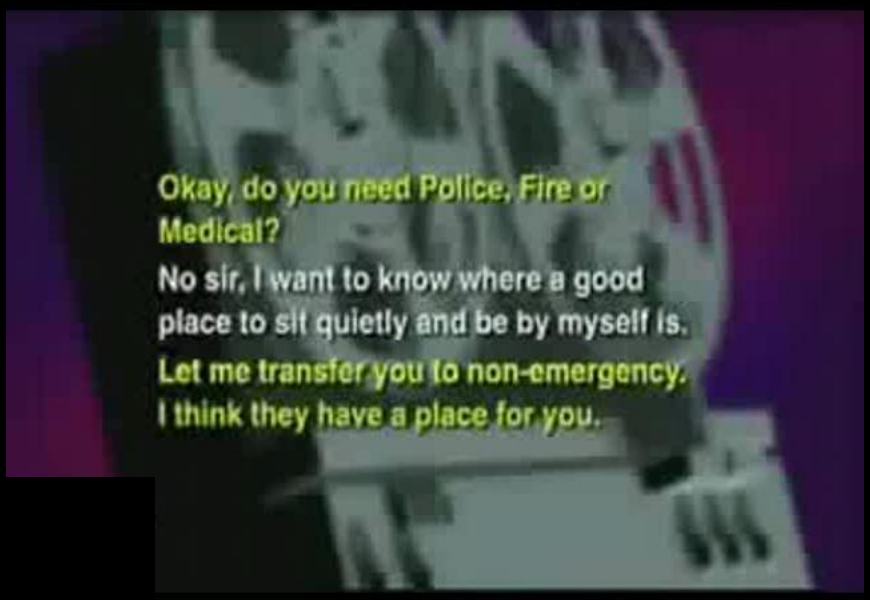
What's new in COPD?

Y. Michael Shim, MD
Division of Pulmonary and Critical Care Medicine
School of Medicine
University of Virginia

Disclosure

- I do not have any financial conflict with topics in this presentation.

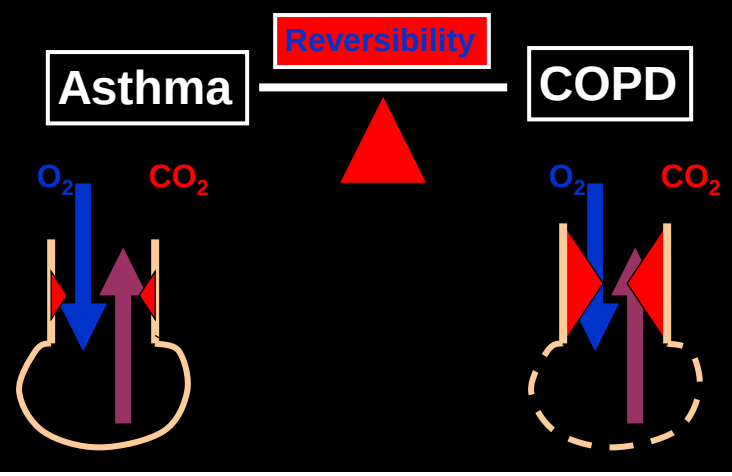


Learning objectives:

1. COPD Diagnosis
   - COPD is a disease with IRREVERSIBLE airway obstruction
   - Sometime with and other times without gas exchange abnormalities
   - COPD presents with VERY DIFFERENT findings….Be VERY CAREFUL with these differential diagnosis.

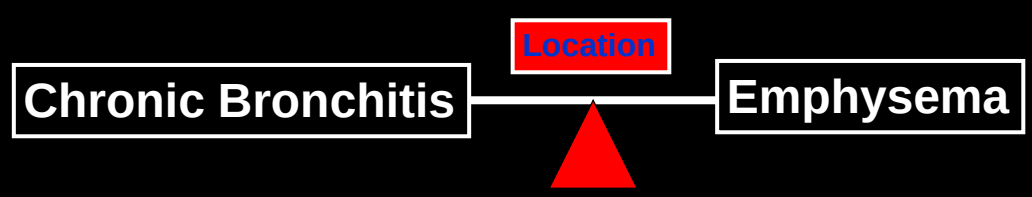
Diagnostic Paradigm

A number of airway diseases can present with symptoms and complaints similar to COPD



Diagnostic Paradigm

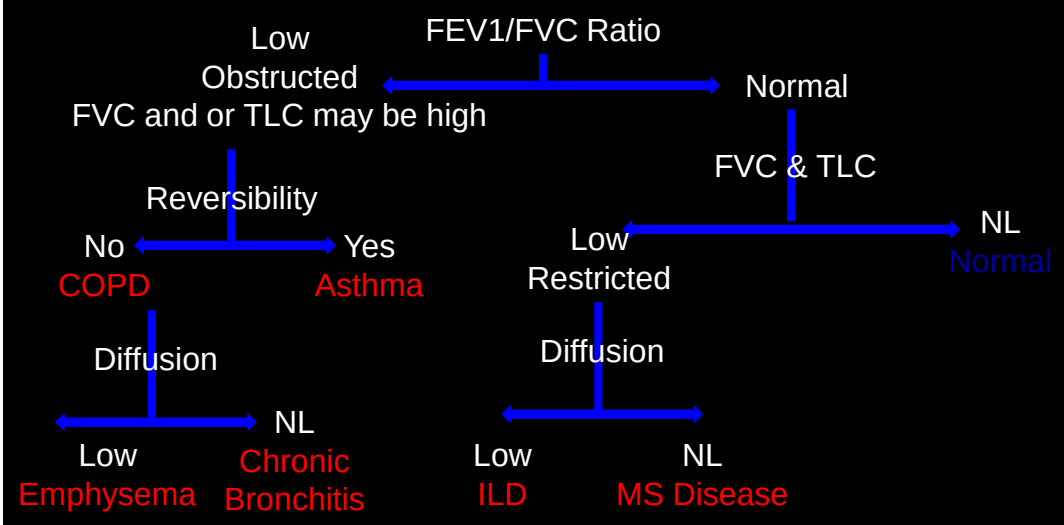
(Chronic Bronchitis vs Emphysema)



- Clinical Diagnosis
- Two consecutive years of two months a year cough, sputum production

- Anatomic Diagnosis
- Destruction & enlargement of the terminal airways and alveoli

PFT Interpretation



Question

Is there a disease other than COPD?

- Question #1
  - Would a discovery of other concurrent disease alter my clinical management?
- Question #2
  - Would such discovery change the clinical outcome of my patient?
- How about approaching this in a reverse order…: from the therapeutics to the diagnosis…

Diagnostic Consideration
Why does it matter

- Clinical guideline per GOLD and FDA approval
  - First line: anti-cholinergic, Rehab & O2
  - Second line: beta-agonist, Rehab & O2
  - Frequent exacerbation: consider steroid, Rehab & O2
    - If ICS, prefer medium dose rather than high dose
    - TORCH: high dose fluticasone led to higher respiratory infection, medium dose was the best middle of the way (500 MCG total per day)
  - Official FDA approval: 250 fluticasone + 50 salmeterol

Learning objectives:

1. COPD Diagnosis
2. Smoking Cessation is VERY Important
   - Chantix is effective but with significant side effects.

Smoking Cessation (verenicline)

- Verenicline (Chatix): partial α4ß2 nicotinic acetylcholine receptor
- Bupropion (Zyban)
- Nicotine replacement: patch, gum, inhaler
- Cytisine: a natural plant alkaloid, a partial agonist to α4ß2 receptor: RECENT Study Suggesting potentials…
- All of these are at least somewhat effective.

Smoking Cessation (verenicline)

Side effects have recently decreased the usage.

Table 4. Treatment-Emergent Adverse Events (Including Those Not Necessarily Related to Study Drug)*

	No. (%)		
	Varenicline (n = 349)	Bupropion SR (n = 329)	Placebo (n = 344)
Any adverse event	275 (78.8)	258 (78.4)	257 (74.7)
Most Frequent Adverse Events*			
Gastrointestinal disorders			
Nausea	98 (28.1)	41 (12.5)	29 (8.4)
Dry mouth	23 (6.6)	29 (8.8)	19 (5.5)
Flatulence	20 (5.7)	14 (4.3)	10 (2.9)
Constipation	19 (5.4)	23 (7.0)	13 (3.8)
Psychiatric disorders			
Insomnia	49 (14.0)	72 (21.9)	44 (12.8)
Abnormal dreams†	36 (10.3)	18 (5.5)	19 (5.5)
Irritability	21 (6.0)	17 (5.2)	20 (5.8)
Sleep disorder	20 (5.7)	13 (4.0)	13 (3.8)
Nervous system disorders			
Headache	54 (15.5)	47 (14.3)	42 (12.2)
Dizziness	21 (6.0)	19 (5.8)	20 (5.8)
Nasopharyngitis	20 (5.7)	17 (5.2)	18 (5.2)
Study Drug Treatment Discontinuations Due to Adverse Events‡			
All causes	30 (8.6)	50 (15.2)	31 (9.0)
Nausea	9 (2.6)	6 (1.8)	1 (0.3)

Table 4. Adverse Events Occurring More Frequently in Treatment Participants*

	No. (%) of Adverse Events		
	Varenicline (n = 343)	Bupropion SR (n = 340)	Placebo (n = 340)
Nausea	101 (29.4)	25 (7.4)	33 (9.7)
Constipation	31 (9.0)	22 (6.5)	5 (1.5)
Flatulence	20 (5.8)	7 (2.1)	8 (2.4)
Dry mouth	19 (5.5)	26 (7.6)	11 (3.2)
Dyspepsia	19 (5.5)	10 (2.9)	12 (3.5)
Vomiting	18 (5.2)	7 (2.1)	6 (1.8)
Insomnia	49 (14.3)	72 (21.2)	42 (12.4)
Abnormal dreams†	45 (13.1)	20 (5.9)	12 (3.5)
Sleep disorder	16 (4.7)	23 (6.8)	9 (2.6)
Anxiety	15 (4.4)	18 (5.3)	13 (3.8)
Headache	44 (12.8)	27 (7.9)	43 (12.6)
Dizziness	22 (6.4)	25 (7.4)	24 (7.1)
Fatigue	25 (7.3)	13 (3.8)	22 (6.5)

Learning objectives:

1. COPD Diagnosis
2. Smoking Cessation is VERY Important
3. Oxygen for those with hypoxemia is the most effective therapy.

O_2 Therapy

- Increases life expectancy
- When used in conjunction with Pulmonary Rehabilitation it also improves quality of life.
- Reduces need for hospitalization
- Enhanced cardiac function
- Increased body weight
- Reversal of polycythemia
- Improved neuropsychiatric function
- Improved exercise performance
- Improved skeletal muscle metabolism

Learning objectives:

1. COPD Diagnosis
2. Smoking Cessation is VERY Important
3. Oxygen for those with hypoxemia is the most effective therapy.
4. Pulmonary rehab is the second most effective therapy.

Pulmonary rehabilitation is expected to achieve

1. Reduced dyspnea
2. Improved QOL
3. Improved 6 minute walk
4. Improved ability to do ADLs
5. Reduced hospitalization rates
6. Reduced exacerbations associated with MD visits

Learning objectives:

1. COPD Diagnosis
2. Smoking Cessation is VERY Important
3. Oxygen for those with hypoxemia is the most effective therapy.
4. Pulmonary rehab is the second most effective therapy.
5. Details on Pharmacotherapies…

Pharmacotherapy

***No pharmacologic agent has been known to prolong survival

1. Short & long acting bronchodilators
   - Anticholinergic agents (ipratropium bromide, tiotropium, Glycopyrrolate)
   - ß2 agonists (albuterol, salmeterol, fomoterol, arfomoterol, Indacaterol)
2. Inhaled corticosteroids
3. Phosphodiesterase 4 inhibitor
   - Daliresp
4. Leukotriene modifiers

UPLIFT: Tiotropium in COPD

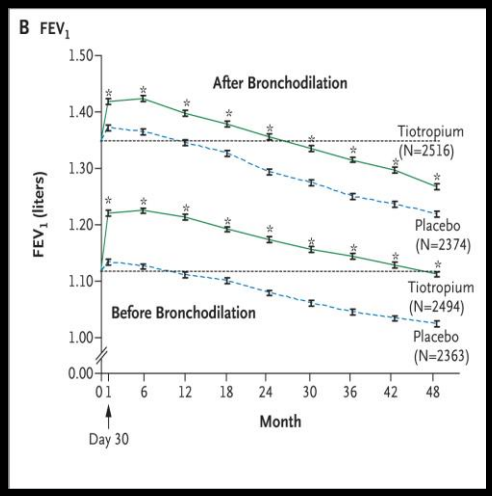
NEJM, 2008 Oct 9;359(15):1543-54

- Randomized, double-blind trial for 4 years
- Groups
  - Tiotropium (n=2987)
  - Placebo (n=3006)
- Co-Primary Endpoints
  - Rate of decline in the mean FEV1 b/f and a/t bronchodilator 30 days post trial initiation
- Secondary Endpoints
  - FVC
  - Change in SGRQ
  - COPD exacerbation
  - Mortality

UPLIFT: Tiotropium in COPD

NEJM, 2008 Oct 9;359(15):1543-54

Rate of FEV1 decline is NOT the best outcome!



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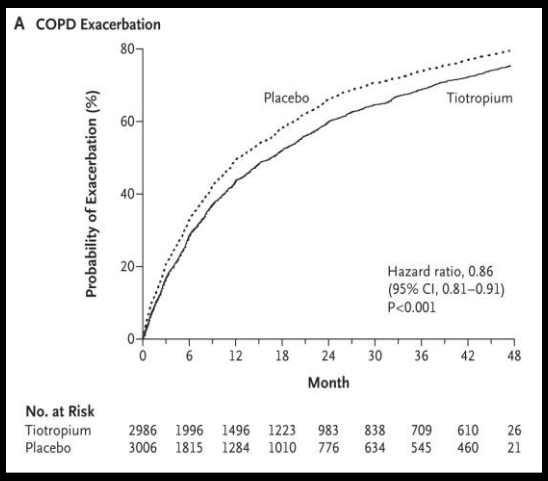
UPLIFT: Tiotropium in COPD

Secondary analysis

?reduction in the rate of COPD exacerbation?



Long-acting Beta2 agonists are additive to anti-cholinergic therapy

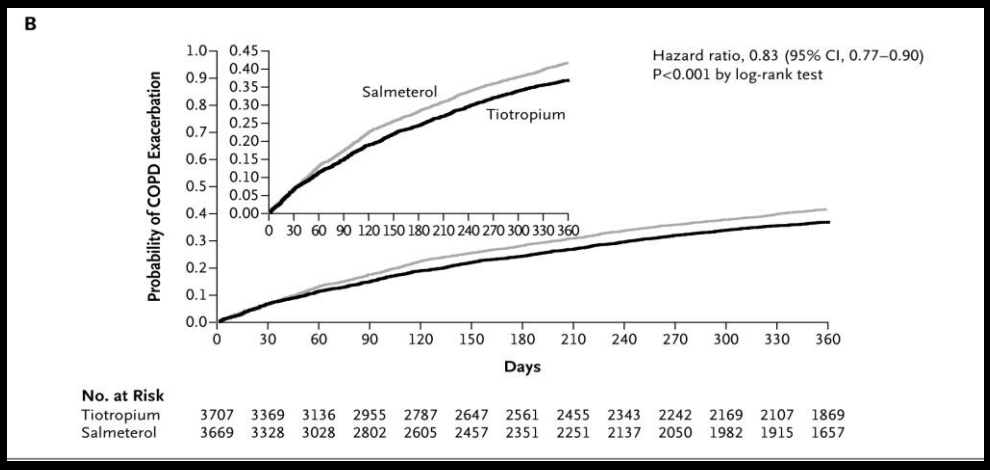
- Improvements in spirometry
- Reductions in dyspnea
- Reductions in exacerbations
- Role should be in combination and not alone.

Tiotropium vs Salmeterol

Secondary analysis

Tiotropium more effectively prevents COPD exacerbation

NEJM 2011;364:1093-1103



Inhaled Corticosteroids in COPD

Level 1: Prevent frequent exacerbation

- Large studies show ICS to be appropriate in those patients with:
  - Significant symptoms and documented spirometric response with baseline $FEV_1 < 50\%$
  - To prevent repeated exacerbations requiring treatment with antibiotics or oral steroids
- Steroids appear to be additive to LABA
  - Unsure of benefit of steroids over tiotropium as both reduce exacerbations (TORCH).

Pharmacotherapy

What is the right dose of ICS?

- TORCH, NEJM 2007
  - Comparison between high fluticasone (1000 vs 500 mcg per day)
  - High dose with more side effects (i.e. respiratory infection)
  - Middle dose approved by FDA (500 mcg per day)
  - Middle of the road is better than maximum dose

High prevalence of bone density reduction regardless of ICS

TORCH Chest.2009;136:1456-1465

- If high dose Fluticasone given (1000 mcg per day)
  - Male: 18% (osteoporosis)
  - Male: 42% by BMD scan (osteopenia)
  - Female: 30% (osteoporosis)
  - Female: 41% by BMD scan (osteopenia)
- Long term high dose ICS is associated with increased incidence of bone density loss, and this is independently associated with cigarette smoking.

Comparative Effectiveness

Budesonide + Fomoterol vs Fluticasone + Salmeterol
J Med Econ. 2011 Sept 27.

- Retrospective administrative claims data
  - Budesonide + Fomoterol decreases albuterol
    - Fewer albuterol (34.7% vs 39.5%), P < 0.001
    - Fewer ipratropium (7.8% vs 9.8%): p < 0.005
  - No difference in
    - Tiotropium, nebulizer albuterol, COPD-related outpatient visit, exacerbation rates
    - Same COPD-related medical cost

COPD & Azithromycin

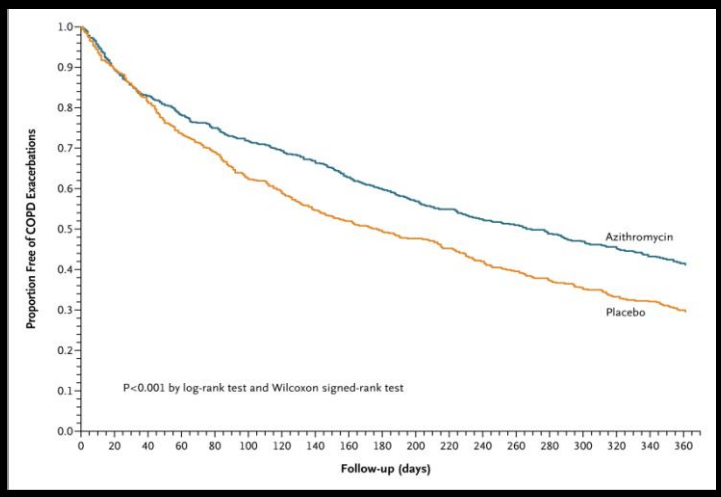
NEJM 2011:365(8):689-698

- Randomized, placebo-controlled
- N=1142
  - Zithromax 250mg (n=570) vs Placebo (n=572)
- Primary Endpoint
  - Time to first exacerbation was reduced.
    - 266 days vs 174 days
- Secondary Endpoint
  - 1.48 exacerbation/patient-year vs 1.83

COPD & Azithromycin

Azithromycin may reduce COPD exacerbation

NEJM 2011:365(8):689-698

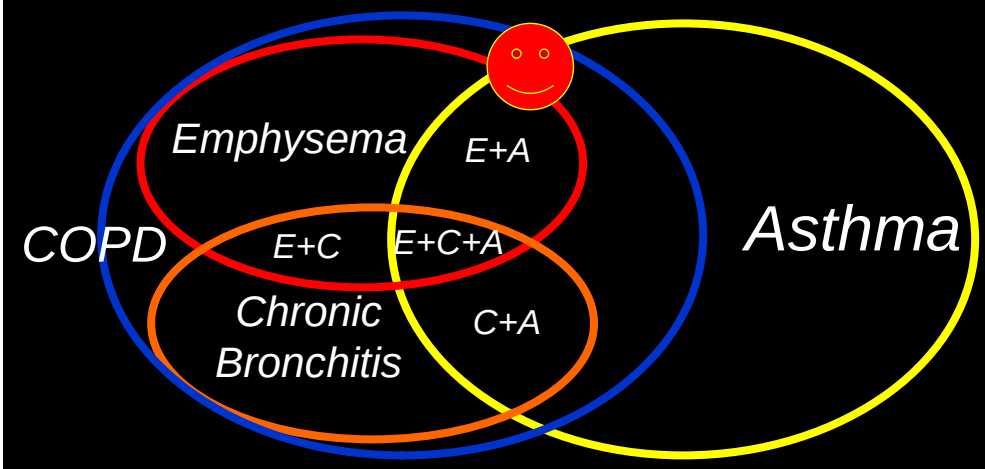


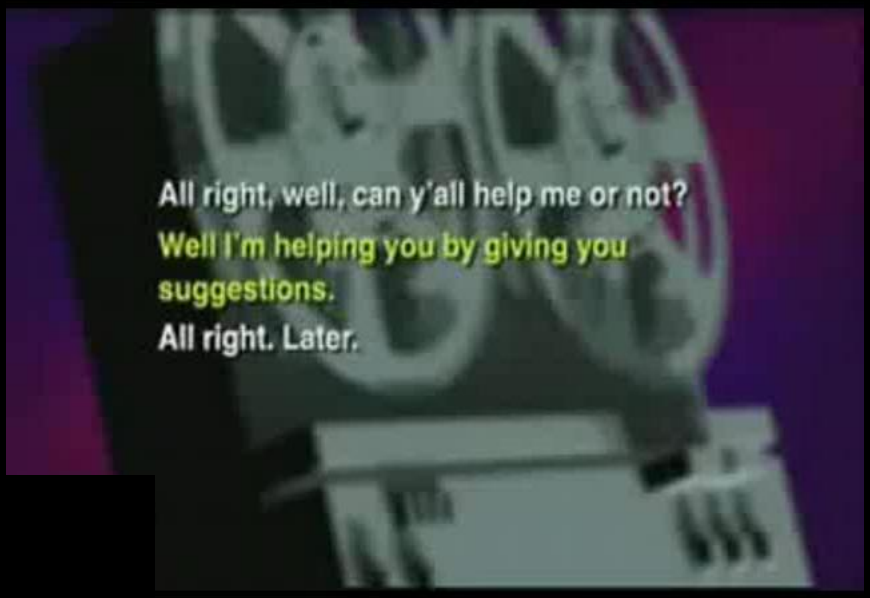
Interventional Options

- Lung Transplant
  - Usually not an option for geriatric population
    - Age limit < or = 65 years
    - Case by case exceptions
- Lung Volume Reduction Surgery
  - NETT study

Incredible Heterogeneity of COPD

Revision of diagnosis is NOT uncommon





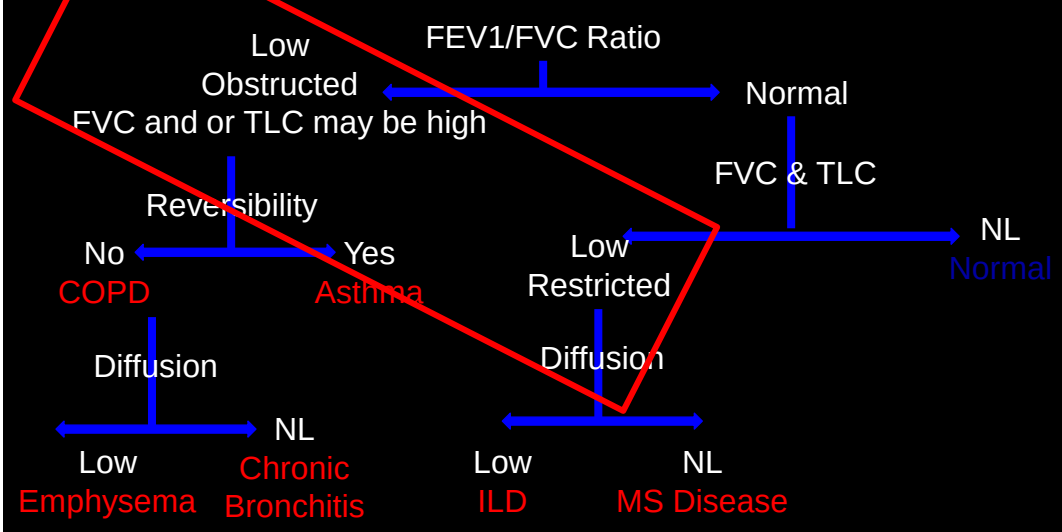
What is the airway physiology?

85 yo lady from CT, still independent, living alone, previous Dx of COPD, has been on budesonide/fomoterol, tiotropium, and PRN rescue inhaler. Still unsatisfactory relief, and came in with her daughter who lives in Charlottesville area. She is 4'11" and was previously 5'3" when she was "young". She is a 30 PkYR smoker who quit about 20 years ago.

	Pre-bronchodilator
FVC	1.57L (2.77 – 3.78, 67%)
FEV1	0.82L (2.12 – 2.95, 45%)
FEV1/FVC	0.52 (0.71 – 1.02 66%)
TLC	6.21L (6.76 – 9.25, 78%)

1. Obstructive
2. Restrictive
3. Mixed (obstructive & restrictive)
4. Normal

PFT Interpretation



IMPORTANT: FEV1/FVC ratio < 70% or outside of the 95%CI (Confidence Interval) is considered abnormal.

1. First number to look: FEV1/FVC ratio.
2. Pre-bronchodilator FEV1/FVC are lower than reference value. Next slide, we will talk about the meaning of the post-bronchodilator study result!
3. This is OBSTRUCTIVE lung disease
4. FVC is low. TLC is low. This indicates low lung volume, consistent with restrictive lung disease.
5. She has a MIXed disease!: Kyphosis

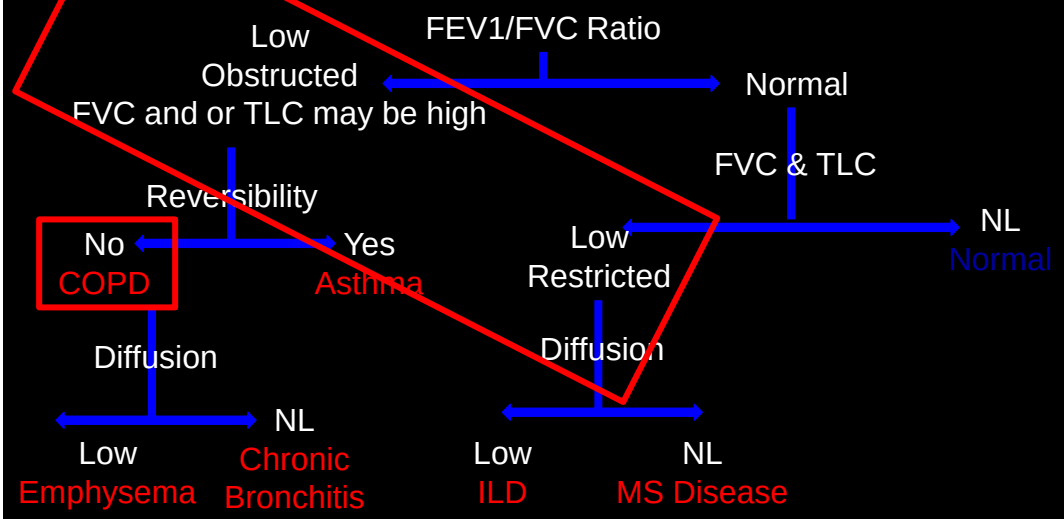
Does this patient have…?

85 yo lady from CT, still independent, living alone, previous Dx of COPD, has been on budesonide/fomoterol, tiotropium, and PRN rescue inhaler. Still unsatisfactory relief, and came in with her daughter who lives in Charlottesville area. She is 4'11" and was previously 5'3" when she was "young". She is a 30 PkYR smoker who quit about 20 years ago.

	Pre-bronchodilator	Post-bronchodilator
FVC	1.57L (2.77 – 3.78, 67%)	2.23L (2.77 – 3.78, 81%)
FEV1	0.82L (2.12 – 2.95, 45%)	1.5L (2.12 – 2.95, 67%)
FEV1/FVC	0.52 (0.71 – 1.02 46%)	0.67 (0.71 – 1.02, 61%)
TLC	6.21L(6.76 – 9.25, 78%)	6.05L(6.76 – 9.25, 72%)

1. Reversible obstructive
2. Irreversible obstructive
3. Mixed lung disease

PFT Interpretation



IMPORTANT: FEV1/FVC ratio < 70% or outside of the 95%CI (Confidence Interval) is considered abnormal.

IMPORTANT: FEV1 OR FVC improvement by 200 cc or greater AND 12% or greater is considered "POSITIVE Bronchodilator Response".

1. We established that this is "OBSTRUCTIVE LUNG DISEASE".
2. Post-bronchodilator FEV1/FVC are still not normal.
3. This indicates that this OBSTRUCTIVE lung disease was not reversed to "NORMAL RANGE" after bronchodilator. And "POSITIVE BRONCHODILATOR RESPONSE"
4. This is "IRREVERSIBLE OBSTRUCTIVE LUNG DISEASE"

EXTRA: Hope you got it by now, that bronchodilator response is just a descriptive term related to improvement in airflow (spirometry) after bronchodilator. Reversibility means that a patient normalizes his/her airflow. Sometimes bronchodilator assists to demonstrate that they can normalize the airflow problem associated with obstructive lung disease!

What is the most likely diagnosis?

85 yo lady from CT, still independent, living alone, previous Dx of COPD, has been on budesonide/fomoterol, tiotropium, and PRN rescue inhaler. Still unsatisfactory relief, and came in with her daughter who lives in Charlottesville area. She is 4'11" and was previously 5'3" when she was "young". She is a 30 PkYR smoker who quit about 20 years ago.

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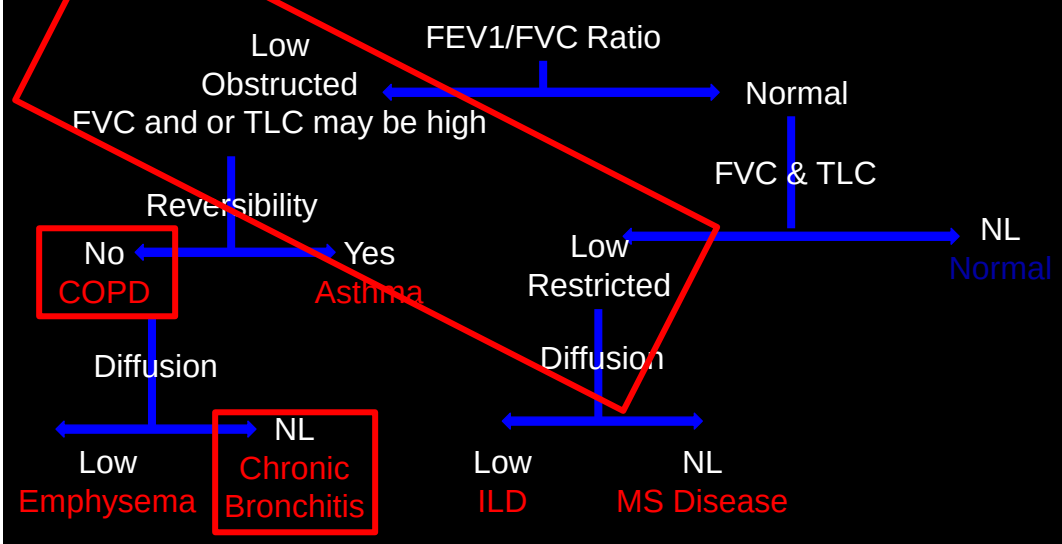
FEV1/FVC	0.52 (0.71 – 1.02 46%)	0.67 (0.71 – 1.02, 61%)
TLC	6.21L (6.76 – 9.25, 78%)	6.05L (6.76 – 9.25, 72%)
DLCO	27.56 (22.45 – 29.76, 91%)	

1. Chronic Bronchitis
2. Emphysema
3. Asthma

PFT Interpretation



IMPORTANT: DLCO outside of 95%CI or < 80% predicted is considered abnormal.

1. We established that this is "OBSTRUCTIVE LUNG DISEASE".
2. We established that this is "IRREVERSIBLE OBSTRUCTIVE LUNG DISEASE"
3. DLCO is normal. Chronic bronchitis primarily occurs at the airway with airflow problems, thus, have normal gas exchange.
4. This indicates that the diagnosis is "Chronic bronchitis"

BUT WAIT!!!!!

What is the most likely diagnosis?

85 yo lady from CT

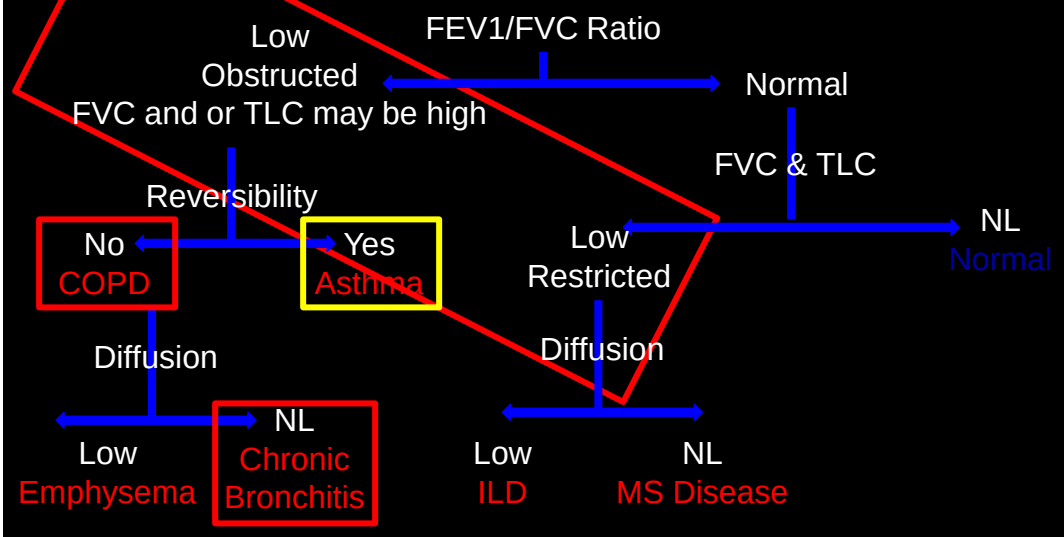
	Pre-bronchodilator	Post-bronchodilator
FVC	1.57L (2.77 – 3.78, 67%)	2.23L (2.77 – 3.78, 81%)
FEV1	0.82L (2.12 – 2.95, 45%)	1.5L (2.12 – 2.95, 67%)
FEV1/FVC	0.52 (0.71 – 1.02 46%)	0.67 (0.71 – 1.02, 61%)
TLC	6.21L(6.76 – 9.25, 78%)	6.05L(6.76 – 9.25, 72%)
DLCO	27.56 (22.45 – 29.76, 91%)	

She was also found to have significant sinus disease (by sinus CT), and positive RAST for dust mite, pollens, and grass. After 5 months of aggressive anti-inflammatory therapy (ICS + Nasal Steroid)

	Pre-bronchodilator
FVC	2.2L (2.77 – 3.78, 81%)
FEV1	1.87L (2.12 – 2.95, 75%)
FEV1/FVC	0.85 (0.71 – 1.02, 91%)
TLC	6.1L(6.76 – 9.25, 79%)
DLCO	28.56 (22.45 – 29.76, 99%)

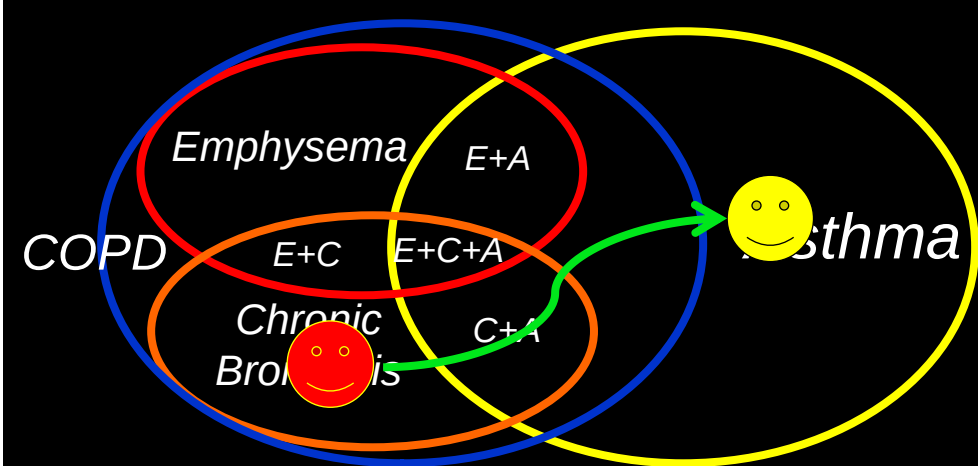
1. Chronic Bronchitis
2. Emphysema
3. Asthma & concurrent restrictive lung disease

PFT Interpretation



Incredible Heterogeneity of COPD

Revision of diagnosis is NOT uncommon

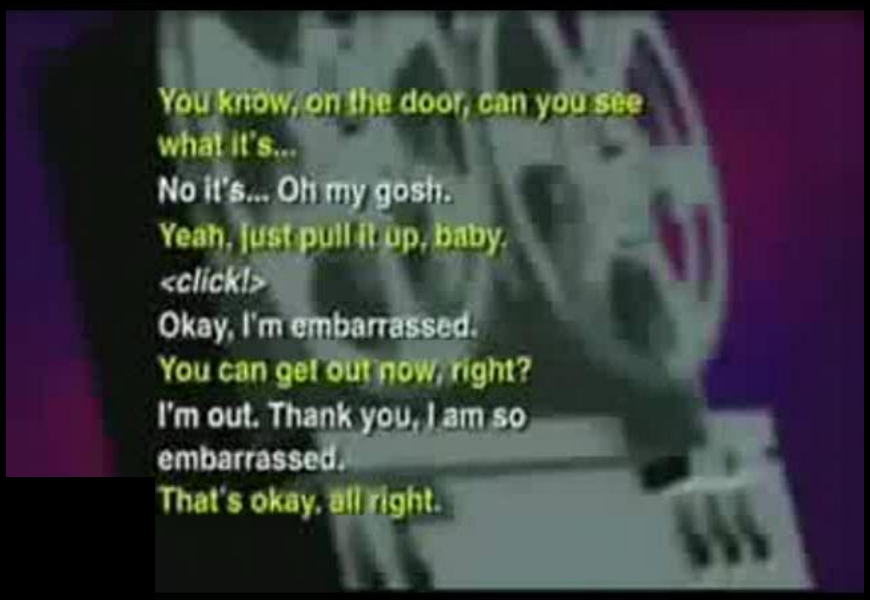


Remember …

- Smoking ≠ COPD
  - Dirty little secret: only 30 – 60% of smokers develop COPD: Raherison, C. Epidemiology of COPD. *Eur Respir Rev* **18**, 213-221, 2009. Postma, D. S. Epidemiology of Chronic Obstructive Pulmonary Disease. *Eur Respir Mon*, 41-73, 1998.
- In case of patients at risk (i.e. smokers)
  - Always consider alternative diagnosis
    - Sinusitis, uncontrolled asthma, environmental factors
    - Cigarette leading to cardiac/vascular diseases
    - Muscular or physical deconditioning
  - Always consider an objective diagnostic study
    - Spirometry is ALWAYS a good starting point

Thank you!

ANY QUESTIONS?



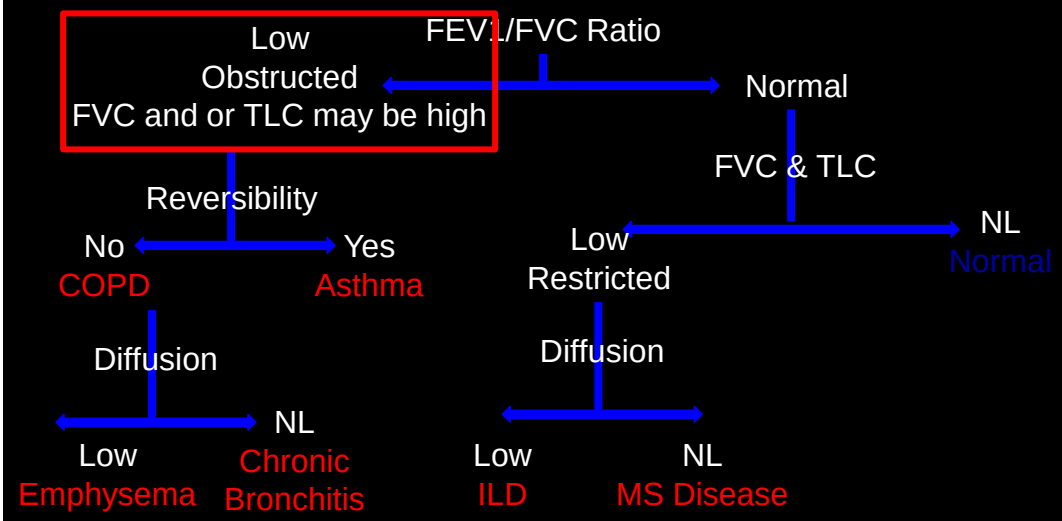
What is the airway physiology?

73 yo female, a retired librarian from Brown University, complaining of breathlessness while walking her two dogs. Hx of 35 PkYR smoking, quit 15 years ago

	Pre-bronchodilator	
FVC	3.2L	(2.77 – 3.78, 98%)
FEV1	1.4L	(2.21 – 3.15, 34%)
FEV1/FVC	0.44	(0.71 – 1.02 66%)

1. Obstructive
2. Restrictive
3. Mixed
4. Normal

PFT Interpretation



IMPORTANT: FEV1/FVC ratio < 70% or outside of the 95%CI (Confidence Interval) is considered abnormal.

1. First number to look: FEV1/FVC ratio.
2. Pre-bronchodilator FEV1/FVC are lower than reference value.
3. This is an OBSTRUCTIVE lung disease
4. FVC is normal-high. This indicates hyperinflation, consistent with obstructive lung disease.

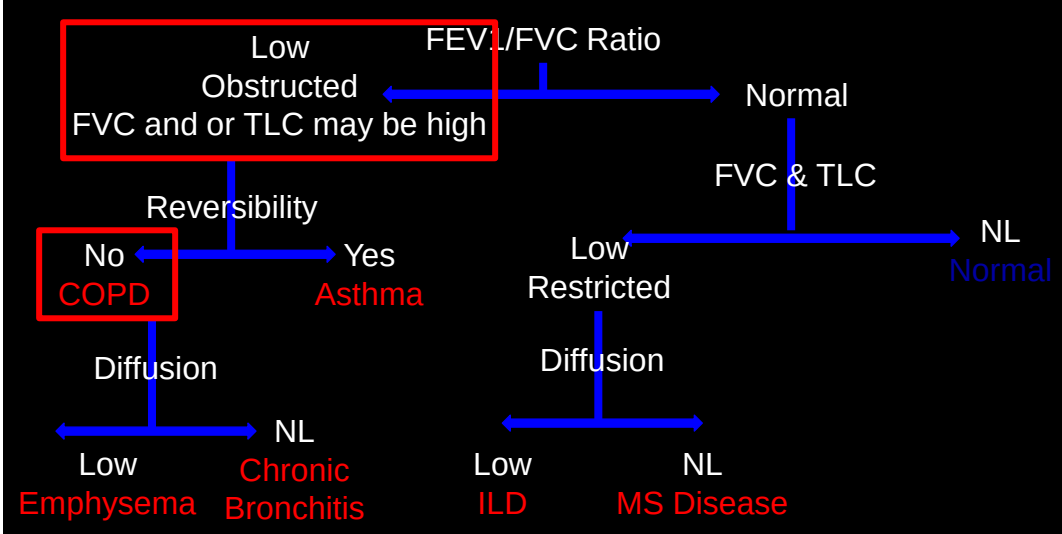
Is it reversible?

73 yo female, a retired librarian from Brown University, complaining of breathlessness while walking her two dogs. Hx of 35 PkYR smoking, quit 15 years ago

	Pre-bronchodilator		Post-bronchodilator	
FVC	3.2L	(2.77 – 3.78, 98%)	3.50L	(2.77 – 3.78, 135%)
FEV1	1.4L	(2.21 – 3.15, 34%)	1.95L	(2.21 – 3.15, 67%)
FEV1/FVC	0.44	(0.71 – 1.02 66%)	0.56	(0.71 – 1.02, 69%)
TLC	9.5L	(6.76 – 8.25, 155%)	8.75L	(6.76 – 8.25, 125%)

1. Reversible obstructive
2. Irreversible obstructive
3. Mixed lung disease

PFT Interpretation



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2. Post-bronchodilator FEV1/FVC are lower than reference value.
3. This indicates that this OBSTRUCTIVE lung disease was not reversed to "NORMAL RANGE" after bronchodilator. But "POSITIVE BRONCHODILATOR RESPONSE"
4. This pattern is consistent with "IRREVERSIBLE OBSTRUCTIVE LUNG DISEASE"

EXTRA: However, some patients normalize their Spirometry PFT after a few months of therapy. Obviously if that occurs, you would need to revise your diagnosis!

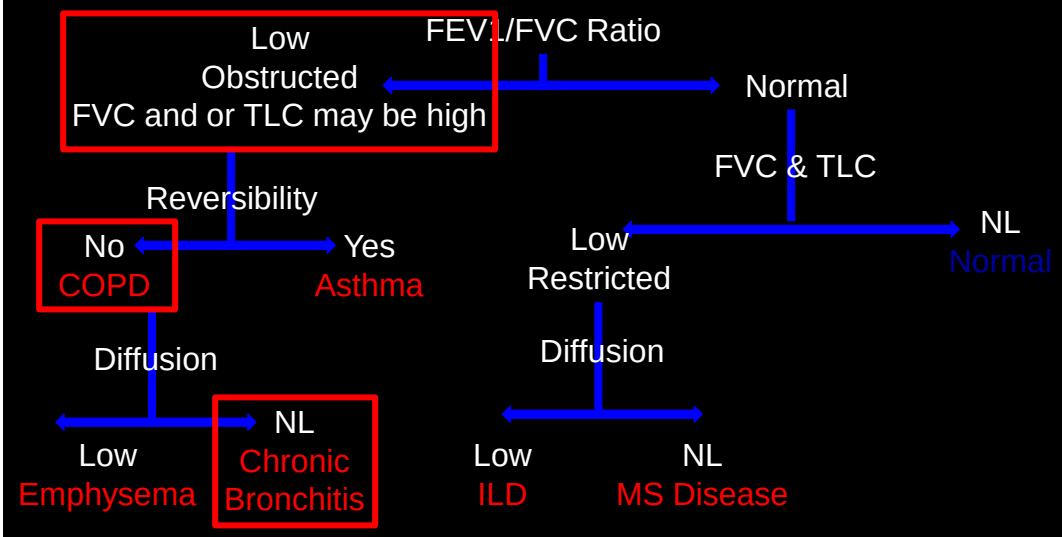
What is the diagnosis?

73 yo female, a retired librarian from Brown University, complaining of breathlessness while walking her two dogs. Hx of 35 PkYR smoking, quit 15 years ago

	Pre-bronchodilator		Post-bronchodilator	
FVC	3.2L	(2.77 – 3.78, 98%)	3.50L	(2.77 – 3.78, 135%)
FEV1	1.4L	(2.21 – 3.15, 34%)	1.95L	(2.21 – 3.15, 67%)
FEV1/FVC	0.44	(0.71 – 1.02 66%)	0.56	(0.71 – 1.02, 69%)
TLC	9.5L	(6.76 – 8.25, 155%)	8.75L	(6.76 – 8.25, 125%)
DLCO	27.56	(22.45 – 29.76, 91%)		

1. Chronic Bronchitis
2. Emphysema
3. Asthma
4. Normal

PFT Interpretation



IMPORTANT: DLCO outside of 95%CI or < 80% predicted is considered abnormal.

1. This is "OBSTRUCTIVE LUNG DISEASE".
2. We established that this is "IRREVERSIBLE OBSTRUCTIVE LUNG DISEASE"
3. This is consistent with COPD. Now question is what kind of COPD?
4. DLCO is normal. Chronic bronchitis does not touch alveolar epithelium, thus, have normal gas exchange.
5. This indicates that the diagnosis is "Chronic Bronchitis"

EXTRA: However, there is a substantial number of patients with MIXed COPD (having both chronic bronchitic and emphysema). This is relevant for you to know in real world, but for now we will focus on pure COPD patients.

Current Guideline: GOLD

Global initiative for chronic Obstructive Lung Disease

Management of COPD

GOLD Stage 0: At Risk

Characteristics

- Chronic symptoms
  - cough
  - sputum
- No spirometric abnormalities

Recommended Treatment

Avoidance of risk factors

SMOKING CESSATION

Influenza vaccination

Above recommendations apply to all stages

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Management of COPD

GOLD Stage 1

Characteristics

- $FEV_1/FVC < 70\ \%$
- $FEV_1 \geq 80\ \%$ predicted
- With or without chronic symptoms

Recommended Treatment

- Short-acting bronchodilator as needed

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Management of COPD

GOLD Stage 2

Characteristics

- $FEV_1/FVC < 70\%$
- $50\% \leq FEV_1 < 80\%$ predicted
- With or without chronic symptoms

Recommended Treatment

- Short-acting broncho-dilator as needed
- Regular treatment with one or more long-acting bronchodilators
- Rehabilitation

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Management of COPD

GOLD Stage 3

Characteristics

- $FEV_1/FVC < 70\%$
- $30\% \leq FEV_1 < 50\%$ predicted
- With or without chronic symptoms

Recommended Treatment

- Short-acting broncho-dilator as needed
- Regular treatment with one or more long-acting bronchodilators
- Inhaled glucocortico-steroids if repeated exacerbations
- Rehabilitation

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Management of COPD

GOLD Stage 4

Characteristics

- $FEV_1/FVC < 70\%$
- $FEV_1 < 30\%$ predicted *or* $FEV_1 < 50\%$ predicted *plus* chronic respiratory failure

Recommended Treatment

- Short-acting bronchodilator as needed
- Regular treatment with one or more long-acting bronchodilators
- Inhaled glucocorticosteroids if repeated exacerbations
- Treat complications
- Rehabilitation
- Long-term oxygen therapy if respiratory failure
- Consider surgical options

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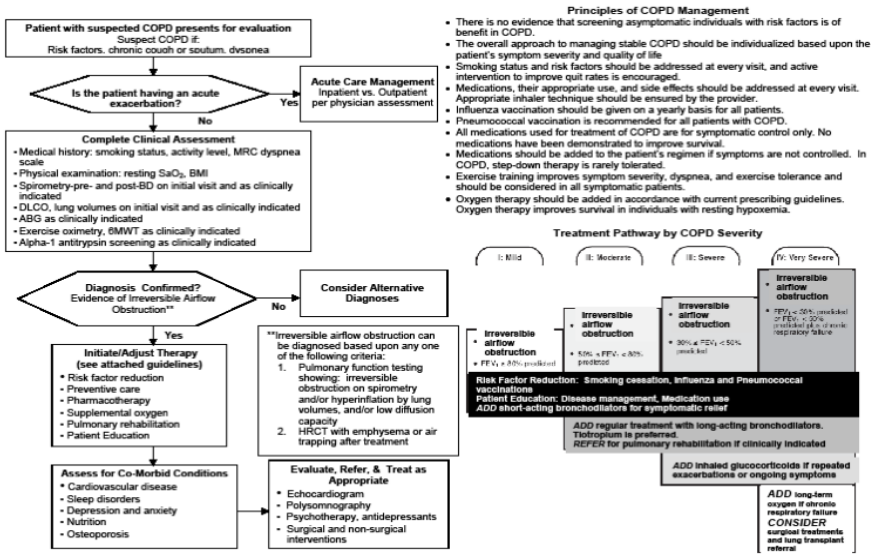
Adopting COPD Guidelines: University of Virginia



Clinical decision tools are general and cannot take into account all of the circumstances of a particular patient. Judgment regarding the propriety of using any specific procedure or guideline with a particular patient remains with that patient's physician, nurse or other health care professional, taking into account the individual circumstances presented by the patient.