New Therapeutic Options in Asthma

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Objectives / Outline

- What is asthma?
- History
- Epidemiology
- Pathophysiology
- NIH Classifications of Severity
- NIH Step Up Therapy
- Severe Persistent Asthma, Step 6
- Current Basic Treatment Options
- Current Advanced Treatment Options
- Looking ahead
- Summary
"A common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment."

Hippocrates named respiratory problem

“Related to the emotions”

“Cured” with Chloroform

1872

IV Pilocarpin

1880

F.H. Bosworth: connection with Hay Fever

1886

Epinephrine

1905

Oral Steroids

1950’s

Inhaled Steroids

1960’s

2015

200 BC

450 BC

1886

1905

1950’s

1960’s

2015

???

Dr. Batty’s Asthma Cigarettes

For the temporary relief of paroxysms of asthma

Effectively treats:

Asthma, Hay Fever, Foul Breath

All Diseases of the Throat,

Head Colds, Canker Sours

Bronchial Irritations

Not recommended for children under 6.
Affects all ages

300 million worldwide as of 2004

By 2025 → 400 million worldwide

Rate of asthma increasing with urbanization

1/250 deaths worldwide.

Expensive
Number & Rate of Asthma Deaths
US, 1980 to 2004
Pathophysiology

Inflammation

Airway Hyperresponsiveness  Clinical Symptoms  Airway Obstruction
Factors Limiting Airflow

Airway Effects
Bronchospasm
Acute Inflammation
Persistent Inflammation
Remodeling

Environmental factors

Th2/Th1 cytokines (e.g., IL-13, TNF-α)

Dendritic cell

B lymphocyte

T lymphocyte

IL-3, IL-4, IL-13, IL-9

GM-CSF

TNF-α

Mast cell

IgE

Neutrophil

Eosinophil

IL-3, IL-5

Pro-inflammatory mediators

Environmental factors and Inflammatory products

Initiation

Amplification

Propagation

Airway microenvironment

Mucus

(myo) fibroblasts

Smooth muscle

Blood vessels

Persistent inflammation and development of remodeling

Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF-α, tumor necrosis factor-alpha
### Classification of Asthma Severity

#### >12 years of age

<table>
<thead>
<tr>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<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>≤2x/month</td>
<td>3–4x/month</td>
<td>&gt;1x/week but not nightly</td>
<td>Often 7x/week</td>
</tr>
<tr>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily, and not more than 1x on any day</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
</tbody>
</table>

#### Components of Severity

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Intermittent</th>
<th>Mild</th>
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<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Lung function</td>
<td>• Normal FEV&lt;sub&gt;1&lt;/sub&gt; between exacerbations</td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt; &gt;80% predicted</td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt; &gt;60% but &lt;80% predicted</td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt; &lt;60% predicted</td>
</tr>
<tr>
<td></td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt;/FVC normal</td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt;/FVC reduced &lt;5%</td>
<td>• FEV&lt;sub&gt;1&lt;/sub&gt;/FVC reduced &gt;5%</td>
<td></td>
</tr>
</tbody>
</table>

#### Exacerbations requiring oral systemic corticosteroids

- 0–1/year (see note)
- ≥2/year (see note)

### Risk

Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.

### Recommended Step for Initiating Treatment

(See “Stepwise Approach for Managing Asthma” for treatment steps.)

- **Step 1:** In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.
- **Step 2:** and consider short course of oral systemic corticosteroids
- **Step 3:** and consider short course of oral systemic corticosteroids
- **Step 4 or 5:**

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Stepwise Approach for Managing Asthma
(Age ≥ 12 years)

**Intermittent Asthma**

**Persistent Asthma: Daily Medication**
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

**Step 1**
Preferred: SABA PRN

**Step 2**
Preferred: Low-dose ICS + LABA
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 3**
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline or Zileuton

**Step 4**
Preferred: High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

**Step 5**
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

**Step 6**
Assess Control
Step up if needed
First check adherence, environmental control, and comorbid conditions

Step down if possible and asthma is well controlled at least 3 months

Each step: Patient education, environmental control, and management of comorbidities.

**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief generally indicates inadequate control and the need to step up treatment.
Severe Persistent Asthma, Step 6

Severe

- throughout the day
- 7x/week
- several times per day
- extremely limited
- FEV1 <60% predicted
- FEV1/FVC reduced >5%

Step 6

Preferred:
High-dose ICS + LABA + oral corticosteroid

AND

Consider Omalizumab for patients who have allergies
Overview of basic treatment options

- Short acting beta agonists – rescue
- Inhaled corticosteroids – low, medium, high doses
- Cromolyn – alternative at Step 2
- Long acting beta agonists – add on therapy at Step 3
- Theophylline – alternative at Step 2-3
- Oral steroid – Steps 5-6

Currently Available Advanced Treatment Options:

- **Anti-Leukotriene Agents**
  - Montelukast (Singulair)
  - Zafirlukast (Accolate)
  - Zilueton (Zyflo)

- **Monoclonal Antibodies**
  - Omalizumab (Xolair)

- **Bronchial Thermoplasty**
Inflammatory mediators
Produced in leukocytes from arachidonic acid
Cysteinyl leukotrienes (cysLTs) contribute to asthma
Smooth muscle contraction
Bronchoconstriction
Vascular leakage, mucous secretion
Synthesized within minutes
Stimulate smooth muscle cell & fibroblast proliferation
Leukotriene Receptor Antagonists

Antagonize cysteinyl leukotrienes (cysLTs) at the cysLT1 receptor

Singulair
1x/ day
> 1 year old
Good choice for allergic asthmatics
Alternative in Step 2

Accolate
2x/ day
> 5 years old

Side Effects:
anaphylaxis, dizziness, dyspepsia, muscle weakness, elevated LFTs, suicidal thinking, behavior or mood changes
Zilueton (Zyflo)

- Direct leukotriene antagonist
- Inhibits 5-lipoxygenase, inhibiting formation of leukotrienes
- Good choice for nasal polyps
- For more severe airflow obstruction

- Monitor ALT
- Avoid alcohol
- Monitor theophylline levels – can increase

Side effects:
- headache, dyspepsia, myalgias, leukopenia, elevated LFTs, sleep disorders & behavior changes
Anti leukotriene vs Placebo

Graphs showing the percent change in FEV1 over weeks for Zileuton and Placebo, and Zafirlukast and Placebo. The graphs indicate a positive effect of active therapy compared to placebo for both Zileuton and Zafirlukast treatments.
Monoclonal Antibodies
Immunoglobulin E (IgE)

- Central to the pathogenesis of many allergic diseases
- Most asthmatics have increased circulating IgE
- Produced by Plasma Cells
- Defends against parasitic diseases
- Receptors on mast cell & basophils; binding leads to degranulation
Monoclonal Antibody Production

Immunization of mouse to stimulate antibody production

Antibody-forming cells isolated from spleen

Tumor cells are grown in tissue culture

Antibody-forming cells are fused with cultivated tumor cells to form hybridomas

Hybridomas screened for antibody production

Antibody-producing hybridomas cloned

Monoclonal antibodies isolated for cultivation
Recombinant humanized IgG1 monoclonal antibody

Binds IgE

Moderate to severe asthma
  • Step 5 or 6

IgE levels 30-700 IU prior to treatment

> 12 years old

Significantly reduces severe exacerbations

Anaphylaxis occurs in 1 per 1000 patients
Applies heat to airways during bronchoscopy
Reduces mass of smooth muscle
Many risks
Modest improvement
Long term effects unknown
Alair approved for adults with severe asthma... but safety and efficacy unknown for FEV1 < 50%
Looking Ahead

- Anti IL-5 treatment (pending FDA Approval)
- Anti IL-13
Pro-inflammatory cytokine

Also known as eosinophil differentiation factor (EDF)

Regulates eosinophil growth, maturation & activation

Plays an important role in diseases associated with increased levels of eosinophils (asthma, allergic rhinitis)

Secreted by Mast Cells/ T h2 Cells
Mepolizumab (Anti IL-5)

- Directed at immuno-inflammatory response
- Anti IL-5
- Decreases eosinophil recruitment
- May reduce exacerbations and decrease steroid use in severe asthma
- SIRIUS, MENSA and DREAM trials all show positive results
- FDA approval is pending

NEJM 2014.
Promotes:
- IgE production by B Cells
- Generation of eosinophil chemoattractants
- Contractility of airway smooth muscle cells
Anti IL-13 vs placebo
3 trials, ~200 patients each

Increased FEV1 at 12 weeks, no difference at 24 weeks

Additional trials have not been successful at improving outcomes with Anti IL-13

More work is needed
Exciting scientific discoveries have occurred recently in the field of allergic diseases including asthma.

It is necessary that general practitioners keep abreast of this knowledge to familiarize oneself with newer modalities of therapy that will be rapidly introduced within the near future.
Asthma is a chronic lung disease marked by variable symptoms, obstruction & bronchial hyperresponsiveness with inflammation.

It is classified based on severity & therapy is tailored to degree of symptoms.

Mainstays of therapy include inhaled glucocorticoids & beta agonists, however there are many alternative treatments available, and many exciting new treatment options to look forward to in the near future.
Questions? Thank you!