

Lecture Outline

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

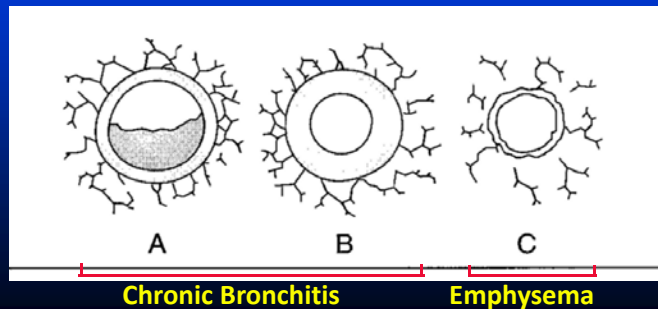


COPD: Defining Terms

- **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

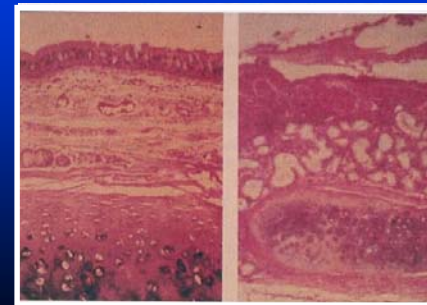


Mechanisms of Airflow Obstruction



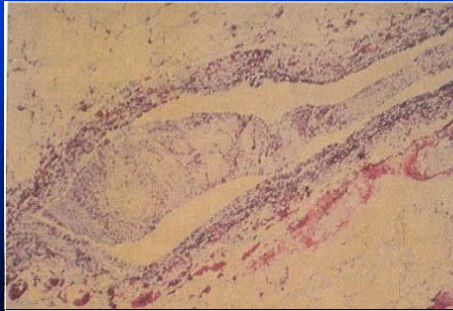
Pathology of Chronic Bronchitis - Large Airways

Normal



Chronic
Bronchitis

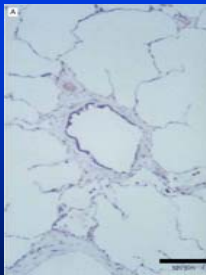
Pathology of Chronic Bronchitis - Small Airways



Pathology of Emphysema



Schematic of Emphysema Pathology



Normal



Emphysema

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



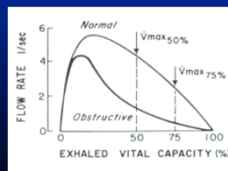
Diagnosis of COPD

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



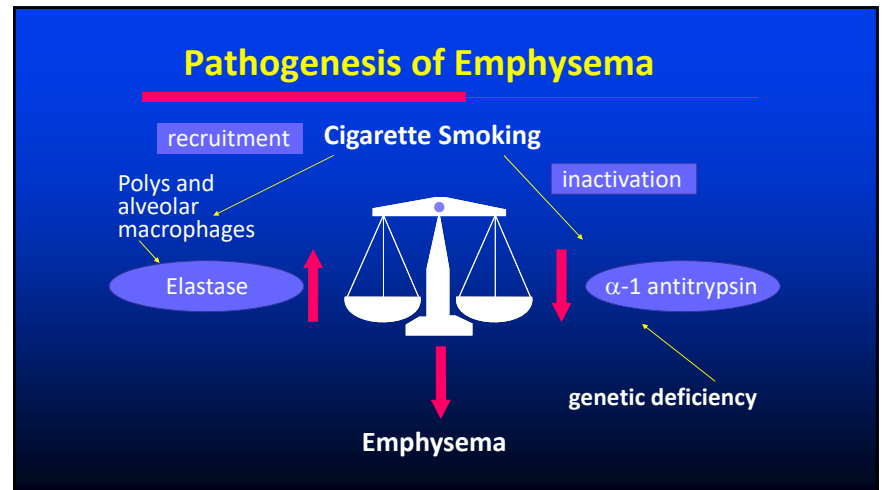
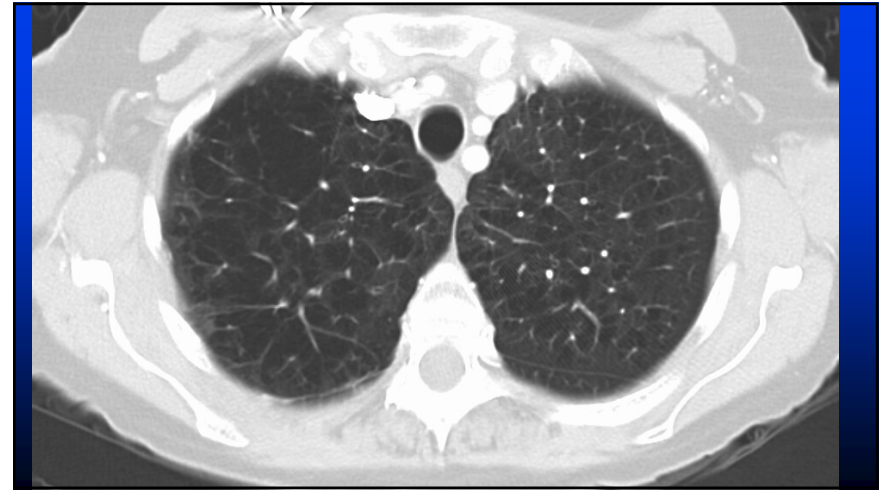
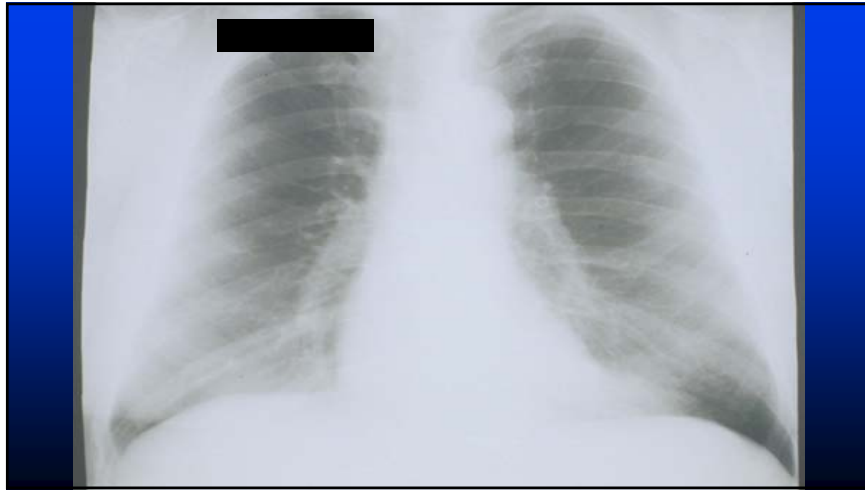
Defining (and Quantifying) an Obstructive Abnormality: Role of Spirometry

- Decreased FEV_1/FVC → Obstructive Defect
- Normal or Increased FEV_1/FVC → No Obstruction



PARTNERS
ASTHMA CENTER





Diagnosis of Alpha-1 Antitrypsin (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



Grading Severity (GOLD 2017): Airflow Obstruction

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

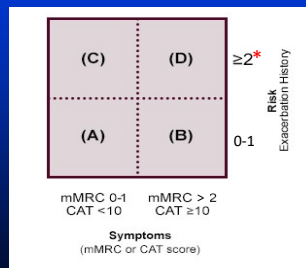
Other systems: **BODE** index (Body mass index, Obstruction on spirometry, Dyspnea score, and Exercise capacity)



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.

Staging Severity (GOLD 2017): Symptoms / Risk of Exacerbations



* or ≥1 leading to hosp admission

www.goldcopd.org



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:

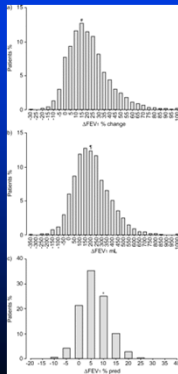
- Bronchodilators
- Corticosteroids
- Antibiotics

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



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:**
 - aclidinium, glycopyrrolate
- **24-hour duration:**
 - tiotropium, umeclidinium,



Combination LABA and ICS

Twice-daily:

- Salmeterol + fluticasone propionate (multi-dose DPI and MDI)
- Formoterol + mometasone (MDI)
- Formoterol + budesonide (MDI)

Once-daily:

- Vilanterol + fluticasone furoate (multi-dose DPI)



Combination Long-Acting Bronchodilators: LABA + LAMA

Twice-daily:

- Formoterol + glycopyrrolate (MDI)
- Indacaterol + glycopyrrolate (single-dose DPI)

Once-daily:

- Vilanterol + umecclidinium (multi-dose DPI)
- Olodaterol + tiotropium (soft-mist inhaler)



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.

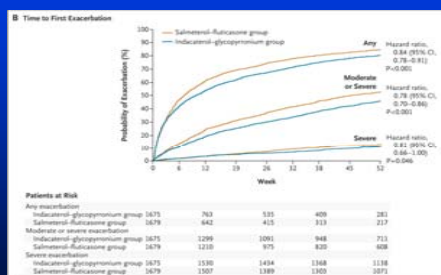
LABA/ICS vs. LABA/LAMA (FLAME)

- 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



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

(My) Current Thinking

- Do not use ICS alone
- LAMA or LABA/ICS similar as first choice
- LABA/LAMA provides greater improvement in lung function than LABA/ICS or LAMA alone
- Eosinophilic phenotype may benefit from ICS, targeted therapy



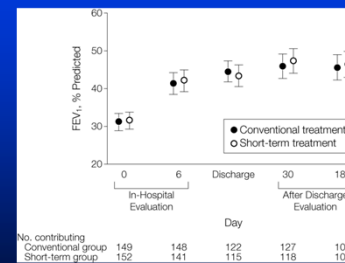
Initiating Therapy in Moderate-Severe COPD (cont.)

- Inhaled steroids may help reduce mucus hypersecretion and steroid-requiring exacerbations, but are more often associated with antibiotic-associated exacerbations.
- Other considerations:
 - Delivery system (MDI, DPI, soft-mist inhaler)
 - Once- or twice-daily dosing
 - Cost / insurance coverage



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.



Treatment of Exacerbations: Antibiotics

	Placebo	Antibiotics
	% (n)	% (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.
Intern Med 1987; 106:196.

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Antibiotic Therapy in Exacerbations of COPD

Typical pathogens:

- Streptococcus pneumoniae*
- Hemophilus influenzae*
- Moraxella catarrhalis*

Appropriate antibiotics:

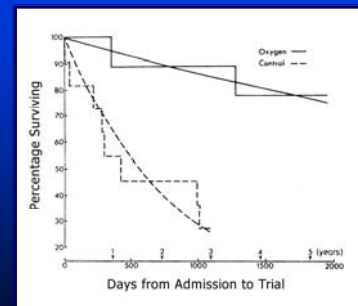
- Trimethoprim-sulfa
- Amoxicillin-clavulanate
- Macrolides
- Cephalosporins (2nd gen.)
- Doxycycline
- Quinolones

Prevention of Frequent Exacerbations of COPD

- Roflumilast
 - Phosphodiesterase-4 inhibitor; once-daily tablet.
 - Weak bronchodilator properties.
 - GI side effects are common
- Azithromycin
 - Daily administration of 250 mg
 - Prolongs QT interval; increased risk of hearing loss

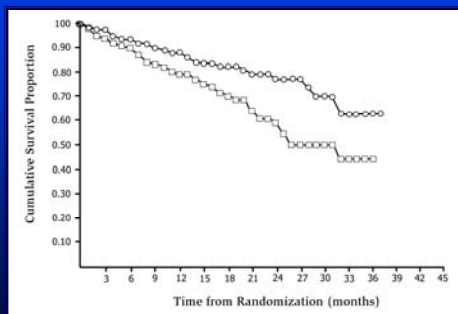


Home Oxygen Therapy: Effect on Survival



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:

- $\text{PaO}_2 \leq 55 \text{ mm Hg}$ ($\text{SaO}_2 \leq 88\%$); or
- $\text{PaO}_2 \leq 59 \text{ mm Hg}$ ($\text{SaO}_2 \leq 90\%$) with
 - P pulmonale on ECG
 - Peripheral edema
 - Secondary erythrocytosis.



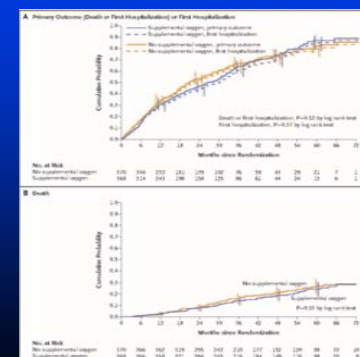
Long-Term Oxygen Treatment Trial (LOTT)

- National RCT in patients with low SaO₂ at rest (but >88%) and/or oxygen desaturation with exertion.
- Random assignment to supplemental oxygen during exercise and sleep vs. observation.
- Primary outcomes: death or hospitalization

N Engl J Med 2016; 375:1617-27.



Mild Resting and Exercise-induced Hypoxemia (LOTT)



COPD with SaO₂ 89-93%
at rest and/or
<90% with exertion

N Engl J Med 2016;
375:1617-27.



Oxygen Delivery Systems

- Stationary
(continuous flow)
- Portable
(continuous or pulsed flow)



Oxygen concentrator



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.

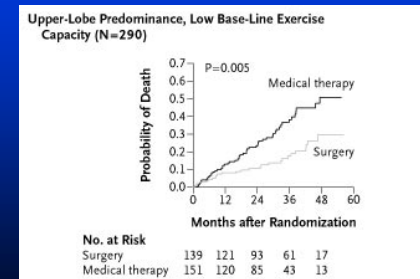


Lung Volume Reduction Surgery

- **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



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



In Summary ...

- Interventions that *prolong survival*:
 - Smoking cessation
 - Supplemental oxygen in the chronically hypoxemic patient
 - Lung volume reduction (in emphysema subset)

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

