Update on Respiratory Pharmacology:

COPD, Asthma, Allergic Rhinitis

Alan P. Agins, Ph.D.
President, PRN Associates
Continuing Medical Education, Tucson, AZ

Objectives:

• Describe risk factors, etiology & pathophysiology of COPD and Asthma
• Define basic and clinical pharmacology of the various classes of medications used for treating COPD, Asthma and allergic rhinitis
• Discuss COPD and Asthma treatment guidelines regarding the uses, priorities and combinations of bronchodilators and inhaled corticosteroids (ICS)
• Describe how spirometry is used to diagnose and differentiate COPD from Asthma and the role of select medications in that process.
• Recognize the potential benefits and disadvantages of at least three recently approved medications for the treatment of obstructive airways diseases and allergic rhinitis

Comparing and Contrasting

Asthma  COPD
Facts about COPD

- 3rd / 4th leading cause of death in US
- 141,075 Deaths in 2008
- Mortality rate still rising
- Economic burden was $42.6 billion (2007)
- COPD drug market > $8.4 billion and growing
- > 80% of cases due to cigarette smoking
- 15% of pts severely symptomatic

Definition of COPD

- Preventable / treatable disease
- Inflammatory response to noxious particles/gases
- Characterized by airflow limitation not fully reversible
- Airflow limitation progressive
- Some significant extrapulmonary effects

Risk Factors for COPD

- Cigarette Smoke
- Occupational dust & chemicals
- Second-hand smoke
- Indoor and outdoor pollution
- Respiratory Infections
- Nutritional Status
- Socio-economic status
- Aging

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Diagnosing COPD

Symptoms
- Cough
- Sputum
- Dypsnea

Risk Factors
- Smoking
- Occupation
- Indoor / Outdoor pollution

Spirometry

COPD

Emphysema

Chronic Bronchitis

Hyperinflation

Chronic Bronchitis
Pathology
- Goblet cell hyperplasia
- Mucus hypersecretion
- Neutrophilic inflammation
- Bacterial infection
- Microaspiration
- CO2 retention
- Airway constriction
- Airway inflammation
- Airway hyperreactivity
Facts about Asthma:

- Estimated that 23.3 million in US currently have asthma (2008)
- Two million ER visits
- 500,000 hospitalizations
- 4,000 deaths/ year
- Annual health care costs estimated > $20 billion
- 90% of asthma cases in children are estimated to be allergic
  - (50-70% in adults)
**Asthma Definition**

- Complex disorder characterized by *variable* & *recurring* symptoms, airflow obstruction and bronchial hyper-responsiveness
- Chronic inflammation
- Reversible-spontaneous or with treatment
- Remodeling
- Symptoms include: wheezing, chest tightness, cough, nocturnal or early AM symptoms.

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**Asthma Pathology**

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**COPD vs Asthma**

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Mid – later life</td>
<td>Early - children</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Chronic cough</td>
<td>Wheezing</td>
</tr>
<tr>
<td></td>
<td>Continuous and slowly progressive</td>
<td>Vary daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Night / early AM worse</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Smoking history</td>
<td>Atopy / allergy Family history</td>
</tr>
</tbody>
</table>
COPD vs Asthma

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitising agent</td>
<td>Noxious agent</td>
</tr>
<tr>
<td>Asthmatic airway inflammation</td>
<td>COPD Airway Inflammation</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Macrophages</td>
</tr>
<tr>
<td>CD4+ T-lymphocytes</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Mast cells</td>
<td>CD8+ T-lymphocytes</td>
</tr>
<tr>
<td>Basophils</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>Mostly reversible</td>
</tr>
<tr>
<td>Bronchoconstriction</td>
<td>Mostly irreversible</td>
</tr>
<tr>
<td>Small airway narrowing</td>
<td>Mostly irreversible</td>
</tr>
<tr>
<td>Alveolar destruction</td>
<td>Mostly irreversible</td>
</tr>
</tbody>
</table>

Airflow limitation

- Mostly reversible
- Mostly irreversible

COPD: Diagnosis and Staging

FEV1/FVC < 0.70 (post bronchodilator)

- Stage I (mild): FEV1 > 80% predicted
- Stage II (Moderate): FEV1 50-80% predicted
- Stage III (Severe): FEV1 30-50% predicted
- Stage IV (Very severe): FEV1 < 30% predicted

With or without chronic symptoms (cough, sputum production)

Asthma: Diagnosis and Staging

Based on:
- Symptom frequency
- Nighttime awakenings
- Frequency of SABA use
- Interferes with normal activity
- Lung Function (FEV1)

Intermittent

- Mild
- Moderate
- Severe
Standard Spirometric Indices

- **FVC** - Forced vital capacity:
  The total volume of air that can be forcibly exhaled in one breath

- **FEV₁** - Forced expiratory volume in one second:
  The volume of air expired in the first second of the blow

- **FEV₁/FVC ratio**
  The fraction of air exhaled in the first second relative to the total volume exhaled
Spirometry: Differential Diagnosis of COPD vs Asthma

Favoring COPD
- Dyspnea, chronic cough, sputum production
- Adult with history of smoking or exposure to noxious particles / gases
- Reduced DLCO (diffusing capacity)

Favoring Asthma
- History of childhood wheezing, atopic symptoms.
- Diurnal variation in peak flows in adult who coughs, wheezes or is short of breath
- Improvement in FEV1 after bronchodilator of 12% (200ml)
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### Bronchodilator Reversibility Testing

<table>
<thead>
<tr>
<th>Bronchodilator</th>
<th>Dose</th>
<th>FEV, before and then after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>200 – 400 µg via large volume spacer</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>500 µg via Turbohaler®</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>160 µg via spacer</td>
<td>45 minutes</td>
</tr>
</tbody>
</table>

### Before performing spirometry:

**Withhold:**
- Short acting β₂-agonists for 6 hours
- Ipratropium for 6 hours
- Long acting β₂-agonists for 12 hours
- Tiotropium for 24 hours

Optimally, subjects should avoid caffeine and cigarette smoking for 30 minutes before performing spirometry

### Contraindications for Spirometry

- Hemoptysis
- Acute disorders affecting test performance
- Pneumothorax
- Recent abdominal or thoracic surgery
- Recent eye surgery
- Recent MI or unstable angina
- Thoracic aneurysms
Why not use peak flow meters for diagnosis or diagnostic screening?

- Predicted values of PEF of little use in detecting lung disease
- In severe obstructive lung disease, the severity of airway obstruction tends to be under-estimated from PEF
- PEF not as good a measure of reversibility (bronchodilator responsiveness) compared to FEV1.

Pharmacotherapy Goals

**COPD**
- Relieve symptoms
- Prevent disease progression
- Improve exercise tolerance
- Improve health status
- Prevent & treat complications
- Prevent & treat exacerbations
- Reduce mortality

**Asthma**
- Reduce impairment
- Decrease symptoms
- Decrease rescue inhaler
- Maintain near normal activity levels
- Maintain <near> normal spirometry
- Reduce risk
- Prevent exacerbations
- Prevent loss of lung function

Provide optimal pharmacotherapy with minimal adverse effects
**Bronchodilators**

Beta Agonists

- **SABA**
  - Albuterol

- **LABA**
  - Formoterol (Foradil, Perforomist)
  - Arformoterol (Brovana)
  - Salmeterol (Serevent)
  - Indacaterol (Arcapta)*

Anticholinergics

- Ipratropium (Atrovent)
- Aclidinium* (Tudorza)
- Tiotropium (Spiriva)

**β₂ receptor locations**

- airway smooth muscle cells
- submucosal glands
- vascular endothelium
- ciliated epithelium
- mast cells, eosinophils, lymphocytes
- cholinergic ganglia

**Indacaterol (Arcapta Neohaler)**

- Long-acting beta agonist (LABA)
- Inhaled (dry-powder)
- Approved only for treatment of COPD
- Once daily dosing (vs bid for other LABAs)
- Fast onset like formoterol
- FDA approved 75 mcg (once daily) dose  
  - One quarter to one half the recommended dose in 2010 GOLD Guidelines and used in Europe
Side Effects – Inhaled Bronchodilators

Beta Agonists
- Tremor
- Tachycardia
- CNS excitation

Extreme cases
- Hypokalemia, Hyperglycemia

Anticholinergics

Better Results in COPD
- Greater parasympathetic (vagal) influence in COPD
- Increased parasympathetic drive increases bronchial smooth muscle tone
- Also contributes to excessive mucus secretion, cough and dypsnea

New Long-acting Anticholinergic
- aclidinium bromide (Tudorza™ Pressair™)
- Twice daily dosing vs once daily for tiotropium (Spiriva)
- No better, no worse than tiotropium in efficacy and safety
**Tudorza Pressair**

- Simpler device than Spiriva Handihaler
- Shorter $t_{1/2} = $ faster to steady state
- May be easier to remember or use in combination with *b.i.d* $b$-agonist inhalers
- Evening dose may provide higher through-the-night drug levels

**Tudorza Pressair**

**versus**

**Spiriva Handihaler**

- Cost differences
- Delivery device differences
- Patient and/or provider preferences

**Side Effects – Inhaled Bronchodilators**

**Anticholinergics**
- Dry mouth
- GI upset
- Upper RT Infections
Combination Therapy – Bronchodilators

**Anticholinergics**
- Reduce cholinergic tone

**Beta Agonists**
- Relax smooth muscles

**Synergy**
1. Different location of maximal effect
2. Different mechanisms
3. Different onsets and durations

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**Combination Therapy - Bronchodilators**

<table>
<thead>
<tr>
<th>Volume (L)</th>
<th>albuterol + ipratropium</th>
<th>ipratropium</th>
<th>albuterol</th>
<th>no drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>Additive Benefit in COPD only</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Inhaled Corticosteroids (ICS)**

**Asthma**
- Early and aggressive
- Improve prognosis
- Can be used as monotherapy in early steps (2 & 3)

**COPD**
- Reserved for severe stages
- Little benefit on lung function and overall mortality
- May reduce exacerbations
- Never used as monotherapy
**Inhaled Corticosteroids (ICS)**
- beclomethasone
- triamcinolone
- flunisolide
- budesonide
- fluticasone
- mometasone
- ciclesonide

**Side Effects – Inhaled Corticosteroids (ICS)**
- Dysphonia
- Cough
- Throat irritation
- Skin bruising
- Oral candidiasis

Conflicting data exists
- Cataracts
- Osteopenia / osteoporosis
- Mild adrenal suppression

**Interactions**
- Strong CYP3A4 Inhibitors
  - Protease inhibitors
    - ritonavir
    - indinavir
    - nelfinavir
    - saquinavir
  - Macrolide antibiotics
    - clarithromycin
  - Azole Antifungals
    - ketoconazole
    - itraconazole

- Fluticasone
- Budesonide
- Ciclesonide
- Mometasone
Additional Agents

**Asthma**
- Leukotriene Antagonists
  - montelukast (Singulair)
  - zafirlukast (Accolate)
- Leukotriene Synthesis Inhibitor
  - Zileuton (Zyflo)
- Cromolyn
- Theophylline

**COPD**
- Roflumilast (Daliresp)
- Theophylline ??

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**Asthma Therapy Guidelines (NAEPP 2007)**

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
<th>Persistent Asthma: Daily Medication</th>
</tr>
</thead>
</table>

- **Step 1**
  - Preferred: SABA PRN
  - Alternative: Ciclesonide, Nedocromil or Theophylline

- **Step 2**
  - Preferred: Low dose ICS + LABA
  - Alternative: Oral corticosteroid

- **Step 3**
  - Preferred: Medium dose ICS + LABA
  - Alternative: Medium dose ICS + LABA

- **Step 4**
  - Preferred: High dose ICS + LABA AND Theophylline
  - Alternative: Medium dose ICS + LABA

- **Step 5**
  - Preferred: High dose ICS + LABA AND Oral corticosteroid
  - Alternative: Medium dose ICS + LABA

- **Step 6**
  - Preferred: High dose ICS + LABA + Oral corticosteroid
  - Alternative: Medium dose ICS + LABA

**COPD Therapy Guidelines (GOLD)**

- **Stage I**: FEV<sub>1</sub> / FVC < 0.70
- **Stage II**: FEV<sub>1</sub> ≥ 80% predicted
- **Stage III**: FEV<sub>1</sub> < 80% predicted
- **Stage IV**: FEV<sub>1</sub> < 70% predicted

- Active reduction of risk factor(s): Influenza vaccination
- Add long-acting bronchodilator (as needed)
- Add inhaled glucocorticosteroids if repeated exacerbations
- Add pulmonary rehabilitation
- Consider surgical treatments for certain advanced cases

**Additional Resources**
- http://www.goldcopd.org/
- http://www.annals.org/content/155/3/179.full.pdf+html
statistics . . .

- 40 to 50 million Americans
- Allergic rhinitis affects between 10 - 30% of all adults and as many as 40% of children.
- > 12 million physician visits annually
- 90% of pediatric asthma cases estimated allergic, 50-70% in adults.
- Key factor in controlling allergic asthma is controlling allergic rhinitis symptoms.

Inflammation of the nasal mucosa characterised by nasal discharge, blockage, sneezing and itching, with two or more symptoms occurring for more than 1 hr on most days.

**Seasonal (intermittent)** when symptoms occur on less than 4 days per week or for less than 4 weeks per year

**Perennial (persistent)** where symptoms occur on at least 4 or more days per week or for more than 4 weeks per year
Seasonal Allergic Rhinitis

Ragweed (& others) - Late Summer and Fall
Tree pollen - Spring
Grass pollen - late Spring and Summer
Fungus / mold - Summer and Fall

Perennial Allergic Rhinitis

• Pet Dander (cats, dogs):
  – Can linger up to 4 months after pet removal.
• House dust mites:
  – Live in bedding, carpets and upholstery.
  – Dietary preference: human epidermal scales.
• Cockroaches:
  – Respiratory allergy
  – Important allergen in inner-city asthma
• Fungi/mold:
  – Exposure peaks accompany activities such as harvesting, cutting grass and leaf raking.

Initial Exposure to Allergen (Sensitization)
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Re-exposure to Allergen (Early Phase)

- Histamine
- Leukotrienes
- Prostaglandin D
- Kinins

Mucus Secretion

Epithelium
- Nasal
- Pulmonary

Plasma exudation

Mast Cell

Basophil

Vasodilation

Re-exposure to Allergen (Late Phase)

- Eosinophils
- Major basic protein (MBP)
- Eosinophil cationic protein (ECP)
- Reactive O2 species
- Leukotrienes
- Cytokines

Epithelial Cell Death

Scarring / remodeling

Chronic Inflammation

Epithelium

Allergic Rhinitis Arsenal

- Oral / Nasal Antihistamines
- Leukotriene Antagonists
- Oral / Nasal Decongestants
- Nasal Cromolyn
- Nasal Steroids
- Nasal Ipratropium

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### Antihistamines

- **H1 receptor**
  - Active Form
  - Inactive Form

**Inverse Agonist**
- "Stabilize histamine receptor in ‘inactive’ state.

**1st Generation**
- Diphenhydramine
- Chlorpheniramine
- Brompheniramine
- Clemastine
- Hydroxyzine
- Cyproheptadine
- Promethazine

**2nd Generation**
- Loratadine
- Desloratadine
- Cetirizine
- Levocetirizine
- Fexofenadine

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**Nasal Antihistamines**
- Azelastine
- Olopatadine
- Histamine
- Leukotriene
- Prostaglandin
- Kinins
- H1 receptor
- Block
- Mast Cell
- IL-4
- TH2-13

**Decongestants**
- Sympathetic nervous system
- Adrenal gland
- Pseudoephedrine
- alpha-1 receptor

**Decongestants (Intranasal)**
- Rebound congestion
- Desensitization
- alpha-1 receptor
- Out of office
- Will Return Tomorrow
Nasal Steroids

Nasal Steroids
Stimulate production of various anti-inflammatory proteins
Suppress synthesis of chemokines (directed chemotaxis) and cytokines (cell signaling – i.e., interleukins).
Provide relief of all nasal symptoms
Congestion
Nasal discharge
Sneezing
Itching
Postnasal drip

Nasal Steroids
Differ in:
  Potency
  Frequency of dosing
  Delivery device
  Systemic bioavailability
  Costs
Similar in:
  Effectiveness for treating symptoms of allergic rhinitis
## Nasal Steroids

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Names</th>
<th>Generation</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>Beconase AQ</td>
<td>1st</td>
<td>~40 – 50%</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Nasacort AQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Nasarel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>Rhinocort Aqua</td>
<td>2nd</td>
<td>~10 - 34%</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Flonase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone</td>
<td>Nasoxex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Omnaris</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Possible Advantages
- Low systemic bioavailability
- Allergic & non-allergic rhinitis

### Possible Disadvantages
- Flowery scent
- Benzalkonium chloride

### Additional Preference Factors:
- Taste
- Smell
- After-taste
- “Throat run-down”
- “Nose run-out”
- Feel of spray

### Sensory Attributes

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Nasal Steroid - Side effects

Nasal irritation
Burning
Stinging
Epistaxis

Interactions

Strong CYP3A4 Inhibitors
- Protease inhibitors
  - ritonavir
  - indinavir
  - nelfinavir
  - saquinavir
- Macrolide antibiotics
  - clarithromycin
- Azole Antifungals
  - ketoconazole
  - itraconazole

Newer Products
- Qnasl (beclomethasone dipropionate)
- Zetonna (ciclesonide)
- Dymista Nasal Spray (azelastine + fluticasone)
QNASL (Beclomethasone)
Aqueous-based taste issues for some throat “rundown” nose “runout” may be useful for moisturizing dry nasal passages
HFA-based (dry) less “throat rundown” less “nose runout” may be useful for watery, dripping noses

Zetonna
Similar indications / efficacies
Similar potential benefits regarding “dry” inhaler for some patients
Systemic bioavailability ciclesonide << beclomethasone
One spray per nostril once daily
Two sprays per nostril once daily

Dymista Nasal Spray
Approved for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older who have significant symptoms that require treatment with both an antihistamine and a corticosteroid for relief
Other Possibilities

Leukotriene Antagonists

Nasal Cromolyn

Nasal Ipratropium

Leukotriene Antagonists

Arachidonic acid

LTC₄

LTD₄

LTE₄

Leukotriene Antagonists

Leukotriene Receptors

- White Blood Cells
- Endothelial cells
- Vascular smooth muscle
- Bronchial smooth muscle
**Cromolyn Sodium (intranasal)**

**Mechanism:**
- Mast cell stabilizer-reduces release of histamine and other mediators

**Use:**
- Prophylactic: start before allergy season or unavoidable/predictable exposures

**Benefits:**
- Reduces nasal pruritis, sneezing, rhinorrhea and congestion

**Disadvantages:**
- Requires frequent dosing (q4hrs)
- Not as effective as steroids/antihistamines
Ipratropium (intranasal)

**Mechanism:**
- Inhibits muscarinic cholinergic receptors

**Uses:**
- Limited to control of rhinorrhea
- Effective at reducing both "cold-air" and "gustatory" rhinitis

**Benefits:**
- Reduces watery rhinorrhea
- Good safety record

**Disadvantages:**
- Irritation, crusting, epistaxis
- No effect on itching, sneezing or congestion

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### Comparing Treatments

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Rhinorrhea</th>
<th>Nasal Itch</th>
<th>Sneezing</th>
<th>Congestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines (oral and nasal)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>-/+</td>
</tr>
<tr>
<td>Nasal steroids</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Decongestants (oral and nasal)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Leukotriene blocker</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Mast cell stabilizer</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>Nasal anticholinergics</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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Thanks for listening.

Alan

- Web: www.gotpharm.com
- www.Pharm1on1.com
- Email: aagins@gotpharm.com
- Facebook: /gotPharm