Take Home Messages in Pulmonary Medicine

Christopher H. Fanta, M.D.
Pulmonary and Critical Care Division
Brigham and Women’s Hospital
Harvard Medical School
Partners Asthma Center

Financial Conflicts of Interest

None.

Topics Covered This Morning

1. Hemoptysis
2. Bronchiectasis/bronchiolitis
3. Solitary Pulmonary Nodule
4. Pleural Disease
5. COPD
6. Sleep Apnea Syndrome
7. Asthma
8. Interstitial Lung Disease

“Brevity is the Soul of Wit”

The Reduced Shakespeare Company
All 37 plays in 97 minutes!

1. Hemoptysis

- Evaluation should include a chest X-ray; further work-up depends on the findings on the chest X-ray.
- A normal chest X-ray does not exclude serious pulmonary pathology (i.e., lung cancer found in 5-7%).
- At risk: cigarette smokers; ≥ age 40; persistent hemoptysis for > 1 week.
- Chest CT and bronchoscopy of complementary value in hemoptysis with negative chest X-ray.

Massive Hemoptysis

- Definition: ≥ 600 ml/24 hr; lesser amounts can cause respiratory insufficiency.
- Think bronchiectasis, TB, cancer, mycetoma, vasculitis.
- Conservative measures include oxygenation, sometimes intubation, positioning with bleeding side down.
- Other: surgical excision; bronchial artery embolization.
- Major complication of the latter: spinal infarct.
2. Bronchiectasis

- Definition: irreversible focal-multifocal dilation of bronchi, predisposing to recurrent/persistent bronchial infection.
- Causes: necrotizing infection/inflammation.
- Multifocal bronchiectasis: think hypogammaglobulinemia, cystic fibrosis, primary ciliary dyskinesia. Most cases remain idiopathic.

Bronchiectasis (cont.)

- Diagnosis: CT scan.
- Typical pathogens: staph, hemophilus, pseudomonas.
- Treatment: bronchodilators, clearance of secretions, and antibiotics, including the option of inhaled antibiotics.
- Choice of antibiotics guided by sputum culture.

Bronchiolitis obliterans

- Definition: chronic cellular inflammation of bronchioles with characteristic intraluminal polypoid tissue.
- Causes: viral infection; noxious gas inhalation; rheumatoid arthritis; ulcerative colitis; s/p transplant.
- Diagnosis: obstructive lung disease – not asthma or COPD or bronchiectasis; occasionally: tree-in-bud small nodules.

Bronchiolitis obliterans (cont.)

- Treatment: bronchodilators, steroids (inhaled and systemic), immunosuppressants.
- Often poorly responsive to treatment.

“Tree-in-bud” pattern
3. **Solitary Pulmonary Nodule**

- Differential diagnosis: benign or malignant.
- Features of benign nodules: calcification; lack of growth (over 2 years).
- Diagnostic test: PET scan for nodules > 8 mm (negative scan indicates benign disease with 95% certainty; other 5%: bronchoalveolar Ca).

**Solitary Pulmonary Nodule (cont.)**

- Other diagnostic tests: bronchoscopy and transthoracic needle aspirate unreliable in excluding malignancy.
- For high-risk patients/larger nodules: surgical excision.
- For low-risk patients/smaller nodules: serial chest imaging over 2 years.
- Screening for lung cancers with chest CT scans: Reduces lung cancer deaths and may soon be recommended as routine practice.

4. **Pleural Effusions**

**(Dr. Anne Fuhlbrigge)**

- **Mechanisms:**
  - Hydrostatic imbalance (transudates)
  - Besides congestive heart failure:
    - Nephrotic syndrome
    - Trapped lung (also can be exudative)
    - Pulmonary embolism (also can be exudative)
    - Myxedema
    - Urinothorax
    - CSF leak

**Thoracentesis**

- **Whom to tap:**
  - More than 1 cm of layering fluid on lateral decubitus chest X-ray.
  - That does not appear typical of CHF.
- **How to tap:**
  - With ultrasound guidance if the effusion is small, hard to percuss on physical exam, esp. in patients on mechanical ventilation.

**Pleural Fluid Analysis**

- **Bloody effusion:**
  - In the absence of chest trauma, think: cancer, pulmonary embolism, pneumonia.
- **Chylous effusion:**
  - Chylomicrons present on lipoprotein analysis; pleural fluid triglycerides > 110 mg/dl.
  - In the absence of thoracic duct trauma, think obstruction due to: tumor, granulomatous disease, LAM, radiation fibrosis, or yellow nails syndrome.
Exudates vs. Transudates

- Light’s criteria for an exudate (any one of the following 3 characteristics):
  - Pleural fluid to serum total protein ratio >0.5
  - Pleural fluid to serum LDH ratio >0.6
  - Absolute pleural fluid LDH >2/3 upper limit of normal of serum LDH
- Albumin gradient:
  - Serum albumin – pleural fluid albumin >1.2 gm/dl indicates a transudate, including in congestive heart failure following diuresis.

White Blood Cell Differential

- Lymphocyte-predominant: think cancer, TB, post-CABG (Dressler’s syndrome), collagen-vascular disease
- Neutrophil-predominant: think parapneumonic, pulmonary embolism, pancreatitis.
- Eosinophilic: not helpful!!

Low Pleural Fluid pH

- Seen in: complicated parapneumonic effusion / empyema; tuberculous pleuritis; rheumatoid and lupus pleuritis; and long-standing malignant pleural effusions.
- Also seen with esophageal rupture; hemothorax; systemic acidosis; urinothorax.
- Most useful in management of parapneumonic effusions.

Pleural Fluid pH in Parapneumonic Effusions

- Results from intense inflammation and anaerobic glucose metabolism leading to production of lactic acid and CO2.

<table>
<thead>
<tr>
<th>Pleural Anatomy</th>
<th>Fluid Micro</th>
<th>Fluid pH</th>
<th>Risk of Poor Outcome</th>
<th>Drain?</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;½ hemithorax, loculated</td>
<td>GS or Cx POS or</td>
<td>pH &lt;7.20</td>
<td>Moderate / High</td>
<td>YES</td>
</tr>
<tr>
<td>≥½ hemithorax, pleural</td>
<td>GS and Cx NEG and</td>
<td>pH &gt;7.20</td>
<td>LOW</td>
<td>No, BUT need to follow</td>
</tr>
</tbody>
</table>

Management of Malignant Effusions

- HIGH functioning and NO lung entrapment: Chest tube + Pleurodesis
- Debilitated or Lung entrapment: Indwelling Pleural Catheter

Unexplained Exudative Effusion

- Special studies in certain cases: amylase, D-DIMER, adenosine deaminase, interferon-gamma, ANA, LE cells, RF.
- Send cytology again.
- Thoracoscopic pleural biopsy.
- Rare indication for closed needle biopsy.
5. COPD (Dr. George Washko)

- Definitions:
  - Chronic bronchitis: daily cough and sputum production for at least 3 months out of the year for at least 2 consecutive years.
  - Emphysema: abnormal dilation of airspaces due to destruction of alveolar walls.
  - COPD: some combination of chronic bronchitis and emphysema, causing airflow obstruction that is not fully reversible.

COPD (cont.)

- Staging severity:
  - FEV<sub>1</sub>
  - BODE index

Stages of Severity in COPD by FEV<sub>1</sub>

- Stage 0 -- At Risk: Spirometry = Normal
- Stage I -- Mild: FEV<sub>1</sub> 80-100%
- Stage II -- Moderate: FEV<sub>1</sub> <80
- Stage III – Severe: FEV<sub>1</sub> <50%
- Stage IV -- Very Severe: FEV<sub>1</sub> <30%

Stages of Severity/Predicting Survival: BODE Index

- B = Body-Mass Index (<21)
- O = Obstruction to airflow (FEV<sub>1</sub>)
- D = Dyspnea (MMRC dyspnea scale)
- E = Exercise tolerance (6-minute walk)

Outcome by Bode Index Score

Therapeutic Interventions: Smoking Cessation

- Smoking cessation counseling
- Nicotine replacement therapy
  - Patch, gum, lozenge, inhaler, nasal spray
  - Bupropion (Wellbutrin, Zyban)
  - Varenicline (Chantix) – a nicotinic acetylcholine receptor antagonist (and partial agonist)
Medical Therapies for COPD

- Bronchodilators
  - Long-acting inhaled beta-agonists
  - Once-daily anticholinergic
  - New: once-daily inhaled beta-agonist (indacaterol)
  - New: oral phosphodiesterase-4 inhibitor (roflumilast)
- Inhaled corticosteroids (do not slow decline in lung function in active cigarette smokers)
- Combination long-acting inhaled beta-agonist bronchodilator and inhaled corticosteroid
  - TORCH study

Towards a Revolution in COPD Health (TORCH)

- Fluticasone 500 mcg plus salmeterol 50 mcg (Advair 500/50) improved FEV₁ more than either component alone or placebo.
- Combination therapy improved overall survival (p=0.052).
- Risk of pneumonia was significantly higher in patients receiving inhaled steroids alone or in combination.

Additional Therapies for COPD

- Supplemental oxygen for the hypoxemic patient
  - Improves exercise capacity, reduces pulmonary hypertension and secondary polycythemia, and prolongs survival
- Pulmonary Rehabilitation
  - Improves exercise tolerance and quality of life
  - No evidence regarding prolonged survival

Additional Therapies for COPD

- Lung volume reduction
  - Improves function and – in a subset of patients – survival in carefully selected patients.
  - Bronchoscopic lung volume reduction
- Lung transplantation
  - Successful transplantation associated with dramatically improved function; overall no increase in survival
Diagnosis of Alpha-1 Antitrypsin Deficiency: History

Suspect alpha-1 antitrypsin deficiency if:
- early onset of emphysema (<age 50)
- emphysema in a non-smoker
- strong family history of emphysema
- basilar predominance to distribution of emphysema

Diagnosis of Alpha-1 Antitrypsin Deficiency: Blood Test

Measure the blood level of alpha-1 antitrypsin:
- Homozygous: 10-20% of normal level;
- Heterozygous: 50% of normal level ... and no disease.

Electrophoretic testing for ZZ phenotype is confirmatory.

Treatment of Alpha-1 Antitrypsin Deficiency: Replacement Therapy

Weekly infusions of alpha-1 antitrypsin protein (Prolastin, Aralast, Zemaira) are thought to protect against the progressive decline in lung function caused by alpha-1 antitrypsin deficiency.

6. Sleep Apnea (Dr. Lawrence Epstein)

**Definitions:**
- Apnea = cessation of airflow ≥10 seconds
- Obstructive apnea = apnea despite respiratory effort
- Central apnea = apnea without respiratory effort
- Mixed apnea = central followed by obstructive apnea

Central Apneas

- Common in CHF (40% of patients with EF <40%) as part of cyclic breathing pattern (Cheyne-Stokes Respiration).
- Treatment of Cheyne-Stokes respiration:
  - Medications: theophylline, acetazolamide
  - Supplemental oxygen
  - CPAP (does not improve survival)

Prevalence of Sleep Apnea Syndrome

- Among working population aged 30-60 yrs:
  - Men: 4%
  - Women: 2%
  - Criteria in this study = apnea-hypopnea index ≥5 plus reported symptoms of daytime hypersomnia.
  - Apnea-hypopnea index (AHI) = # of apneas and hypopneas per hour of sleep.
  - Hypopnea = decreased airflow associated with oxygen desaturation or sleep arousal.
Consequences of Sleep Apnea

Sleep fragmentation + recurrent hypoxemia/hypercapnia

- Daytime hypsomnolence
- Decreased productivity
- Automobile accidents
- Increased morbidity and mortality

Cardiovascular consequences
- Pulmonary HT
- Cardiac arrhythmias
- Systemic HT
- Cerebrovasc. disease

When to Suspect Sleep Apnea

- Snoring (loud, chronic)
- Nocturnal gasping and choking
- Excessive daytime sleepiness
- Automobile- or work-related accidents
- Personality changes or cognitive problems
- Risk factors

Risk Factors for Sleep Apnea

- Obesity (neck size: ≥17” in men; ≥16” in women)
- Increasing age
- Male gender; post-menopausal women
- Anatomic abnormalities of upper airway
- Family history
- Alcohol or sedative use
- Smoking
- Associated conditions

Diagnosis of Sleep Apnea Syndrome

- Overnight polysomnogram

Treatment of Sleep Apnea Syndrome

- Behavioral
  - Weight loss; avoid alcohol/sedatives; avoid sleeping on back; quit smoking
- Medical
  - CPAP/B-PAP
  - Oral appliances
- Surgery
  - UP3; mandibular advancement; others
  - Tracheostomy

Benefits of CPAP/B-PAP

- Decreased hypersomnolence; improved performance
- Improved nocturnal oxygenation
- Decreased systemic hypertension
- Decreased healthcare utilization
- Decreased mortality
7. Asthma (Dr. Jeffrey Drazen)

- Step-care approach to asthma treatment:
  - Old approach: categorize severity of asthma
  - New approach: assess asthma control
    - Do asthma symptoms prevent ADL?
    - Nighttime awakenings?
    - Frequency of rescue inhaler use?
    - Unscheduled visits to physicians?
    - Is lung function near normal?

Asthma (cont.)

- Stepping up therapy in poorly controlled asthma:
  - Complicated Rx: Omalixumab (Xolair)
  - Three controllers
    - ICS+Anti-LT or ICS-LABA
  - Rescue Inhaler Only

Inhaled Corticosteroids

<table>
<thead>
<tr>
<th>Metered-Dose Inhaler</th>
<th>Dry-Powder Inhaler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone (Qvar)</td>
<td>Budesonide (Pulmicort)</td>
</tr>
<tr>
<td>(40, 80 mcg/puff)</td>
<td>(90, 180 mcg/inhal)</td>
</tr>
<tr>
<td>Fluticasone (Flovent HFA)</td>
<td>Fluticasone (Flovent Diskus)</td>
</tr>
<tr>
<td>(44, 110, 220 mcg/puff)</td>
<td>(50, 100, 250 mcg/inhal)</td>
</tr>
<tr>
<td>Ciclesonide (Alvesco HFA)</td>
<td>Mometasone (Asmanex)</td>
</tr>
<tr>
<td>(80, 160 mcg/puff)</td>
<td>(110, 220 mcg/inhal)</td>
</tr>
</tbody>
</table>

Dosing of Inhaled Corticosteroids (mcg/day)

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;400 mcg</td>
<td>400 – 800 mcg</td>
<td>&gt;800 mcg</td>
</tr>
</tbody>
</table>

LABAs Alone and in Combination with ICS

<table>
<thead>
<tr>
<th>Long-Acting Beta-Agonists (LABAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol (Foradil) – Single-dose DPI</td>
</tr>
<tr>
<td>Salmeterol (Serevent) – Multi-dose DPI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination ICS + LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone + salmeterol (Advair) – Multi-dose DPI and HFA-MDI</td>
</tr>
<tr>
<td>Budesonide + formoterol (Symbicort) – HFA-MDI</td>
</tr>
<tr>
<td>Mometasone + formoterol (Dulera) – HFA-MDI</td>
</tr>
</tbody>
</table>

Leukotriene Modifiers

<table>
<thead>
<tr>
<th>Leukotriene Receptor Antagonists:</th>
<th>Montelukast (Singulair)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zafirlukast (Accolate)</td>
</tr>
</tbody>
</table>

| Epoxygenase Inhibitor:           | Zileuton (Zyflo)        |
## Asthma Therapy

When choosing therapy, consider:
- Albuterol p.r.n. = albuterol Q.I.D.
- Albuterol MDI (HFA) = Albuterol MDI (CFC)
- Long-acting beta agonists (SMART study):
  - Should not be used without ICS
  - Should not be used to treat mild asthma
- Environmental control measures:
  - Reduce asthmatic symptoms when applied in a comprehensive and systematic approach

## Environmental Control Measures

- 6 educational modules: dust mites; cigarette smoking; pets; cockroaches; rodents; and mold.
- Equipment and support:
  - Allergen-impermeable bed wraps
  - HEPA-filtered vacuum cleaners
  - HEPA room air filter
  - Cockroach extermination

## Asthma Therapy

Inhaled corticosteroids:
- Prevent asthmatic exacerbations
- Do not alter the natural history of asthma (that is, do not prevent the development of irreversible airflow obstruction)
- Have dose-dependent systemic absorption, impacting:
  - Bone density, cataracts, intraocular pressure, and skin bruising/thinning
- Can be used intermittently in mild, well-controlled asthma

## Trends in Asthma Deaths in U.S.

**Figure 1: Asthma - Age-Adjusted Death Rates Based on the 1940 and 1950 Standard populations, 1979-2006.**


## Interstitial Lung Disease (Dr. Hillary Goldberg)

- **Consider** chronic interstitial lung disease:
  - Exertional dyspnea with non-productive cough
  - Inspiratory crackles
  - Not heart failure
  - Obtain additional history:
    - environmental/occupational exposures
    - collagen-vascular disease

## Interstitial Lung Disease (cont.)

- **Confirm** chronic interstitial lung disease:
  - Linear and nodular infiltrates on CXR, CT scan
  - Restriction on PFTs
    - exceptions: some sarcoidosis, eosinophilic granuloma, LAM
  - Oxygen desaturation with exercise
Interstitial Lung Disease (cont.)

- Establish diagnosis of chronic interstitial lung disease:
  - Thoracoscopic lung biopsy (VATS)
  - Bronchoscopy
    - to Dx sarcoidosis, hypersensitivity pneumonitis, or lymphangitic carcinomatosis
    - to exclude infection, malignancy

Idiopathic Pulmonary Fibrosis vs. Sarcoidosis

<table>
<thead>
<tr>
<th></th>
<th>IPF</th>
<th>Sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>&gt;Middle age</td>
<td>20-50 y.o.</td>
</tr>
<tr>
<td>Radiographic appearance</td>
<td>Bibasilar predominance</td>
<td>Lymphadenopathy; upper lobe predominance</td>
</tr>
<tr>
<td>CT appearance</td>
<td>Characteristic subpleural honeycombing</td>
<td>Variable: ground-glass opacities; peribronchial nodules</td>
</tr>
</tbody>
</table>

Idiopathic Pulmonary Fibrosis vs. Sarcoidosis

<table>
<thead>
<tr>
<th></th>
<th>IPF</th>
<th>Sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-pulmonary involvement</td>
<td>None (except clubbing)</td>
<td>Myriad, including: eyes, liver, skin, calcium metabolism.</td>
</tr>
<tr>
<td>Pathology</td>
<td>UIP: fibrosis interspersed with normal lung</td>
<td>Non-caseating granulomas</td>
</tr>
</tbody>
</table>

Idiopathic Pulmonary Fibrosis vs. Sarcoidosis

<table>
<thead>
<tr>
<th></th>
<th>IPF</th>
<th>Sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural history</td>
<td>50% mortality at 3 years</td>
<td>Progression in small minority</td>
</tr>
<tr>
<td>Treatment</td>
<td>Prednisone + azathioprine increases mortality; Observation and supplemental oxygen; Lung transplantation</td>
<td>Nothing needed; Prednisone; Infliximab (Remicade)</td>
</tr>
</tbody>
</table>