Asthma in the college health setting: diagnosis, treatment, pitfalls
• A 20-year-old college student with a history of asthma and allergic rhinitis, which were diagnosed in childhood, presents with cough and tightness of the chest that interfere with his sleep three or four times per month.

• He requires albuterol two or three times per week.

• He enjoys playing tennis but generally wheezes after a match.

• Last year, during the pollen season, he sought treatment in an emergency department for acute asthma but was not admitted to the hospital.

• His forced expiratory volume in 1 second (FEV₁) is 93% of the predicted value.

• How should this case be evaluated and managed?
Asthma is a chronic inflammatory disease consisting of reversible airflow obstruction and bronchospasm with wheezing and coughing.

Taught widely in North America to be entirely reversible 30 years ago, it is now recognized that chronic uncontrolled asthma can lead to permanent airway remodeling and long term lung damage.
• Uncertain if treatment prevents the hypothetical remodeling process

• Genetic and environmental factors play a role; but the inheritance is complex (ethnicity noted for natives of PR)
• Asthma prevalence varies widely: 27% in Australia, 2% in Vietnam. Specific ethnic groups are notable for particular sensitivities, such as chitin (cockroach) sensitivity in many people from Puerto Rico.
• Allergens and viruses (especially human rhinovirus) can trigger asthma; in children, it is associated with variants of the 17q21 locus (nejm 2013;368:398-1407)
Differential diagnosis: dyspnea, cough. Nocturnal symptoms—minutes, exercise, hours. Response to medications. Age, smoking history. Rhinitis, allergies, allergic shiners, reflux, stridor, eczema?
Diagnosis:

- Symptoms of dyspnea, cough, wheeze and confirmation of reversible (partly or fully) airflow limitation, ?eczema
  - Exclude: wheeze from reflux, sarcoid, cardiac disease, foreign body, early Hodgkins/mass lesions
  - Exclude: dyspnea from anxiety, hyperventilation, rhinitis
    - Caffeine consumption. Sleep deprivation
  - Exclude: stridor – very characteristic
  - Cystic fibrosis, allergic bronchopulmonary aspergillosis–
  - Bronchiectasis – childhood TB as cause if foreign student. Can diagnose on CT chest (noncontrast)
Criteria for Diagnosis

• Descriptions by patient of episodic wheeze, cough, and dyspnea, with or without specific causes (airborne irritants, allergens, or exercise)

• Reversible airflow
  • Increase in FEV1 of >12% from baseline
  • Increase in predicted FEV1 from baseline of >10%
  • Increase in PEF of >20% from baseline
  • Diurnal variation in PEF of more than 10%, measured twice daily
Define asthma: National Asthma Education and Prevention Program

- **Intermittent:** symptoms fewer than 2 days a week, no affect on normal activities
  - Nocturnal symptoms less than 2 days a month
  - Spirometry normal when patient has no symptoms

- **Mild Persistent:** More than 2 days a week and interfere with daily activities
  - Nocturnal symptoms 3-4 times a month
  - Spirometry normal when patient has no symptoms but may show variation morning to evening
Define asthma: National Asthma Education and Prevention Program

• **Moderate Persistent Asthma**: daily symptoms; asthma medication used daily.
  • Symptoms interfere with daily activities
  • Nocturnal symptoms more than once per week.
  • Spirometry is 60% to 80% of predicted; PEF 30% variation

• **Severe Persistent Asthma**: daily symptoms
  • Symptoms severely limit daily activity
  • Nocturnal symptoms often or nightly
  • Spirometry is 60% or less of expected, PEF 30% variation
**Asthma Control Test™**

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?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. During the *past 4 weeks*, how often have you had shortness of breath?

<table>
<thead>
<tr>
<th>More than Once a day</th>
<th>Once a day</th>
<th>3 to 6 times a week</th>
<th>Once or twice a week</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>4 or more nights a week</th>
<th>2 to 3 nights a week</th>
<th>Once a week</th>
<th>Once or twice</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

4. During the *past 4 weeks*, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

<table>
<thead>
<tr>
<th>3 or more times per day</th>
<th>1 or 2 times per day</th>
<th>2 or 3 times per week</th>
<th>Once a week or less</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Clinical assessment: know your patient

- New York State is a heterogeneous environment
- Born and raised on a farm = decreased risk of allergy and asthma
- Obesity, smoking have higher risks
  - Is reflux a cause of asthma in obesity? = PPI had no effect on individuals with poor control of asthma who had reflux (NEJM 360:1487)

Socio-economic status
Clinical assessment: know your patient

• The urban environment: fumes smells, viruses.
  • House mites, danders, chitin from roaches/insects
  • Inner-City Anti-IGE therapy for Asthma (ICATA) study looked at 419 inner city children and young adults age 6 to 20 years. Defined uncontrolled disease as hospitalization or unscheduled urgent are 6 to 12 months before study; needed IGE levels between 30 and 1300u/cc
### Table 2. Adjusted Treatment Effect on Asthma Symptoms and Health Care Use during 48 Weeks of Follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 211)</th>
<th>Omalizumab (N = 208)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma-related symptoms — no. of days in 2 wk preceding visit</td>
<td>1.96±0.10</td>
<td>1.48±0.10</td>
<td>-0.48 (-0.77 to -0.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wheezing</td>
<td>1.76±0.09</td>
<td>1.32±0.09</td>
<td>-0.44 (-0.70 to -0.17)</td>
<td>0.001</td>
</tr>
<tr>
<td>Interference with activity</td>
<td>0.58±0.07</td>
<td>0.70±0.07</td>
<td>-0.28 (-0.47 to -0.09)</td>
<td>0.003</td>
</tr>
<tr>
<td>Nighttime sleep disruption</td>
<td>0.59±0.05</td>
<td>0.42±0.05</td>
<td>-0.17 (-0.31 to -0.03)</td>
<td>0.02</td>
</tr>
<tr>
<td>Missed school — no. of days savory</td>
<td>0.25±0.03</td>
<td>0.16±0.03</td>
<td>-0.09 (-0.18 to -0.01)</td>
<td>0.018</td>
</tr>
<tr>
<td>Asthma control†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-ACT score in previous month, age 4 to 11 yr</td>
<td>22.2±0.21</td>
<td>23.0±0.21</td>
<td>0.78 (0.21 to 1.35)</td>
<td>0.007</td>
</tr>
<tr>
<td>ACT score in previous month, age 12 yr or older</td>
<td>22.3±0.22</td>
<td>22.5±0.22</td>
<td>0.19 (-0.42 to 0.79)</td>
<td>0.54</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ — % of predicted value</td>
<td>91.7±0.64</td>
<td>92.6±0.60</td>
<td>0.92 (-0.81 to 2.64)</td>
<td>0.30</td>
</tr>
<tr>
<td>FEV₁/FVC x100</td>
<td>77.3±0.38</td>
<td>77.3±0.36</td>
<td>-0.13 (-1.16 to 0.91)</td>
<td>0.81</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence — %</td>
<td>88.6±1.80</td>
<td>84.6±1.78</td>
<td>-3.96 (-8.95 to 1.02)</td>
<td>0.12</td>
</tr>
<tr>
<td>Step level equal to 1 or 2 — %</td>
<td>26.7±3.3</td>
<td>43.6±4.0</td>
<td>-16.9 (6.6 to 27.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Step level equal to 4 to 6 — %</td>
<td>50.8±4.0</td>
<td>31.2±2.3</td>
<td>-19.6 (-30.1 to -9.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inhaled glucocorticoids prescribed — mg/day++</td>
<td>77.1±23.5</td>
<td>66.3±23.3</td>
<td>-10.9 (-77.2 to -45.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long-acting β₂ agonists prescribed — %</td>
<td>65.5±2.47</td>
<td>55.4±2.44</td>
<td>-10.1 (-36.8 to -3.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Asthma-related health care use — %††</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>6.3±1.8</td>
<td>1.5±0.9</td>
<td>-4.7 (-8.6 to -0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Exacerbation‡‡</td>
<td>48.8±3.7</td>
<td>30.3±3.3</td>
<td>-18.5 (-28.2 to -8.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

---

* Plus–minus values are means ±SE, adjusted for study site, visit, season, dosing, and baseline levels, unless noted otherwise. FEV₁ denotes forced expiratory volume in one second, and FVC forced vital capacity.
† Unrounded values were used to determine the difference between groups.
‡ The number of days with symptoms was calculated as the largest of the following variables during the previous 2 weeks: number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2-week period.
§ The number of school days missed was available for 329 of the 419 study participants.
†† Scores on the Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT) were measured on scales of 0 to 27 and 0 to 25, respectively. A score of 19 or less on either test indicates that asthma is not well controlled. The minimally important difference for ACT equals 3 points; that for Childhood ACT is not defined.
†‡ Six treatment steps were established, consistent with report 3 of the National Asthma Education and Prevention Program guidelines to standardize prescribing patterns according to levels of asthma severity; these steps are provided in full in the Supplementary Appendix and are summarized here. Steps 1 and 2 apply to mild asthma, step 3 to moderate asthma, and steps 4 through 6 to severe asthma. At step 0, the recommendation is for no asthma-control medication or albuterol as needed: at step 1, budesonide — 180 µg once a day; at step 2, budesonide — 180 µg twice a day; at step 3, budesonide — 360 µg twice a day; at step 4, fluticasone-salmeterol (Advair, GlaxoSmithKline) — 250 µg fluticasone and 50 µg salmeterol twice a day; at step 5, Advair — 250 µg and 50 µg twice a day plus montelukast once a day; and at step 6, Advair — 500 µg and 50 µg twice a day plus montelukast once a day. (The doses for montelukast are 5 mg per day for children ≤14 years of age and 10 mg per day for those ≥15 years of age.)
+++ The dose of inhaled glucocorticoids was converted to the budesonide-equivalent dose.
†† Asthma-related health care use was adjusted for study site and dosing because of the scarce data for baseline levels.
‡‡ An exacerbation was defined as a prednisone burst (a minimum of 20 mg per day of prednisone, or the equivalent, taken for any 3 of 5 consecutive days) or a hospitalization.
Clinical assessment: know your patient

• Home environment:
  • Smoking?
  • Pets?
  • Bedding covers? Pest traps? Regular vacuuming, mopping
  • Multiple triggers usually must be addressed to effect response, as single component interventions show conflicting results
Clinical assessment: know your patient

• Workplace environment
  • Isocyanates – if your university has a chemistry lab
  • Cleaning products
Clinical assessment: know your patient

• Pregnant?
  • Same strategies but get more aggressive
  • Don’t consider methacholine testing
  • Do check RAST and IGE
  • Don’t do skin test as these are associated with systemic reactions
  • Do reinforce the concept that a flare of asthma is worse for gestation than the meds; alterations in pH can have profound effects on placental blood flow; consider the fetus well protected from modest variations in maternal oximetry due to properties of fetal hemoglobin
  • Studies linking bronchodilator with risk of cardiac defects are “confounded by indication”
Presentation with episodes of wheezing, cough, and dyspnea

Clinical assessment including spirometry or PEF and allergy testing

Reversible or variable airflow limitation

No

Positive challenge test with methacholine or exercise

No

Consider alternative diagnosis

Yes

Diagnosis of asthma likely

Start rescue medication

Coexisting rhinitis?

Yes

Start low-dose inhaled glucocorticoid

Evaluate after 1–3 mo with ACQ or ACT

Uncontrolled

Add LABA or LTRA or theophylline

Evaluate after 1–3 mo with

Controlled

Continue low-dose inhaled glucocorticoid

Evaluate after 1–3 mo with

Controlled

Continue LTRA

Uncontrolled

Add low-dose inhaled glucocorticoid

Evaluate after 1–3 mo with
Patient education

• Consider the creation of a written action plan
• Use a peak flow meter and begin treatment if 15 to 30% drop is noted
• Does your patient have a “red flag,” an early warning that asthma may be starting and be progressive?
• Plan on an increase in current medications, including inhaled steroids, or addition of systemic steroids in severe cases – consider escalation if SABAs required more than 2 days a week (NIH 2007 pub 07-4051)
• Consider alternate day prednisone for more severe individuals – an underappreciated approach, more commonly used in New England
<table>
<thead>
<tr>
<th>Table 2. Controller and Rescue Medications for the Treatment of Mild Asthma.†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication and Drug</strong></td>
</tr>
<tr>
<td><strong>Medications for quick relief</strong></td>
</tr>
<tr>
<td>Short-acting beta₂-agonists†</td>
</tr>
<tr>
<td>Albuterol</td>
</tr>
<tr>
<td>Terbutaline§</td>
</tr>
<tr>
<td>Anticholinergic agent: ipratropium bromide¶</td>
</tr>
<tr>
<td><strong>Medications for long-term control</strong></td>
</tr>
<tr>
<td>Inhaled glucocorticoids†</td>
</tr>
<tr>
<td>Beclomethasone</td>
</tr>
<tr>
<td>Budesonide</td>
</tr>
<tr>
<td>Fluticasone</td>
</tr>
<tr>
<td>Ciclesonide</td>
</tr>
<tr>
<td>Leukotrien modifier: oral montelukast</td>
</tr>
<tr>
<td><strong>Cromones</strong></td>
</tr>
<tr>
<td>Sodium cromoglycate</td>
</tr>
<tr>
<td>Nedocromil sodium</td>
</tr>
<tr>
<td><strong>Step-up or add-on medications</strong></td>
</tr>
<tr>
<td>Long-acting beta₂-agonists†</td>
</tr>
<tr>
<td>Salmeterol</td>
</tr>
<tr>
<td>Formoterol</td>
</tr>
<tr>
<td>Oral theophylline</td>
</tr>
</tbody>
</table>

* All drug doses are approximate doses and apply to metered-dose inhalers unless specified otherwise.
† This is a preferred therapy.
‡ Daily use of rescue medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
§ Terbutaline Turbutaline is not available in the United States.
¶ Anticholinergic agents can be used as second-line therapy after therapy with short-acting beta₂-agonists but do not have approval by the Food and Drug Administration for use in treatment of asthma. However, in many European countries, ipratropium bromide is approved for the treatment of asthma. Montelukast can also be used as a step-up medication with inhaled glucocorticoids. Pranlukast or zafluralkast can be substituted for montelukast in adults; doses vary according to medication type.
Treatment: Drug Categorization

• Traditionally based on predominant effect: smooth muscle relaxation (beta agonists), suppression of airway inflammation (ICS).

• Now classifications according to hierarchy of management – LABA, SABA. This strategy is useful when teaching patients
Asthma treatment:

- Mild persistent asthma: Current guidelines begin with a “controller,” in the form of an inhaled steroid, and a SABA. For individuals with unacceptable side effects to beta agonists, consider short acting anticholinergic agents.

- SABA potency does not decline with regular use but action duration is slightly shortened (Lipworth, ARRD, 1989).

- Inhaled corticosteroids are potent and effective: persistent asthma, and those with two or more exacerbations requiring systemic steroids in the prior year.

- Inhaled corticosteroids reduce symptoms, improve quality of life, improve asthma control and reduce severity and frequency of exacerbations.
Asthma treatment: ICS

• Inhaled corticosteroids reduce risk of death from asthma.
• Not yet evidence that childhood intervention alters severity or progression.
• Discontinuation results in asthma control deterioration over weeks or months.
• Dosage range is broad: quadruple dose for 1 to 2 weeks if worsening asthma is anticipated.
Asthma treatment:

- Corticosteroids may be usable on an off and on basis with results similar to continuous use in adults, but this may not be reproducible from drug to drug. However, a meta analysis of other studies suggests better overall control with used daily both in adults and children, with reduction in airway inflammation, improved lung function, and decreased need for rescue inhalers.

- Long term use shows airway improvements: fewer mast cells, eosinophils, T lymphocytes, and dendritic cells; reduced goblet-cell hyperplasia, decreased vascularity.
Asthma treatment:

- Some studies suggest that inhaled steroids may be best utilized if given in an afternoon dose (depending on medication).
- This may reflect low serum cortisol levels in humans at around 3pm.
- A single inhalation in afternoon may comparable in efficacy to a more traditional bid dosage.
- “Tea time” dosage hard for most people to accommodate.
- Active smoking neutralizes benefits.
Asthma treatment: side effects

• Beta agonists: SABA dose dependent side effects = tremor, anxiety, palpitations, tachycardia, but NOT hyptertension. No improvement in side effect profile from the more expensive Xopenex, the levo form of albuterol

• Atropinic inhaler side effects: dry mouth. Worsening of glaucoma in severe cases. Urinary retention in older males with enlarged prostates. Dry mouth

• Inhaled steroids: oral thrush, hoarse or weakened voice. Some have systemic side effects in high doses, and can decrease final height in children by 1.2cm with chronic use. Therefore use lowest dose possible. Education tip: “toothbrush medicine.” Systemic side effects only in the highest doses: bruising, intraved intraocular pressure, accelerated loss of bone mass
Asthma treatment side effects

• Long acting beta-agonists (LABAs) used long-term may be associated with increased exacerbations and deaths. FDA warns must be used in combination with ICS

• Fomotorol vs salmeterol: faster onset, higher receptor affinity, possible less downregulation of receptors, used in Europe as rescue inhaler

• FDA suggests de-escalation of LABAs in well controlled asthmatics to low or medium dose glucocorticoids and “rescue inhaler” or addition/maintenance of leukotriene antagonists
Leukotriene blockers, inhibitors

- Alternatives or adjunct treatment
- Suitable for asthma and approved for rhinitis
- Montelukast provides protection against exercise induced asthma, as effectively as salmeterol (without the tachyphylaxis)
- Useful in aspirin-sensitive asthma, but inconsistent
- Symptoms reduced in 60 to 80% of patients,
- Improvement in lung function in only 35 to 50%
Leukotriene blockers, inhibitors: some effects of Leukotrienes on different organs

<table>
<thead>
<tr>
<th>Type of Cell</th>
<th>Asthma</th>
<th>Cardiovascular Disease</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte</td>
<td>Increases recruitment of T cells, eosinophils, mast cells; Increases Th2 responses, cytokines or chemokines, and reactive oxygen species</td>
<td>Increases monocyte and T-cell recruitment; Increases differentiation of macrophages or foam cells; Increases chemokines (e.g., MCP-1 and MIP-1α) and proteases</td>
<td>Increases recruitment of monocytes; Increases cytokines or chemokines and reactive oxygen species</td>
</tr>
<tr>
<td>Dendritic cell</td>
<td>Increases cell recruitment and activation</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Epithelial cell</td>
<td>Increases mucus release and goblet cells</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fibroblast or myofibroblast</td>
<td>Increases collagen release</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Smooth-muscle cell</td>
<td>Increases contractility and proliferation</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>Increases vascular permeability</td>
<td>Increases vascular permeability; Increases intimal hyperplasia; Increases chemokines (e.g., MIP-2); Increases thrombosis</td>
<td>Increases vascular permeability and angiogenesis</td>
</tr>
<tr>
<td>Malignant cell</td>
<td>NA</td>
<td>NA</td>
<td>Increases proliferation (e.g., kinase or β-catenin signaling); Increases transcriptional activity of oncogenic genes; Increases expression of adhesion molecules; Decreases apoptosis (by increasing Bcl-2) to increase tumor-cell survival</td>
</tr>
</tbody>
</table>

* Th2 denotes type 2 helper T cell, MCP-1 monocyte chemoattractant protein 1, MIP-1α macrophage inflammatory protein 1α, MIP-2 macrophage inflammatory protein 2, and NA not applicable.
† Biologic action is most closely attributable to both leukotriene B4 and cysteiny1 leukotrienes.
‡ Biologic action is most closely attributable to leukotriene B4.
§ Biologic action is most closely attributable to cysteiny1 leukotrienes.
Leukotriene blockers, inhibitors

• Add a leukotriene blocker or synthesis inhibitor.
• Leukotrienes are compounds originating from arachidonic acid. Synthesis is predominantly an action of WBC’s. Act on binding receptors of structural and inflammatory cells. Serve to reduce cAMP, the opposite of theophyllines, beta agonists, etc
• Montelukast, zafirlukast are antagonists.
• Zileuton is a direct inhibitor of 5-lipoxygenase, must be give 4 times daily (2 times with an ER version)
Asthma treatment side effects

- Montelukast was associated with a rise in eosinophils but it was uncertain if this was an “unmasking” as patients reduced their steroids. Medication interactions are minimal
- Zafirlukast has more potential medication interactions and requires intermittent liver function testing both at onset of treatment and during therapy
- Zileuton must have LFTs watched for hepatic injury.
Leukotriene blockers, inhibitors

• May be similar in efficacy to inhaled glucocorticoids in the “real world” as there is increased compliance with a once or twice daily pill than for inhalers.
Step-down therapy

• De-escalate where possible
• If asthma controlled for 3 to 4 months on low dose ICS, consider intermittent ICS – or
• Consider once daily LABA/ICS combination
• Use LRA’s
• Data remains uncertain
Maturing therapies (?)

• Bronchoscopic thermoplasty: RF ablation of smooth muscle down to the 3rd generation of airways. Tedious, time consuming, multiple procedures required; best reserved for young, pure asthmatic who are severe

• Mepolizumab (humanized monoclonal anti-interleukin-5): improved severe asthma resistant to high dose ICS +/- systemic steroids, who have elevated eosinophils (150 cells in peripheral blood at screening or 300 cells within prior year)

• Dupilumab (fully human antibody to interleukin-4 alpha subunit) improved persistent, moderate to severe asthma where eosinophils over 300 and sputum over 3% eosinophils