Evaluation and Treatment of Severe Asthma

John Prpich, MD
Pediatric Pulmonary Specialists
Tampa, FL

No one told him that he can breathe underwater
Pediatric Pulmonary Specialists

- Providing care at St Josephs for over 25 years.
  - Dave Rosenberg, MD
  - John Prpich, MD – joined about 10 yrs ago
  - 3 ARNP’s
  - 1 Pediatric Respiratory Therapist

- St Joseph’s Children’s Hospital recently recognized as an Asthma Friendly Hospital
Severe Asthma in Children

• Asthma affects over 6 million children in USA
  – Approx 10% of children < 15 y/o
  – About 5-10% of these children have severe or difficult to treat asthma.

• Medical expenditure for asthma is about 10 billion annually
  – 50% of these costs are due to severe/difficult to control asthma
Severe Asthma

• Heterogeneous disorder with similar clinical features.
  – Increased symptom frequency
  – Increased symptom severity, more persistent symptoms
  – Increased hi-risk outcomes
    • ED visits
    • Hospitalizations
    • ICU admissions
    • Intubations
  – Greater need for medications
  – Lower lung function
Age Matters — factors change with age

- **Infancy**
  - Little agreement on definition — Diagnosis is hard
  - Underlying pathophysiology poorly understood
  - Objective measurement/evaluation harder
  - More risk for severe sx due to small airway size

- **Preschool**
  - Still hard to measure
  - Compliance dependant on parents
  - Virus is major trigger
  - Sensitization to aeroallergens beginning
  - Exercise/activity can be a trigger

- **School age**
  - Easier to measure lung function
  - Allergy is an increasing factor
  - Compliance still depends on parents

- **Adolescent**
  - Poor symptom perception/denial is a problem
  - Psychological factors more of an issue
  - Personal compliance and parental compliance now a challenge
Severe Asthma in Children

- Usually begins in the first year of life
- Associated with severe viral illness in someone with atopic features
  - Early evidence of allergic pattern is a predictor of disease progression
  - Tends to persist into adulthood
  - Variability within this group
    - Bronchodilator response/use
    - Lung function
    - Pattern of symptom
- Current pharmacologic agents not as effective.
- Lower quality of life scores
Evaluation

• **Must try to separate:**
  – **Not asthma** – wrong diagnosis
  – **Difficult to treat asthma** due to reversible factors
  – Asthma is exacerbated by one or more co-morbidities - **“asthma plus”**
  – **Severe therapy resistant asthma**

• Unfortunately, there can be cross-over between these categories
Problematic severe respiratory symptoms, unresponsive to prescribed asthma therapy

Asthma?  
Yes → Asthma plus (co-morbidities)  
No → New diagnosis

Yes → Severe, therapy resistant asthma

Yes → Difficult asthma
Some of the ways

- **Detailed** history and physical exam
- Lung function testing
  - PFT’s, Lung Volumes – pre and post bronchodilator
  - Provocative testing (Mch, exercise)
  - IOS
  - FeNO
- Allergy testing
  - SPT
  - Immunocap
- Home visit
- EMR (refill hx, hospital/ED visits etc)
Not Asthma

• May suspect if severe or frequent symptoms without atopy
  – Sweat test
  – CT chest
  – Bronchoscopy
  – Swallow study
  – Immune evaluation
Difficult to control asthma due to reversible factors

- Poor medication compliance
  - Most common reason
- Poor medication technique
  - Even after MULTIPLE attempts at training
- Cultural barriers
- Split household
- Cost of clinic visits and medications
Fig. 1. Drug deposition of radiolabeled salbutamol in a young child. A: Inhaling with a pressurized metered-dose inhaler (pMDI)/spacer through a loosely fitted face mask. B: Inhaling with a nebulizer through a loosely fitted face mask. C: Inhaling with a pMDI/spacer through a tightly fitted face mask and screaming during inhalation. D: Inhaling with a nebulizer through a tightly fitted face mask and screaming during inhalation. E and F: Inhaling with a pMDI/spacer through a tightly fitted face mask and quietly inhaling. G and H: Inhaling with a nebulizer through a tightly fitted face mask and quietly inhaling. From Reference 10, with permission.
“Asthma Plus”

- GERD – hard to determine cause vs effect
  - Clear link has been hard to identify
  - If history is suggestive, consider treatment
- Obesity
  - Can worsen or cause GERD
  - Risk for OSA
  - Can mimic asthma – wheeze/dyspnea
  - Linked to steroid resistance
- Home environment
  - Allergen exposure
  - Mold sensitization
  - Stress, anxiety
  - Cigarette smoke
  - Food allergy
- Rhinosinusitis – allergic or infectious
- Dysfunctional breathing
  - VCD
  - Hyperventilation
- Poor symptom perception
And then, your left with

Severe Therapy Resistant Asthma.

Now what?
New Treatment Considerations

• High-Dose ICS
  – Steroid resistance may be more of a spectrum than a “all or nothing” phenomenon.
  – The dose response curve may be shifted in the more severe patient.
  – May consider addition of a “small particle” ICS in addition to current ICS regimen.
  – May allow reduction in OCS tx

• Addition of a LAMA
  – Tiotropium (spiriva) once daily
  – Improves lung function, trend toward improved control
  – Additional bronchodilation and may help inflamm.
• Oral steroid Tx
  – Limited literature to recommend starting dose
  – Consider 0.5 mg/kg daily or every other day
  – Taper as symptoms permit

• Low dose Theophylline
  – Typical dosing has increased risk of side effects and drug interactions – blood level 10-20 mol/L
  – Low dose – blood level 5-10 mol/L
    • Immunomodulatory
    • May help “neutrophilic asthma”
    • May help with acquired steroid resistance and down regulation of beta receptors by too much albuterol use
  – Easier – no worry about monitoring levels
• IM triamcinolone trial
  – Can help to identify true steroid resistant patient
  – May help identify poor control due to compliance issues

• Macrolide antibiotics (M/W/F zithromax)
  – Immunomodulatory properties/neutrophilic asthma
  – Possible effect on GERD
  – Impact on respiratory tract flora
• Anti-fungal therapy
  – Severe Asthma with Fungal Sensitization (SAFS)
  – Growing awareness that fungal sensitization with exposure is associated with increased morbidity and mortality in severe asthma.
  – Need both SPT and Blood allergy testing
  – Tx: eliminate the exposure and consider antifungal

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Fungi implicated in severe asthma with fungal sensitisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus fumigatus</td>
<td></td>
</tr>
<tr>
<td>Alternaria alternate</td>
<td></td>
</tr>
<tr>
<td>Cladosporium herbarum</td>
<td></td>
</tr>
<tr>
<td>Penicillium chrysogenum</td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td></td>
</tr>
<tr>
<td>Trichophyton mentagrophytes</td>
<td></td>
</tr>
<tr>
<td>Botrytis cinerea</td>
<td></td>
</tr>
</tbody>
</table>
New inhalers

• ICS/LABA/LAMA combinations
  – Not yet approved for asthma yet (or children) but seems to be a natural fit.
    • Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) – approved for COPD in the US
    • Trimbow (Beclomethasone/formotorol/glycopyrronium) – approved for COPD in the UK.
Novel and New Treatments
<table>
<thead>
<tr>
<th>Drug (Trade Name) and Dosage</th>
<th>Biologic Mechanism of Action</th>
<th>Suggested Clinical Population</th>
<th>Clinical Effects</th>
<th>Effects on Biomarkers</th>
<th>Adverse Effects and Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab (Xolair), subcutaneous injection every 2 to 4 wk depending on dose (for dosing according to weight and IgE, see <a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf">www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf</a>)</td>
<td>Anti-IgE; binds to Fc receptor of free IgE (also reduces production of IgE)</td>
<td>Persons with IgE ≥30 IU/ml (upper limit of IgE varies according to weight and regulatory authority), positive skin test or elevated specific IgE level in response to perennial aeroallergen; best response in those with FENO ≥20 ppb</td>
<td>Reduced exacerbations, small reduction in symptoms, minimal effect on FEV₁</td>
<td>Small reduction in FENO, no reduction in circulating total IgE (measured by available assays)</td>
<td>Anaphylaxis (in an estimated 0.2% of patients); monitor for helminthic infection</td>
</tr>
<tr>
<td>Mepolizumab (Nucala), 100 mg given by monthly subcutaneous injection</td>
<td>Anti-interleukin-5; binds circulating interleukin-5</td>
<td>Best response in those with two or more exacerbations in past year and ≥300 eosinophils/μl†</td>
<td>Reduced exacerbations, reduced symptoms small or moderate effect on FEV₁</td>
<td>Reduction in circulating eosinophils, no change in FENO</td>
<td>Cases of zoster (rare); avoid in persons with active helminthic infection</td>
</tr>
<tr>
<td>Reslizumab (Cinquaer), 3 mg/kg given by monthly intravenous infusion</td>
<td>Anti-interleukin-5; binds circulating interleukin-5</td>
<td>Tested primarily in patients with more than one exacerbation in the past year and ≥400 eosinophils/μl</td>
<td>Reduced exacerbations, reduced symptoms small or moderate effect on FEV₁</td>
<td>Reduction in circulating eosinophils, no change in FENO</td>
<td>Oropharyngeal pain slightly greater than with placebo, anaphylaxis (rare); avoid in persons with active helminthic infection</td>
</tr>
<tr>
<td><strong>Phase 3 testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benralizumab, given by subcutaneous injection</td>
<td>Anti-interleukin-5; binds interleukin-5 receptor with resultant lysis of eosinophils</td>
<td>Phase 3 efficacy primarily in those with two or more exacerbations in past year and ≥300 eosinophils/μl</td>
<td>Reduced exacerbations, reduced symptoms moderate effect on FEV₁</td>
<td>Reduction in circulating eosinophils, no change in FENO</td>
<td>Not yet available</td>
</tr>
<tr>
<td>Dupilumab, given by subcutaneous injection</td>
<td>Anti-interleukin-4 and interleukin-13 receptor subunit for interleukin-4 and interleukin-13 receptor</td>
<td>Tested primarily in patients with more than one exacerbation in the past 1 or 2 yr and ≥300 eosinophils/μl‡</td>
<td>Reduced exacerbations, improved FEV₁</td>
<td>Temporary increase in eosinophils, reduction in FENO by approximately 30%</td>
<td>Reports of eosinophil counts &gt;5000, may affect metabolism of CYP450 substrates; avoid live vaccines, most likely should avoid in persons with active helminthic infection</td>
</tr>
<tr>
<td>Fevipiprant, pill taken by mouth</td>
<td>Anti-CRTH2; blocks signaling at CRTH2 (the PGD₂ receptor)</td>
<td>To be defined; most likely type 2</td>
<td>Most likely improved FEV₁ and reduced symptoms</td>
<td>Reduction in sputum eosinophils, no effect seen in peripheral blood or FENO</td>
<td>Not yet available</td>
</tr>
</tbody>
</table>

*The drugs listed have been approved by the Food and Drug Administration or are in phase 3 testing for asthma. CRTH2 denotes chemoattractant receptor homologue expressed by type 2 helper T cells, FEV₁ forced expiratory volume in 1 second, and PGD₂ prostaglandin D₂.
†In patients with at least three exacerbations, this drug may be effective if the eosinophil count is at least 150 per microliter.
Omalizumab (Xolair)

• Approved in 2016 (first in 2003 > 12 y/o)
  – Children > 6 y/o
  – With severe atopic asthma – driven by a type-2 inflammatory response.
  – Allergen in the airway drives the polarization of TH-2 cells leading to recruitment/activation of mast cells, eosinophils, basophils, B-cell Ig class switching and generation of allergen specific IgE

• Monoclonal IgE antibody – binds to the Fc receptor of freely circulating IgE
  – Blocks the binding of free IgE to mast cells, basophils and APC.
  – Down regulates high-affinity receptor for Fc-region of Ig-E
Xolair

– Children > 6y/o with IgE 30 - 1,300
– Given every 2 weeks to 1 X month
– Reduces exacerbation rates, health care utilization and improves quality of life
– Immunomodulatory effects may modify long-term effects of allergen-induced airway remodeling
**xolair**

- In most studies – when added to typical tx
  - reduced severe exacerbation by at least 45% and hospitalizations by 85%
  - Allowed lower doses of inhaled steroids
  - Inconsistent effect on lung function
  - Baseline IgE level is not predictive of response
  - Elevated FeNo does seem to predict a better response.

- Link between allergy and viral triggered Sx
  - Allergic sensitization increases the risk and severity of virus-induced wheeze.
  - Fall exacerbations (linked to RV) are more closely associated with sensitization to perennial allergens.
  - *Xolair* has been shown to decrease this fall increase in exacerbations (ICATA)
  - *Xolair* has been shown to decrease the duration of rhinoviral infections, viral shedding and the risk of illness in atopic children. (PROSE)
  - *Xolair* may improve virus induced dendritic cell IFN-α response improving anti-viral activity in the airway.
• **Targeting eosinophils**
  – IL-5 is key cytokine involved in eosinophillic driven inflammation
  – Eosinophils plays a key role in determining asthma severity, exacerbation rate, and response to steroid tx.
  – Eosinophil activation and degrannulation releases cytotoxic proteins and further inflammatory cytokines
  – Triggers local tissue damage and recruitment of other inflammatory cells
  – Decreased exacerbation rates needing OCS in half
  – Small improvement in FEV1
  – Improved quality of life scores
Targeting the Eosinophil

- For use in patients with severe eosinophil driven asthma.
  - Elevated peripheral eosinophils (> 150 cell/μl)

- Targeting this pathway
  - Decreased exacerbation rates needing OCS in half
  - Small improvement in FEV1
  - Improved quality of life scores
• Mepolizumab (Nucala)
    • Humanized monoclonal antibody against IL-5
    • Prevents IL-5 from binding to the receptor on the eosinophil
      – Prevents differentiation, recruitment, activation, growth and survival of the eosinophil.
    • Given IM once a month
    • Ages > 12y/o
    • Well tolerated
    • Decreases severe exacerbation rate by 40-60%
    • 50% reduction in need for oral steroid
    • Response improves with:
      – The higher the number of previous exacerbations
      – higher the baseline eosinophil count
• Benralizumab (Fasenra)
  – Humanized antibody against IL-5 receptor (alpha subunit)
  – Inhibits proliferation of IL-5 dependant cell lines
  – Induces eosinophil apoptosis (95% depletion within 24 hrs of first injection)
  – Results In significant drop in eosinophil counts
  – Given IM once every 2 mo
  – Ages > 12 y/o
Lebrikizumab – monoclonal antibody targeting IL-13.

- IL-13: cytokine involved in Th2 inflammation
  - Released by activated basophils, mast cells, and eosinophils
  - Major role in allergic driven airway inflammation
  - Induces airway epithelial cells to secrete periostin
    - Periostin is a matricellular protein effecting local epithelial cells and fibroblasts
    - May play a role in airway remodeling
  - Inhibited by ICS

- Effects
  - Improve lung function
  - More effect on patients with high serum periostin levels
  - Not a clear impact on asthma exacerbation rates or symptoms
Tezepelumab

- TSLP (thymic stromal lymphopoeitin)
  - Cytokine with effects on lymphocyte maturation through activation of APC.
  - TSLP is central to regulation of Th2 inflammation affecting
    - Dendritic cells
    - T & B cells
    - Innate immune cells
  - TSLP expression is higher in airways of asthmatics
    - Levels correlate with Th2 cytokine/chemokine expression and disease severity
  - Tezepelumab binds to TSLP and inhibits interaction with its receptor
  - Effect is likely upstream from current available Tx
Tezepelumab

• Effects
  – Greater reduction in exacerbation rates – up to a 71% reduction
  – Effect was independent of baseline eosinophil count
  – Improvement in lung function

  – Reduce eosinophil count, FeNO and IgE lvs (first one to show impact on all markers)

  – Indicates it may impact IL-4, IL-5 and IL-13 pathways and may have broader physiologic effect than targeting individual cytokine

  – Effective in reducing exacerbation in multiple asthma phenotypes
    • Eosinophilic (allergic and non-allergic) asthma
    • Non-eosinophilic asthma

  – Non allergic factors – smoke, diesel particles, viruses have been shown to trigger TSLP release and inflammation

  – Many cells that are activated/respond to TSLP (mast cells, basophils, NKT cells, innate lymphoid cells and neutrophils) may play a role in inflammation/asthma beyond Th2 pathways
That’s it, time for discussion

1. Role of personalized asthma tx.

1. New treatments force us to better understand our patients.

1. Cost-benefit considerations.

1. monoclonal tx allows for directly observed tx in non-compliant patients.