Sometimes it’s COPD . . . Sometimes it’s not

Jacqueline Chang, MD, FCCP
Chief, Division of Pulmonary/Critical Care
Scripps Clinic
La Jolla, California
“Not everyone who wheezes or coughs has COPD”

1. Give due diligence to COPD: update on this common disease with emphasis on diagnosis
2. Discuss other diseases which can mimic COPD:
   - chronic obstructive asthma
   - bronchiectasis
Why COPD remains important

- 4th leading cause of death in US and Europe
- COPD mortality in women has doubled over the last 20 years
- Cost of COPD: $87 per capita (1992 dollars)
- 75% of these costs are for exacerbations
What is COPD and how do we diagnose it?

*COPD is a preventable and treatable disease, with some significant extrapulmonary effects, whose pulmonary component is characterized by airflow limitation that is not fully reversible.*

*COPD should be considered in anyone with dyspnea and cough with risk factors for the disease and should be confirmed with spirometry.*
Diagnosing COPD

Prevalence of COPD in general adult population (age 25-75): 7% mild disease, 7% moderate disease

Less than 50% of patients with COPD by spirometric criteria had the diagnosis

Why is the diagnosis of COPD being missed?
Case example

J.K. is a 68 y/o never smoker with SOB, wheezing with “severe asthma”. She presented for a second opinion because her previous physician felt she was non compliant since she was not responding to the medications: singulair, advair, albuterol, allergy shots

Why is she not responding?
History:
She denies associated allergic rhinitis, eczema or atopy.
Upon specific questioning, she reports a lifetime exposure to second hand smoke. Growing up both parents smoked. Her husband of 40 years smokes and continues to do so.
PFTs: FEV1/FVC =60%. FEV1 = 68%. No BDR. Methacholine challenge: negative

Dx: COPD
The “face” of COPD
Risk factors for COPD

Risk is related to the total burden of inhaled particles over a lifetime

1. Tobacco smoke: cigars, cigarettes, pipe, environmental smoke
2. Occupational dusts and chemical (vapors, irritants, and fumes)
3. Indoor pollution: biomass fuels
4. Outdoor pollution
Non-tobacco related exposures and COPD

Occupational exposure estimated to account for 19% of COPD cases overall and 31% cases in non-smokers (MMWR 2002)

European Community Respiratory Health Study: Dust, fumes, gases, or vapor exposure increases risk of chronic bronchitis 30%

Copenhagen study: OR for chronic bronchitis
- Long term dust exposure and organic solvents, OR = 1.5
- Occupational smoke inhalation, OR = 1.7
Treatment for COPD

• Behavioral: Smoking cessation and exposure reduction
• Pharmacologic: Short acting bronchodilators, long acting bronchodilators, phosphodiesterase-4 (PDE4) inhibitors
• Adjunctive: pulmonary rehabilitation
Don’t forget smoking cessation
Lung Health Study

Most important study for COPD
  Sponsor NHLBI

RCT of 6000 patients to smoking cessation intervention vs placebo

Mild-moderate COPD

Only study
  Reduction in mortality
  Meaningful effect on lung function

Only RCT to demonstrate that smoking kills
TORCH Trial: Salmeterol and Fluticasone propionate and Survival in Chronic Obstructive Pulmonary Disease

NEJM 2007. 356: 775-789

Randomized, double-blind trial comparing salmeterol (50 µg) plus fluticasone propionate (500 µg twice daily) combination regimen, salmeterol alone, or fluticasone propionate alone versus placebo for a period of 3 years.

Primary outcome: death from any cause
Other outcomes: frequency of exacerbations, health status, and spirometric values
SFC Combination Therapy versus Placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SFC vs Placebo: hazard ratio</th>
<th>P value</th>
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<tbody>
<tr>
<td>Probability of death at 3 yr</td>
<td>0.825</td>
<td>0.052</td>
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<tr>
<td>Mod/severe exacerbation</td>
<td>0.75</td>
<td>&lt;0.001</td>
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<td>Exacerbation requiring steroids</td>
<td>0.57</td>
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<td>Exacerbation requiring hospitalization</td>
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25% reduction in exacerbation (NNT=4)
Improved quality of life
Improved lung function: For all time points, FEV1 was highest in SFC
SHINE study: randomized double blind multicenter trial of budesonide/formoterol in moderate-severe COPD
ERS 2003. 21: 74-81

Comparison of budesonide/Formoterol 160/4.5 versus Formoterol versus placebo

Primary outcome: reduction in severe exacerbations and FEV1
Other outcomes: QOL, reduction in mild exacerbations

Moderate -severe COPD: FEV1 <=50%
Mean FEV1 = 1L
Average smoking history: 44 pack years
SHINE study results

Budesonide/formoterol reduced number of severe exacerbation 24% vs placebo and 23% versus formoterol

Budesonide/formoterol improved FEV1 15% compared with placebo and formoterol

Budesonide/formoterol improved symptom scores
Tiotropium in Chronic Obstructive Pulmonary Disease (UPLIFT)

NEJM. 2008. 359: 1543-54

4 year study with tiopropium or placebo in patients with COPD who were permitted to use all other respiratory medications
Primary endpoint: rate of decline in FEV1
Other endpoints: QOL, exacerbations, mortality

“Placebo” group were actually aggressively treated.
Almost 70% of both groups on steroids
60% of both groups on LABA
Almost 30% of both groups on theophylline
UPLIFT Study Results

A COPD Exacerbation

- **Placebo**
- **Tiotropium**

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo</th>
<th>Tiotropium</th>
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<td>8</td>
<td>2249</td>
<td>2306</td>
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Hazard ratio, 0.86
(95% CI, 0.81–0.91)
P<0.001

B Death from Any Cause

- **Placebo**
- **Tiotropium**

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Hazard ratio, 0.89
(95% CI, 0.79–1.02)
P<0.001
UPLIFT Summary

Primary endpoint: No difference in the rates of decline in FEV1 between the two groups

Important secondary outcomes:
1. Consistently higher lung function
2. Improved quality of life
3. Reduced number of exacerbations and delay in time to first exacerbation
4. Lower mortality (RR: 0.76-0.99)
5. Lower respiratory failure (RR 0.51-0.89)
Roflumilast in symptomatic COPD
Lancet 2009;374:685-94

Phosphodiesterase inhibitors provide a novel treatment for certain patients with COPD: reduce airway inflammation

Two placebo controlled multi-center trial: moderately severe patients randomised to 500 micrograms roflumilast versus placebo for 52 weeks

Severe airflow obstruction: FEV1 < 50%
Bronchitic symptoms
H/o exacerbations in prior year: steroids or hospitalization
Roflumilast study results

Primary endpoints: Change in FEV1 during treatment, rate of exacerbations

3091 patients randomized between the 2 studies: mean FEV1 = 1 L

Change in FEV1: in the roflumilast group, FEV1 increased 40-50 ml; in the placebo group, FEV1 decreased 9 ml (p<0.0001)

Exacerbations: roflumilast group experienced 16% fewer moderate or severe exacerbations (p<0.0003)
Roflumilast Side Effects

Higher incidence of study withdrawal in roflumilast group in first 12 weeks: centrally mediated effects (insomnia, nausea, HA) and GI (diarrhea)

Roflumilast group experienced greater weight loss: average approx. 5 lbs, attenuated after 6 months

No difference between roflumilast and placebo for the following:
pneumonia and pulmonary infections
cardiac events and arrhythmia
"Well, you see, I went to one of those progressive medical schools with no formal classes or credits and the students plan their own course of study so I never learned anything about the lungs, breathing and all that."
COPD versus Asthma

Reversibility of airflow obstruction

COPD: partially reversible airflow obstruction
Asthma: significant, if not total, reversibility of airflow obstruction

Can we always make that distinction?
Chronic Obstructive Asthma

Copenhagen study (NEJM 1998; 339:1194-1200): 15 year longitudinal study of ventilatory function in 19,698 adults with asthma.

Rate of decline greater for patients with asthma than for those without asthma (38 ml/year versus 22 ml/year)

Extrapolation: a 60 y/o man with asthma could have an FEV1=1.99L compared with a man without asthma who would have an FEV1=3.05L

Confirmed that chronic obstruction could develop in long standing asthma
Chronic Obstructive Asthma

Epidemiologic studies show that 30% of patients with fixed airflow obstruction have a history of asthma.

Some international guidelines recommend classifying asthma with fixed obstruction COPD.

Does it matter? Are they essentially the same disease?

Yes ... No ...
Case example

55 y/o man diagnosed with adult asthma 20 years ago. He used Advair in the distant past but for the last 5 years has been on no controlling agents. Now he has daily asthma symptoms of SOB and tightness and has stopped exercising as a result.

Social history: Smoked lightly for 3-4 years. However worked 28 years as a firefighter, including 14 years working on wild fires on West Coast

Family history: strong history of asthma (both parents, sister)

What type of obstructive disease does he have?
Case example: 55 y/o man

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<th>Pre-</th>
<th>Post-</th>
<th>% change</th>
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<tbody>
<tr>
<td>FVC</td>
<td>4.2 L (79%)</td>
<td>6.2 L (117%)</td>
<td>+ 49%</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.1 L (27%)</td>
<td>2.5 L (61%)</td>
<td>+122%</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.26</td>
<td>0.40</td>
<td></td>
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Asthma with fixed obstruction is still asthma and distinct from COPD

Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. Fabbri, et al. Am J Resp Crit Care Med 2003. 167 (3); 418-424

46 patients with similar fixed airflow obstruction and bronchial responsiveness: 27 COPD and 19 Asthma patients were compared

PFTs
Clinical features
HRCT

BAL and bronchial bx characteristics
Asthma with fixed obstruction is still asthma and distinct from COPD.

Asthma patients still have prominent airway eosinophilia.

Fixed obstruction: different mechanism in asthma (basement membrane thickening).
Asthma with fixed obstruction is still asthma and distinct from COPD

Inflammatory markers: consistently higher in asthma patients
PFTs: asthma patient have lower residual volumes (less hyperinflation) and higher DLCO and pO2 in blood
HRCT: asthma patients had lower emphysema scores
Clinical features: asthma patients still had better response to bronchodilators and steroids and had a better prognosis

Proof of principle: within a group of patients with fixed airflow obstruction, those with a history of asthma have distinct airway inflammation as compared with those with a history of smoking-induced COPD. This finding suggests that asthmatic airway inflammation does not change with the development of fixed airflow obstruction and thus does not become similar to the airway inflammation characteristic of COPD.
Asthma with fixed obstruction has similarities to COPD but is distinct from COPD

Many of the same bronchodilators are used in advanced asthma and COPD: short acting bronchodilators, inhaled corticosteroids/LABA combinations, tiotropium (a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease)
Tiotropium bromide step-up therapy for adults with uncontrolled asthma. NEJM 2010; 363 (18) 1715-26

NHLBI Asthma Clinical Network study: three-way, double-blind, triple-dummy crossover trial involving 210 patients with asthma not well controlled on low-moderate doses if ICS

Three arms: (1) addition of tiotropium bromide to an inhaled glucocorticoid compared with (2) doubling of the dose of the inhaled glucocorticoid or (3) addition of LABA (salmeterol)

Tiotropium added to ICS improved symptoms and lung function

Tiotropium was as effective as salmeterol for all outcomes including symptom control and was superior in its effects on FEV1
Asthma with fixed obstruction has similarities to COPD but is distinct from COPD

Because ongoing eosinophilic and lymphocytic inflammation is ongoing, inhaled corticosteroids remain essential

Montelukast is helpful in asthma but has no role in COPD

Patients may still have allergic triggers and may benefit from any IGE therapy (Xolair)

Adjunctive therapies such as bronchial thermoplasty may be helpful in asthma but have no role in COPD
LABA and the risk of death in asthma


Comparison: Salmeterol versus placebo
Study stopped because of interim analysis in 26,355 patients

Small increase in respiratory related death: 24 vs 1
RR=2.16 (CI 1.05-4.41)
Small increase in asthma related deaths: 13 vs 3
RR= 4.37 (CI 1.25-15.34)
Small increase in asthma related death or life threatening experiences: 37 vs 22
RR= 1.7 (CI 1.01-2.89)
Safety of LABA among patients with asthma using inhaled corticosteroids: systematic review and meta-analysis

Rational: Given the increase risk of LABAs as monotherapy in asthma, does the same risk exist in patients using ICS/LABA

Study cohort: 62 studies with > 29,000 patients looking at the effects on mortality and morbidity of LABAs in patients taking ICS

15,710 patients taking LABAS, >8000 patient-years exposure
3 asthma related death, 2 intubations
No difference in asthma related hospitalizations: OR = 0.74 (CI 0.53-1.03)
No difference in asthma serious events OR = 0.75 (CI 0.54-1.03)
Anti-Immunoglobulin E (omalizumab) therapy in Allergic Asthma
Am J Resp Crit Care Med 2001; 164: S 12-17

Randomized double blind placebo controlled trial:

ICS
Placebo or omalizumab +ICS
Placebo or omalizumab ICS withdrawal
Placebo or omalizumab ICS

Run -in phase
Efficacy phase
Extension phase

Safety phase

Primary endpoint: Asthma exacerbations in stable steroid and steroid withdrawal phase
Anti-Immunoglobulin E (omalizumab) therapy in Allergic Asthma

The reduction in asthma exacerbations in the omalizumab group occurred despite the significantly greater reduction of BDP dose from baseline to the end of treatment in the omalizumab group compared with the placebo group.

Omalizumab group associated with more significant ICS dose reduction or total ICS dose withdrawal.
New therapies: bronchial thermoplasty in severe asthma
AIR2 TRIAL. Am J Resp Crit Care Med 2010; 181:116-124

Rationale: Increases airway smooth muscle (ASM) mass and contractility cause increased bronchospasm and obstruction and contribute to asthma morbidity

Bronchial thermoplasty delivers controlled thermal energy to bronchial wall decreasing ASM mass

Randomized (2:1) double blind sham controlled trial in 225 adult patients with severe asthma

Primary endpoint: change in asthma symptoms (AQLQ)
Secondary endpoints: PEF, rescue medication use for 12 months, health care utilization
Bronchial thermoplasty in severe asthma

Mean change in AQLQ score was higher in thermoplasty group compared with the sham group

Reduced severe exacerbations and ER visits in thermoplasty group compared with sham group
Bronchial thermoplasty - adverse events

Events during the treatment period: higher in thermoplasty group
Airway irritation/bronchospasm = asthma symptoms
Upper respiratory tract infection
8.4% thermoplasty group required hospitalization
2% sham group required hospitalization
Majority of these events occurred within 1 day of the procedure and resolved by 7 days post procedure

Events during post procedure period: fewer in thermoplasty group
36% risk reduction of asthma symptoms
84% risk reduction of ER visits
Case: a second opinion for shortness of breath, wheezing, and cough

61 y/o retired farmer from Bakersfield, CA
Treated for the last 5 years for asthma with Advair, singulair, albuterol desensitization therapy. None have helped. Steroid pulse did not help.

Outside workup: allergy testing (allergic to most weeks, trees and grasses, less so to mold and dust mites)

Peak flow self monitoring: varies by 150 and albuterol changes is minimally

One of his biggest complaints: chronic cough

Is his diagnosis asthma?
Asthma versus COPD versus Bronchiectasis?

COPD risk factors:
1. ppd for 20 years, quite 30 years ago
2. Lifetime exposure to dust and organic materials (cotton and wheat)

Exam: O2 sat 97% and lungs were clear
PFTs: FEV1 = 75% predicted, DLCO WNL, no BD response

Serum IgE level normal
HRCT scan: bronchiectasis

Conclusion: COPD with bronchiectasis
Bronchiectasis in COPD patients

Prospective study assessing the prevalence of bronchiectasis in patients with moderate-severe COPD: 106 patients over 2 year period with COPD but w/o any prior dx of bronchiectasis

All patients evaluated with clinical questionnaires, PFTs, sputum samples, and HRCT

Bronchiectasis by HRCT was found in 57% of moderate COPD patients and 73% of severe COPD patients
Bronchiectasis in COPD patients

COPD patients with bronchiectasis:
more symptoms of chronic cough
more exacerbations
more likely to have positive sputums for pathogenic organisms

Bronchiectasis may be an incidental finding with implications for prognosis and therapy
Some estimates of prevalence:
All ages: 25 per 100,000
Elderly 75+ years old: 272 per 100,000

Economic burden is great (2001 estimated annual cost to care for a patient)
Bronchiectasis $13,244*
COPD $11,000-13,000
Heart disease $12,000

*Cost is greater in patients with resistant organisms requiring IV antibiotics
Bronchiectasis: a vicious cycle of damage

Bronchial damage causes chronic enlargement

- Decreased ability to clear secretions
  - Collection of microbes and particles
    - Further secretions and inflammation
      - Further damage to airways
Diagnosing bronchiectasis

Clinical index of suspicion:
symptoms- chronic cough, sputum, prior unusual pathogens, recurring infection
compatible personal history- prior infection (childhood illness, pertussis, tuberculosis), pneumonia
family history- cystic fibrosis, immunodeficiencies

Pulmonary function testing: NOT UNIQUE
Obstructive
May show strong bronchodilator response

Imaging:
CXR insensitive
HRCT scan is the gold standard
Bronchiectasis on CT scan

Bronchial dilation and thickening: signet ring sign
Bronchiectasis treatments

Similarities to other obstructive lung diseases:
Bronchodilators (nebulized treatments over MDIs or powder inhalers)

Differences from other obstructive lung diseases:
Antibiotics (early administration, importance of culture directed therapy, screening for atypical organisms)
Secretion mobilization or “pulmonary toilet”
- hypertonic saline, mucomist
- clearance mechanisms: exercise, acapella valve, fluter device, vibratory vest
**Take home points**

*“Not every patient who wheezes has COPD”*
*Try to define the phenotype based upon clinical features, risk factors, PFTs, and imaging*

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<tr>
<th><strong>COPD</strong></th>
<th><strong>Asthma</strong></th>
<th><strong>Bronchiectasis</strong></th>
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</thead>
</table>
| - risk factors: lifetime burden of inhaled irritants  
- symptoms of chronic bronchitis  
- PFTs: Less often strong bronchoreactivity  
- CT: emphysema | - Atopic history  
- symptoms of bronchoreactivity  
- PFTs: more likely bronchoreactivity, preserved DLCO  
- CT: air trapping without emphysema | - risk factors: prior infections/ pna or immunodeficiency  
- more prominent cough and frequent infections  
- atypical organisms  
- CT scan: bronchial dilation and thickening  
- Bronchoscopy: airway thinning and pitting |