Childhood Asthma: Management Challenges

Timothy J. McCloskey, D.O.
POMA – 111th Annual Clinical Assembly
May 3, 2019

Disclosures

• None

References

Expert Panel Report – 3
• Allergy & Asthma Network Mothers of Asthmatics
  www.breatherville.org
• American Academy of Allergy, Asthma and Immunology
  www.aaaai.org
• American College of Allergy, Asthma, and Immunology
  www.Acaai.Org
• National Heart, Lung, and Blood Institute Information Center
  www.nhlbi.nih.gov
• National Jewish Medical and Research Center www.njc.org
Objectives

- Review asthma historical perspective
- Review and discuss the pathophysiology of asthma both anatomical and cellular involvement and interaction
- Therapeutic management based on both national and international guidelines
- Use of asthma action plans and shared decision making to improve care.
- Cost, quality and value of care modalities.

Historical Perspective

Asthma in Antiquity

Greek verb – ἀαζεῖν – aazein to exhale with open mouth, to pant

Asthma triad – medical school

Bronchospasm

Inflammation

Mucus
Expert Panel Report - 3 (EPR-3)

1. Update on National Asthma Education and Prevention Program (NAEPP) Guidelines for the Diagnosis and Management of Asthma

The Development of Guidelines Has Evolved With Our Understanding of Asthma

1989 First expert panel convened
1991 Expert Panel Report (EPR-1) - Guidelines for the Diagnosis and Management of Asthma issued
1993 EPR-2 issued
1997 Expert Panel Report (EPR-2) - Guidelines for the Diagnosis and Management of Asthma issued
1999 NAEP (EPR-3) updated guidelines issued
2002 Updates of selected topics (EPR-update)
2007 NAEP (EPR-3) updated guidelines issued


Diagnosis: Is this Asthma?

- Clinical diagnosis:
  - Asthma is an airway disease not a lung disease
  - Chest x ray is helpful to eliminate lung disease
  - Spirometry +/- bronchodilator response
  - Provocation studies
    - Methacholine challenge study demonstrates "hyper responsive airways"
    - Allergen challenge
    - Mannitol challenge


EPR-3: Heterogeneity of Asthma

- Variability in inflammation
  - Pattern of inflammation
  - Phenotypic differences that may influence treatment response
- Gene-environment interactions
  - Development of sensitization and atopy
  - Viral respiratory infections (to pathogenesis and exacerbations)
- Hence the need to individualize therapy

EPR-3: Co-morbidities

- Treating co-morbidities may have may help improve asthma control:
  - rhinitis and sinusitis
  - laryngeal pharyngeal and gastro esophageal reflux
  - BMI ≥ 30
  - obstructive sleep apnea,
  - stress, anxiety and depression

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EPR-3: Medications.

1. The use of a stepwise approach to control asthma, in which medication doses or types are stepped up as needed and stepped down when possible.
2. Treatment is adjusted based on the level of asthma control.
3. Initial treatment of asthma is based on severity of asthma.

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EPR-3: Distinguishing between Classifying Asthma Severity and Assessing Asthma Control

- Asthma Severity:
  - the intrinsic intensity of the disease process.
  - Assess asthma severity to initiate therapy.

- Asthma Control:
  - the degree to which the manifestations of asthma are minimized by therapeutic interventions
  - and the goals of therapy are met.
  - Assess and monitor asthma control to adjust therapy.

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Asthma Severity and Control: Impairment Domain

Impairment = Frequency and Intensity of Symptoms and Functional Limitations

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nighttime awakenings</td>
<td></td>
</tr>
<tr>
<td>• Need for short-acting β2-agonists (SABAs)</td>
<td></td>
</tr>
<tr>
<td>• Quick relief of symptoms</td>
<td></td>
</tr>
<tr>
<td>• Work/school days missed</td>
<td></td>
</tr>
<tr>
<td>• Ability to engage in normal daily activities or desired activities</td>
<td></td>
</tr>
<tr>
<td>• Quality-of-life assessments</td>
<td></td>
</tr>
</tbody>
</table>

Available at: http://www.nhlbi.nih.gov/guidelines/asthma/epr3

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
  – Lung function
  – Noninvasive biomarkers may play an increased role in future

Available at: http://www.nhlbi.nih.gov/guidelines/asthma/epr3/resource.pdf

Goal of Asthma Therapy: Achieve Control

- Prevent chronic and troublesome symptoms
- Require infrequent use of inhaled SABA (≤2 days/week)
- Maintain (near) "normal" pulmonary function
- 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

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Asthma Severity chart

<table>
<thead>
<tr>
<th>Components of severity</th>
<th>Intermittent “rule of 2's”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use</td>
<td>≤2 x / week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>none</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal FEV₁, between exacerbations</td>
</tr>
</tbody>
</table>

Asthma Control Chart

<table>
<thead>
<tr>
<th>Components of control</th>
<th>Well Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</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</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75*</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
</tr>
</tbody>
</table>

Stepwise Approach for Managing Asthma in Patients Aged ≥12 Years:

- Special considerations for this age group include the following:
  - For youths:
    1. Involve adolescents in the development of their written asthma action plans and reviewing their adherence.
    2. Encourage students to take a copy of their plan to school, after school programs, and camps.
    3. Encourage adolescents to be physically active.
Stepwise Approach for Managing Asthma in Patients Aged ≥12 Years:

• For older adults:
  1. Consider a short course of oral systemic corticosteroids to establish reversibility and the extent of possible benefit from asthma treatment.
  2. Chronic bronchitis and emphysema may coexist with asthma.
  3. Adjust medications as necessary to address coexisting medical conditions.
     — calcium and vitamin D supplements for patients who take ICS and have risk factors for osteoporosis.

Stepwise Approach for Managing Asthma in Patients Aged ≥12 Years:

1. Increased sensitivity to side effects of bronchodilators
2. Increased possibilities for drug interactions with theophylline.
3. NSAIDs prescribed and OTC for arthritis
4. β-blockers prescribed for hypertension or glaucoma may exacerbate asthma.
5. Review the patient’s technique and adherence in using medications, and make necessary adjustments.
6. Physical or cognitive impairments may make proper technique difficult. (RA with decreased grip and deformity)

Evidence Supporting ICS Use in Patients Aged ≥12 Years

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily long-term controller medication is recommended for patients with persistent asthma. Of the available medications, ICS is the most effective single agent</td>
<td>A</td>
</tr>
<tr>
<td>Step 2: Preferred treatment is daily ICS at a low dose</td>
<td>A</td>
</tr>
<tr>
<td>Step 3: Preferred options are to</td>
<td></td>
</tr>
<tr>
<td>• Continue the ICS by increasing the dose to the medium-dose range or</td>
<td>A</td>
</tr>
<tr>
<td>• Add a LABA to a low dose of ICS</td>
<td></td>
</tr>
<tr>
<td>Step 4: Preferred option is to increase the dose of ICS to the medium-dose range and add a LABA</td>
<td>B</td>
</tr>
<tr>
<td>Step 5: High-dose ICS and LABA are preferred</td>
<td>B</td>
</tr>
</tbody>
</table>
Assessment of risk factors for poor asthma outcomes

Risk factors for exacerbations include:
- Uncontrolled asthma symptoms
- Additional risk factors, even if the patient has few symptoms:
  - High SABA use (≥3 canisters/year)
  - Having ≥1 exacerbation in last 12 months
  - Low FEV₁; higher bronchodilator reversibility
  - Incorrect inhaler technique and/or poor adherence
  - Smoking
  - Obesity, chronic rhinosinusitis, pregnancy, blood eosinophilia
  - Elevated FeNO in adults with allergic asthma taking ICS
  - Ever intubated for asthma

Risk factors for fixed airflow limitation include:
- No ICS treatment, smoking, occupational exposure, mucus hypersecretion, blood eosinophilia; pre-term birth, low birth weight

Risk factors for medication side-effects include:
- Frequent oral steroids, high dose/potent ICS, P450 inhibitors

Exhaled nitric oxide (FeNO)
- FeNO is becoming more widely available in some countries
- All sections on FeNO have been reviewed and updated
- Decisions about initial asthma treatment
  - GINA recommends at least low dose ICS in almost all patients with asthma, to reduce risk of asthma exacerbations and death
    - SABA-only treatment considered only if symptoms < twice/month, no night waking, and no risk factors for exacerbations
  - In non-smoking patients, FeNO >50 ppb is associated with a good short-term response to ICS in symptoms and lung function
  - There are no studies examining the long-term safety (i.e., for risk of exacerbations) of withholding ICS if initial FeNO is low
  - In patients with a diagnosis or suspected diagnosis of asthma, FeNO can support the decision to start ICS, but cannot safely be recommended for deciding against treatment with ICS
Exhaled nitric oxide (FeNO)

- **FeNO-guided treatment**
  - Updated to reflect new meta-analyses (Petsky Cochrane 2016; Petsky Cochrane 2016) that separately analyzed studies in which the control algorithm was reasonably close to current clinical recommendations, and therefore provided a clinically relevant comparator.
  - **Children/adolescents**: FENO-guided treatment was associated with significantly fewer exacerbations and lower exacerbation rate than treatment based on current guidelines.
  - **Adults**: no significant difference in exacerbations with FENO-guided treatment compared with treatment based on current guidelines.
  - FENO-guided treatment is not recommended for the general asthma population at present.
  - Further studies are needed to identify the populations most likely to benefit, and the optimal frequency of monitoring.

Exhaled nitric oxide (FeNO)

- In children ≤5 years with recurrent coughing and wheezing
  - Elevated FeNO recorded >4 weeks from any URTI predicts physician-diagnosed asthma at school age (Singer 2013).
  - Elevated FeNO at age 4 increases the odds for wheezing, physician-diagnosed asthma and ICS use by school age, independent of clinical history and presence of specific IgE (Caudri JACI 2010).

Children aged ≤5 years – key changes

- **Step 2 (initial controller treatment)** for children with frequent viral-induced wheezing and with interval asthma symptoms
  - A trial of regular low-dose ICS should be undertaken first.
  - As-needed (prn) or episodic ICS may be considered.
  - The reduction in exacerbations seems similar for regular and high dose episodic ICS (Kaiser Pediatr 2015).
  - **LTRA is another controller option**.
- **Step 3 (additional controller treatment)**
  - First check diagnosis, exposures, inhaler technique, adherence.
  - Preferred option is medium dose ICS.
  - Low-dose ICS + LTRA is another controller option.
    - Blood eosinophils and atopy predict greater short-term response to moderate dose ICS than to LTRA (Brandt, Muir 2016).
    - Relative cost of different treatment options in some countries may be relevant to controller choices.
Treatment steps – changes in 2018

- **Step 1**
  - It is explained that the reason ICS should be considered for patients with mild asthma (rather than prescribing SABA alone) is to reduce their risk of serious exacerbations (Pauwels, Lancet 2003; O’Byrne AJRCCM 2001; Reddel Lancet 2017).

- **Steps 3-4**
  - From the large FDA LABA safety studies: adding LABA to ICS in a combination inhaler reduces risk of exacerbations and improves symptoms and lung function, compared with the same dose of ICS alone, but with only a small reduction in reliever use (Stempel NAM 2016, Peters NEJM 2016).

- **Step 5 and Box 3-14: management of severe asthma**
  - Subcutaneous benralizumab (monoclonal anti-IL5 receptor α antibody) is another add-on treatment for patients aged ≥12 years with severe eosinophilic asthma.

Other changes

- **Primary prevention of asthma**
  - A systematic review of randomized controlled trials on maternal dietary intake of fish or long-chain polyunsaturated fatty acids during pregnancy showed no consistent effects on the risk of wheeze, asthma or atopy in the child (Best Am J Clin Nutr 2016).
  - One recent study demonstrated decreased wheeze/asthma in pre-school children at high risk for asthma when mothers were given a high dose fish oil supplement in the third trimester (Bisgard NEJM 2016), but ‘fish oil’ is not well defined, and the optimal dosing regimen has not been established.

Asthma heterogeneity:

**Allergic asthma**

- Eosinophilia
- IgE production
- Mucus
- Airway hyper responsiveness

Treatment options: medical versus biologic
Allergic Asthma:

Pediatric biological FDA approved

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Monoclonal antibody</th>
<th>Mechanism of action</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic asthma</td>
<td>Omalizumab</td>
<td>Anti-IgE antibody</td>
<td>SQ every 4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;6 years of age</td>
</tr>
</tbody>
</table>

Immunoglobulin structure
Omalizumab

- Allergic asthma patients on ICS had decreased exacerbations 0.28 per patient treated group versus 0.54 placebo group decreased asthma symptoms, improved FEV1, morning PEFR and rescue medication use. (Busse, et al)
- Other studies demonstrate decreased exacerbation rate 25%, improve Asthma QOL scores. (Hannia, et al)
- Meta analysis of pediatric and adult patients show reduction in exacerbation 38 per 100 patient years compared to 70 per 100 patient years.
- Decreased biomarker values:
  - decreased FeNO (56% versus 16%)
  - Decreased peripheral eosinophils (32% versus 9%)
  - Decrease periostin (30% versus 3%)

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Omalizumab

- Adverse effects
  - Nasopharyngitis, headache, sinusitis and upper respiratory infections
- Anaphylaxis
  - 0.14% versus 0.07%
- Malignancy
  - Initial pooled data increased malignancy rate (2003)
  - Subsequent pooled data decrease crude rate of malignancy

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Pediatric biological FDA approved

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Monoclonal antibody</th>
<th>Mechanism of action</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-high Asthma</td>
<td>Mepolizumab</td>
<td>Anti IL-5</td>
<td>SQ &gt;12 years</td>
</tr>
<tr>
<td></td>
<td>Reslizumab</td>
<td>Anti IL-5</td>
<td>IV &gt;18 years</td>
</tr>
<tr>
<td></td>
<td>Benralizumab</td>
<td>Anti IL-5 receptor</td>
<td>SQ &gt;12 years</td>
</tr>
</tbody>
</table>

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T2-high asthma treatment

- **Mepolizumab**
  - Humanized IgGK1 anti IL 5 antibody inhibits receptor binding on the eosinophil which inhibits eosinophil recruitment, growth, differentiation and activation

- **Clinical studies:**
  - Decreased exacerbations, decrease oral corticosteroids and improved QoL.

- **Adverse reactions:**
  - Hypersensitivity reactions, herpes zoster infections, vaccinate if indicated. Headache, injection pain, backache, fatigue, influenza, UTI, abdominal pain, pruritus, muscle spasms and eczema

No anaphylaxis has occurred.

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![Graph showing decreased exacerbations with Mepolizumab](image)

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![Graph showing improved QoL with Mepolizumab](image)
Anti IL5/IL5r antibodies

- Reslizumab
  - Dosed on weight
  - 18 years old
  - IV every 4 weeks
  - >400 eosinophils/μL

- Benralizumab
  - SQ every 4 weeks x 3, then every 8 weeks
  - Decreased exacerbations, improved Fev1
  - ER one time dose 50% decrease exacerbation rate for 12 weeks

Pediatric biological FDA approved

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Monoclonal antibody</th>
<th>Mechanism of action</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis</td>
<td>Dupilumab</td>
<td>Anti IL-4r and anti IL-13</td>
<td>SQ (at home)</td>
</tr>
<tr>
<td>Asthma – recent indication</td>
<td></td>
<td></td>
<td>Adults &gt;12 years of age</td>
</tr>
</tbody>
</table>

Figure 5-2. Type 1 and 2 receptors. Type 1 IL-4 receptors are heterodimers of IL-4Rα and IL-13Rα. Type 2 IL-4 receptors are homodimers of IL-4Rα. They have a shared chain and bind only IL-4. Type 1 and 2 receptors are expressed in Th1 and Th2 cells and are involved in the pathogenesis of allergic asthma.
Pharmacoeconomics:

- Average cost-effectiveness is calculated
  - Cost of drug + resulting effect = cost per unit of effect achieved

\[
\frac{\text{Cost (option B) - cost (option A)}}{\text{Effect (option B) - Effect (option A)}} = \text{Cost to achieve one unit of effect}
\]

- Cost
  - Minimization: identical outcomes
  - Effectiveness: natural years
  - Utility: quality of life years
  - Benefit: dollars

Value? Quality report cards?

Medicine Adherence Studies

- Studies consistently show that less than 50% of patients adhere to daily medication regimens.
- Clinicians cannot predict better than chance which patients will be compliant.
- Therefore, all patients need to be educated to ensure adherence to the medical regimen.
- Communicating well and providing education are as important as prescribing the right medicine.

<table>
<thead>
<tr>
<th>Method of Measuring Medication Use</th>
<th>Bender et al., 2000</th>
<th>Smith et al., 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controller</td>
<td>Metered dose inhaler (MDI)</td>
<td>Steroid inhaler</td>
</tr>
<tr>
<td>Compliance</td>
<td>80%</td>
<td>39%</td>
</tr>
<tr>
<td>Measuring Tool</td>
<td>43%</td>
<td>Telephone interviews with parents of children 2-12 years. Long term control medication underuse was defined as suboptimal control and parent report of 6 days/week of inhaled steroid use</td>
</tr>
<tr>
<td>Measure</td>
<td>Mother report, child report</td>
<td>Canister weight, raw doser, adjusted doser</td>
</tr>
</tbody>
</table>

- Studies consistently show that less than 50% of patients adhere to daily medication regimens.
- Clinicians cannot predict better than chance which patients will be compliant.
- Therefore, all patients need to be educated to ensure adherence to the medical regimen.
- Communicating well and providing education are as important as prescribing the right medicine.

Shared Decision Making

1. Non verbal attentiveness
2. Reassuring messages
3. Identifying fears
4. Address immediate concerns
5. Interactive conversation
6. Tailoring regimes
7. Nonverbal encouragement
8. Initiate long term treatment plan
9. Reach agreement on short term
10. Plan for decision making

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Asthma triad – medical school

Bronchospasm

Inflammation

Mucus

Asthma pathology

Figure 15-41 Bronchus from an asthmatic patient showing goblet cell hyperplasia (green arrowhead), subbasement membrane fibrosis (black arrowhead), eosinophilic inflammation (yellow arrowhead), and muscle hypertrophy (blue arrowhead).

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Asthma triad – medical school

Bronchospasm

Inflammation

Mucus

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Asthma pathology

Figure 15-11 Bronchus from an asthmatic patient showing goblet cell hyperplasia (green arrowhead), submucosal membrane fibrosis (black arrowhead), eosinophilic inflammation (yellow arrowhead), and muscle hypertrophy (blue arrowhead).

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**Conclusions**

- Severity, control, and responsiveness to treatment are key elements of asthma assessment and monitoring.
- The goal of asthma therapy is to achieve control, based on NAEPP guidelines.
- Clinical assessment and patient self-assessment are primary methods for monitoring asthma control.
- ICSs are preferred monotherapy for controller therapy in patients with persistent asthma, across all ages.
- LABAs are preferred adjunctive agents in patients aged ≥12 years who cannot be controlled with ICS monotherapy.

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**Asthma pathology**

![Image: Immunology and Allergy Clinics 2017 37, 233-246 DOI: (10.1016/j.iac.2017.01.001)](Image)

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References

- Expert Panel Report – 3
- Allergy & Asthma Network Mothers of Asthmatics
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  www.nhlbi.nih.gov
- National Jewish Medical and Research Center www.njc.org

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