

UPDATE IN COPD EXACERBATION

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Disclosures

- Forest Pharmaceuticals (Speaker's Bureau)
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Objectives

- Recognize at risk patients for COPD exacerbations.
- Identify pharmacological therapy for patients with recurrent COPD exacerbations.
- Identify non-pharmacological therapy for patients with recurrent COPD exacerbations.

COPD & EXACERBATIONS

- Epidemiology
- Staging COPD
- Prevention
- Management

COPD

- COPD is the third leading cause of mortality
- 60-85 % patients with COPD (mostly mild/moderate severity) are undiagnosed
- \$49.9 Billion – total yearly cost related to COPD

STAGING COPD

Staging Severity of Airflow

In patients with $FEV_1/FVC < 0.70$

GOLD 1	Mild	$FEV_1 > 80\%$
GOLD 2	Moderate	$50\% < FEV_1 < 80\%$
GOLD 3	Severe	$30\% < FEV_1 < 50\%$
GOLD 4	Very severe	$FEV_1 < 30\%$

GOLD 2011 Guidelines

Figure 1. COPD Patient Staging Assessment Tool

RISK GOLD Classification	3-4	C High Risk, Less Symptoms	D High Risk, More Symptoms	≥ 2	RISK Exacerbation History
	1-2	A Low Risk, Less Symptoms	B Low Risk, More Symptoms	0-1	
		mMRC 0-1 CAT <10	mMRC ≥ 2 CAT ≥ 10		
SYMPTOMS					
<p><i>CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: Modified British Medical Research Council. Source: Reference 4.</i></p>					

Symptoms

Modified Medical Research Council (MMRC) 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

Adapted from: Fletcher CM, Elmes PC, Fairbairn MB, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. British Medical Journal 1959; 2:257.

Table 3. Pharmacotherapy by COPD Patient Stage

Stage	A	B	C	D
First-line therapy	SABA prn <i>or</i> SAMA prn	LAMA <i>or</i> LABA	ICS + LABA <i>or</i> LAMA	ICS + LABA <i>and/or</i> LAMA
Second-line therapy	LAMA <i>or</i> LABA <i>or</i> SABA + SAMA	LAMA + LABA	LAMA + LABA <i>or</i> LAMA + PDE4i <i>or</i> LABA + PDE4i	ICS + LABA <i>and</i> LAMA <i>or</i> ICS + LABA <i>and</i> PDE4i <i>or</i> LAMA + LABA <i>or</i> LAMA + PDE4i

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting beta₂ agonist; LAMA: long-acting anticholinergic; PDE4i: phosphodiesterase-4 inhibitor; prn: as needed; SABA: short-acting beta₂ agonist; SAMA: short-acting anticholinergic. Source: Reference 4.

COPD EXACERBATIONS

- 30 day mortality 3x greater than for an acute MI
- 90 day readmission rate – 35 %
- Leads to faster decline in lung function

Severity of Exacerbation

- Mild – requiring increased BD only
- Moderate – requiring systemic steroids
- Severe - requiring hospitalization

Who is at risk?

- Severe COPD (severe air flow obstruction)
- History of exacerbations (single best predictor)
- Associations with:
 - Poorer quality of life
 - Elevated WBC
 - ***GERD***

COPD EXACERBATION PREVENTION

Smoking Cessation

- ⦿ Varenicline, Bupropion, Nicotine replacement
- ⦿ Electronic cigarettes
 - Delivers nicotine vapor
 - Equal smoking cessation rates to nicotine patch
 - Trace “toxic chemicals”
 - FDA regulations likely coming soon

Smoking Cessation

● VARENICLINE

- 525 adult smokers with **stably** treated current/past major depression
- Excluded patients with untreated depression or with co-occurring psychiatric conditions
- Smoking cessation - Varenicline - 20.3 % vs placebo 10.4 %
- No differences in suicidal ideation/behavior or worsening of depression or anxiety

COPD EXACERBATION PREVENTION

- Inhaled Steroids
- Inhaled Long Acting Beta Agonists (LABA)
- Inhaled Combined LABA/Inhaled Steroid
- Inhaled Long Acting Muscarinic Agent (LAMA)

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COPD Exacerbation Prevention

- Roflumilast
- N-Acetylcysteine
- Azithromycin

ROFLUMILAST

- Oral phosphodiesterase-4 inhibitor
- Severe COPD with chronic bronchitis with h/o exacerbation
- Reduced moderate/severe COPD exacerbations by 17%/year (NNT- 4.35)
- Did not reduce hospitalizations

ROFLUMILAST

- ⦿ Dose: 500 mcg once daily
- ⦿ Contraindications: liver disease
- ⦿ Side effects
 - Weight loss (7.5 %)
 - Diarrhea (9.5%)

Calverley PMA. Lancet. 2009

Freeman. Consult Pharm. 2012

Daily Azithromycin

- Anti-inflammatory effects
- Severe COPD
 - Azithromycin 250 mg vs placebo daily for 1 year
- Azithromycin group - 25% reduction in exacerbations
 - NNT – 3 pts
- Hearing decrements more frequent in azithromycin group
- Cardiac complications of azithromycin (even 5 day course)
 - QT prolongation, Vtach, Torsades de pointes

Albert RK et al. NEJM. 2011
Ray WA. Et al. NEJM .2012

Azithromycin M, W, F

- ⦿ At least 2 COPD exacerbations in the previous year
- ⦿ QTc < 450 msec on ECG, and not taking other QTc-prolonging drugs
- ⦿ No cardiovascular disease (heart failure, coronary artery disease, PVD, CVA)
- ⦿ No hearing loss on formal audiology testing
- ⦿ Heart rate < 100 / min

Oral N-Acetylcysteine (NAC)

- ⦿ Antioxidant
- ⦿ Most previous studies were negative (600 mg **daily**)
- ⦿ Mild/moderate COPD
 - NAC 600 mg po **BID** vs placebo x 1 year
- ⦿ Improved lung function and reduction in exacerbations
 - (NAC 1/year vs placebo 1.7/year)

VACCINES

- Flu Vaccine
- Pneumococcal Vaccine
- Possible additive effect in prevention of COPD exacerbations

NONPHARMACOLOGICAL THERAPY

Pulmonary Rehabilitation

- ⦿ Comprehensive intervention
 - Education, exercise, breathing techniques
- ⦿ 6-8 weeks
- ⦿ May reduce and shorten exacerbations/health care utilization
- ⦿ Need to have follow up program to maintain benefits

LUNG VOLUME REDUCTION SURGERY (LVRS)

- National Emphysema Treatment Trial (NETT) 2003
- LVRS vs continued medical therapy
- Survival advantage
 - Upper lobe emphysema
 - Low exercise capacity
 - $FEV_1 > 20\%$ and $DLCO > 20\%$
- LVRS reduced the death rate from 0.13 deaths-per-person-year with medical management to 0.11
- 2.2 % 30 day mortality

- 30 % reduction in exacerbations in surgical cohort
- Bronchoscopic methods investigational

Treatment of COPD Exacerbation

Antibiotics

- ⦿ Not recommended for mild exacerbations
 - Not requiring hospitalization
 - Having **only one** of the three cardinal symptoms:
 - increased dyspnea
 - Increased sputum purulence
 - increased sputum production

Roede et al. EJR. 2009
GOLD Guidelines 2013

Antibiotics

- ⦿ Recommended in moderate/severe COPD exacerbations
- ⦿ In hospitalized & mechanically ventilated patients reduces mortality

Stockley et al..CHEST. 2000

Quon et al. CHEST. 2008

Procalcitonin

- Released by tissues in response to bacterial toxins
- Rises quickly as bacterial infections develop
- Does not rise in viral infections

Stolz D et al. CHEST. 2007
Scheutz et al. Cochrane Database. 2012
Tolkmn et al. ERAIT. 2011

Procalcitonin

- Using procalcitonin algorithm - antibiotics (42%)
- Standard care - antibiotics (72 %)
- Outcomes similar in both groups
 - Hospital stay, exacerbations, ICU stay, death

Length of Steroids

- ⦿ Expert guidelines: 30-40 mg prednisone for 10 -14 days
- ⦿ REDUCE TRIAL
 - 40 mg prednisone
 - **5 days vs 14 days of treatment**
 - Severe COPD exacerbations in patients with severe COPD
 - Primary end point – time to next exacerbation
 - Results: 5 days of prednisone non-inferior to 14 days

CONCLUSIONS

- COPD exacerbations are common and burdensome
- Exacerbation history is part of new COPD staging
- Inhaler therapy is cornerstone in prevention
- Roflumilast, Azithromycin, NAC can be considered in recurrent exacerbations
- Length of steroids and antibiotic coverage for exacerbations debatable

EXTRA SLIDES

of severe chronic respiratory failure. (See ["Noninvasive positive pressure ventilation in acute respiratory failure in adults"](#), [section on 'COPD exacerbation'](#) and ["Nocturnal ventilatory support in COPD"](#).)

Noninvasive positive pressure ventilation — Noninvasive ventilatory support is sometimes useful in the treatment of acute or severe chronic respiratory failure. (See ["Noninvasive positive pressure ventilation in acute respiratory failure in adults"](#), [section on 'COPD exacerbation'](#) and ["Nocturnal ventilatory support in COPD"](#).)

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Vitamin D

- ◎ The effect of high dose vitamin D supplementation on the incidence of COPD exacerbations was assessed in patients with moderate or more severe COPD who were randomly assigned to take vitamin D 100,000 IU or placebo orally every four weeks for a year [56]. The median time to first exacerbation did not differ between the groups, nor did exacerbation rates, FEV₁, hospitalization, quality of life, or death. However, patients with severe vitamin D deficiency (serum 25-[OH] D levels <10 ng/mL) at baseline had a significant reduction in exacerbations. Further research is needed to determine whether daily dosing of vitamin D supplementation for a longer period would be beneficial and whether this effect is dependent on the baseline vitamin D level