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Advanced COPD:

Evidence-based Approaches to Our Sickest Patients

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Disclosures or Conflicts of Interest: None

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Agenda/Learning Objectives

- Review the Clinical Features and prognostic indicators of advanced COPD, including tools for assessing disease severity and trajectory
- Discuss evidence-based pharmacologic and non-pharmacologic therapies for symptom control in late-stage disease
- Identify strategies for interprofessional collaboration to improve care transitions, reduce exacerbations, and support patient self-management in COPD

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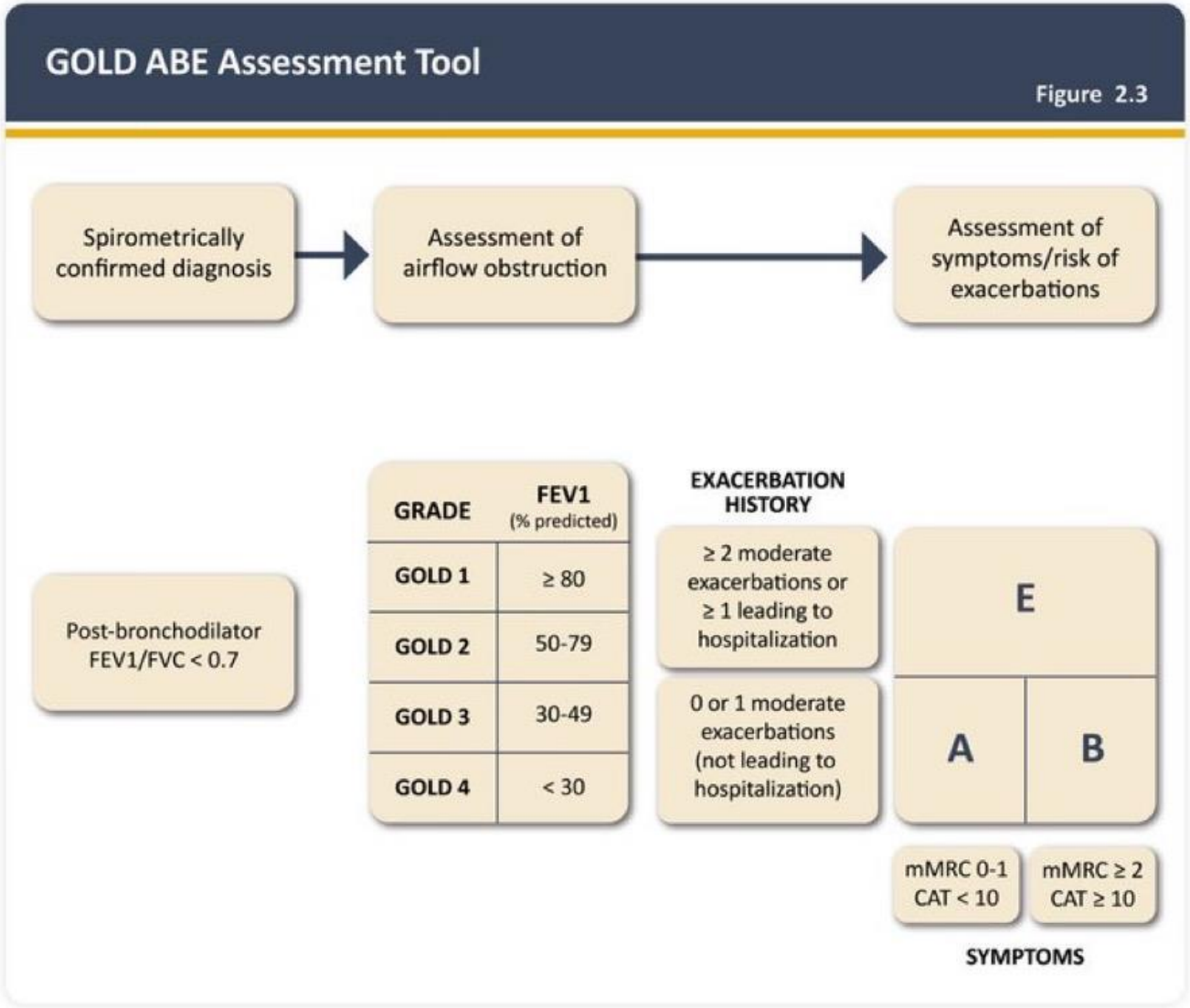
COPD Assessment

1. Assess degree of airflow limitation
   - Spirometry and PFTs. For patient's with severe disease, reasonable to repeat at least annually, and more frequently for patients with progressive symptoms or frequent exaccerbations/hospitalizations.
   - Also for patients with more severe disease, consider referral for formal PFTs, as DLCO and lung volumes are often qualifications for transplant or advanced surgical/valve interventions
2. Assess symptoms
   - COPD Assessment Test (CAT)
   - Modified Medical Research Council (mMRC)
3. Assess history of moderate/severe exacerbations
4. Assess comorbidities

GOLD Combined Assessment for COPD



Assess Degree of Airflow Limitation Using Spirometry

- In patients with $FEV_1/FVC < 0.70$

GOLD Stage	Classification	FEV1
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$
GOLD 4	Very Severe	$FEV_1 < 30\%$ predicted

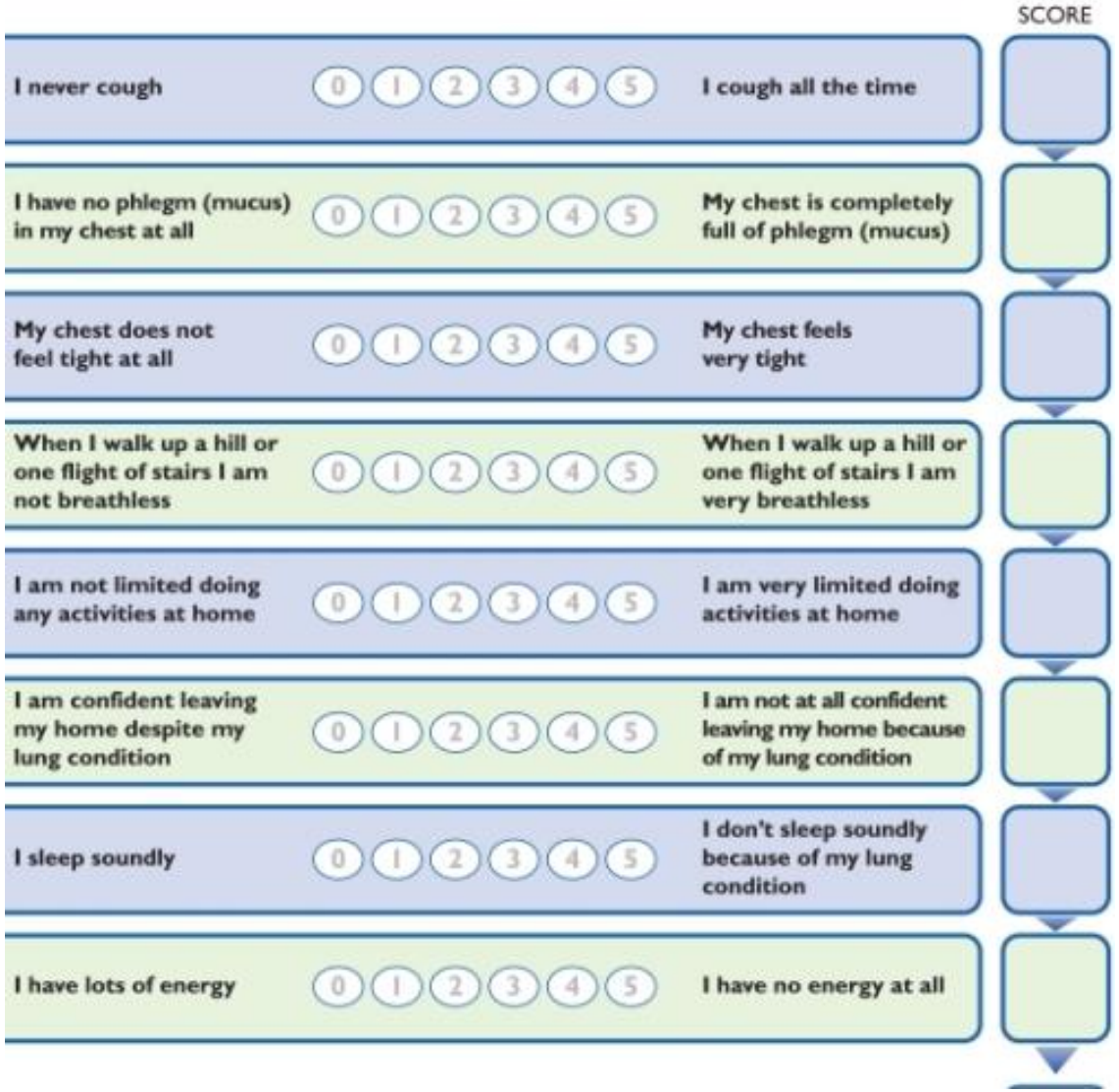
Assess Symptoms: Modified Medical Research Council (mMRC)

- mMRC 0-1 = Less Symptoms
- mMRC ≥2 = More Symptoms

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

Fletcher CM. *BMJ* 1960;2:1662

Assess Symptoms: COPD Assessment Test (CAT)



<10 = Less Symptoms

≥10 = More Symptoms

Predictors of Mortality in COPD

- BODE Index

Points	Approximate 4 Year Survival
0-2	80%
3-4	67%
5-6	57%
7-10	18%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease

Bartolome R. Celli, M.D., Claudia G. Cote, M.D., Jose M. Marin, M.D., Ciro Casanova, M.D., Maria Montes de Oca, M.D., Reina A. Mendez, M.D., Victor Pinto Plata, M.D., and Howard J. Cabral, Ph.D.

Table 2. Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*

Variable	Points on BODE Index			
	0	1	2	3
FEV_1 (% of predicted)†	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale‡	0–1	2	3	4
Body-mass index§	>21	≤21		

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Identify strategies for interprofessional collaboration to improve care transitions, reduce exacerbations, and support patient self-management in COPD

> I have maximized all inhalers, ensured appropriate inhaler technique and my patient remains symptomatic or continues to exacerbate…

Evaluate for Co-Morbid Conditions

- Other pulmonary process: asthma, bronchiectasis, lung cancer
- Environmental allergies
- Gastroesophageal reflux
- Chronic rhinosinusitis
- Dysphagia/aspiration
- Immune deficiency
- Coronary heart disease or congestive heart failure
- Pulmonary hypertension
- Cardiac arrhythmia
- Thromboembolic disease
- Sleep disordered breathing

Acute Exacerbations of COPD

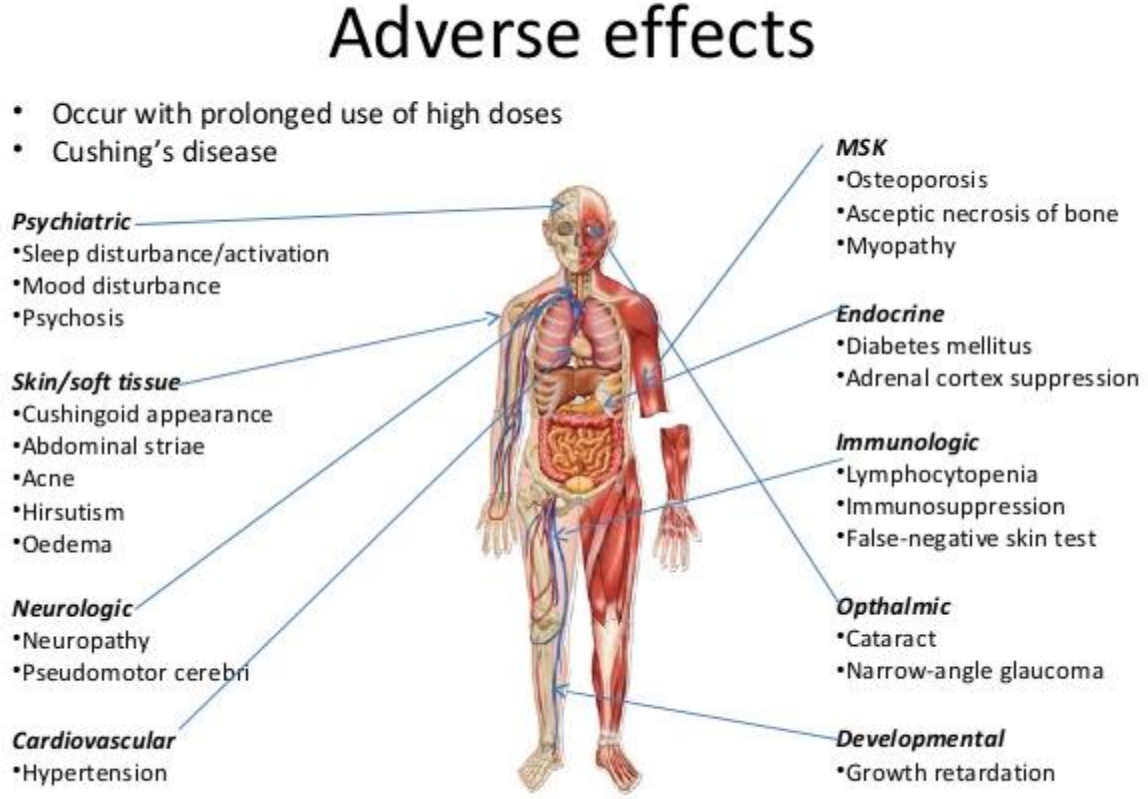
- Increased respiratory symptoms (cough, dyspnea, sputum production, purulent sputum, wheezing) resulting in additional therapy
- Classification:
  - Mild: Short acting beta agonists (i.e. albuterol)
  - Moderate: short acting beta agonists + antibiotics and/or steroids
  - Severe: Hospitalization or ER visit
- Etiology: URI, noxious inhalation, non-compliance w/ meds, bad inhaler technique, upper airway cough syndrome/post-nasal drip, GERD, CHF/arrhythmia, PE?
- Reminder, patients are considered frequent exacerbators by having 2 outpatient exacerbations requiring steroids/antibiotics, or 1 inpatient hospitalization

COPD Exacerbations

- Treatment
  - Oxygen (goal Spo2 88-92%)
  - Inhaled short-acting bronchodilators
  - Antibiotics 5-7 days (fluoroquinolones, macrolides)
    - Shorten recovery time, reduce risk of early relapse, treatment failure and hospital LOS
  - Systemic steroids 5-7 days
    - Improve lung function (FEV_1), oxygenation, and shorten recovery time and hospital LOS
  - NIV if respiratory acidosis (hold if obtunded, vomiting, secretions)
    - Improves gas exchange, reduces work of breathing and the need for intubation, decrease hospital LOS and improves survival
  - Consider concurrent comorbidities and treatments, like diuresis, arrythmia control, or if PE, anticoagulation
  - **Patients with advanced COPD may have difficulty generating inspiratory efforts for MDI, consider nebulized medications as less technique dependent**

Systemic Glucocorticoids

- Good for acute exacerbations (~5 day course typically, though you will at times see tapers used in select patients)
- Chronic use associated with increased M&M
- **NOT** recommended for chronic COPD



Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

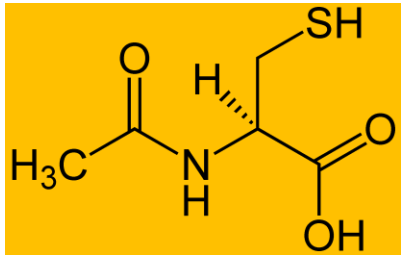
The REDUCE Randomized Clinical Trial

- Double blind, placebo-controlled, non-inferiority trial (n=314)
- Patients presenting to ER in AECOPD and admitted to the hospital
- 40 mg prednisone daily for 5d vs. 14 d
- Outcome: Time to exacerbation within 180d
- 37.2% re-exacerbation in the 5d
- 38.4% re-exacerbation in the 14d

JAMA, June 5, 2013—Vol 309, No. 21

Methylxanthines (i.e. Theophylline)

- Modest bronchodilator effect and provides symptomatic relief
- Can be added as additional therapy in any GOLD stage of COPD
- Rx: low dose theophylline 100-600 mg/day
- Less effective than inhaled bronchodilators
- Less well tolerated, liver metabolism, many medication interactions, monitor drug levels, and has fallen somewhat out of favor in recent years given better tolerated alternatives.



Mucoactive Agents

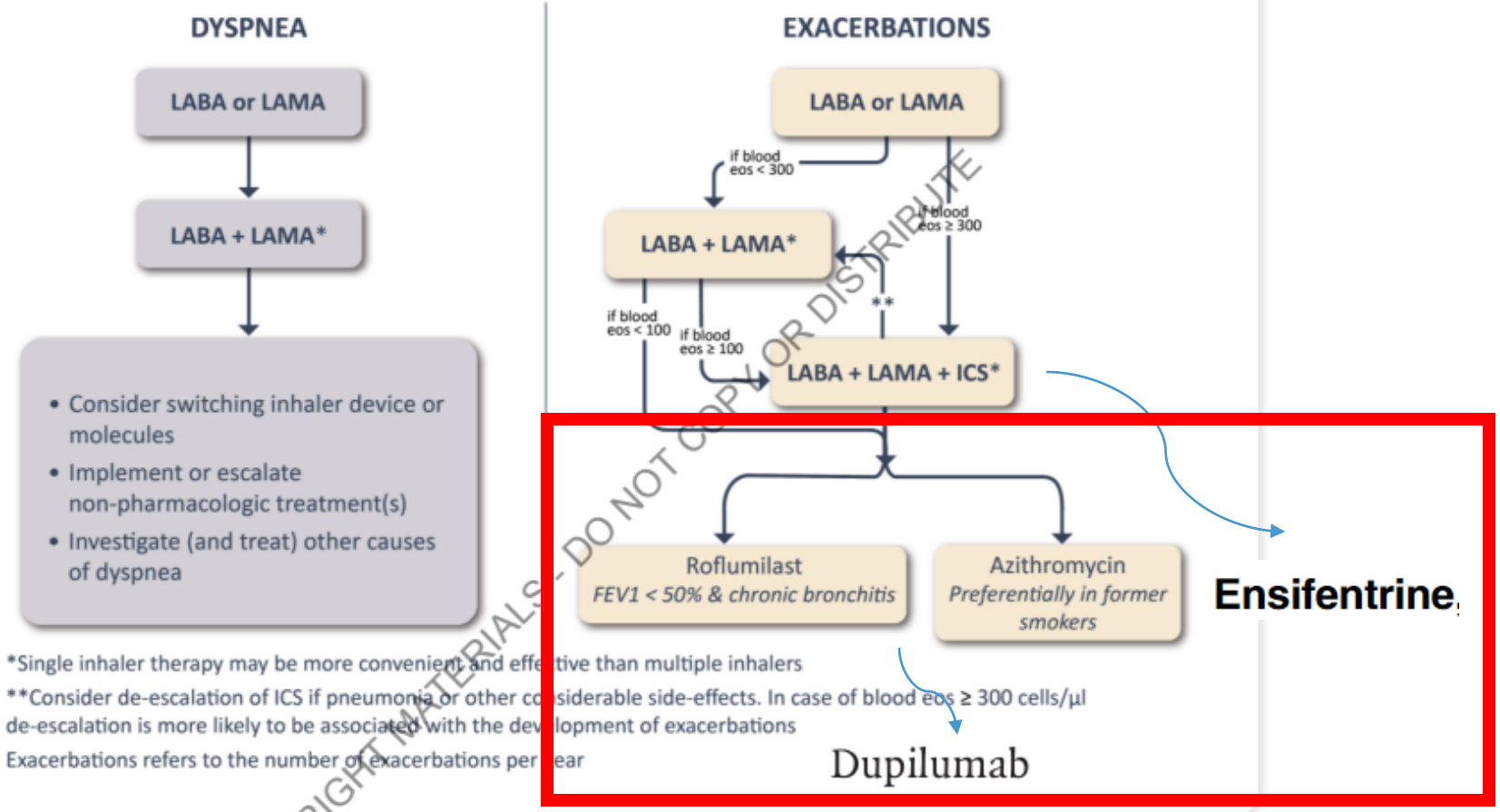
- N-acetylcysteine 600 mg PO twice daily can reduce risk of exacerbations in patients with moderate to severe COPD and more chronic bronchitis/sputum symptoms*
- Do NOT use inhaled NAC→ bronchospasm
- Oral expectorants (i.e. guaifenesin) limited benefit
- Dornase alfa (DNAse) has not been adequately studied
- Hydration, nebulized water, hypertonic saline without benefit

*PANTHEON Study. *Lancet Respir Med* 2014;2(3):187-94

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 ABE assessment at 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/µl de-escalation is more likely to be associated with the development of exacerbations

Exacerbations refers to the number of exacerbations per year

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

- RCT, n=1557
- >40, COPD with FEV_1<80%, history of exacerbations or O2 dependent
- Azithromycin 250 mg daily vs. placebo + usual care for 1 year (though in practice we also dose 500 mg MWF)
- Decreased median time to first exacerbation
- Decreased frequency of exacerbations
- Improved quality of life
- Decrease in nasopharyngeal colonization with respiratory pathogens, but increased colonization with macrolide-resistant organisms
- NO effect on exacerbation or pneumonia rates
- Some increased hearing decrement in the azithromycin arm 5%

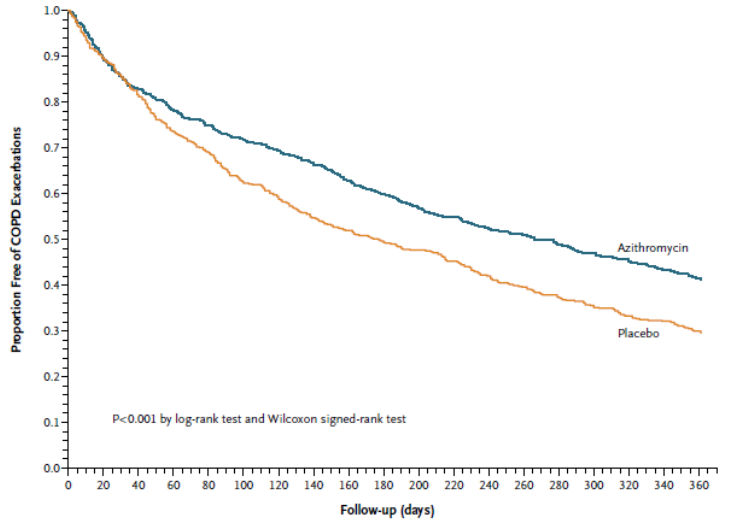


Figure 2. Proportion of Participants Free from Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) for 1 Year, According to Study Group.

N Engl J Med 2011;365:689-98.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 20, 2023 VOL. 389 NO. 3

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

S.P. Bhatt, K.F. Rabe, N.A. Hanania, C.F. Vogelmeier, J. Cole, M. Bafadhel, S.A. Christenson, A. Papi, D. Singh, E. Laws, L.P. Mannent, N. Patel, H.W. Staudinger, G.D. Yancopoulos, E.R. Mortensen, B. Akinlade, J. Maloney, X. Lu, D. Bauer, A. Bansal, L.B. Robinson, and R.M. Abdulai, for the BOREAS Investigators*

- Dupilumab, 300 mg every other week vs. placebo
- IL-4 receptor mAb
- Add on therapy in patients with refractory eosinophilic (>300) COPD inadequately controlled on standard therapies
- *more biologics on the way

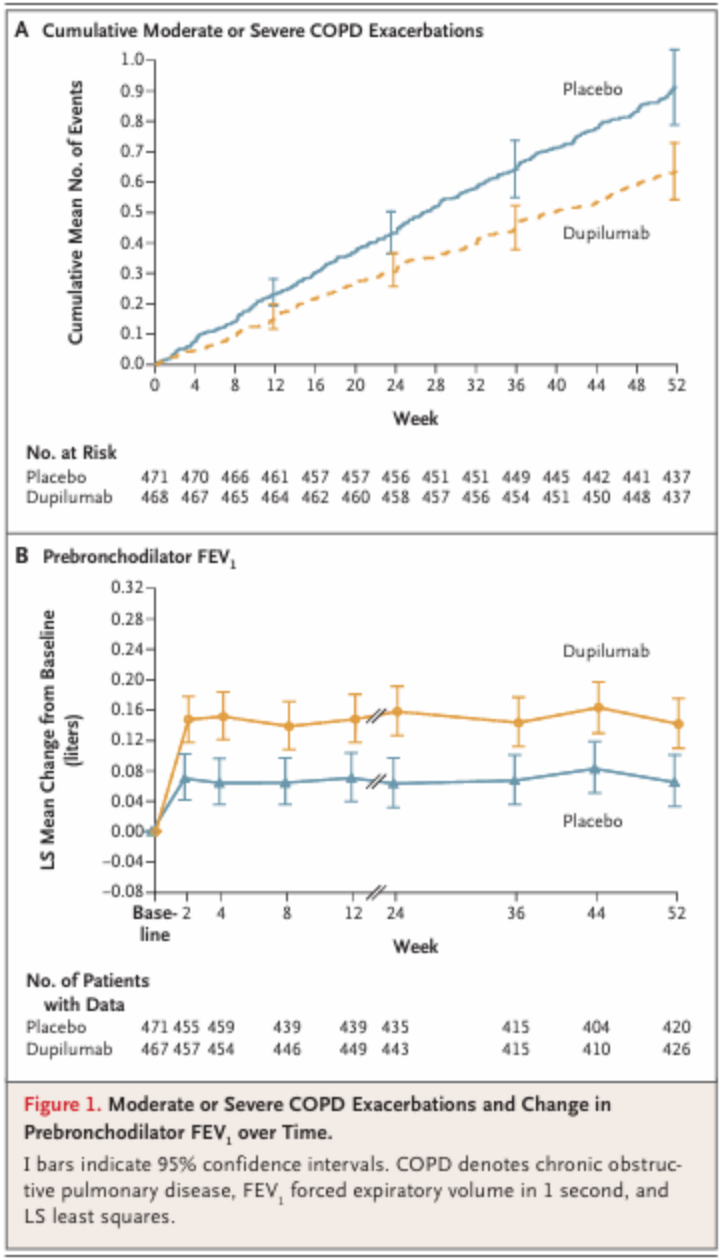


Figure 1. Moderate or Severe COPD Exacerbations and Change in Prebronchodilator FEV_1 over Time.

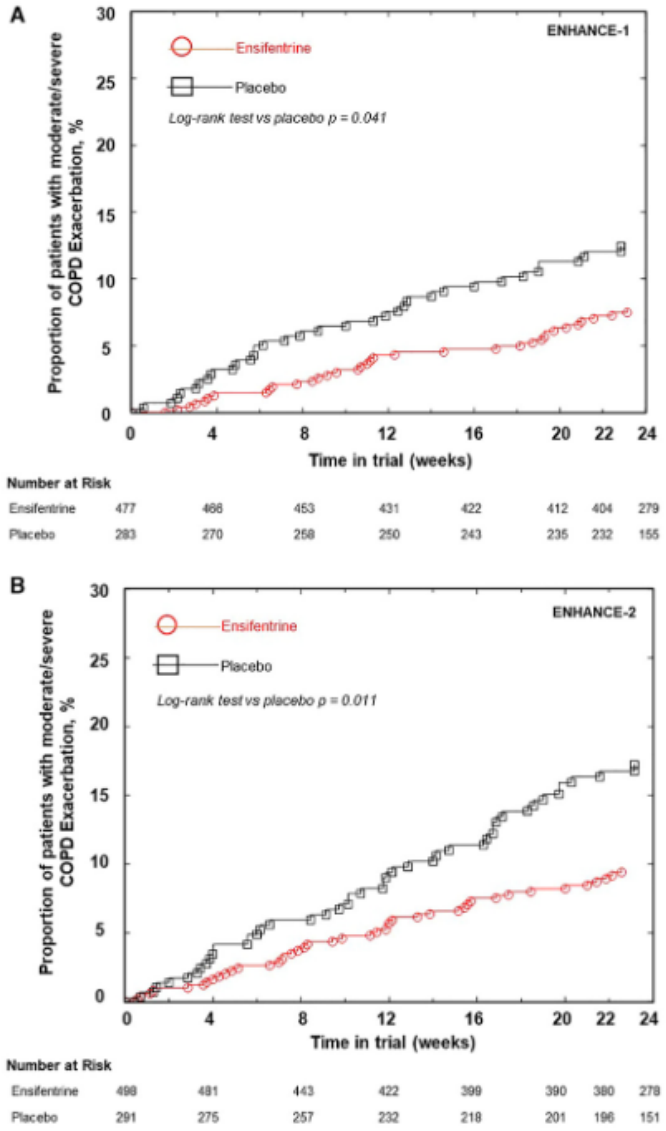
I bars indicate 95% confidence intervals. COPD denotes chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, and LS least squares.

Roflumilast (Daliresp, Daxas, Zoryve, etc)

- PDE4-inhibitor, PO (500 mg, start at 250mg)
- Decreases inflammation and promote smooth muscle relaxation by inhibiting the breakdown of intracellular cyclic AMP
- Reduces exacerbations in:
  - Severe to very severe COPD patients with:
    - Recurrent exacerbations and
    - Chronic bronchitis phenotype
- Avoid in patients with unstable mood symptoms, depression, suicidality
- Other AEs: diarrhea, nausea, reduced appetite, weight loss, abdominal pain

Ensifentrine (Ohtuvayre)

- Nebulized PDE3 and PDE4 inhibitor, BID
  - Airway smooth muscle relaxation
  - Inflammatory response suppression
- Add on to LAMA or LABA with or w/o ICS but not studied on LAMA/LABA
- Improves lung function
- Improves Sx/QoL
- Reduces exacerbations

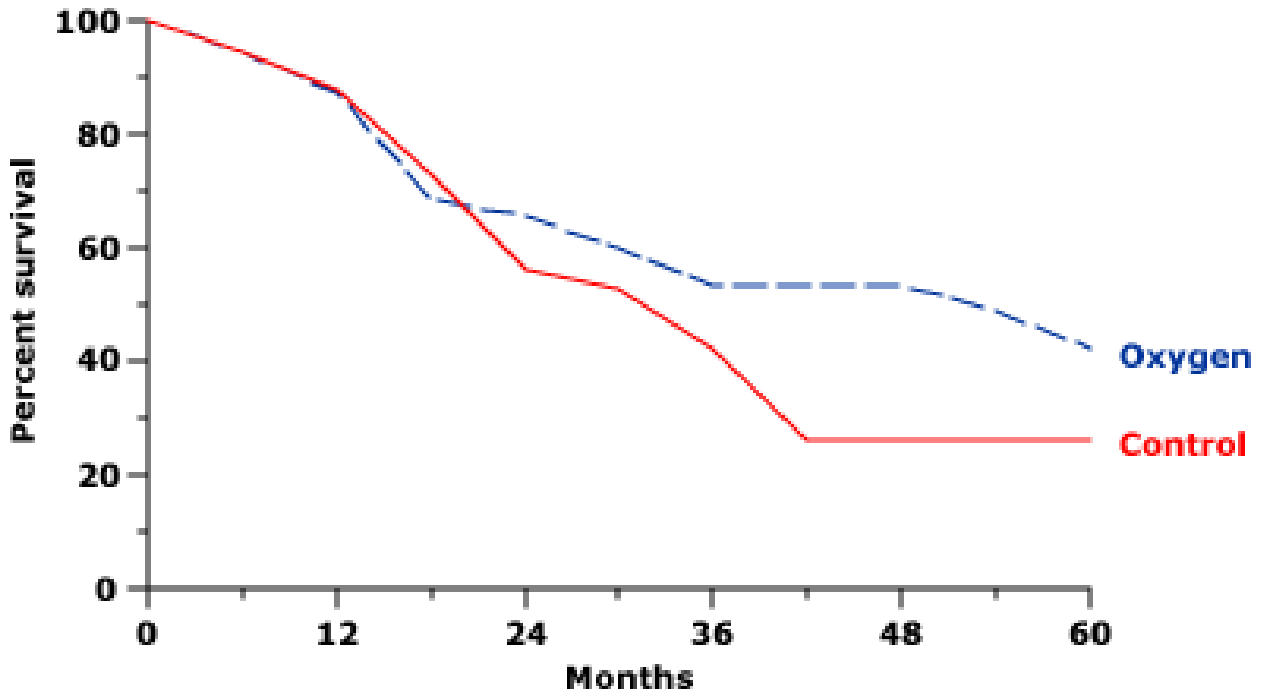


AJRCCM Vol 208 (4) Aug 15, 2023

Long Term Oxygen Therapy

- Apart from smoking cessation, the only medical therapy that improves survival in patients with COPD is oxygen
- Long term oxygen therapy when given for > 15 hours per day improved survival in patients with COPD and chronic hypoxemia, with or without hypercapnea.
  - UK LOTT, *Lancet*; 1981
  - US NOTT, *Ann Intern Med*; 1980

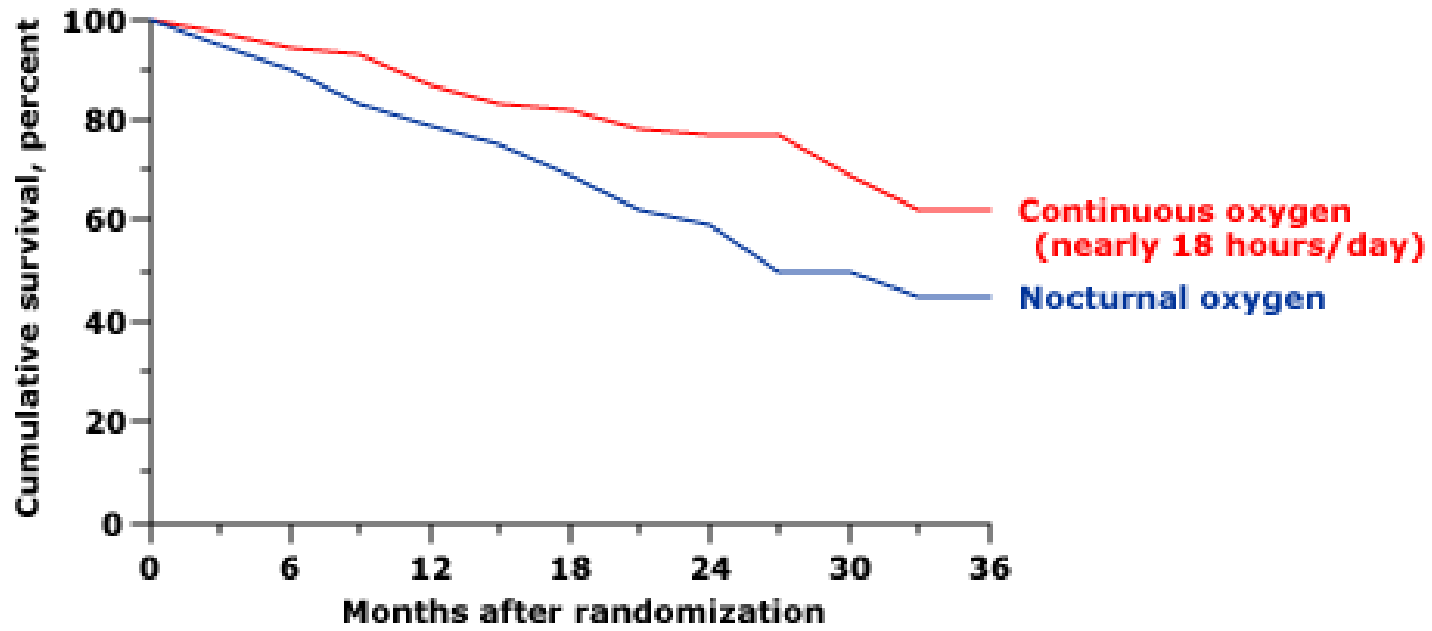
Survival benefit of long-term oxygen therapy in COPD



Medical Research Council Trial in which 87 patients with chronic obstructive pulmonary disease, severe hypoxemia, hypercapnia, and a history of heart failure were randomized to treatment with oxygen therapy for at least 15 h/day (blue dashed line) or no oxygen (red line). Continuous oxygen therapy led to a significant survival benefit.

Report of the Medical Research Council Working Party, Lancet 1981; 1:681.

Survival benefit of continuous long-term oxygen therapy in COPD



The Nocturnal Oxygen Therapy Trial randomly assigned 203 patients with chronic obstructive pulmonary disease complicated by hypoxemia to treatment with nearly continuous oxygen therapy (red line) or nocturnal oxygen alone (blue line). Continuous oxygen therapy was associated with a significant survival benefit ($p = 0.01$).
Redrawn from Nocturnal Oxygen Trial Therapy Group, Ann Intern Med 1980; 93:391.

Indications for Long Term Oxygen Therapy

- Resting PaO2 ≤ 55 or SpO2 ≤ 88%
- Resting PaO2 55-59 or SpO2 < 89% in the setting of…
  - Cor pulmonale
  - Right heart failure
  - Polycythemia with HCT > 55
- Resting Pa O2 ≥ 56 or SpO2 ≥ 89% in the setting of…
  - Desaturation with exercise
  - Sleep desaturation not corrected with CPAP/APAP
- Lung disease with severe dyspnea that responds to O2 (palliative)

* In a NEJM 2016 study, stable COPD patients with moderate resting and exercise-induced desaturation, there was no improvement in time to death or first hospitalization with long term O2 therapy

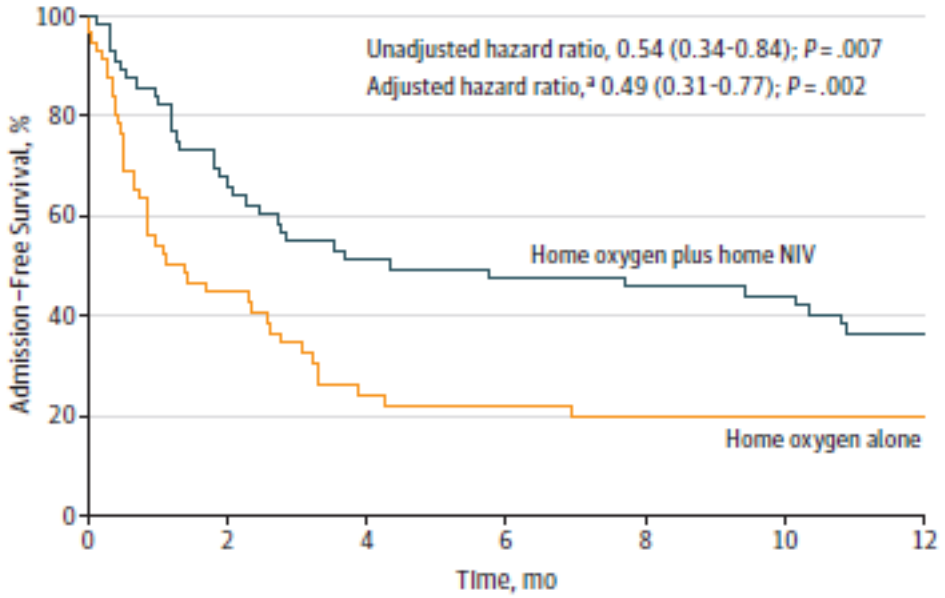
Nocturnal Non-Invasive Ventilation (NIV)

- Home non-invasive ventilation w/ oxygen vs. oxygen therapy alone following an acute COPD exacerbation w/ persistent hypercapnia
  - Included:
    - Persistent hypercapnia ($PaCO_2$ >53 mm Hg)
    - Hypoxemia (PaO_2 <55 mm Hg or <60 mm Hg; ≥1 of polycythemia, pulmonary hypertension, or cor pulmonale; >30% of sleep time with O_2 saturation <90%)
    - pH>7.30 ambient air
  - Excluded: BMI >35, OSA, other causes of respiratory failure

JAMA June 6, 2017 Volume 317, Number 21

Non-Invasive Ventilation (NIV)

Figure 2. Kaplan-Meier Survival Plot of Time to Readmission or Death From Randomization to the End of Trial Follow-up at 1 Year



No. at risk							
Home oxygen plus home NIV	57	37	28	26	25	24	16
Home oxygen alone	59	23	11	10	8	8	6

JAMA June 6, 2017 Volume 317, Number 21

- NIV prolonged time to readmission or death at 12 months

Interventional & Surgical Therapies for COPD

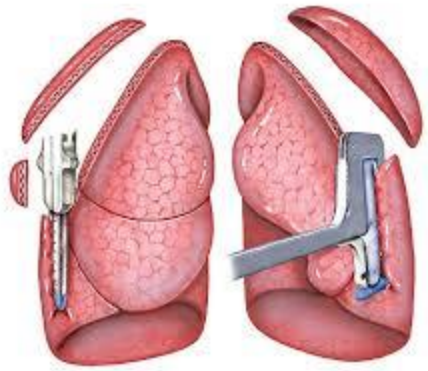
- Refer to Pulmonary or an advanced therapeutic center for evaluation for patients who may benefit
- Bullectomy
- Large airway stenting
- Endoscopic Lung Volume Reduction: endobronchial one-way valves, coils, vapor ablation, sealants, referral to Interventional Pulmonary
- Lung Volume Reduction Surgery, referral to Thoracic Surgery
- Lung Transplant. Remember workup and listing can be a prolonged process, so refer early enough for patients to work their way through the systems/consultants/committee's
- Phase 3 for chronic bronchitis: endobronchial cryospray, rheoplasty, lung denervation

The NEW ENGLAND JOURNAL of MEDICINE

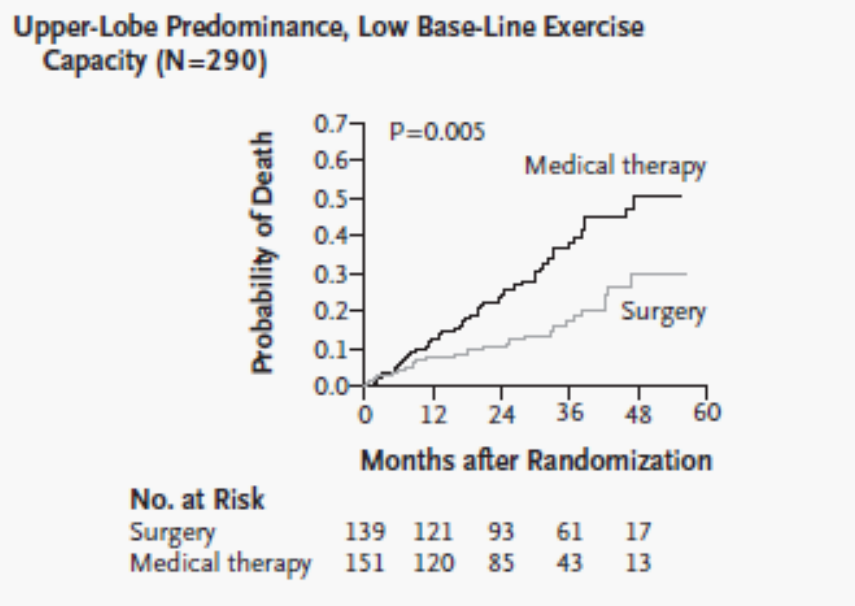
ESTABLISHED IN 1812 MAY 22, 2003 VOL. 348 NO. 21

A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema

National Emphysema Treatment Trial Research Group*



- NETT trial, n=1218, severe emphysema
- LVRS vs. medical therapy
- All patients underwent mandatory pulmonary rehab
- Survival benefit in patients with upper lobe emphysema and low exercise capacity
- Increased mortality with LVRS if FEV1 <20% or DLCO <20%



Lung Transplantation

- No mortality benefit assured
- May improve health-care QOL
- Often need to get to patient “just in time”, when they are sick enough to have benefit, but not so sick as to be too sick to transplant. Consider getting formal PFTs to check DLCO and referral to a transplant center sooner for patients you are worried about.
- Indications:
  - Progressive dyspnea despite maximal medical therapy, pulmonary rehab and oxygen
  - Not a candidate for LVRS
  - BODE Index 7-10
  - 1 or more severe exacerbations with acute hypercapnic respiratory failure (P_{CO2}>50)
  - Pulmonary hypertension and/or cor pulmonale, despite oxygen therapy
  - FEV_1 <20% or homogenous distribution of emphysema

Agenda

Review the Clinical Features and prognostic indicators of advanced COPD, including tools for assessing disease severity and trajectory

Discuss evidence-based pharmacologic and non-pharmacologic therapies for symptom control in late-stage disease

Identify strategies for interprofessional collaboration to improve care transitions, reduce exacerbations, and support patient self-management in COPD

Critical to Engage QOL and EOL Discussions Early

- Goals of care discussion, POLST forms. End-stage COPD is similar survival to an advanced stage cancer diagnosis.
- Breathlessness: chest wall vibration, fans blowing face, oxygen (if helps), opiates as palliation
- Malnourished: Nutritional supplementation
- Fatigue: **pulm rehab**, **nutrition**, CBT and mind-body interventions
- Consider referral to Palliative Care or hospice

- COPD Survival based on BODE

Points	Approximate 4 Year Survival
0-2	80%
3-4	67%
5-6	57%
7-10	18%

- Non-Small Cell Lung Cancer Survival

SEER stage	5-year relative survival rate
Localized	67%
Regional	40%
Distant	12%
All SEER stages combined	32%

Take-Aways for Frontline Providers

1. COPD patients merit an assessment of airflow obstruction (spirometry at minimum, formal PFTs with DLCO and 6 minute walk test for patients with advanced disease considering advanced interventions), symptoms, exacerbation risk, and comorbidities/mortality risk
   - Calculate BODE, and for high mortality patients, consider starting advanced directive/EOL discussions early
2. Assure appropriate inhaler technique, and consider poor inspiratory effort can compromise effectiveness, consider nebulizer meds as alternative
3. Check baseline CBC w/ diff, A1AT, bicarb (as indicator of possible chronic hypercapnia, confirm with blood gas if suspected)
4. Remember referral for pulmonary rehabilitation (GOLD B, E and post exacerbation) can have a significant improvement for patients!
5. Ensure vaccinations are up to date (influenza, COVID, pneumonia, Tdap, Shingles, RSV)

Take-Aways for Frontline Providers (continued)

6. Assess for comorbid conditions
   - Baseline EKG
   - +/- Cardiac stress test to evaluate for ischemic heart disease
   - +/- 2D ECHO to evaluate for heart failure, pulmonary hypertension
   - LDCT to screen for pulmonary malignancy if qualifies and/or LVRS candidacy
   - GERD screening, Chronic rhinitis/sinusitis screening, sleep disordered breathing screening
   - Referral for nutrition counseling and DEXA if low BMI
7. For patients with high exacerbation risk or advanced COPD unresponsive to LABA/LAMA (+/- ICS), referral to pulmonary for co-management very much appropriate. Add on therapies may be beneficial.
8. Chronic O2 supplementation the only medical therapy with mortality benefit in patients with advanced disease who qualify
9. Non-invasive ventilation may be appropriate with patients with chronic hypercapnic respiratory failure, may be suggested by chronically elevated bicarb on labs. Refer to pulm and/or sleep medicine as appropriate.
10. For patients with minimal comorbidities and advanced disease, consider referral to an advanced center for lung transplant, LVRS, or endobronchial therapies/valves. There is a window to hit, with patients sick enough to qualify but not so sick as to be poor surgical candidates.

Thank you!

Happy to answer any questions.

CME Survey