Strategies to Break the Cycle of Severe COPD Exacerbation

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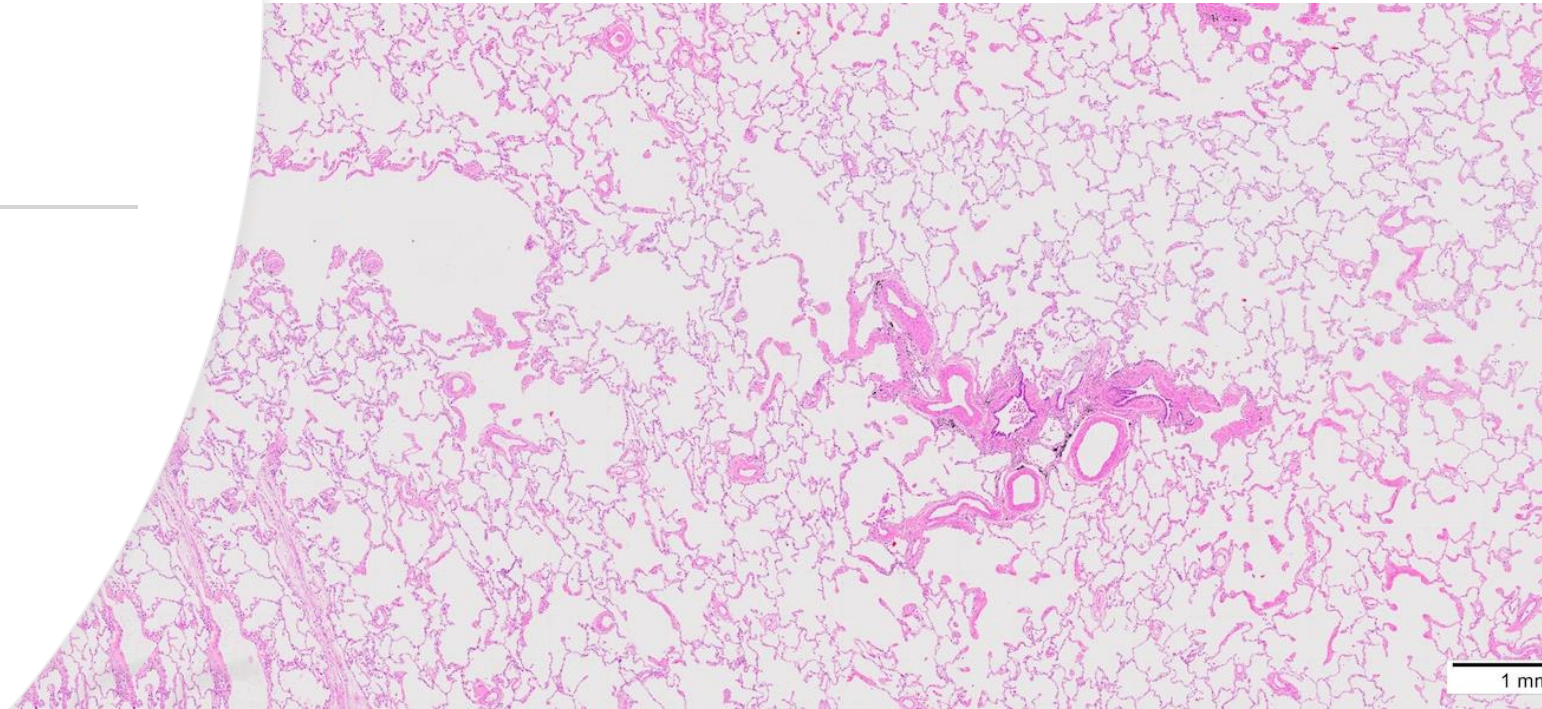


Disclosures

- I have no pertinent financial disclosures
- The opinions and slides in this presentation are my own

RESPIRATORY CARE

Research Article | Reviews

Efficacy and Safety of Different Doses of Systemic Corticosteroids in COPD Exacerbation

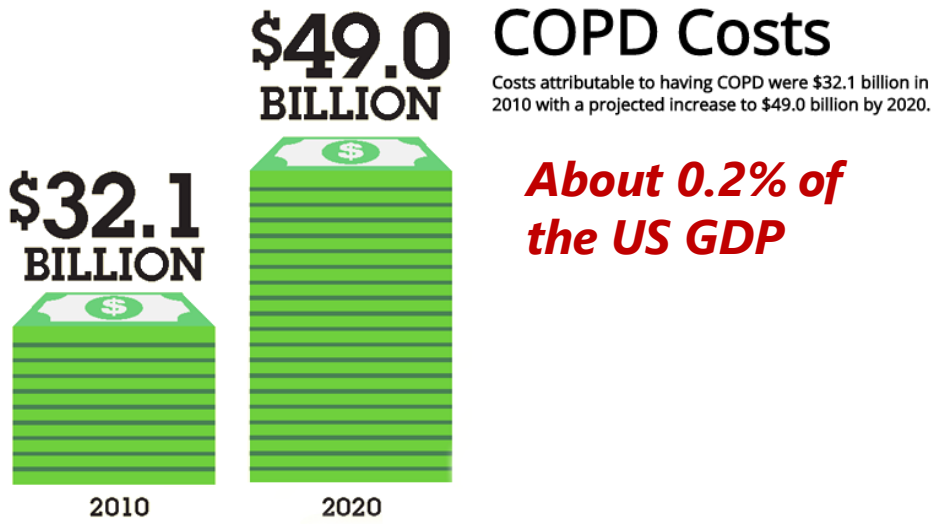
Xiaofeng Pu, Liang Liu, Bimin Feng, Maolin Wang, Limei Dong, Zhengji Zhang, Qingze Fan, Ying Li and Guojun Wang

Respiratory Care October 2020, respcare.07925; DOI: https://doi.org/10.4187/respcare.07925

http://rc.rcjournal.com/content/early/2020/10/13/respcare.07925.abstract

US COPD Epidemiology

- Prevalent
- Mortality
- $

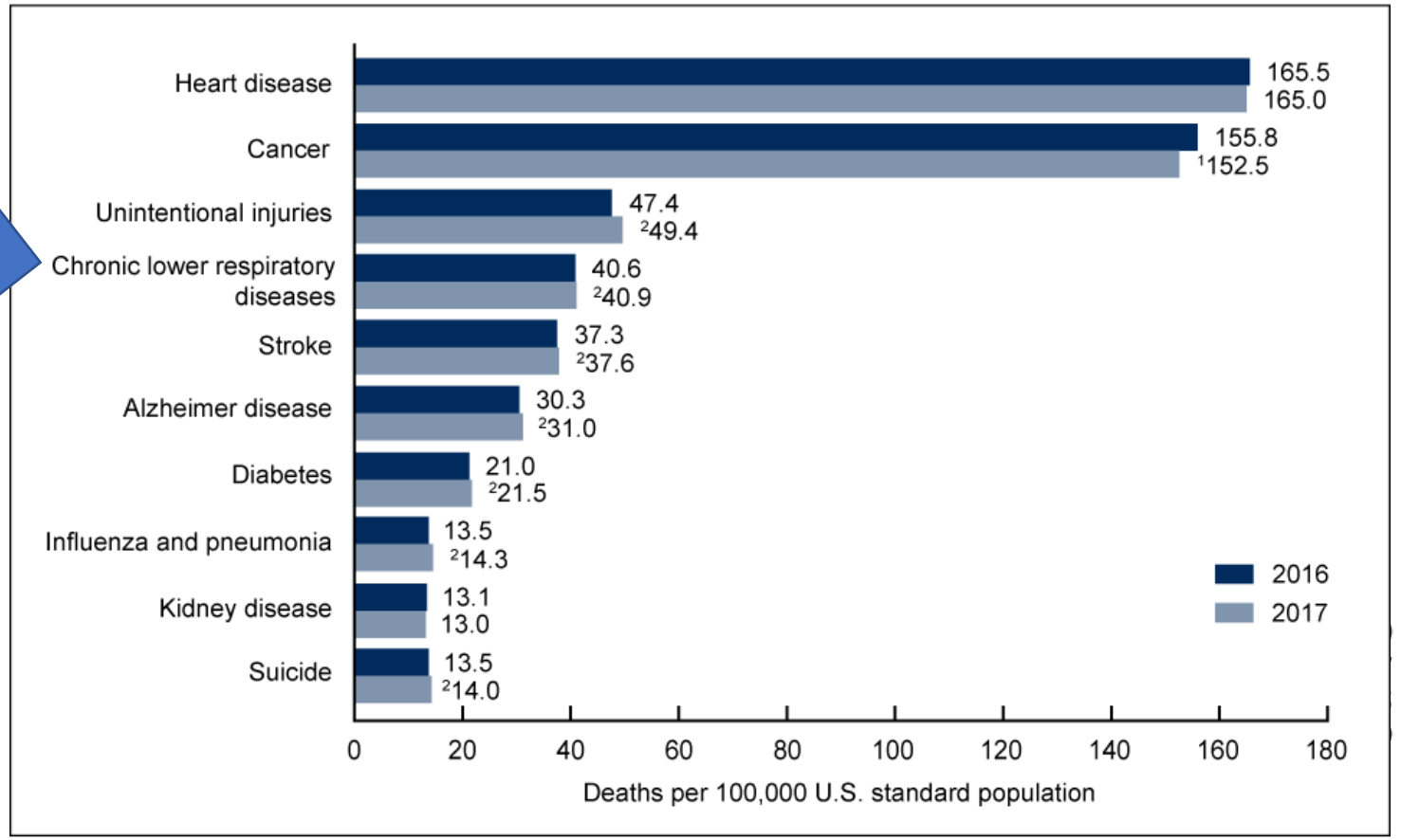


COPD Costs

Costs attributable to having COPD were $32.1 billion in 2010 with a projected increase to $49.0 billion by 2020.

About 0.2% of the US GDP

Figure 4. Age-adjusted death rates for the 10 leading causes of death: United States, 2016 and 2017

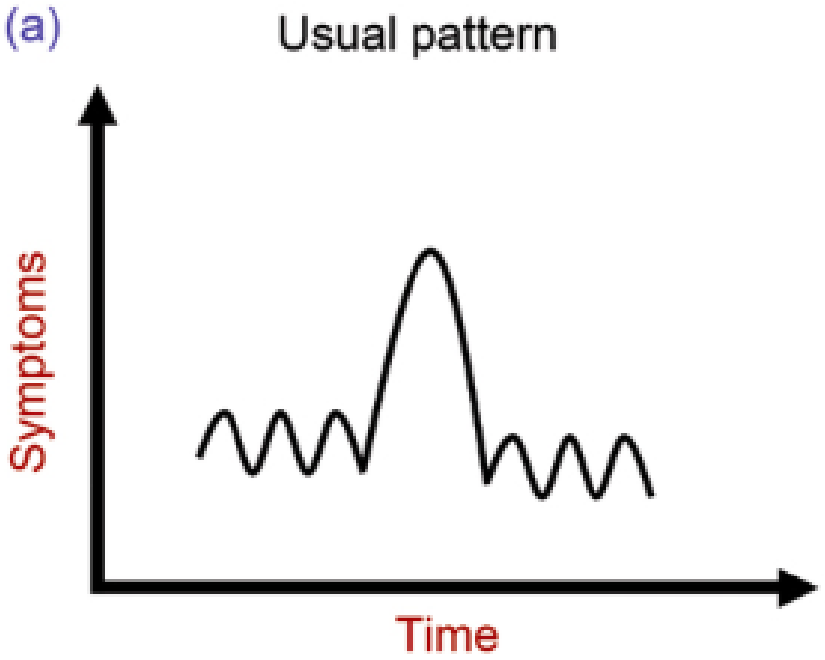


[1]Statistically significant decrease in age-adjusted death rate from 2016 to 2017 ($p < 0.05$).
[2]Statistically significant increase in age-adjusted death rate from 2016 to 2017 ($p < 0.05$).
NOTES: A total of 2,813,503 resident deaths were registered in the United States in 2017. The 10 leading causes accounted for 74.0% of all deaths in the United States in 2017. Causes of death are ranked according to number of deaths. Rankings for 2016 data are not shown. Data table for Figure 4 includes the number of deaths for leading causes. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db328_tables-508.pdf#4.
SOURCE: NCHS, National Vital Statistics System, Mortality.

Murphy SL, Xu JQ, Kochanek KD, Arias E. Mortality in the United States, 2017. NCHS Data Brief, no 328.
CDC. Chronic obstructive pulmonary disease among adults— United States, 2011. MMWR. 2012; 61(46):938-943.

Acute COPD Exacerbation (AECOPD) Definition

- GOLD definition:
  - "Acute worsening of symptoms requiring escalation in treatment, often with corticosteroids and/or antibiotics"



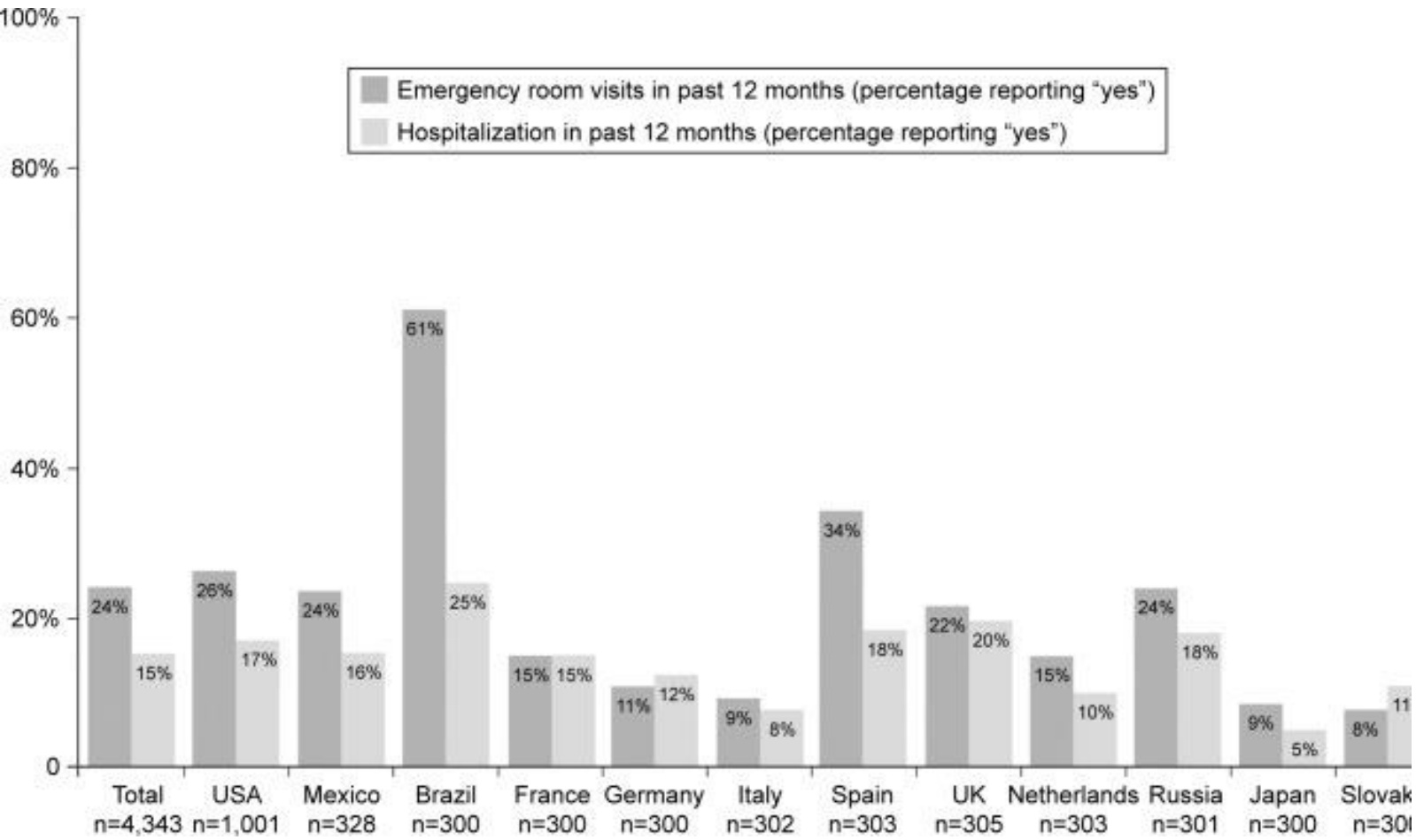
- Mild

- Moderate

- Severe

GOLD Criteria, https://goldcopd.org/

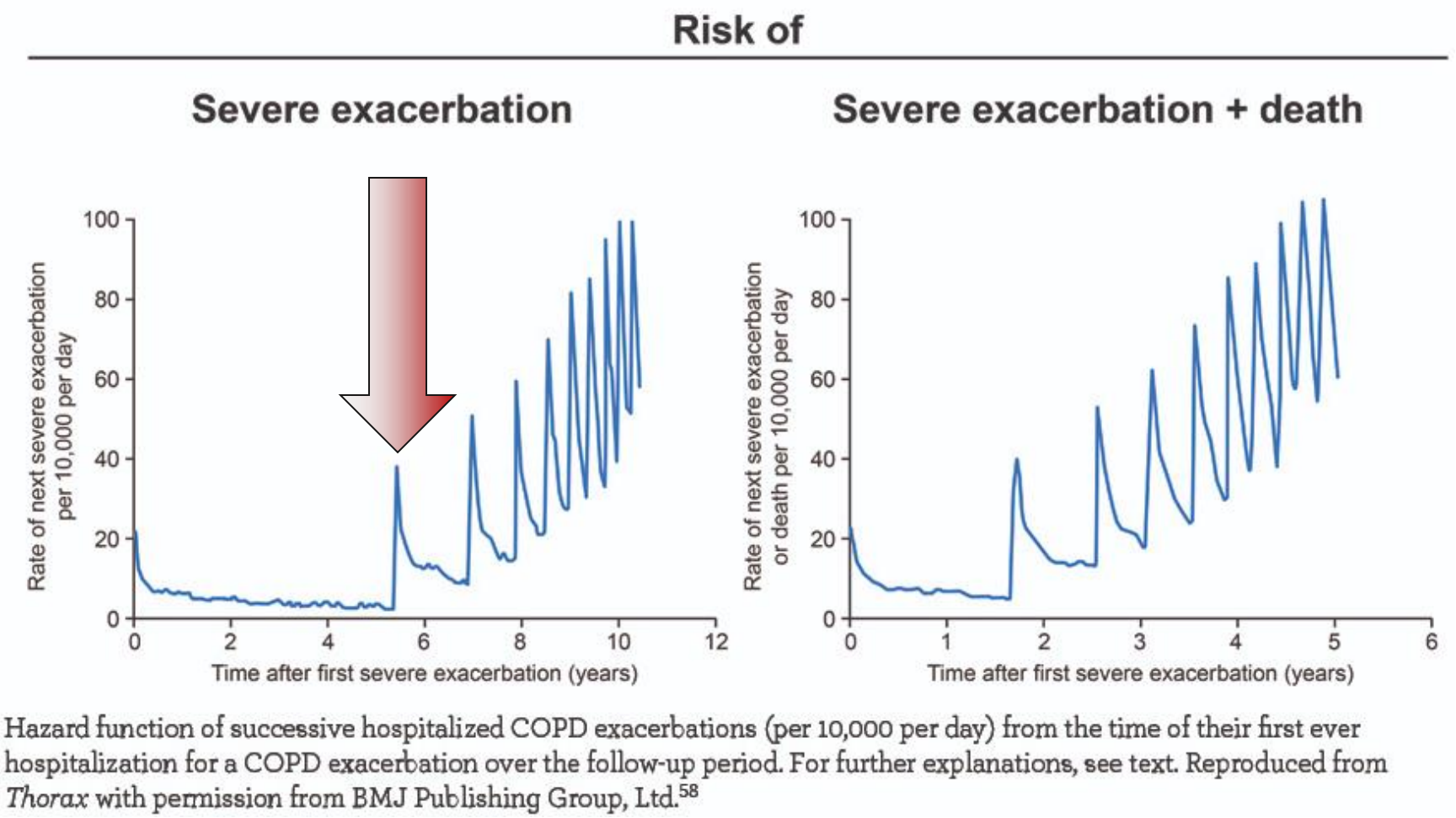
Severe Exacerbation Epidemiology



- In 2006, there were **1,254,703 hospitalizations** for COPD exacerbations, with total inpatient **costs of $11.9 billion** (and $9,545 per hospitalization)
- Contrary to overall in-patient trends within the period 2001–2012, there has been **no significant improvement** in: the number of hospital discharges, ED visits, and 30-day readmissions.
- Patients who have been admitted to hospital for a severe exacerbation of COPD are at **substantial risk for rehospitalization (15-25%)**

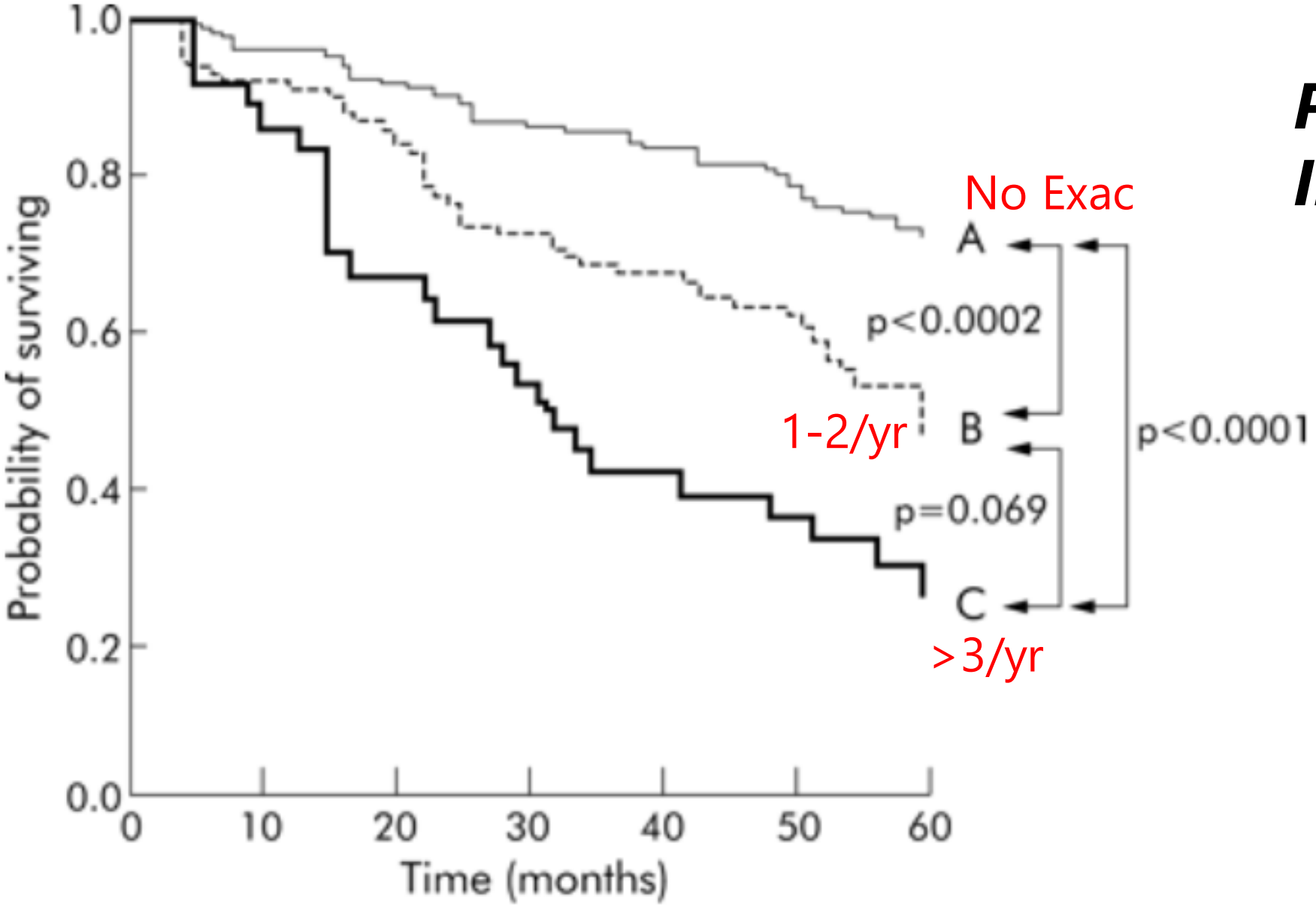
Halpin DM, Miravitlles M, Metzdorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2891-2908. Published 2017 Oct 5. doi:10.2147/COPD.S139470

Exacerbations beget exacerbations



Hazard function of successive hospitalized COPD exacerbations (per 10,000 per day) from the time of their first ever hospitalization for a COPD exacerbation over the follow-up period. For further explanations, see text. Reproduced from *Thorax* with permission from BMJ Publishing Group, Ltd.[58]

Agusti A, Calverley PM, Decramer M, Stockley RA, Wedzicha JA. Prevention of exacerbations in chronic obstructive pulmonary disease: knowns and unknowns. *Chronic Obstr Pulm Dis*. 2014; 1(2): 166-184. doi:

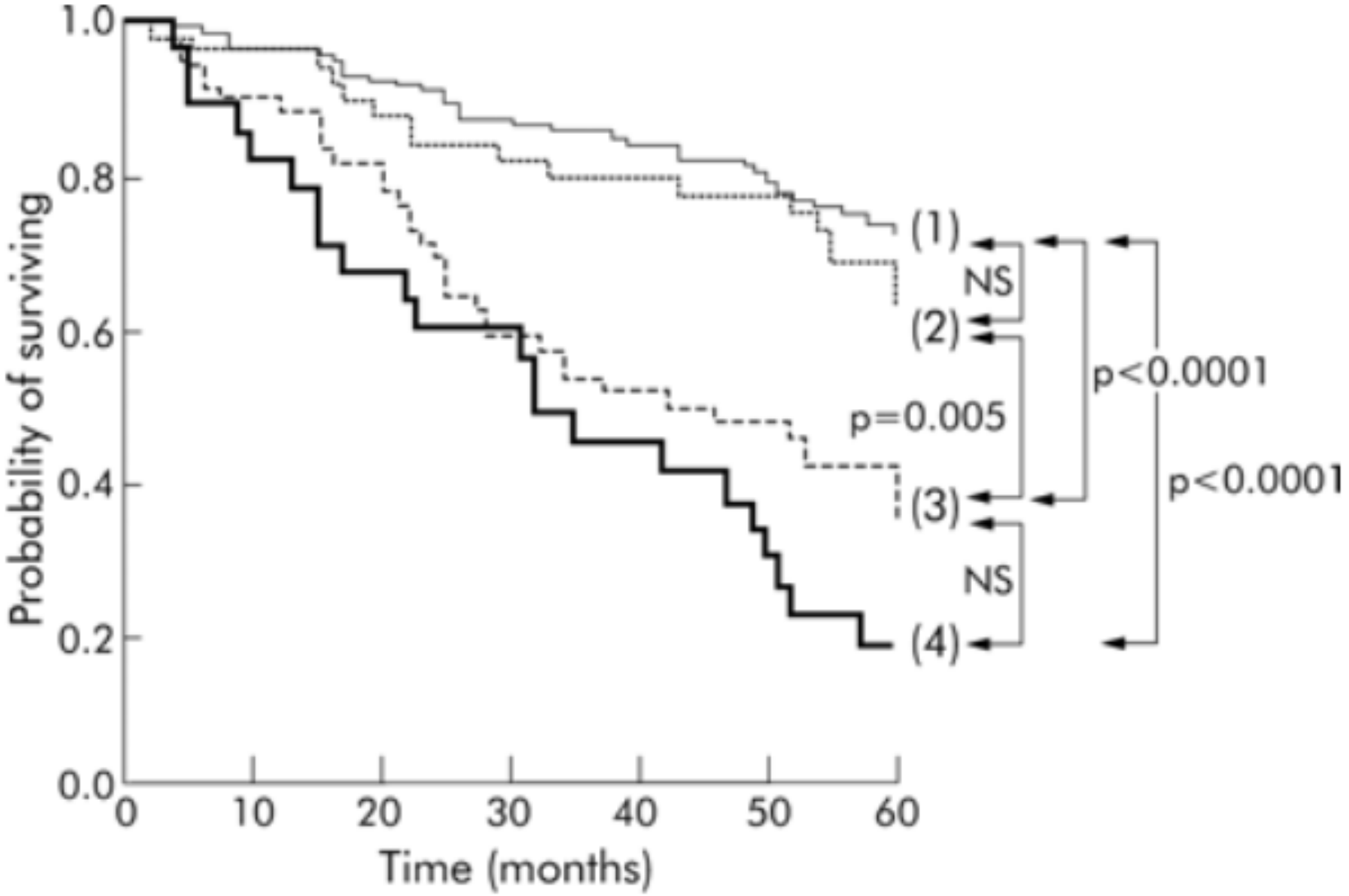


Persistent Negative Impact:

- Decreased quality of life and functional status.
- Increase in healthcare utilization and cost.
- Increased morbidity and mortality.

Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, *et al*
Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease
Thorax 2005;**60:**925-931.

Severity of COPD Exacerbations Matter



1) No exacerbations
2) ED visits
3) Admitted
4) Readmissions

Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, *et al.* Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease.*Thorax* 2005;**60:**925-931.

Scope of this Presentation

- Common pitfalls in diagnosis and management of COPD
- Optimal inpatient care of COPD exacerbations
- Strategies to break the cycle of exacerbation

Common scenario

https://lungdiseasenews.com/2015/04/21/day-tiotropium-respimat-dose-proven-effective-24-hour-bronchodilator-asthma-patients/

Strategies in Management of Severe AECOPD

- Confirm the Diagnosis of COPD
- Characterize the patient's COPD
  - Identify phenotype/endotype of COPD
  - Assess for associated comorbidities/confounding causes of dyspnea
- Identify the Exacerbating Cause
- Pharmacotherapy For COPD
  - Role of inhaled corticosteroids
  - Role of systemic corticosteroids
  - Bronchodilators: Medication and Delivery
  - Antibiotics
  - Other medications: Beta blockers, roflumilast, chronic macrolides, Vitamin D
- Respiratory Support
  - Hypercapnic "death spiral"
  - Acute and nocturnal mechanical ventilation

Confirm/Challenge the Diagnosis of COPD

- Is this actually COPD?
  - COPD is both **OVER**-diagnosed and **UNDER**-diagnosed

Common Pitfall:

+

=

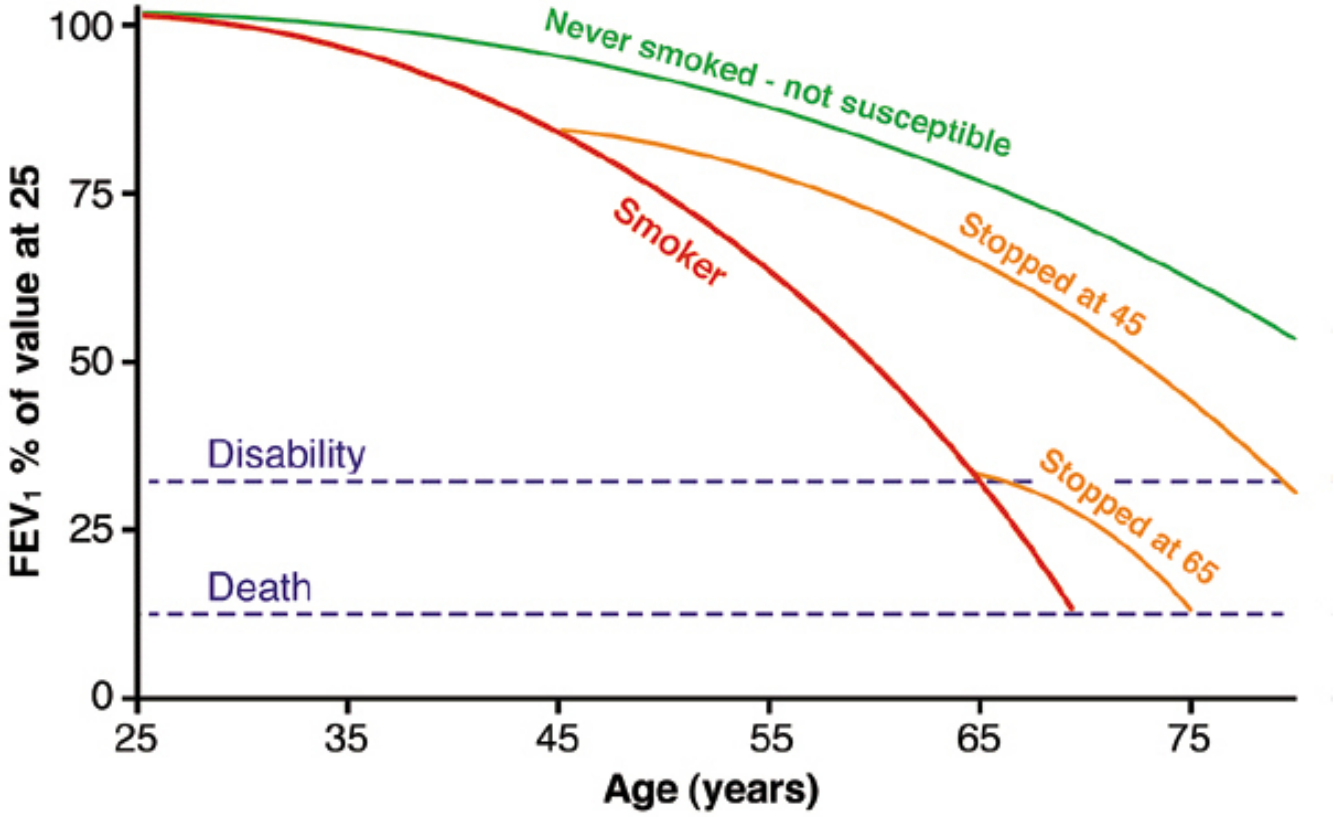
COPD

Image: https://www.medicalnewstoday.com/articles/324644.php

UNDER-diagnosis of COPD

- Much of COPD is *UNDER-diagnosed* until it's *advanced*
  - Early COPD is often asymptomatic
    - FEV1 ~ 60% when symptoms start

- What's the effect?
  - Worse quality of life
  - Higher mortality rate from diagnosis,\
  - *More exacerbations*



Fletcher & Peto. Brit Med J; 1977(1):1645-48

Gender Bias in the Diagnosis of COPD*

Kenneth R. Chapman, MD, FCCP; Donald P. Tashkin, MD, FCCP; and David J. Pye, PhD

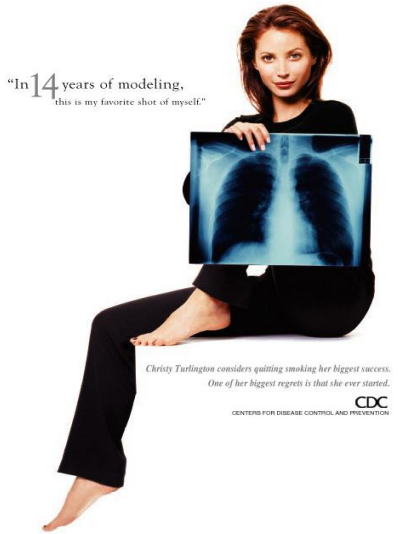


Table 1. Percentage of Diagnoses Offered at Each Stage of the Survey Process

Diagnosis	History and Physical		Spirometry		Oral Steroid Trial	
	Male	Female	Male	Female	Male	Female
COPD	64.6	49.0	76.0	64.6	85.4	78.1
Asthma	32.3	43.8	21.9	32.3	10.4	17.7
Other, nonrespiratory	3.1	7.3	2.1	3.1	4.2	4.2

OVER-diagnosis of COPD

- Among 16,177 participants, 919 (5.7%) reported a previous medical diagnosis of COPD.
- Postbronchodilator spirometry was unobstructed in 569 subjects ***(61.9%): false positive COPD.***
  - 37.7% with "emphysema" or "chronic bronchitis" had no airflow limitation.
- Among the subjects with false positive COPD, ***45.7% reported current use of respiratory medication***

CHEST
Volume 156, Issue 2, August 2019, Pages 277-288

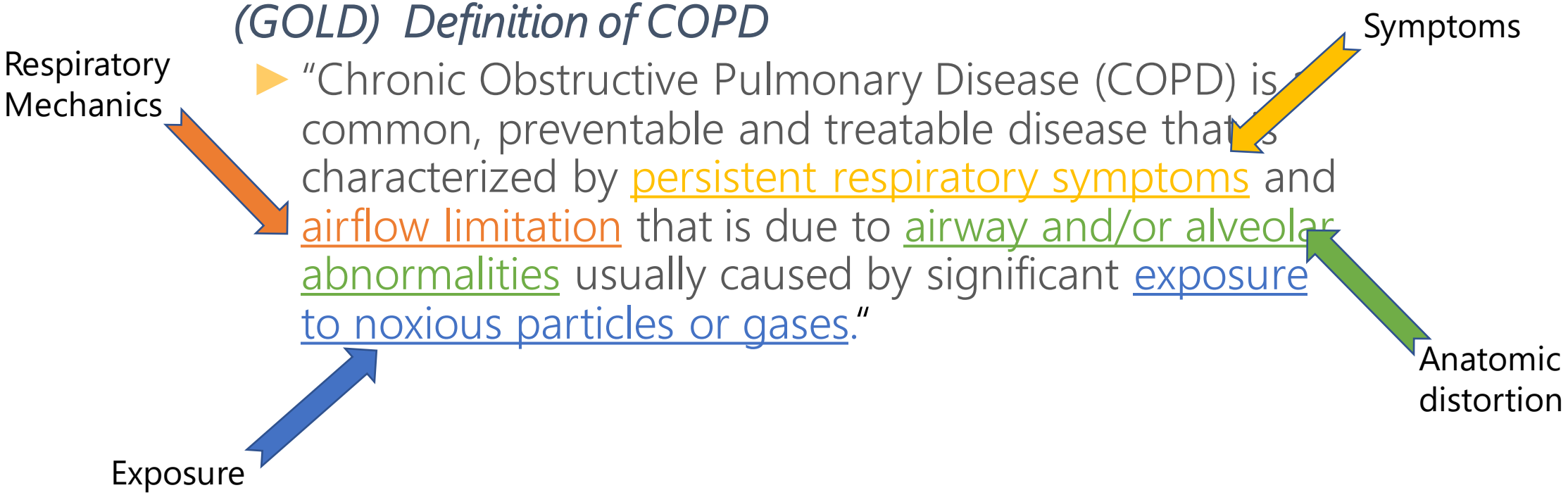
Original Research: COPD

Overdiagnosis of COPD in Subjects With Unobstructed Spirometry: A BOLD Analysis

Lea Sator MD [a], Andreas Horner MD [b, c, d], Michael Studnicka MD, FCCP [a], Bernd Lamprecht MD [b, c], Bernhard Kaiser MSc [b], Mary Ann McBurnie MD [e], A. Sonia Buist MD [f], Luisa Gnatiuc MSc [g], David M. Mannino MD, FCCP [h], Christer Janson MD, PhD [i], Eric D. Bateman MD [j], Peter Burney MD [g]
BOLD Collaborative Research Group*

What is Chronic Obstructive Pulmonary Disease (COPD)?

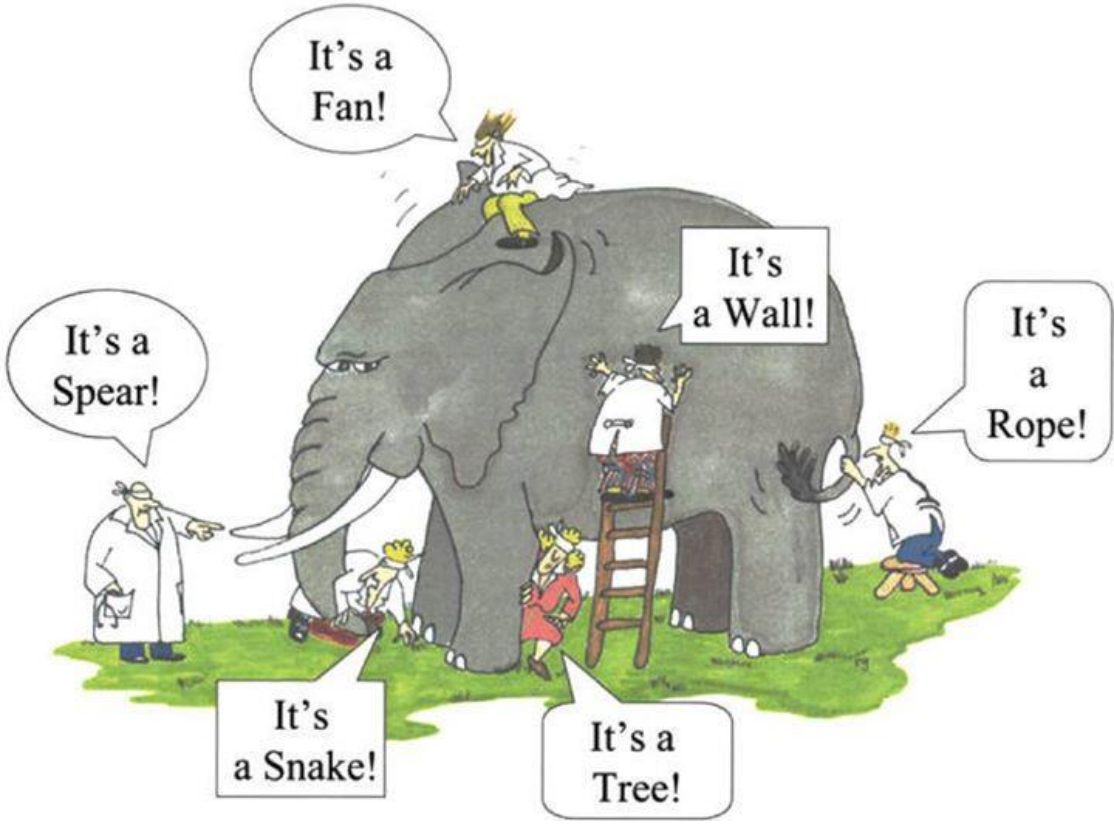
- *Global Initiative for Chronic Obstructive Lung Disease (GOLD) Definition of COPD*
  - "Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."



Global Initiative for Chronic Obstructive Lung Disease (GOLD)
Accessed June 2019 at www.goldcopd.org

What is Chronic Obstructive Pulmonary Disease (COPD)?

- *Symptoms*
- *Respiratory Mechanics (ie, Spirometry/PFT)*
- *Anatomic Distortion*
- *Exposure*



https://www.patheos.com/blogs/driventoabstraction/2018/07/blind-men-elephant-folklore-

Symptoms

- Chronic dyspnea/shortness of breath
- Cough
  - with or without sputum production
- Weight loss, cachexia
- Emotional stress
- Acute Exacerbations

Fletcher & Peto. Brit Med J; 1977(1):1645-48
https://www.pharmacytimes.com/publications/health-system-edition/2015/march2015/copd-improving-disease-mana

Why spirometry?

- Make the diagnosis
  - And identify potential alternative diagnoses
- Identify rapid decliners, hyperinflated patients, *etc.*
- Grade degree of obstruction correlated with symptom/exacerbation burden
- Candidacy for certain therapies (endobronchial valves, lung volume reduction surgery)

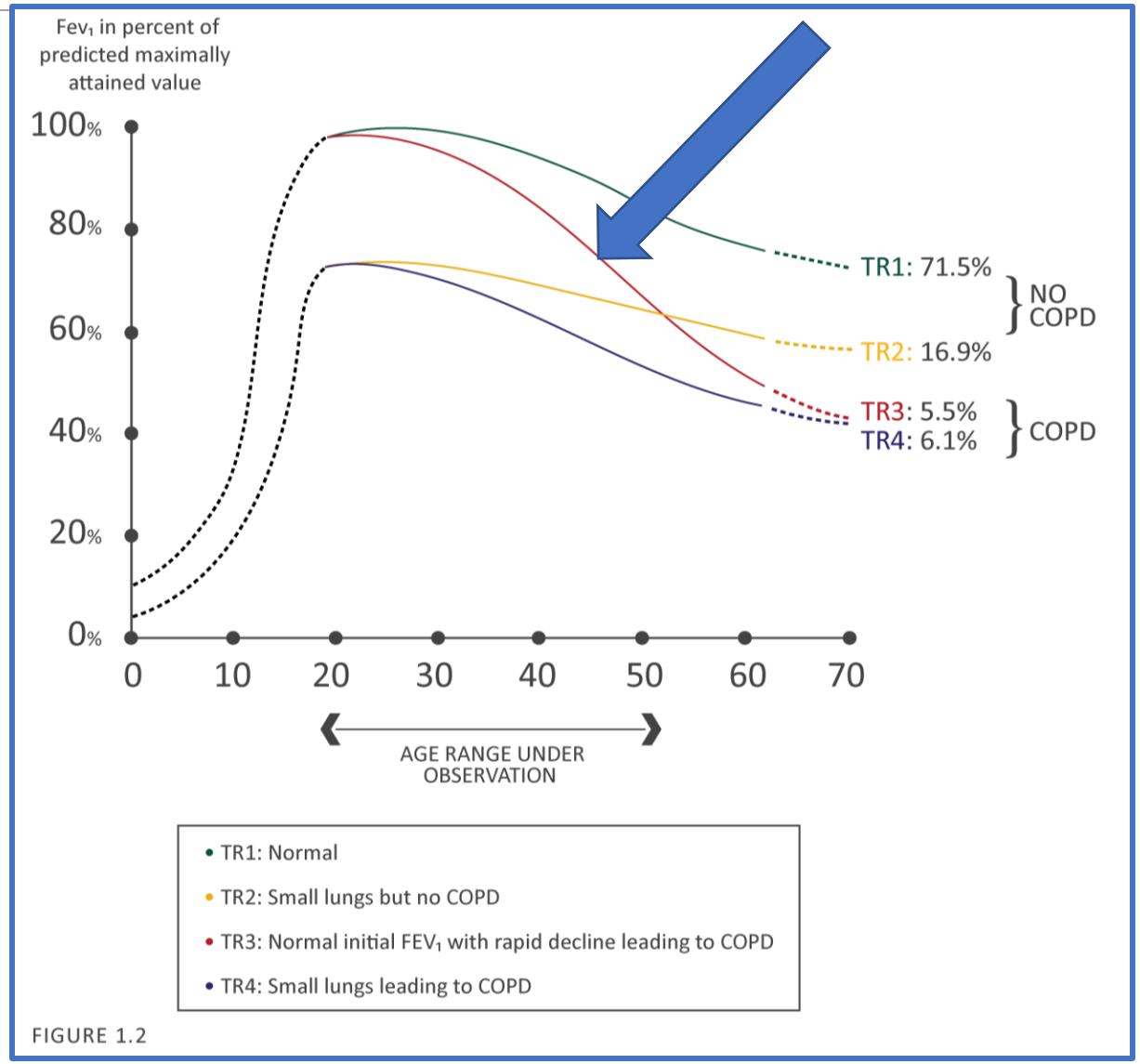
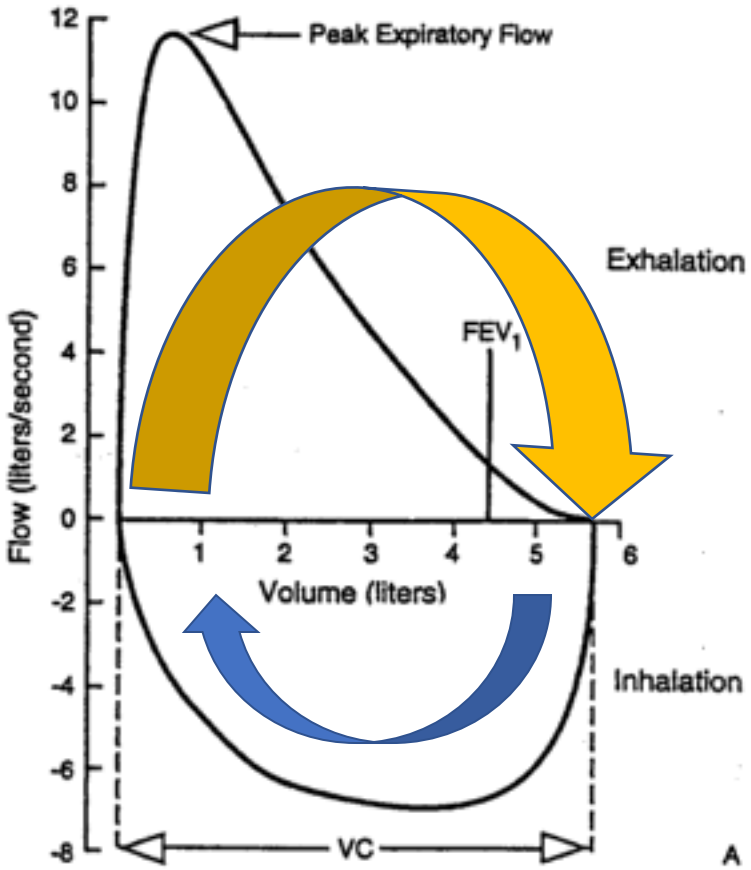


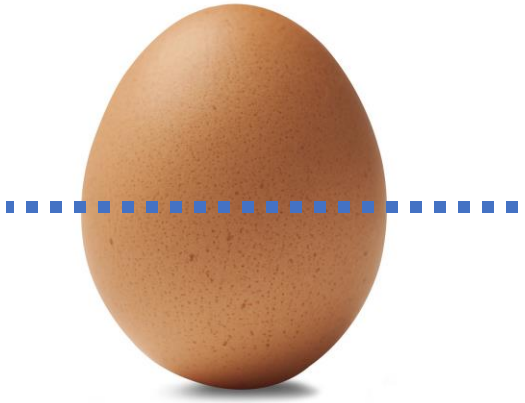
FIGURE 1.2

Spirometry Interpretation

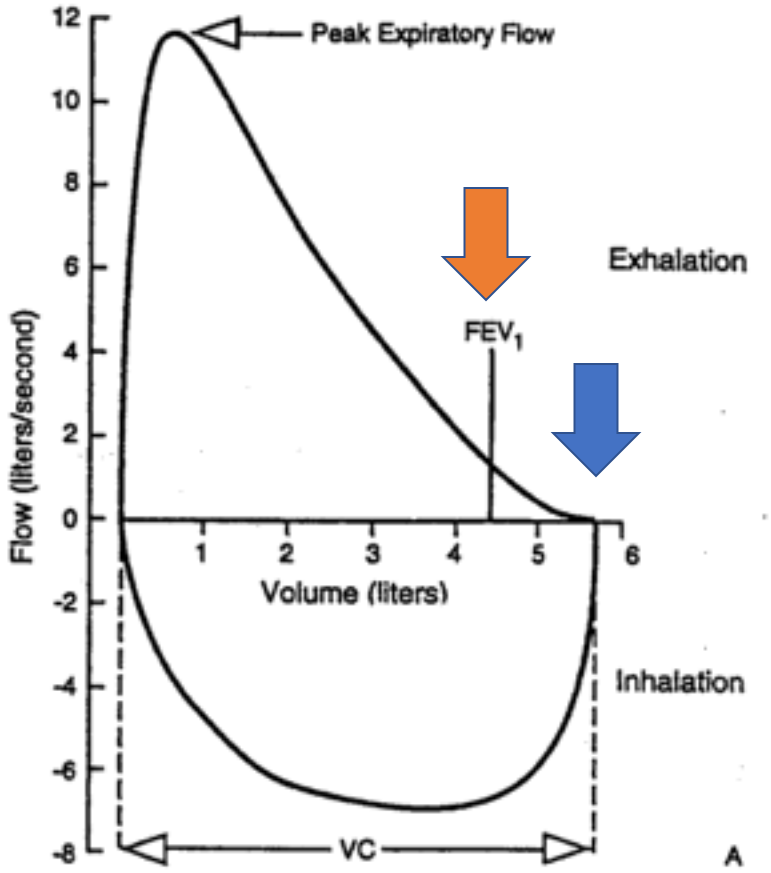
Exhalatory Flow



Inspiratory Flow

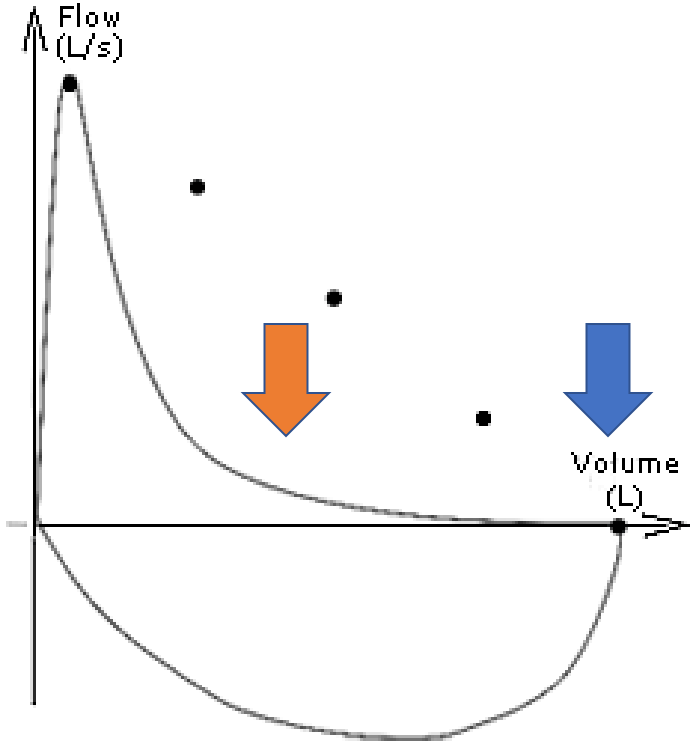


Normal vs. Obstruction Spirometry



FEV1=Forced exhalatory volume at 1 second

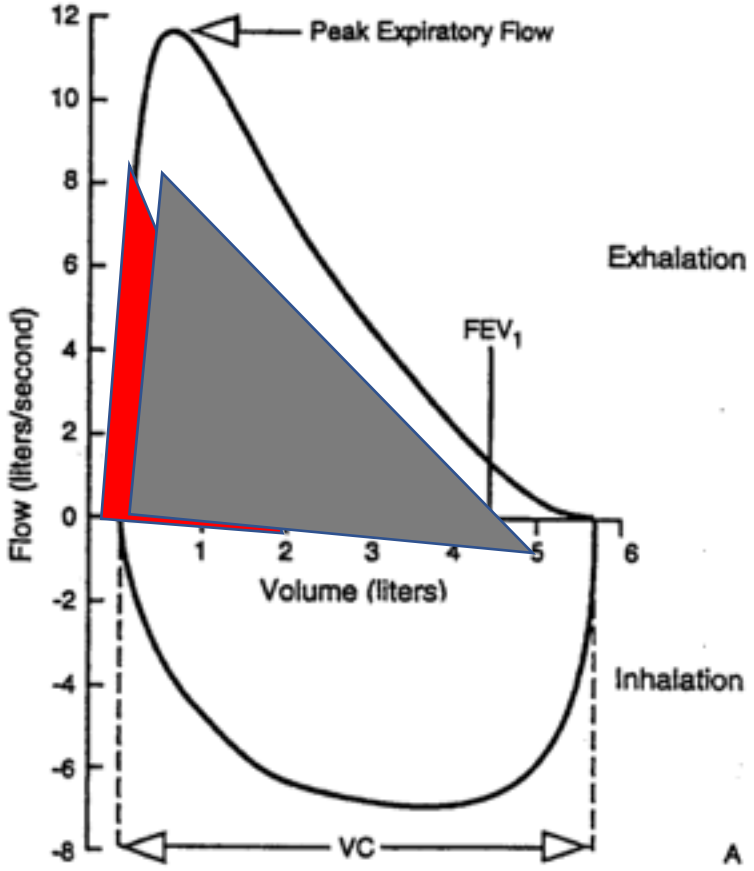
FVC= Forced vital capacity

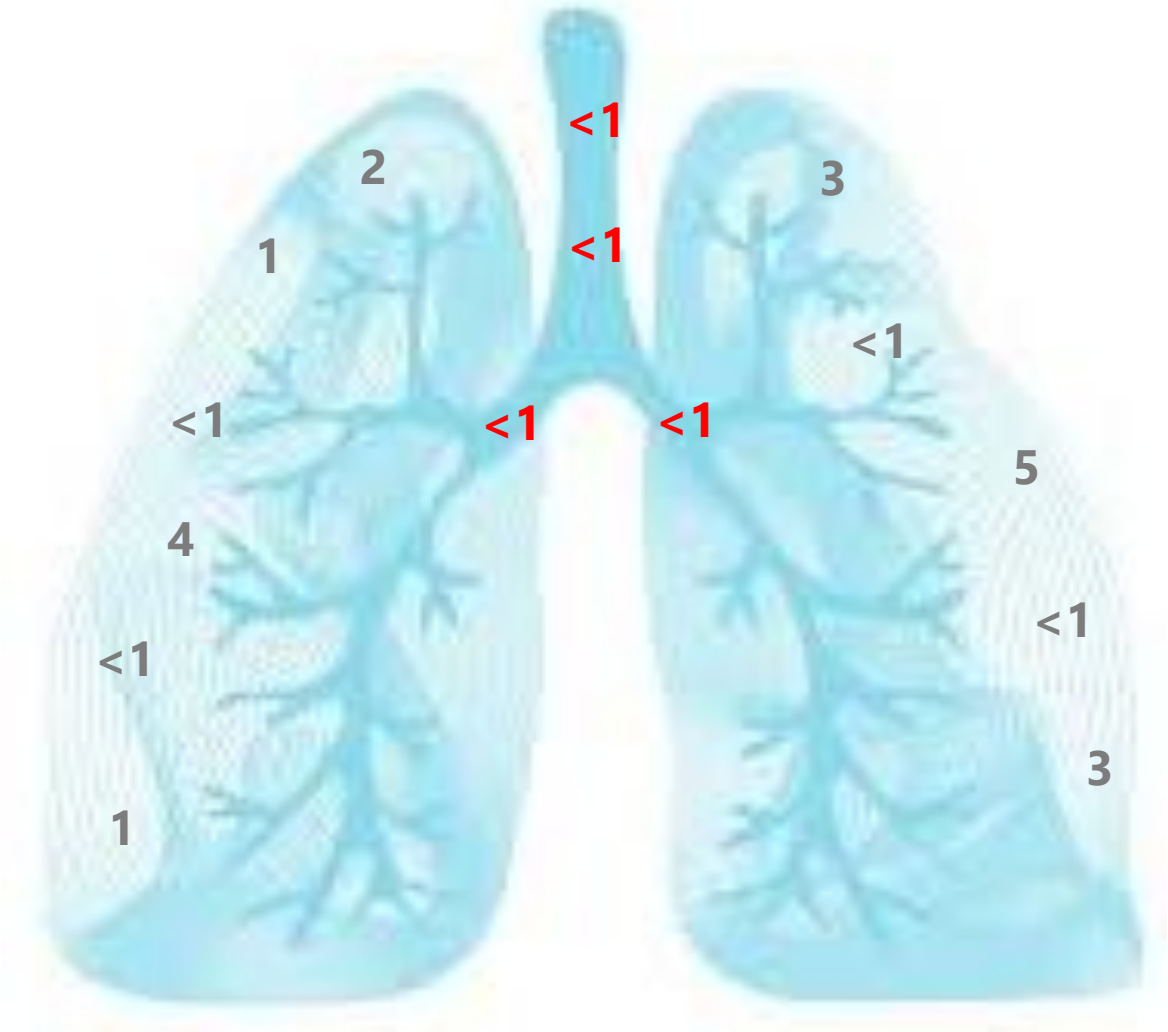


Obstruction: FEV1/FVC <0.7 (or lower than 95% LLN)

Normal Spirometry

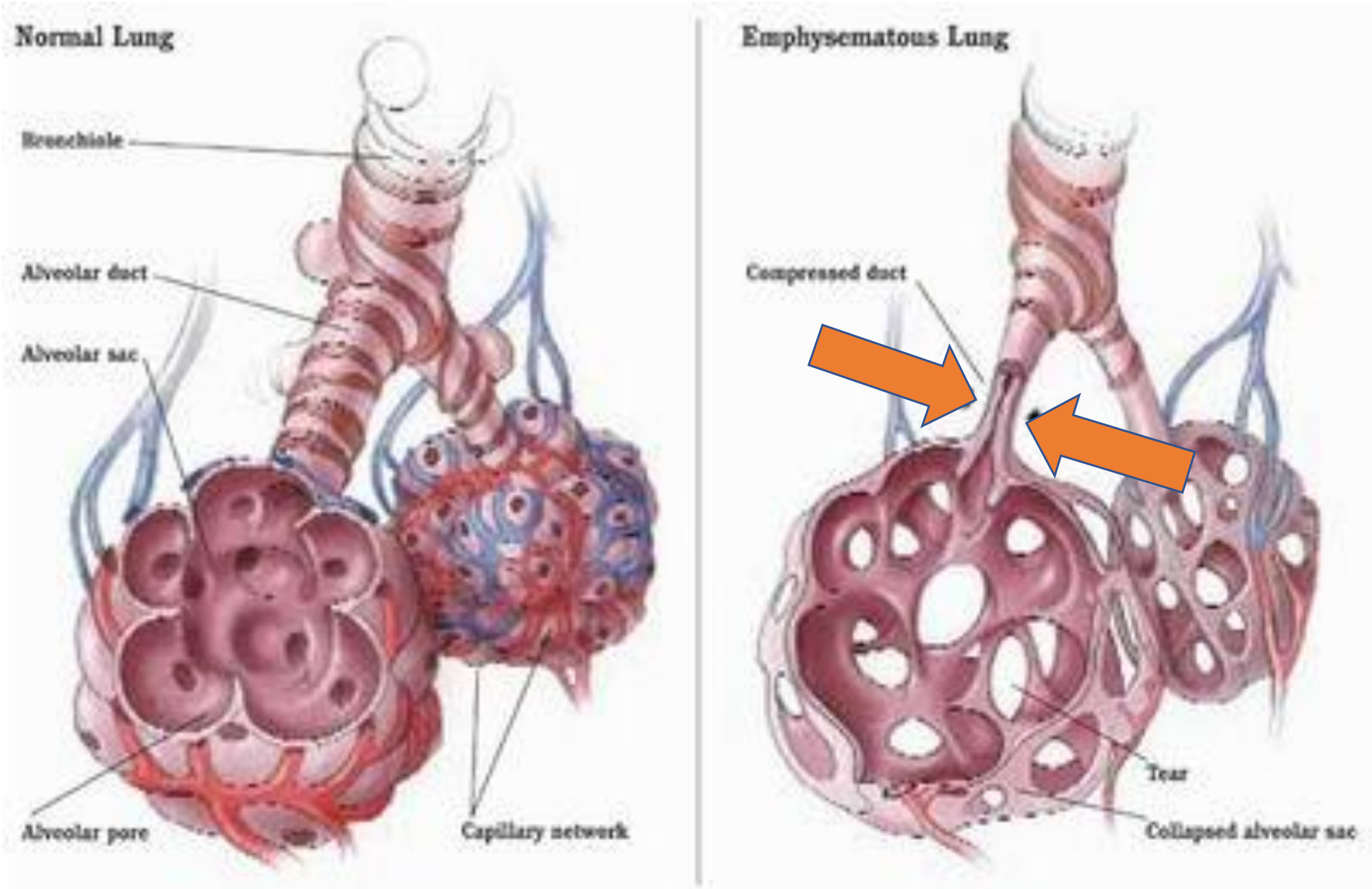
Time Constant = time to exhale a lung unit = Airway Resistance x Alveolar Compliance





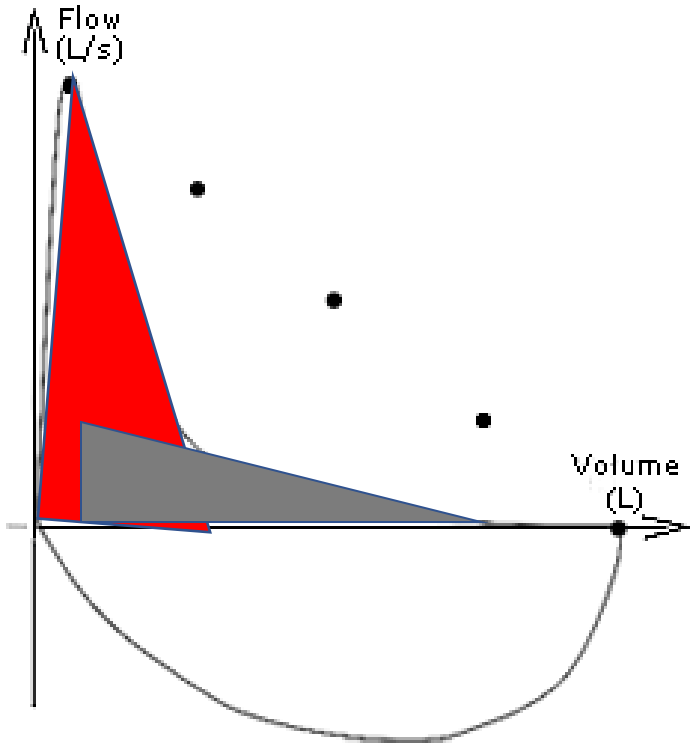
Red= Proximal Airway Green=Small Airways

COPD Airway Physiology

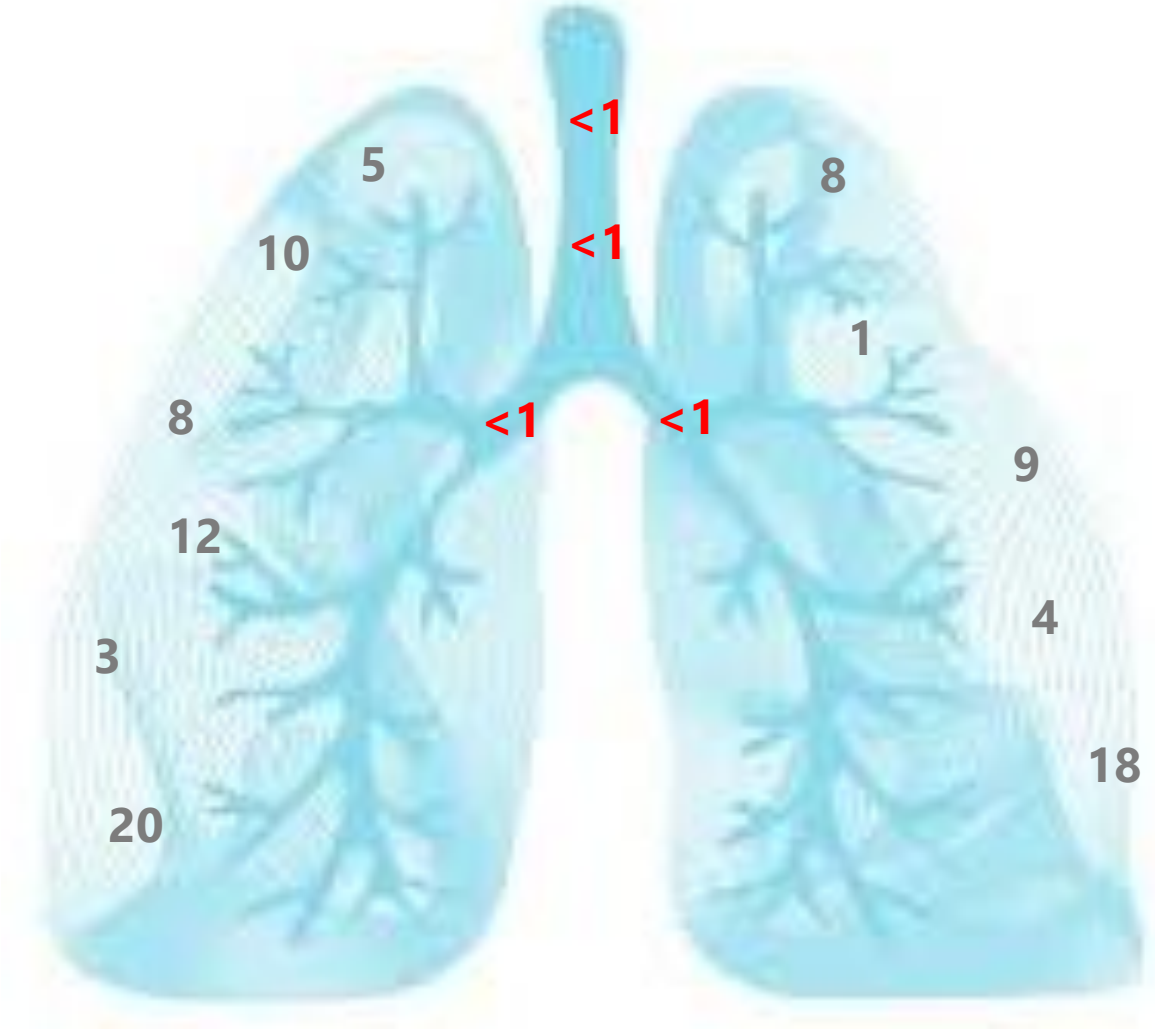


http://www.medicalook.com/Lung_diseases/Copd.html

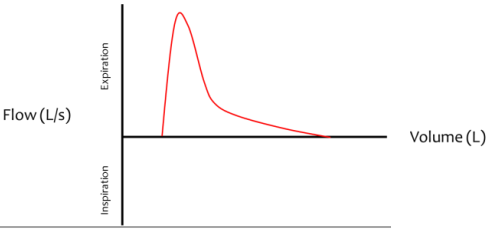
Obstruction

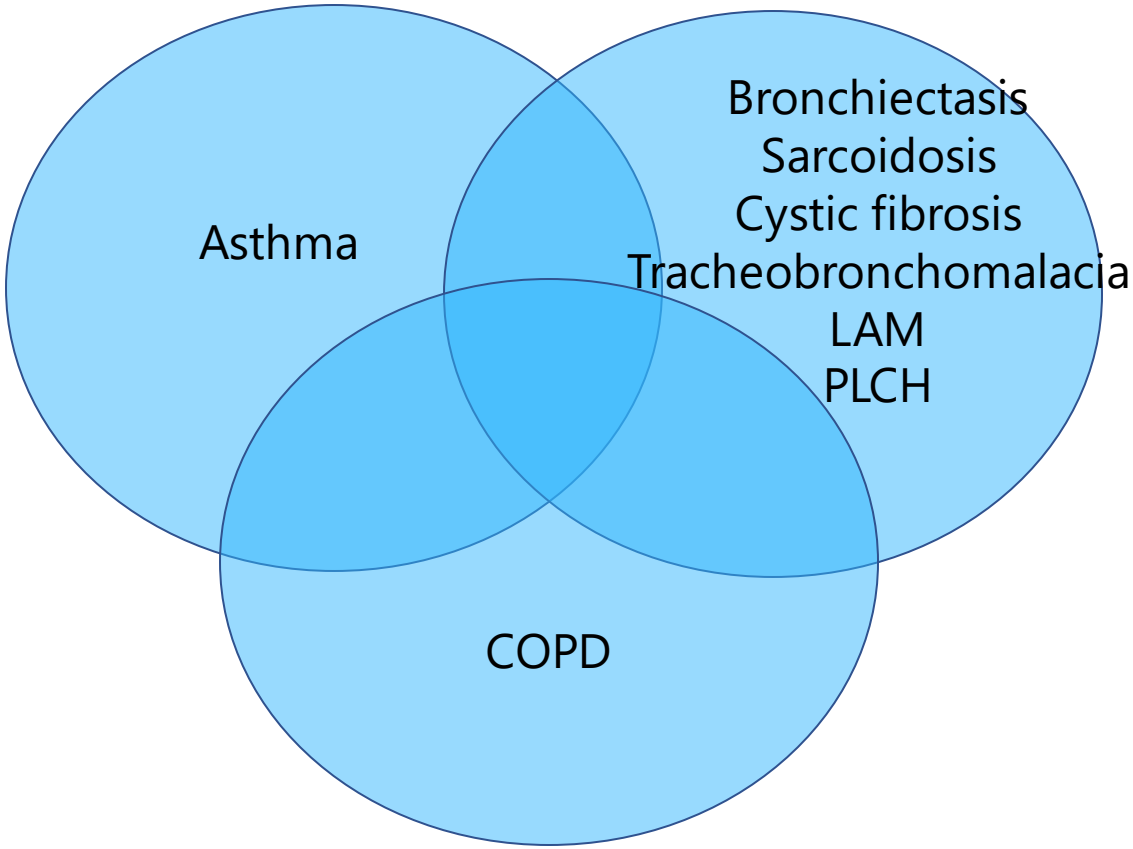


Obstruction: FEV1/FVC <0.7
(or lower than 95% LLN)



Obstructive Lung Disease vs COPD

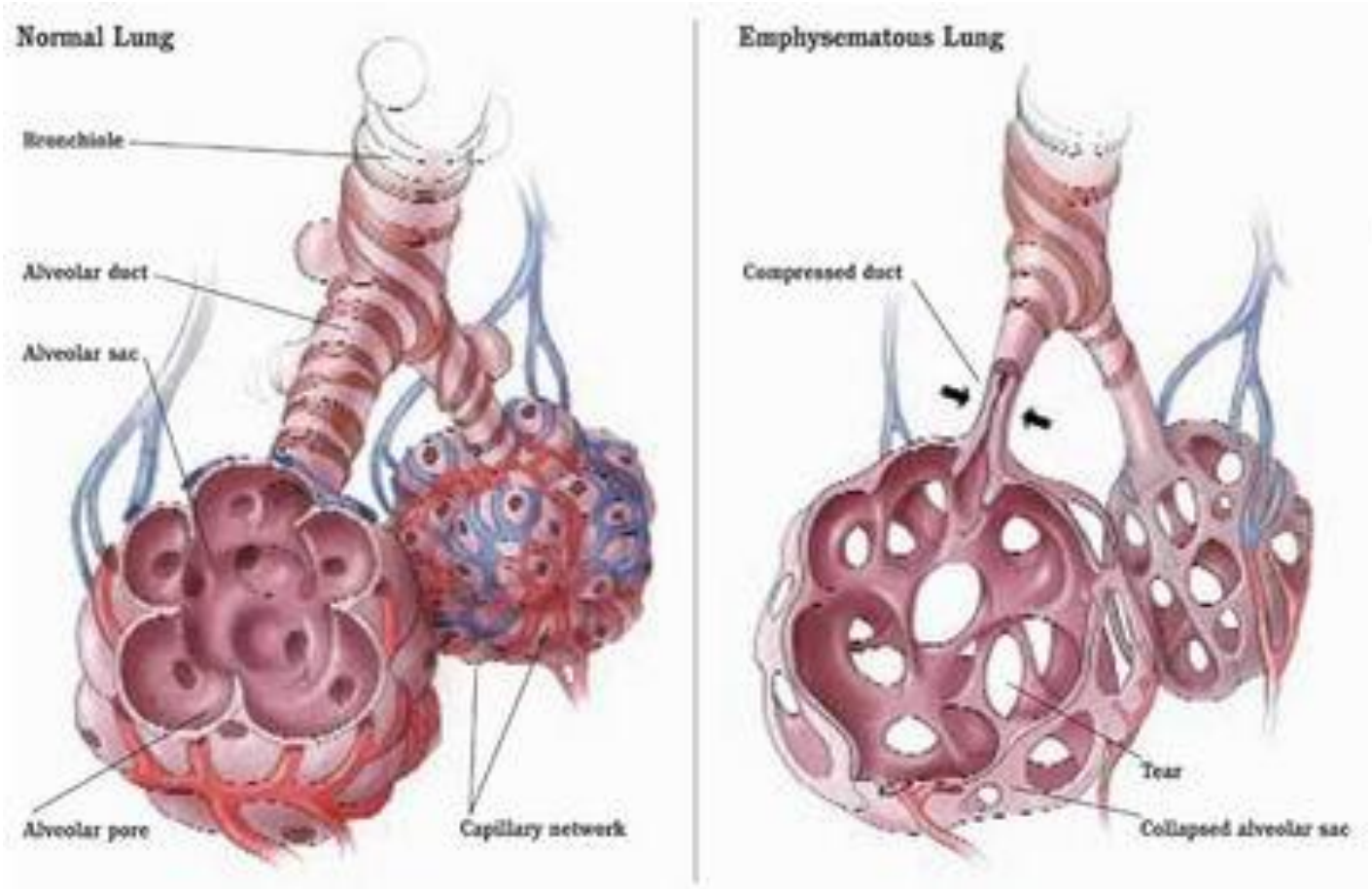


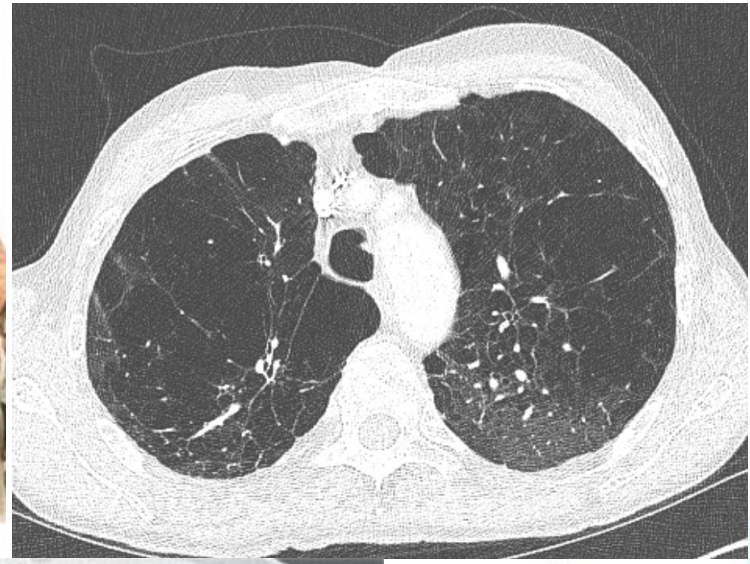


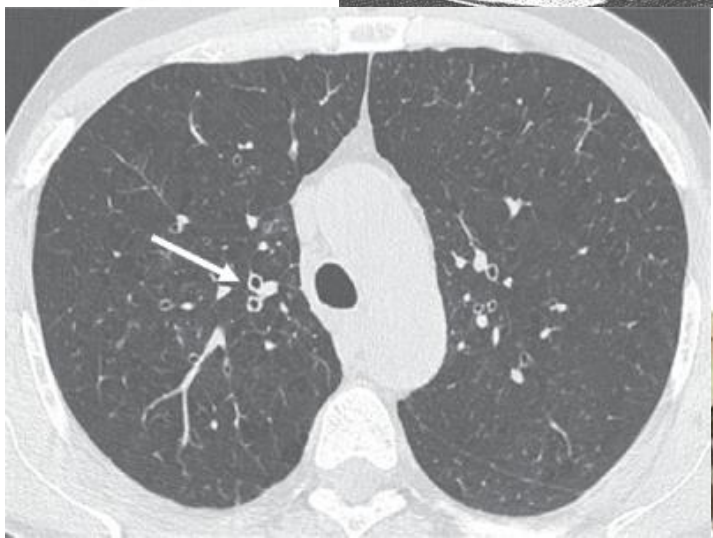
COPD= chronic obstructive pulmonary disease; LAM=lymphangiolyomyomatosis; PLCH=pulmonary Langerhans cell histiocytosis (aka eosinophilic granulomatosis)

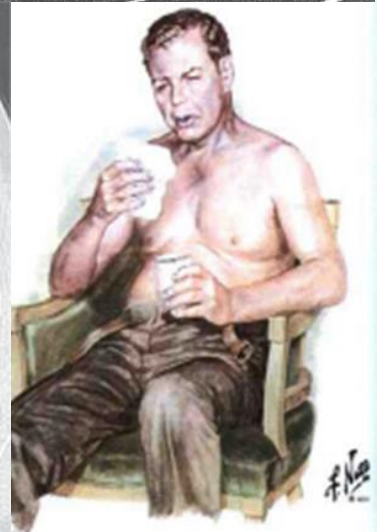
Slide adapted from presentation by Dr. Michael Schivo

Anatomic Distortion









http://www.medicalook.com/Lung_diseases/Copd.html

Exposures

- Tobacco smoke
- Wildfire smoke
- Indoor pollution/smoke from biomass fuels
- Industrial air pollution
- Infections

https://www.vox.com/energy-and-environment/2018/11/16/18098461/aqi-san-francisco-worst-air-quality-world-epa

Alternative Diseases Misdiagnosed as COPD

- Aspiration pneumonitis/bronchitis
- Obesity hypoventilation syndrome
- Asthma
- Coronary artery disease
- Pulmonary edema/heart failure
- Bacterial pneumonia (important if on inhaled corticosteroids)
- Vocal cord dysfunction
- Bronchiectasis
- Lung Cancer
- Arrythmia/valvular disease
- Pulmonary embolism
- .....

Any smoking ever + Age >50 + Dyspnea ≠ COPD

Spirometry/PFTs are crucial in tackling this differential

Does this patient have COPD?

- You are called to the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

- In the ED patient has been given 125 mg of solumedrol, azithromycin 500 mg IV, albuterol via nebulizer, and the patient is on BiPAP at 15/5, 40% FiO2.
  - Temperature: 99 F, HR 100, BP 133/75, RR 26, SpO2 99%
  - CXR and CT chest performed demonstrating left lower lobe pneumonia with significant centrilobular emphysema, no PE
  - Labs: CBC with no peripheral eosinophilia

Probably…..

Imaging in Diagnosis

Figure 1. Features Used to Define COPD in the COPDGene® Study

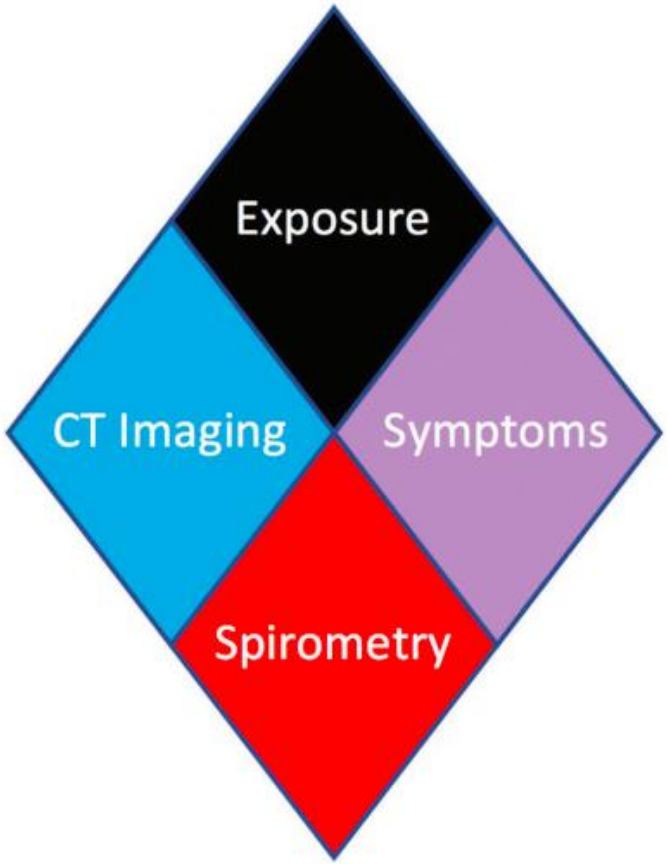


Table 1. COPDGene® 2019 Categories

Category	Description	Symbol	# of Disease Features
A	Exposure		1
B	Exposure + CT Abnormal		2
C	Exposure + Symptoms		2
D	Exposure + Spirometry Abnormal		2
E	Exposure + Symptoms + CT Abnormal		3
F	Exposure + Spirometry Abnormal + Symptoms		3
G	Exposure + Spirometry Abnormal + CT Abnormal		3
H	Exposure + Spirometry Abnormal + Symptoms + CT Abnormal		4

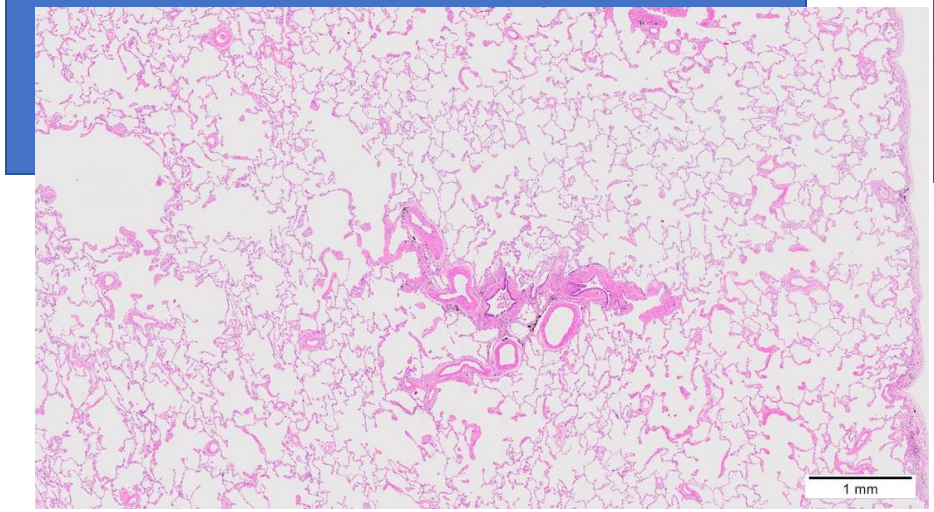
Lowe KE, Regan EA, Anzueto A, et al. COPDGene 2019: redefining the diagnosis of chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis*. 2019; 6(5): 384-399. doi: http://doi.org/10.15326/jcopdf.6.5.2019.0149

What is the phenotype/endotype of COPD?

- In 2010, Han *et al.* proposed the following definition of COPD Phenotypes:
  - "a single or combination of **disease attributes** that describe differences between individuals with COPD as they **relate to clinically meaningful outcomes** (symptoms, exacerbations, response to therapy, the rate of disease progression, or death)"

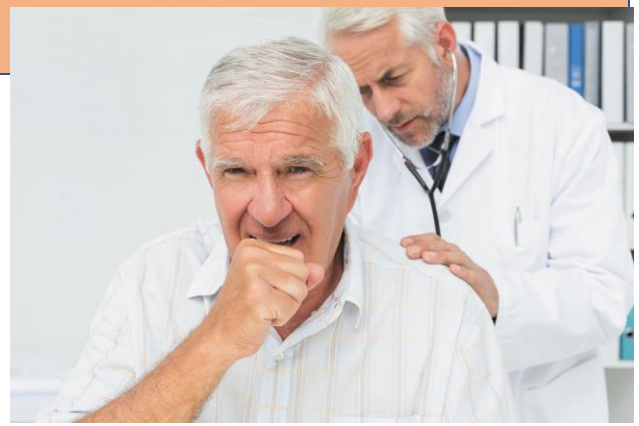
Endotype

- A condition defined by a distinct pathobiological mechanism (*e.g.* emphysema)



Phenotype

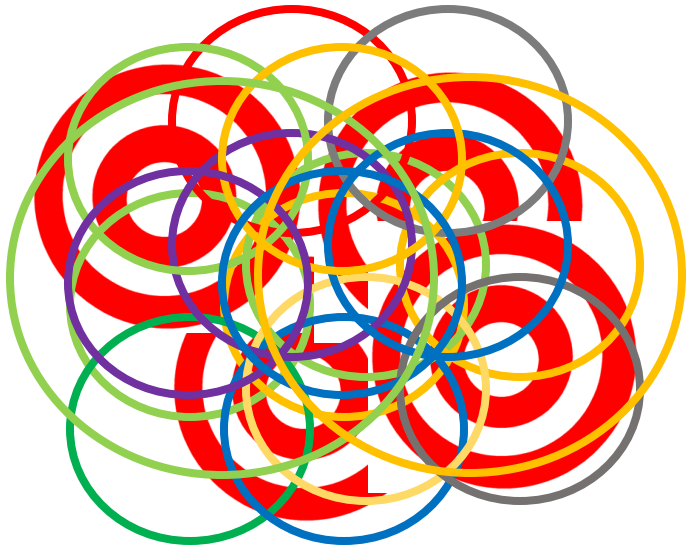
- The observable characteristics of an individual resulting from the interaction of its endotype with the environment (*e.g.* dyspnea)



Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010; 182(5):598–604.

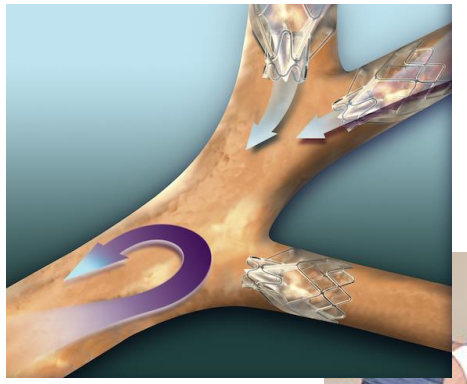
How many phenotypes?

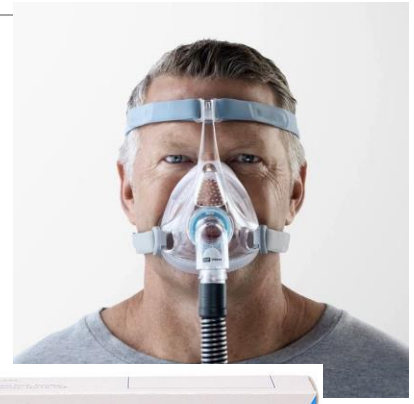
- Miravitlees *et al.*
  - "***no consensus*** on the number and definition of the different COPD phenotypes, being anywhere from ***two to 328 million*** (the estimated number of patients worldwide)"

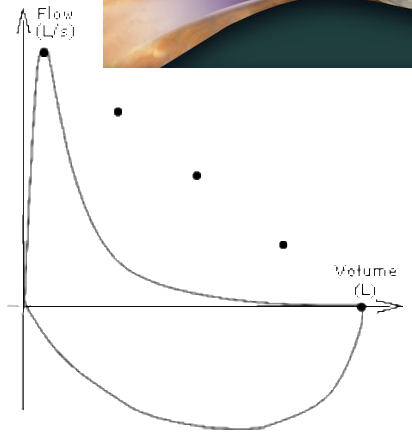


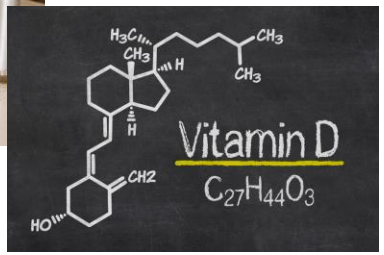
Miravitlees et al., Eur Respir J 2013; 41: 1252–1256

PERSONALIZED Treatment









https://breatheeasycpap.com/fisher-paykel-vitera-full-face-cpap-mask-with-headgear/

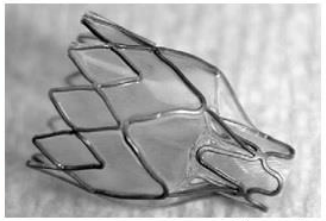
https://lungdiseasenews.com/2015/04/21/day-tiotropium-respimat-dose-proven-effective-24-hour-bronchodilator-asthma-patients/

https://lungdiseasenews.com/2015/04/22/vitamin-deficiency-may-cause-poorer-lung-function-exercise-ability-copd/

Endobronchial valves for severe emphysema

Jorine E. Hartman[1,2], Lowie E.G.W. Vanfleteren[3,4,5], Eva M. van Rikxoort[6], Karin Klooster[1,2] and Dirk-Jan Slebos[1,2]

PERSONALIZED Treatment



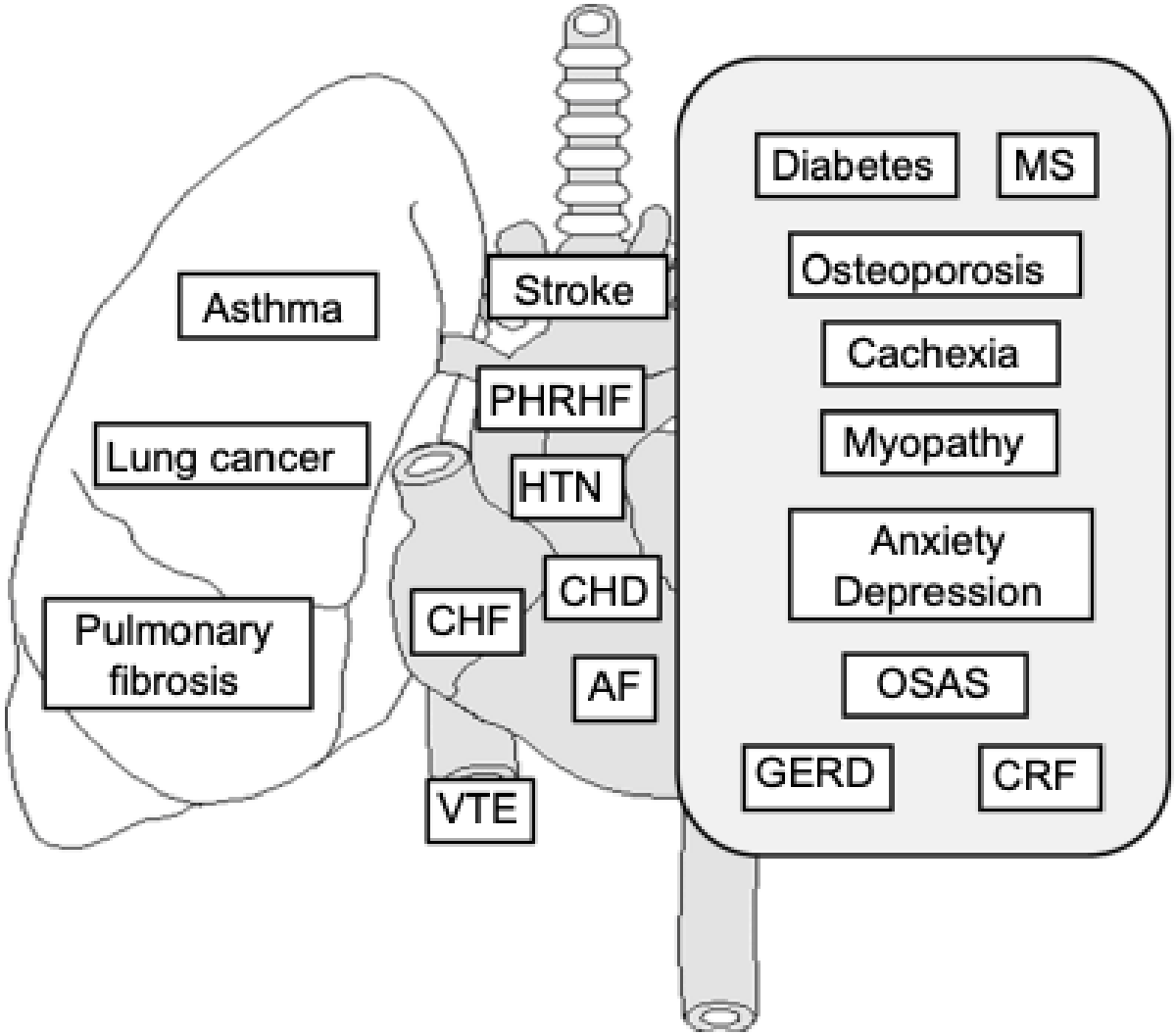
COPD CLINICAL PHENOTYPES/ENDOTYPES

- Frequent exacerbator
- Chronic bronchitis
- High peripheral eosinophils
- Asthma-COPD overlap
- Depression/anxiety
- Pulmonary hypertension
- Cardiac disease
- Alpha-1 Antitrypsin deficiency
- HIV emphysema
- Obstructive Sleep Apnea
- Obesity
- Hyperinflation +/- Giant bullae
- CO2 retainer
- Pulmonary Cachexia
- Active smoker
- ……

https://lungdiseasenews.com/2015/04/21/day-tiotropium-respimat-dose-proven-effective-24-hour-bronchodilator-asthma-patients/

Diseases with Higher Prevalence in COPD

- **Heart failure**
- **Coronary artery disease**
- **Pulmonary vascular disease**
- **Arrhythmias**
- **Pulmonary fibrosis**
- **Peripheral vascular disease**
- Hypertension
- Osteoporosis
- **Aspiration**
- **Anxiety and depression**
- **Lung cancer**
- Diabetes
- GERD
- **Bronchiectasis**
- Obstructive sleep apnea



Hillas et al., International Journal of COPD 2015:10 95–109

How can we better phenotype our patient?

- You are called to the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

- In the ED patient has been given 125 mg of solumedrol, azithromycin 500 mg IV, albuterol via nebulizer, and the patient is on BiPAP at 15/5, 40% FiO2.
  - Temperature: 99 F, HR 100, BP 133/75, RR 26, SpO2 99%
  - CXR and CT chest performed demonstrating left lower lobe pneumonia with significant centrilobular emphysema, no PE
  - Labs: CBC with no peripheral eosinophilia

  - ***What phenotype does this patient have?***
    - ***Frequent exacerbator***
  - ***Endotype:***
    - ***Pauci-immune (low eos)…?inhaled corticosteroids?***

Identify the CAUSE of the exacerbation?

- COPD exacerbation is not a manifestation of the underlying disease itself
  - e.g. myocardial infarction:coronary artery disease
- What pushed them over the edge?

Causes of Exacerbation

- Mainly triggered by viral infections
- Infectious tracheitis/bronchitis makes up ~50-60% of severe acute exacerbations
  - The most common bacterial pathogens isolated from sputum and bronchoscopic samples are *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis*.
  - In patients with more severe disease and/or exacerbations, Gram-negative pathogens, such as *Pseudomonas aeruginosa*, are common.
- Short term exposure to high PM2.5 increases COPD admissions/mortality
- Aspiration is common, especially in very frequent exacerbators
- Remember the non-COPD/non-pulmonary etiologies

What is driving the exacerbation?

- You are called form the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

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  - CXR and CT chest performed demonstrating left lower lobe pneumonia with significant centrilobular emphysema, no PE
  - Labs: CBC with no peripheral eosinophilia

Pneumonia, likely bacterial
- ***Is this an exacerbation?***

Corticosteroids

- Several studies have demonstrated an improvement of several outcomes in AECOPD patients using systemic steroids, including:
  - Length of hospital stay
  - In-hospital oxygen requirement
  - FEV_1
  - Dyspnea
  - Risk of relapse/treatment failure
- The **oral administration is as effective** as intravenous administration
- A **short duration** of treatment is preferred to a long duration
  - A recent meta-analysis suggested that a 5-day course of oral CSs not inferior to those with longer (10- to 14-day) courses
  - Worse outcomes with high dose steroids
- **Keep dose modest** (~0.5 mg/kg)
  - Beware the lure of solumedrol 125 mg (size of the vial)

Crisafulli, E., Barbeta, E., Ielpo, A. *et al.* Management of severe acute exacerbations of COPD: an updated narrative review. *Multidiscip Respir Med* **13,** 36 (2018). https://doi.org/10.1186/s40248-018-0149-0

ICS in Acute Exacerbations of COPD (AECOPD)

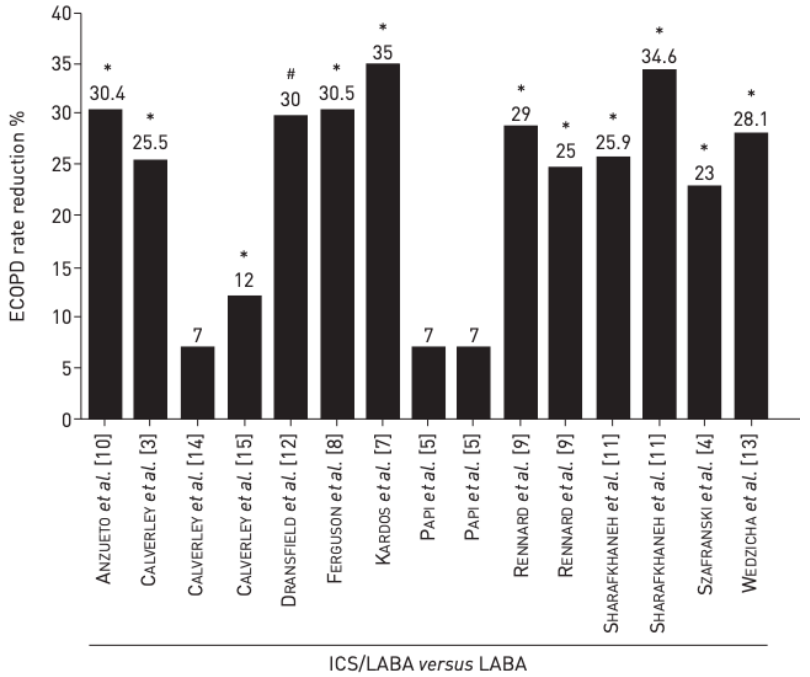
- Early RCTs focused on FEV1 as a primary outcome and enrolled patients with a relatively low exacerbation rate (and hence showed little benefit for ICS)
- More recent RCTs showed ICS + LABA reduced AECOPD by 25-35% when compared to

BENEFITS of ICS in COPD:

- Exacerbation rate
- FEV1
- Symptoms

RISKS of ICS in COPD:

- **Pneumonia** in those with:
  - older age
  - lower body mass index (BMI)
  - greater overall fragility
  - receiving higher ICS doses
  - those with blood eosinophils <100



Agusti *et al.* Summary of ICS/LABA vs. LABA alone on rates of AECOPD

Inhaled corticosteroids in COPD: friend or foe? Alvar Agusti, Leonardo M. Fabbri, Dave Singh, Jørgen Vestbo, Bartolome Celli, Frits M.E. Franssen, Klaus F. Rabe, Alberto Papi
European Respiratory Journal Dec 2018, 52 (6) 1801219; **DOI:** 10.1183/13993003.01219-2018

THE LANCET
Respiratory Medicine
Volume 6, Issue 2, February 2018, Pages 117-126

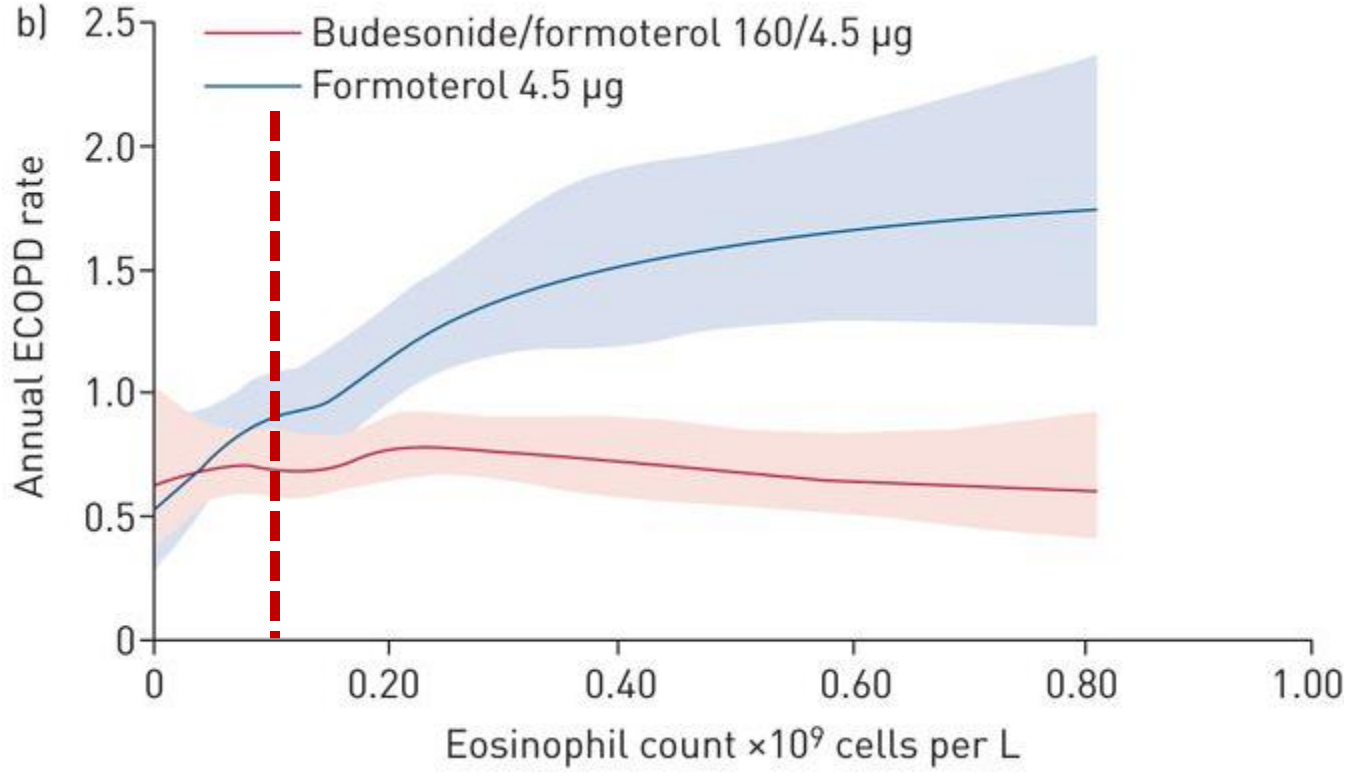
Blood Eosinophils as Biomarkers

Articles

Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials

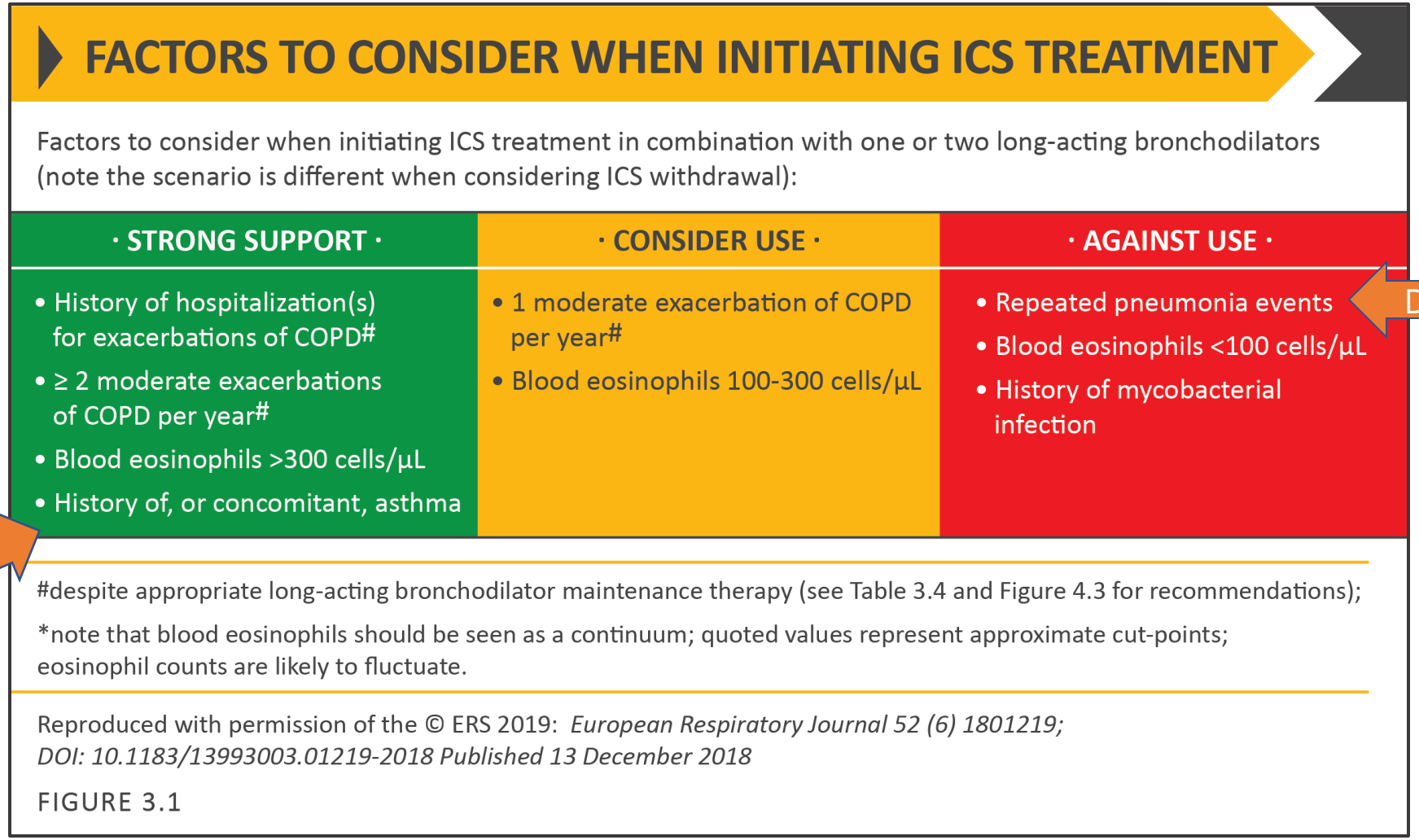
Mona Bafadhel PhD [a], Stefan Peterson PhD [b], Miguel A De Blas MSc [d], Prof Peter M Calverley DSc [e], Prof Stephen I Rennard MD [c, f], Kai Richter MD [g, h], Malin Fagerås PhD [g]

- Analyzed data from three AstraZeneca randomized controlled trials of budesonide-formoterol in patients with COPD with a history of exacerbations and available blood eosinophil counts.
- Patients with any history of asthma were excluded.
- At eosinophil counts >100, a significant treatment effect was recorded for exacerbation reduction with budesonide-formoterol compared with formoterol alone (rate ratio 0·75, 95% CI 0·57-0·99; $p_{interaction}$=0·015)



Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med 2018;

Pharmacotherapy: Who should be treated with an ICS?



Don't Forget!!!

Don't Forget!!!

Treatment of stable COPD

INITIAL PHARMACOLOGICAL TREATMENT

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator	**Group B** A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1 CAT < 10	mMRC ≥ 2 CAT ≥ 10

FIGURE 4.1

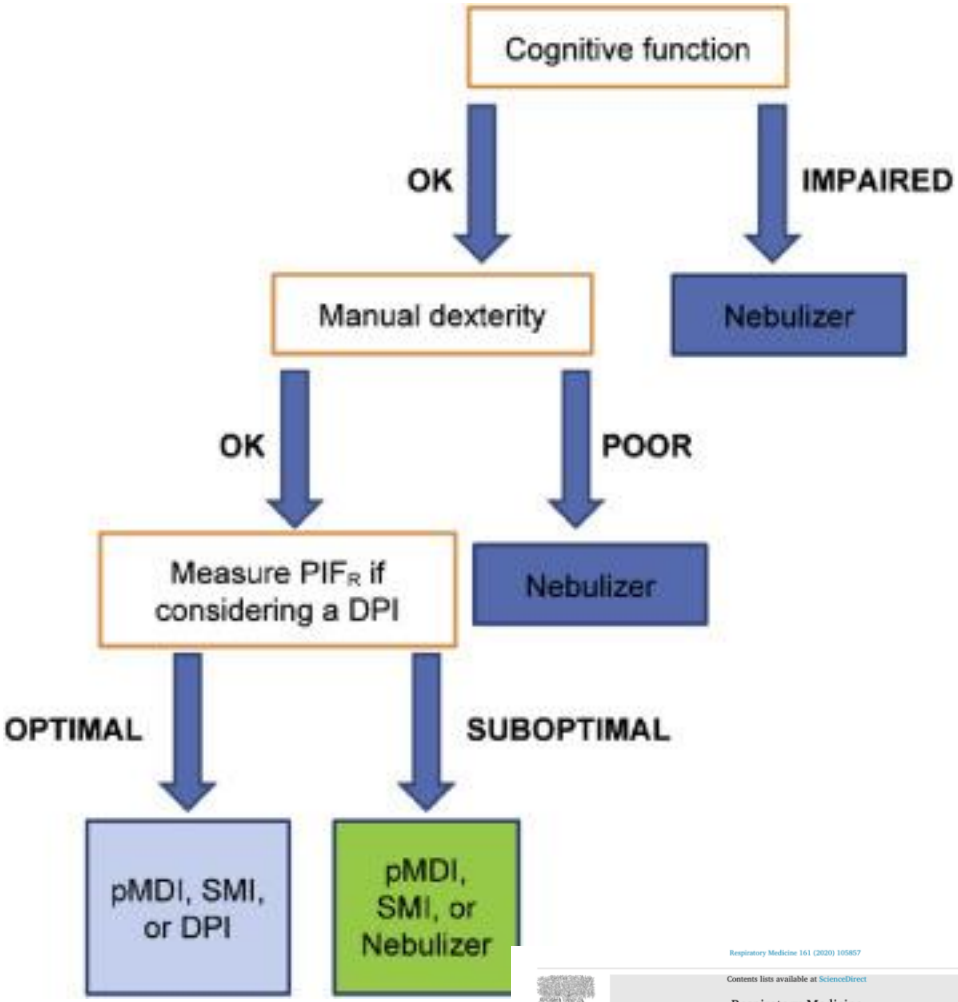
Bronchodilators

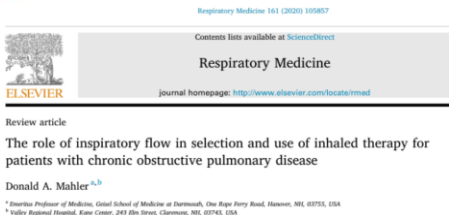
- Nebulizers > Metered Dose Inhalers (MDI) > Dry powder inhalers (DPI)?
  - A Canadian meta-analysis found no difference in the effect of bronchodilator delivery by a metered-dose inhaler (MDI) or wet nebulizer based on objective measurements
  - Cochrane review comparing the effects of nebulizers versus pressurized MDI (pMDI) plus spacer or dry powder inhalers (DPI) found no significant difference in the change in FEV_1 at 1 h after dosing between nebulizers versus pMDI plus spacer
    - there was a trend for greater improvement in FEV_1 when treating with nebulizers
  - Consider measuring peak inspiratory force

Crisafulli, E., Barbeta, E., Ielpo, A. *et al.* Management of severe acute exacerbations of COPD: an updated narrative review. *Multidiscip Respir Med* **13,** 36 (2018). https://doi.org/10.1186/s40248-018-0149-0

Don’t forget about the device!

- Types:
  - Metered dose inhaler (MDI, e.g. albuterol)
  - Dry powder inhaler (DPI, e.g. tiotropium or Spiriva handihaler)
  - Slow mist inhaler (SMI, e.g. tiotropium or Spiriva Respimat)
  - Nebulizers (e.g. budesonide)
- Risk factors for insufficient drug delivery
  - Age
  - Cognitive or manual impairment
  - Impaired peak inspiratory force (InDial)
  - Crowded upper airway
  - Patient in the American healthcare system




Respiratory Medicine 161 (2020) 105857

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Review article

The role of inspiratory flow in selection and use of inhaled therapy for patients with chronic obstructive pulmonary disease

Donald A. Mahler[a,b]

Bronchodilators

- Short-acting β_2 agonists (SABA) and short acting anticholinergics (SAMA) have no high-quality evidence from randomized-control trials
  - ~furosemide in heart failure
- Continuous helpful pragmatically, but high risk for adverse effects

Crisafulli, E., Barbeta, E., Ielpo, A. *et al.* Management of severe acute exacerbations of COPD: an updated narrative review. *Multidiscip Respir Med* **13,** 36 (2018). https://doi.org/10.1186/s40248-018-0149-0

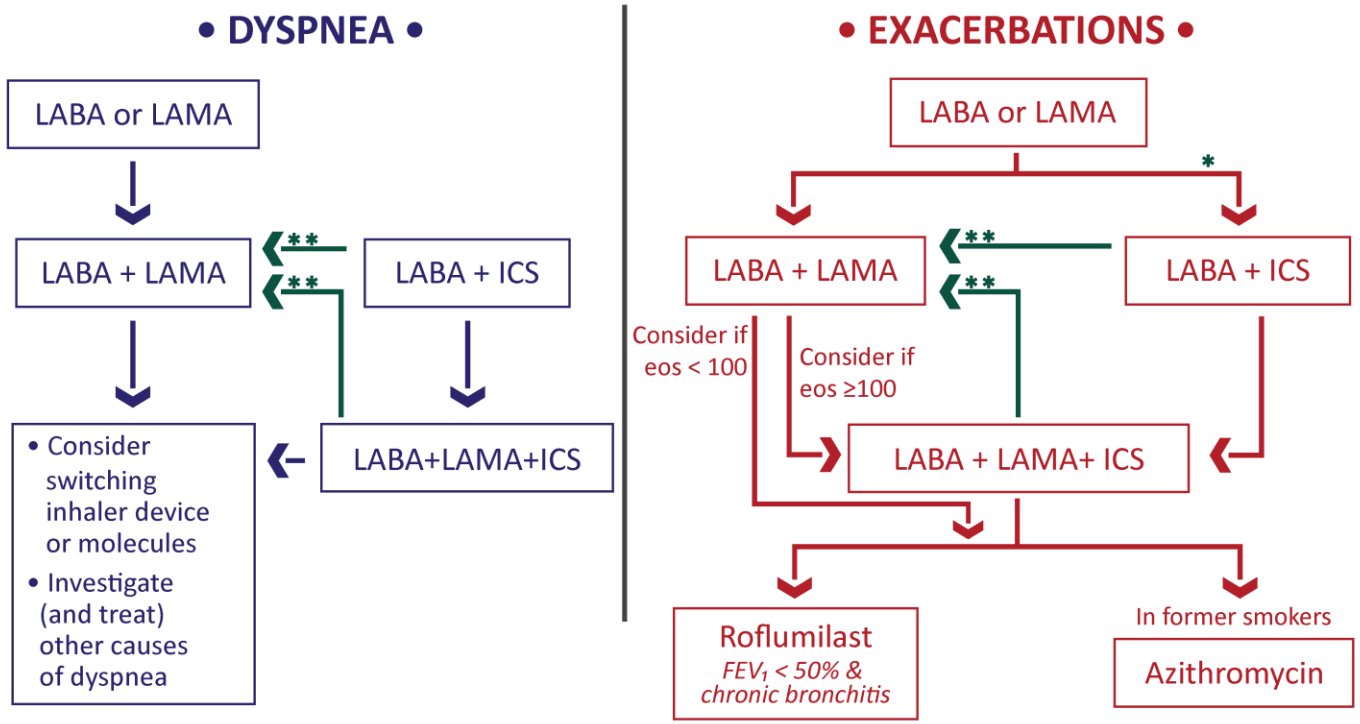
Antibiotics

- In AECOPD **with history of purulent sputum** an antibiotic is suggested
- A Cochrane review showed that in **severe AECOPD**, antibiotics:
  - reduce treatment failures (risk ratio 0.77, 95% CI 0.65 to 0.91: high)
  - …but not the length of hospital stay or mortality (low grade of evidence)
- In **very severe AECOPD**:
  - Nouria et al. showed a reduction in:
    - mortality (4% versus 17%, $p = 0.05$)
    - deaths in hospital (4% versus 22%, $p = 0.01$)
    - need for additional course of antibiotics (6% versus 35%, $p = 0.0006$)
- Azithromycin is not magic
  - Not significant evidence for one antibiotic over another (Bactrim, FQ, doxycycline, macrolides have all been studied with no superiority even in some head to head studies)

Crisafulli, E., Barbeta, E., Ielpo, A. *et al.* Management of severe acute exacerbations of COPD: an updated narrative review. *Multidiscip Respir Med* **13,** 36 (2018). https://doi.org/10.1186/s40248-018-0149-0

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



Don't Forget!!!

eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

Roflumilast (Brand: Daliresp)

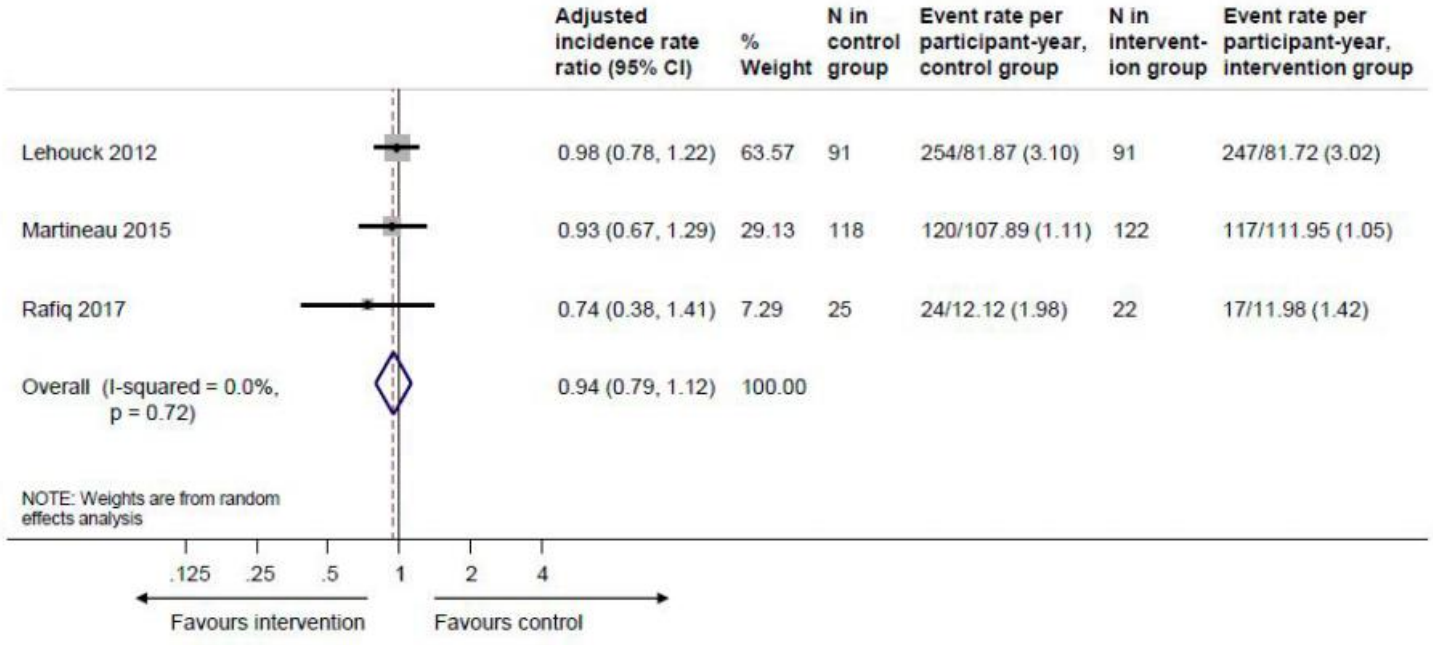
- **Mechanism**: PDE4 inhibitor that decreases inflammation by impairing intracellular cAMP degradation. No bronchodilator effects.
- **Dosing**: Non-efficacious initial dosing to avoid ADE (250 mcg daily), then 500 mcg daily orally
- **Indication**: recurrent exacerbations with FEV_1 <50% predicted and chronic bronchitis (best in patients with severe exac. history)
- **ADE**: diarrhea, weight loss (~2-3kg)
- **Effect**: decreases exacerbations (RR ~0.8) in high risk patients

Chronic azithromycin

- **Dosing** 250 mg daily or 250/500 mg TIW oral azithromycin
- **Indication**: former smokers with recurrent exacerbations
- **ADE**: hearing loss, drug resistance, and QTc prolongation
- **Effect**: decreases exacerbations (RR ~0.8) in high risk patients
  - Less effect in active smokers
  - Only data at 1 year

Vitamin D Deficiency

- Biomarker vs. treatable trait?
- In SPIROMICS cohort of 1609 patients;
  - Each 10-ng/mL decrease in 25-OH-vitamin D was associated with lower baseline lung function (–1.04% predicted; 95% CI, –1.96% to –0.12% predicted; *P* = .03) and increased odds of any exacerbation in the year before enrollment (OR, 1.11; 95% CI, 1.01-1.22; *P* = .04)
- Metanalysis by Joliffee et al.;
  - "Vitamin D supplementation safely and substantially reduced the rate of moderate/ severe COPD exacerbations in patients with baseline 25-hydroxyvitamin D levels"
- GOLD guidelines recommend treatment in frequent exacerbators with levels less than 25 nmol/L



Milne et al. Vitamin D Deficiency in COPD. Chest. 2020;157(4):755-756. doi:10.1016/j.chest.2019.12.007.

Burkse et al. Associations Among 25-Hydroxyvitamin D Levels, Lung Function, and Exacerbation Outcomes in COPD. Chest. 2020;157(4):755-756. https://doi.org/10.1016/j.chest.2019.11.047

Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. Thorax. 2019;74(4):337-345. doi:10.1136/thoraxjnl-2018-212092.

Beta Blockers in COPD

- *Beta blockers likely cause a mild decrease in FEV1*
- *Retrospective Data Supporting Benefit of Beta Blockers in COPD*
  - Du *et al.*, 2014, meta-analysis of 15 retrospective of COPD patients → beta-blockers are associated with 38% reduction in AECOPD and 28% decrease in mortality
- *Beta-blockers are underutilized in COPD patients even when clear cardiac indications exist*
  - Lipworth *et al.*, 2016 and van der Woude *et al.*, 2005 → Patients post-MI with COPD are prescribed beta blockers only 20-60% of the time
  - Negative effects on FEV1 and symptoms are minimal, especially in cardio selective beta blockers
- *Potential mechanism of action in COPD?*
  - Reducing systemic inflammation
  - The number of goblet cells and their mucous release
  - Inhibition of neutrophil chemotaxis

Lipworth B, Skinner D, Devereux G, et al. Underuse of β-blockers in heart failure and chronic obstructive pulmonary disease. Heart 2016;102:1909-1914.
Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. PLoS One 2014;9(11):e113048-e113048
van der Woude HJ, Zaagsma J, Postma DS, Winter TH, van Hulst M, Aalbers R. Detrimental effects of beta-blockers in COPD: a concern for nonselective beta-blockers. Chest 2005;127:818-824..
Dransfield et al. N Engl J Med 2019; 381:2304-2314

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Metoprolol for the Prevention of Acute Exacerbations of COPD

Dransfield *et al.* N Engl J Med 2019; 381:2304-2314

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Design

Metoprolol for the Prevention of Acute Exacerbations of COPD

	BLOCK
DESIGN	Multicenter (US) RCT
COHORT	COPD patients (FEV1<80) without indications for BBs (MI, CHF) and at risk for AECOPD (mod or sev AECOPD in past year or home O2)
INTERVENTION	Dose adjusted Metoprolol
PRIMARY OUTCOMES	Time to AECOPD

Lipworth B, Skinner D, Devereux G, et al. Underuse of β-blockers in heart failure and chronic obstructive pulmonary disease. Heart 2016;102:1909-1914.
Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. PLoS One 2014;9(11):e113048-e113048
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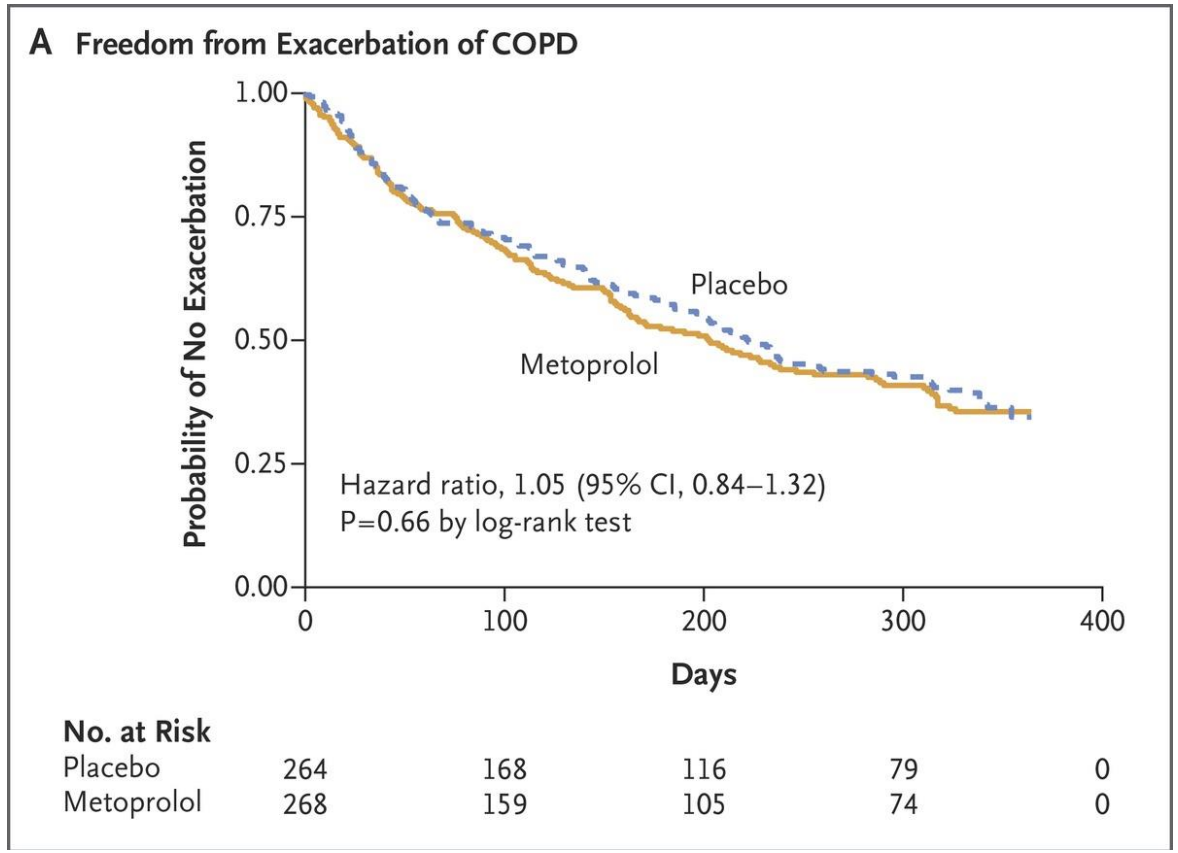
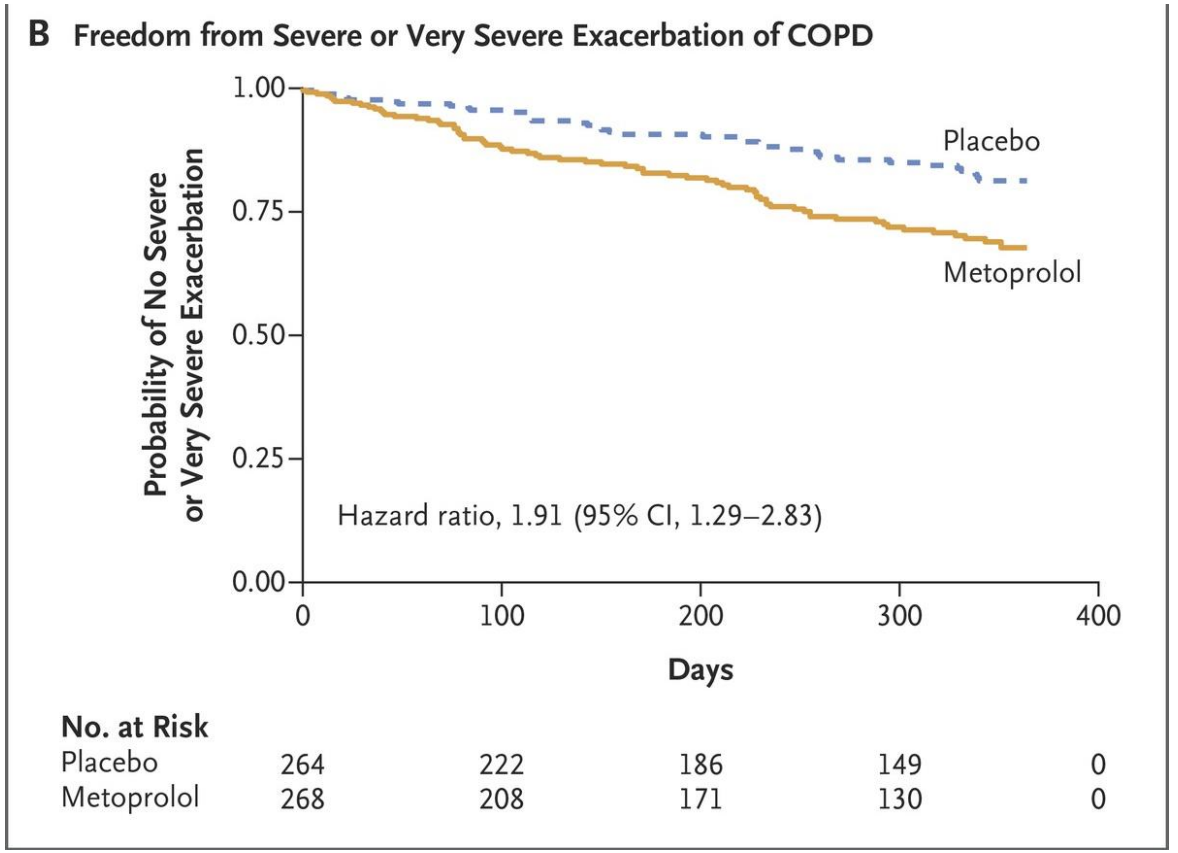
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

COPD Exacerbations

Metoprolol for the Prevention of Acute Exacerbations of COPD





Severity of Exacerbations

Table 2. Rate of Exacerbation of COPD, According to Severity.

Severity of Exacerbation	Metoprolol (N=268)		Placebo (N=264)		Rate Ratio (95% CI)
	Events	Rate (95% CI)	Events	Rate (95% CI)	
	no.	*no. of events/person-yr*	*no.*	*no. of events/person-yr*	
Any severity	289	1.40 (1.21–1.61)	272	1.33 (1.15–1.54)	1.05 (0.85–1.28)
Mild	163	0.78 (0.65–0.94)	178	0.88 (0.74–1.05)	0.89 (0.69–1.15)
Moderate	34	0.17 (0.11–0.25)	36	0.18 (0.12–0.26)	0.94 (0.53–1.65)
Severe	81	0.40 (0.30–0.52)	55	0.26 (0.19–0.36)	1.51 (1.00–2.29)
Very severe	11	0.05 (0.03–0.10)	3	0.01 (0.00–0.05)	3.71 (1.10–16.98)
Moderate or greater	126	0.62 (0.50–0.77)	94	0.45 (0.35–0.58)	1.36 (0.98–1.91)
Severe or very severe	92	0.45 (0.35–0.58)	58	0.28 (0.21–0.38)	1.63 (1.10–2.42)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Metoprolol for the Prevention of Acute Exacerbations of COPD

Results

- ***Stopped*** early due to inefficacy (and potential harm)
  - Among patients with moderate or severe COPD who did not have an established indication for beta-blocker use, the time until the first COPD exacerbation was similar in the metoprolol group and the placebo group.
  - Hospitalization for exacerbation was more common among the patients treated with metoprolol.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Metoprolol for the Prevention of Acute Exacerbations of COPD

Conclusions

- No role for beta-blockers for the ***treatment*** of COPD
- This study should not deter the use of beta-blockers in COPD patients with a cardiac indication
  - Consider withholding beta-blockers in patients with very severe COPD at high risk for severe exacerbation

Are the medications for this patient optimized?

- You are called to the ED to admit a 67-year-old 30 pack year former smoker for COPD exacerbation. The patient complains of increased dyspnea and new, higher volume yellow sputum. Past medical history includes coronary artery disease and osteoporosis. Patient has had 3 outpatient exacerbations in past year, two ED visits, and two admissions for COPD. Outpatient medications include tiotropium handihaler daily, fluticasone 250/salmeterol diskus twice per day, propranolol. No spirometry is available in chart.

- In the ED patient has been given 125 mg of solumedrol, azithromycin 500 mg IV, albuterol via nebulizer, and the patient is on BiPAP at 15/5, 40% FiO2.
  - Temperature: 99 F, HR 100, BP 133/75, RR 26, SpO2 99%
  - CXR and CT chest performed demonstrating left lower lobe pneumonia with significant centrilobular emphysema, no PE
  - Labs: CBC with no peripheral eosinophilia

  - ***Selective BB***
  - ***ICS likely not indicated***
  - ***Should consider azithromycin/daliresp***
  - ***Vit D testing?***

Supplemental Oxygen Therapy

- GOLD recommends titrating supplemental oxygen therapy to achieve a target saturation of 88%–92%

- MYTH: excessive oxygen in COPD leads to hypoventilation
- FACT: Uncontrolled oxygen administration in acute exacerbation of severe COPD has a limited effect on minute ventilation and thus does not explain the total increase in PaCO2

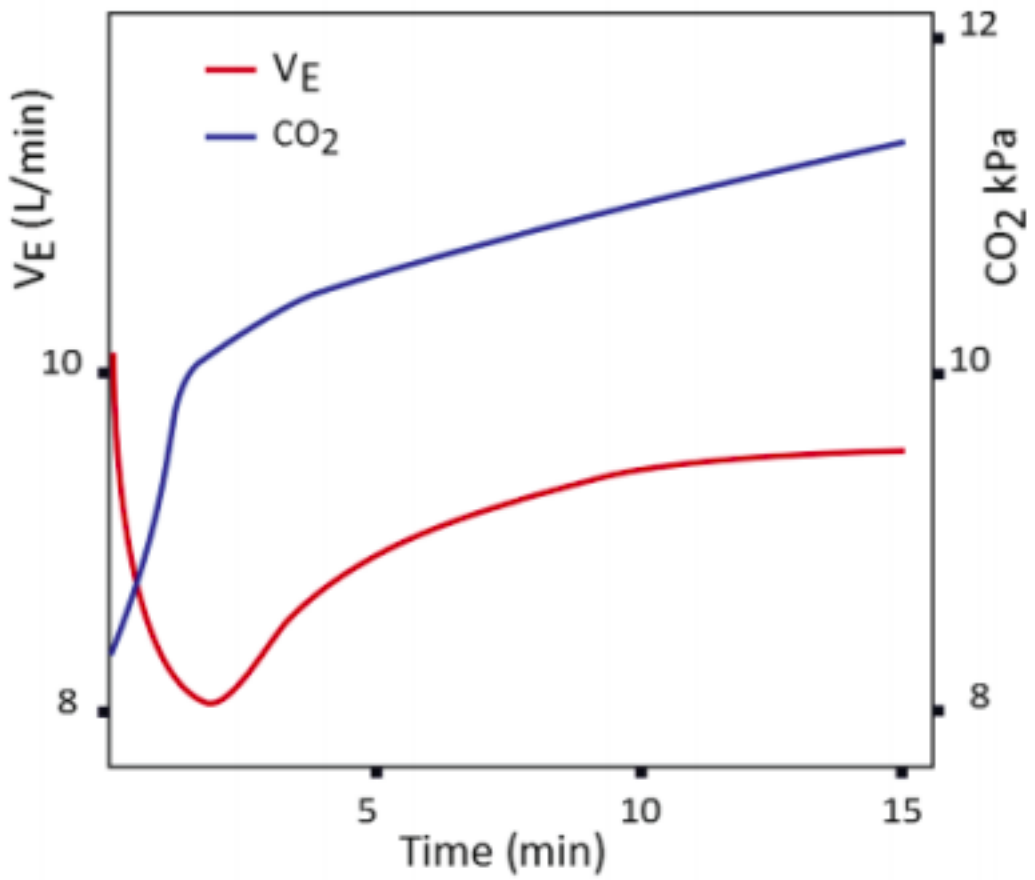
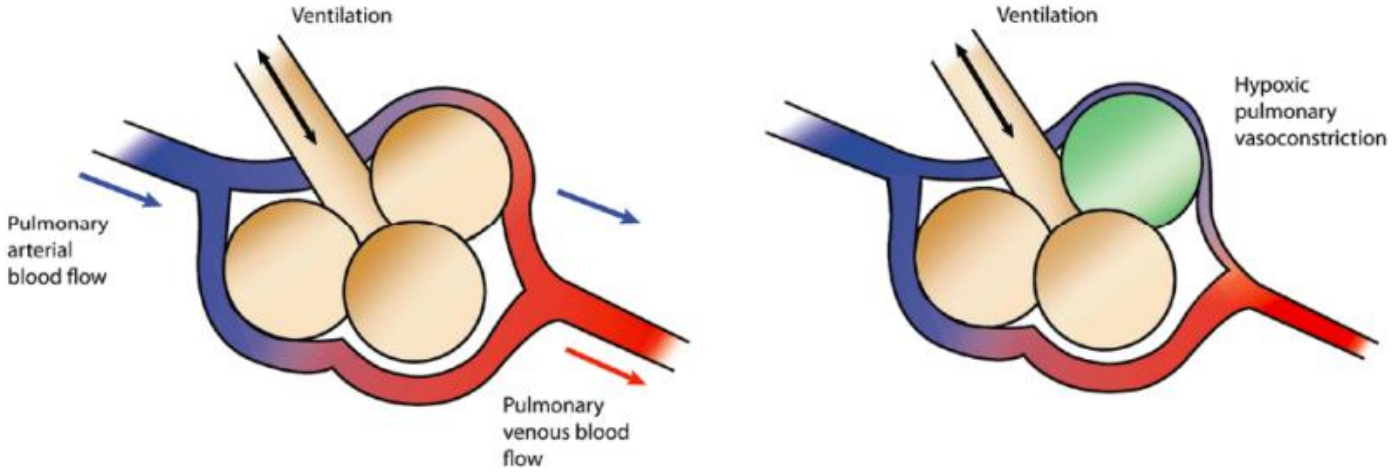


Figure 1. Effect of minute ventilation during oxygen-induced hypercapnia. During 15 minutes of high oxygen administration, an initial decrease in minute ventilation, which recovers substantially, is seen in patients with acute exacerbation of chronic obstructive pulmonary disease. However, the oxygen-induced hypercapnia does not recover. CO_2, carbon dioxide; V_E, minute ventilation. Based on data of Aubier and colleagues [4].

Abdo and Heunks *Critical Care* 2012, **16**:323
http://ccforum.com/content/16/5/323

Hypoxic vasoconstriction

- Two factors predominantly lead to worsening hypercapnia in COPD
  - Haldane effect
  - V/Q mismatch due to hypoxic vasoconstriction



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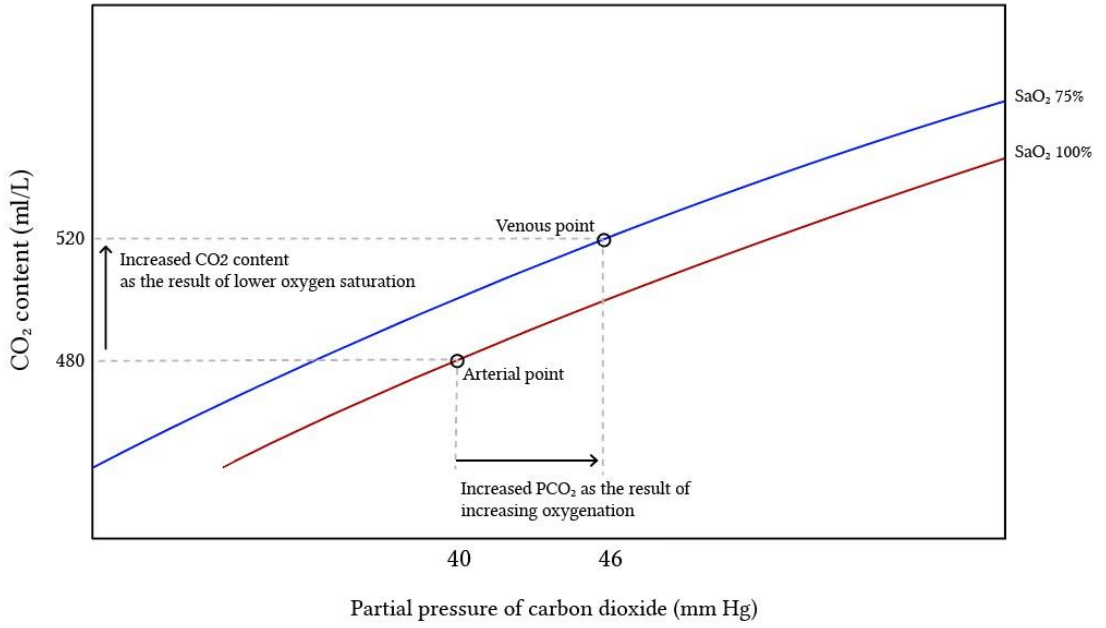

Teboul, Jean-Louis, and Thomas Scheeren. "Understanding the Haldane effect." *Intensive care medicine* 43.1 (2017): 91-93.

Non-Invasive Positive Pressure Ventilation (NIPPV)

- *NIPPV*
  - Decreases RR and work of breathing
  - Reduced mortality and intubation compared when oxygen alone
  - Preferred over high flow nasal canula, although the latter does improve hypercapnia and work of breathing
- *Tips for "Not Tolerating BIPAP"*
  - Mask fit
  - Increase EPAP/CPAP
  - Decreasing inspiratory pressure (more does not equal better)

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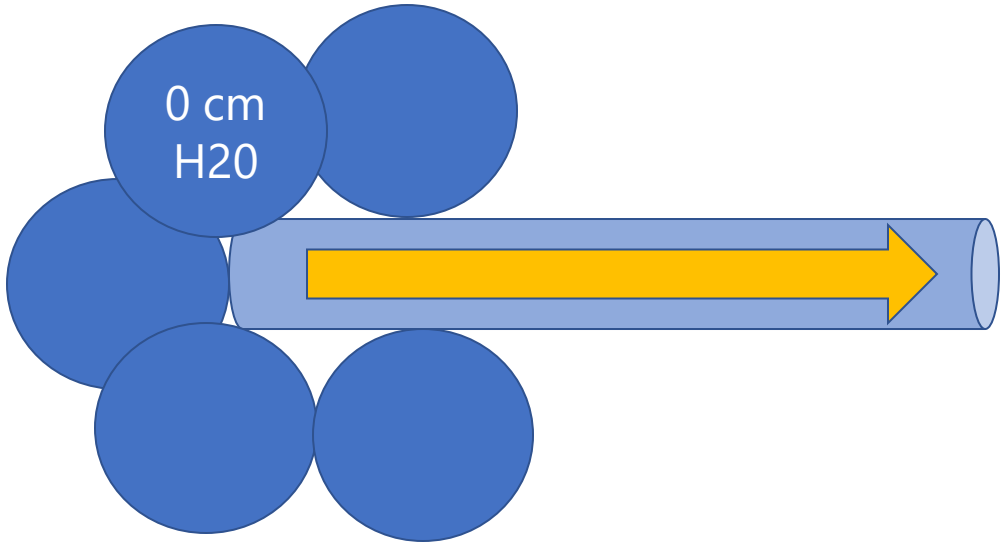
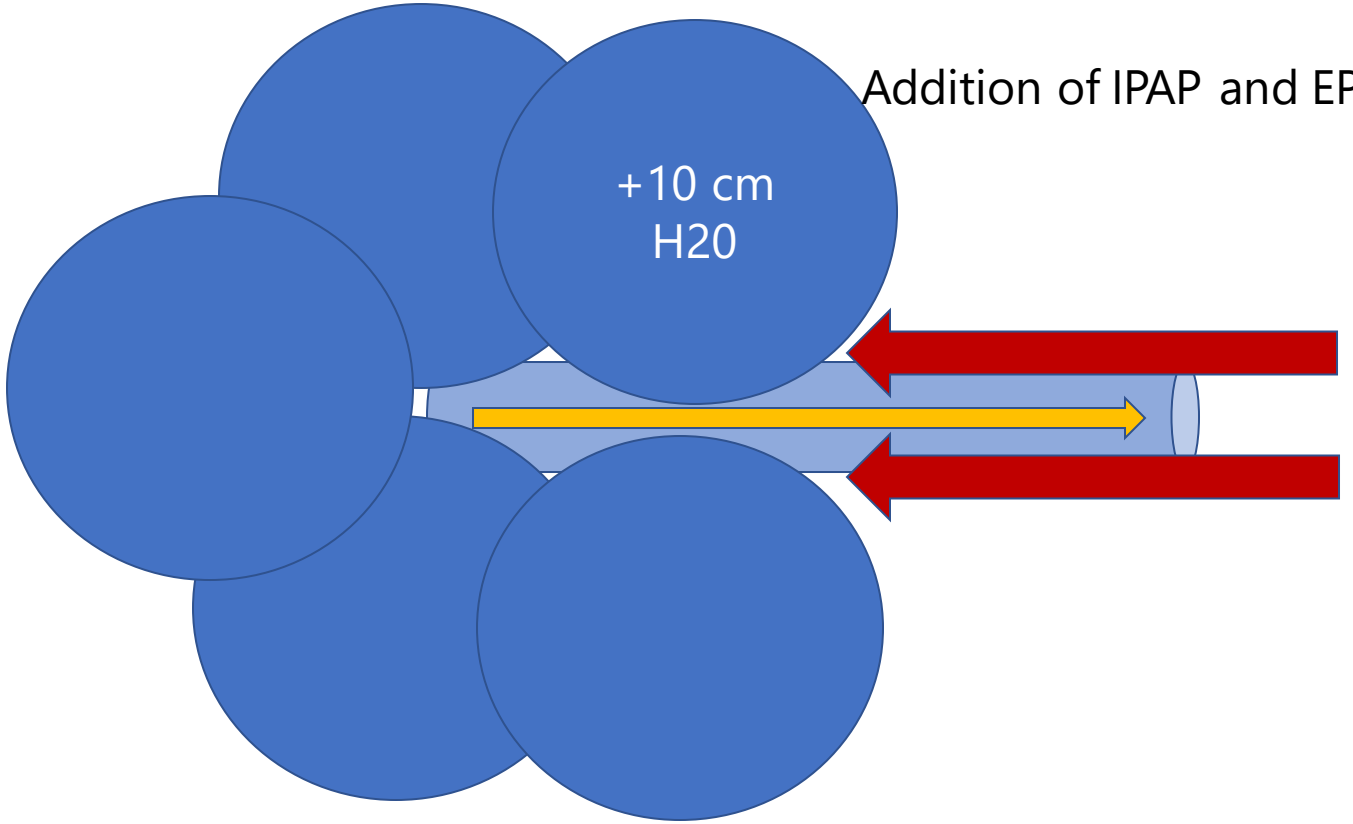
  - Mask fit
  - Increase EPAP/CPAP
  - Decreasing inspiratory pressure (more does not equal better)

Non-Invasive Positive Pressure Ventilation (NIPPV)

- High EPAP/IPAP to overcome hyperinflation
- IPAP still necessary often when patients near failure



Normal Lung During Exhalation



COPD with Severe Hyperinflation

Pulmonary Rehabilitation

Cochrane Library

Cochrane Database of Systematic Reviews

Pulmonary rehabilitation for chronic obstructive pulmonary disease (Review)

McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y

- Pulmonary rehabilitation (PR) is a comprehensive non-pharmacological treatment
  - Monitored exercise
  - ~Occupational Therapy for Dyspnea (pursed lip breathing, pant breathing, etc.)
  - In depth RT evaluation (DME, O2 qualification/titration)
  - Education
  - Community
- PR has optimal benefit in COPD patients both during and immediately after AECOPD
- Reduces readmission, AECOPD, increases QOL/functional status

McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD003793.

ONLY 48.8% of Medicare patients had annual flu vaccine

Effectiveness of Influenza Vaccination on Hospitalizations and Risk Factors for Severe Outcomes in Hospitalized Patients With COPD

CHEST

- Existing data suggests clear benefit reducing lower respiratory tract infections requiring *moderate AECOPD and mortality*
  - Poole *et al.* 2010 Cochrane review:
    - "It appears, from the limited number of studies performed, that inactivated vaccine reduces exacerbations in COPD patients."
- Flu vaccination is an ATS 1b recommendation

Malpura et al. CHEST 2019 155, 69-78DOI: (10.1016/j.chest.2018.10.044)

Effectiveness of Influenza Vaccination on Hospitalizations and Risk Factors for Severe Outcomes in Hospitalized Patients With COPD

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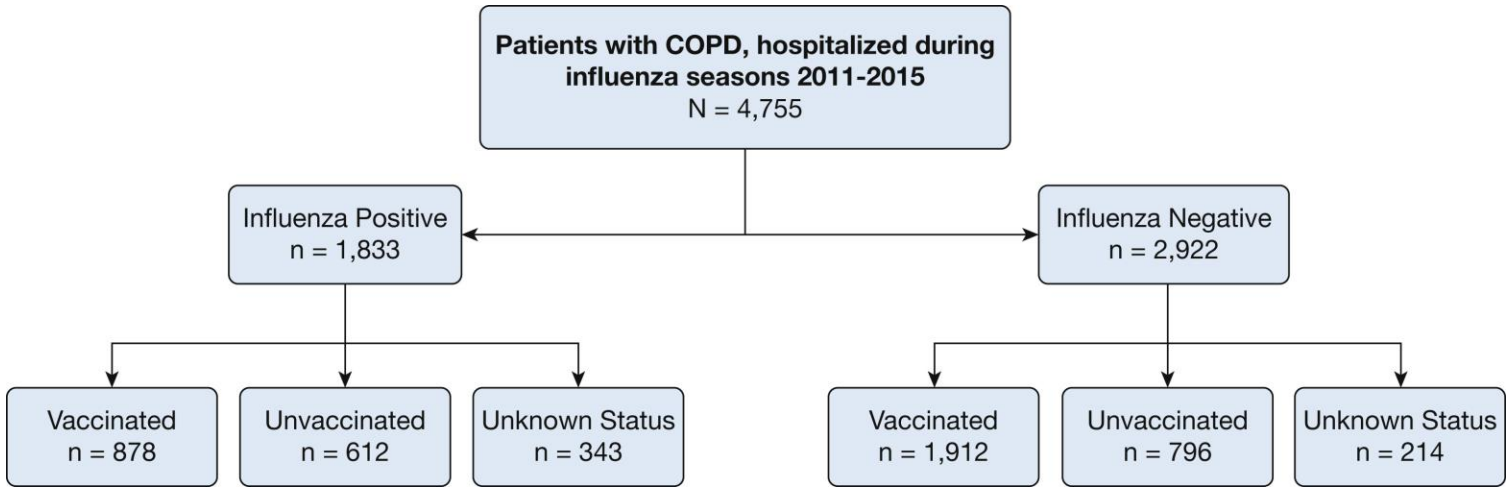


TABLE 2] Outcomes for Influenza-Related Hospitalizations Among Adult Patients With COPD and Known Vaccination Status Who Were Hospitalized Between the 2011 and 2015 Influenza Seasons

Variable	Influenza Positive (n = 1,490)	Influenza Negative (n = 2,708)	Total (N = 4,198)
30-d mortality	145 (9.7%)	215 (7.9%)	360 (8.6%)
ICU admission	257 (17.2%)	329 (12.1%)	586 (14.0%)
Use of NIV during hospitalization	159 (10.7%)	366 (13.5%)	525 (12.5%)
Mechanical ventilation	130 (8.7%)	142 (5.2%)	272 (6.5%)
Length of hospital stay, median (IQR), d	7 (5-13)	7 (5-11)	7 (5-12)

IQR = interquartile range; NIV = noninvasive ventilation.

- **Influenza-positive patients** experienced ***higher crude mortality*** (9.7% vs 7.9%; P = .047) and ***critical illness*** (17.2% vs 12.1%; P < .001) compared with influenza-negative patients.
- ***38% reduction in influenza-related hospitalizations*** in vaccinated vs unvaccinated individuals

Conclusions:

- Exacerbations secondary to influenza have higher mortality and critical illness
- Vaccination reduces influenza-related hospitalization

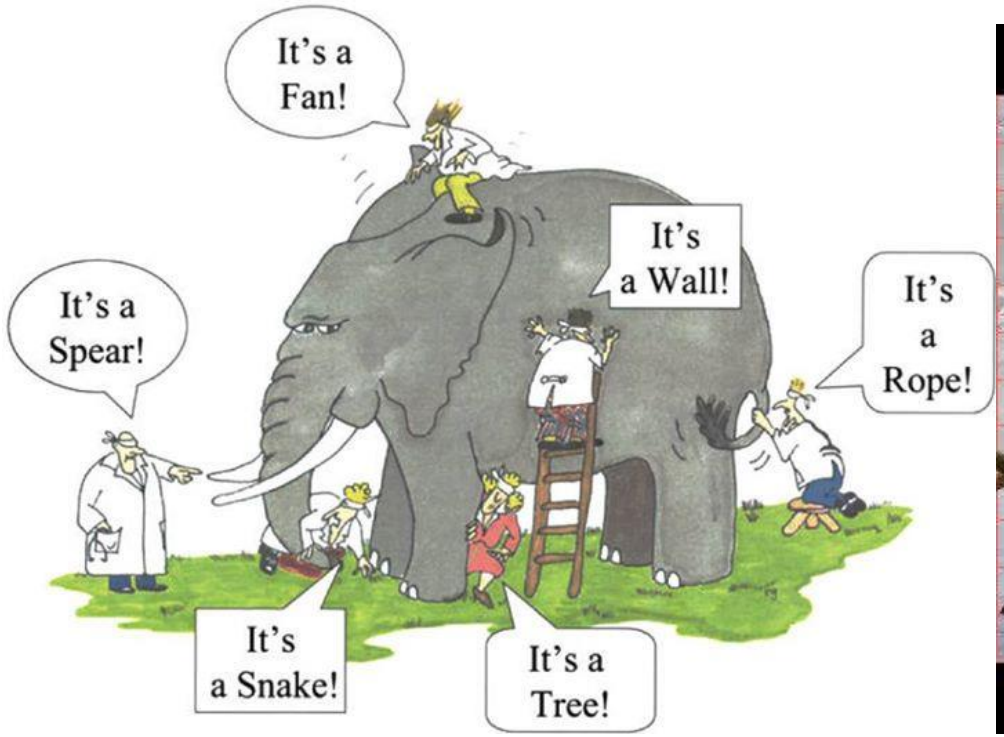
CHEST 2019 155, 69-78DOI: (10.1016/j.chest.2018.10.044)

Recommendations for our patient

- Likely COPD, but need to arrange PFTs/spirometry (even inpatient)
- Screen for cause of exacerbation (including aspiration)
- Prednisone 0.5 mg/kg instead of 125 methylprednisone
- BiPAP: increase EPAP, consider evaluating for nocturnal MV on follow up
- Judicious lorazepam a reasonable idea to avoid hypercapnia spiral
- Decrease Fio2 to goal saturation 88-92%
- STOP inhaled corticosteroids
- Consider alternative inhaler device
- Start chronic azithromycin or roflumilast
- Ok to use betablocker, but consider selective BB
- Influenza vaccine
- Pulmonary rehabilitation referral

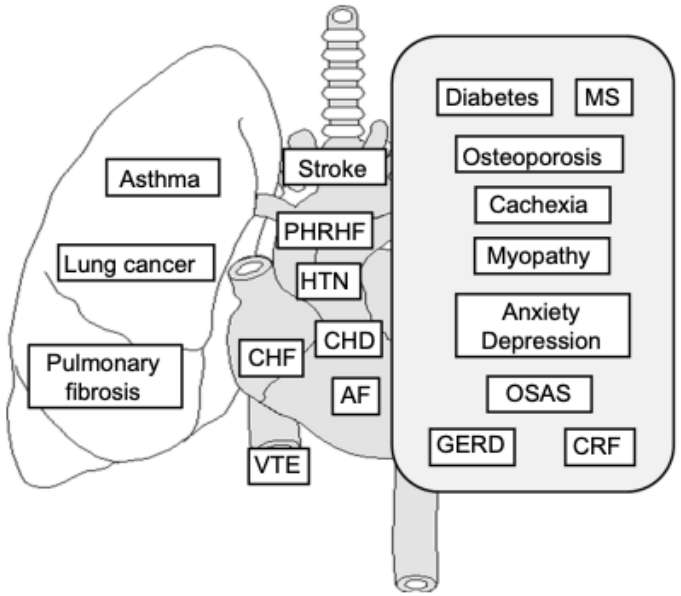
Take Home Points:

- Move beyond the thinking of COPD as a single disease



Take Home Points:

- Phenotype for personalized care



CLINICAL PHENOTYPES
- Frequent exacerbator
- Chronic bronchitis
- Asthma-COPD overlap
- Depression/anxiety
- Pulmonary hypertension
- Cardiac disease
- Alpha-1 Antitrypsin deficiency
- HIV emphysema
- Obstructive Sleep Apnea
- Obesity
- Hyperinflation
- Giant bullae
- CO2 retainer
- Cachexia
- Active smoker
- ……

Take Home Points:

- Identify the exacerbating cause/contributors

Exacerbation cause
- Bacterial or viral infection
- Aspiration
- Pulmonary embolism
- Heart failure
- Coronary disease
- Asthma overlap

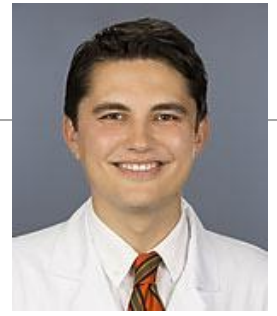
Take Home Points:

- Hospital admission is a symptom of failed outpatient therapy:
  - Start measures to prevent recidivism immediately and aggressively prior to and at discharge

- Appropriate bronchodilators/ICS if indicated
- Chronic Azithromycin
- Roflumilast (daliresp)
- Mucolytics
- Smoking cessation
- Vaccinations
- Pulmonary rehabilitation
- ?Vitamin D?
- ?beta blockers?
- Comorbidities identified and optimized
- Social determinants of health

COPD takes a team

- ROAD RT team (for patients admitted with AECOPD)
- Comprehensive COPD Clinic
- Pulmonary rehabilitation
- COPD Foundation (www.COPDfoundation.org)
  - COPD Pocket Tool for Providers and Patients
  - Great educational resource on inhaler technique







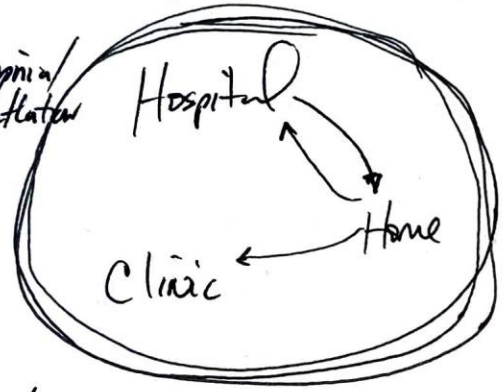

AECOPD

Pitfalls

1. Drug delivery devices
2. Excessive prednisone/solumedrol
3. Inhaler cost/education/rapid cycling
4. Missed/Wrong Diagnosis
5. Death spiral of hypercapnia/hyperinflation
6. Superimpose asthma/CAD/aspiration/PHTN
7. Following O_2 Sat to tackle severity/progress
8. Inappropriate ICS use/PNA
9. Missed vaccinations

Myths

1. O_2 therapy ↓ resp drive
2. "Anxiety" ± hypercapnia
3. O_2 symptoms > mortality
4. "Magic" anti-inflamm azithro
5. Avoid BiPAP



Strategies

1. Identify the precipitant ; treat accordingly
2. Initiate therapies to ~~break~~ prevent future exac (az-thro, roflumilast)
3. Assure COPD is the correct diagnosis!
4. Phenotype the COPD
5. Mechanical Ventilation
6. CXR or anthracosis cirrhosis

RESOURCES

- Epaper for AECOPD Evaluation:
  - GOLD
- EHR dot phrase for AECOPD note

COPD Paradigm

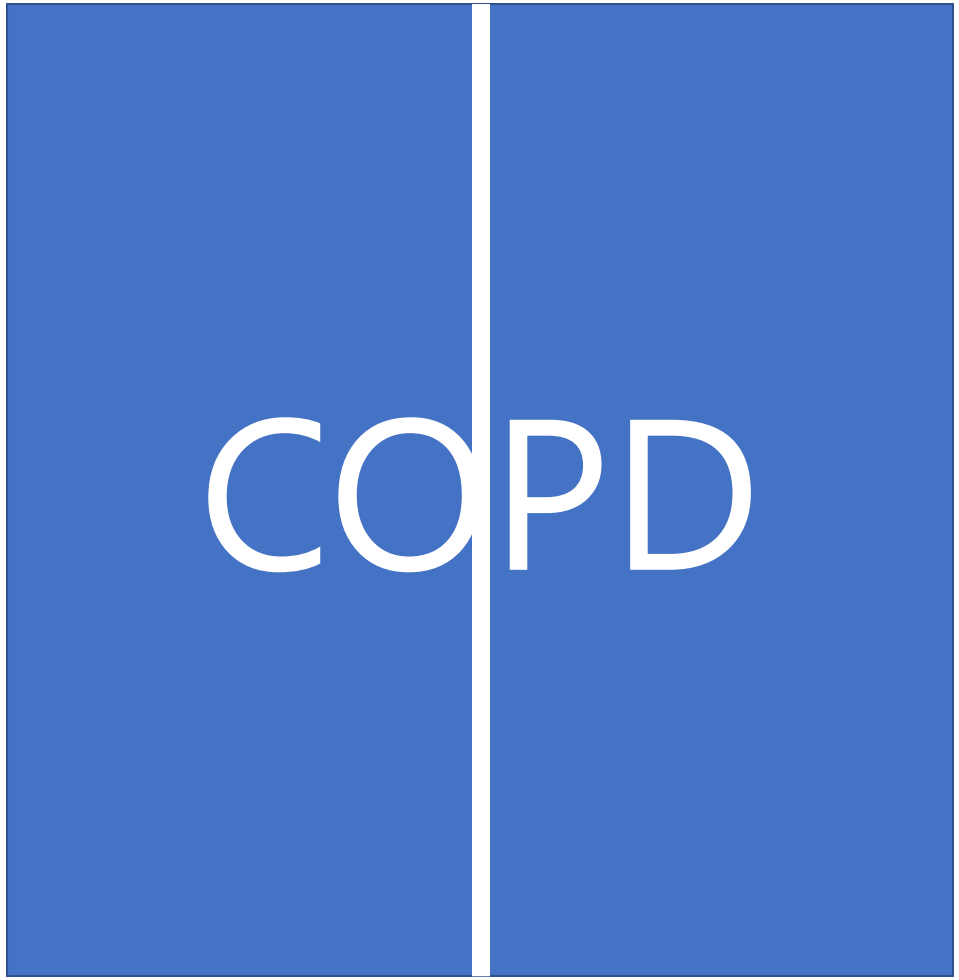
COPD

https://lungdiseasenews.com/2015/04/21/day-tiotropium-respimat-dose-proven-effective-24-hour-bronchodilator-asthma-patients/

COPD Phenotypes

Chronic Bronchitis

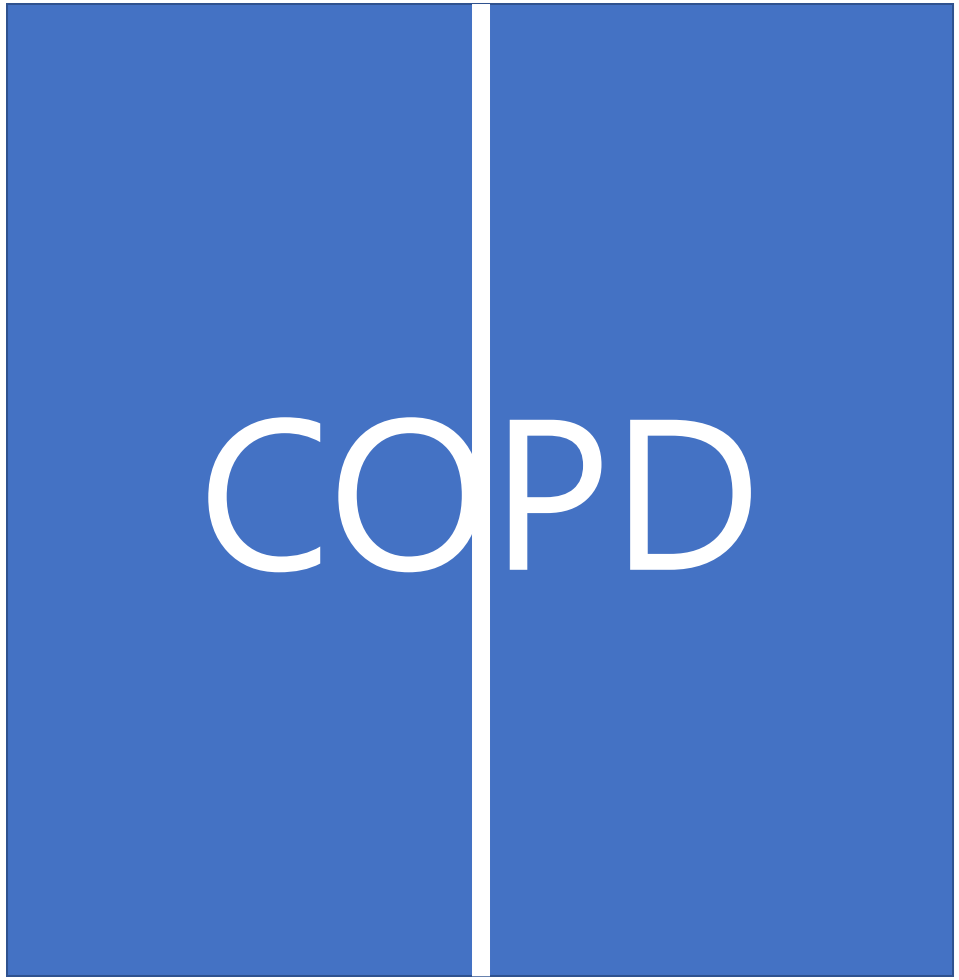
Emphysema



COPD Phenotypes

Chronic Bronchitis
- Frequent exac
- Bronchiectasis
- Asthma overlap
- Active smokers

Emphysema
- Alpha1 ATD
- HIV
- Environmental factors
- Giant bullae



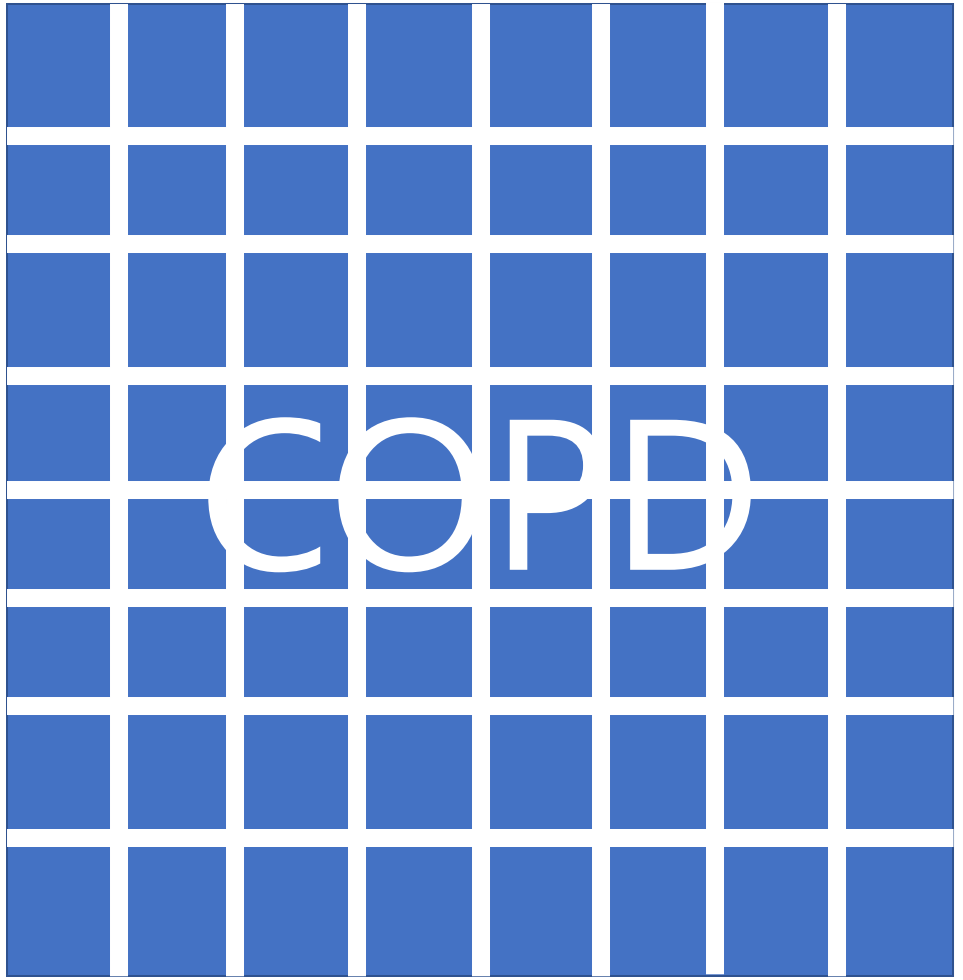
COPD Phenotypes

Chronic Bronchitis

Emphysema

Overlapping Dx:
- Asthma (ACOS)
- CAD
- Heart failure
- Pulm Htn
- Depression
- Pulmonary fibrosis

Mimics:
- Obesity hypoventilation
- Aspiration
- Bronchiectasis



INPATIENT COPD EXACERBATION CONSULTATION AND DISCHARGE FOLLOW-UP

U.S. Department of Veterans Affairs

PCCM=pulmonary critical care medicine
HBPC=home based primary care
HIH=hospital in home
AECOPD=acute exacerbation of COPD
O/P= Outpatient
IP= Inpatient
MSA=medical support assistant (*i.e.*, clerk)

AECOPD Admission

WARD Housestaff/ Attendings
Huddle/NP/RN/Hospitalist/RT Identifies Potential High Risk "Missed Case"
ICU team once patient on floor

IP Pulmonary Evaluation
(Outlined in COPD note)

Alert Pulm RN (and PCP) via co-signer on note

PULMONARY NURSE

Assists in Pulm Clinic Follow Up

"Meet and Greet" and Education during hospitalization

Telephone F/u By Pulmonary RN

IP & O/P Treatment Rec's

Additional CONSULT INFO
1. Diagnostics (e.g. PFTs, TTE, IgE, RAST)
2. DME recs (e.g. BIPAP)
3. Exacerbating causes
4. Comorbid evaluation
5. Initiation of advanced therapies
6. Medication recommendations

Hospitalist ultimately decides and places order

OUTPATIENT RESOURCES

HBPC
Palliative Care
HIH
Telehealth

OUTPATIENT PULM DISPO

RTC order placed with specific pulmonary or PCP disposition delineated by PCCM

Inpatient MSA

Severe COPD Clinic

Fellows Pulm Clinic

Urgent Pulmonary
If Non-urgent full

ASSIGNED PRIMARY CARE

CC PCP to IP Note regardless of dispo. OK to refer back to PCP if no escalation necessary

Jan 08, 2020

Effectiveness of Influenza Vaccination on Hospitalizations and Risk Factors for Severe Outcomes in Hospitalized Patients With COPD

CHEST

TABLE 1] Risk Factors for Influenza-Related Hospitalizations Among Adult Patients With COPD and Known Vaccination Status Who Were Hospitalized Between 2011 and 2015 Influenza Seasons

Variable	Influenza Positive (n = 1490)	Influenza Negative (n = 2708)	*P* Value
Age categories			.001
16-49 y	41 (2.8%)	57 (2.1%)	
50-64 y	309 (20.7%)	513 (18.9%)	
65-75 y	383 (25.7)	848 (31.3%)	
> 75 y	757 (50.8%)	1,290 (47.6%)	
Female sex	771 (51.7%)	1,360 (50.2%)	.35
Aboriginal ethnicity[a]	23 (1.5%)	32 (1.2%)	.31
Current smoker[b]	501 (34.4%)	725 (27.2%)	< .001
Comorbidities			
Heart disease	769 (51.6%)	1,528 (56.4%)	.003
Diabetes	381 (25.6%)	710 (26.2%)	.83
Renal or liver disease	249 (16.7%)	469 (17.3%)	.62
Cancer	297 (19.9%)	578 (21.3%)	.28
Solid organ transplant	9 (0.6%)	15 (0.6%)	.84
Rheumatic disease	67 (4.5%)	99 (3.7%)	.18
Long-term care resident	137 (9.2%)	189 (7.0%)	.01
Assisted living	172 (11.5%)	230 (8.5%)	.001
Oxygen use at home[c]	151 (10.1%)	556 (20.5%)	< .01
Prior physician or ED visit for current illness	490 (32.9%)	669 (24.7%)	< .01
Influenza vaccination[d]	878 (58.9%)	1,912 (70.6%)	< .01
>4 Medications at admission	1,203 (80.7%)	2,320 (85.7%)	< .001

[a]Aboriginal ethnicity not known in 42 of 1,490 case subjects and in 53 of 2,708 control subjects.
[b]Smoking status unknown in 32 of 1,490 case subjects and 40 of 2,708 control subjects.
[c]Oxygen use at home unknown in 1 of 1,490 case subjects, and 1 of 2,708 control subjects.
[d]Indicates trivalent influenza vaccine given in influenza season during which patient was admitted to the hospital.

- **Influenza-positive patients** experienced ***higher crude mortality*** (9.7% vs 7.9%; *P* = .047) and ***critical illness*** (17.2% vs 12.1%; *P* < .001) compared with influenza-negative patients.
- ***38% reduction in influenza-related hospitalizations*** in vaccinated vs unvaccinated individuals

Conclusions:

- Exacerbations secondary to influenza have higher mortality and critical illness
- Vaccination reduces influenza-related hospitalization

CHEST 2019 155, 69-78DOI: (10.1016/j.chest.2018.10.044)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2019 VOL. 381 NO. 2

C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations

Christopher C. Butler, F.Med.Sci., David Gillespie, Ph.D., Patrick White, M.D., Janine Bates, M.Phil., Rachel Lowe, Ph.D., Emma Thomas-Jones, Ph.D., Mandy Wootton, Ph.D., Kerenza Hood, Ph.D., Rhiannon Phillips, Ph.D., Hasse Melbye, Ph.D., Carl Llor, Ph.D., Jochen W.L. Cals, M.D., Ph.D., Gurudutt Naik, M.B., M.S., M.P.H., Nigel Kirby, M.A., Micaela Gal, D.Phil., Evgenia Riga, M.Sc., and Nick A. Francis, Ph.D.

Butler *et al.* N Engl J Med 2019; 381:111-120

Background

- The evidence supporting antibiotics in the treatment of moderate COPD exacerbations is mixed, despite many AECOPD events being caused by infection
- Unwarranted use of antibiotics drives antimicrobial resistance, may negatively affect the microbiome, and distracts from potentially more effective interventions.
  - More than 80% of AECOPD patients receive antibiotic prescriptions in the United States and in Europe
- Recommendations for antibiotic prescribing in primary care practice are generally based on clinical features alone
  - i.e., the Anthonisen criteria: increased sputum volume, increased dyspnea, change in sputum color)

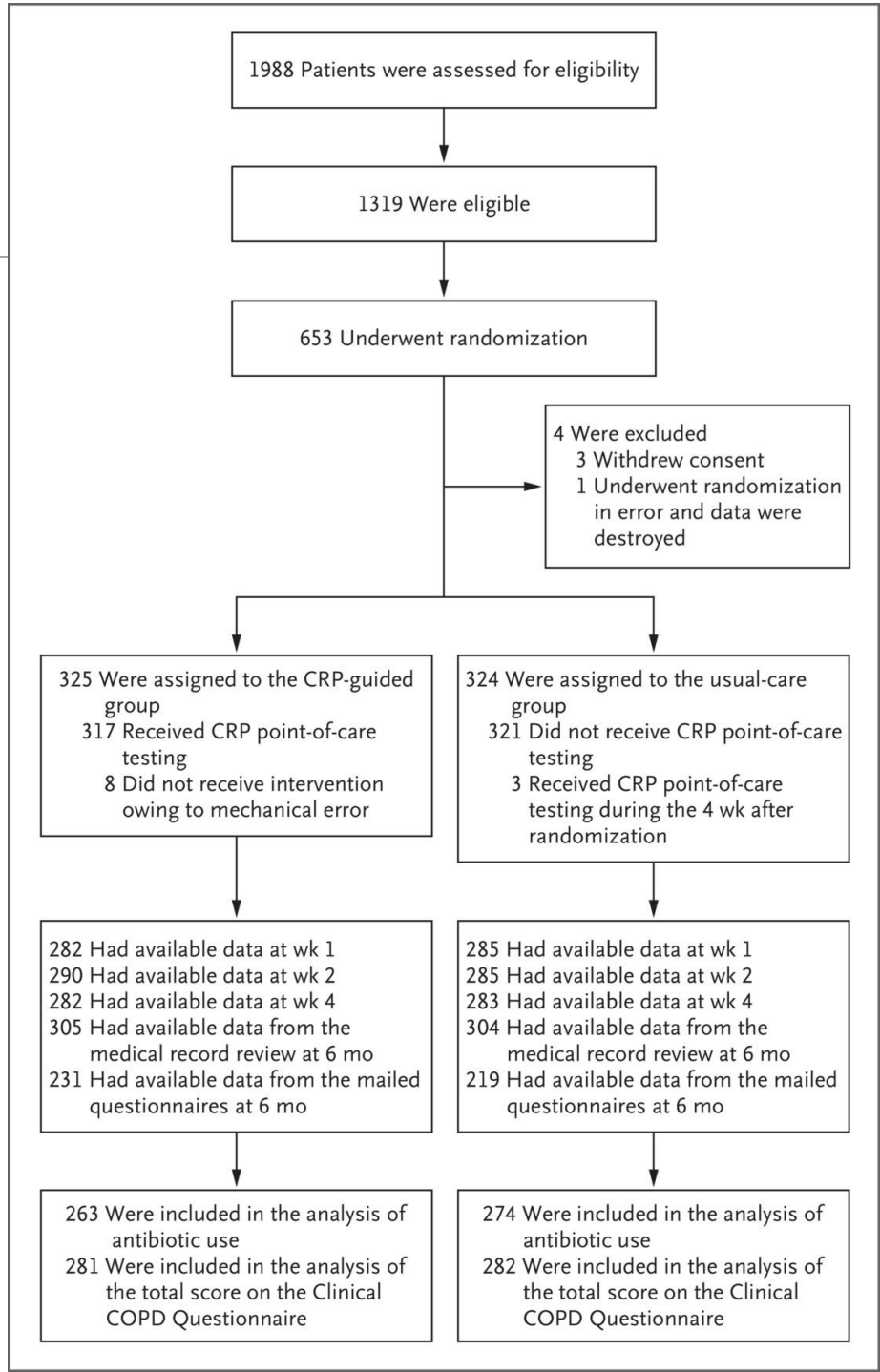
Question:

Can testing for C-reactive protein (CRP) lower antibiotic prescribing without compromising clinical outcomes?

Butler et al. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. N Engl J Med 2019; 381:111-120

The Role of CRP

	Butler *et al.* CRP for Exacerbations
DESIGN	Multicenter, open-label, RCT 2015-2017
COHORT	OUTPATIENT: 86 general medical practices in the UK, total 633 events randomized. COPD patients presenting for AECOPD. Mean FEV1 60.
INTERVENTION	CRP POC and guidance for antibiotic use in exacerbation. CRP<20: no ABX, CRP>40: ABX, CRP 20-40: may be beneficial especially if purulent sputum
DEVICE	Afinion (Alere, now Abbott) desktop devices for CRP point-of-care testing
PRIMARY OUTCOMES	Patient-reported antibiotic use for an acute exacerbation of COPD within 4 weeks after randomization ***AND*** COPD-related health status, as measured by the Clinical COPD Questionnaire at 2 weeks after randomization



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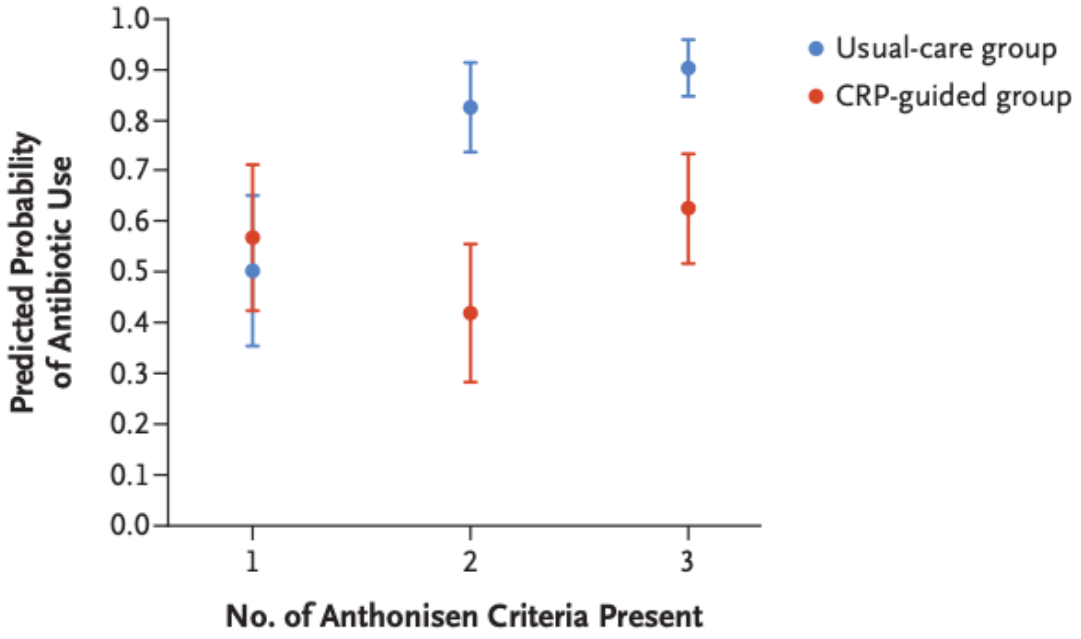

Figure 2. Differential Effect of the Interventions on the Use of Antibiotics during the First 4 Weeks.

Shown is the predicted probability of antibiotic use for acute exacerbations of COPD during the first 4 weeks according to the number of Anthonisen criteria present. The Anthonisen criteria include increased dyspnea, increased sputum volume, and increased sputum purulence. I bars denote 95% confidence intervals.[29]

- Between-group differences in the scores on the Clinical COPD Questionnaire during follow-up were smaller than the published minimal clinically important difference of 0.4
- The proportion of patients receiving antibiotics was ***significantly lower in the CRP group*** than in the usual-care group (57% vs. 77%).
  - Differences only seen if Anthonisen 2 or more
- Not a clinically significant difference in symptom scores
- No higher risk of hospital admission

The Role of CRP

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Conclusion:

- POC CRP can help reduce the prescription and usage rates of antibiotics in AECOPD without negatively affecting patient health

Limitations:

- Need ***point-of-care*** CRP measurement

Butler et al. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. N Engl J Med 2019; 381:111-120