Asthma State Of The Art

Sandy Khurana, MD, FCCP
Director, Mary Parkes Asthma Center
University of Rochester, NY
Disclosures

Grant support – GSK

I will not be discussing off-label use for any drugs or devices
Objectives

- Describe recent advances in our understanding of asthma
- Identify factors contributing to poor control of asthma
- Discuss a systematic approach to phenotyping asthma, and applying traditional & advanced therapies
Prevalence of symptoms of asthma worldwide (World Health Survey 2002–03)

Asthma definitions over time…

Corpus Hippocraticum, 4th century BC
Ailments characterised by spasms of breathlessness occurring more frequently in anglers, tailors, and metal workers.

Sir John Floyer, 1698
“...the Muscles labour much for Inspiration and Expiration thro’ some Obstruction, or Compression of the Bronchia, etc. This we properly call a Difficulty of Breath: but if this Difficulty be by the Constriction of the Bronchia, it is properly the Periodic Asthma. And if the Constriction be great, it is with Wheezing: but if less, the Wheezing is not so evident.”

Sir William Osler, 1894
Osler highlighted the following features: spasm of the bronchial muscles; swelling of the bronchial mucous membrane; a special form of inflammation of the smaller bronchioles; similarities with hay fever; running in families; often beginning in childhood and sometimes lasting into old age; symptoms occurring in a variety of circumstances which at times induce a paroxism; a relationship with climate, atmosphere (ie, hay, dust, cat), violent emotion, diet, and colds; and distinctive sputum containing rounded gelatinous masses (periles), Curschmann spirals, and octahedral crystals of Leyden.

Global Initiative for Asthma, 2002
Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread airflow obstruction that is typically reversible either spontaneously or with treatment.

″Global Initiative for Asthma 2017″
Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.
Consider low dose ICS
Leukotriene receptor antagonists (LTRA)
Low dose theophylline*
Low dose ICS/LABA**
As-needed SABA or low dose ICS/formoterol#
Low dose OCS

STEP 1
Low dose ICS
STEP 2
Leukotriene receptor antagonists (LTRA)
Low dose theophylline*
Med/high dose ICS/LABA
Add tiotropium*
Add low dose ICS/LABA
Add low dose OCS

STEP 3
Low dose ICS/LABA**
Add tiotropium*
Add high dose ICS/LABA
Add low dose OCS

STEP 4
Med/high ICS/LABA

STEP 5
Add on treatment

Other controller options
Consider low dose ICS
Leukotriene receptor antagonists (LTRA)
Low dose theophylline*
Med/high dose ICS/LABA
Add tiotropium*
Add low dose OCS
Question

What percentage of patients with doctor-diagnosed asthma may not have current asthma?

A. Less than 10 percent
B. Less than 20 percent
C. 30-40%
D. Greater than 60%
What percentage of patients with doctor-diagnosed asthma may not have current asthma?

A. Less than 10 percent
B. Less than 20 percent
C. 30-40%
D. Greater than 60%
Reevaluation of Diagnosis in Adults
With Physician-Diagnosed Asthma

Shawn D. Aaron, MD; Katherine L. Vanderheen, MScn; J. Mark FitzGerald, MD; Martha Ainslie, MD; Samir Gupta, MD; Catherine Lemière, MD; Stephen K. Field, MD; R. Andrew McVor, MD; Paul Hernandez, MD; Irvin Meyers, MD; Sunita Mulbuna, MD; Gonzalo G. Alvarez, MD; Smita Pakhale, MD; Ranjeeta Mallick, PhD; Louis-Philippe Boulet, MD, for the Canadian Respiratory Research Network

Visit 1 (study day 1): spirometry before and after bronchodilator

- FEV₁ improves by ≥12% and ≥200 mL after use of bronchodilator
  - Asthma confirmed

Visit 2 (study week 1): bronchial challenge test with methacholine

- PC₂₀ ≥8 mg/mL
  - Asthma confirmed

- Halve all inhaled corticosteroids and all long-acting bronchodilators; discontinue antiasthmatic therapy; retest in 3 wk

Visit 3 (study week 4–5): bronchial challenge test with methacholine

- PC₂₀ ≥8 mg/mL
  - Asthma confirmed

- Discontinue all inhaled corticosteroids and long-acting bronchodilators; retest in 3 wk

Visit 4 (study week 7–8): bronchial challenge test with methacholine

- PC₂₀ ≥8 mg/mL
  - Asthma confirmed

- Normal airway responsiveness; no physiological evidence of current asthma

- Participant is assessed by study pulmonologist (study week 8–12) and workup is initiated to determine alternative diagnosis

- Participant enters 12-mo follow-up, and all asthma medications are held; bronchodilator challenge tests at 6 and 12 mo

613 Completed all study assessments and could be conclusively evaluated for a diagnosis of asthma

410 Current asthma confirmed

- Reversible airflow obstruction at first study visit

- Bronchial hyperresponsiveness at visit 2, 3, or 4

- Acute worsening of asthma during medication tapering period

- Asthma diagnosed by study pulmonologist

203 Current asthma ruled out

Current Asthma ruled-out in 33%!
Nonadherence in the era of expensive advanced therapies

All patients
n=69

Patients eligible for novel therapy n=47
Validated questionnaires can improve detection of comorbidities in difficult asthma. N=86

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Comorbidity</th>
<th>Items</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNQ [32,33]</td>
<td>Sino-nasal disease</td>
<td>5</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>SFAR [34]</td>
<td>AR</td>
<td>8</td>
<td>74</td>
<td>83</td>
</tr>
<tr>
<td>NIJMEGEN [35,26]</td>
<td>DB</td>
<td>16</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>PVC [37]</td>
<td>VCD</td>
<td>4</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td>BERLIN [38,39]</td>
<td>OSA</td>
<td>10</td>
<td>86</td>
<td>77</td>
</tr>
<tr>
<td>HADS [40]</td>
<td>Anx/Dep</td>
<td>14</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>GERD-Q [41,42]</td>
<td>GORD</td>
<td>6</td>
<td>65</td>
<td>71</td>
</tr>
</tbody>
</table>

The average time for questionnaire administration was approximately **40 minutes**.
## Association, prevalence and treatment outcomes of comorbidities in difficult asthma

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Associated with asthma?</th>
<th>Prevalence in asthma</th>
<th>Does treatment improve asthma?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sino-nasal disease AR</td>
<td>Yes</td>
<td>80% *</td>
<td>Yes</td>
</tr>
<tr>
<td>Sino-nasal disease CRS</td>
<td>Yes</td>
<td>70-74% *</td>
<td>Yes</td>
</tr>
<tr>
<td>GERD</td>
<td>Yes</td>
<td>59% *</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>OSA</td>
<td>Yes</td>
<td>75-95% *</td>
<td>Yes</td>
</tr>
<tr>
<td>VCD</td>
<td>Yes</td>
<td>75% *</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>DB</td>
<td>Yes</td>
<td>29% *</td>
<td>Yes</td>
</tr>
<tr>
<td>Anx/Dep</td>
<td>Yes</td>
<td>49% *</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Difficult asthma
# All asthma

Adapted from Radhakrishna N. Journal of Asthma. 2016
Suggested stepwise approach to mitigate impairment and risk

**STEP 1**
- Low dose ICS
- Consider low dose ICS

**STEP 2**
- Leukotriene receptor antagonists (LTRA)
- Low dose theophylline*

**STEP 3**
- Low dose ICS/LABA**
- Med/high dose ICS/LABA

**STEP 4**
- As-needed SABA or low dose ICS/formoterol#
- Add tiotropium*+
- High dose ICS + LTRA (or + theoph*)
- Add low dose OCS

**STEP 5**
- Refer for add-on treatment e.g. tiotropium,** anti-IgE, anti-IL5*
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O’Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jonup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.
SYGMA 1: Budesonide/Formoterol given as needed in mild asthma

In terms of weeks of well controlled asthma, budesonide-formoterol was:
 Superior to as needed terbutaline
 Inferior to Budesonide maintenance

In terms of exacerbations:
As-needed budesonide/formoterol was non-inferior to maintenance ICS with 1/5th of the ICS dose

Register now at congress.chestnet.org

O'Byrne PM et al. NEJM 2018; 378: 1865
Progress against key outcomes has stalled
Pitfalls in diagnosis…absent ‘gold standard’
Better understanding of complex pathophysiology
Identification of different treatable traits
Management guided by these traits appears more effective
Francis Rackemann did a detailed longitudinal clinical study of asthma in the first half of the 20th century and was the first to highlight the heterogeneity of asthma.

“surely it is hard to believe that the wheeze that comes to the young school girl for a day or two in the ragweed season is the same disease as that which develops suddenly in the tired business man or in the harassed housewife and pushes them down to the depths of depletion and despair. The problem is still wide open: the approach is not at all clear”
Complex gene/environment interactions...
…result in different clinical expressions
And variable treatment responses

Comparative effect sizes for exacerbation rates (Mepolizumab)

Zeiger RS. J Allergy Clin Immunol. 2006; 117: 45-52

Pavord ID et al. Lancet 2018; 391: 350
Allergic Eosinophilic
Nonallergic Eosinophilic
Neutrophilic
Currently available biologic therapies DO NOT target

A. Eosinophilic asthma
B. Allergic Asthma
C. T2 low asthma
D. All of the above
Currently available biologic therapies DO NOT target

A. Eosinophilic asthma
B. Allergic Asthma
C. T2 low asthma
D. All of the above
Type 2 Biomarkers

These biomarkers may reflect Type 2 cytokines that are released as part of the inflammatory response.

- **IL-13**: Secretion of periostin leads to induction of iNOS, leading to increases in FeNO that can be measured in the breath.
- **IL-5**: IL-13/IL-4 induces eosinophil maturation.
- **EOSINOPHILS**: Eosinophils migrate into the airway lumen and can be measured in sputum.
- **FeNO**: FeNO can be measured in the blood.

*Register now at congress.chestnet.org*
Type 2 asthma and therapeutic targets
# Biologics for Type 2 Asthma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Mechanism</th>
<th>FDA Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab (Xolair®, Genentech)</td>
<td>75-375 mg SC Q 2-4 weeks</td>
<td>Anti-IgE</td>
<td>Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mepolizumab (Nucala®, GlaxoSmithKline)</td>
<td>100 mg SC Q 4 weeks</td>
<td>Anti-IL-5</td>
<td>Age ≥ 12 years with severe asthma and eosinophilic phenotype&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reslizumab (Cinqair®, Teva)</td>
<td>3 mg/kg IV Q 4 weeks</td>
<td>Anti-IL-5</td>
<td>Age ≥ 18 years with severe asthma and eosinophilic phenotype&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Benralizumab (Fasenra™, AstraZeneca)</td>
<td>30 mg SC Q 4 weeks x 3, then Q 8 weeks</td>
<td>Anti-IL-5Rα</td>
<td>Age ≥ 12 years with severe asthma and eosinophilic phenotype&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dupilumab (Dupixent®, Sanofi/Regeneron)</td>
<td>200 mg SC Q 2 weeks 300 mg SC Q 2 weeks</td>
<td>Anti-IL-4Rα</td>
<td>Age ≥ 12 years with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
# Biologics for Type 2 Asthma - Efficacy

## Rate Ratio for exacerbations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.52 (0.37-0.73)</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>0.45 (0.36-0.55)</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>0.43 (0.33-0.55)</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>0.59 (0.51-0.68)</td>
</tr>
<tr>
<td>Dupilumab 200 mg</td>
<td>0.44 (0.34-0.58)</td>
</tr>
<tr>
<td>Dupilumab 300 mg</td>
<td>0.40 (0.31-0.53)</td>
</tr>
</tbody>
</table>

## Mean Difference AQLQ

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.26 (0.05-0.47)</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>NR</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>0.28 (0.17-0.39)</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>0.23 (0.11-0.35)</td>
</tr>
<tr>
<td>Dupilumab 200 mg</td>
<td>0.29 (0.15-0.44)</td>
</tr>
<tr>
<td>Dupilumab 300 mg</td>
<td>0.26 (0.12-0.40)</td>
</tr>
</tbody>
</table>

## Mean Difference ACQ

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>NR</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>-0.42 (-0.56 to -0.28)</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>-0.27 (-0.36 to -0.19)</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>-0.23 (-0.34 to -0.12)</td>
</tr>
<tr>
<td>Dupilumab 200 mg</td>
<td>-0.39 (-0.53 to -0.25)</td>
</tr>
<tr>
<td>Dupilumab 300 mg</td>
<td>-0.22 (-0.36 to -0.08)</td>
</tr>
</tbody>
</table>

Register now at congress.chestnet.org
Blood eosinophil count predicts response to omalizumab

Casale TB et al. Allergy 2017
Blood eosinophil count predicts response to mepolizumab
Effect of dupilumab on exacerbation and lung function by baseline Eos and FeNO

Castro et al. NEJM 2018; 378:2486
Which of the following biologics has NOT been studied for steroid sparing efficacy?

A. Mepolizumab  
B. Reslizumab  
C. Benralizumab  
D. Dupilumab
Question

Which of the following biologics has NOT been studied for steroid sparing efficacy?

A. Mepolizumab
B. Reslizumab
C. Benralizumab
D. Dupilumab
Steroid-sparing effect of biologics

Register now at congress.chestnet.org
Tezepelumab in Adults with Uncontrolled Asthma
Anti-TSLP: Effect by Th2 status

Corren J et al. NEJM 2017
Azithromycin & Asthma

N=420
Symptomatic asthma despite ICS/LABA
Azithromycin 500 mg thrice weekly vs placebo for 48 weeks
Azithromycin asthma AMAZES

<table>
<thead>
<tr>
<th>Number</th>
<th>Exacerbations per person-year</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Non-eosinophilic asthma</td>
<td>224</td>
<td>1.74</td>
</tr>
<tr>
<td>Eosinophilic asthma</td>
<td>196</td>
<td>1.98</td>
</tr>
<tr>
<td>Inhaled corticosteroid dose adjustment</td>
<td>420</td>
<td>1.86</td>
</tr>
<tr>
<td>Frequent exacerbators</td>
<td>140</td>
<td>2.79</td>
</tr>
<tr>
<td>Cough and sputum VAS</td>
<td>48</td>
<td>1.72</td>
</tr>
<tr>
<td>Bacteria-negative</td>
<td>188</td>
<td>1.85</td>
</tr>
<tr>
<td>Bacteria-positive</td>
<td>48</td>
<td>2.64</td>
</tr>
</tbody>
</table>
Bronchial Thermoplasty PAS 2 Study
Real world effectiveness – 3 year follow-up
‘Traditional’ vs. ‘Personalized’

**Traditional Guidance-Based Asthma Management**

- Diagnosis
  - Assessment of asthma severity
    - Avoidance of triggers and management of comorbidities:
      - Laryngopharyngeal reflux
      - Subacute bacterial infection
      - Sinus disease
      - Sleep apnea
      - Vocal cord dysfunction
  - Stepwise approach to therapy:
    - SABA, ICS alone, ICS + LABA, ICS + LTRA, oral corticosteroids, biologic therapy

**Personalized Approach to Asthma**

- Diagnosis
  - Determination of whether asthma is refractory
  - Characterize subtype
  - Phenotype
    - Gender
    - Age
    - Obesity
    - Ethnicity
    - Smoking Hx
  - Endotype
    - Blood biomarkers
      - IgE
      - Eosinophils
      - Periostin
      - Cytokines
    - Sputum biomarkers
      - Eosinophils
      - Neutrophils
      - Cytokines
  - Genotype
    - Other
      - FeNO

- Assess comorbidities

- Tailored therapy
Summary

- Burden of asthma remains high and mortality rates have stalled

- Heterogeneity and complex pathophysiology increasingly recognized. Multiple mechanisms in play. Therefore, a ‘one-size’ approach is no longer appropriate.

- Before pursuing advanced therapies, a systematic assessment is critical to evaluate correct diagnosis and address modifiable risk factors

- Recent studies suggest a role for as needed ICS/fast acting LABA for mild asthma

- Several biologics targeting type 2 pathways are effective in reducing exacerbations and steroid dependence. Limited options for non-eosinophilic asthma.
Join colleagues from around the region to gain access to the CHEST learning and training experience at our regional congress. This unique program will go beyond the classroom-style setting to connect you to leading experts who will teach and develop you and your team.

Learn More: athens.chestnet.org