

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: Brigham and Women's Hospital
- Associate Professor of Medicine at HMS
 - Clinical focus: COPD, Alpha-1 antitrypsin deficiency
 - Research focus: COPD epidemiology and genetics

Disclosures

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- Consulting fees:
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Outline

- COPD exacerbations
- Assessment of stable COPD
- Treatment of stable COPD
 - Preventing exacerbations
- Lung volume reduction
- New concepts in COPD diagnosis

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*Case #1

A 72F former smoker presents to the ED with 3 days of dyspnea, productive cough, and chest tightness. She is tachycardic, tachypneic, SaO₂ 88% on room air, and 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
- E. All of the above

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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

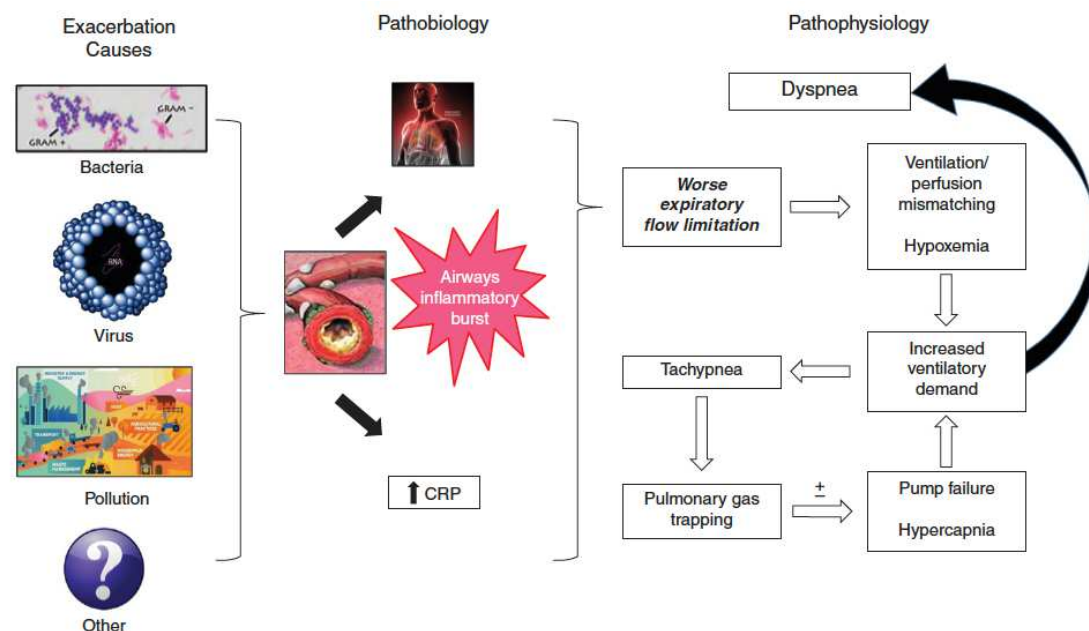
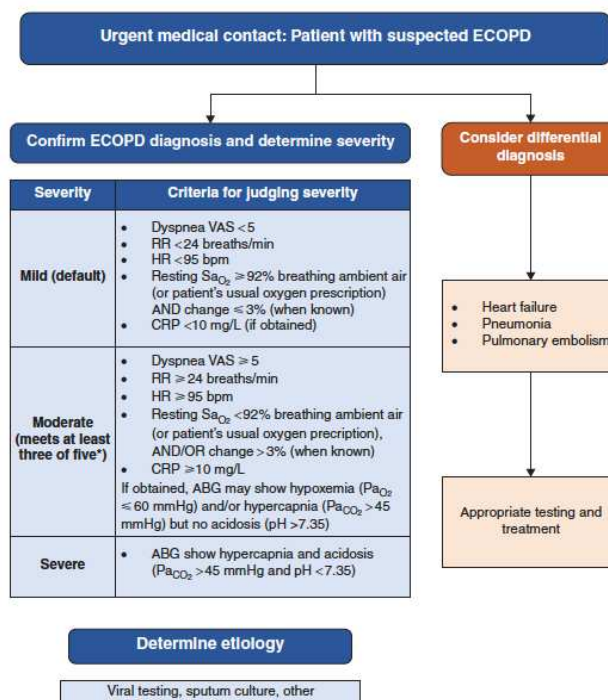
Utilization-based

- 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

Rome proposal

Celli BR et al, AJRCCM 2021;204:1251

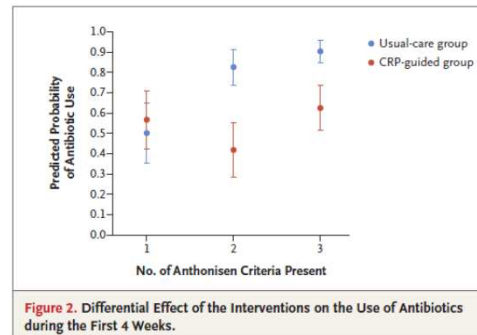
- Modified Delphi method
- Goal: more objective
- Limitations
 - Arbitrary cutoffs
 - Change from baseline?
 - Discounts some symptoms
 - ED/hospital-based
 - No clinical validation



Celli BR et al, AJRCCM 2021;204:1251

CRP to guide antibiotic prescription

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



Less antibiotic use
No evidence of harm

Butler et al, NEJM 2019;381:111

Procalcitonin in COPD inpatients

- Pre/post intervention
 - <0.1 µg/L antibiotics strongly discouraged
 - 0.1-0.25 discouraged
 - 0.25-0.5 recommended
 - >0.5 strongly recommended

Less antibiotic use
Shorter LOS
No difference in readmission rate

Small studies – not consistent results

Table 2 Antibiotic Durations and Secondary Outcomes of Total Cohort

Variable	Pre-intervention (n = 166)	Post-intervention (n = 139)	P value
Duration of total antibiotics, mean (SD), days	5.3 (3.2)	3.0 (2.9)	0.01
Duration of IV antibiotics, mean (SD), days	2.5 (2.4)	1.9 (1.8)	0.02
Total antibiotic duration, n (%)			
0 to 1 day	24 (14.5)	61 (43.8)	
2 to 5 days	73 (44.0)	48 (34.6)	
6 to 7 days	37 (22.3)	18 (13.0)	
8 to 10 days	23 (13.8)	10 (7.2)	
11 to 14 days	8 (4.8)	2 (1.4)	
More than 14 days	1 (0.6)	0 (0)	
Inpatient LOS, mean (SD), days	4.1 (3.9)	2.9 (2.0)	0.01
All-cause 30-day readmission, n (%)	24 (14.5)	23 (16.6)	0.25
Respiratory-related 30-day readmission, n (%)	18 (10.8)	13 (9.4)	0.18

Bremner, J Gen Internal Med 2018

Pulmonary embolism in exacerbations

- Meta-analyses: 16-17% of unexplained acute exacerbations, mostly ER or inpatient

Aleva FE, Chest 2017;151:544. Fu X, PLoS ONE 2021;16:e0256480

- French multi-center study

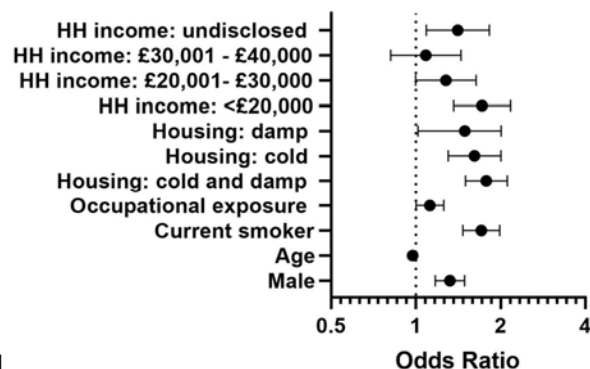
Couturaud F, JAMA 2021;325:59

- Hospital admissions
- Geneva score: age, previous VTE, surgery, cancer, tachycardia, hemoptysis, LE pain, edema
 - High → CT-PE, LE ultrasound
 - Low → d-dimer, 2/3 led to CT and US
- PE in 5.9%: segmental or more proximal
 - 11.7% in patients with suspected PE
 - 4.3% in patients without suspected PE

Le Gal G, Ann Intern Med. 2006;144:165

Social determinants of health

- Current smoking
- Low SES, income
- Air pollution
- Housing, indoor exposures
- Medication non-adherence
 - Inhaler technique
 - Polypharmacy
 - Triple therapy inhalers ~\$600 /30d



Hogea SP, Clin Respir J 2019; Pasquale CB, JCOPDF 2021; Williams PJ, BMJ Open Respir Res 2022
<https://www.gskforyou.com/gsk-pricing-information/>
<https://www.breztri.com/cost-affordability.html>

*Case # 2

68M presents to the ED with a COPD exacerbation. He is treated with nebulized albuterol/ipratropium and supplemental O₂ via nasal cannula.

ABG: pH 7.32, PaCO₂ 55 mmHg, PaO₂ 100 mmHg, SaO₂ 99% on 6 lpm O₂

Which of the following will reduce his risk of mortality?

- A. Prednisone 40 mg daily
- B. Azithromycin x 5 days
- C. Bilevel positive airway pressure (BiPAP)
- D. Reducing supplemental O₂ to keep SaO₂ 89-93%
- E. Intubation and mechanical ventilation

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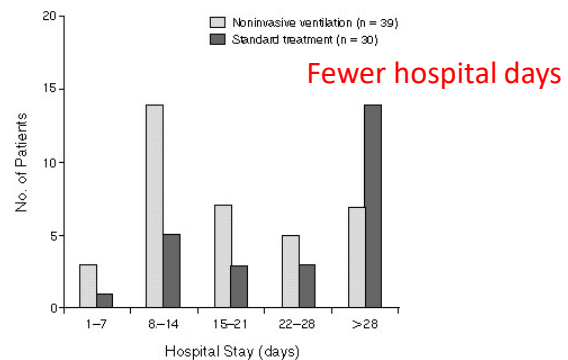
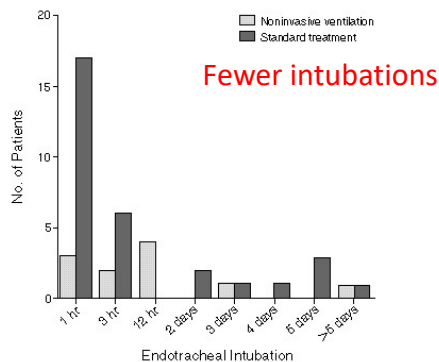
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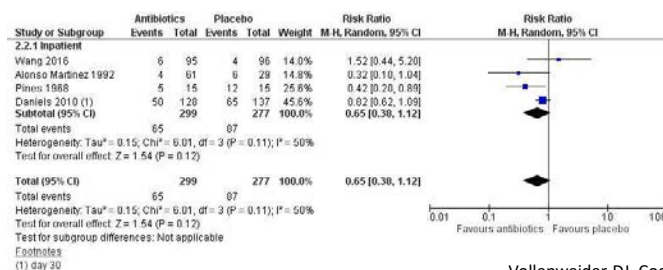
Non-invasive ventilation for AE-COPD

- Acute hypercapneic respiratory failure
 - RR > 25-30
 - Respiratory acidosis: pH < 7.35
- *Caution in severe acidosis, altered mental status, hemodynamic instability*



Brochard, NEJM 1995

Exacerbations treatment: Antibiotics



Vollenweider DJ, Cochrane Database Syst Rev 2018:CD010257

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

Exacerbations treatment: Systemic steroids

Benefits:

- ↓ treatment failure, symptoms, LOS
- ↑ FEV₁

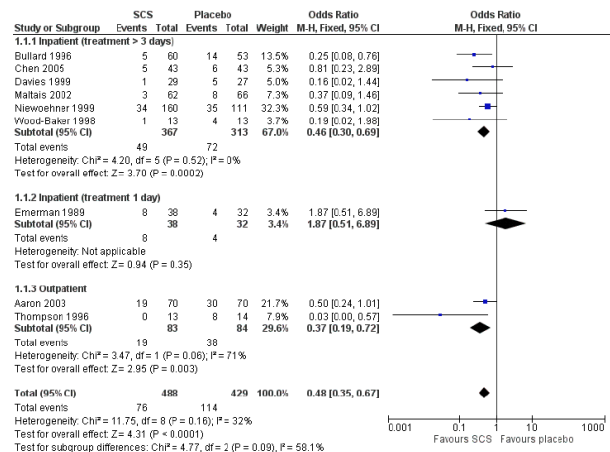
Dose/duration:

Benefit of lower doses

No difference in oral vs IV

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

Side effects: hyperglycemia, etc.



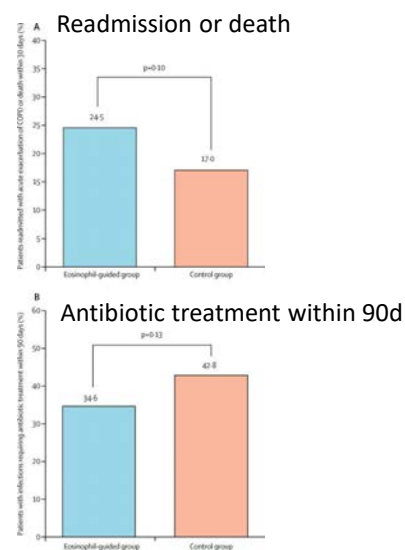
Walters JAE, Cochrane Database Syst Rev 2014;CD001288.

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

- Inpatients (Denmark) n=318
 - All received IV steroids x 1 dose
 - Oral steroids only if daily BEC ≥ 300
 - 5 days max
- Non-inferior
 - Days alive out of hospital (at 14d)
 - Readmission
- Mean 2 vs 5 days of steroids
 - Lower cumulative dose
 - Improved diabetes control
- Similar non-inferiority in UK outpatients



Sivapalan P, Lancet Respir Med 2019; Ramakrishnan S, Lancet Respir Med 2024

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*Case #3

You are discharging a 70F after a COPD exacerbation. At baseline, she has daily cough and sputum and has to stop walking after a few minutes. She uses supplemental oxygen at 2 lpm. She was treated with antibiotics for acute bronchitis 6 months ago. Her last FEV₁ was 45% predicted. She still smokes. Which of the following is her strongest risk factor for a COPD exacerbation in the next year?

- A. Chronic bronchitis symptoms
- B. FEV₁ < 50% predicted
- C. History of two or more exacerbations in the past year
- D. Use of supplemental O₂
- E. Current smoking

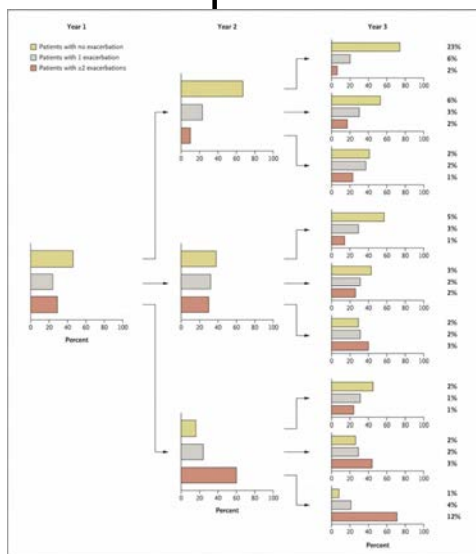
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- B. FEV₁ < 50% predicted
- C. History of two or more exacerbations in the past year
- D. Use of supplemental O₂
- E. Current smoking

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



High risk:

2 or more exacerbations in previous year, or
1 or more hospitalizations

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



Global Strategy for Diagnosis, Management and Prevention of COPD

Classification of Severity of Airflow Limitation in COPD*

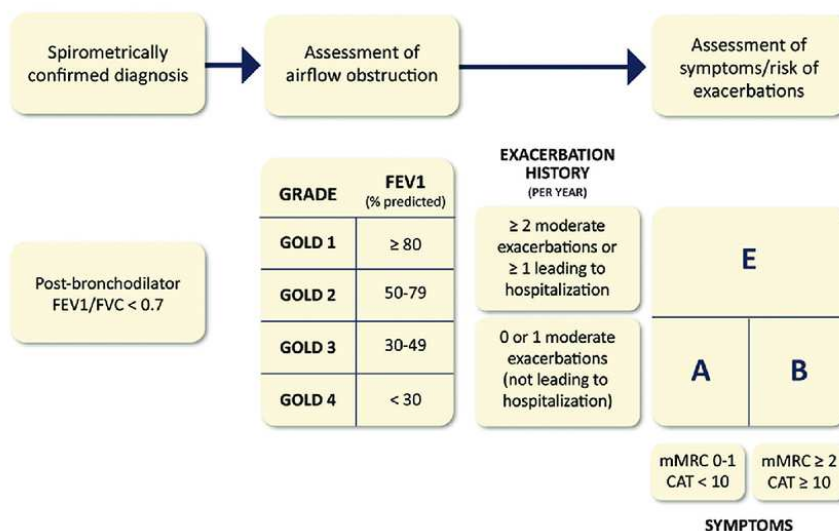
In patients with $FEV_1/FVC < 0.70$:

- 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*

© 2014 Global Initiative for Chronic Obstructive Lung Disease

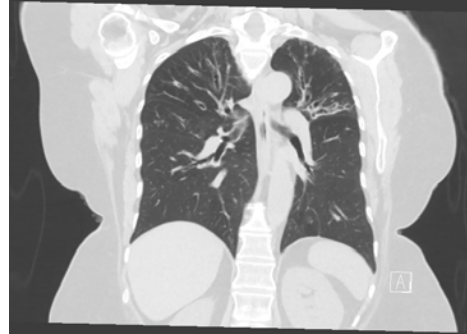
GOLD ABE Assessment Tool



www.goldcopd.org

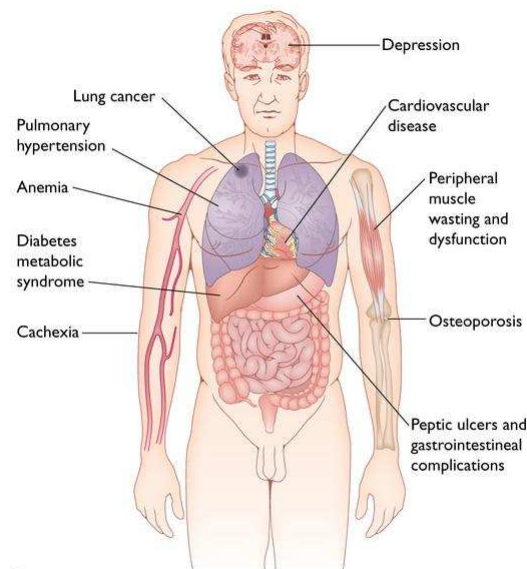
Other assessments

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



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

Comorbidities: COPD is a systemic disease



Crapo J, ed.,
Atlas of COPD, 2009

© Current Medicine

*Case #4

A 65 year old male current smoker with presents with cough and exertional dyspnea (MMRC 2). He had one exacerbation last year. Spirometry: FEV_1 55% predicted, FEV_1/FVC 0.6.

Appropriate treatments include:

- A. LABA+LAMA inhaler
- B. Triple therapy inhaler (LABA+LAMA+ICS)
- C. Nicotine replacement therapy
- D. All of the above
- E. (A) and (C) only

Case #4

A 65 year old male current smoker with presents with cough and exertional dyspnea (MMRC 2). He had one exacerbation last year. Spirometry: FEV_1 55% predicted, FEV_1/FVC 0.6.

Appropriate treatments include:

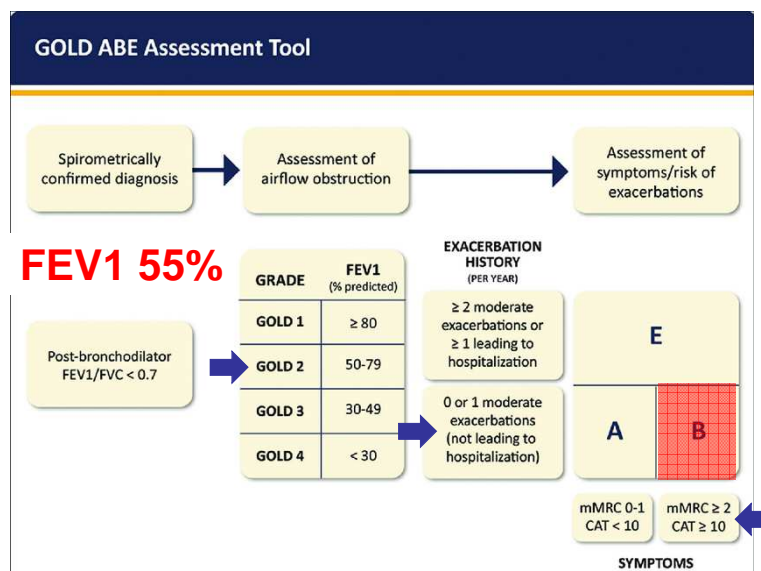
- A. LABA+LAMA inhaler
- B. Triple therapy inhaler (LABA+LAMA+ICS)
- C. Nicotine replacement therapy
- D. All of the above
- E. (A) and (C) only

COPD treatment: overview

- Goals of treatment
 1. Reduce symptoms
 2. Reduce risk
- Smoking Cessation
- Supplemental oxygen
- Pulmonary Rehabilitation
- Vaccinations
 - Influenza, Pneumococcal, COVID-19, RSV

Poole PJ, Cochrane Database Syst Rev 2006; Dransfield MT, AJRCCM 2009;180:499;
Kobayashi M, MMWR 2022;71:109

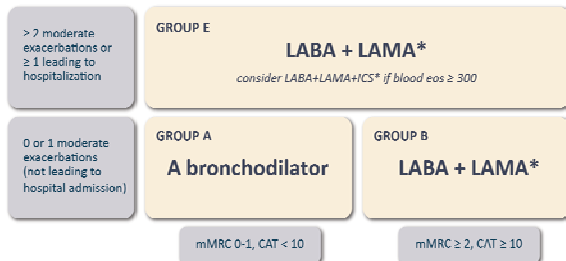
GOLD grade 2, group B



COPD pharmacotherapy

Initial Pharmacological Treatment

Figure 4.2



*Single inhaler therapy may be more convenient and effective than multiple inhalers

www.goldcopd.org

Bronchodilators are first-line

Long-acting: LABA or LAMA

Dual bronchodilators: LAMA+LABA

Short-acting bronchodilators in all patients

Targeted use of inhaled corticosteroids

GOLD E, blood eosinophils ≥ 300

Triple therapy: LABA+LAMA+ICS

Risk of pneumonia

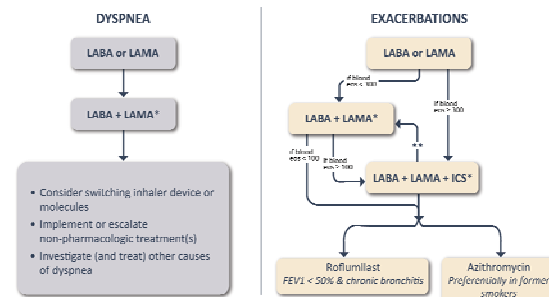
Qaseem, Ann Intern Med 2011; Tashkin, NEJM 2008; Rodrigo, Int J COPD 2017; Calverley, NEJM 2007; Ernst, AJRCCM 2007; Magnussen, NEJM 2014

Follow-up algorithm

Follow-up Pharmacological Treatment

Figure 4.4

- 1 IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
- 2 IF NOT:
 - Check adherence, inhaler technique and possible interfering comorbidities
 - 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 ARF assessment, a) diagnosis



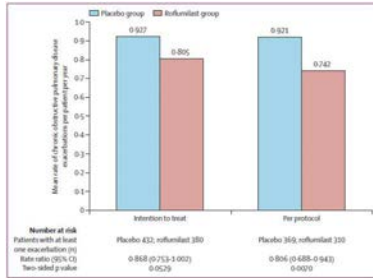
*Single inhaler therapy may be more convenient and effective than multiple inhalers

**Consider de-escalation of ICS if pneumonia or other considerable side effects. In case of blood eos ≥ 300 cells/ μ l de-escalation is more likely to be associated with the development of exacerbations

www.goldcopd.org

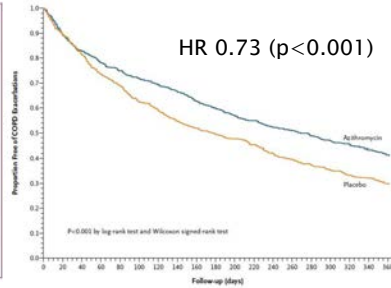
Oral therapies to decrease exacerbation risk

Roflumilast



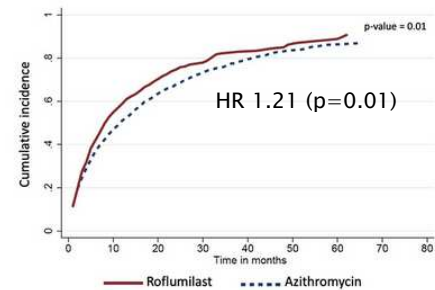
Severe COPD (FEV₁<50%)
chronic bronchitis
exacerbation history
GI side effects

Azithromycin 250mg daily



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

Comparison



VA database study:
Prefers azithromycin

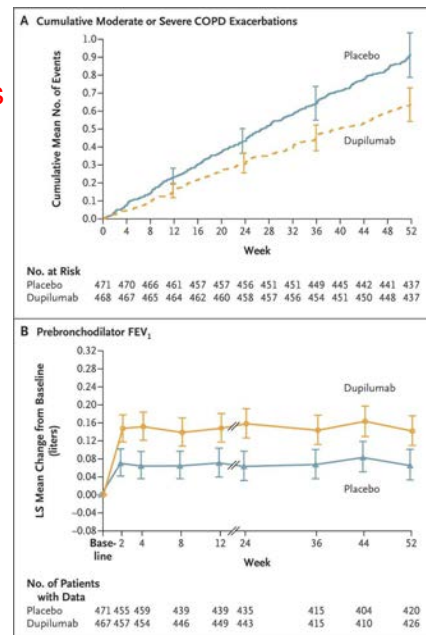
Martinez, Lancet 2015;385:857
Albert, NEJM 2011;365:689
Lam, JCO 2021;39:450

Dupilumab

- Anti-IL4/13 mAb
 - FEV₁ 30-80%
 - Blood eos ≥ 300
 - Exacerbation history
 - On LABA/LAMA/ICS
- 300mg sc q2wks vs. placebo

Reduced
exacerbations
RR 0.70

Improved
FEV1

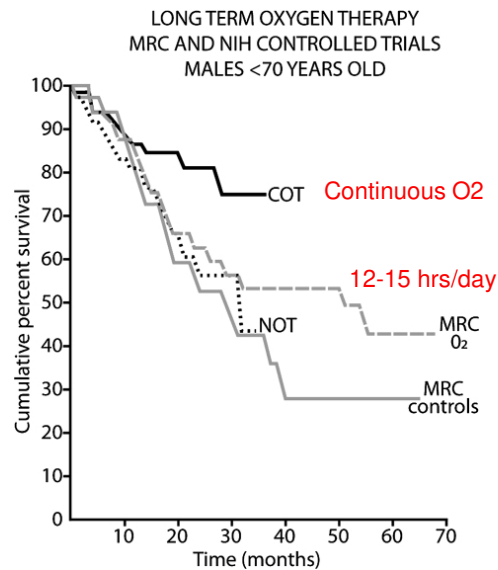


Bhatt SP, NEJM 2023;389:205

Supplemental oxygen reduces mortality in hypoxemic COPD patients

Criteria, at rest:

- $\text{PaO}_2 \leq 55 \text{ mmHg}$ or $\text{SaO}_2 \leq 88\%$, or
- $\text{PaO}_2 \leq 60 \text{ mmHg}$ or $\text{SaO}_2 \leq 89\%$,
 - with cor pulmonale, right heart failure or polycythemia

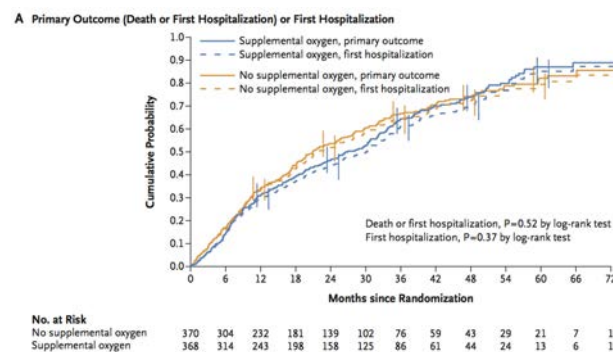


Stoller J, Chest 2010

Long Term Oxygen Treatment Trial

NEJM 2016;375:1617-27

- 1) Moderate hypoxemia
 - SpO_2 89-93%
 - Randomized to 24 hr O₂
- 2) Exertional hypoxemia
 - $\text{SpO}_2 < 90\%$
 - Randomized to O₂ with exercise and sleep



No difference in death or hospitalization

No change in secondary outcomes:

- exercise capacity, quality of life, exacerbations, lung function

Long-Term Noninvasive Ventilation in Chronic Stable Hypercapnic Chronic Obstructive Pulmonary Disease

An Official American Thoracic Society Clinical Practice Guideline

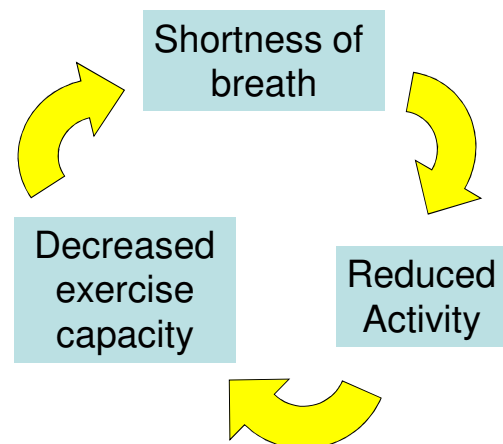
Madalina Macrea, Simon Oczkowski, Bram Rochweg, Richard D. Branson, Bartolome Celli, John M. Coleman III, Dean R. Hess, Shandra Lee Knight, Jill A. Ohar, Jeremy E. Orr, Amanda J. Piper, Naresh M. Punjabi, Shilpa Rahangdale, Peter J. Wijkstra, Susie Yim-Yeh, M. Bradley Drummond, and Robert L. Owens; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

- Hypercapnic respiratory failure: $\text{PaCO}_2 > 45 \text{ mmHg}$
- Suggest nocturnal NIV
 - Stable, not exacerbation
 - Screen for OSA prior to starting
 - Target normal PaCO_2
- Benefit: improve QoL, possibly reduce exacerbations and mortality
- Barriers to implementation

AJRCCM 2020;202:e74-87

Pulmonary Rehabilitation

- Multidisciplinary
- 6-12 weeks outpatient
 - 2-3 times/week
- Exercise
 - Lower body
 - Upper body
 - Respiratory Muscle Training
- Education
- Psychosocial Support



Spruit MA, AJRCCM 2013;188:e13

*Case #5

You are discharging a 72F with stable COPD (FEV₁ 55%, GOLD B) after an acute MI, treated with PCI. Her LV function is normal.

In addition to anti-platelet therapy, statin, and ACE-inhibitor, which of the following would you prescribe?

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

Case #5

You are discharging a 72F with stable COPD (FEV₁ 55%, GOLD B) after an acute MI, treated with PCI. Her LV function is normal.

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

Managing comorbidities

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

Metoprolol

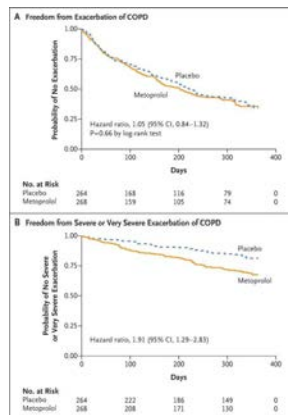
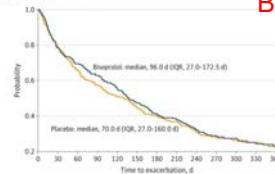


Figure 3. Freedom From Exacerbation of Chronic Obstructive Pulmonary Disease in the 2 Trial Groups

Bisoprolol



Cardioselectivity: β_1/β_2 ratio

Bisoprolol 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

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*Case #6

A rapid response is called on a 66yo F who underwent bronchoscopic lung volume reduction with LUL endobronchial valves earlier today. She is tachypneic and tachycardic, SaO₂ 88% on 6 lpm nasal cannula.

The most likely cause of her acute worsening is:

- A. Aspiration
- B. Reaction to general anesthesia
- C. COPD exacerbation
- D. Pneumothorax
- E. Pulmonary embolism

Case #6

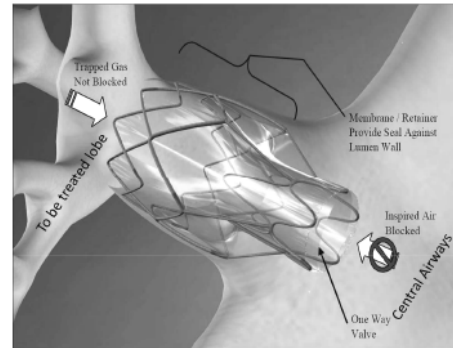
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Surgical or interventional treatments for COPD

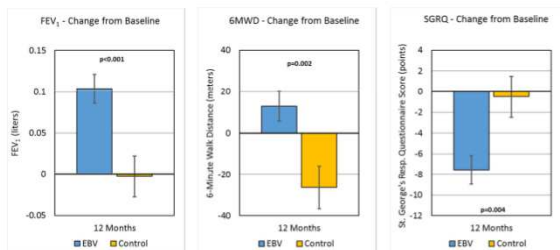
- Lung volume reduction
 - Reduce hyperinflation
 - Improve respiratory mechanics
- Surgical
 - Upper lobe predominant
 - Low exercise capacity
- Bronchoscopic valves
- Lung transplantation



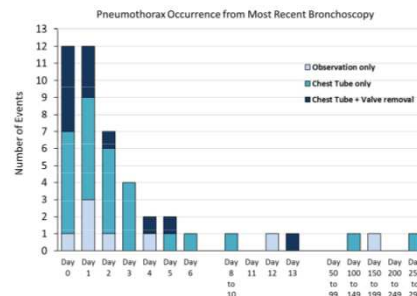
NETT, NEJM 2003;348:2059
 *Klooster K, NEJM 2015;373:2325
 Davey C, Lancet 2015;386:1066
 Yusen R, J Heart Lung Transplant 2015;34:1264

Bronchoscopic Lung Volume Reduction

- Severe airflow obstruction with emphysema
- Hyperinflated lung volumes



- Improvement in lung function, exercise capacity, quality of life
- Carefully selected patients



- Pneumothorax in 25%
- Most within 2-3 days

Criner, AJRCCM 2018;198:1151

Outline

- COPD exacerbations
- Assessment of stable COPD
- Treatment of stable COPD
 - Preventing exacerbations
- Lung volume reduction
- New concepts in COPD diagnosis

*Case #7

You are discharging a 70M former smoker admitted for “COPD exacerbation”.

At baseline, he has daily cough, sputum, and exertional dyspnea.

Work-up in the past year:

Spirometry: normal

Blood eosinophil count 50

Lung screening CT scan: 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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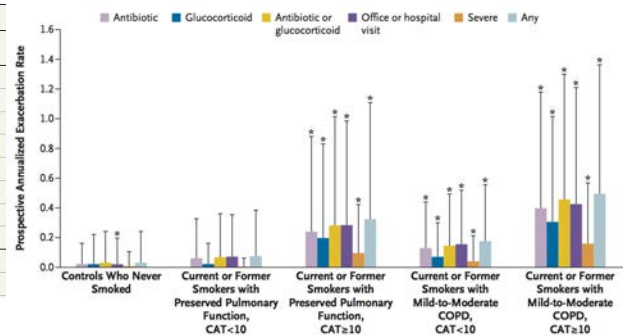
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Current/former smokers with normal spirometry

Variable	No. (%)	Never Smokers (n = 108)	GOLD 0 (n = 4288)	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



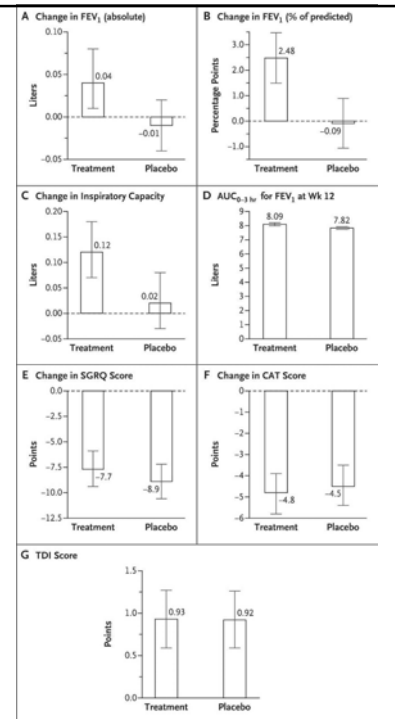
Increased exacerbation risk

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



Summary: COPD exacerbations

- No objective definition or biomarkers
 - Consider differential diagnosis
- Treatment
 - Oxygen and bronchodilators
 - Antibiotics and systemic steroids have small effects
 - Non-invasive ventilation in hypercapneic respiratory failure

Summary: Stable COPD

- Multidimensional assessment
 - symptoms and exacerbation risk
- Assessment and management of comorbidities
- Non-pharmacologic treatments
 - Smoking cessation
 - Pulmonary rehab
 - Vaccines
 - Supplemental O₂ - not clearly beneficial for exercise induced desaturation

Summary: Stable COPD (2)

- COPD medications
 - Bronchodilators are first line therapy: LAMA-LABA
 - Inhaled steroids are add-on - elevated blood eosinophils
 - Daily azithromycin or roflumilast for frequent exacerbators
- Lung volume reduction
 - Selected patients, specialized centers
- 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.