COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project
Sub-Intern Name: Samantha Shapiro **Date:** July 31, 2013

Case SIGNOUT:

88 yr old Domincan man with a history of COPD, HTN, and CKD presented to the ED with 3 months of worsening dyspnea and a cough productive of white/yellow phlegm and was admitted in acute respiratory failure secondary to a COPD exacerbation. The patient was initially treated according to the CUMC COPD pathway: albuterol and Ipratropium via nebulizer q4, as well as budesonide-formoterol, azithromycin and Methylprednisolone 40 mg IV every 6 hours until improved. After receiving a pulmonology consult we transitioned the patient from methylprednisolone to prednisone and decreased the length of glucocorticoid therapy from 10-14 day to 5-7. The patient gradually improved over the course of his admission, and has not required oxygen for the past few days.

Clinical Question: *What is the appropriate dose and duration of glucocorticoid therapy when treating patients with COPD exacerbations?*

Background: Chronic Obstructive Pulmonary Disease

- **Definition**: A group of progressive, chronic respiratory conditions, characterized by airway inflammation & airflow limitation
- **Epidemiology**: COPD is the 3rd-ranked cause of death in the US, killing more than 120,000 each year
- **Pathology**: The predominant effects can be seen in the airways, consisting of chronic inflammation, fibrosis, mucus gland hyperplasia + airway collapse. The lung parenchyma + pulmonary vasculature can be affected be affected as well
- **Clinical Features**: dyspnea, chronic cough, and sputum production
- **Risk Factors**: Exposure to toxins (ie. cigarette smoke), impaired lung growth + development, socioeconomic status, bronchial hyper-reactivity, pulmonary infection.
- **Diagnosis**: Spirometry measures forced expiratory volume in one sec (FEV_1) + forced vital capacity (FVC)
    - Both FEV_1 and FVC are decreased, but FEV_1 is decreased disproportionally
    - FEV_1/FVC ratio < 0.70 is diagnostic (post-bronchodilator)
- **Staging / Prognosis**: based on severity of symptoms, number of exacerbations per year, and FEV_1
- **Morbidity**: Traditional measures include physician visits, ER visits, + hospitalizations
- **Main Therapeutic Options**: Beta-blockers (albuterol), Anticholinergic (ipratropium), Inhaled corticosteroids (fluticasone), and Systemic corticosteroids (prednisone)
- Recently published Cochrane review on the *Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease*
    - Pooled data from 7 studies, including 288 patients
    - Most patients with COPD exacerbations are treated according to guidelines that recommend 7-14 days of corticosteroid therapy
    - Presumption: pts should be given the shortest effective course of corticosteroids in order to minimize side effects from treatment
    - Findings: there is no significant increase in tx failure with corticosteroid tx for ≤7 days or less
    - However, analysis was not robust enough to recommend change in clinical practice

Search Strategy: Database: PubMed
((((((copd[Title]) OR chronic obstructive pulmonary disease[Title]) AND chronic obstructive pulmonary disease[MeSH Terms]) AND steroid[MeSH Terms]) AND exacerbation) AND randomized controlled trial[Publication Type]) AND english[Language] → 59 results

Leuppi JD, Schuetz P, Bingisser R, Bodmer M, et al. Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *Journal of the American Medical Association*: 2013;309(21):2223-2231.

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened.	Consecutive patients with exacerbated COPD seen between 3/2006 – 2/2011 in the ED of 5 Swiss teaching hospitals	717
Inclusion criteria	At least 2 of the following: (a) change in baseline dyspnea, cough, or sputum quantity or purulence (b) age >40y (c) A smoking hx ≥20 pack yrs	314
Exclusion criteria	(a) hx of asthma (b) FEV_1 / FVC > 70%, (c) pneumonia (d) estimated survival of < 6m (e) pregnancy / lactation (f) inability to give written informed consent	403
Treatment group	Short-term therapy: 40mg IV methylprednisolone (day 1), 40 mg oral prednisone daily (day 2-5), matching prednisone placebo tablet daily (day 6-14)	157
No treatment group	Conventional Therapy: 40mg IV methylprednisolone (day 1), 40 mg oral prednisone daily (day 2-14)	157

Primary endpoints: Time to next COPD exacerbation (acute clinical deterioration, beyond day-to-day variation, requiring interaction w a clinician) during a 6m follow-up period.

Secondary endpoints: (a) All-cause mortality (b) change in FEV_1 (c) cumulative glucocorticoid dose (d) clinical performance (based on the medical Research Council dyspnea scale, bronchitis-associated quality-of-life score, patient-reported overall performance) (e) duration of hospital stay (f) time to open-label glucocorticoid therapy (g) need for mechanical ventilation during index exacerbation (h) glucocorticoid-associated adverse effects (i) new or worsening hyperglycemia (ii) new or worsening hypertension (iii) newly diagnosed infection

- **Are the Results of the Trial Valid?**
  - **Randomized?** YES. Computer generated randomization list
  - **All patients accounted for at end?** YES
    - All of the following were equally balanced between groups: (a) 3 patients were excluded after randomization because of erroneous initial COPD diagnosis (b) 15 pts withdrew consent and (c) 3 were lost to follow-up
  - **Intention to treat?** YES
  - **Blinding?** YES. Placebo used. Patients, caregivers, outcome assessors, data collectors, the biostatistician, + all other investigators remained blinded until the primary analysis was complete
  - **Groups similar at start of trial?** YES
    - Computer generated randomization was based on (a) age-stratified blocks (b) use of systemic glucocorticoid treatment within 2 days of randomization (c) severity of COPD according to GOLD classification (d) trial site
    - Patients were well matched for age, smoking hx, FEV_1, GOLD COPD grade, Medical Research Council dyspnea scale, home O2 therapy, pretreatment w systemic glucocorticoids or abx, and clinical variables (BP, HR, O2 sat, WBC).
    - **not gender**: there were more woman than man in the conventional therapy group
  - **Equal treatment of groups?** YES
    - All pts received: (a) broad-spectrum antibiotic for 7 days (b) an inhaled, nebulized, short-acting bronchodilators q4-q6 prn while hospitalized (c) inhaled combo of glucocorticoids + B_2-agonist bid (d) tiotropium 18µg daily
    - Physiotherapy, supplemental O2 + ventilator support were provided to both groups according to international guidelines
    - Additional glucocorticoids could be administered at the discretion of the treating physician
    - Endpts were assessed daily during hospitalization, + on days 6, 15, 30, 90, and 180.
  - **Did randomization work?** YES.

- **Are the Results of the Trial important?**
  - **Size of treatment effect and Precision of the estimate of the effect?** YES it was important and significant (P-0.006).
    - This was a non-inferiority study, for which they defined a 15% difference in the percentage of patients with a re-exacerbation during the 6 months of follow-up as the clinically tolerable upper limit. This translates to a hazard ratio of 1.515. Said another way, they assumed that 50% of patients would have an exacerbation within the follow-up period, so as long as fewer than 65% of the patients in the treatment arm experienced an exacerbation, the trial would pass the non-inferiority criteria.
    - A total of 56 patients (35.9%) reached the primary endpoint of COPD exacerbation in the short-term therapy group and 57 patients (36.8%) in the conventional therapy group. The hazard ratio of 0.95 between the short-term and conventional therapy groups.

Primary Endpoint	Event Frequency, No. (%)		Hazard Ratio (90% CI)	P value
	Conventional	Short term		
# of pts w/ re-exacerbation during 6m follow-up	57 (36.8%)	56 (35.9%)	HR 0.95 (0.70-1.29)	0.006
Time to re-exacerbation	29 days	43.5 days		
Glucocorticoid-related Adverse Effect	**No. (%) of Patients**		**Comparison Measure (95% CI)**	**Fisher exact test**
	Conventional	**Short term**		
Diagnosis of Infection	44 (28.4)	44 (28.2)	OR, 0.99 (0.59-1.67)	>.99
New or worsening hyperglycemia	74 (57.4)	74 (56.9)	OR, 0.98 (0.58-1.66)	>.99
New or worsening HTN	23 (17.8)	15 (11.6)	OR, 0.61 (0.28-1.29)	.22
Secondary Endpoints	**Event Frequency, No. (%)**		**Comparison Measure (95% CI)**	**Significance**
	Conventional	**Short term**		
Need for mechanical ventilation	21 (13.6)	17 (11.0)	OR, 0.78 (0.37-1.63)	0.49[a]
Cumulative Prednisone dose (mg)	560	200		<0.001[b]
Duration of hospital stay (days)	9	8	HR, 1.25 (0.99-1.59)	0.04[c]

a – Fisher exact test
b – Mann-Whitney *U* test
c – Log-rank test

- **Can I apply these results to my patient?**
  - **Comparison of my patient to trial patients?** YES. My patient met inclusion criteria: he had 3 months of worsening dyspnea + cough and was in his 80s.
  - **All clinically important outcomes considered?** YES. Increasing time between exacerbations and decreasing the length of the hospital stay were two of the most important outcomes for this patient. The time until patient's returned to their baseline activity could have also been a useful outcome.
  - **Likely benefits outweigh potential harms and cost?** YES. In this inferiority study, the "treatment arm" was exposed to less of the potentially harmful treatment (14 days of glucocorticoids). The benefit was less steroid exposure and the study demonstrated that patients on the shorter dose of steroids did not have an increased rate of exacerbations or any increased morbidity.

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