Brigham and Women's Hospital
Founding Member, Mass General Brigham

Chronic Obstructive Pulmonary Disease

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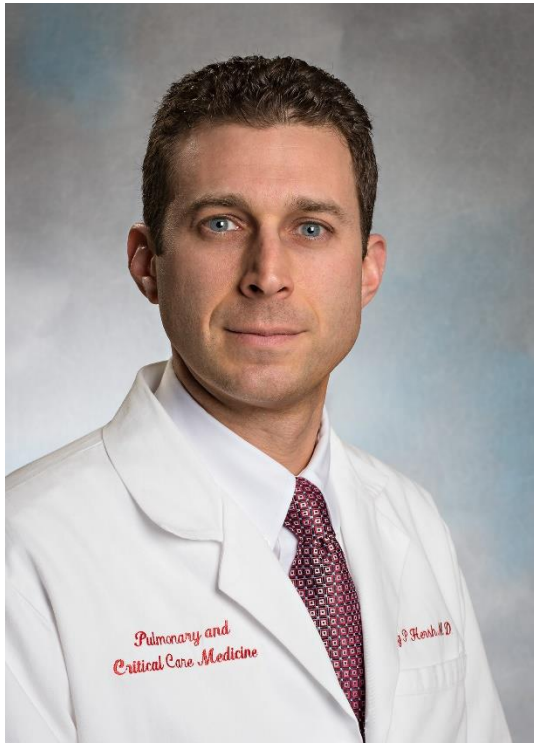

- Medical School: Univ of Pennsylvania
- Medical Residency: Univ of Pennsylvania
- Pulmonary and Critical Care fellowship: Harvard combined program
- Respiratory epidemiology fellowship: BWH
- Associate Professor of Medicine at BWH
  - Clinical focus: COPD, Alpha-1 antitrypsin deficiency
  - Research focus: COPD epidemiology and genetics

Disclosures

- Grant support:
  - Bayer
- Consulting fees:
  - Apogee Therapeutics, Chiesi, Genentech, Ono Pharma, Sanofi, Takeda, Verona Pharma

Learning Objectives

- Review the assessment and current treatments for stable COPD
- Describe the evaluation and management of COPD exacerbations
- Highlight new concepts in COPD diagnosis

Case

A 70 year old woman with no prior respiratory diagnosis sees you after a hospital admission for a COPD exacerbation. She was discharged on triple inhaled therapy (LAMA/LABA/ICS). She stopped smoking 20 years ago but still has daily cough and sputum.

Which of the following tests should you order:

a) Spirometry
b) Chest CT scan
c) Blood eosinophil count
d) All of the above
e) (a) and (c) only

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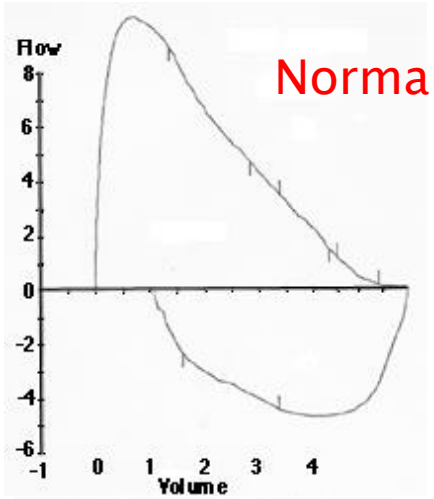
Chronic obstructive pulmonary disease

- Heterogeneous lung condition
- Chronic respiratory symptoms
- Abnormalities of the airways and/or alveoli
- Persistent airflow obstruction, often progressive

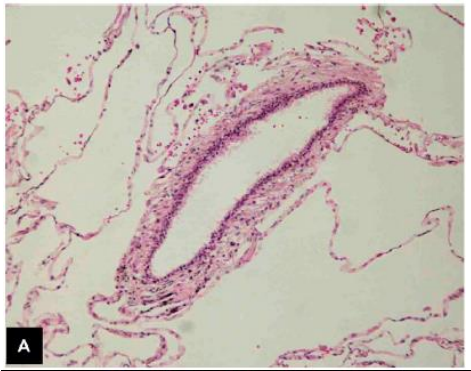
Global Initiative for Chronic Obstructive Lung Disease 2025
www.goldcopd.org

Multiple pathologies of COPD



Normal spirometry

Emphysema



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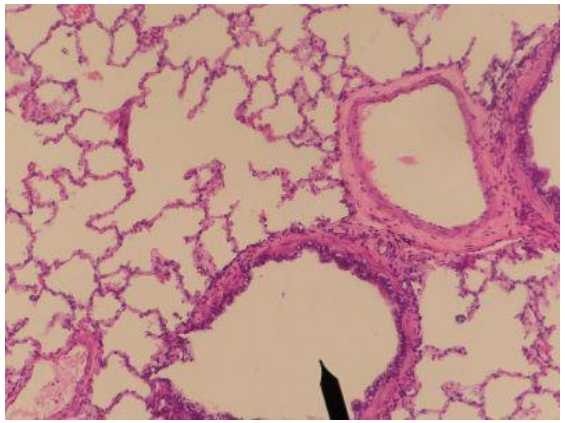
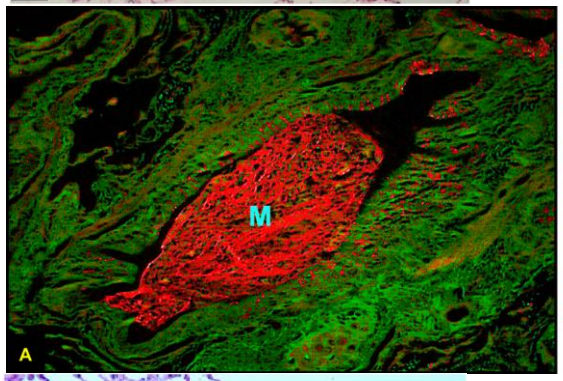
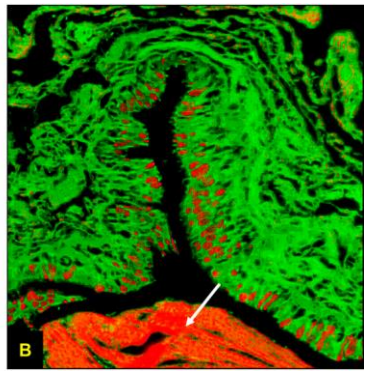
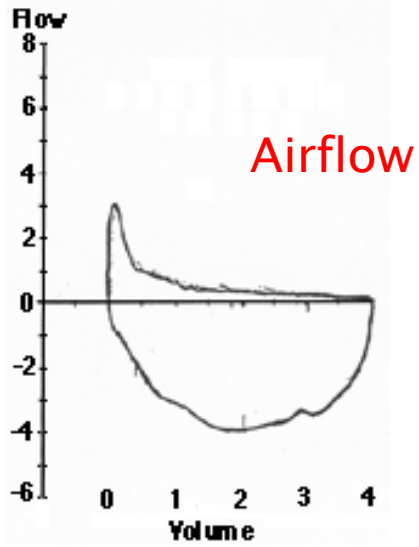


histology-world.com

Mucus metaplasia

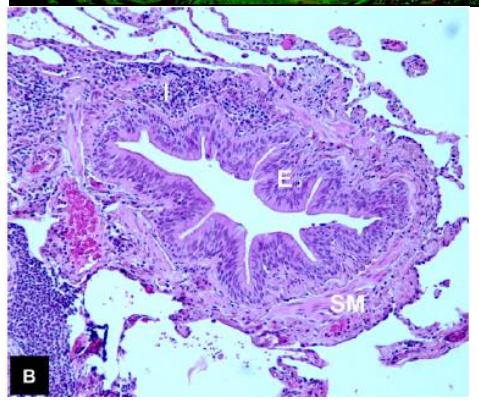






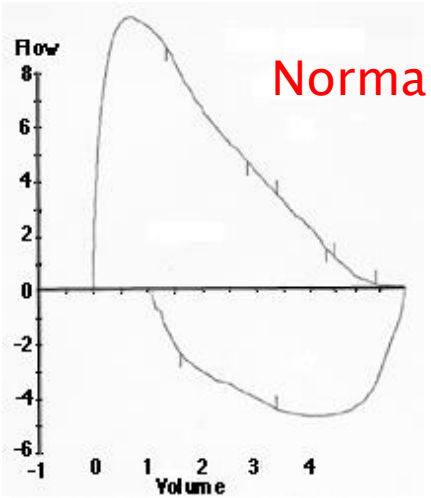
Airflow obstruction

Small airway disease

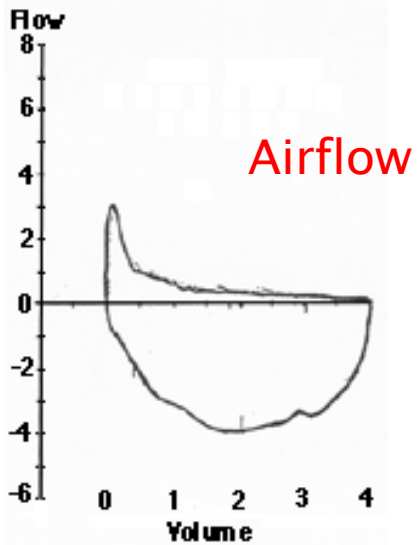


Kim V, Proc Am Thorac Soc 2008;5:478

Mechanisms of airflow limitation



Normal spirometry



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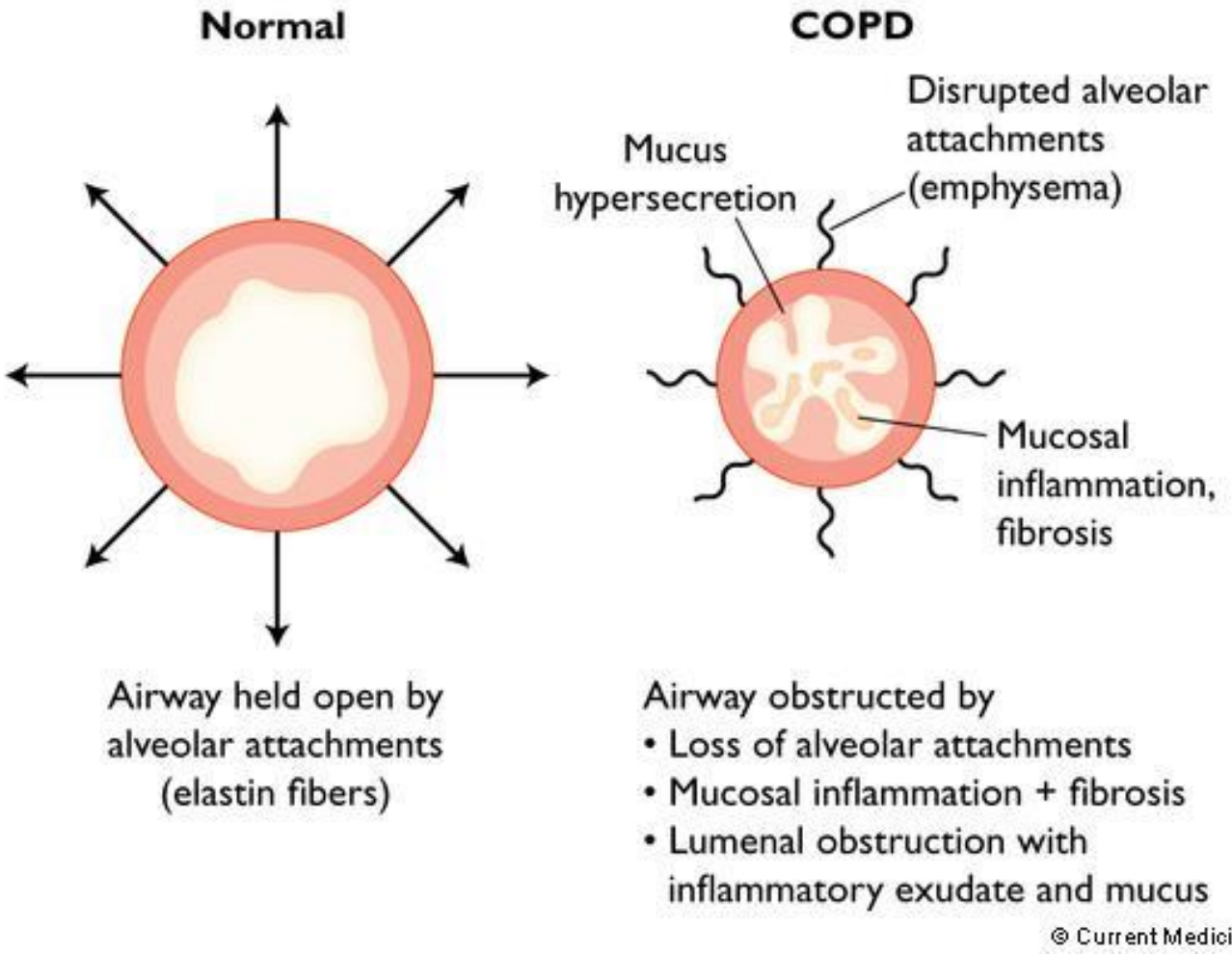


Crapo J, ed. Atlas of COPD, 2009

Assessment: Symptoms and Signs of COPD

Symptoms

Cough

Sputum

Dyspnea

Wheeze

Chest tightness

Weight loss

Muscle weakness

Edema

Depression

Physical Exam

Tripod posture

Skin: cyanosis

Breathing: tachypnea, pursed lip breathing, prolonged expiration, accessory muscle use

Barrel Chest

Breath Sounds: distant, wheezes

Cardiac: distant, increased P2, JVD, edema

Cachexia

COPD Assessment Test (CAT)

I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	0 1 2 3 4 5	I have no energy at all

Modified MRC Dyspnea scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

Mahler DA, Chest 1988;93:580
Jones P, ERJ 2009;34:648

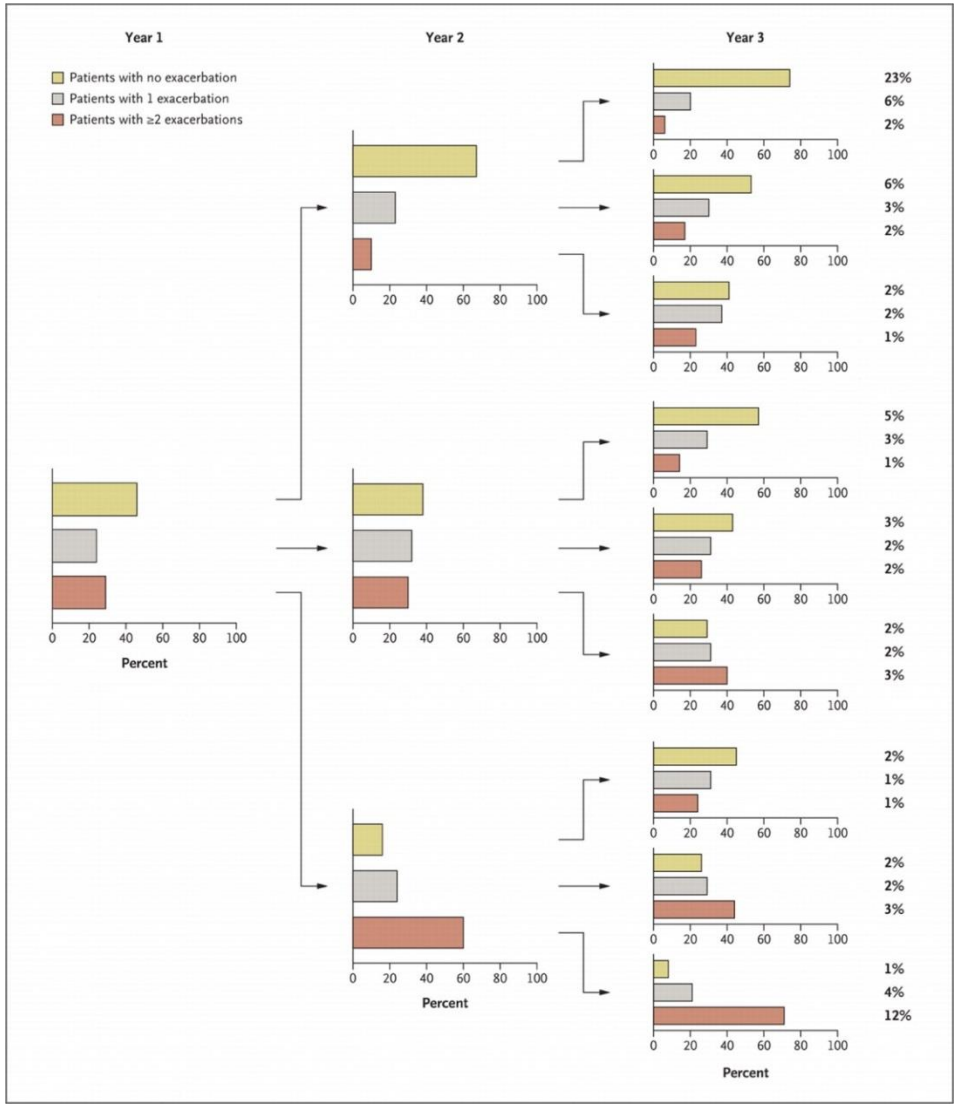
Classification of Severity of Airflow Limitation in COPD*

In patients with $FEV_1/FVC < 0.70$:

GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

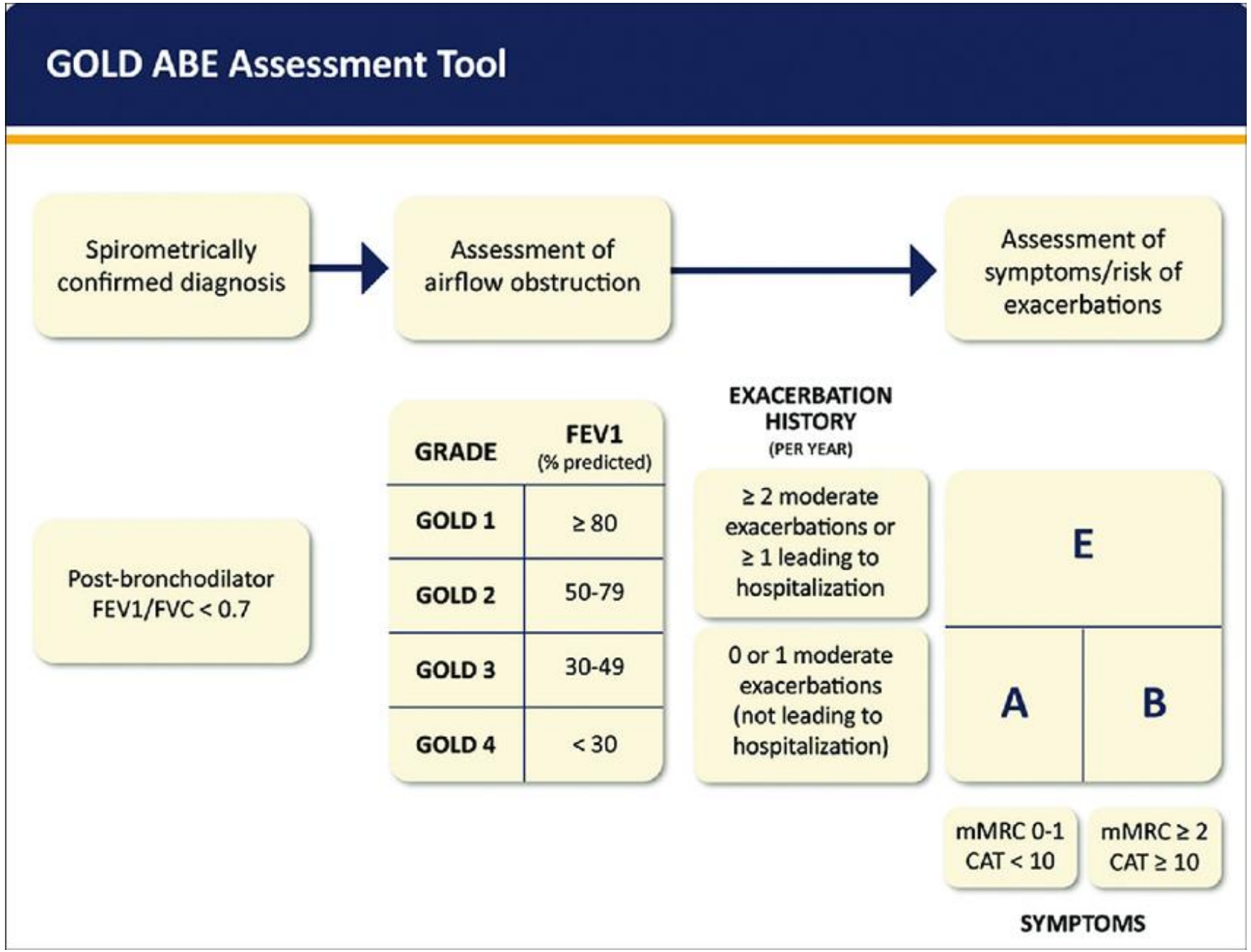
**Based on Post-Bronchodilator FEV_1*

Exacerbation Risk: Past exacerbations are the best predictor of future exacerbations



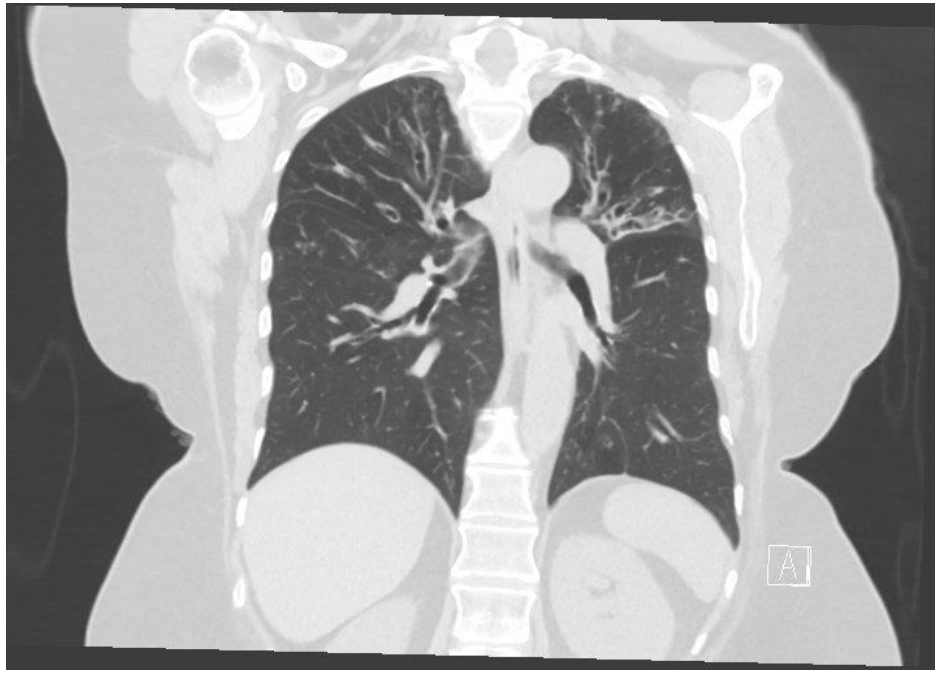
Hurst JR, NEJM 2010; 363:1128

GOLD ABE Assessment Tool



Other assessments

- Chest CT scan
  - Differential diagnosis
    - Bronchiectasis
    - “symptoms out of proportion”
  - Lung cancer screening
  - Lung volume reduction
- CBC with differential
- Alpha-1 antitrypsin deficiency
  - 1-2% of COPD in USA
  - AAT level +/- genotype or protein phenotype



Sandhaus RA, JCOPDF 2016; 3(3): 668-682

Case, 2 month follow-up

Spirometry: FEV_1 55% predicted, FEV_1/FVC 0.6.
Blood eosinophils 350 cells/µl
In the interim, she was treated with antibiotics for bronchitis.
What would you add to her regimen?

a) Roflumilast
b) Azithromycin 250mg daily
c) Dupilumab
d) Ensifentrine

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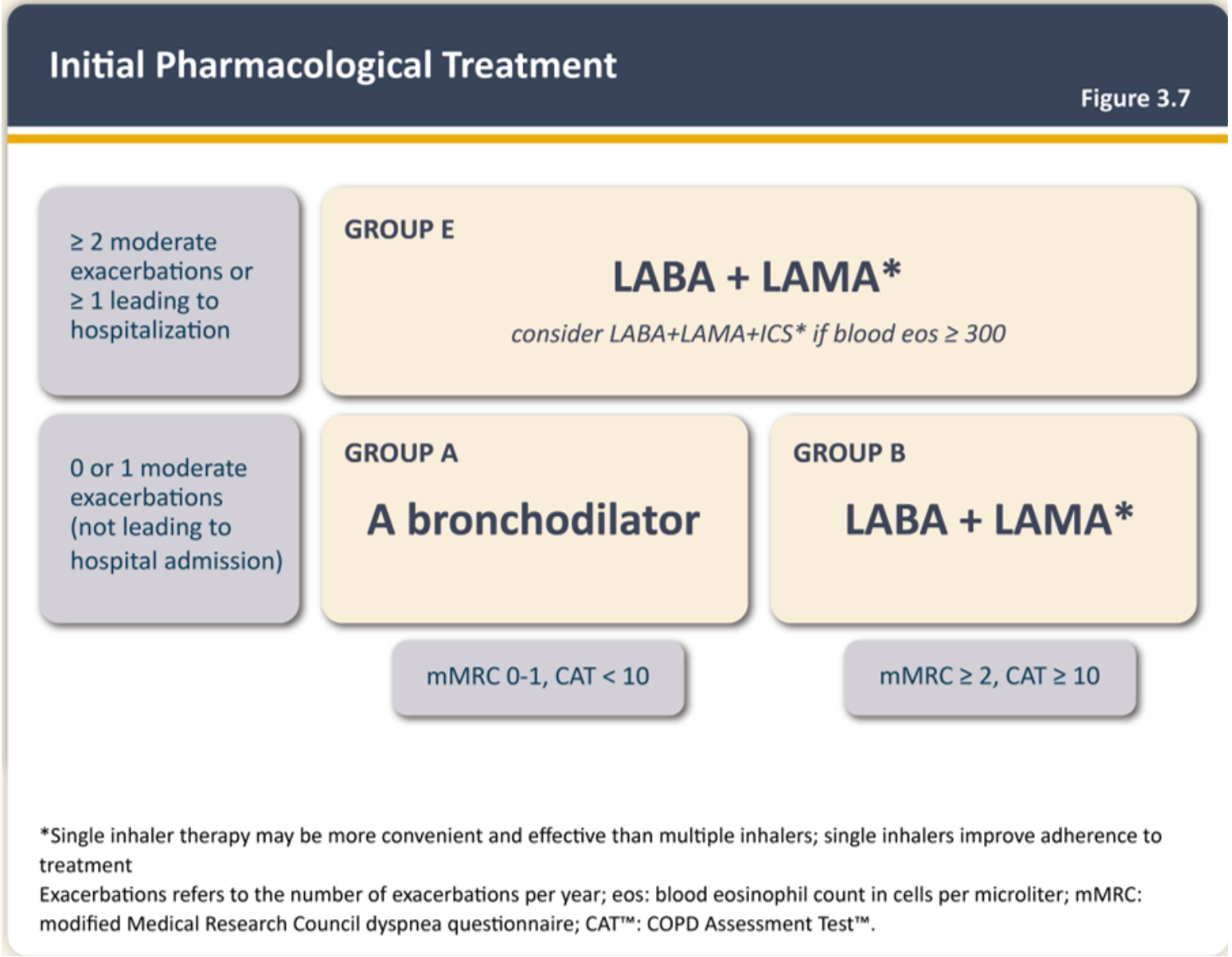
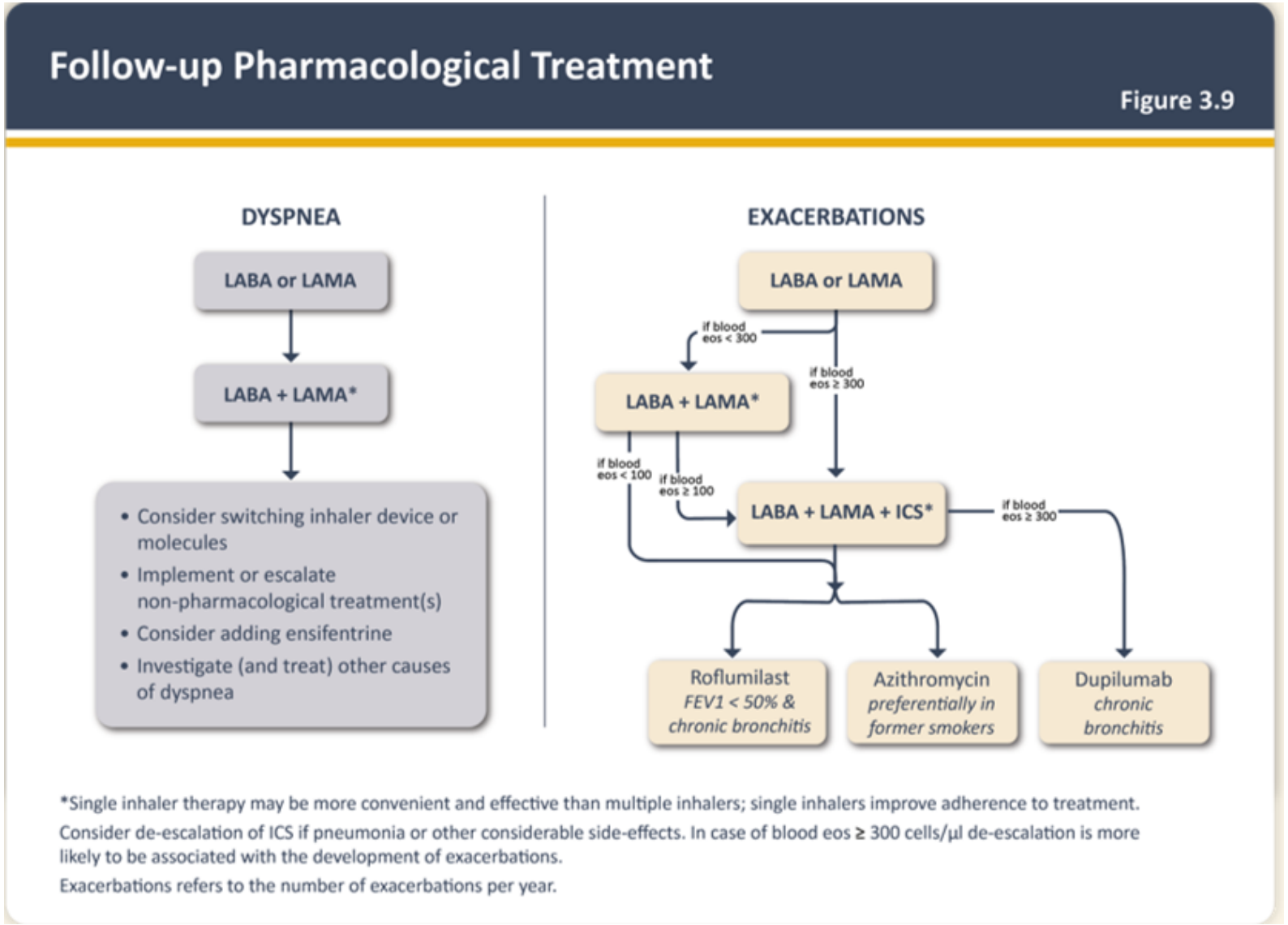
Medication algorithm: initial



Medication algorithm: follow-up



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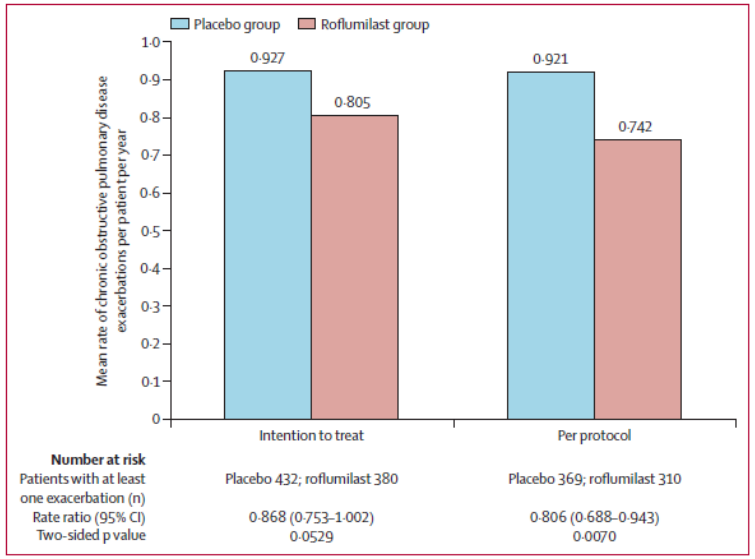
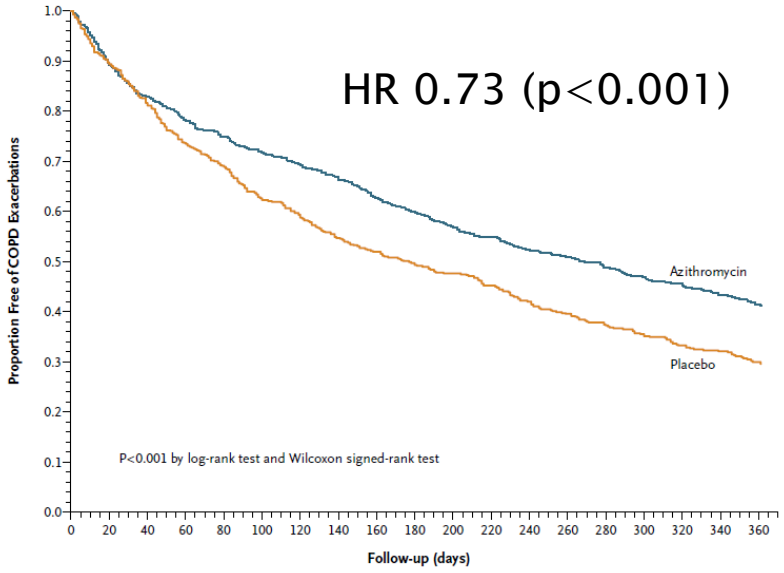
Oral therapies to decrease exacerbation risk

Roflumilast



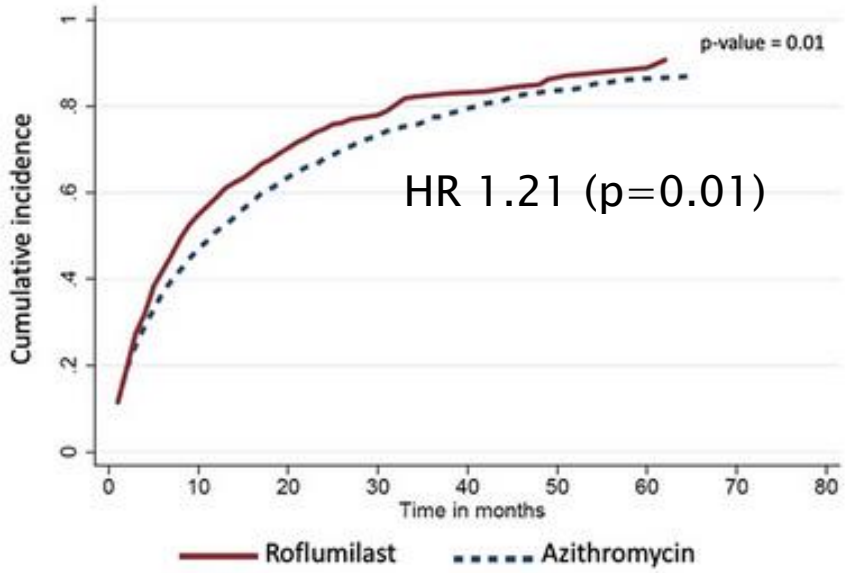
Severe COPD (FEV_1<50%)
chronic bronchitis
exacerbation history
GI side effects

Azithromycin 250mg daily



More effective: older, ex-smokers, milder COPD
Adverse effect: hearing loss

Comparison



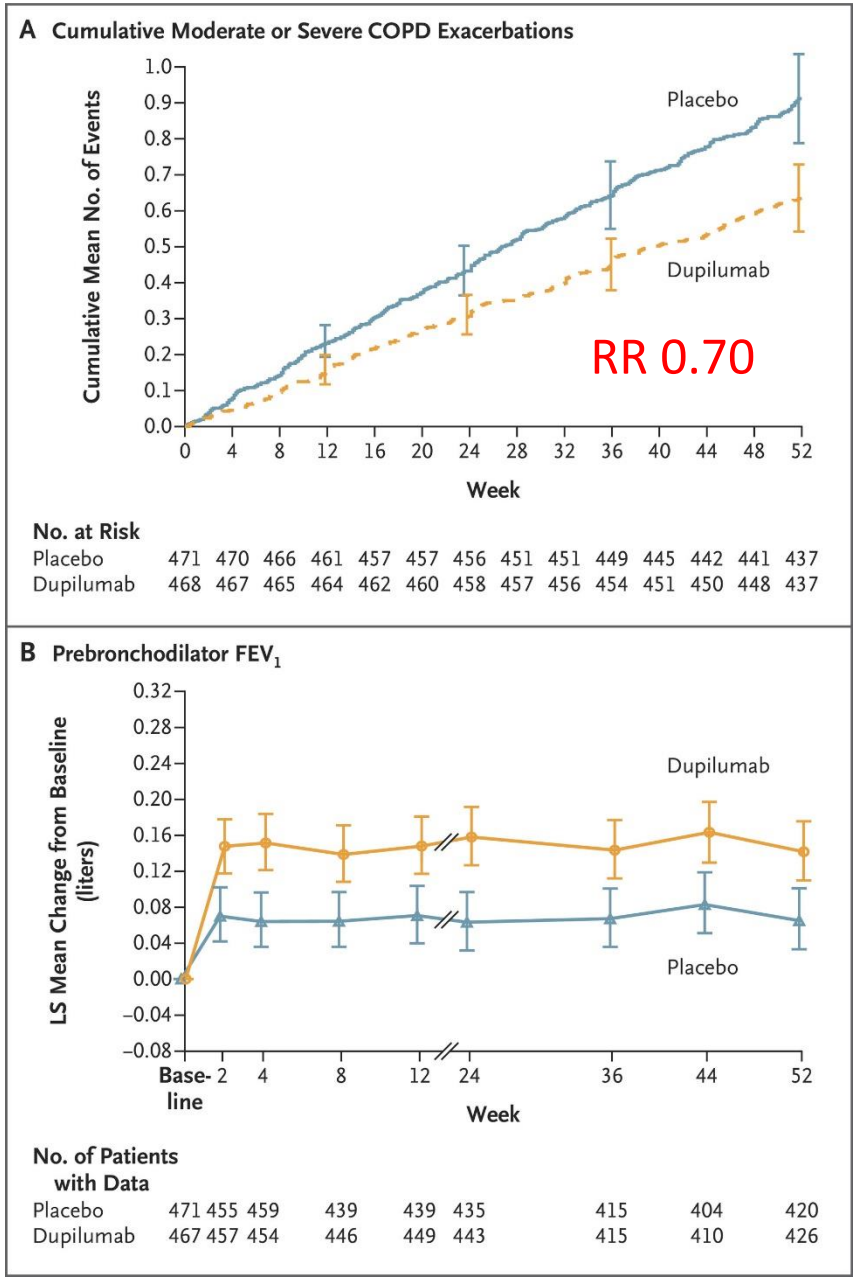
VA database study:
Prefers azithromycin

Martinez, Lancet 2015;385:857
Albert, NEJM 2011;365:689
Lam, JCOPDF 2021;8:450

Dupilumab in COPD

- BOREAS Trial
- Current/former smokers (N=939)
  - FEV1 30-80%
  - Blood eos ≥300
  - Exacerbation history
  - On LABA/LAMA/ICS
- Dupilumab 300mg sc q2wks vs. placebo
- Findings largely replicated in NOTUS trial

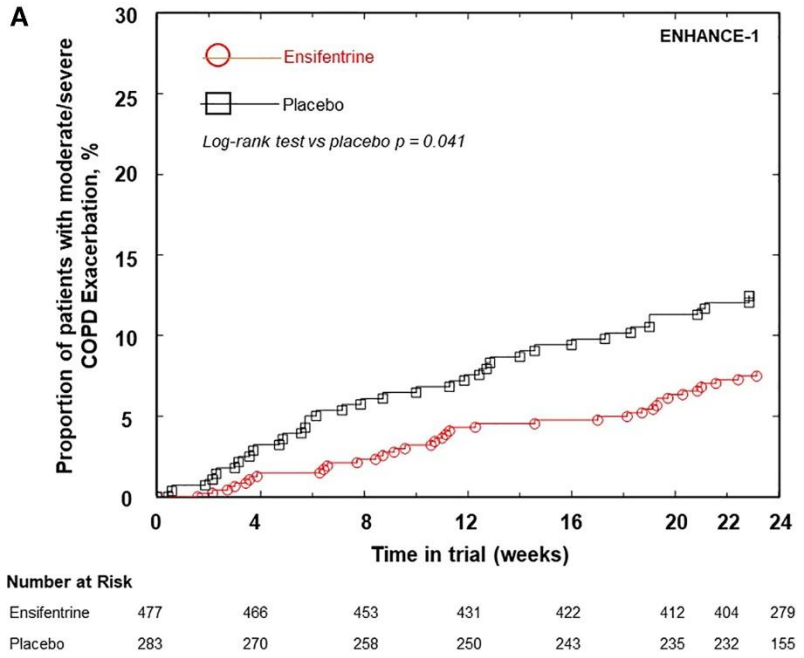
Bhatt SP, NEJM 2024

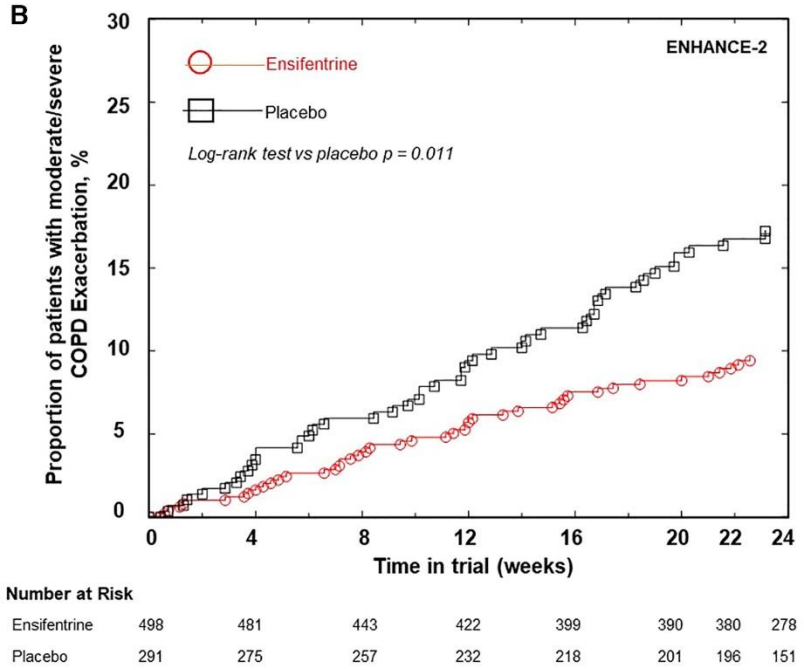


Bhatt SP, NEJM 2023;389:205

Ensifentrine

- Nebulized PDE3/4 inhibitor
  - Bronchodilator and anti-inflammatory
- ENHANCE 1 and 2 trials
  - FEV1 increase ~90ml
  - Improved symptoms
  - Reduced exacerbations
- Caveat:
  - Maintenance therapy 68%, 55%
  - None on triple therapy





Anzueto, AJRCCM 2023;208:406

Case, part 3

She was admitted for an acute MI, treated with PCI. Her LV function is normal. The cardiologist asks you if she can start a β-blocker. Which of the following would you prescribe?

A. Carvedilol
B. Bisoprolol
C. Diltiazem
D. Any of the above
E. (A) or (B) only

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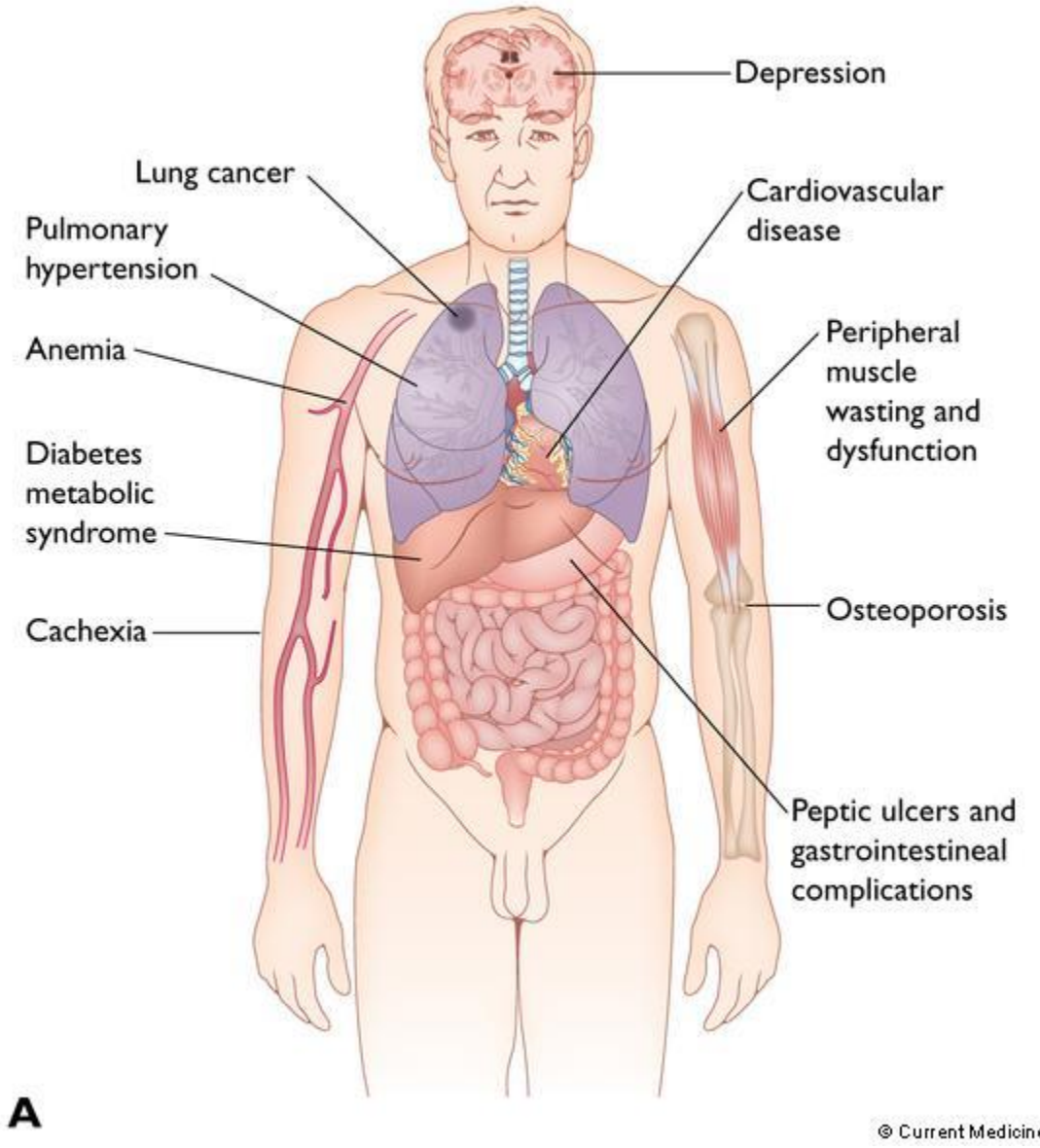
Comorbidities: COPD is a systemic disease

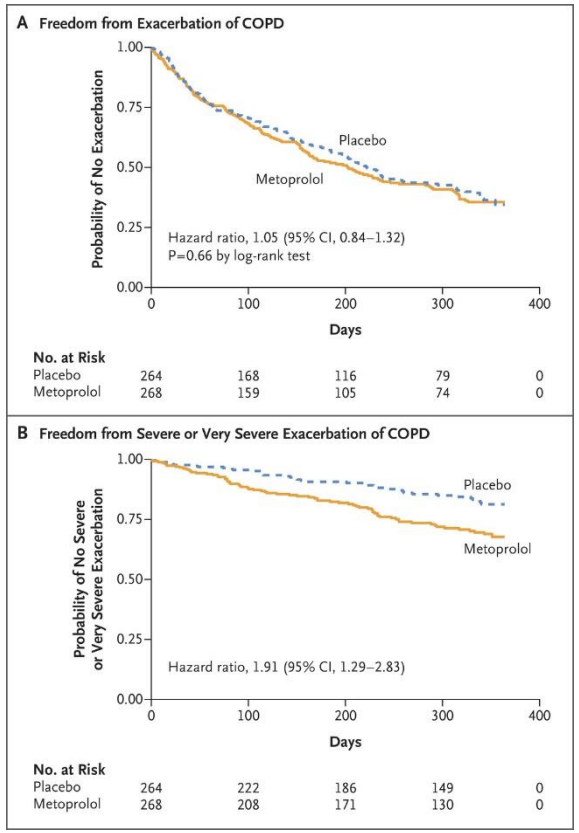


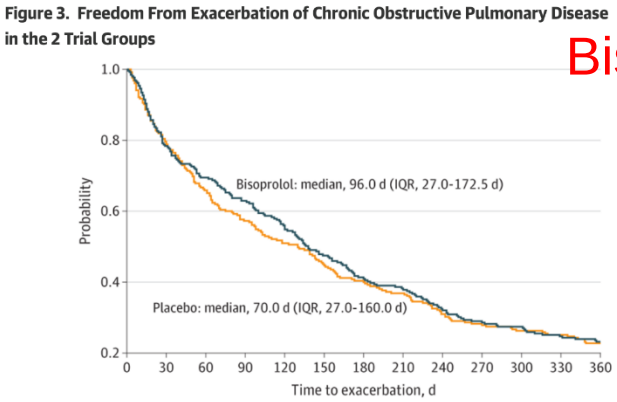
Crapo J, ed.,
Atlas of COPD, 2009

Managing comorbidities

- General rule: treat comorbidities as you normally would
- β-blockers in COPD:

Metoprolol





Bisoprolol

Cardioselectivity: β1/β2 ratio

Bisprolol	14
Metoprolol	2
Carvedilol	0.2

Metoprolol increased risk of severe exacerbations

no increase in total exacerbations

Bisoprolol – no increased risk

Dransfield M, NEJM 2019; Devereux G, JAMA 2024

Baker J, Br J Pharmacol 2005

Case, a few years later

She notes progressive dyspnea. O_2 sat is 88% on room air at rest. To reduce future adverse events, you prescribe supplemental O_2

A. 24 hours/day

B. 15 hours/day (e.g. nighttime)

C. Either A or B

D. No supplemental O_2

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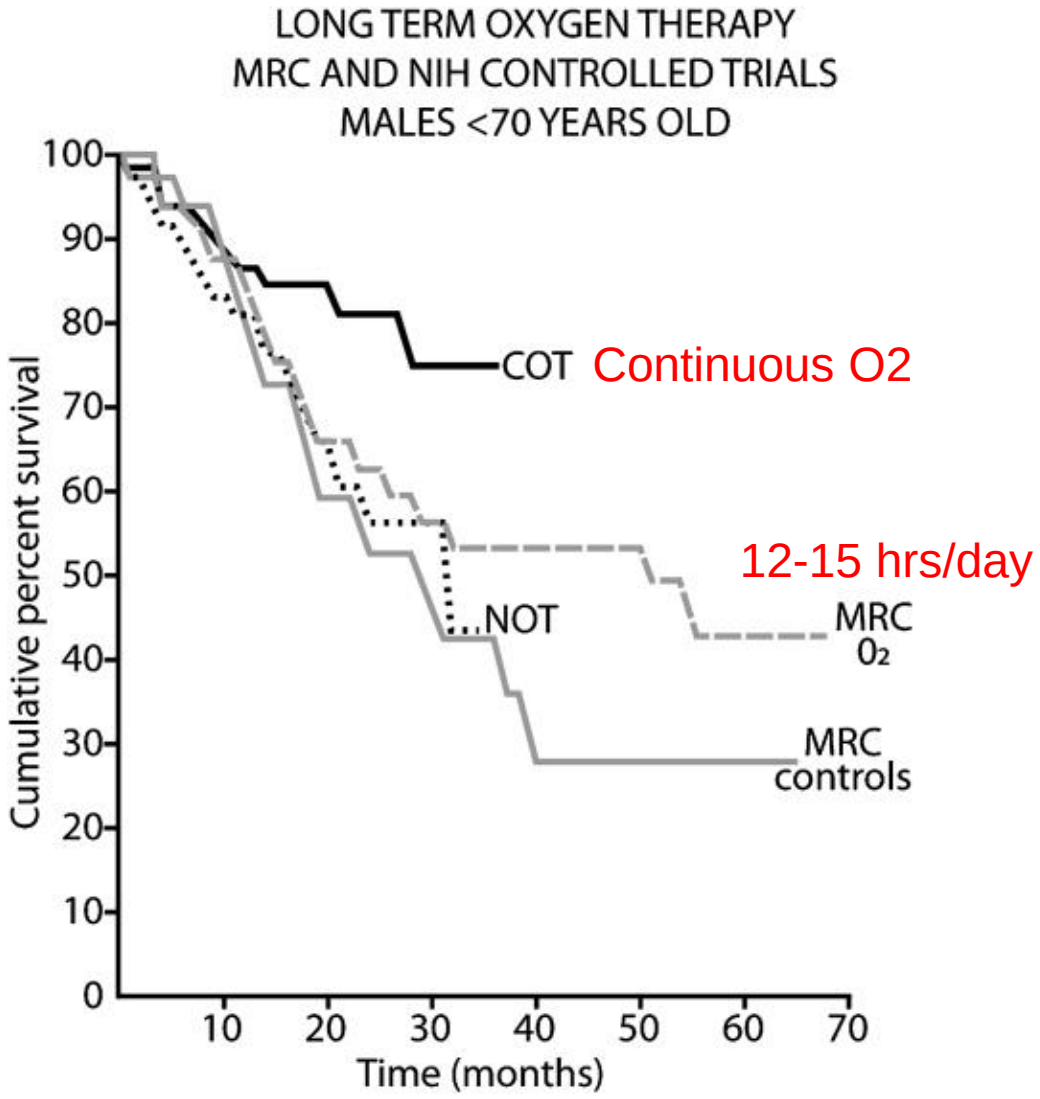
Supplemental oxygen reduces mortality in hypoxemic COPD patients

Criteria, at rest:

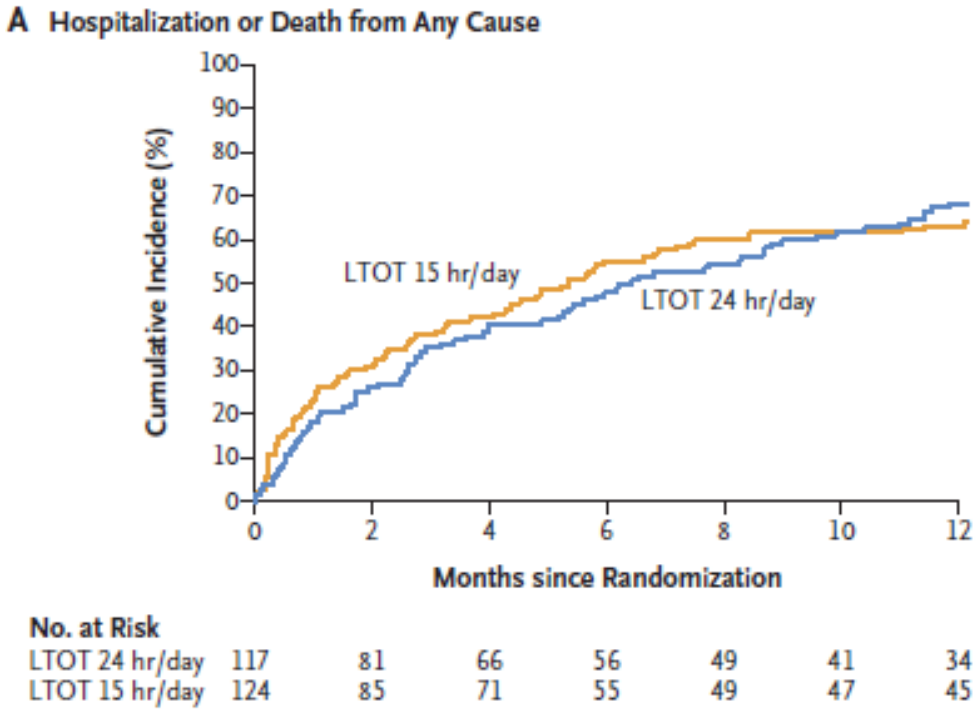
- PaO_2 ≤55 mmHg or SaO_2 ≤88% or
- PaO_2 ≤60mmHg or SaO_2 ≤89%
  - with cor pulmonale, right heart failure or polycythemia



Stoller J, Chest 2010

Do you need supplemental O_2 24hrs/day?

- REDOX trial
- N=241
- ~70% COPD
- Randomized O_2 24 vs 15 hr/d



Ekstrom M, NEJM 2024;391:977

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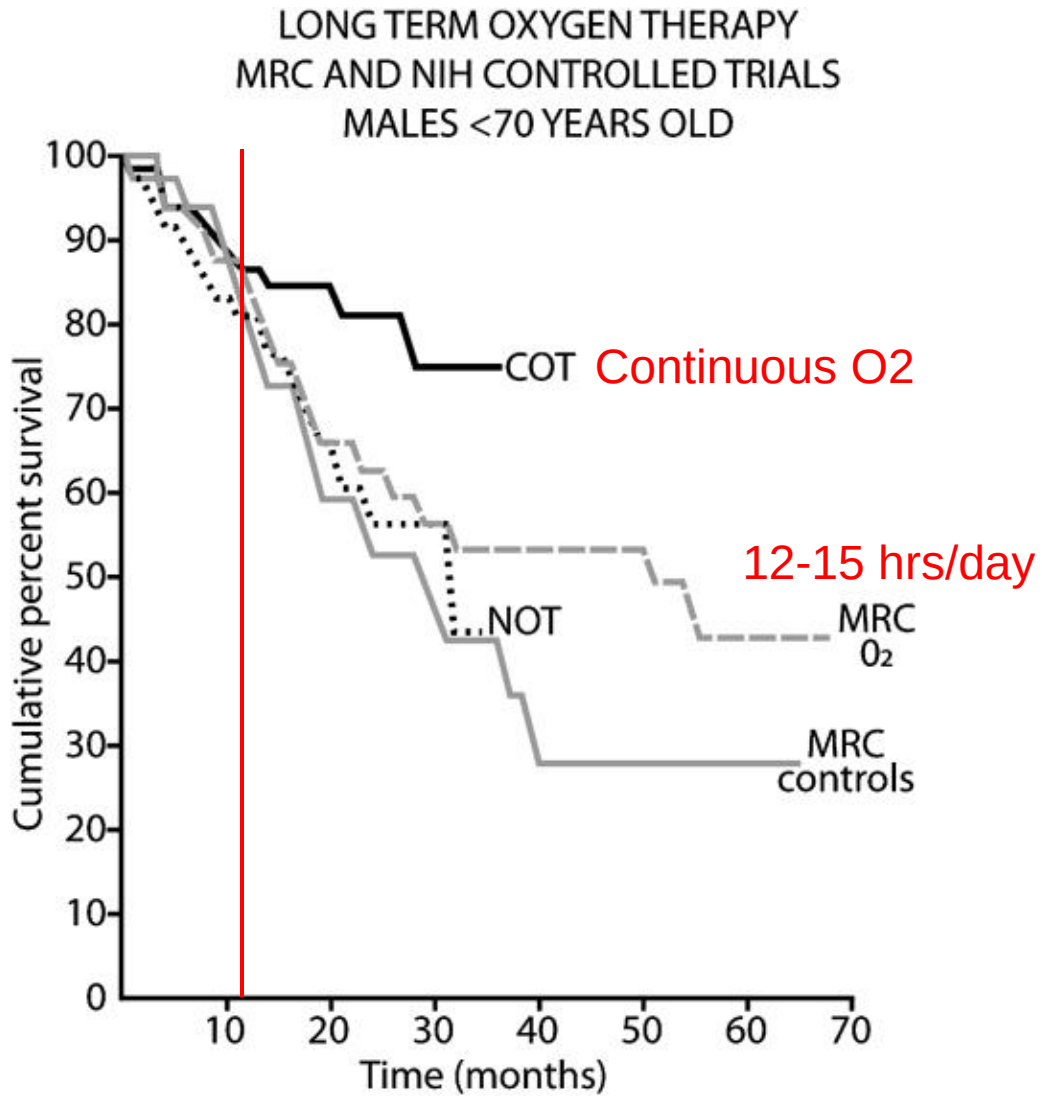
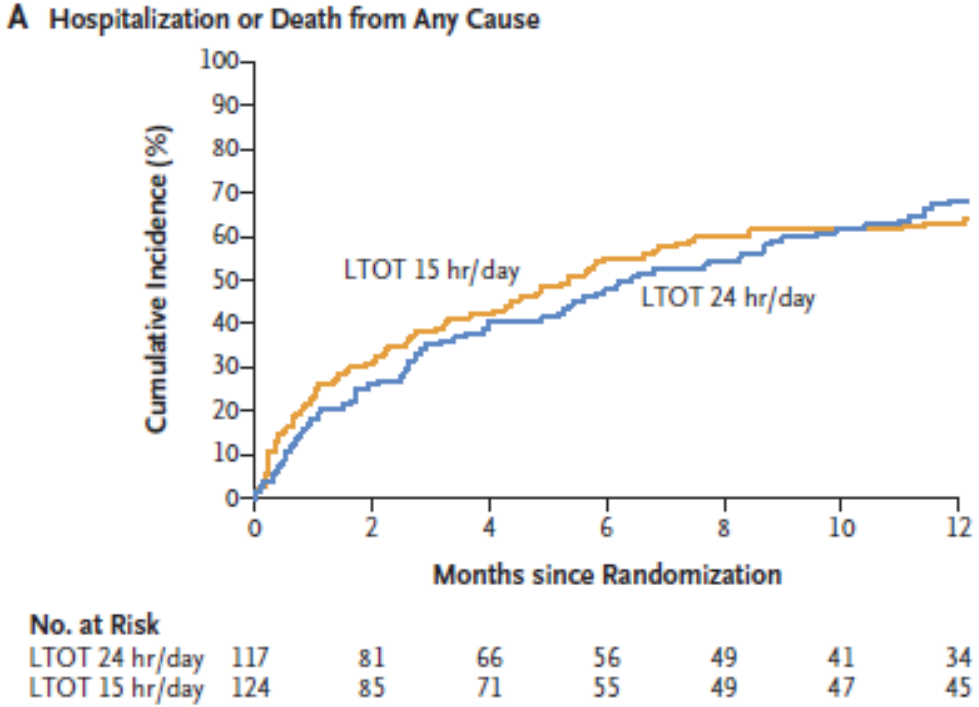
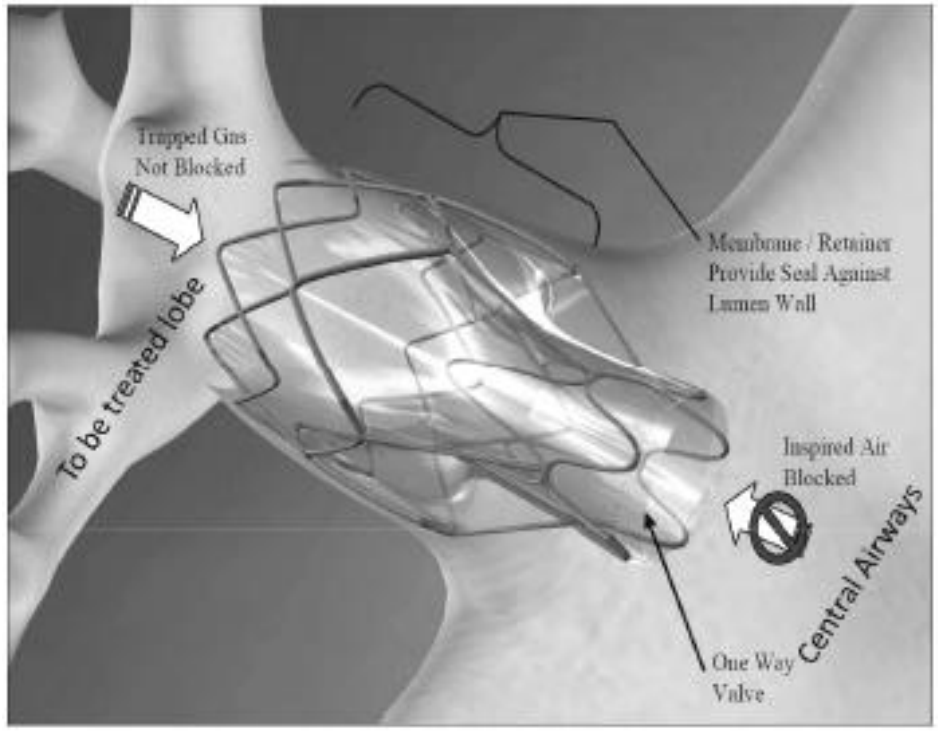




Ekstrom M, NEJM 2024;391:977

Surgical or interventional treatments

- Lung volume reduction surgery
  - Upper lobe predominant
  - Low exercise capacity
- Bronchoscopic lung volume reduction
- Lung transplantation



NETT, NEJM 2003;348:2059
*Klooster K, NEJM 2015;373:2325
Davey C, Lancet 2015;386:1066
Yusen R, J Heart Lung Transplant 2015;34:1264

Case, urgent visit

She has 3 days of dyspnea, productive cough, and chest tightness. She is tachycardic, tachypneic, O_2 sat 87% on her baseline 2 lpm, and she is wheezing on exam.

Besides COPD exacerbation, the differential diagnosis includes:

A. Community acquired pneumonia
B. Pulmonary embolism
C. Acute decompensated heart failure
D. (A) and (C) only
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COPD exacerbation: definitions

Symptom-based (Anthonisen)

- Increased dyspnea
- Increased sputum volume
- Increased sputum purulence

- Mild → Moderate → Severe
  - 1 → 2 → 3 symptoms

- Limitations
  - subjective
  - non-specific

Utilization-based

- Acute worsening of symptoms
- Requires additional therapy
  - Mild: short-acting bronchodilators
  - Moderate: antibiotics and/or systemic corticosteroids
  - Severe: ED visit or hospitalization

- Limitations
  - post-hoc
  - healthcare access
  - local medical practices

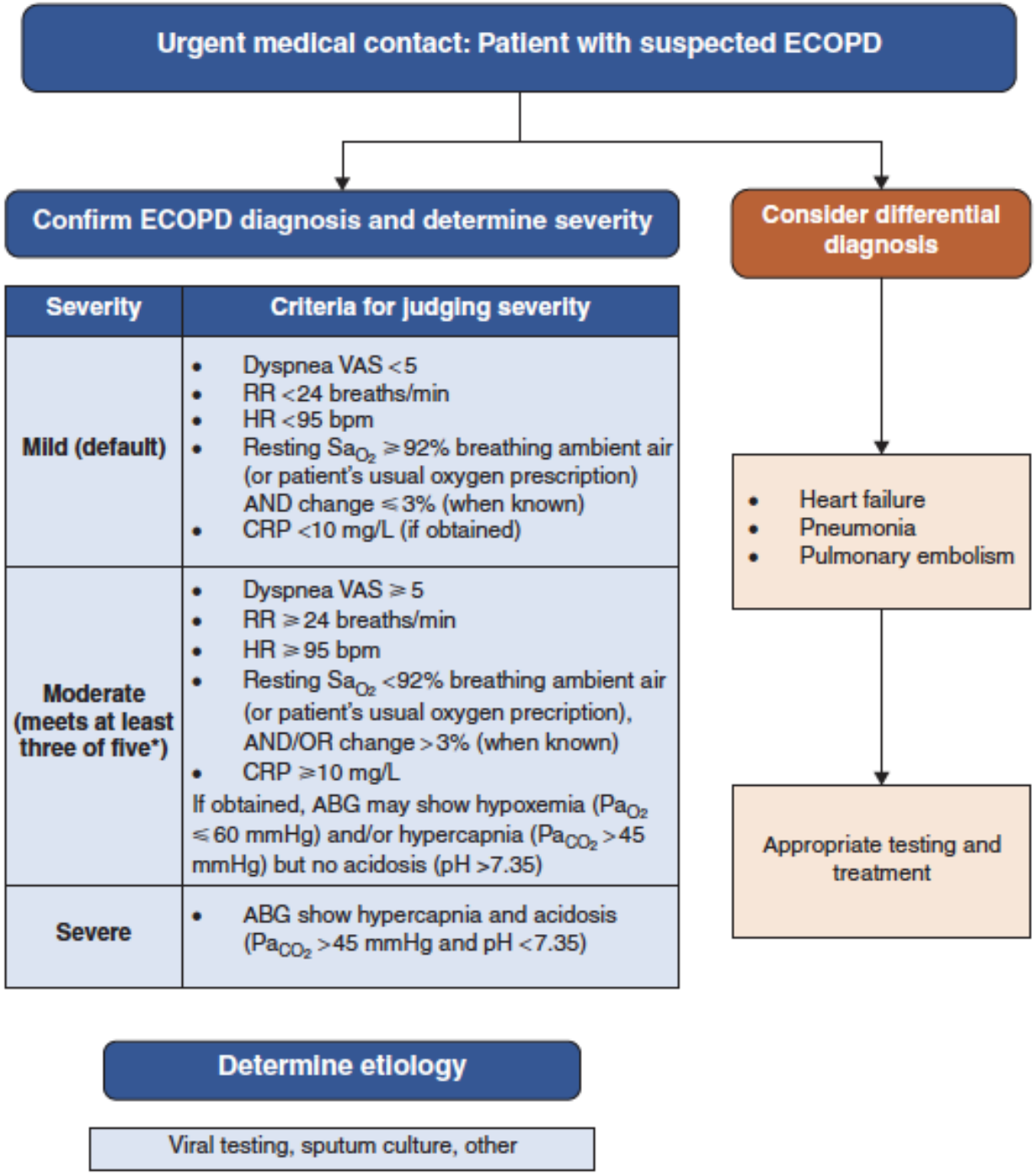
Anthonisen NR, Ann Intern Med 1987;106:196

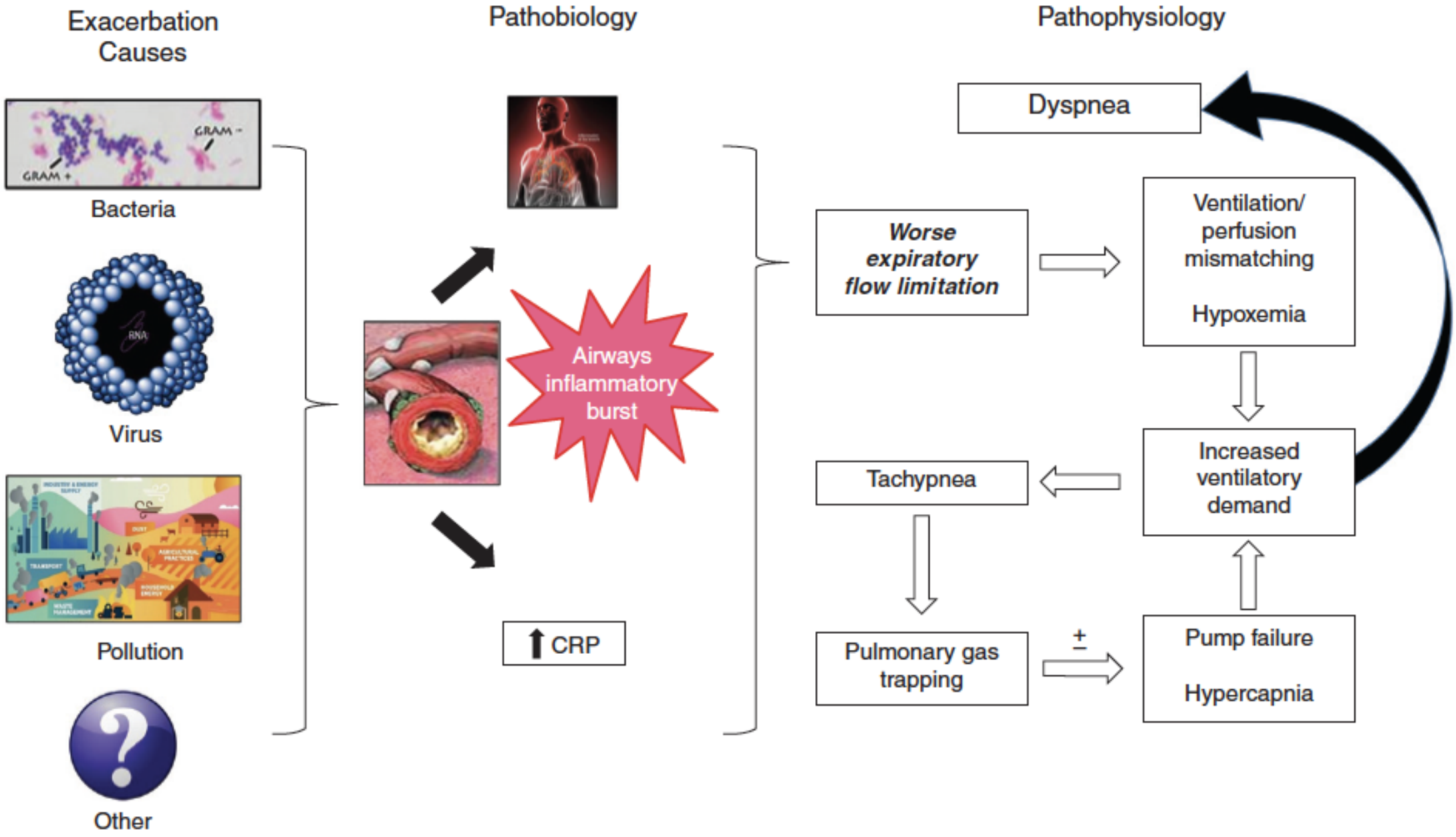
Calverley P, COPD 2005;2:143

Rome proposal

Celli BR et al, AJRCCM 2021;204:1251

- Modified Delphi method
- Goal: more objective
- Limitations
  - Arbitrary cutoffs
    - Change from baseline?
  - Discounts some symptoms
  - ED/hospital-based
  - No clinical validation



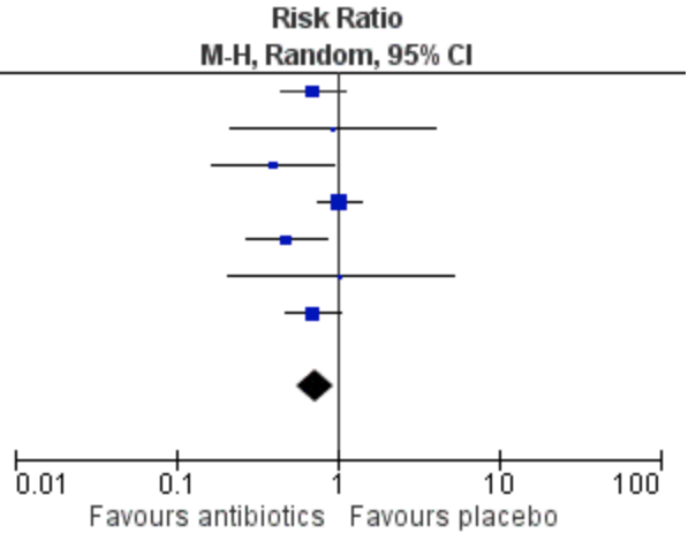


Celli BR et al, AJRCCM 2021;204:1251

Exacerbations treatment: Antibiotics

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Anthonisen 1987 (1)	19	57	28	59	19.8%	0.70 [0.45, 1.11]
Brusse-Keizer 2009 (2)	3	18	3	17	3.0%	0.94 [0.22, 4.05]
Hassan 2015 (3)	6	50	15	50	7.8%	0.40 [0.17, 0.95]
Jørgensen 1992 (4)	49	132	49	136	28.8%	1.03 [0.75, 1.41]
Llor 2012 (5)	15	158	30	152	14.5%	0.48 [0.27, 0.86]
Sachs 1995 (6)	4	40	2	21	2.5%	1.05 [0.21, 5.27]
van Velzen 2017 (7)	32	150	46	151	23.6%	0.70 [0.47, 1.03]
Total (95% CI)		**605**		**586**	**100.0%**	**0.72 [0.56, 0.94]**
Total events	128		173			

Heterogeneity: Tau² = 0.04; Chi² = 8.76, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 2.42 (P = 0.02)



Vollenweider DJ, Cochrane Database Syst Rev 2018:CD010257

- Reduce treatment failure
- Usually 5-7 days
- Respiratory flora: *H.influenzae, S.pneumoniae, M.catarrhalis*
  - E.g., Amox/clav, macrolides, doxycycline, quinolones
- Risk factors for pseudomonas
  - Previous sputum isolate, severe COPD, bronchiectasis, prior hospitalization

CRP to guide antibiotic prescription

- Primary care, N=653
- Point of case testing
  - < 20 mg/L should not use antibiotics
  - 20-40 mg/L may be beneficial
  - > 40 mg/L likely to be beneficial

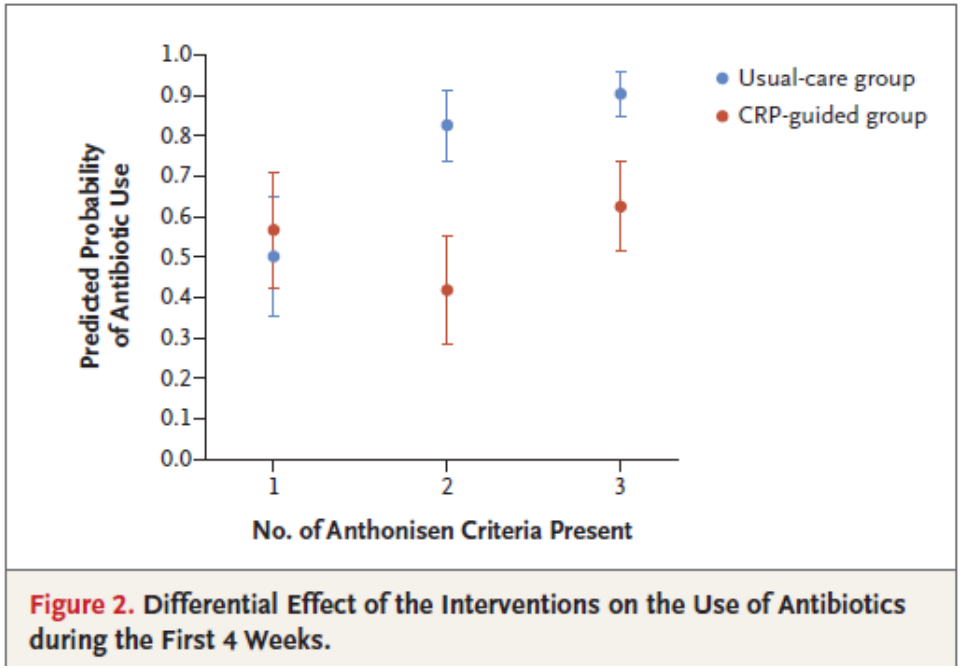


Figure 2. Differential Effect of the Interventions on the Use of Antibiotics during the First 4 Weeks.

Less antibiotic use
No evidence of harm

Butler et al, NEJM 2019;381:111

Exacerbations treatment: Systemic steroids

Benefits:

↓ treatment failure, symptoms, LOS

↑ FEV_1

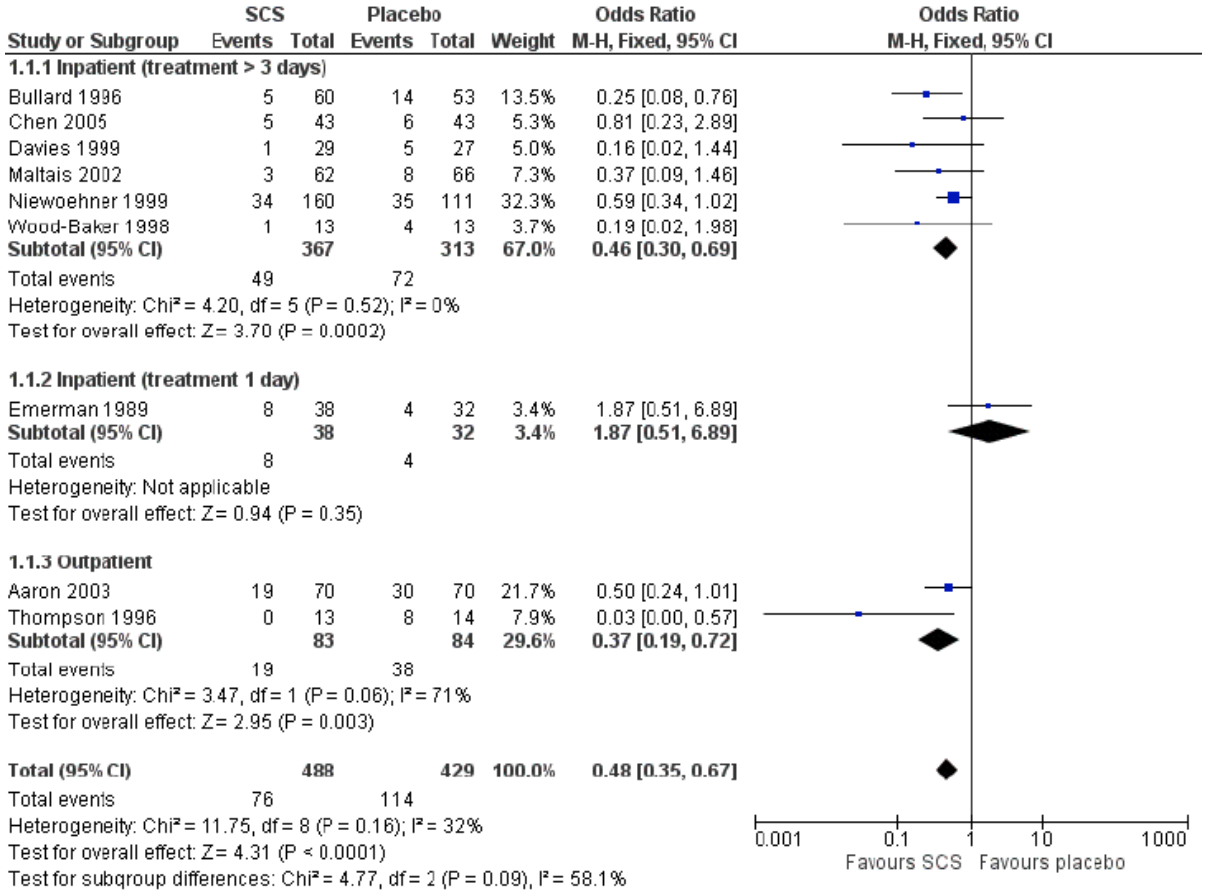
Dose/duration:

Benefit of lower doses

No difference in oral vs IV

Prednisone 40 mg x 5d non-inferior to 14d

Side effects: hyperglycemia, etc.

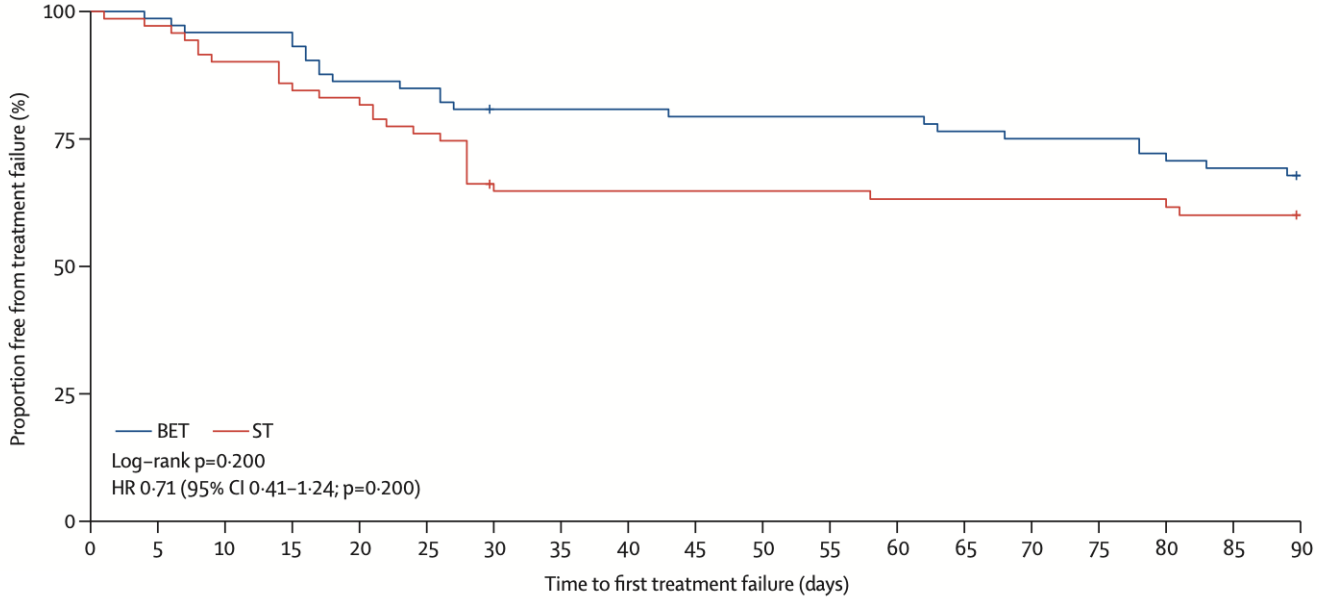


Walters JAE, Cochrane Database Syst Rev 2014:CD001288.
Davies L, Lancet 1999;354:456. Leuppi JD, JAMA 2013;309:2223.
Sivapalan P, Lancet Respir Med 2019;7:699

Eosinophil-guided oral steroid use

- STARR2: UK primary care practices
- 144 exacerbations, 93 subjects
- Point of care blood eos count
  - >2% prednisolone 30mg daily x 14d
  - <2% placebo
- Compared to standard care
  - prednisolone 30mg daily x 14d
- All received antibiotics

33% reduction in prednisolone Rx
Non-inferior



Ramakrishnan S, Lancet Respir Med 2024

Case #2

You see a 70 male former smoker after admission for “COPD exacerbation”.

At baseline, he has daily cough, sputum, and exertional dyspnea. He has no history of asthma. Work-up includes normal spirometry and a blood eosinophil count of 50 cells/μl. Lung screening CT scan within the past year showed mild bronchial wall thickening.

Which of the following is most likely to improve his symptoms?

A. LAMA-LABA inhaler
B. Triple therapy (LAMA-LABA-ICS)
C. Azithromycin 250mg daily
D. Roflumilast
E. None of the above

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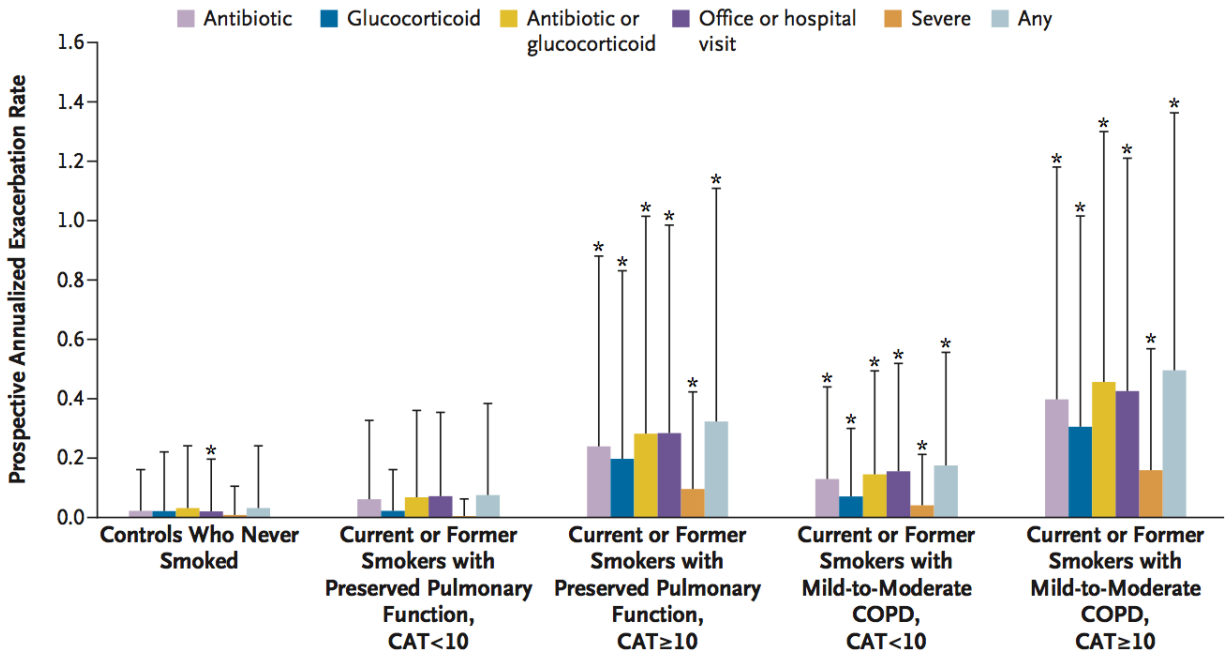
Current/former smokers with normal spirometry

Variable	No. (%) Never Smokers (n = 108)	GOLD 0 (n = 4388)	GOLD 1 (n = 794)
Individual Scores			
Chronic bronchitis, by criteria	0	552 (12.6)	125 (15.7)
History of ≥1 severe exacerbation	0	190 (4.3)	39 (4.9)
St George's Respiratory Questionnaire total score >25	4 (3.7)	1143 (26.0)	226 (28.5)
Six-minute walk distance <350 m	4 (3.7)	674 (15.4)	109 (13.7)
Modified Medical Research Council dyspnea score ≥2	4 (3.7)	1029 (23.5)	175 (22.0)
Emphysema >5%	9 (8.3)	428 (9.8)	273 (34.4)
Gas trapping >20%	11 (10.2)	536 (12.2)	319 (40.2)
Sums			
Any impairment	26 (24.1)	2375 (54.1)	585 (73.7)

COPD-like symptoms
CT scan changes

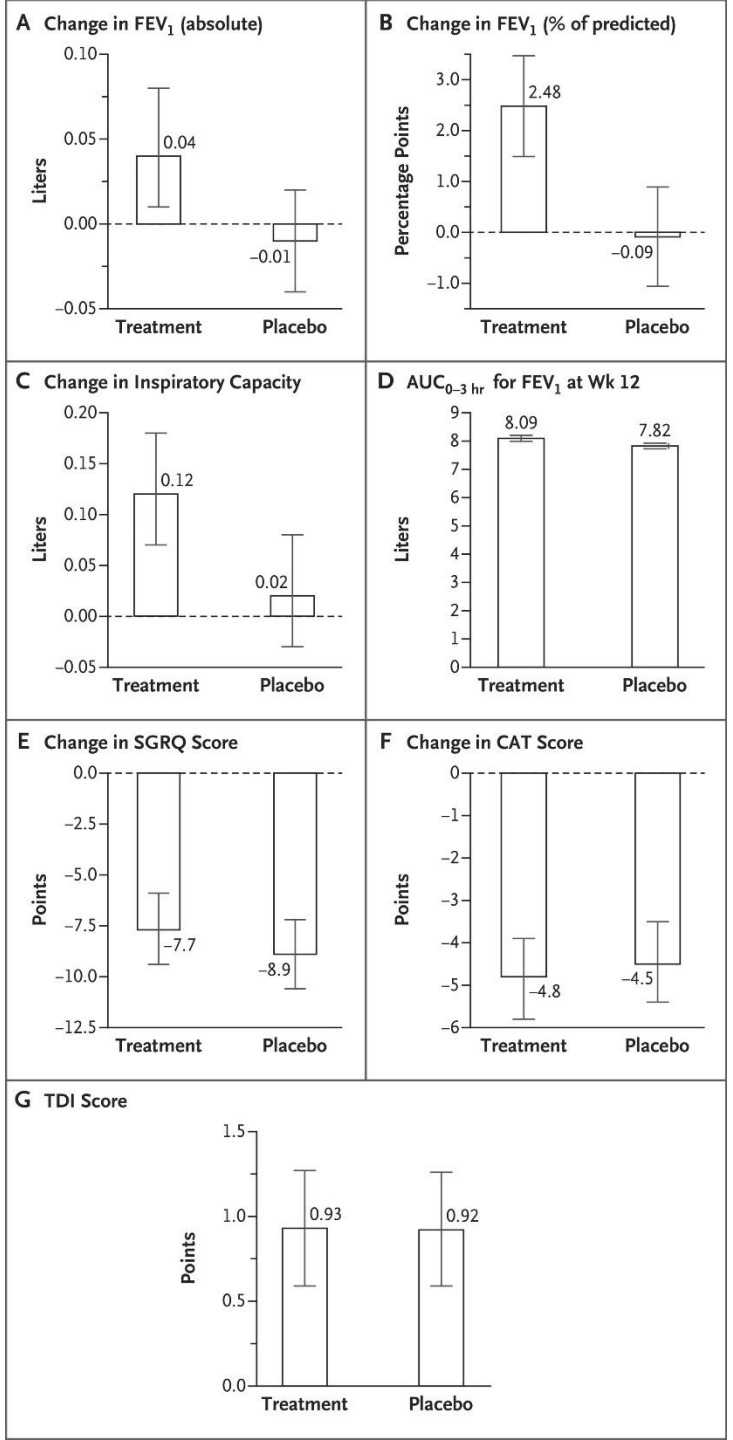


Increased exacerbation risk

COPDGene: Regan, JAMA Intern Med 2015;175:1539
SPIROMICS: Woodruff, NEJM 2016;374:1811

“Tobacco-exposed persons with symptoms and preserved lung function”

- How to treat?
  - Symptoms
    - CAT score ≥ 10
  - No airflow obstruction
    - $FEV_1/FVC \geq 0.7$
  - Asthma excluded
- LAMA-LABA inhaler did not improve symptoms vs placebo



Han MK, NEJM 2022;387:1173

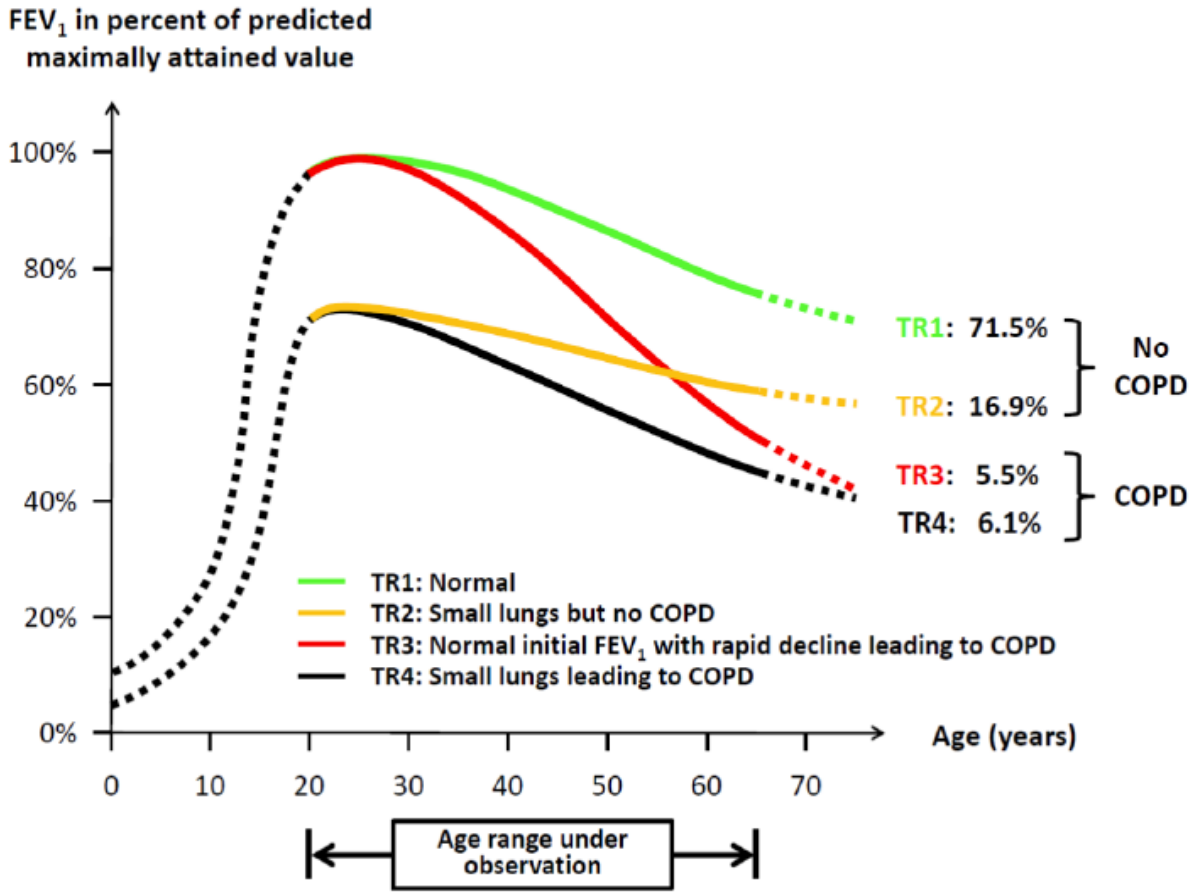
COPD Etiotypes

Proposed Taxonomy (Etiotypes) for COPD

Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)



www.goldcopd.org

Lange P, NEJM 2015;373:111

COPD Summary

- Multidimensional assessment
  - Symptoms and exacerbation risk
  - Assessment and management of comorbidities
- Non-pharmacologic treatments
  - Smoking cessation, pulmonary rehab, vaccines, supplemental O_2
- Medications
  - Bronchodilators are first line therapy: LAMA-LABA
  - Inhaled steroids are add-on - elevated blood eosinophils
  - Daily azithromycin or roflumilast for frequent exacerbators
  - New therapies: dupilumab, ensifentrine

COPD Summary (2)

- Lung volume reduction
  - Selected patients, specialized centers
- Acute exacerbations
  - No objective definition or biomarkers
  - Consider differential diagnosis
  - Antibiotics and systemic steroids have small effects
- New concepts in COPD diagnosis
  - Tobacco-exposed persons with symptoms and preserved lung function

References

- Global Initiative for Chronic Obstructive Lung Disease, Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, available at www.goldcopd.org
- COPD Foundation, www.copdfoundation.org
  - Patient information, including inhaler instructional videos
- Nici L, et al., Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020;201:e56-e69
- Celli B, et al., An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. Am J Respir Crit Care Med 2021; 204:1251-1258.