

Original Article

## SYNERGIES AND CONSIDERATIONS: BUDESONIDE NEBULIZERS AND SYSTEMIC CORTICOSTEROIDS IN COPD EXACERBATION MANAGEMENT

*Emily Grace Johnson, PhD and Sarah Lynn Anderson, PharmD*

<sup>1</sup>West Virginia University School of Pharmacy, Morgantown, West Virginia, United States. Corresponding author: literature search, data collection, study design, analysis of data, and manuscript preparation.

<sup>2</sup>Department of Clinical Pharmacy, West Virginia University School of Pharmacy, Morgantown, West Virginia, United States. Coauthor: study design, analysis of data, and review of manuscript.

**Abstract:** Chronic Obstructive Pulmonary Disease (COPD) is a major global health concern, with increasing prevalence and significant morbidity and mortality. This paper explores COPD exacerbations, which are characterized by a worsening of symptoms and often lead to hospitalization. We investigate the clinical features, impact on health status, and management of these exacerbations. COPD exacerbations are associated with increased airway inflammation, mucus production, and gas trapping, leading to symptoms like dyspnea, increased sputum, cough, and wheezing. Exacerbations tend to cluster, increasing the risk of recurrent events. The duration of these episodes is typically 7-10 days, resulting in adverse outcomes, including hospitalization and disease progression. This paper reviews the pharmacological approaches to managing exacerbations, which include systemic corticosteroids, bronchodilators, and antibiotics. Systemic corticosteroids have been shown to be effective in reducing recovery time, improving lung function, and reducing the risk of early relapse. Understanding and effectively managing COPD exacerbations are essential in improving the quality of life and clinical outcomes for patients with COPD.

**Keywords:** COPD exacerbation, airway inflammation, systemic corticosteroids, bronchodilators, antibiotics

### Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that comes from abnormalities in the alveolar cells due to exposure to noxious particles and/or gases.<sup>1</sup> These alveolar abnormalities are often characterized by persistent respiratory symptoms such as shortness of breath, chronic cough, sputum and airflow limitation.<sup>1</sup> COPD is currently the fourth leading cause of death in the world, but is projected to be the third leading cause by 2020.<sup>2</sup> Patients with COPD typically have one to two exacerbations annually with the frequency increasing as the disease progresses.<sup>3</sup> COPD exacerbations are complex events that typically involve an increase in airway inflammation, production of mucus, and gas trapping.<sup>1</sup> Exacerbation symptoms commonly

## **Original Article**

involve an increase in dyspnea, sputum volume, cough and wheezing. Exacerbations have the potential to cluster in time and after each event, patients are at an increased risk of having another event.<sup>4,5</sup>

COPD exacerbation symptoms typically last 7-10 days and negatively impact health status, rates of hospitalization and readmission, and disease progression.<sup>1,6,7</sup> Pharmacologic management of an exacerbation typically includes systemic corticosteroids, bronchodilators, and potentially antibiotics.<sup>1</sup> Systemic corticosteroid use has been shown to shorten recovery time, improve lung function, reduce risk of early relapse, reduce risk of treatment failure, and hasten 2

Vol. 7, No. 2, December 2019

International Journal of Medicine and Pharmacy,

symptomatic improvement.<sup>1,8</sup> A dose of 40 mg of prednisone per day for five days is currently recommended by guidelines.<sup>1,9</sup> Other studies have shown that nebulized budesonide appears to be equivalent to systemic corticosteroids such as methylprednisolone and prednisone in improving pulmonary function, forced expiratory volume in 1 second (FEV<sub>1</sub>), saturation of peripheral oxygen (SpO<sub>2</sub>), in reducing symptoms, and treating COPD exacerbations.<sup>10-15</sup> Recent practice trends within certain institutions have included utilizing nebulized budesonide in addition to systemic corticosteroids during a COPD exacerbation. Currently, only one study has evaluated this particular corticosteroid combination therapy and showed that hospital length of stay was longer in patients receiving both systemic and inhaled corticosteroids.<sup>16</sup>

Additionally, inhaled corticosteroids could lead to more adverse effects when used concomitantly with systemic corticosteroids including hyperglycemic events. Inhaled corticosteroids have also been shown to increase incidence of oral candidiasis.<sup>17</sup> Another potential negative consequence is cost, with another study demonstrating a cost savings if inhaled corticosteroids were not used during treatment of COPD exacerbations.<sup>18</sup>

The objectives of this retrospective analysis were to evaluate the benefits and risks with concomitant use of nebulized budesonide and systemic corticosteroids during COPD exacerbations. The primary objective was to compare hospital length of stay for patients with concomitant use of nebulized budesonide and systemic corticosteroids versus patients who received solely systemic corticosteroids for a COPD exacerbation. Secondary objectives were to evaluate adverse effect rates (i.e., incidence of hyper-/hypoglycemia or oral thrush).

## **Methods**

This study was conducted retrospectively by reviewing electronic medical records of subjects at West Virginia University (WVU) Medicine, an academic medical center, admitted between September 20, 2015- July 30, 2017 with a COPD exacerbation based off ICD9 and/or ICD10 codes. Approval was obtained from the institution's Institutional Review Board (IRB) prior to initiation of the study. Inclusion criteria included receipt of at least 40 mg of prednisone equivalents per day for at least 48 hours during hospitalization and receipt of

## **Original Article**

nebulized budesonide for at least 48 hours during hospitalization, if in the budesonide arm. Subjects were excluded if they had a past medical history (PMH) of Cushing's syndrome, cystic fibrosis, concomitant asthma, active cancer or any other immunosuppressive disorder, if they previously received systemic corticosteroids within the past 4 weeks, if they did not have an actual diagnosis of a COPD exacerbation per chart review, or if they had an active fungal infection. Regarding the secondary outcomes, hyperglycemia was defined as blood glucose readings above 180 mg/dl and hypoglycemia was defined as blood glucose readings below 60 mg/dl.

### **Statistical analyses:**

The unpaired T-test was used to evaluate non-parametric continuous variables, such as age. Mann-Whitney U test was used to evaluate non-parametric ordinal variables, such as length of hospitalization and Charlson Comorbidity Index. Fisher's exact test was used to evaluate non-parametric nominal variables, such as inhaler usage in each group, incidence of oral thrush, and gender. All statistical data analyses were performed using GraphPad InStat version 3.10, 32 bit for Windows, (GraphPad Software, San Diego California USA, www.graphpad.com). A significant result was set at a two-sided  $\alpha$ -level of less than 0.05.

### **Results**

Charts of 645 subjects were reviewed based off ICD9 and/or ICD10 diagnosis codes signifying a COPD exacerbation. Of those reviewed, 75 subjects met inclusion criteria. Figure 1 describes why subjects were excluded from the study. Demographic data of subjects included in the study are contained in Table 1, with no statistically significant differences between the groups.

Regarding the primary outcome, mean length of stay for non-budesonide and budesonide groups was 3.62 (95% CI 3.20 to 4.06) and 4.63 (95% CI 3.84 to 5.42) days ( $p=0.18$ ), respectively. Regarding secondary outcomes, incidence of hyperglycemic events (i.e., blood glucose readings greater than 180 mg/dL) for non-budesonide and budesonide groups were 92 and 164 ( $p=0.02$ ), while oral thrush diagnoses were noted in 0 and 4 subjects ( $p=0.12$ ), respectively. Detailed results for primary and secondary outcomes are included in Table 2.

J. Ben Hill & Jon P. Wietholter

3

### **Discussion**

## **Original Article**

The findings from this study suggest no difference in length of stay between groups receiving nebulized budesonide combined with systemic corticosteroids versus just receiving systemic corticosteroids during a COPD exacerbation. Exclusion criteria were rigorous to attempt to eliminate as many confounding factors as possible and this led to inclusion of only subjects receiving corticosteroids for COPD exacerbations. Additionally, baseline characteristics were comparable in the two groups, including the Charlson Comorbidity Index score, suggesting that there was no difference in baseline severity of illness between the groups upon admission. In addition to this noted lack of efficacy, the number of hyperglycemic events in the group receiving concomitant budesonide and systemic corticosteroids was significantly higher. These findings suggest that there is no noticeable benefit with the addition of nebulized budesonide to systemic corticosteroids during COPD exacerbations and potentially some detriment.

One difference noted in the groups was those in the non-budesonide group were significantly more likely to receive a long-acting beta agonist (LABA) than those in the budesonide group (65% vs. 10%,  $p = < 0.001$ ). This was likely due to the hospital system not having a nebulized LABA agent on the formulary at the time of this review; because of this, those in the non-budesonide group received combination LABA/inhaled corticosteroid (ICS) inhaler therapy and thus significantly more LABA therapy overall.

When comparing and contrasting the existing literature, our findings appear to support that nebulized budesonide may not be beneficial in treatment for COPD exacerbations when added to systemic corticosteroids. One study recently analyzed systemic corticosteroid therapy with and without ICS for COPD exacerbation management.<sup>16</sup> Their study found that hospital length of stay was significantly increased in subjects receiving both ICS and systemic corticosteroids.<sup>16</sup> The main differences when comparing our studies were the lack of evaluation of hyperglycemic events and inclusion of subjects with concurrent asthma or those who recently received systemic corticosteroids in their study.<sup>16</sup> However, even with these noted differences, our findings support theirs in that it appears there is no decrease in hospital length of stay when using combination corticosteroid therapy with a potential increase in adverse effects. Furthermore, a separate study analyzed the potential for cost savings when not combining ICS with systemic corticosteroids during a COPD exacerbation and concluded that institutions could save money by avoiding combination corticosteroid therapy.<sup>18</sup>

Limitations of this study include its retrospective nature and the fact that it encompassed data from only one institution. Due to the rigorous exclusion criteria utilized, this study did not encompass a huge sample size leaving the possibility that the primary outcome would have been significantly different between groups if more subjects had met inclusion criteria. In fact, our findings combined with the recent publication by Pearce and colleagues suggest that there may actually be an increase in hospital length of stay when using combination corticosteroid therapy during a COPD exacerbation.<sup>16</sup> GOLD classifications and FEV<sub>1</sub> data were not collected during this study, due to limited documentation of these data points. This information could have further strengthened the fact that both groups were well balanced in terms of severity of disease. Lastly, the primary outcome could potentially have been influenced by the aforementioned difference in LABA usage between

## **Original Article**

groups. Increased LABA usage could be a potential explanation why length of stay was shorter in the non-budesonide group.

In summary, this study showed nebulized budesonide does not appear to provide any benefit on hospital length of stay for a COPD exacerbation when added to systemic corticosteroid therapy. Additionally, there were significantly more hyperglycemic events in the combination group. This falls in line with the current literature, but future prospective trials are necessary to confirm the findings.

## **Acknowledgements:**

The authors received no financial support for the conduct of this research and authorship. We do credit the West Virginia University School of Pharmacy's Arthur I. Jacknowitz Foundation for financial support towards the publication fee for this article.

## **References:**

- GOLD Science Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2019. Available at: <http://www.goldcopd.com>. Accessed April 15<sup>th</sup> 2019.
- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380(9859):2095-2128.
- 4 International Journal of Medicine and Pharmacy, Vol. 7, No. 2, December 2019
- Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:2355–2365.
- Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010; 363(12):1128-1138.
- Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;179(5): 369-374.
- Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet*. 2007; 370(9589): 786796.
- Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157:1418-1422.
- Ceviker Y, Sayiner A. Comparison of two systemic steroid regimens for the treatment of COPD exacerbations. *Pulm Pharmacol Ther*. 2014;27:179–183.

## **Original Article**

- Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA*. 2013; 309(21): 2223-2231.
- Sun X, He Z, Zhang J, Deng J, Bai J, Li M, Zhong X. Compare the efficacy of inhaled budesonide and systemic methylprednisolone on systemic inflammation of AECOPD. *Pulm Pharmacol Ther*. 2015;31:111-116.
- Ding Z, Li X, Lu Y, Rong G, Yang R, Zhang R, et al. A randomized, controlled multicentric study of inhaled budesonide and intravenous methylprednisolone in the treatment on acute exacerbation of chronic obstructive pulmonary disease. *Respir Med*. 2016;121:39-47.
- Gunen H, Mirici A, Meral M, Akgun M. Steroids in acute exacerbations of chronic obstructive pulmonary disease: are nebulized and systemic forms comparable? *Curr Opin Pulm Med*. 2009;15(2):133-137.
- Makarova EV, Varvarina GN, Menkov NV, Czapaeva MY, Lazareva ES, Kazatskaya ZA, et al. Nebulized budesonide in the treatment of exacerbations of chronic obstructive pulmonary disease: Efficacy, safety, and effects on the serum levels of soluble differentiation molecules. *Ter Arkh*. 2016;88(3):24-31.
- Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med*. 2002;165(5):698-703.
- Yilmazel Ucar E, Araz O, Meral M, Sonkaya E, Saglam L, Kaynar H, et al. Two different dosages of nebulized steroid versus parenteral steroid in the management of COPD exacerbations: a randomized control trial. *Med Sci Monit*. 2014;20:513-520.
- Pearce JA, Shiltz DL, Ding Q. Effectiveness and safety comparison for systemic corticosteroid therapy with and without inhaled corticosteroids for COPD exacerbation management. *Ann Pharmacother*. 2018;52(11): 10701077.
- Fukushima C, Matsuse H, Tomari S, Obase Y, Miyazaki Y, Shimoda T, Kohno S. Oral candidiasis associated with inhaled corticosteroid use: comparison of fluticasone and beclomethasone. *Ann Allergy Asthma Immunol*. 2003;90(6):646-651.
- Steuber T, Shiltz D. Single-Center retrospective evaluation of inhaled corticosteroid use for chronic obstructive pulmonary disease exacerbation patients receiving systemic corticosteroids. *Hosp Pharm*. 2016;51(10):841846.

Quick Look text:

### *Current Knowledge*

Systemic corticosteroids and nebulized budesonide have been shown to be effective in treating COPD exacerbations in the hospital setting. Currently, only one study has looked at the use of inhaled corticosteroids in combination with systemic corticosteroids in COPD exacerbations in the inpatient setting.

### *What This Paper Contributes To Our Knowledge*



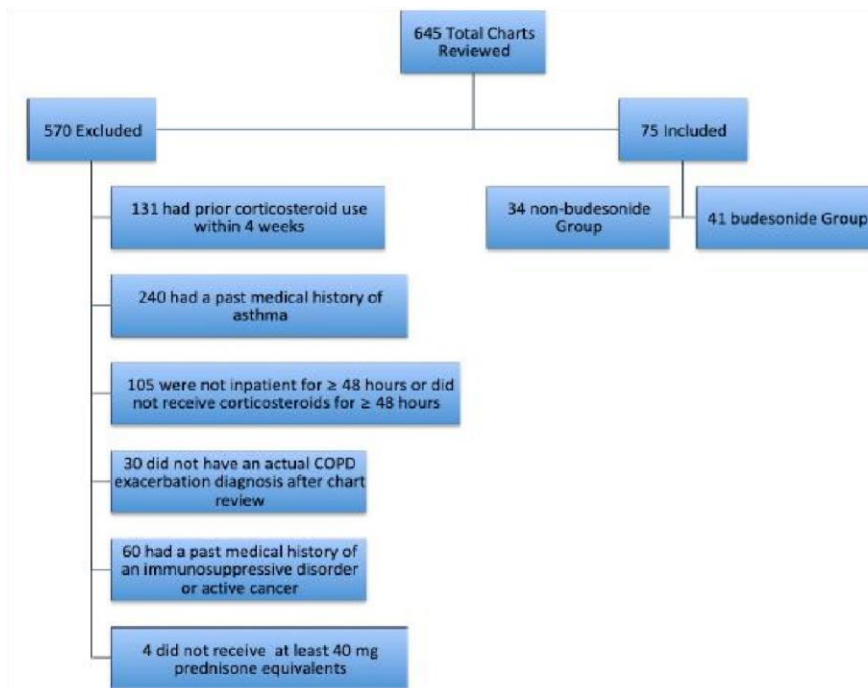
## Original Article

Giving nebulized budesonide along with systemic corticosteroids in the inpatient setting for COPD exacerbations does not shorten and may in fact lengthen hospital length of stay. Patients might be at an increased risk for hyperglycemic events in the inpatient setting if receiving both nebulized budesonide and systemic corticosteroids for COPD exacerbations.

J. Ben Hill & Jon P. Wietholter

5

**Figure 1: Reasons for exclusion**



**Table 1. Demographic Data**

	Non-budesonide group (n = 34)	Budesonide group (n = 41)	p-value
Males (%)	20 (59%)	27 (66%)	0.63
Mean Age (95% Confidence Interval)	63.6 (62.4 to 68.9)	65.7 (60.5 to 66.8)	0.37

## Original Article

Mean Charlson Comorbidity Index(95% Confidence Interval)	4.21 (3.96 to 5.30)	4.63 (3.54 to 4.88)	0.44
Pre-Existing Diabetes (%)	8 (24%)	9 (22%)	1.00

**Table 2.Adverse Effects**

	Non-budesonide group (n = 34)	Budesonide group (n = 41)	p-value
Oral candidiasis diagnosed during hospitalization	0	4	0.12
Hyperglycemic events/Total glucose readings during hospitalization	92/322 (29%)	164/446 (37%)	0.02
Patients with at least one hyperglycemic event	16	19	1.00
Hypoglycemic events/Total glucose readings during hospitalization	1/322 (0.3%)	3/446 (0.7%)	0.64

**Table 3.Concomitant Respiratory Medications Used During Hospitalization**

	Non-budesonide group (n = 34)	Budesonide group (n = 41)	p-value
Short-acting antimuscarinic (SAMA)	32	40	0.59
Long-acting antimuscarinic (LAMA)	3	2	0.65
Long-acting beta agonist (LABA)	22	4	< 0.001
Inhaled corticosteroid (ICS)	23	41	< 0.001
Montelukast	6	9	0.78
Roflumilast	1	4	0.37
Theophylline	0	5	0.060