Pediatric Asthma, an Update on Pharmacotherapy and Drug Delivery; Where We’ve been and Where We’re Going

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Objectives

• Recognize the key features of asthma and some aspects of proposed pathophysiology
• Describe basic pharmacologic options for acute and chronic asthma management, mechanisms of action, pros and cons, and options for drug delivery
• Describe a basic strategy for initiating and adjusting asthma pharmacotherapy based on classification of severity and assessment of ongoing control

Introduction and Background

• Hallmarks of Asthma:
  • Obstruction of the lower airways that is:
    – Recurrent
    – Reversible
    – Reactive (to a specific trigger)
    – The “three R’s”
    – (Re-modeling)
    – Inflammation

NHBLI Definition

• Asthma is a chronic inflammatory disease of the airways in which many cell types play a role, in particular mast cells, eosinophils and T lymphocytes. In susceptible individuals, the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or early morning. These symptoms are usually associated with widespread and variable airflow obstruction that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli

Morphologic Changes in Asthma

Basement Membrane
Thickening/Fibrosis
Smooth Muscle
Hyper trophy
Mucous Gland
Hyper trophy and Hypersecretion
Vascular Dilation
Edema
Inflammatory Cell Infiltration
Epithelial Damage

Effects of Inhaled Corticosteroids

Pre- and post-3-month treatment with budesonide (BUD) 600 mcg b.i.d.
Pediatric Asthma Prevalence


The Hygiene Hypothesis

• Shift to Th2 cytokine profile
• Favors eosinophilic airway inflammation
• Increased IgE
• Initial Th2 profile shifts with infections, exposure to older children, less frequent antibiotics

Asthma – Who and When?

Asthma Predictive Index

Was shown to be highly predictive of wheezing in later childhood

Patients Overestimate Their Asthma Control

• Of patients who report symptoms that meet NIH criteria for moderate-persistent asthma
  – 61% still consider their asthma to be “well controlled” or “completely controlled”
• Of patients who report symptoms that meet NIH criteria for severe-persistent asthma
  – 32% still consider their asthma to be “well controlled” or “completely controlled”

Assessing Flows with Spirometry

“Normal” “Obstructed”
Pulmonary Function Tests

Spirometry

Pre- and Post-Bronchodilator Testing

Pre- and Post-Bronchodilator Testing

Initial Evaluation

Follow Up

Severe Obstruction & Significant Airway Hyper-responsiveness
Final diagnoses of 117 children/adolescents, referred for dyspnea or “asthma”

Spirometry in VCD

Treatment

Goals of Therapy of Asthma

• Control chronic symptoms
• Maintain normal activity levels
• Maintain “normal” pulmonary function
• Prevent exacerbations
• Minimize ER visits and hospitalizations
• Avoid adverse effects of medications
• Maximize adherence

Therapeutic Options: Pharmacotherapy

Long-Term Controllers
- Corticosteroids (inhaled)
- Cromones
- Leukotriene modifiers
- Long-acting β₂-agonists (LABAs)
- Theophylline

Quick Relief Medications
- Short-acting β₂-agonists
- Anticholinergics
- Systemic corticosteroids

Other
- Omalizumab (monoclonal IgE ab)
Acute Asthma Symptoms

- Dyspnea
- Shortness of breath
- Air hunger
- Chest tightness
- Cough
- Choking sensation
- Exercise intolerance

Beta Receptor Agonists

- Bind to beta adrenergic receptors
- Several tissue specific subtypes:
  - $\beta_1$ receptors – mainly cardiac
  - $\beta_2$ receptors – smooth muscle $\rightarrow$ relaxation
  - $\beta_3$ receptors – adipose tissue, lipolysis
- Include albuterol, levalbuterol, salbutamol, terbutaline (short-acting)

Short-Acting Inhaled $\beta_2$-Agonists

- Drug of choice for relief of acute symptoms and bronchospasm
- Beneficial when used early and often with exacerbations or with exercise
- Excessive use indicates inadequate asthma control
- Increasing use indicates need for anti-inflammatory therapy

Beta receptors

- Coupled to G proteins
- Activate adenylyl cyclase
- Formation of cAMP and end effects

$\beta_2$ receptors

- ADRB2 receptor
- Polymorphisms and Pharmacogenetics
- Some polymorphisms in the beta receptor may influence asthma responsiveness
- Arginine/Glycine genotype at amino acid position 16
- May influence downstream effects

Anticholinergic Agents

- Ipratropium Bromide
- Bronchodilation via inhibition of muscarinic ($M_3$) cholinergic receptors
- NOT a first line choice for treatment of acute exacerbations
- Helpful as an adjunct to albuterol in treatment of acute severe asthma
Inhibition of M$_3$ receptor

Inhaled Corticosteroids
- Reduce symptom severity
- Prevent exacerbations
- Improve lung function
- Diminish airway hyperresponsiveness
- Prevent airway remodeling
- Need to be taken daily!

EPR-3
Inhaled Steroids: The Most Potent and Consistently Effective Long-Term-Control Medication for Asthma

Pathogenesis of Asthma

Effect of Corticosteroids

Glucocorticoids
- Steroids named for role in glucose metabolism, synthesis in cortex
- Bind to glucocorticoid receptor to influence gene transcription
- Anti-inflammatory effect
- Use in numerous disease states
  - Immune system pathology (Autoimmunity)
  - Asthma, Allergies/Atopy
  - Cancer
  - Transplantation
  - Sepsis
Steroid Mechanism of Action

Cortisol
Dexamethasone

Effect of Long-term Treatment with ICS on Adult Height in Children with Asthma

- 142 children with asthma treated with inhaled budesonide (412 μg/day) for 3-13 years (mean: 9.2 years)
- Reduced growth rate during the first years of treatment
- Similar adult height (dependent on the child’s height before treatment)
- Children with asthma who receive long-term treatment with ICS attain normal height


Steroids for an Exacerbation

- Assume about 40mg daily for 5 days:
  - 200,000 micrograms
  - 200 days of budesonide 0.5 mg bid
  - 227 days of fluticasone 440 mcg bid
  - 454 days of fluticasone 220 mcg bid
  - 400 days of fluticasone/salmeterol 250/50mcg bid
  - 625 days of beclomethasone 160 mcg bid
  - 1,250 days of beclomethasone 80 mcg bid
- Of which only <10% is bioavailable

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Long Acting β₂-Agonists

- Relax airway smooth muscle by stimulating β₂-adrenergic receptors
- Slower onset of action (30 min)
- Duration of 12 hours after single dose
- Should not be used for acute exacerbations
### Long Acting $\beta_2$-Agonists

- Helpful as an *adjunct* to anti-inflammatory therapy for long term control of symptoms
- Should not be used in place of anti-inflammatory therapy
- Especially helpful for control of nocturnal symptoms and EIB

### SMART and LABAs

**The Salmeterol Multicenter Asthma Research Trial**

*CHEST, 2006; 129*

- No difference in primary outcomes
- Concurrent use of ICS not controlled
- Follow up: 7 months study drug supplied
- Delay in care with LABA use alone

### LABAs

- Provide sustained bronchodilation and improve asthma control
- In combination ICS:
  - improve asthma control and decrease the frequency of asthma exacerbations more effectively than doubling the dose of ICS
- Retrospective case-control studies of asthma exacerbations and deaths have failed to implicate LABAs as a risk factor for hospitalization, intensive care unit admissions, or deaths
- May be more cost-effective than increased doses of ICS

### Leukotriene Modifiers

- Include leukotriene receptor antagonists (LTRA) montelukast and zafirlukast
- As well as the 5-lipoxigenase inhibitor zileuton
  - Not recommended under 12 years of age
Leukotriene Modifiers

- Modest improvement in lung function and symptoms, reduced use of rescue medication
- Attenuate allergen-induced bronchial responsiveness and EIB
- May be considered as an alternative in mild persistent asthma
- Should not be used as substitutes for ICS in the management of moderate-severe asthma

Cromones

- Cromolyn and Nedocromil
- Known to have anti-inflammatory properties
- Mechanism of action:
  - Blockade of calcium channels
  - Modulation of mast cell mediator release
  - Inhibition of eosinophil activation
- Adjunctive therapy for exercise symptoms

Cromones

- Reduce airway hyperresponsiveness
- Inhibit the early and late asthmatic response to allergen challenge and EIB
- Nedocromil more potent in inhibiting EIB
- Cromolyn requires QID dosing, Nedocromil can be used BID

Theophylline

- Methylxanthine class, similar to caffeine
- Exact mechanism of action is unknown
- Some role in smooth muscle relaxation as well as a weak anti-inflammatory effect
- Sustained-release theophylline may be considered as an alternative for nocturnal asthma symptoms
- Drug interactions, side effects and need for serum concentration measurements

Theophylline

**TABLE 1. PROPOSED MECHANISMS OF ACTION OF THEOPHYLLINE**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Phosphodiesterase inhibition (nonselective)</td>
</tr>
<tr>
<td>Adenosine receptor antagonism (A&lt;sub&gt;1&lt;/sub&gt;, A&lt;sub&gt;2A&lt;/sub&gt;, A&lt;sub&gt;3&lt;/sub&gt;-receptors)</td>
</tr>
<tr>
<td>Increased interleukin-10 release</td>
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<tr>
<td>Stimulation of catecholamin (epinephrine) release</td>
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<tr>
<td>Mediator inhibition (prostaglandins, tumor necrosis factor α)</td>
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<tr>
<td>Inhibition of intracellular calcium release</td>
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<tr>
<td>Inhibition of nuclear factor-κB (κB nuclear translocation)</td>
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<tr>
<td>Increased apoptosis</td>
</tr>
<tr>
<td>Histone deacetylation activity (efficacy of corticosteroids)</td>
</tr>
</tbody>
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Azithromycin

- Macrolides have been shown to have anti-inflammatory and immunomodulating effects
  - Macrocyclic lactone ring (similar to Tacrolimus)
- Most evidence from studies in Cystic Fibrosis
  - Inhibits quorum sensing in Pseudomonas
- May downregulate IL-5 in Th2 cells
- Decreases airway cell mucus secretion/viscosity
- Applicable to CF, COPD, DPB, Bronchiectasis, Bronchiolitis Obliterans

EPR 3: Guidelines for the Diagnosis and Treatment of Asthma

- New additions & recommendations
  - In patients >5yo with moderate asthma equally weigh addition of LABA versus increased ICS
  - Emphasis on impairment and risk
  - Assess severity; assess control
  - Periodic assessment of control emphasized
  - Inflammation, cellular level, phenotypic variety
  - Age stratification
  - Omalizumab

Mild Intermittent Asthma
- Symptoms < 2 times/week
- Nocturnal symptoms < 2 times/month
- Normal FEV1 and PEF (>80%)
- Brief and mild exacerbations

Mild Persistent Asthma
- Symptoms > 2 times/week
- Exacerbations may affect activity
- Nocturnal symptoms > 2 times/month
- Normal FEV1 (>80%)
- Increased PEF variability (20-30%)

Moderate Persistent Asthma
- Daily symptoms + use of β2 agonists
- Frequent exacerbations that affect activity
- FEV1 or PEF: 60-80%
- PEF variability: > 30%

Severe Persistent Asthma
- Daily symptoms
- Frequent exacerbations
- Limited physical activity
- FEV1 and PEF: <60%
**Children 0-4 years of age**

**Children 5-11 years of age**

**Children > 12 years of age**

**Stepwise Approach**

- Gain control as quickly as possible
- Step down -- Review treatment every 1 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible (e.g. steroid wean by 25%)
- Step up if control is not achieved (Review environment, compliance and technique)

**Drug Delivery**

**Characteristics of Ideal Respiratory Inhalation Delivery System**

- Reproducible dose delivery to lungs across wide range of inspiratory flows
- Small particle size (1-5 microns)
- Ease of use, small size, easy to carry
- Multiple-dose capability
- Cost-effectiveness
- Dose counter
Particle Deposition in Airways According to Size

MDIs in Children
- With proper technique, even 4-6 month old patients can achieve good drug delivery to the lower airways with an MDI and holding chamber with face mask (15-20%)
- Using a spacer or holding chamber offers advantages
  - increased drug delivery to the lower airways
  - decreased drug deposition on the oral mucosa
  - administration time

MDIs in Children: Technique
- Drugs should be administered as single actuations into the spacer
- The canister should be shaken before and between actuations
- A single, slow and deep inspiration or series of smaller breaths are equally effective
- To eliminate static charge spacer should be washed with a washing liquid and air dried without rinsing or wiping every 4 weeks

Nebulizers
- Two types:
  - Jet nebulizers
  - Ultrasonic nebulizers
- Patient cooperation is not required
- Better drug delivery when used with a mouthpiece compared to face mask
- Drug deposition to the lungs <10%
- Main use: treatment of acute severe asthma

Factors Affecting Nebulizer Performance
- Design of the nebulizer chamber
- Flow of the driving gas
- Performance characteristics of the compressor
- Fill volume
- Time taken to nebulize the solution
- Viscosity, surface tension and concentration of the drug
- Residual volume
- Tapping of the nebulizer chamber
- Distance from the face

Effect of Distance of the Mask from the Face
Factors that Effect Deposition in Infants and Young Children

- Behavior and adherence
  - 4 to 6 fold decrease in lung deposition when child is crying
  - Increased extrathoracic and gastrointestinal deposition
- Face-mask seal and design
  - A tight seal of the face-mask is extremely important
  - Round face-mask with flexible rim is the best
- Particle size
  - MMAD of 1.1 micron had 4 fold more deposition than MMAD of 3-4 microns
- Anatomy and physiology:
  - Narrow nasal passages increase impaction in nose
  - High RR decrease sedimentation in lower respiratory tract

A Comparison of Commercial Jet Nebulizers

Respiratory Particle Delivery Rate

Future of Aerosol Therapy

- Nanoparticles loaded with anti-TB antibiotics
- Inhaled Tacrolimus and Cyclosporine
- Gene therapy for CF (liposomes or viral vectors)
- Inhaled chemotherapy for lung cancer
- Hormone replacement (Insulin, GH, TSH, FSH...)
- GM-CSF for alveolar proteinosis, GM-CSF for neutropenia
Limitations of Peak Flow Monitoring

- In mild exacerbations symptoms may deteriorate before PEFR
- There is a big variation in PEFR readings among commercially available devices
- PEF underestimates airflow obstruction measured by FEV1
- Compliance is satisfactory in short term but falls considerably after a few months
- PEFM is an extra device to teach, makes therapy more complicated

Outpatient monitoring

Summary

- Asthma is a complex disease, the etiology of which involves many factors related to infection, atopy, and genetics
- Objective evaluation is important for appropriate treatment
- Inhaled corticosteroids and aggressive and early treatment of exacerbations are the mainstay of good asthma therapy

Summary

- Adjunctive therapies are important in addition to further investigation when symptoms are not controlled
- An array of current pharmacologic options are used to treat asthma in a stepwise fashion
- Carefully consider drug delivery in addition to patient education and other non-pharmacologic management

Thank you!

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