Diagnosis and Differential Diagnosis of Asthma

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Disclosures: None
Disclosures

• Nothing to disclose
Objective

• Delineate the steps to accurately identify patients with refractory asthma and to rule out other conditions and comorbidities that may mimic the disease
Difficult to Control Asthma: Case Study

- 29 yo physician referred by Pulmonologist
  - Recurrent wheezing/SOB/ chest tightness lasting up to 2 hrs
  - Symptoms worse x 8 months

- PMHx
  - Age 8-10: nocturnal awakening with dyspnea
  - Age 19: episodic bronchitis/wheeze the wk before menses
  - Severe exacerbation: 1 month ago (ER x 24 hours)

- ROS
  - Triggers: cold air, perfume, dust, ETS
  - Unable to walk up 1 flight of stairs
Case Study

• Social: lifetime non-smoker
• Allergies: Sulfa, ASA, Ibuprofen
• Meds: BCP, LABA/high dose ICS combination, LTRA, Albuterol nebs prn
• PE: 138/78 RR 14 WNL including normal lung exam
• Prior w/u
  – Echo – nl LV fxn with PASP 16 (normal); stress test- negative
  – PFTs:
    • WNL
    • FEV₁ 3.04 L (98%), FEV₁/FVC (91%), FEF₂⁵⁻⁷⁵ (134%); DLCO (102%)
  – Labs: normal CBC, BNP, D-dimer, total eosinophil count, Ig-E
  – CXR and HRCT both WNL
Diagnosis of Refractory Asthma
Pathobiology of Asthma: Why Different Patients Need Different Therapies

Neutrophilic Asthma
- Severe asthma
- Occupational asthma
- Obesity
- Hyper acute asthma

- Does our patient have refractory asthma?
- What is the differential diagnosis to consider in patients with refractory asthma?
- What happened to our patient?
Definition of Asthma: Making Sure the Patient Really Is Asthmatic

- Symptoms: Cough, dyspnea, and/or wheeze
- Reversible airflow obstruction
  - By spirometry (obstruction with 12%/200cc increase in FEV$_1$ post-BD)
  - Methacholine/mannitol challenge test
- Ruling out other disorders that mimic asthma
Definition of Refractory Asthma

• Diagnosis of asthma confirmed & comorbidities treated
• Requiring high dose ICS and second controller (LABA)
  – To prevent asthma from being “uncontrolled”
  – Remains “uncontrolled”
• Uncontrolled asthma is defined by:
  – Poor Sx control: ACQ consistently > 1.5; ACT < 20
  – Two or more burst of oral steroids/yr
  – At least one hospitalization/yr
  – Persistent airflow limitation (FEV₁ < 80%; FEV₁/FVC < LLN)

Eur Respir J 2014; 43:343-373
Definition of High Dose Inhaled Corticosteroids

<table>
<thead>
<tr>
<th>Inhaled corticosteroid</th>
<th>Threshold daily dose in µg considered as high</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Age 6–12 years</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>≥800 (DPI or CFC MDI)</td>
</tr>
<tr>
<td></td>
<td>≥320 (HFA MDI)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>≥800 (MDI or DPI)</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>≥160 (HFA MDI)</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>≥500 (HFA MDI or DPI)</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>≥500 (DPI)</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>≥1200</td>
</tr>
</tbody>
</table>

- **Ciclesonide** > 320 mcg/day HFA or DPI
- **Beclomethasone** > 640 mcg/day HFA
- **Fluticasone propionate** > 880 HFA; 1000 mcg/day DPI
- **Mometasone** > 1000mcg/day HFA or DPI
- **Budesonide** > 1600 mcg/day HFA or DPI
Differential Diagnosis of Refractory Asthma
Differential Diagnosis in Asthma

• Vocal Cord Dysfunction (ILO)
• Bronchiectasis (ABPA/Cystic Fibrosis)
• Hypersensitivity pneumonitis/Sarcoidosis
• Churg-Strauss Syndrome
• COPD/Overlap Syndrome
• Obstructive Bronchiolitis
• Pulmonary emboli
• Congestive Heart Failure (Cardiac asthma)
• Tracheal stenosis/Airway tumors
Features of VCD

Common Triggers

- **Exercise** 25-30%
- **Irritants** 20%
  - GERD
  - Rhinosinusitis
  - Dust, fumes, vapors
- **Psychogenic** 20%
  - Depression
  - Sexual abuse
- **Neurogenic** 5% (*ALS, MG*)
Vocal Cord/Laryngeal Dysfunction

- Vocal Cord dysfunction
  - Adduction of anterior 2/3 of vocal cords
    - Usually inspiratory (60-70%)
    - Expiratory (20-30%)
    - Bilateral (5%)
  - Co-existent asthma: 32%
  - Not present during sleep
  - FEV$_1$ out of proportion to airway resistance
- Rx: Speech pathology, Biofeedback
Question: 45 y.o. male with hx of stable asthma for 5 years. Recent asthma exacerbations 2-3 times/month. New hobby- woodworking. A possible cause of his exacerbations is:

A. Acute hypersensitivity pneumonitis
B. Sub-acute hypersensitivity pneumonitis
C. Chronic hypersensitivity pneumonitis
D. Acute Bacillus subtilis infection
E. Chronic Bacillus subtilis infection
### Hypersensitivity Pneumonitis

#### Table 1. Some common inciting antigens for hypersensitivity pneumonitis

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Source</th>
<th>Exposure risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Saccharopolyspora rectivirgula</em></td>
<td>Moldy hay and compost</td>
<td>Farmers</td>
</tr>
<tr>
<td>Avian proteins</td>
<td>Bird droppings and feathers</td>
<td>Bird fanciers and pigeon breeders</td>
</tr>
<tr>
<td><em>Thermoactinomyces sacchar</em></td>
<td>Sugar cane residue (bagass)</td>
<td>Sugar cane workers</td>
</tr>
<tr>
<td><em>Amoeba (Naegleria gruberi)</em></td>
<td>Contaminated HVAC systems and humidifiers</td>
<td>Office workers</td>
</tr>
<tr>
<td><em>Bacillus subtilis</em> proteins</td>
<td>Contaminated wood dust</td>
<td>Woodworkers</td>
</tr>
<tr>
<td>Penicillium casei</td>
<td>Cheese mold</td>
<td>Cheese workers</td>
</tr>
<tr>
<td><em>Aspergillus clavatus</em></td>
<td>Contaminated barley</td>
<td>Malt workers and brewers</td>
</tr>
<tr>
<td><em>Mycobacterium avium intracellulare</em></td>
<td>Hot tubs</td>
<td>Hot tub users</td>
</tr>
<tr>
<td><em>Trichosporon cutaneum</em></td>
<td>Mold in Japanese homes</td>
<td>Japanese house dwellers during summer months</td>
</tr>
<tr>
<td>Rodent proteins</td>
<td>Rodent dander</td>
<td>Animal handlers and laboratory workers</td>
</tr>
<tr>
<td>Soybean hull antigens</td>
<td>Soybeans in animal feed</td>
<td>Farmers and animal feed handlers</td>
</tr>
<tr>
<td>Wheat weevil protein</td>
<td>Infected wheat</td>
<td>Wheat workers and silo fillers</td>
</tr>
<tr>
<td>Anhydrides</td>
<td>Plastic components</td>
<td>Plastic workers</td>
</tr>
<tr>
<td>Isocyanates</td>
<td>Paint hardeners</td>
<td>Painters</td>
</tr>
<tr>
<td>Pyrethrum</td>
<td>Insecticides</td>
<td>Farmers and gardeners</td>
</tr>
</tbody>
</table>

- Granulomatous inflammation secondary to organic particles or fumes
- Over 200 antigens have been identified
- Not an atopic disorder (no increase in IgE or Eosinophils)
- 95% of HP cases occur in nonsmokers

*Curr Opin Pulm Med 2004; 10: 401-411*
Hypersensitivity pneumonitis

• Acute HP
  – Flu-like sx 4-8 hours after exposure
  – Peak 24-48 hours: fever; elevated WBC; mixed obstruction/restriction
  – CXR: GGO or patchy infiltrates
• Subacute HP
  – Dyspnea, fatigue, cough
  – Mimics asthma or acute bronchitis
• Chronic HP (5%: may progress to IPF)

Treatment: Avoidance of antigen exposure and corticosteroids
Allergic Bronchopulmonary Aspergillosis

• ABPA
  – Allergic immune response to Aspergillus
  – Frequency: 2% asthma; 2-15% CF

• Clinical features
  – Cough, wheeze, +/- ↑sputum
  – Hallmark: serum IgE > 1000 IU/ml
  – Radiographic features
    • Fleeting infiltrates or nodules
    • Mucus plugging +/- atelectasis
    • Central bronchiectasis
Allergic Bronchopulmonary Aspergillosis

- Consider in refractory asthma
  - Diagnostic criteria
    - Asthma with IgE >1000 IU/ml
    - Immediate skin test positive
    - IgE or IgG to Aspergillus positive
    - Central bronchiectasis
  - Therapy for ABPA
    - Prednisone .5 mg/kg x 2 wks
    - Convert to .5 mg/kg QOD x 8 wks
    - Taper 5-10 mg every 2 weeks
    - Monitor IgE q2 months x 1yr
    - Two fold rise suggest relapse

Chest 2009;135:805-826
Eosinophilic granulomatosis with polyangiitis: (Churg-Strauss/EGPA)

- Clinical features
  - Asthma (adult onset/poorly controlled)
  - Eosinophilia (> 1,500/L or 10%)
  - Necrotizing vasculitis

- EGPA Subtypes
  - ANCA (MPO) positive
    - Kidney: necrotizing GN
  - ANCA negative (asthma phenotype)
    - More cardiac involvement

Pathologic features:
- Extravasc granulomas
- Necrotizing vasculitis
- Tissue eosinophilia

CT: EGPA

EGPA/CSS
CXR: nl 35%
CT: GGO +/- nodules
Eosinophilic granulomatosis with polyangiitis

• Pulmonary involvement with EGPA
  – Worsening or refractory asthma
  – Severe sinusitis +/- polyposis

(Note: HRCT: GGO 86% in EGPA vs. 4% in asthma)

Other organs frequently involved: nerve; abdomen, kidney, cardiac (eosinophilic infiltration or vasculitis)

• Treatment
  – Prednisolone 1 mg/kg/day
  – Cytoxan .6 gm/m2 monthly (Hemorrhagic cystitis: Cellcept)
  – Salvage therapy: retuximab or mepolizumab
What happened to our patient?

Fiberoptic laryngoscopy – *Gold Standard*

**Case study:** Exercised up/down steps then carried her into PFT lab (flow-volume loop)

*Exercise prior to bronchoscopy:*
- Contraction of vocal cords inspiration/expiration
- Biopsy: thickening of basement membrane
- BAL: 4% eosinophils
CASE STUDY: Follow-up

- Patient seen by ENT (Speech Therapist)
  - Trained in control of breathing/airway relaxation
- Did well for 18 months; became pregnant
- Asthma worsened last trimester/post-partum
  - Rx with high dose ICS, LABA, LTRA
  - Visiting ER every 1-2 months
- Re-evaluated patient in clinic (3 months post-partum)
  - Sent sputum eosinophils, IgE
  - Sent repeat RAST/Immunocap for aeroallergens
Questions to be considered:

• What would you do with this patient at this point?
• What pharmacologic therapies could be added to improve her asthma control?
• If her asthma remains poorly controlled, is she a candidate for bronchial thermoplasty?
• What future therapies are likely to be available to control refractory asthma?
Question: 45 y.o. male with hx of stable asthma for 5 years. Recent asthma exacerbations 2-3 times/month. New hobby- woodworking. A possible cause of his exacerbations is:

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Questions?
Dr. William Calhoun

• Current pharmacological therapies
• Future pharmacological therapies
Dr. Diego Maselli

- Non-pharmacological management of Refractory Asthma
  - Treating comorbidities
  - Bronchial Thermoplasty