Chronic Obstructive Pulmonary Diseases
(Diagnosis and Treatment of Asthma)

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Classification of Pulmonary Diseases

- Obstructive Diseases
- Restrictive Diseases
- Infectious Diseases
- Pulmonary Vascular Diseases
- Neoplastic Disease
- Diffuse Alveolar Diseases
Clinical Manifestations of Pulmonary Alterations

• Symptoms
  – Dyspnea
  – Cough and expectoration
  – Chest Pain

• Signs
  – Abnormal breathing patterns
  – Cyanosis
  – Adventitious breath sounds
  – Clubbing of the digits
Pulmonary Diagnostic Studies

• Mechanics of Breathing
  – Spirometry and lung volume studies

• Chest Radiographs/Lung Scans
  – A-P, lateral X-rays
  – V/Q scans

• Arterial Blood Gas Analysis
  – pH, PaCO₂, and PaO₂ measurements

• Bronchoscopy
Chronic Obstructive Pulmonary Diseases (COPD)

- Asthma
- Chronic Bronchitis
- Emphysema

Rate/1,000 Persons

Age (years)
- <18
- 18-44
- 45-64
- 65+
- Total (All Ages)

Year

85 86 87 88 89 90 91 92 93 94 95 96
Hospitalization Rates for Asthma by Age, U.S., 1974 - 1997

Rate/100,000 Persons

Year

74 76 78 80 82 84 86 88 90 92 94 96
Pathophysiology of Asthma

- Airway inflammation
- Bronchial hyperresponsiveness
- Airflow limitation
Pathologic Findings

- Bronchoconstriction
- Hyperinflation of the lungs
- Hyperplasia of the smooth muscle surrounding the bronchial and bronchiolar walls
- Thickening of the basement membrane
- Mucosal edema
Etiology

- Genetic factors
  - Atopy

- Environmental factors
  - Viruses
  - Allergens
  - Occupational exposure
Major Cells Implicated in Inflammatory Response

- Mast cells
- Lymphocytes
- Eosinophils
- Neutrophils
Chemicals Involved in Inflammation

- IgE
- Histamine
- Tryptase
- Leukotrienes (LTC₄)
- Platelet activating factor (PAF)
- Prostaglandins (PGD₂)
- Interleukins (IL-4, IL-5)
- Granulocyte-macrophage colony stimulating factor (GM-CSF)
- Tumor Necrosis Factor (TNF)
- Major Basic Proteases (MBP)
- Eosinophil Cationic Protein (ECP)
## Classification of Asthma Severity: Clinical Features Before Treatment

<table>
<thead>
<tr>
<th>Severity</th>
<th>Days with Symptoms</th>
<th>Nights with Symptoms</th>
<th>PEF or FEV$_{1.0}$</th>
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<tbody>
<tr>
<td><strong>Severe Persistent</strong></td>
<td>Continual</td>
<td>Frequent</td>
<td>≤ 60%</td>
</tr>
<tr>
<td><strong>Moderate Persistent</strong></td>
<td>Daily</td>
<td>≥ 5/month</td>
<td>&gt;60% &lt; 80%</td>
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<tr>
<td><strong>Mild Persistent</strong></td>
<td>3-6/week</td>
<td>3-4/month</td>
<td>≥ 80%</td>
</tr>
<tr>
<td><strong>Mild Intermittent</strong></td>
<td>≤ 2/week</td>
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</table>
Part 4: Long-term Asthma Management

Stepwise Approach to Asthma Therapy - Adults

Outcome: Asthma Control
- Controller: Daily inhaled corticosteroid
- Daily long-acting inhaled β2-agonist
- Reliever: Rapid-acting inhaled β2-agonist prn

Outcome: Best Possible Results
- Controller: Daily inhaled corticosteroid
- Daily long-acting inhaled β2-agonist
- Theophylline-SR
- Leukotriene
- Oral corticosteroid

Steps:
- STEP 1: Intermittent
- STEP 2: Mild Persistent
- STEP 3: Moderate Persistent
- STEP 4: Severe Persistent
- STEP Down

When asthma is controlled, reduce therapy
Monitor

Alternative controller and reliever medications may be considered (see text).
Treatment of Asthma

- NIH Guidelines for the treatment of asthma
- Reliever (Rescue) Drugs
  - Bronchodilators
    - Sympathomimetic amines
    - Xanthine derivatives
    - Parasympatholytics
- Controller Drugs
  - Corticosteroids/Mast cell stabilizers
  - Leukotriene Inhibitors
  - Anti-IgE antibodies
“Relievers”
Adrenergic Bronchodilators – Short-Acting Agents

- Catecholamines
  - Epinephrine
  - Isoproterenol
  - Isoetharine

- Resorcinol agents
  - Metaproterenol

- Saligenin agents
  - Albuterol

- Pirbuterol

- Bitolterol
Beta-2 Adrenergic Agonists – Short-acting agents

- **Role in therapy**
  - Medication of choice for treatment of acute exacerbations of asthma and useful in the pretreatment of exercise-induced bronchospasm (EIB)
  - Used to control episodic bronchoconstriction
    - Increased used – or even daily use of these agents is a warning of deterioration of asthma and indicates the need to institute or to intensify regular anti-inflammatory therapy.
Anticholinergic (Parasympatholytic) Bronchodilators

- Tertiary Ammonium Compounds
  - Atropine sulfate
  - Scopolamine

- Quaternary Ammonium Compounds
  - Ipratropium
  - Tiotropium
Anticholinergic (Parasympatholytic) Bronchodilators

- **Mode of administration**
  - Inhaled

- **Mechanisms of action**
  - Block the effects of acetylcholine released from cholinergic nerves in the airways (i.e., reduce intrinsic vagal cholinergic tone to the airways).
  - Block reflex bronchoconstriction caused by inhaled irritants.
  - They do not diminish the early and late allergic reactions and have no effect on airway inflammation.
  - Less potent bronchodilators than inhaled beta-2 agonists, and in general, have a slower onset of action (30-60 min to maximum action).
Anticholinergic (Parasympatholytic) Bronchodilators

- **Role in therapy**
  - Additive effect when nebulized together with a rapid-acting beta-2 agonist for exacerbations of asthma
    - Combivent®
  - It is recognized that Ipratropium can be used an alternative bronchodilator for patients who experience adverse effects such as tachycardia, arrhythmias, and tremors from beta-2 agonists.

- **Side effects**
  - Dryness of the mouth and bitter taste
“Controllers”
Controllers

- Corticosteroids
- Long-Acting bronchodilators
  - $\beta_2$-adrenergic agents
  - Methylxanthines
- Cromolyn sodium/Nedrocromil
- Leukotriene inhibitors
- Anti-IgE monoclonal antibodies
Inhaled Glucocorticoids

- **Mechanisms of action**
  - Reduces pathologic signs of airway inflammation mediated in part by inhibition of production of inflammatory cytokines
  - Airway hyperresponsiveness continues to improve with prolonged treatment

- **Role in therapy**
  - Most effective anti-inflammatory medication for the treatment of asthma
Inhaled Glucocorticoids

- **Side effects**
  - Local adverse effects include oropharyngeal candidiasis, dysphonia, and occasional coughing from upper airway irritation.
  - Because there is some systemic absorption, the risks of systemic adverse effects will depend on the dose and potency of the glucocorticoid as well as its bioavailability, absorption in the gut, metabolism by the liver, and the half-life of its systemically absorbed fraction.
Inhaled Glucocorticoids

- Beclomethasone dipropionate
  - Dosage: 200-1000µg
- Budesonide
  - Dosage: 200-800µg
- Flunisolide
  - 500-2000µg
- Fluticasone
  - 100-500µg
- Tramcinolone acetonide
  - 400-2000µg
Systemic Glucocorticoids

- Mode of administration
  - Oral
  - Parenteral

- Mechanisms of action
  - Same as for inhaled glucocorticoids however systemic glucocorticoids may reach different target cells than inhaled drugs

- Role in therapy
  - Long-term oral glucocorticoid therapy (daily or alternate-day) may be required to control severe persistent asthma.
Systemic Glucocorticoids

- Side effects
  - Osteoporosis
  - Arterial hypertension
  - Diabetes
  - Hypothalamic-pituitary axis suppression
  - Cataracts
  - Glaucoma
  - Obesity
  - Skin thinning leading to cutaneous striae
  - Easy bruising
  - Muscle weakness
  - Fatal herpes virus infections have been reported among patients who are exposed to these viruses when they are taking systemic glucocorticoids
Adrenergic Bronchodilators – Long-Acting Agents

- Sustained-released albuterol
- Salmeterol
- Formoterol
Adrenergic Bronchodilators – Long-Acting Agents

- Modes of administration
  - Inhaled
  - Oral

- Mechanisms of action
  - Same as short-acting beta-2 agonists
  - Effects persists for at least 12 hours
Adrenergic Bronchodilators – Long-Acting Agents

- Role in therapy
  - Long-acting inhaled beta-2 agonists should be considered when standard introductory doses of inhaled glucocorticoids fail to achieve control of asthma before raising the dose of inhaled glucocorticoids.
  - Because long-term treatment with these agents does not appear to influence the persistent inflammatory changes in asthma, this therapy should be combined with inhaled glucocorticoids
    - Fluticasone propionate – salmeterol and bedesonide-formoterol inhalers
Adrenergic Bronchodilators – Long-Acting Agents

- Side effects
  - Inhaled beta-2 agonists cause fewer systemic adverse effect (e.g., cardiovascular stimulation, skeletal muscle tremors, and hypokalemia) than oral therapy particularly if the oral regimen includes theophylline.
Xanthine Agents

- Naturally Occurring Agents
  - Caffeine (Coffee and kola beans; tea leaves)
  - Theophylline (Tea leaves)
  - Theobromine (Cocoa seeds or beans)

- Synthetic Derivatives
  - Dyphylline
  - Proxyphylline
  - Enprophylline
Methylxanthines

- Mode of administration
  - Oral or Parenteral
- Mechanisms of action
  - The bronchodilator effect may be related to phosphodiesterase inhibition (>10mg/L); anti-inflammatory effect is due to an unknown mechanism and may occur at lower concentrations (5-10mg/L). This latter mechanism may involve the inhibition of cell surface receptors for adenosine, which modulate adenylyl cyclase activity (contraction of isolated smooth muscle and to provoke histamine release from mast cells).
  - Most studies show little or no effect on airway hyperresponsiveness
- Role in therapy
  - Sustained release theophylline is effective in controlling asthma symptoms and improving lung function (i.e., nocturnal symptoms; may be used as an add-on therapy to low or high doses of glucocorticoids)
Methylxanthines

- **Side effects (serum concentrations > 15µg/mL)***
  - Gastrointestinal symptoms – nausea, vomiting
  - CNS – Seizures
  - Cardiovascular – tachycardia, arrhythmias
  - Pulmonary – stimulation of the respiratory center

*Monitoring theophylline levels is advised when high-dose therapy (>10mg/kg body weight is used or when a patient develops an adverse effect on the usual dosage*
Cromolyn and Nedrocromil Sodium

- **Mode of administration**
  - Inhaled

- **Mechanisms of action**
  - Exact mechanisms of action are not fully understood, although these nonsteroidal anti-inflammatory medications partly inhibit the IgE-mediated release from mast cells in a dose-dependent way and they have a cell-selective and mediator-selective suppressive effect on other inflammatory cells (e.g., macrophage, eosinophils, monocytes).
  
  - There is some evidence that these medications alter the function of delayed chloride channels in the cell membrane.
Cromolyn and Nedrocromil Sodium

- **Role in therapy**
  - May be used as a controller in mild persistent asthma.
  - Administered prophylactically, these medications inhibit early and late-phase allergen-induced airflow limitation and acute after exposure to exercise, cold dry air, and sulfur dioxide.
  - Inconclusive data at present on the effectiveness of these drugs on reducing airway hyperresponsiveness.
  - A 4-6 week therapeutic trial may be required to determine the efficacy for individual patients.

- **Side effects**
  - Minimal side effects – coughing, throat irritation, wheezing, chest tightness, and mouth dryness
Leukotriene modifiers

- A new class of anti-asthma drugs that include cysteinyl leukotriene 1 (CysLT1) receptor antagonists (e.g., montelukast, zafirlukast) and 5-lipoxygenase inhibitor (zileuton)
Leukotriene modifiers

- **Mode of administration**
  - Oral

- **Mechanism of action**
  - Receptor antagonists block the CysLT1 receptors on airway smooth muscle and thus inhibit the effects of cysteinyi leukotrienes that are release from mast cells and eosinophils
  - 5-lipoxygenase inhibitors block synthesis of leukotrienes.
Leukotriene modifiers

Role in therapy

- These agents have a small and variable bronchodilator effect, reduce symptoms, improve lung function, and reduce asthma exacerbations.
- Effect of these drugs is less than that of low-doses of inhaled glucocorticoids. There is evidence that the use of these drugs as an add-on may reduce the dose of inhaled glucocorticoid required by patients with moderate to severe asthma.
- Note that leukotriene modifiers are less effective than long-acting inhaled beta-2 agonists as an add-on therapy.
Leukotriene modifiers

- Side effects
  - These drugs are usually well tolerated, and few if any class-related effects have been recognized.
    - Zileuton has been associated with liver toxicity and monitoring liver test is recommended
    - There are several reports of Churg-Strauss syndrome associated with the leukotriene modifier therapy (typically associated with a reduction of systemic glucocorticoids)
IgE Antibodies
Anti-IgE Antibodies

- Agents directed at diminishing the production of IgE through effects on interleukin 4 or on IgE itself have been evaluated
  - Soluble recombinant IL-4 receptor that can be delivered by aerosol
  - Recombinant human monoclonal antibody that forms complexes with free IgE (rhuMAb or omalizumab blocks the interaction of IgE with mast cells and basophils.
    - Attenuates the early-phase and late phase airway obstruction response to allergen and suppressed the accumulation of eosinophils in the airways
Treatment Protocols
## Classification of Asthma Severity:
Clinical Features Before Treatment

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Peak Flow Meter
Routes of Administration

- Inhaled
  - Metered dose inhalers (MDI)
    - “Spacers”
  - Dry powder inhalers (DPI)
  - Nebulized (“wet”) aerosols

- Oral

- Parenteral
  - Subcutaneous
  - Intramuscular
  - Intravenous
GREEN means GO - use preventive (anti-inflammatory) medicine

YELLOW means CAUTION - use quick-relief (short-acting bronchodilator) medicine in addition to preventive medicine

RED means STOP! - get help from a doctor
Your GREEN ZONE is 80 to 100% of your personal best. GO!
Breathing is good with no cough, wheeze, or chest tightness during work, school, exercise, or play.

ACTION:
• Continue with medications listed in your daily treatment plan.
Your YELLOW ZONE is 50 to less than 80% of your personal best.

CAUTION!

Asthma symptoms are present (cough, wheeze, chest tightness).
Your peak flow number drops below _______ or you notice:
  • Increased need for inhaled quick-relief medicine
  • Increased asthma symptoms upon awakening
  • Awakening at night with asthma symptoms
  • _______________________________________

ACTIONS:
  • Take _____ puffs of your quick-relief (bronchodilator) medicine
    ______________________________________. Repeat _____ times.
  • Take _____ puffs of _______________ (anti-inflammatory)
    _______________times/day.
  • Begin/increase treatment with oral steroids: Take _____mg of
    _______________ every a.m. _____p.m. ______.
  • Call your doctor (phone) _______________ or emergency room
    __________.
Your RED ZONE is ________ 50% or less of your best. DANGER!!

Your peak flow number drops below _____, or you continue to get worse after increasing treatment according to the directions above.

ACTIONS:
Take _____ puffs of your quick-relief (bronchodilator) medicine
Repeat _____ times.
Begin/increase treatment with oral steroids: Take _____mg now.
Call your doctor now (phone) _________________. If you cannot contact your doctor, go directly to the emergency room (phone) ________________.
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<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control (5–11 years of age)</th>
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<tr>
<td><strong>Impairment</strong></td>
<td><strong>Well Controlled</strong></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week but not more than once on each day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤1x/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</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>Lung function</td>
<td></td>
</tr>
<tr>
<td>• FEV₁ or peak flow</td>
<td>&gt;80% predicted/ personal best</td>
</tr>
<tr>
<td>• FEV₁/FVC</td>
<td>&gt;80%</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0–1/year</td>
</tr>
<tr>
<td>Reduction in lung growth</td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td></td>
</tr>
<tr>
<td><strong>Recommended Action for Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>(See figure 4–1b for treatment steps.)</td>
<td></td>
</tr>
<tr>
<td>• Maintain current step.</td>
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</tr>
<tr>
<td>• Regular followup every 1–6 months.</td>
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<tr>
<td>• Consider step down if well controlled for at least 3 months.</td>
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<tr>
<td>• For side effects: consider alternative treatment options.</td>
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### Components of Control

#### Classification of Asthma Control (≥12 years of age)

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<tr>
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<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
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</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>1–3x/week</td>
<td>≥4x/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times per day</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/ personal best</td>
<td>60–80% predicted/ personal best</td>
<td>&lt;60% predicted/ personal best</td>
</tr>
<tr>
<td>Validated questionnaires</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>0</td>
<td>1–2</td>
<td>3–4</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75*</td>
<td>≥1.5</td>
<td>N/A</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
<td>16–19</td>
<td>≤15</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0–1/year</td>
<td>≥2/year (see note)</td>
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<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term followup care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
<td></td>
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</table>

### Recommended Action for Treatment

(see figure 4–5 for treatment steps)

- Maintain current step.
- Regular followups every 1–6 months to maintain control.
- Consider step down if well controlled for at least 3 months.
- Step up 1 step and reevaluate in 2–6 weeks.
- For side effects, consider alternative treatment options.
- Consider short course of oral systemic corticosteroids.
- Step up 1–2 steps, and reevaluate in 2 weeks.
- For side effects, consider alternative treatment options.
References

• http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm