

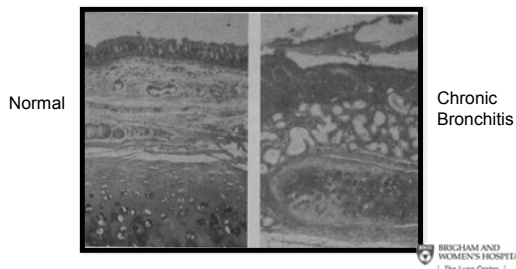
Lecture Outline

- I. Diagnosis and staging
- II. Prevention
- III. Treatment
 - A. Pharmacologic (including exacerbations)
 - B. Non-pharmacologic

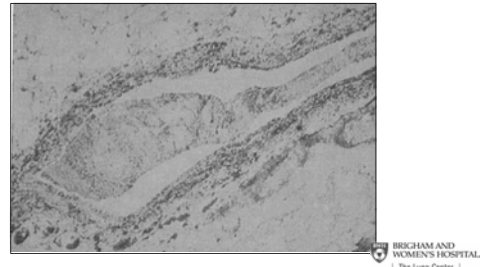
COPD: Defining Terms

- **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

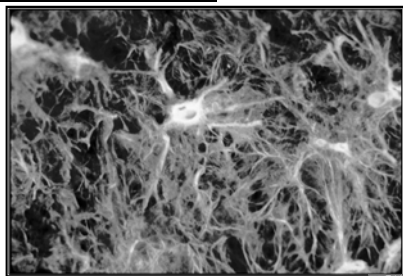
Pathology of Chronic Bronchitis - Large Airways



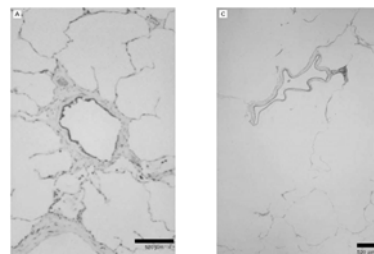
Pathology of Chronic Bronchitis - Small Airways



Pathology of Emphysema



Schematic of Emphysema Pathology



Normal

Emphysema

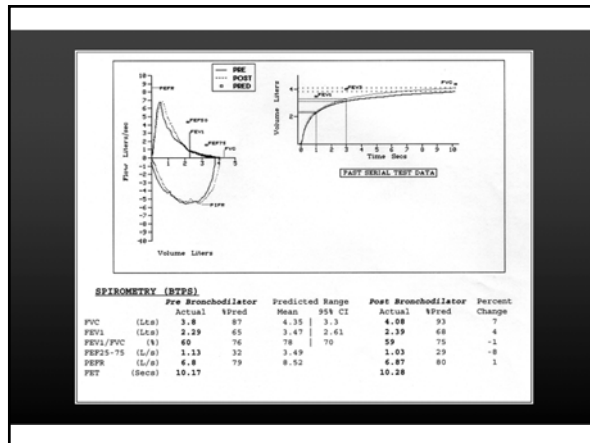
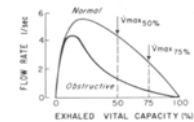
Barnes PJ, *NEJM* 2000;343:269-80.

Diagnosis of COPD

- Risk factors ... cigarette smoking
- Symptoms
- *** Spirometry ***
- In young person, consider alpha-1 antitrypsin deficiency

Defining (and Quantifying) an Obstructive Abnormality: Role of Spirometry

- Decreased $FEV_1/FVC \Rightarrow$ Obstructive Defect
- Normal or Increased $FEV_1/FVC \Rightarrow$ No Obstruction



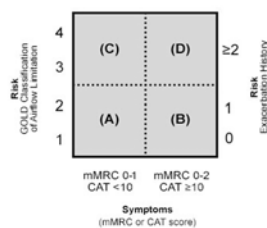
Staging Severity of COPD (ATS)

- Stage 1: $FEV_1 \geq 80\%$ of predicted
- Stage 2: $FEV_1 \geq 50-80\%$
- Stage 3: $FEV_1 \geq 30-50\%$
- Stage 4: $FEV_1 < 30\%$

Other systems: BODE index (Body mass index, Obstruction on spirometry, Dyspnea score, and Exercise capacity)

Staging Severity of COPD (GOLD)

When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history



www.goldcopd.org

Definitions – GOLD 2011

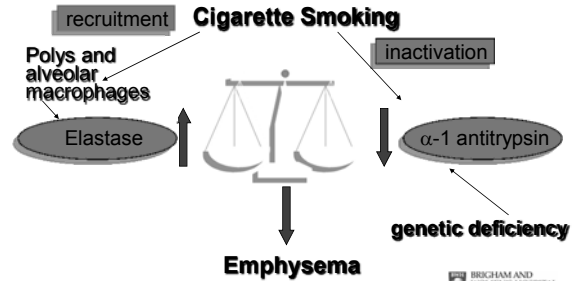
“... a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with a chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

www.goldcopd.org

Extrapulmonary Effects

- Weight loss
- Nutritional abnormalities
- Skeletal muscle dysfunction
- ... and frequent co-morbidities:
 - CAD, respiratory infections, lung cancer, osteoporosis, depression, diabetes, sleep disorders, anemia, glaucoma.

Pathogenesis of Emphysema



Screening for Alpha-1 Antitrypsin (AAT) Deficiency

- Early-onset emphysema
- Emphysema in a non-smoker
- Strong family history of emphysema
- Bibasilar bullae
- ?All patients with COPD

Diagnosis of AAT Deficiency

- Measurement of blood AAT level (homozygous deficiency causes blood levels 10-20% of normal).
- Confirmation with protein electrophoresis (MM = normal; ZZ = most common abnormal pattern)

Treatment of AAT Deficiency

- Alpha-1 augmentation therapy (weekly infusions of purified AAT protein)
- Test family members

Prevention of COPD

- Preventing *onset* of disease
 - Smoking abstinence
- Preventing *progression* of disease
 - Smoking cessation
 - Alpha-1 antitrypsin augmentation therapy

Prevention of COPD (cont.)

- Preventing *exacerbations* of disease
 - Long-acting bronchodilators
 - Inhaled corticosteroids
 - Other medications

Treatment of COPD

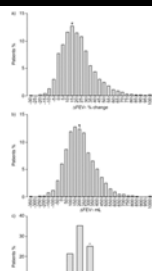
Pharmacologic:

- Bronchodilators
- Corticosteroids
- Antibiotics

Non-pharmacologic:

- Home oxygen
- Pulmonary rehab
- Lung volume reduction

Bronchodilator Response in Stable COPD



Percent change in FEV_1

Absolute change in FEV_1 (ml)

Absolute change in % pred. FEV_1

5,756 patient with COPD, following medication washout, given ipratropium 4 puffs followed by albuterol 4 puffs

Tashkin DP, et al. *Eur Resp J* 2008; 31:742-50.

Bronchodilator Strategy in COPD: For Mild Disease

Quick-Acting Bronchodilators

• Beta-Agonists:

- Albuterol, levalbuterol

• Anticholinergics:

- Ipratropium

• Combination:

- Albuterol + ipratropium

Soft mist inhaler

Bronchodilator Strategy in COPD: For More Severe Disease

Long-Acting Beta-Agonists (LABAs):

• 12-hour duration:

- Formoterol, salmeterol

• 24-hour duration:

- Vilanterol, olodaterol, indacaterol

Long-Acting Muscarinic Antagonists (LAMAs)

• 12-hour duration:

- Acclidinium

• 24-hour duration:

- Tiotropium, umeclidinium, glycopyrronium

Combination Long-Acting Bronchodilators

Once-Daily Long-Acting Beta-Agonist and Long-Acting Muscarinic Antagonist Combinations (LABA/LAMA):

- Vilanterol + umeclidinium (multi-dose DPI)
- Olodaterol + tiotropium (soft-mist inhaler)
- Indacaterol + glycopyrronium (single-dose DPI)

Combination LABA and ICS

Twice-daily:

- Salmeterol plus fluticasone propionate (DPI and MDI)
- Formoterol plus mometasone (MDI)
- Formoterol plus budesonide (MDI)

Once-daily:

- Vilanterol plus fluticasone furoate (DPI)



Towards a Revolution in COPD Health (TORCH) Trial: Study Design

- 6112 patients current and former smokers
- Avg. FEV₁ = 1.12 L (44%)
- Avg. age = 65 years; Gender = 3:1 male
- Randomized to fluticasone-salmeterol (500/50), salmeterol alone, fluticasone alone, or placebo
- Primary endpoint: all-cause mortality at 3 yrs.

Calverley P, et al., *NEJM* 2007; 356:775.



TORCH Trial: Findings

Key findings:

1. Mortality:

- Fluticasone-salmeterol combination reduced mortality by 17.5% (p=0.052) compared to placebo

Calverley P, et al., *NEJM* 2007; 356:775.



TORCH Trial: Findings

Key findings:

2. Other health outcomes:

- Fluticasone-salmeterol combination reduced COPD exacerbations and improved lung function and health status scores more than placebo or monotherapy with salmeterol or fluticasone.

Calverley P, et al., *NEJM* 2007; 356:775.



TORCH Trial: Findings

Key findings:

3. Complications:

- Probability of pneumonia was sig. greater with combination therapy and with fluticasone alone than with salmeterol or placebo.
- Cataracts and bone fractures did not differ among groups.

Calverley P, et al., *NEJM* 2007; 356:775.



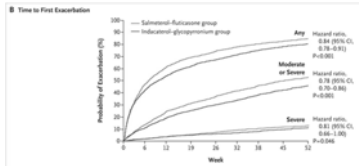
LABA/LAMA vs. LABA/ICS (FLAME)

- 3,300 patients with COPD.
- Randomly assigned to salmeterol-fluticasone (LABA/ICS) twice-daily vs. indacaterol-glycopyrronium (LABA/LAMA) once daily.
- 52-week, double-blind, double-dummy trial.

Wedzicha JA, et al., *NEJM* 2016; 374:2222-34.



LABA/LAMA vs. LABA/ICS (FLAME)



- LABA/LAMA caused significantly greater bronchodilation.
- Fewer pneumonias in LABA/LAMA group

BRIGHAM AND WOMEN'S HOSPITAL
The Lung Center

Wedzicha JA, et al., *NEJM* 2016; 374:2222-34.

Initiating Therapy in Moderate-Severe COPD

- Choices include single or combination long-acting bronchodilators vs. long-acting bronchodilator with inhaled steroid;
- Inhaled steroids may help reduce mucus hypersecretion and steroid-requiring exacerbations, but are more often associated with antibiotic-associated exacerbations.

BRIGHAM AND WOMEN'S HOSPITAL
The Lung Center

Initiating Therapy in Moderate-Severe COPD (cont.)

- Other considerations:
 - Delivery system (MDI, DPI, soft-mist inhaler)
 - Once- or twice-daily dosing
 - Cost / insurance coverage

BRIGHAM AND WOMEN'S HOSPITAL
The Lung Center

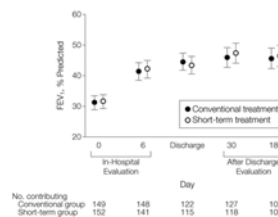
Other Medications for COPD

- Roflumilast
 - Phosphodiesterase-4 inhibitor; once-daily tablet.
 - Weak bronchodilator.
 - Associated with reduced frequency of exacerbations.
 - GI upset a common side effect.

BRIGHAM AND WOMEN'S HOSPITAL
The Lung Center

Treatment of Exacerbations: Steroids

A 5-day course of prednisone 40 mg/day is equally effective as a 14-day course at the same dose (the REDUCE trial).



Leuppi JD, et al. *JAMA* 2013; 309:2223-31.

BRIGHAM AND WOMEN'S HOSPITAL
The Lung Center

Treatment of Exacerbations: Antibiotics

	Placebo % (n)	Antibiotics % (n)
Success	55.0 (99)	68.1 (124)*
No Resolution	23.3 (42)	18.7 (34)
Deterioration	18.9 (34)	9.9 (18)*
Other	2.9 (5)	3.2 (6)

* p < 0.05

Anthonisen NR, et al.
Ann Intern Med 1987; 106:196.

BRIGHAM AND WOMEN'S HOSPITAL
The Lung Center

Antibiotic Therapy in Exacerbations of COPD

Typical pathogens:

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*

Appropriate antibiotics:

- Trimethoprim-sulfa
- Amoxicillin-clavulanate
- Macrolides
- Cephalosporins (2nd gen.)
- Doxycycline
- Quinolones

Chronic Antibiotic Therapy for Prevention of Exacerbations

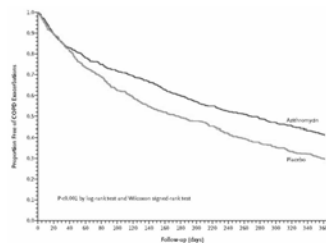
Randomized trial of azithromycin 250 mg/day vs. placebo for 1 year:

Inclusion: COPD and 1) chronic suppl. O₂; or 2) exacerbation within the past year requiring systemic steroids or ED visit or hosp'n.

Exclusion: resting tachycardia, prolonged QTc interval, medicines prolonging QTc, or impaired hearing.

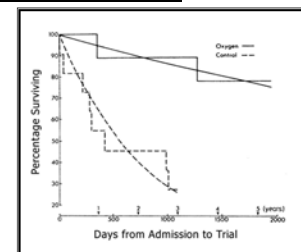
Albert RK, et al., *NEJM*
2011; 365:689-98.

Chronic Antibiotic Therapy for Prevention of Exacerbations



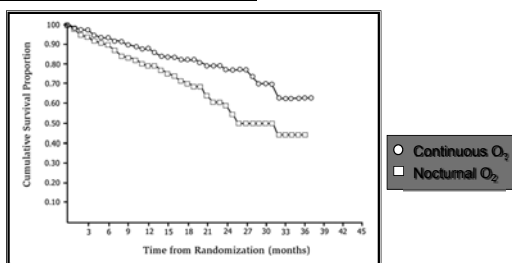
Albert RK, et al., *NEJM*
2011; 365:689-98.

Home Oxygen Therapy: Effect on Survival



Medical Research Council. *Lancet* 1981; 1(8222):681-6.

Nocturnal Oxygen Treatment Trial: Nocturnal vs. Continuous Oxygen Therapy



Nocturnal Oxygen Therapy Trial Group.
Ann Intern Med 1980; 93:391-8.

Criteria for Home Oxygen

Following maximal medical therapy; measured at rest:

- PaO₂ ≤ 55 mm Hg (SaO₂ ≤88%); or
- PaO₂ ≤ 59 mm Hg (SaO₂ ≤90%) with
 - P pulmonale on ECG
 - Peripheral edema
 - Secondary erythrocytosis.

Oxygen Delivery Systems

- Stationary
(continuous flow)



Oxygen concentrator

- Portable
(continuous or pulsed flow)



Compressed gas



Liquid O2



Portable oxygen concentrator

Outpatient Pulmonary Rehabilitation

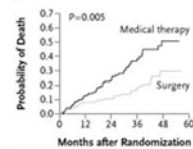
- Two Sessions per week for 8 weeks:
 - supervised exercise with O₂ monitoring;
 - patient education about COPD;
 - social interaction with other persons with COPD.
- Outcomes:
 - increased exercise capacity, and
 - improved sense of well-being.

Lung Volume Reduction Surgery

- Operation: resection of 25-30% of the most severely involved emphysematous lung tissue.
- Purpose: improved elastic recoil of remaining lung tissue and improved diaphragmatic function.
- Risks: prolonged bronchopleural fistula; ventilator dependence; death

NETT: Favorable Outcome in Subgroup Analysis

Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)



No. at Risk
Surgery 139 121 93 61 17
Medical therapy 151 120 85 43 13

National Emphysema Treatment Trial Research Group,
N Engl J Med 2003; 348:2059-2073

Bronchoscopic Approach to Lung Volume Reduction

- Novel, non-surgical approaches to lung volume reduction are being developed, including:
 - One-way endobronchial valves
 - Shape-memory coils
 - Tissue engineering techniques to induce lung scarring

In Summary ...

- Interventions that *prolong survival*:
 - Smoking cessation
 - Supplemental oxygen in the chronically hypoxemic patient
 - Lung volume reduction (in emphysema subset)
 - Medications (ICS/LABA or LAMA) - almost

In Summary ...

- Interventions that *decrease exacerbations*:
 - Medications (ICS, LABA, LAMA)
 - Chronic antibiotic suppression (azithromycin)
 - Roflumilast

In Summary ...

- Interventions that *improve quality of life*:
 - All of the above, and
 - Outpatient pulmonary rehabilitation