine 73%
  - Peak expiratory flow monitoring 34%
  - Asthma action plans 9%

Moving beyond the guidelines

- New roles for old therapies
- Alternate treatment approaches
- Personalized asthma care?
Salmeterol Multi-center Asthma Research Trial (SMART)

- Large placebo-controlled US study of salmeterol vs. placebo added to usual asthma therapy
- Increase in asthma-related deaths
  - Salmeterol group: 13 deaths in 13,176
  - Placebo: 3 deaths in 13,179

Safety considerations for LABAs

Black box warning for LABAs

“Physicians should only prescribe...for patients not controlled on other asthma-controller medications or whose disease severity warrants initiation of treatment with 2 maintenance therapies”
Tiotropium for uncontrolled asthma

- 3-way, double-blind, triple dummy crossover trial
- 210 patients with uncontrolled, mild-moderate asthma
- Compared three regimens
  - Tiotropium + ICS
  - Double dose ICS (beclomethasone 160 µg BID)
  - Salmeterol + ICS
- Primary outcome: AM peak expiratory flow (PEF)
- Secondary outcomes: control, symptoms, healthcare utilization

Tiotropium for uncontrolled asthma cont.

- Tiotropium vs. double dose glucocorticoid
  - AM PEF 25.8 L/min higher (p<0.001)
  - PM PEF 35.3 L/min higher (p<0.001)
  - Proportion of asthma-control days with a difference of 0.079 (p=0.01)
  - Score for daily symptoms with difference of -0.11 (p<0.001)
  - Score on ACQ with difference of -0.18 (p=0.02)

Tiotropium for uncontrolled asthma cont.

- Tiotropium vs. salmeterol
  - AM PEF 6.5 L/min higher (p=0.26)
  - PM PEF 10.6 L/min higher (p=0.05)
  - Proportion of asthma-control days with a difference of -0.009 (p=0.78)
  - Score for daily symptoms with difference of -0.04 (p=0.10)
  - Score on ACQ with difference of 0.0.09 (p=0.18)

Tiotropium for uncontrolled asthma cont.

- Conclusions
  - Tiotropium improved lung function and asthma symptoms when added to inhaled corticosteroid
  - Effects appeared similar to addition of salmeterol
  - Additional studies are needed but results are sufficient to establish clinical equipose
  - Treatment arms 14 weeks limited ability to evaluate effect on exacerbations

Moving beyond the guidelines

- New roles for old therapies
- Alternate treatment approaches
- Personalized asthma care?
Single inhaler therapy?

- Combination of formoterol & budesonide has allowed exploration of single inhaler as controller and for relief of symptoms
- Single Maintenance And Reliever Therapy (SMART)
- Single inhaler Therapy (SiT)
- Why do it?
  - Convenience for patients
  - Lower daily doses of ICS
  - Improved outcomes?
Cochrane review of SMART dosing

- 9 trials of SMART vs. best practice
- No effect on rates of hospital admission
  - OR 0.81 (CI 0.45-1.44)
- Reduced rates of exacerbations needing oral steroids
  - OR 0.83 (CI 0.70-0.98)
- No effect on time to severe exacerbation needing intervention
  - OR 0.94 (CI 0.85-1.04)
- Most studies demonstrated reduction in total daily doses of ICS

Problems with SMART/SiT

- Most studies are open label
- Guideline-recommended control rarely achieved in studies
- How to titrate maintenance medications when up to 8 puffs/day of LABA/ICS allowed?
- FDA concerns regarding LABA
- Long-term effects of SMART?
Changes from baseline following 1-year of SMART

Original data Pavard et al. JACI 2009; 123:1083.
Moving beyond the guidelines

- New roles for old therapies
- Alternate treatment approaches
- Personalized asthma care?
Phenotyping in asthma

- Effective care complicated by heterogeneity of disease
- Current strategies of characterization can identify severe patient but will not differentiate phenotypes of severe disease
- A classification system that incorporates the multidimensionality of the disease is needed
  - Identify subgroups with consistent disease patterns
  - Predict response to specific therapies
  - Focus research for biologics & genetics
Is there a role for FeNO?

- Qualitative, noninvasive method to indirectly assess airway inflammation in asthma
- Methods for measuring FeNO standardized
- Guidelines now available for application in clinical practice

Potential role
- Detecting eosinophilic airway inflammation
- Predicting likelihood of response to steroids
- Long term monitoring
  - Titration of steroids, nonadherence to therapy

Dweik et al. AJRCCM 2011; 184(5):602.
Cluster analysis & clinical phenotypes

- Cluster analysis in 2 populations
  - 184 mild-moderate asthma from primary care
  - 187 refractory asthma from specialist clinics (secondary care)
- Evaluated relevance of clusters in relation to asthma outcomes in a 3rd population
  - 68 refractory asthmatics enrolled in prospective, randomized trial of inflammation guided therapy
  - Titrated ICS to maintain normal sputum eosinophil vs. standard care

Haldar et al. AJRCCM 2008;178:218.
Clinical phenotypes of asthma

- Discordant Symptoms
  - EARLY SYMPTOM PREDOMINANT
    - Early onset, atopic
    - Normal BMI
    - High symptom expression.
  - OBESE NON-EOSINOPHILIC
    - Later onset, female preponderance
    - High symptom expression.

- Concordant Disease
  - Symptom-based approach to therapy titration may be sufficient.

- Discordant Inflammation
  - Monitoring inflammation allows targeted corticosteroids to lower exacerbation frequency.
  - EARLY ONSET ATOPIC ASTHMA
    - Concordant symptoms, inflammation & airway dysfunction.
  - BENIGN ASThma
    - Mixed middle-aged cohort
    - Well controlled symptoms and inflammation. Benign prognosis.
  - INFLAMMATION PREDOMINANT
    - Late onset, greater proportion of males
    - Few daily symptoms but active eosinophilic inflammation.

Halder et al. AJRCCM 2008;178:218.
Clinical asthma phenotypes and outcomes

- 3 clusters identified in prospective cohort of refractory asthma
  - Obese non-eosinophilic female
  - Inflammation predominant
  - Early symptom predominant
- Original study demonstrated reduction in exacerbations in sputum targeted arm
  - All benefit in the inflammation-predominant cluster
  - 0.38 vs. 3.53 exacerbation/patient/year (p=0.002)

Haldar et al. AJRCCM 2008;178:218.
Conclusions

- Current asthma guidelines
  - Systemic approach to management
  - Patient-centered approach, not necessarily based on objective patient characteristics
- Identification and correction of practice gaps provide an opportunity to improve care
- Next stages will focus on developing personalized treatment strategies that consider the heterogeneity of the disease