Recent Advances In Management Of Adult Asthma

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Definition of Asthma

• A Chronic inflammatory disorder of the airways

• Many cells and cellular elements play a role

• Chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing

• Widespread, variable, and often reversible airflow limitation
Asthma Inflammation: Cells and Mediators

1. Allergen
   - Macrophage/Dendritic cell
   - Mast cell
   - Neutrophil
   - Th2 cell
   - Eosinophil

2. Mucus plug
   - Mucus hypersecretion
   - Hyperplasia

3. Nerve activation
   - Epithelial shedding
   - Plasma leak
   - Edema
   - New vessels (angiogenesis)
   - Hypertrophy/hyperplasia
   - Subepithelial fibrosis
   - Sensory nerve activation
   - Cholinergic reflex

4. Airway smooth muscle

Source: Peter J. Barnes, MD
Pathophysiology of Asthma
Immunohistopathologic Features

- **Eosinophils**: Increased in airways of most persons with asthma
- **Lymphocytes**: May contribute to production of proinflammatory cytokines, increased eosinophils, and development of airway hyperresponsiveness
- **Mast-cell activation**: Leads to release of bronchoconstrictor mediators (e.g., histamine, cysteinyi leukotrienes, PGD$_2$)
- **Neutrophils**: Increased in airways and sputum of persons with severe asthma, in smokers, and during acute exacerbations
- **Epithelial cell injury**: May be exacerbated by the presence of an abnormal repair process

PG = prostaglandin.

Recurrent episodes of wheezing
Troublesome cough at night
Cough or wheeze after exercise
Cough, wheeze or chest tightness after exposure to airborne allergens or pollutants
Colds “go to the chest” or take more than 10 days to clear
Symptoms respond to anti-asthma treatment
Hx of eczema or hay fever or family history of atopic diseases
Symptoms worsen on seasonal pattern
Asthma Triggers

- **Allergens**
  - Dust mites, mold spores, animal dander, cockroaches, pollen, indoor and outdoor pollutants, irritants (smoke, perfumes, cleaning agents)
- **Pharmacologic agents (aspirin, beta-blockers)**
- **Physical triggers (exercise, cold air)**
- **Physiologic factors**
  - Stress, GORD, viral and bacterial URI, rhinitis
Differential diagnosis of BA

With out air flow obstruction

- Chronic cough syndromes
- Hyperventilation syndromes
- Vocal cord dysfunction
- Rhinitis
- GORD
- Heart failure
- Pulmonary fibrosis
With air flow obstruction

- COPD
- Bronchiectasis
- Inhaled foreign body
- Obliterative bronchiolitis
- Large air way stenosis
- Lung cancer
- Sarcoidosis
- Tuberculosis
Diagnostic Testing

- Peak expiratory flow (PEF)
  - Important in both diagnosis and monitoring
  - Patients can use at home
  - Ideally used to compare patients own previous measurement.
  - An improvement of $>60\text{l/min} (>20\% \text{ of pre bronchodilator PEF})$ after inhalation of bronchodilator, or diurnal variation of PEF $> 20\%$ suggest a diagnosis of asthma.
  - Effort and technique dependent
Spirometry

- Recommended to do spirometry pre- and post-use of bronchodilator to establish reversibility of airflow obstruction
- \( \geq 12\% \) reversibility or an increase in FEV1 of 200cc is considered significant
- Obstructive pattern: reduced FEV1/FVC ratio
- Restrictive pattern: reduced FVC with a normal FEV1/FVC ratio
Spirometry

- Can be used to identify reversible airway obstruction due to triggers
- Can diagnose Exercise-induced asthma (EIA) or Exercise-induced bronchospasm (EIB) by measuring FEV1/FVC before exercise and immediately following exercise, then for 5-10 minute intervals over the next 20-30 minutes looking for post-exercise bronchoconstriction
Spirometry

- National Asthma Education and Prevention Program (NAEPP) recommends spirometry:
  - For initial assessment
  - Evaluation of response to treatment
  - Assessment of airway function at least every 1-2 years
Methacholine challenge

- Most common bronchoprovocative test in US
- Patients breathe in increasing amounts of methacholine and perform spirometry after each dose
- Increased airway hyperresponsiveness is established with a 20% or more decrease in FEV1 from baseline at a concentration < 8mg/dl
- May miss some cases of exercise-induced asthma
Other Diagnostic Testing

- CXR – usually normal, exclude other causes
- Indirect challenge - inhaled mannitol, saline or exercise challenge
- Skin test with allergen or measurement of specific IgE in serum.
- Test of eosinophilic airway inflammation induced sputum differential eosinophil count, exhaled nitric oxide concentration (FENO)
Diagnostic trial of anti-inflammatory medication (preferably corticosteroids) or an inhaled bronchodilator

- Especially helpful in very young children unable to cooperate with other diagnostic testing
- There is no one single test or measure that can definitively be used to diagnose asthma in every patient
Asthma Phenotypes

The evolution from clinical to molecular approaches
Overview

- Asthma has been considered as a single disease for years,
- Recent studies have increasingly focused on its heterogeneity.
- The characterization of this heterogeneity has promoted the concept that asthma consists of multiple phenotypes or consistent groupings of characteristics.
- Asthma phenotypes were initially focused on combinations of clinical characteristics, but now evolving to involve pathobiology.
Factors Contributing to Variability of Asthma and Response to Treatment

Variability of Asthma

Genetic Factors
- Presence of specific HLA alleles
- Polymorphisms of FcεRI-β
- Polymorphisms of the interleukin-4 family of cytokine genes
- Polymorphisms of CD14
- Polymorphisms at other loci

Environmental Factors
- Allergen sensitization
- Having few siblings
- Excessive hygiene
- Receipt of antibiotics in the first 2 years of life
- Vaccination and prevention of disease

Defects in Target Organs
- Bronchial epithelium

Triggers
- Viral infections
- Exposure to allergens
- Occupational exposure
- Tobacco smoke
- Aspirin
- Indoor and outdoor pollutants

Variability of Treatment Response
- Genetics
- Race and ethnicity
- Obesity
- Smoking
- Comorbidities

Atopy and Asthma Hyperresponsiveness

HLA = human leukocyte antigen; FcεRI-β = receptor for immunoglobulin E (IgE).

1. Adapted with permission from Kay AB. N Engl J Med. 2001;344:30–37. Copyright © 2001 Massachusetts Medical Society. All rights reserved.
Phenotype

Observable properties of an organism that are produced by the interactions of the genotype and the environment

The definition of a true phenotype requires,

- a unifying and consistent natural history
- consistent clinical and physiological characteristics
- an underlying pathobiology with identifiable biomarkers
- genetics and a predictable response to general and specific therapies
Asthma phenotypes

- Early-onset allergic TH2 asthma
- Late-onset persistent eosinophilic asthma
- Exercise induced asthma
- Obesity related asthma
- Neutrophilic asthma
TH2 Asthma
Pathophysiology of an allergic reaction
Early-onset allergic TH2 asthma

- Most people with asthma are likely to have this phenotype
- Early-onset allergic asthma can present with mild to severe disease
- But it is unclear whether mild allergic asthma progresses to severe disease or whether severe allergic asthma arises in childhood and remains severe
- Both genetic and environmental factors are important in asthma pathogenesis
- Associated with AR, AD
- 40% get AD compare to later onset 4%
- Higher allergen specific IgE, Total IgE, Eosinophil
- Strong family history, genetic background
- Place of treatment – CST, Anti IgE.
- Monoclonal antibody to IL13, lebrikizumab, place for treatment
- Serum periostin, IgE, Blood Eosinophils, FeNO, biomarkers
Late-onset persistent eosinophilic asthma

- Eosinophilic asthma is characterized by the presence of eosinophils in higher numbers than normal as determined by sputum, bronchoscopic or blood analysis.
- A proportion of sputum eosinophils greater than 2% of all sputum inflammatory cells
- Can distinguish individuals with eosinophilic asthma from healthy individuals and those with noneosinophilic asthma, suggesting eosinophils as a target for therapeutic intervention.
- Mild to severe asthma suggest that it may be around 50%.

- In severe asthma, high numbers of eosinophils can persist despite treatment with inhaled and oral corticosteroids and appear to be consistent over at least 5 years.
• Persistent sputum eosinophilia (≥2%) despite corticosteroid therapy is associated with an adult-onset, less allergic form of asthma.
• Often associated with sinusitis, nasal polyps and sometimes AERD,
• But there is little to suggest that clinical allergic responses are occurring, despite positive allergen skin tests in ~75% of individuals.
• Related to IL 33, IL17.
A family history of asthma is also less commonly observed than in early-onset disease.

AERD associated adult onset, sinusitis, nasal polyps, life threatening, non Ig E mediated response to aspirin.

Genetics of this phenotype have not been specifically studied.

This phenotype is often severe from onset.
Treatment

- High dose systemic CST
- CST refractory
- Leucotrient antagonist treatment
- Antibody to IL5
Exercise induced asthma

- Symptoms are experienced primarily after exercise.
- Often have mild asthma and experience reactive bronchoconstriction (a decline in FEV1 of 10–15%) in response to sustained exercise, and this decline is more frequent and severe in cold, dry conditions.
- More common in atopic athletes and pathologically associated with high percentages of eosinophils in both sputum and tissue.
- EIA has also been associated with mast cells and their mediators, and these cells are consistently associated with TH2 processes.

- No distinct genetic factors or biomarkers for EIA have been described.
• Drugs that modify the **cysteinylic leukotrienes**

• **Monoclonal antibody blockade** of the mast cell–promoting cytokine IL-9

• **Bronchodilators**
Non TH2 Asthma
Obesity related asthma

- Obesity has been suggested to have a substantial role in the development, control and severity of asthma

- Controversial issue
  - ? Development of asthma
  - ? A cofounder
  - ? A comorbidity
- Misdiagnosis of asthma in obese
- Obesity is associated with
  - greater energy expenditure during breathing
  - Deconditioning
  - shortness of breath
  - greater likelihood for gastroesophageal reflux and associated coughing and chest tightness
Factors favouring obesity related asthma

- an association with a generalized proinflammatory state involving high expression of certain inflammatory mediators such as TNF-α, IL-6 and leptins

- weight loss was recently shown to enhance TH2 (and TH1 and TH17) cytokine production from peripheral blood lymphocytes
Biomarkers and treatment responses

- Adipokines have been proposed
  - No specific biomarkers
  - Define obesity-related asthma, perhaps because the role of obesity differs between TH2 and non-TH2 asthma.
Treatment responses

- Profound weight loss
- Improvements in symptoms, quality of life and bronchial hyperresponsiveness.
- In contrast, similar weight loss in obese individuals with allergic (TH2) asthma did not improve bronchial hyperresponsiveness, and the high TH2 cytokine production in these individuals suggests that weight loss may even worsen TH2 asthma

- Antioxidant
- Hormonal therapy
Neutrophilic Asthma

- Neutrophilia has been inconsistently associated with asthma.

- Data to support neutrophilic asthma as a specific phenotype remain modest, and no consensus exists as to what level of neutrophilia should define the phenotype.
Neutrophilia is generally seen in corticosteroid-treated patients.

Corticosteroids inhibit neutrophil apoptosis and, in some settings, contribute to neutrophil activation, suggesting that corticosteroid treatment itself is likely to have some role in the development of neutrophilia.
In affected individuals, lung neutrophilia has been associated with lower lung function, more trapping of air, thicker airway walls and greater expression of matrix metalloproteinases than are seen in people with non-neutrophilic asthma.

It has not been associated with airway hyperresponsiveness.
Treatment

- Responsive to macrolides
- CST refractory
Brittle asthma

- Brittle asthma sufferers are often chronic, severe and very difficult to treat as well as proving unresponsive to medicines and other treatments.

- Brittle asthmatics are also very susceptible to sudden and often unpredictable changes in their condition, and this is where the term 'brittle' is used.
Type 1 Brittle asthma

• suffer chronically every day with their asthma, even though they are on large amounts of medication and treatment and this often includes the use of daily steroids.
• life-threatening asthma attacks which come on suddenly and often with little or no warning.
• May need frequent admission to hospital when their condition is exacerbated.
Type 2 Brittle asthma

- Often appear to be reasonably well with their asthma well controlled.
- Type 2 sufferers can also have severe and often life threatening attacks that come on very suddenly with little or no advanced warnings and they too may require frequent hospital admission.
Cough variant asthma

- Cough-variant asthma is a type of asthma in which the main symptom is a dry, non-productive cough.

- People with cough-variant asthma, often have no other "classic" asthma symptoms, such as wheezing or shortness of breath.
Cough variant asthma

- Cough-variant asthma is somewhat difficult to diagnose because the cough may be the only symptom, and cough itself may appear to be bronchitis or cough associated with post nasal drip.
- However, people with cough-variant asthma often have normal physical examination, chest X-rays, and spirometry.
- Cough-variant asthma is treated in the same way that typical asthma is treated.
# Asthma phenotypes

<table>
<thead>
<tr>
<th>Natural history</th>
<th>Clinical and physiological features</th>
<th>Pathobiology and biomarkers</th>
<th>Genetics</th>
<th>Response to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset allergic</td>
<td>Early onset; mild to severe</td>
<td>Allergic symptoms and other diseases</td>
<td>Specific IgE; T(_H)2 cytokines; thick SBM</td>
<td>17q12; T(_H)2-related genes</td>
</tr>
<tr>
<td>Late-onset eosinophilic</td>
<td>Adult onset; often severe</td>
<td>Sinusitis; less allergic</td>
<td>Corticosteroid-refractory eosinophilia; IL-5</td>
<td></td>
</tr>
<tr>
<td>Exercise-induced</td>
<td>Mild; intermittent with exercise</td>
<td></td>
<td>Mast-cell activation; T(_H)2 cytokines; cysteinyl leukotrienes</td>
<td></td>
</tr>
<tr>
<td>Obesity-related</td>
<td>Adult onset</td>
<td>Women are primarily affected; very symptomatic; airway hyperresponsiveness less clear</td>
<td>Lack of T(_H)2 biomarkers; oxidative stress</td>
<td></td>
</tr>
<tr>
<td>Neutrophilic</td>
<td></td>
<td>Low FEV1; more air trapping</td>
<td>Sputum neutrophilia; T(_H)17 pathways; IL-8</td>
<td></td>
</tr>
</tbody>
</table>
Goals of Asthma Treatment

- Control chronic and nocturnal symptoms
- Maintain normal activity, including exercise
- Prevent acute episodes of asthma
- Minimize ER visits and hospitalizations
- Minimize need for reliever medications
- Maintain near-normal pulmonary function
- Avoid adverse effects of asthma medications
Four component of asthma care

- Component 1: develop patient /doctor partnership
- Component 2: identify and reduce exposure to risk factors
- Component 3: assess, treat, and monitor asthma
- Component 4: manage asthma exacerbations
Current therapy for Asthma

Current therapy for asthma

**Relievers (bronchodilators)**
- β₂-agonists
- Theophylline
- Anticholinergics

**Controllers (anti-inflammatory treatments)**
- Corticosteroids
- Anti-leukotrienes
- Cromones
- Theophylline
- Anti-immunoglobulin E
- Methotrexate
- Gold
- Ciclosporin A
- Roflumilast
Short-acting inhaled $\beta_2$-agonists

- e.g. salbutamol, terbutaline, Albuterol
- Duration of action - 3 to 4 hours (less in severe asthma).
- When inhaled from pMDIs in standard doses, they are convenient, easy to use, rapid in onset of action and without significant adverse effects.
- They also protect against the effects of bronchoconstrictor stimuli such as exercise, cold air and allergen.
- Bronchodilators of choice in acute severe asthma, in the treatment of which the nebulized route of administration is as effective as intravenous use.
• **Albuterol**
  
  o **Short-acting beta2-agonist**
    - ATP to cAMP leads to relaxation of bronchial smooth muscle, inhibition of release of mediators of immediate hypersensitivity from cells, especially mast cells
  
  o **Should be used prn not on a regular schedule**
    - Prior to exercise or known exposure to triggers
    - Up to every 4 hours during acute exacerbation as part of a written action plan
Long-acting beta2-agonists (LABA)

- Beta2-receptors are the predominant receptors in bronchial smooth muscle
- Stimulate ATP-cAMP which leads to relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity
- Inhibits release of mast cell mediators such as histamine, leukotrienes, and prostaglandin-D2
- Salmeterol (Serevent)
- Salmeterol with formeterol
- Should only be used as an additional treatment when patients are not adequately controlled with inhaled corticosteroids
- Should not be used as rescue medication
- Can be used age 4 and above with a DPI
Corticosteroids

- Anti-inflammatory (but precise MOA not known)
- Act locally in lungs
  - Some systemic absorption
  - Risks of possible growth retardation thought to be outweighed by benefits of controlling asthma
- Not intended to be used as rescue medication
- Benefits may not be fully realized for 1-2 weeks
- Preferred treatment in persistent asthma
Effects of corticosteroids on inflammatory and structural cells in the airways

**Inflammatory cells**
- Eosinophil: ↓ Numbers (apoptosis)
- T lymphocyte: ↓ Cytokines
- Mast cell: ↓ Numbers
- Macrophage: ↓ Cytokines
- Dendritic cell: ↓ Numbers

**Structural cells**
- Epithelial cell: ↓ Cytokines, ↓ Mediators
- Endothelial cell: ↓ Leak
- Airway smooth muscle: ↑ $\beta_2$-receptors
- Mucus gland: ↓ Mucus secretion

**Glucocorticosteroids**
Flat Dose Response of ICS

Response vs. Dose

Favorable Benefit-Risk Ratio

Wanted Effects

Unwanted Effects

1600mcg budesonide
## Estimate Comparative Daily Dosages for inhaled Glucocorticosteroids by Age

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose (µg)</th>
<th>Medium Daily Dose (µg)</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>200-500</td>
<td>100-200</td>
<td>&gt;500-1000</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;200-400</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Budesonide</td>
<td>200-600</td>
<td>100-200</td>
<td>600-1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;200-400</td>
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<td></td>
<td></td>
<td></td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Budesonide-Neb Inhalation Suspension</td>
<td>250-500</td>
<td></td>
<td>500-1000</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>80 – 160</td>
<td>80-160</td>
<td>&gt;160-320</td>
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<td></td>
<td></td>
<td></td>
<td>&gt;160-320</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;320-1280</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500-1000</td>
<td>500-750</td>
<td>&gt;1000-2000</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;750-1250</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;2000</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>100-250</td>
<td>100-200</td>
<td>&gt;250-500</td>
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<td></td>
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<td></td>
<td>&gt;200-500</td>
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<td></td>
<td></td>
<td></td>
<td>&gt;500</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>200-400</td>
<td>100-200</td>
<td>&gt; 400-800</td>
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<td></td>
<td></td>
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<td>&gt;200-400</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;800-1200</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400-1000</td>
<td>400-800</td>
<td>&gt;1000-2000</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;800-1200</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;2000</td>
</tr>
</tbody>
</table>
Mast cell stabilizers (cromolyn/nedocromil)

- Inhibits release of mediators from mast cells (degranulation) after exposure to specific antigens
- Blocks Ca2+ ions from entering the mast cell
- Safe for pediatrics (including infants)
- Should be started 2-4 weeks before allergy season when symptoms are expected to be effective
- Can be used before exercise (not as good as ICS)
- Alternate medication for persistent asthma
Leukotriene receptor antagonists

- Leukotriene-mediated effects include:
  - Airway edema
  - Smooth muscle contraction
  - Altered cellular activity associated with the inflammatory process
- Receptors have been found in airway smooth muscle cells and macrophages and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells) and nasal mucosa
Leukotriene receptor antagonists

- No good long-term studies in pediatrics
- Montelukast as young as 2; zarfirlukast age 7
- Alternate, but not preferred medication in persistent asthma and as addition to ICS
- Showed a statistically significant, but modest improvement when used as primary medication
**Cys-LT1 receptor antagonists**-Montelukast, zafirlukast

- Reduce allergen, exercise and cold air-induced asthma by about 50-70%
- Inhibit aspirin-induced responses in aspirin-sensitive asthmatics almost completely.

**5-lipoxygenase inhibitors**

- Only clinically available drug-zileuton.
- Efficacy is similar to that of receptor antagonists.
- Anti-leukotrienes have also been shown to have weak anti-inflammatory effects and may reduce eosinophilic inflammation, which may be provoked by Cys-LTs.
Effects of cysteinyl-leukotrienes on the airways and their inhibition by anti-leukotrienes

1. Allergens lead to the activation of inflammatory cells.
2. Exercise can also cause the release of leukotriene B4.
3. 5-lipoxygenase is involved in the production of leukotriene B4.
4. Platelet-activating factor is another trigger for leukotriene production.
5. Aspirin is effective in inhibiting leukotriene production in aspirin-sensitive asthmatics.
6. Leukotriene antagonists can block the action of cysteinyl-leukotrienes.
7. Eosinophil recruitment and mucus secretion are downstream effects of cysteinyl-leukotrienes.
8. Bronchoconstriction is also a consequence of these mediators.
# Anti-leukotrienes

<table>
<thead>
<tr>
<th>Name</th>
<th>Usual doses</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antileukotrienes. Monteleukast (M) Pranlucast (P) Zafirlucast (Z) Zileuton (Zi)</td>
<td>Adults- M 10mg qhs P 450 bid Z 20mg bid Zi 600mg qid Children M- 5mg qhs (6-14Y) 4mg qhs (2-5Y) Z -10mg bid (7-11Y)</td>
<td>No specific side effects to date due to recommended doses. Elevated liver enzymes with Zafirlukast and Zileuton and limited case reports of reversible hepatitis and hyperbilirubinemia with zileuton and liver failure with Zafirlukast.</td>
<td>Most effective for patients with mild persistent asthma. They provide additive benefit when added to ICS though not as effective as inhaled long acting $\beta_2$ agonists.</td>
</tr>
</tbody>
</table>
Theophylline

- Narrow therapeutic index/Maintain 5-20 mcg/mL
- Variability in clearance leads to a range of doses that vary 4-fold in order to reach a therapeutic dose
- Mechanism of action
  - Smooth muscle relaxation (bronchodilation)
  - Suppression of the response of the airways to stimuli
  - Increase force of contraction of diaphragmatic muscles
- Interacts with many other drugs
Theophylline has effects on several other cells in addition to airway smooth muscle; some of these effects are mediated via inhibition of phosphodiesterases.
Anticholinergics

- Atropine is a naturally occurring compound that was introduced for the treatment of asthma but, because of adverse effects (particularly drying of secretions), less soluble quaternary compounds (e.g. ipratropium bromide) were developed.

Mode of action

- Specific antagonists of muscarinic receptors - inhibit cholinergic nerve-induced bronchoconstriction.
- A small degree of resting bronchomotor tone is present because of tonic cholinergic nerve impulses, which release acetylcholine in the vicinity of airway smooth muscle.
- Cholinergic reflex bronchoconstriction may be initiated by irritants, cold air and stress.
Anticholinergics

- Although anticholinergics protect against acute challenge by sulphur dioxide and emotional factors, they are less effective against antigen, exercise and fog.
- Inhibit reflex cholinergic bronchoconstriction only.
- No significant blocking effect on the direct effects of inflammatory mediators such as histamine and leukotrienes.
- In COPD, cholinergic tone is the only reversible element of airway narrowing.
Effects of anticholinergic drugs

Normal

Vagus nerve

Acetylcholine

Vagal ‘tone’

COPD

Anticholinergic

\[ R \propto \frac{1}{r^4} \]

Anticholinergic drugs inhibit vagally mediated airway tone, leading to bronchodilatation. This effect is small in normal airways, but greater in the airways of patients with chronic obstructive pulmonary disease, which are structurally narrowed.
Anticholinergics

Clinical use.

- Ipratropium bromide, oxitropium bromide-administered 3 or 4 times daily via inhalation.
- Tiotropium bromide-inhaled once daily.
- In asthmatics, anticholinergic drugs are less effective than $\beta_2$-agonists-offer less protection against various bronchial challenges.
- Nebulized anticholinergics-effective in acute severe asthma, but less effective than $\beta_2$-agonists.
- Anticholinergic drugs may have an additive effect with $\beta_2$-agonists in acute and chronic treatment and should therefore be considered when control of asthma is inadequate, particularly when theophylline or inhaled $\beta_2$ agonists have caused adverse effects.
Recent studies have demonstrated that tiotropium is an effective add-on bronchodilator in patients with severe asthma.

bronchodilators of choice in COPD.

once-daily tiotropium bromide is the most effective bronchodilator for COPD

useful additive effects with long-acting $\beta_2$-agonists.
Bronchial Thermoplasty

Theory

- Resistance to airflow in the airways is additive.
- Major source of resistance to airflow in the normal bronchial tree is in the “conducting” airways down to about the fourth generation.
  - 4th generation airway diameter is approximately 4 mm.

Remember: BT targets airways 3 to 10 mm in diameter.
Easier Breathing
People with chronic asthma often develop a thickening of the smooth muscle lining the airways. Now, a procedure called bronchial thermoplasty can reduce the size of the smooth muscle, allowing many patients to cut back on medication and lead more active lives.

The Problem
Smooth muscle

NORMAL AIRWAY

ASTHMATIC AIRWAY

ASTHMATIC AIRWAY DURING AN ASTHMA ATTACK Smooth muscle (contracted)

The Procedure
A bronchoscope with a thermoplasty device inside is inserted into the patient’s mouth or nose as far as possible down each airway. Electrodes on the tip are then heated with radiofrequency energy, shrinking the muscle and creating a larger opening in the airway.

Bronchoscope

Source: Asthmatx Inc.
In April 2010, the FDA approved the Alair Bronchial Thermoplasty System from Asthmatx, Inc.

- A catheter-electrode system that provides radiofrequency thermal energy to ASM
Catheter-electrode system is inserted in side port of bronchoscope

Radiofrequency thermal energy applied to airways 3–10 mm in diameter
  - Systematic and distal to proximal direction

At end, airway inspection and recovery for 2 – 4 hrs

Total procedure time: <1 hr

Bronchial Thermoplasty

- BT targets intraparenchymal airways distal to the mainstem bronchi down to airways 3 mm in diameter
Bronchial Thermoplasty

BT is performed in 3 separate treatment sessions each scheduled approximately 3 weeks apart.
Contraindications to Bronchial Thermoplasty

- Patients that have a pacemaker, internal defibrillator, or other implantable electronic device
- A known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines
- Patients that have previously been treated with the Alair® System
Selective inhibitors of phosphodiesterase 4

- A promising class of novel anti-inflammatory treatments for asthma are the selective inhibitors of phosphodiesterase 4 (PDE$_4$). PDE4 is expressed in macrophages, neutrophils, T cells and airway smooth muscle cells.
- cilomilast and roflumilast
- There are controlled clinical trials suggesting some efficacy of roflumilast in mild to moderate asthma and to prevent exercise-induced asthma in adults.
Roflumilast

- A once-daily oral phosphodiesterase (PDE)-4 inhibitor.
- Has anti-inflammatory effects in COPD patients.
- Its dose is limited by adverse effects (nausea, vomiting, diarrhoea, headaches) - so its clinical efficacy is relatively small.
- Weight loss may also occur but this is non-progressive and reversible.

**Indications.**

In COPD patients with,

1. severe disease (forced expiratory volume in 1 second (FEV1) < 50% predicted).
2. Chronic bronchitis.
3. Frequent exacerbations.
Roflumilast

- There is a small improvement in lung function and a reduced incidence of severe exacerbations.
- It is therefore used as an add-on therapy in a subpopulation of patients with COPD.
- Should never be co administered with theophylline, which also has PDE4- inhibitory effects.
Numerous antibodies, receptor blocking mutant chemokines and small molecules are now being evaluated for the treatment of asthma.

Chemokines have proven to be amenable drug targets for the development of low molecular weight antagonists.

- CCR3,4 antagonists
- CR8 antagonists
- CRTH2 antagonists
New inhaled long-acting bronchodilators and corticosteroids

- Inhaled ultra long-acting $\beta_2$-agonists (ultra-LABAs) such as **Indacaterol**, currently licensed for COPD, have a longer half-life than current LABAs and are suitable for once daily administration.

- Fixed combinations of ultra-LABAs with once daily inhaled corticosteroids as well as once daily inhaled corticosteroids alone are at an advanced stage of development for the treatment of asthma.

- Once daily administration should be more convenient for patients and may improve adherence.

- New inhaled long-acting antimuscarinic agents (LAMAs) agents such as **Aclidinium**, may also have a role in the treatment of severe asthma associated with persistent airflow obstruction.
severe asthma with fungal sensitization (SAFS)

- The oral anti-fungal drug itraconazole administered for 32 weeks resulted in improvement in AQLQ scores.
- However the risk of adrenal suppression with long-term treatment with itraconazole in patients also receiving inhaled corticosteroids has led to some caution in adopting this management strategy.
The first and as yet only biological agent licensed for the treatment of asthma is omalizumab.

**Mode of action**

- A humanized recombinant monoclonal antibody binds to circulating IgE.
- Blocks high-affinity IgE receptors on mast cells.
- Low-affinity IgE receptor on other inflammatory cells.
- This results in reduced responses to allergens.
- Over time the blocking of IgE reduces its synthesis from B cells and results in a sustained reduction in IgE.
IgE play a central role in allergic diseases and blocking IgE using an monoclonal antibody omalizumab is beneficial in some patients with severe asthma. IgE may activate high affinity receptors (FcεRI) on mast cells as well as low affinity receptors (FcεRII, CD23) on other inflammatory cells so that anti-IgE therapy inhibits mast cell mediated effects as well as reducing chronic inflammation.

IL, interleukin; cys-LT, cysteinyl-leukotriene; PG, prostaglandin.
**Anti-IgE therapy- Omalizumab**

**Clinical use**

1. Reduces airway inflammation in patients with mild to moderate asthma.
2. Reduces the incidence of asthma exacerbations.
3. Improves control in patients maintained on reduced doses of inhaled corticosteroids.

- Omalizumab is most useful in patients with **severe asthma** who are not controlled by maximal doses of inhaled therapy.
- Only about 30% of patients show a good response and this is not predictable by any clinical features, so a trial of therapy over 4 months is indicated.
- Should be given only to patients with serum IgE concentrations of 20-700 IU/ml.
- It is not possible to give enough antibody to neutralize higher IgE concentrations.
- The dose of omalizumab is determined by the serum IgE level
- Once or twice a month.
- Because of its high cost only patients at steps 4 (severe) and 5 (very severe) of the BTS guidelines who have frequent exacerbations are suitable for this therapy.

**Adverse effects**
- Occasionally local reactions occur at the injection sites.
- Very rarely anaphylactoid reactions.
### Anti-IgE therapy- Omalizumab

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>Adults- dose administered SC every 2-4 weeks depend on weight and IgE level.</td>
<td>Pain and bruising at injection site (5-20%) Very rarely anaphylaxis (0.1%)</td>
<td>Need to be stored in refrigeration (2-8°C) and maximum of 150mg administered at one injection site.</td>
</tr>
</tbody>
</table>
5-Lipoxygenase Inhibitor

- **Mechanisms**: Inhibits the production of leukotrienes from arachidonic acid, both LTB4 and the cysteinyl Leukotrienes. Zileuton tablets

- **Indications**
  - □ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age.
  - □ May be used with ICS as combination therapy in moderate persistent asthma in patients ≥12 years of age.

Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia. □ Zileuton is microsomal P450
Allergy shots /Immunotherapy

- It is a way of modulating the patient’s immune response.
- Allergen immunotherapy is the administration of gradually increasing quantities of an allergen vaccine to an allergic subject, reaching a dose which is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen.
Figure 1 Potential targets for selected novel therapies for treatment resistant asthma. The figure summarizes targets for a selection of therapies that are recently licensed or under clinical development for patients with severe treatment resistant asthma. Abbreviations: CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; FLAP, lipooxygenase-activating protein; IL-, interleukin-; PPAR, proliferator-activated receptor; PDE, phosphodiesterase; PGD₂, prostaglandin D₂.
Various severities of asthma

- Step-wise pharmacotherapy treatment program for varying severities of asthma
  - Mild Intermittent (Step 1)
  - Mild Persistent (Step 2)
  - Moderate Persistent (Step 3)
  - Severe Persistent (Step 4)
- Patient fits into the highest category that they meet one of the criteria for
## CLASSIFYING ASTHMA SEVERITY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Classifying severity for patients who are not currently taking long-term control medications.

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (Youths ≥12 years of age and adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</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>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal FEV₁, between exacerbations</td>
</tr>
<tr>
<td></td>
<td>FEV₁/FVC normal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>Exacerbations requiring oral systemic corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–1/year (see note)</td>
</tr>
</tbody>
</table>

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

Relative annual risk of exacerbations may be related to FEV₁.

- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
**TREATMENT STEPS**

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
<th>STEP 4</th>
<th>STEP 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>CONTROLLER OPTIONS</strong></td>
<td><strong>SELECT ONE</strong></td>
<td><strong>SELECT ONE</strong></td>
<td><strong>TO STEP 3 TREATMENT, SELECT ONE OR MORE:</strong></td>
<td><strong>TO STEP 4 TREATMENT, ADD EITHER</strong></td>
</tr>
<tr>
<td>asthma education</td>
<td>as needed rapid-acting $\beta_2$-agonist</td>
<td>as needed rapid-acting $\beta_2$-agonist</td>
<td>medium- or high-dose ICS plus long-acting $\beta_2$-agonist</td>
<td>oral glucocorticosteroid (lowest dose)</td>
</tr>
<tr>
<td>environmental control</td>
<td></td>
<td></td>
<td>leukotriene modifier</td>
<td>anti-IgE treatment</td>
</tr>
<tr>
<td>as needed rapid-acting $\beta_2$-agonist</td>
<td>low-dose ICS</td>
<td>low-dose ICS plus long-acting $\beta_2$-agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>leukotriene modifier**</td>
<td>medium- or high-dose ICS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>low-dose ICS plus leukotriene modifier</td>
<td>sustained-release theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>low-dose ICS plus sustained-release theophylline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*inhaled glucocorticosteroids
**receptor antagonist or synthesis inhibitors

Shaded green - preferred controller options
# Levels of Asthma Control

**(Assess patient impairment)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (All of the following)</th>
<th>Partly controlled (Any present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>Twice or less per week</td>
<td>More than twice per week</td>
<td></td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms / awakening</td>
<td>None</td>
<td>Any</td>
<td>3 or more features of partly controlled asthma present in any week</td>
</tr>
<tr>
<td>Need for rescue / “reliever” treatment</td>
<td>Twice or less per week</td>
<td>More than twice per week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV₁)</td>
<td>Normal</td>
<td>&lt; 80% predicted or personal best (if known) on any day</td>
<td></td>
</tr>
</tbody>
</table>

Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side effects)
LEVEL OF CONTROL

- controlled
- partly controlled
- uncontrolled
- exacerbation

TREATMENT OF ACTION

- maintain and find lowest controlling step
- consider stepping up to gain control
- step up until controlled
- treat as exacerbation

TREATMENT STEPS

- STEP 1
- STEP 2
- STEP 3
- STEP 4
- STEP 5
Reasons for Failure to Achieve Asthma Control

- Problems with patient adherence to treatment plan
- Problems with patient technique in using medications
- Coexisting conditions (e.g., sinusitis, allergen or irritant exposure, gastroesophageal reflux)
- Psychosocial or family barriers
- Need for temporary increase in anti-inflammatory medication (e.g., short course of a corticosteroid)
Diagnostic challenges

- Cough variant asthma – LFT, airway hyperresponsiveness test are needed.
- Exercise induced bronchoconstriction – exercise with 8 min running protocol.
- Children < 5 years
- Asthma in elderly
- Occupational asthma
ASTHMA CONTROL TEST
Monitoring Control in Clinical Practice: Asthma Control Test™ for Patients Aged ≥12 Years¹

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?</td>
<td>All of the time  Most of the time  Some of the time  A little of the time  None of the time</td>
</tr>
<tr>
<td>2. During the past 4 weeks, how often have you had shortness of breath?</td>
<td>More than once a day  Once a day  3 to 6 times a week  Once or twice a week  Not at all</td>
</tr>
<tr>
<td>3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?</td>
<td>4 or more nights a week  2 or 3 nights a week  Once a week  Once or twice  Not at all</td>
</tr>
<tr>
<td>4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?</td>
<td>3 or more times per day  1 or 2 times per day  2 or 3 times per week  Once a week or less  Not at all</td>
</tr>
<tr>
<td>5. How would you rate your asthma control during the past 4 weeks?</td>
<td>Not controlled at all  Poorly controlled  Somewhat controlled  Well controlled  Completely controlled</td>
</tr>
</tbody>
</table>

Level of Control Based on Composite Score²

- ≥20 = Controlled
- 16-19 = Not Well Controlled
- ≤15 = Very Poorly Controlled

Regardless of patient’s self assessment of control in Question 5

1. Asthma Control Test™ copyright, QualityMetric Incorporated 2002, 2004. All rights reserved.
Asthma Action Plan

- Developed with the physician
- Tailor to meet individual needs
- Educate patients and families about all aspects of plan
  - Recognizing symptoms
  - Medication benefits and side effects
  - Proper use of inhalers and Peak Expiratory Flow (PEF) meters
Sample Asthma Action Plan

Describes medicines to use and actions to take

<table>
<thead>
<tr>
<th>Medicine Type</th>
<th>How Much To Take</th>
<th>How Often</th>
<th>Other Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-Term Control Meds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quick-Relief Meds</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Special instructions when I feel:

- **Good**: 
  - Prevent asthma symptoms everyday.
  - Take my long-term control medicines (above) every day.
  - Before exercise, take _______ puffs of...
  - Avoid things that make my asthma worse like...

- **Not Good, but still feeling fine**: 
  - Prevent asthma symptoms everyday.
  - If my peak flow is not back in the Green Zone within 1 hour, then I should...
  - Take _______ puffs of...
  - Increase...
  - Add...
  - Call...

- **Awful**: 
  - Medical Alert! Get help!
  - Take ___ until I get help immediately...
  - Call 9-1-1 if you have trouble breathing or talking due to shortness of breath or lips or fingers are gray or blue.

---

THANK YOU