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Original Article

Evaluation of the Impact of Corticosteroid Dose on the Incidence of Hyperglycemia in Hospitalized Patients with an Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Purpose: Guidelines recommend systemic corticosteroids for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) albeit in lower doses than studies that cemented corticosteroids' place in therapy. Corticosteroids potentiate hyperglycemia, however it is undetermined how corticosteroid dose impacts hyperglycemia incidence.

Objectives: To establish whether a greater incidence of steroid-induced hyperglycemia (SIHGLY) exists for high- versus low-dose corticosteroids.

Methods: Patients with primary discharge diagnosis 491.21/491.22 in a community hospital were retrospectively reviewed and divided into tertiles based on corticosteroid dosage. Baseline characteristics and primary endpoint were statistically assessed between tertiles using logistic regression analysis. A Cox proportional hazards (CPH) model adjusted for potential covariates. Post hoc analysis for primary outcome and CPH model was run removing non-insulin dependent diabetics because of disproportionate event count. A secondary endpoint used a Kaplan-Meier curve to evaluate time to event between tertiles.

Results: Tertile divisions were 125 and 187.5 mg methylprednisolone equivalents. The primary outcome for incidence of SIHGLY was insignificant; post hoc analysis removing non-insulin-dependent diabetics narrowly missed significance between tertiles 1 and 3 (P = .056). CPH analysis found significant differences in SIHGLY between tertiles 1 and 2 (hazard ratio [HR], 1.68; 95% CI, 1.02-2.76) and tertile 1 and 3 (HR, 1.79; 95% CI, 1.13-2.84), further post hoc analysis resulted in a loss of significance for the CPH analysis. Of 21 non-insulin-dependent diabetics, 20 met event status. The Kaplan-Meier analysis results were insignificant.

Conclusions: Study results suggest that a link between larger corticosteroid doses and hyperglycemia incidence may exist, but it requires further study. Results in non-insulin-dependent diabetics provide evidence for increased glucose monitoring upon initiation of corticosteroid therapy.

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Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States and has been diagnosed in 12.7 million adults in the United States as of 2013, with estimates projecting that up to 24 million could be afflicted.[1] COPD is marked by recurrent exacerbations potentially necessitating hospitalization and routinely requiring systemic corticosteroid administration. Systemic orticosteroids were cemented as a cornerstone of therapy for hospitalized patients based on data from a 1999 randomized controlled trial conducted by the Veterans Administration System comparing

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methylprednisolone against placebo for treatment of acute exacerbations of COPD (AECOPD). Results of this work showed reduced treatment failure (defined as readmission for AECOPD, need for intubation or mechanical ventilation, death, or intensification of drug therapy).[2]

Additional evidence is given in a 2014 Cochrane Review; Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease favored administration of corticosteroids to prevent treatment failure versus placebo (odds ratio [OR], 0.48; 95% CI, 0.35-0.67).[3] While the studies in the review had individual strengths and weaknesses that need to be evaluated independently, they were all successful on some level in providing evidence that corticosteroids are beneficial in treating AECOPD. This was significant as every study used a different dosing scheme, ranging from a low of 30 mg of prednisolone daily to the high end of 125 mg methylprednisolone every 6 hours. With the ambiguity in these studies about dosing, it is understandable why the range of doses currently administered in the hospital setting varies such a great deal.

Systemic corticosteroids present a myriad of potential acute side effects (eg, insomnia, hyperglycemia, anxiety) that may or may not be linked to the dose of corticosteroid. Additional information in the Cochrane Review showed the overall risk of hyperglycemia for patients receiving corticosteroids during AECOPD to be increased (OR, 2.79; 95% CI, 1.86-4.19).[3] While a universal definition for the potential side effect of hyperglycemia is lacking, guidelines provide recommendations for inpatient blood glucose values to be less than 180 mg/dL.[4,5] Using this target as an event definition for steroid induced hyperglycemia (SIHGLY), this study was designed to evaluate whether the initial dosing of corticosteroids played a significant role in patients experiencing SIHGLY during their inpatient stay. Demonstration of a link between the corticosteroid dosage and SIHGLY would highlight the need for further investigation as to what the appropriate dose of corticosteroids is for patients experiencing AECOPD to provide the most benefit with the least amount of side effects.

METHODS

A retrospective review was conducted in a 451-bed Midwestern community hospital in a major metropolitan area with approval from the facility institutional review committee. Patients were screened for study inclusion if they carried a primary discharge diagnosis for AECOPD (ICD-9 code 491.21/491.22) over a 31-month period from December 2010 to June 2013. This time period allowed for assessment of all available patients after the facility moved to an electronic medical record (while allowing for an acclimation period) up to the time of data synthesis. A data screening tool programmed by the Clinical Informatics Department located patients with the target ICD-9 codes along with their admit/discharge dates, mortality, intensive care unit (ICU) admission, age, sex, blood glucose values, and comorbidities. To exclude patients with other causes of hyperglycemia, any patient with a blood glucose level greater than 180 mg/dL in the first 12 hours of hospitalization was excluded. Individuals who were hospitalized for less than 48 hours and those with only one blood glucose value available during their stay were also considered to be lacking enough information for inclusion. Those who did not receive corticosteroids in the first 24 hours of hospitalization or who had a length of stay greater than 3 *SD* from the population mean were considered to be outlier cases. Additionally any patients who were noted at any point to be insulin-dependent diabetic prior to hospitalization were excluded from further analysis. For individuals still available for assessment following application of the screening tool (see **Table 1**), further review was continued manually on the individual patient level (all data collection was done by the same individual). Additional data that were collected included home medications and intravenous/oral corticosteroid doses. Data collection was terminated at discharge, after a patient experienced SIHGLY (each patient could only account for one event), or when 7 days length of stay was reached, whichever came first. Data collection was limited to 7 days, as daily doses were stabilized by day 7 and few patients' length of stay extended beyond 7 days.

Specific attention was given to the amount of intravenous and oral corticosteroids patients received on a daily basis (all doses were either oral prednisone or intravenous methylprednisolone). Cumulative corticosteroid dose in milligrams of methylprednisolone equivalents received on day 2 of the hospital stay was used to separate the patients into tertiles for comparison. Day 2 was seen as the optimal timeframe to group patients as it would constitute a full 24 hours for medication administration. A blood glucose value of 180 mg/dL was used to define an event based on the

Table 1. Exclusion criteria with corresponding numbers of excluded patients

Criteria	No. of patients excluded[a]
Elevated blood glucose (>180) during first 12 hours of hospitalization	154
Length of stay <48 hours	134
Only one blood glucose lab available	69
Diabetics on insulin therapy	49
No corticosteroids administered in first 24 hours of hospitalization	41
Incomplete data	7
Length of stay >3 *SD* from study population	7
Patients available for assessment	245

[a]706 patients were available for initial assessment.

recommended target for hospitalized non-critically ill patients in the practice guidelines from the American Diabetes Association and the Endocrine Society. Administration of insulin at any point was also considered an event regardless of the blood glucose value.

Patient characteristics (comorbidities, home medications, inpatient medications) were compared between tertiles using descriptive statistics to determine whether the groups were equally distributed. Analysis using binary logistic regression was performed on the patient characteristics to establish whether there were differences between the tertiles for any of the items collected including the primary study outcome of incidence of SIHGLY. Division points for population tertiles were 125 mg and 187.5 mg total methylprednisolone dose on day 2; any individual who had a dose equivalent to the division point was included in the lower tertile. This produced 3 distinct dosing groups of low (0-125 mg), moderate (126-187.5 mg), and high (188-500 mg). In an effort to evaluate the potential impact of the cumulative dose of corticosteroids, a secondary outcome was investigated to compare the time to event between tertile displayed as a Kaplan- Meier curve. Kaplan-Meier results were further analyzed using a Cox proportional hazards model to adjust for several potential covariates that were established a priori. Covariates were chosen due to their potential to impact study results based on other study data or known influences, such as on oral corticosteroids prior to admission, patients with controlled non-insulin-dependent type II diabetes prior to admission, or receipt of atypical antipsychotics, fluoroquinolones, or dextrose in intravenous fluids while an inpatient. [6,7]

All statistical tests were run using IBM SPSS version 22 (IBM, Inc., Armonk, NY). The significance level established a priori for logistic regression analysis and Kaplan-Meier was $P < .05$. Following review of the data, an unplanned analysis was completed for the primary study outcome with all diabetic patients removed to evaluate the impact this subgroup had on the overall findings.

RESULTS

Table 2 illustrates the patient populations based on their comorbidities, home medications, hospital medications, and demographics using descriptive statistics. Statistical analysis to determine whether the low tertile differed from the moderate or high tertile yielded only 2 significant values based on the binary regression model (hypertension and dextrose in intravenous fluids between the low- and high-dose groups).

Table 3 highlights additional population characteristics including the average and cumulative amount of corticosteroids received during the patient stay across the tertiles along with the average length of stay. Also shown is the primary study outcome of incidence of SIHGLY, which showed a 7% increase between the low and moderate tertile ($P = .33$) and a 12% increase between the low and high tertiles ($P = .10$).

Figure 1 illustrates the Kaplan-Meier curve of the time to SIHGLY. The individuals in the low-dose tertile showed a decreased incidence and potentially a longer time to evolution of SIHGLY when compared to the moderate- and high-dose tertiles. The results for this analysis however failed to show a significant difference between groups ($P > .05$).

Further analysis for covariates was completed using a Cox proportional hazards model (shown in **Figure 2**) controlling for patients who were diabetic, were on oral corticosteroids as a home medication, or

Table 2. Baseline characteristics by tertile [frequency (percentage)] unless otherwise noted

		Tertile (dose range in mg)		
		Low (0-125)	**Moderate (126-187.5)**	**High (188-500)**
Demographics	Female	52 (57)	44 (60)	50 (62)
	Age,[a] years	70 (±11.9)	67 (±12.9)	65 (±12.8)
	ICU admission	2 (2)	0 (0)	4 (5)
Comorbidities	Diabetes	11 (12)	5 (7)	5 (6)
	Depression	14 (15)	18 (25)	17 (21)
	Hypertension*	67 (74)	50 (68)	47 (58)
	Congestive heart failure	20 (22)	9 (12)	9 (11)
	Lung cancer	1 (1)	2 (3)	1 (1)
	Smoker	39 (43)	39 (53)	43 (53)
Home medications	Oral corticosteroids	18 (20)	18 (25)	23 (28)
	Inhaled corticosteroids	44 (48)	41 (56)	36 (44)
	Long-acting beta agonist	39 (43)	38 (52)	39 (48)
	Short-acting beta agonist	59 (65)	37 (51)	48 (59)
	Fluoroquinolone	2 (2)	8 (11)	7 (9)
	Other antibiotic	10 (11)	6 (8)	10 (12)
	Long-acting anticholinergic	19 (21)	14 (19)	24 (30)
	Short-acting anticholinergic	27 (30)	21 (29)	21 (26)
	Oral diabetes medication	8 (9)	4 (5)	5 (6)
	Atypical antipsychotics	4 (4)	9 (12)	3 (4)
Hospital medications	Inhaled corticosteroids	51 (56)	51 (70)	57 (70)
	Long-acting beta agonist	48 (53)	50 (68)	58 (72)
	Short-acting beta agonist	88 (97)	72 (99)	79 (97)
	Fluoroquinolone	45 (50)	34 (47)	37 (46)
	Other antibiotic	48 (53)	46 (63)	44 (54)
	Long-acting anticholinergic	27 (30)	15 (21)	31 (38)
	Short-acting anticholinergic	70 (77)	60 (82)	70 (86)
	Oral diabetes medication	7 (8)	5 (7)	4 (5)
	Atypical antipsychotics	4 (4)	11 (15)	3 (3)
	Dextrose in IV fluids**	23 (26)	10 (14)	8 (10)

Note: Values expressed as frequency (percentage), unless otherwise noted. ICU = intensive care unit; IV = intravenous.
[a]Measures of central tendency [average (*SD*)] used to assess these variables.
*P = .03 comparing low to high dose tertiles.
**P = .01 comparing low to high dose tertiles.

Table 3. Results divided by patient tertile

	Tertile (dose range in mg)		
	Low (0-125)	Moderate (126-187.5)	High (188-500)
No. (%) of patients	91 (37)	73 (30)	81 (33)
Average daily dose of corticosteroids,[a] mg	84 (±34)	121 (±30)	170 (±51)
Average cumulative dose of corticosteroids,[a] mg	395 (±251)	572 (±234)	875 (±329)
Length of stay,[a] days	4.25 (±2.0)	4.24 (±1.7)	4.8 (±2.6)
Hyperglycemic event[b]	38 (42)	36 (49)	44 (54)

[a]Measures of central tendency [average (*SD*)] used to access these variables.
[b]Primary study outcome: low to moderate dose, $P = .33$; low to high dose, $P = .10$.

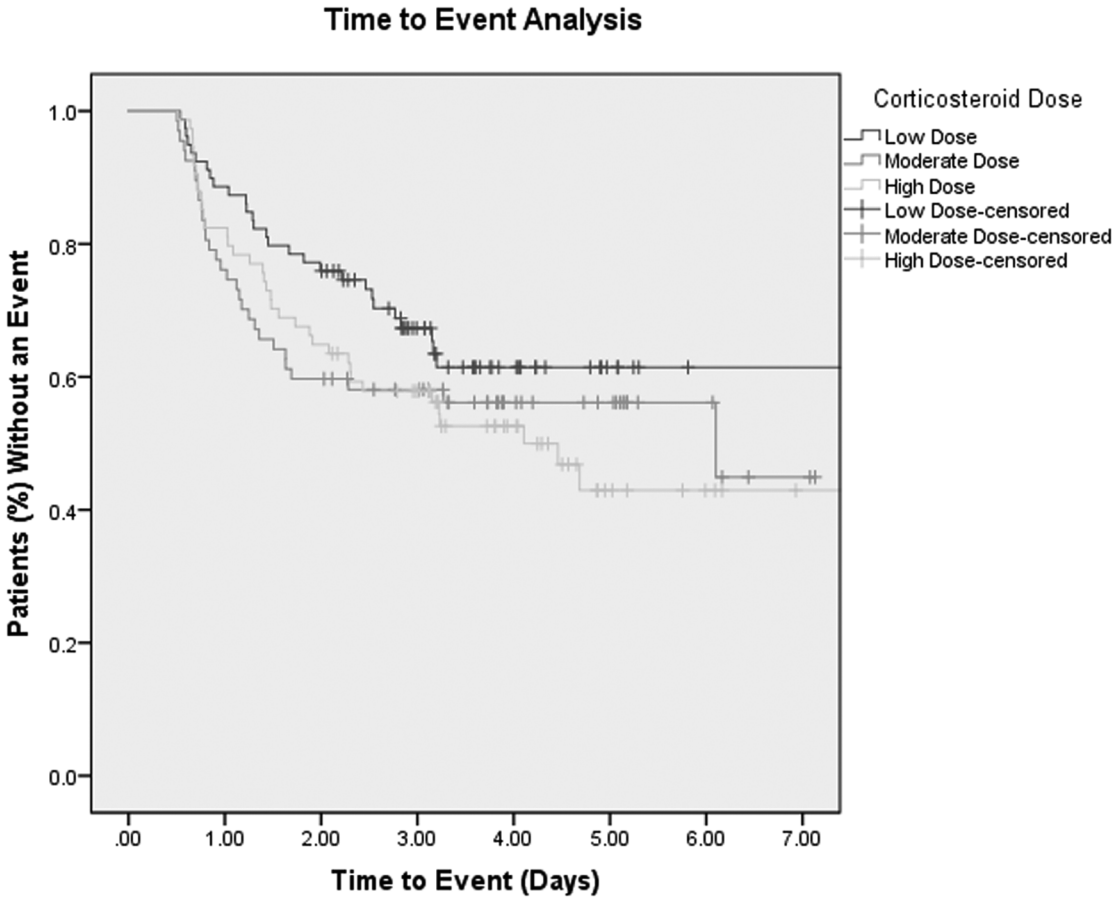

Figure 1. Kaplan-Meier curve showing the time to event analysis. Censored denotes patients no longer available for follow-up who did not experience an event. No statistical comparisons reached significance ($P > .05$) for the Kaplan-Meier curve analysis.

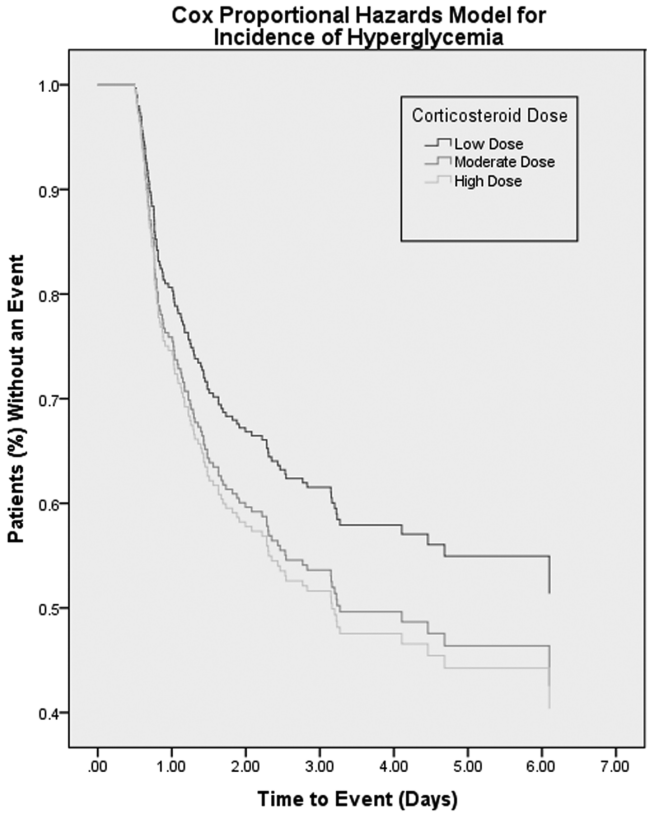

Figure 2. Cox proportional hazards model adjusting for predetermined covariates. Both the low to moderate dose (hazard ratio [HR], 1.68; 95% CI, 1.02-2.76) and low to high dose (HR, 1.79; 95% CI, 1.13-2.84)) comparisons achieved significance.

received fluoroquinolones, atypical antipsychotics, or any amount of dextrose in their intravenous fluids during hospitalization. Hazard ratios (HRs) generated from this model showed a statistically significant difference for SIHGLY between the low-dose and moderate-dose tertiles (HR, 1.68; 95% CI, 1.02-2.76) as well as the low-dose and high-dose tertiles (HR, 1.79; 95% CI, 1.13-2.84).

During review of patients meeting study event criteria, it was noted that 20 of 21 patients with diabetes experienced an event. A post hoc subanalysis was completed with these 21 patients excluded to determine their overall impact on results. With diabetic patients removed, the primary study outcome of incidence of SIHGLY showed a 10% increase between low and moderate tertiles (P = .25) and a 15% (P = .056) increase in SIHGLY between low and high tertiles in the subanalysis. The Cox proportional hazards model was also reapplied while controlling for the same covariates as the initial model. Results failed to reach statistical significance for either low versus moderate tertile (HR, 1.41; 95% CI, 0.83-2.39) or low versus high tertile (HR, 1.56; 95% CI, 0.95-2.57).

DISCUSSION

This retrospective study illustrates a possible relationship between the dose of systemic corticosteroid used to treat an AECOPD and the incidence of SIHGLY. Although statistical analysis did not reach significance for the primary study endpoint, a consistent rise in hyperglycemic events when going from the low- to moderate- to high-dose tertiles was present. Additionally when results for the primary study endpoint were analyzed further with diabetic patients

removed, the comparison between the low-dose tertile and the high-dose tertile narrowly missed significance (P = .056). Significance may have been reached under more controlled (prospective) conditions or with a larger sample size.

Recent articles have highlighted the differences in approach to dosing systemic corticosteroids for AECOPD based on the studies that established corticosteroids as efficacious versus current guideline recommendations.[8] While the Veterans Administration study utilized a dosing scheme that started with 125 mg of methylprednisolone intravenously every 6 hours, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines currently recommend 40 mg prednisone daily and the American Thoracic Society COPD guidelines currently recommend 30 to 40 mg of oral prednisone daily.[9,10] As suggested by Shweiger et al,[8] the answer probably lies somewhere in the middle to balance therapeutic outcomes with deleterious side effects.

Even though the optimal corticosteroid dosage to treat AECOPD is not known, corticosteroids can cause hyperglycemia. Multiple mechanisms are responsible for the induction of SIHGLY. Overt insulin resistance occurs due to increased hepatic gluconeogenesis coupled with decreased glucose uptake and utilization in skeletal muscle tissue. In addition, secretion of insulin from the pancreatic beta cells is impaired, further compounding the matter.[11]

Little data regarding the true incidence of SIHGLY is available. Three of the studies in the previously mentioned Cochrane Review evaluated hyperglycemia as a side effect of corticosteroid therapy during inpatient stay (OR, 8.0; 95% CI, 2.96-21.63).[2,12,13] Each study utilized only one dose of corticosteroid versus placebo, so there is no way to infer whether a relationship exists between higher doses and increased hyperglycemia. One additional small retrospective study detailed 50 patients on a general medicine ward to evaluate risk factors for SIHGLY in patients receiving at least 40 mg per day of prednisone. Of those 50 patients, 32 (64%) were considered to have had a hyperglycemic episode (glucose level >200 mg/dL) and 25 (50%) experienced multiple episodes. Although SIHGLY was prevalent in this setting, there was no attempt to correlate it with corticosteroid dosage.[14] A 2015 study reviewed 30 patients admitted for AECOPD and attempted to correlate initial and maximal glucose levels to maximum dose of methylprednisolone using a similar study design to this work. The results did not reach statistical significance but were likely hampered by the small sample size.[15]

Conversely the impact of the length of corticosteroid dose was evaluated in the REDUCE trial that compared 2 different lengths of therapy (5 or 14 day) following an AECOPD while using a single strength of prednisone 40 mg throughout the study. The incidence of new or worsening hyperglycemia at hospital discharge was a secondary endpoint for this study in an effort to determine whether cumulative corticosteroid dose played a significant role. Both groups experienced a significant amount of hyperglycemia (56.9% and 57.4%), however neither group had a greater risk (OR, 0.98; 95% CI, 0.58-1.66). Mean length of hospital stay for each group was 9.3 days for the study (5 day) group and 10.8 for the protocol (14 day) group. The study group received a much lower cumulative dose but still experienced an equal amount of new or worsened hyperglycemia.[16]

In our findings, the comparison between the low- to moderate- to high-dose tertiles using the Kaplan-Meier analysis was intended to show when events occurred and whether dose accumulation played a role. The Kaplan-Meier analysis did not show significant statistical results and the Cox proportional hazards model showed conflicting results depending on whether diabetic patients were included. The lack of evidence adds doubt about the effect of cumulative corticosteroid dose established in the REDUCE trial and provides further evidence that the effect of the corticosteroid alone may be enough to derange glycemic control.

The subanalysis group of 21 diabetic patients does lend further support to the evidence for managing all inpatient diabetics experiencing an AECOPD with insulin therapy at the initiation of corticosteroid therapy. Of the 21-patient subgroup, 11 had blood glucose values above 180 mg/dL prior to insulin administration, 9 were switched to insulin therapy prior to having a blood glucose value of 180 mg/dL or greater at provider discretion, and one did not have an event. Current guidelines recommend that patients receiving therapies associated with hyperglycemia be monitored for at least the first 24 to 48 hours of hospitalization with bedside point of care testing.[4] Further recommendations for those who are diabetic suggest sole management with insulin while they are inpatients.[4] Both of the aforementioned guideline recommendations were valid in this 21-patient subgroup

based on a uniform need for intense monitoring and consideration of immediate initiation of insulin therapy at the outset of corticosteroid therapy in diabetic patients with AECOPD.

LIMITATIONS

Only 35% of patients identified with AECOPD were available for assessment based on study exclusion criteria. This is a smaller sample of a much larger population, so those assessed should have been at a much lower risk of meeting the study criteria for an event. Potential covariates discussed in the methods section that could not be controlled for with exclusion criteria were accounted for with statistical analysis to provide a more accurate depiction of the role of corticosteroid dose in event attainment. This analysis resulted in wide confidence intervals, indicating that negative findings might be a result of inadequate sample size and resultant lack of power.[17,18]

Patients receiving oral prednisone on day 2 were grouped with patients receiving intravenous methylprednisolone. Overall 78% of the total doses received in the study were intravenous methylprednisolone (a majority of the oral doses were administered just prior to discharge). Converting patients on oral prednisone to methylprednisolone equivalents based on 80% prednisone to methylprednisolone equivalency did not alter the tertile division points of 125 mg and 187.5 mg.[19] This is due to the small percentage of the population receiving oral therapy on day 2 at very low doses, resulting in minimal adjustment.

Prescribers may have decided on a dosage based on a patient's severity of illness or perceived risk of adverse events. The patient tertiles were evenly dispersed, as shown in **Table 2**, so it is unlikely that this played a significant role in the results of this study. Although several comorbidities, including diabetes, were more frequently seen in the low-dose group, these results were not statistically significant. Patients with diabetes were included in the analysis if they had not reached the point of receiving insulin therapy. These patients may be at increased risk for hyperglycemia, but they either had managed the disease in a manner to control it prior to admission or were newly diagnosed. Statistical analysis controlled for both variables in the initial analysis, but a subanalysis was performed with diabetic patients removed to evaluate their impact on the results. Counting patients who were administered insulin prior to event occurrence as having experienced an event may have increased the total number of events in the study. Insulin administration was considered significant; in a number of cases, it likely prevented the patients from meeting the established glucose value as event criteria. The willingness of the prescriber to add insulin therapy was also deemed significant, as insulin is considered a high-alert medication when used in acute care settings by the Institute for Safe Medication Practices.[20]

The number of covariates controlled for in the final statistical model was limited based on the number of events assessed. It takes approximately 10 to 15 study events for every one variable that is to be individually analyzed, therefore every possible scenario could not be tested.[21] It was evident upon event analysis that the inclusion of patients with diabetes in data collection was questionable as every diabetic patient but one experienced an event. This was further illustrated when the results of the Cox proportional hazards analysis went from statistically significant to statistically nonsignificant following their removal. Initial consideration for inclusion was given because these patients were controlled prior to admission and did not meet the event definition within the first 12 hours of hospitalization.

It is unclear whether the patients who received lower doses experienced the same outcomes regarding exacerbation cessation. This is a valid point that is difficult to fully assess without pulmonary function tests, which are not routinely recommended during an exacerbation, or data regarding the time to next AECOPD, which is beyond the scope of this study. Patient length of stay is the best marker available; it did not differ excessively based on the average length of stay amongst these 3 groups, as shown in **Table 3**.

CONCLUSIONS

This study was not intended to question the utility of corticosteroids for AECOPD, as it has been thoroughly proven. However appropriate dosing is up for debate; current guidelines recommend much more conservative dosing than what is commonly used in practice. Coupled with the numerous side effects of corticosteroids (eg, insomnia, anxiety, and hyperglycemia) that may be dose related, the risk versus benefit of larger doses is a valid concern. Although the primary study outcome did not yield statistically significant results, the data provide indications that higher corticosteroid dosing potentiates hyperglycemia. Results also provide further evidence of the need

to closely monitor and treat diabetics with insulin when corticosteroids are initiated. To fully determine the impact corticosteroid dosing has on hyperglycemia and other adverse effects, a prospective study with controlled dosing will likely be necessary.

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