COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

SubIntern Name: Cindy Cai **Block:** **Date: March 29, 2013**

Case SIGNOUT:

80-year-old woman with a PMHx of **COPD** (FEV1 **1.61**, FEV1/FVC **76%** in 2012; history of multiple admissions for hypercarbic respiratory failure requiring **intubation** in 2008, 2010, 2012; **non-compliant** on home **oxygen** 3L or **medications**: advair, albuterol, iptratroipum, tiotroprium; and **current smoker** 1/2ppd for 30 years), **HOCM** with dCHF preserved EF and LVOT obstruction, **HTN**, and **DM2** who presented with increasing **shortness of breath** x2 days. On presentation: RR16 with **SpO2 91%** on RA, **BNP 2356**, CXR showed mild **interstitial edema**. SOB of unclear etiology (acute CHF exacerbation versus mild COPD exacerbation). Patient was given albuterol/ipratropium nebulizers, put on 3L oxygen with subsequent SpO2 95%, and started on furosemide with marked improvement in her symptoms.

Clinical Question: Systemic steroids are the standard of care in the treatment of acute COPD exacerbation. Given that the precise diagnosis was unclear in this case, should systemic glucocorticoids (gc) have been administered anyway?

Background:

- COPD Management Guidelines:
  - GOLD (Global initiative for chronic Obstructive Lung Disease)
  - Other guidelines: National Clearinghouse, University of Michigan System
- Acute COPD exacerbation: defined as: "acute event characterized by a worsening of the patient's respiratory symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation and leads to a change in medication"
- Treatment options:
  - Short-acting inhaled beta2 agonist +/- short-acting anticholinergic: no controlled trial but preferred treatment
  - Antibiotics: only if moderately/severely ill and has evidence of bacterial infection (i.e. increase in sputum purulence)
  - Oxygen therapy: improve hypoxemia to saturation of 88-92%
  - Corticosteroids: shorten recovery time, improve lung function (FEV1), and reduce treatment failure and length of hospital stay: SCCOPE trial
    - Standard of care: not dependent on severity
    - Optimal dose and duration unclear: 30-40mg prednisolone per day for 10-14 days; oral preferred over nebulized

Search Strategy

Database:

Pubmed: (keywords) systemic steroids COPD → 199 results → randomized controlled trials
Cochrane database
National Clearinghouse Guidelines
GOLD guidelines
University of Michigan Health System Guidelines

Study Chosen:

Niewoehner et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *NEJM* (1999) vol. 340 (25)

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened.	All patients admitted to 25 participating Veterans Affairs medical centers for exacerbations of COPD (November 1994-October 1996)	1840
Inclusion criteria	-Clinical diagnosis of COPD exacerbation -50 years or older -History of 30 pack-years or more of cigarette smoking -FEV1 <1.5L or inability to undergo spirometry because of dyspnea	271
Exclusion criteria	-Diagnosis of asthma -Use of systemic glucocorticoids within the preceding 30 days -Coexisting medical condition that makes survival for at least 1 year unlikely -Inability to give informed consent	1569
Treatment group	-8 weeks of glucocorticoid therapy -2 weeks of glucocorticoid therapy	80 80
No treatment group	-Placebo	111

Primary endpoints:

- Treatment failure: 1) death from any cause, 2) need for intubation and mechanical ventilation, 3) hospital readmission because of COPD, or 4) intensification of pharmacologic therapy (prescription of open-label systemic glucocorticoids, high-dose inhaled glucocorticoids, theophylline)

Secondary endpoints:

- 1) Change in FEV1, 2) length of hospital stay, 3) death from any cause during the 6-month follow-up
- Complications: hyperglycemia, GI bleeding, secondary infection, psychiatric disorder, other adverse events

- **Are the Results of the Trial Valid**? Double-blinded, randomized, placebo-controlled trial
  - Randomized? Yes
  - All patients accounted for at end? Yes, for the most part
    - Study drugs discontinued for reasons other than a primary end point in: 10 placebo (9%), 10 2w-gc (12%), 5 8w-gc (6%)
    - Follow-up data complete for 19 of the 25: data included in analysis
  - Intention to treat? Yes
  - Blinding? Yes
  - Groups similar at start of trial? Yes, for the most part well matched by demographics, symptoms, risk of exacerbations, medications, and other illnesses with the following exceptions:
    - Total cigarette smoking (pack-year): 77 placebo, 67 2w-gc, 80 8w-gc
    - Prior use of systemic glucocorticoids: 52 placebo, 30 2w-gc, 46 8w-gc
    - Diabetes mellitus: 5 placebo, 12 2w-gc, 11 8w-gc
  - Equal treatment of groups? Yes

- 3days of IV + pills for the rest of the 57d, 7d of broad-spectrum antibiotic, 6mo of inhaled β-adrenergic agonist, 6mo of inhaled ipratropium, starting d4 inhaled triamcinolone acetonide
- Not allowed: theophylline, high-dose inhaled glucocorticoids, open-label systemic glucocorticoids
- Spirometry at baseline, on days 1, 2, 3; and the 2w, 8w, and 6mo visits

o Did randomization work? Yes

Endpoint	**Result**			**Significance**	**ARR**	**NNT**
	Placebo	**2w-gc**	**8w-gc**	**p-value**		
Treatment Failure						
30d	37(33%)	19(24%)	18(22%)	0.04	14%	7.1
90d	53(48%)	30(38%)	29(36%)	0.04	11%	9.1
182d	60(54%)	39(49%)	42(52%)	0.58	--	--
FEV1					--	--
d0	0.75L	0.775L		--		
d1	0.775L	0.9L		<0.05		
d2	0.875L	0.975L		<0.05		
d3	0.86L	0.97L		<0.05		
w2	1.02L	1.10L		--		
Hospital Length	9.7d	8.5d		0.03	--	--
All-cause mortality	11	16		0.61	--	--
Morbidity	**Result**			**Significance**	**ARI**	**NNH**
	Placebo	**2w-gc**	**8w-gc**	**p-value**		
Hyperglycemia	4(4%)	14(18%)	10(12%)	0.002	11%	9.1
GI bleed	5(5%)	0	3(4%)	0.21	--	--
Secondary infection	19(17%)	12(15%)	18(22%)	0.73	--	--
Hypertension	4(4%)	6(8%)	4(5%)	0.33	--	--
Psychiatric disorder	3(3%)	5(6%)	2(2%)	0.47	--	--
Other adverse events	16(14%)	18(22%)	21(26%)	0.04	10%	10

TABLE 2. CUMULATIVE PRIMARY OUTCOMES ACCORDING TO TREATMENT ASSIGNMENT.

OUTCOME	PLACEBO (N=111)	GLUCOCORTICOIDS FOR 2 WK (N=80)	GLUCOCORTICOIDS FOR 8 WK (N=80)	P VALUE*
	number (percent)			
30 days				
Death	3 (3)	0	2 (2)	
Intubation	3 (3)	2 (2)	1 (1)	
Readmission for COPD	5 (5)	4 (5)	2 (2)	
Intensification of therapy	26 (23)	13 (16)	13 (16)	
Total	37 (33)	19 (24)	18 (22)	0.04
90 days				
Death	4 (4)	2 (2)	2 (2)	
Intubation	3 (3)	3 (4)	1 (1)	
Readmission for COPD	13 (12)	8 (10)	6 (8)	
Intensification of therapy	33 (30)	17 (21)	20 (25)	
Total	53 (48)	30 (38)	29 (36)	0.04
182 days				
Death†	4 (4)	2 (2)	3 (4)	
Intubation	3 (3)	3 (4)	2 (2)	
Readmission for COPD	17 (15)	12 (15)	13 (16)	
Intensification of therapy	36 (32)	22 (28)	24 (30)	
Total	60 (54)	39 (49)	42 (52)	0.58

*P values are for comparisons of the placebo group with the combined glucocorticoid groups, by the log-rank test.

†Only deaths that were counted as primary outcomes are listed. The total numbers of deaths during six months of follow-up were 11 in the placebo group and 13 in the glucocorticoid groups.

- **Are the Results of the Trial important**? Yes
  - Size of treatment effect? The study clearly shows that glucocorticoids are associated with decreased treatment failure even up to 3mo after initial exacerbation, improved FEV1 (by 0.1L), and decreased hospital stays (by 1.2 days) (all statistically significant).

- Precision of the estimate of the effect? Confidence intervals were not reported so it is difficult to estimate the spread of the data. However, theoretically, the precision of the estimates are less than optimal since many patients in the placebo group who experienced treatment failure went on open-label glucocorticoids thus diminishing any differences between the placebo and glucocorticoid groups (especially later on during the trial). This issue did not affect demonstrating differences in the primary and secondary endpoints but is likely the reason no differences were shown in numerous categories of morbidity from glucocorticoid use.

- **Can I apply these results to my patient**?
  - Comparison of my patient to trial patients.
    - My patient would not have been included in this study: less than 30-pack-year smoking history, FEV1 >1.5
  - All clinically important outcomes considered.
    - The trial demonstrates the placebo results in more treatment failure but the clinical significance of what they define as treatment failure is questionable. The study does not specifically show the p-value associated with each item of treatment failure, i.e. death, intubation, etc. However, it seems that most of the difference between the groups are due to intensification of therapy. The clinical significance of this is an issue. Even the article itself concludes that "the principle consequence of withholding glucocorticoids in patients receiving placebo was to delay their administration to about half these patients. The other half recovered and received no glucocorticoids during the full six months of follow-up."[1]
    - Although FEV1 abnormalities correlate poorly with the sensation of dyspnea, exercise limitation, it has been shown to be highly predictive of clinical outcomes during exacerbations of COPD.[2]
    - Otherwise, the significance of all-cause mortality, and the side-effects of glucocorticoid therapy are considered
  - Likely benefits outweigh potential harms and cost?
    - Although the GOLD guidelines recommend steroids and this study shows that glucocorticoids results in decreased treatment failure, improved FEV1, and decreased hospital stays, given the considerable side effects of glucocorticoid therapy and the questions of clinical significance of the study's endpoints, it is reasonable to withhold systemic glucocorticoid therapy in certain cases such as this one.

References:

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