Management of COPD
Update

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Overview/Objectives

- Overview of COPD and disease impact
- Classification of COPD Severity
- Treatment Recommendations for acute exacerbations of COPD
  - Pharmacological
  - Non pharmacological
- What’s new in inhaler therapy
Survival Data in COPD Exacerbations

- COPD is the third leading cause of death in adults in USA
- Over 133,000 people died from COPD in 2009
- In 2009 COPD exacerbations lead to 8 million clinic visits, 1.5 million ER visits and 715,000 hospitalizations.
- Single best predictor of COPD exacerbation is prior history of exacerbation regardless of severity of COPD

Chest. 2015;147(4):883-893
COPD Exacerbations and Survival

The graph shows the probability of surviving over months for different categories of severe exacerbations. The categories are:

- No Severe Exacerbations
- 1-2 Severe Exacerbations
- >3 Severe Exacerbations

* indicates *p ≤ 0.05.
COPD Exacerbations and Hospitalizations

- Any COPD exacerbation requiring hospitalization predicts about a 28% mortality at 1 year.
- 20% of patients hospitalized for COPD exacerbations will be re-admitted in 30 days.
- Attempts to reduce re-admissions require much resources.
- Hospital Readmission Reduction Program penalizes hospitals for 30 day readmissions and this was extended to COPD in October 2014.
COPD Exacerbations and Readmission to Hospital.

- Randomized control trial, single center
- 172 pt randomized to standard of care vs bundle (smoking cessation counseling, screen for GERD, depression/anxiety, inhaler education, 48hr post discharge call)
- Results: 22% in control and 19% in bundle re-admitted in 30 days, time to readmission in 30 and 90 days same.

Bode Index: Predicts 4 Year Survival in Patient with COPD

- Validated index in a cohort of 625 patients prospectively studied
- > 20 pack yr smoking hx
- FEV1/FVC < 70%
- Each variable independently evaluated
- Follow up at 6wk, then every 3-6 month for 2 years or until death
- End point was death from any cause and death from respiratory failure

Bode Index:

**MMRC Dyspnea Scale**
- MMRC 0: Dyspneic on strenuous excercise (0 points)
- MMRC 1: Dyspneic on walking a slight hill (0 points)
- MMRC 2: Dyspneic on walking level ground; must stop occasionally due to breathlessness (1 point)
- MMRC 3: Must stop for breathlessness after walking 100 yards or after a few minutes (2 points)
- MMRC 4: Cannot leave house; breathless on dressing/undressing (3 points)

**FEV1 % After Bronchodilator**
- $\geq 65\%$ (0 points)
- 50-64\% (1 point)
- 36-49\% (2 points)
- $\leq 35\%$ (3 points)

**Body Mass Index**
- $> 21$ (0 points)
- $\leq 21$ (1 point)

**6 Minute Walk Distance**
- $\geq 350$ Meters (0 points)
- 250-349 Meters (1 point)
- 150-249 Meters (2 points)
- $\leq 149$ Meters (3 points)

**4 yr Survival in patient with COPD**
- 0-2 points 80%
- 3-4 points 67%
- 5-6 points 57%
- 7-10 points 18%

Kaplan–Meier Survival Curves for the Four Quartiles of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity Index (Panel A) and the Three Stages of Severity of Chronic Obstructive Pulmonary Disease as Defined by the American Thoracic Society (panel B)

Survival
0-2 points 80%
3-4 points 67%
5-6 points 57%
7-10 points 18%
Triggers for COPD Exacerbations

- 70% of time infectious cause
  - Viral: rhinovirus, coronavirus, influenza, parainfluenza, adenovirus, RSV
  - Bacteria: H. Flu, Moraxella catarrhalis, Streptococcal Pneumoniae, Pseudomonas
- 30% Environmental pollution, Pulmonary embolism, unknown cause.
  - Prospective cohort study demonstrated a 25% prevalence of PE in patients hospitalized with COPD presenting with severe exacerbation of unknown cause.

Gold Guidelines

- Global Initiative for chronic obstructive lung disease.
- Disease collaborative project of the NHLBI and the WHO.

Goals
- Increase awareness of COPD
- Decrease morbidity and mortality
GOLD Guidelines for COPD

Stage O: At Risk

- Chronic cough/sputum
- PFT within normal limits
- No symptoms
- Avoid risk factors
- Smoking cessation
GOLD Guidelines for COPD

Stage 1: Mild

- $\text{FEV}_1 > 80\%$
- $\text{FEV}_1/\text{FVC} < 70\%$, with/without symptoms
- Avoid risk factors
- Short-acting bronchodilator PRN
GOLD Guidelines for COPD

Stage 2: Moderate

- FEV₁ 50%-79%
- FEV₁/FVC < 70%, with/without symptoms
- Avoid risk factors
- Regular therapy with one or more bronchodilators
- Pulmonary Rehabilitation
GOLD Guidelines for COPD

Stage 3: Severe

- FEV$_1$ 30%-49%
- FEV$_1$/FVC < 70%
- Avoid risk factors
- Regular therapy with one or more bronchodilators
- Pulmonary Rehabilitation
- Inhaled corticosteroid with frequent exacerbations
GOLD Guidelines for COPD

Stage 4: Very Severe

- FEV₁ < 30%; or
- Respiratory failure
- Right heart failure
- FEV₁/FVC < 70%

- Avoid risk factors
- Regular therapy with one or more bronchodilators
- Inhaled steroids for repeated exacerbations
- Long-term O₂ therapy if qualifies
- Evaluate for surgical treatment
Inpatient Treatment of COPD Exacerbation

- Bronchodilators: nebs or MDI
- Antibiotics
- Steroids
- Non invasive ventilation
- Other things
- Smoking cessation
Inpatient Antibiotics in Acute Exacerbations of COPD

- Standard recommendations: levofloxacin or moxifloxacin or ceftriaxone or cefotaxime.
- If pseudomonas suspected: levofloxacin or ceftazidime or cefepime or piperacillin-tazobactam
- Duration 3-7 days only
  - Meta analysis of 7 RCTs comparing 5 days vs 7-10 days of antibiotics demonstrated no difference in outcomes

Steroids in Routine Hospitalized COPD Exacerbation

- Short term vs conventional glucocorticoid therapy in acute exacerbation of COPD: REDUCE trial
- Randomized clinical trial of 314 patients
- 5 days vs 14 days of steroids
- Average dose 379 mg vs 793 mg (roughly 60mg daily)
- 5 days was not inferior to 14 days with regard to re-exacerbation rate at 6 months but much less steroid exposure and side effects such as hyperglycemia and hypertension
- TAKE HOME POINT: 125mg Q6 hr solumedrol is OUT and less is better.

JAMA 2013; 309 (21): 2223-31
Steroids in the Critically Ill Patient with COPD exacerbation

- Observational Cohort 17,000 patient admitted to ICU with COPD exacerbation.
- Optimal dose of corticosteroids in critically ill patient with acute exacerbation of COPD.
- Methylprednisolone 240mg/day vs >240mg/day.
- Lower dose associated with decreased hospital length of stay, decreased cost, decreased length of invasive ventilation, decreased insulin needs and decreased fungal infections.

Am J Respir Crit Care Med 2014;189 (9):1052-64
Non Invasive Positive Pressure Ventilation (BiPAP) in COPD Exacerbations

- 17 Randomized Controlled Trials
  - 9 trials demonstrate lower intubation rates
  - 3 trials demonstrate lower hospital mortality
Non Invasive Positive Pressure Ventilation in COPD Exacerbations

- COPD vs conventional therapy
  - ↓ Need for intubation (16% vs 33%)
  - ↓ Mortality (11% vs 21%)
  - ↓ Length of stay
  - Ventilatory mode of choice

Cochrane Database Syst Rev 2004
Non Invasive Positive Pressure Ventilation

- **Starting Settings:**
  - IPAP: 8-12 cm H2O
  - EPAP: 3-5 cm H2O
  - Goal TV 300-500 mL

- Improves gas exchange
  - Decrease CO2
  - Improves oxygenation

- Decrease work of breathing
Non Invasive Positive Pressure Ventilation

- No airway protection
- Patient should be NPO
- Should not be used in setting of decreased LOC.
- Causes skin breakdown if used >24-48 hr
Other things.....

- Mucolytics
- Guaifenesin
- NAC: nebulize may cause bronchospasm
- NAC: oral
- Nebulized hypertonic saline
- Hydration if patient is dehydrated
Non Pharmacological Treatment of COPD

- Smoking cessation
- Vaccinations: influenza and pneumococcal
- Pulmonary rehabilitation
  - Meta analysis of 9 trials evaluating pulmonary rehabilitation post hospitalization for AECOPD.
  - Decreased admissions rates OR 0.22, NNT 4
  - Decreased mortality OR 0.28, NNT 6
  - Increased quality of life

Cochrane Database 2011
Oxygen Therapy for COPD

- Mortality benefits for oxygen therapy in COPD severe resting hypoxia. PaO2 ≤ 55 mmHg or PaO2 ≤ 59 mmHg and cor pulmonale
  - Lancet 1981
  - Annals Internal Medicine 1980
- Currently no good randomized control trial demonstrating mortality benefit in moderate hypoxia.
- LOTT: Current on going randomized control trial on oxygen therapy in patients with hypoxia with activity and at night.
- Oxygen: goal oxygen saturations 88-92%

LONG TERM OXYGEN THERAPY
MRC AND NIH CONTROLLED TRIALS
MALES <70 YEARS OLD

Cumulative percent survival

Time (months)

COT
NOT
MRC O₂
MRC controls
Future for COPD

- Lung volume reduction surgery
- Stent placement
- Lung Transplantation
- Stem cell research
- Smoking cessation....
What are all those new inhalers?
Long Acting Anticholinergic Bronchodilators AKA Long Acting Muscarinic Antagonists (LAMA)

- Tiotropium (Spiriva Respimat)
- Aclidinium (Tudorza)
- Umeclidinium (Incruse Ellipta)

Short acting agents
- Combivent Respimat has replaced Combivent MDI
Tiotropium Bromide: Spiriva Respimat

- No capsule to load or eat
- Binds to muscarinic receptors
- Dilates smooth muscle
- Once daily dosing of 2 puffs
- 5mcg per dose
Aclidinium Bromide: Tudorza

- Indications: moderate to severe COPD
- Relaxes smooth muscle around large airways
- 400 mcg Bid dosing
Umecclidinium: Incruse Ellipta

- **LAMA**: relax smooth muscle around large airways
- **62.5 mcg once daily**
- **Half life 11 hours**
- **Onset of action 5-15 minutes**
Combivent Respimat vs Combivent MDI

- Respimat has replaced combivent
- Dosing 1 puff QID pm
- Combivent MDI no longer available in USA
Long Acting Beta Agonist Bronchodilators (LABA)

- salmeterol (Serevent)
- formoterol (Foradil, Perforomist)
- arformoterol (Brovana)
- indacaterol (Arcapta)
- Olodaterol (Striverdi Respimat)
- Vilanterol (combination product only)
Indacaterol: Arcapta Neohaler

- LABA
- 75 mcg puff Daily
- COPD maintenance
  - Chronic bronchitis or emphysema
  - Not asthma (yet)
Olodaterol: Striverdi Respimat

- Olodaterol: LABA
- Once daily inhaler
- 2 actuations = 5mcg
- Onset 10-20 minutes
- Half life about 7.5 hours
Combination Products

- Fluticasone + Salmeterol: Advair BID dosing
- Mometasone + Formoterol: Dulera BID dosing
- Budesonide + Formoterol: Symbicort BiD dosing
- Fluticasone + Vilanterol: Breo once daily
- Umeclidinium + Vilanterol: Anoro Ellipta once daily
- Tiotropium bromide + Olodaterol: Stiolto
Fluticasone + Vilanterol: Breo Ellipta

- Once daily use of ICS/LABA
- Fluticasone furoate 100mcg + vilanterol 25mcg
- Dry powder inhalation
- Onset of LABA 10 minutes
- Half life 24hr/21hr
Umecclidinium + Vilanterol: Anoro Ellipta

- First LAMA + LABA
- Onset 5-15 minutes
- 1 puff daily 62.5mcg/25mcg
- Half life 11 hours
Tiotropium Bromide + Olodaterol: Stiolto

- **LAMA + LABA**
- Tiotropium 2.5mcg + Olodaterol 2.5mcg
- 2 puffs once a day
Tiotropium vs Salmeterol for the Preventions of Exacerbations of COPD

- NEJM 2011; 364: 1093-1103
  - 1 year multicenter randomized double blind, double dummy, parallel group
  - 7376 patients randomized to salmeterol vs tiotropium
  - Time to first exacerbation was longer in tiotropium group. 17% risk reduction
- Cochrane Data meta analysis of 7 studies 2012: Tiotropium vs LABA for stable COPD.
  - Quality of life same but tiotropium may decrease exacerbation rate and hospitalization.
2691/7376 (36%) had 4411 exacerbations
↓
Annual exacerbations 11%
↓
Severe exacerbations 27%

Hazard ratio, 0.72 (95% CI, 0.61–0.85)
P<0.001 by log-rank test

No. at Risk

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NEJM 2011
Multiple Trials involving ICS + LABA

- Fluticasone/salmeterol/tiotropium vs salmeterol/tiotropium vs tiotropium
  - No difference in exacerbations or pneumonia rate
  - Fluticasone arm ↑ lung function; ↓ hospitalizations
    (Ann Intern Med 2007;146:545)

- Fluticasone/salmeterol vs. fluticasone vs. salmeterol vs Placebo
  - ↑ Lung function, ↓ dyspnea in fluticasone/salmeterol
    (Chest 2003;124:834)

- TORCH (Towards a Revolution in COPD Health)
  - ↓ 17.5% mortality vs. placebo (primary endpoint)
  - ↓ yearly exacerbation
  - ↑ pulmonary function
  - ↑ pneumonia rate (19.6%, 18.3, vs. 12.3 placebo)
Roflumilast (Daliresp)

- Phosphodiesterase-4 inhibitor
- PDE 4 inhibitors expressed in airway smooth muscle and pro-inflammatory cells
- Pill taken daily 500mcg
- Side effects: diarrhea, weight loss
Clinical Efficacy of Roflumilast

- 6 randomized, double-blind, placebo-controlled studies
- Moderate/severe COPD
- 6-12 months
- Exacerbations ↓ 30% (RR 0.82)
  - Mostly GOLD IV
- FEV₁ ↑ 40-60 ml vs placebo ↓ 5-35 ml

J Chronic Obstructive Pulmonary Disease 2010;7:141-153
References

- Kiser et al. Outcomes associated with corticosteroid dosage in critically ill patients with acute exacerbations of COPD. American J Respiratory Critical Care Med 2014;189 (9):1052-64
- Global initiative for Chronic obstructive lung disease (GOLD). http://www.goldcopd.org
- Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD. NEJM 2011; 364: 1093-1103
References

References

- Long Term domiciliary Oxygen Therapy in Chronic Hypoxic Cor Pulmonale Complicating Chronic Bronchitis and Emphysema. The Lancet: March 1981: 317; 681-686