

Use of glucocorticoids in patients with COPD exacerbations in China: a retrospective observational study

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Abstract

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are common in patients with underlying moderate to severe COPD and are associated with increased health and economic burden. International and Chinese guidelines recommend using glucocorticoids for the management of AECOPD because glucocorticoid therapy has been shown to benefit clinical outcomes. However, only scant data are available for current status of glucocorticoid therapy in hospitalized AECOPD patients in China. The aim of the study was to identify current use of glucocorticoids for the treatment of AECOPD in China.

Methods: This retrospective, multicenter, noninterventional study evaluated the treatment pattern of AECOPD in patients hospitalized from January 2014 to September 2014 at 43 sites (41 tertiary hospitals and two secondary hospitals) in China. The endpoints of the study were the percentage of patients receiving glucocorticoids by different routes of administration, doses and duration, mortality, and the mean length of hospitalization.

Results: A total of 4569 patients (90.17%) received glucocorticoids for AECOPD treatment. A combination of nebulized and systemic route was most frequently used (40.51%), followed by using nebulized route alone (38.00%), systemic route alone (15.45%), and *inhaled route* other than nebulization (6.04%). Furthermore, the most commonly prescribed glucocorticoids of the nebulized, intravenous, inhaled (other than nebulized) and oral route was budesonide (69.4%), methylprednisolone sodium succinate (45.31%), fluticasone propionate (19.54%), and prednisone acetate (11.90%), respectively. The in-hospital mortality rate was 1.24% and the mean length of hospitalization was 12.22 ± 6.20 days (\pm SD).

Conclusions: Our study was the first study of the treatment pattern of glucocorticoids in the management of hospitalized AECOPD patients in China. Data indicates that there is a gap in the implementation of international guidelines for the treatment of AECOPD in China. Further studies are warranted to clarify the appropriate glucocorticoids strategy for the management of AECOPD to determine the optimal route of administration, dose and duration, and resulting clinical outcomes.

Keywords: COPD, exacerbation, glucocorticoids, nebulization

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Introduction

Chronic obstructive pulmonary disease (COPD) is a significant public health concern, affecting approximately 64 million people globally.^{1,2} According to the World Health Organization, COPD was the third leading cause of deaths in 2012.³ In China, COPD affects 8.2% of the

population over the age of 40 years.⁴ In 2008, COPD was the fourth leading cause of death in urban areas and third in rural areas of China. Although COPD-associated mortality rates declined since 1990, hospitalization rates rose from 1.0% in 1998 to 1.6% in 2008.⁵ The clinical course of COPD is complicated by exacerbations

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with frequent episodes in severe COPD patients.^{6,7} Acute exacerbations of COPD (AECOPD) quickly deteriorate lung functions and impose significant morbidity, mortality and a great burden on health systems.^{8,9} Exacerbations occur about 0.5–3.5 times every year in COPD patients.¹⁰ Patients who have frequent exacerbations have shown poor prognosis and increased mortality.¹¹

The primary goal of management of patients with AECOPD is to reduce the impact of the current exacerbation and prevent the development of following exacerbations. Current guidelines recommend glucocorticoids as a mainstay of therapy for the treatment of AECOPD along with bronchodilators and antibiotics.¹ For example, duration of systemic glucocorticoid therapy should be used no more than 5–7 days and a dose of 40 mg prednisone daily for 5 days is recommended; nebulized budesonide alone can be a replacement of oral corticosteroids.¹ Glucocorticoids not only shorten recovery time, improve lung function (forced expiratory volume; FEV1) and oxygenation, but also decrease treatment failure, the risk of early relapse and the length of hospitalization in COPD exacerbations.¹ Although corticosteroids form an integral part in the management of acute exacerbations in COPD,¹ there are scant data regarding their use in AECOPD in the Chinese population.¹² Therefore, this study focused on the treatment pattern of glucocorticoids in hospitalized AECOPD patients in China. This study was aimed to understand current clinical practice of glucocorticoids in AECOPD management in China.

Patients and methods

Study design and population

This retrospective, multicenter (the majority are tertiary hospitals in 24 large cities in 17 provinces), non-interventional study [ClinicalTrials.gov identifier: NCT02051166] was designed to collect data from medical records of hospitalized patients with an acute exacerbation of COPD from January 2014 to September 2014 at 43 sites in China. The primary objective was to determine the use of glucocorticoids in hospitalized AECOPD patients. The patients were included in the study if patients: (1) were aged \geq 40 years; (2) were hospitalized due to AECOPD; (3) had COPD for at least 3 months before the acute

exacerbation [diagnosis of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013]; and (4) provided informed consent or for whom informed consent was waived. The patients were excluded from the study if patients: (1) had participated in any interventional study within 3 months of recruitment; (2) had ongoing AECOPD during the recruitment period; (3) were discharged against medical advice; and (4) had the primary diagnosis of hospitalization other than AECOPD. All hospitalized patients received standard bronchodilator treatment. In addition, medical history of COPD and AECOPD, smoking history, duration of hospitalization, etc. were collected from medical records. Lung function tests and blood gas analysis were recorded. Particular therapeutic strategies were not assigned to patients in advance but fell within current clinical practice. The study was approved by the institutional review board at each participating center. Informed consent was obtained from all participating patients or informed consent waiver was obtained from the local ethics committee in case patients were discharged.

Study endpoints

The primary endpoint was the percentage of patients receiving glucocorticoids for AECOPD management. The secondary endpoints were percentage of patients receiving glucocorticoids *via* different routes of administration including nebulization, intravenous, oral, or inhalation (except nebulization) and the mean dosage and duration of glucocorticoids. Other secondary endpoints were inpatient mortality rate and the mean length of hospitalization.

Determination of sample size

The sample size for the study was analyzed using an unpublished marketing research report in 2013 which stated that 33% patients received nebulized corticosteroid. Using Dixon and colleagues¹³ approach, a sample size of 5000 was determined, which provided an estimated 95% confidence interval (CI) of \pm 1.3%.

Statistical analysis

Statistical analysis was performed using the SAS statistical software 9.3. All results were descriptively analyzed. Quantitative variables were

Table 1. Demographic characteristics of the study population ($n = 5067$).

Characteristics of the study population	n (%) or mean \pm SD
Age (years)	72.70 \pm 9.50
Male	3837 (75.76)
Body mass index (kg/m ²)	22.20 \pm 4.21
Habitat ($n = 5008$)	
Passive smoking for a long time	390 (7.79)
Long-term exposure to occupational dust and smoke	296 (5.91)
Air pollution	1831 (36.56)
Damp, cold, or foggy environment	662 (13.22)
None of the above	2446 (48.84)
Smoking status ($n = 5012$)	
No smoking history	1575 (31.42)
Current smoking	1288 (25.70)
Quit smoking	2149 (42.88)
Duration of COPD (years)	9.76 \pm 9.40
Comorbidities (excluding COPD)	3469 (68.46)
Surgical history	1482 (29.25)
COPD, chronic obstructive pulmonary disease; SD, standard deviation.	

expressed as mean, median, standard deviation, 25 and 75 percentiles, and minimum and maximum, whereas qualitative variables were described by the absolute and relative frequencies (%) of each modality and number of missing data. Two-sided 95% CIs were provided, as appropriate, for the endpoints reported as proportions. All hypotheses (if not specified) were tested at the 0.05 significance level and were two-sided.

Results

Patient disposition

Of 5091 patients, 5067 were included in the full analysis set (FAS). A total of 24 patients were excluded from the study due to unfulfillment of inclusion criteria in 20 patients, repeated enrollment in 3 patients, and misplacement of the original medical record in 1 patient. The FAS population consisted of 3837 (75.76%) men and 1230 (24.24%) women at a mean age of 72.70

years. Comorbidities were present in the majority of the patients (68.50%) and cardiovascular disease was most prominent. Most patients had a smoking history (68.58%). In 1575 patients with no smoking history, more than half (896 patients) had either exposure to environmental or occupational pollution, smoke, dust, gas, passive smoking, damp, cold, foggy environment, or a combination of these (Table 1).

Treatment with glucocorticoids

In 5067 patients, 4569 (90.17%) patients received glucocorticoids and 498 (9.83%) patients did not receive glucocorticoid treatment. For 4569 patients who received glucocorticoids, the combination of nebulized and systemic (intravenous and oral) route was most frequently used (40.51%), followed by using nebulized route alone (38.00%), and systemic route alone (15.45%), and *inhaled route* other than nebulization (6.04%) (Table 2).

Table 2. Distribution of glucocorticoids treatment strategies ($n = 4569$).

Treatment strategies	<i>n</i> (%)
Nebulized + systemic	1851 (40.51)
Nebulized	1736 (38.00)
Systemic (oral/intravenous)	706 (15.45)
Inhaled (other than nebulized)	276 (6.04)

The most commonly prescribed glucocorticoid in nebulized, intravenous, oral, inhaled (other than nebulized) route was budesonide, methylprednisolone sodium succinate, prednisone acetate, and fluticasone propionate, respectively (Table 3). Table 3 also showed mean daily dose and mean duration in different routes of administration.

Among 3514 patients who received nebulized budesonide, the most common daily dose was 2 mg (1493 patients, 42.49%), followed by 4 mg (1162 patients, 33.07%) and 6 mg (657 patients, 18.70%). Among 2296 patients who received methylprednisolone sodium succinate injection, the most common daily dose was 40 mg (2078 patients, 90.51%), followed by 80 mg (422 patients, 18.38%) and 20 mg (359 patients, 15.64%). In oral therapy, 603 patients received prednisone and 177 received methylprednisolone. Among these 177 patients, the most common daily dosage was 20 mg (61 patients, 34.36%), followed by 16 mg (50 patients, 28.25%) and 8 mg (41 patients, 23.16%). Furthermore, the in-hospital mortality rate was 1.24% and the overall discharge rate was 98.76%. The mean length of hospitalization was 12.22 ± 6.20 days (\pm SD).

Discussion

This study aimed to demonstrate current treatment pattern of prescribing glucocorticoids in AECOPD patients in Chinese hospitals. Acute exacerbations extensively increase the disease burden of COPD. Using appropriate treatment of glucocorticoids can reduce the rate of relapse, the rate of treatment failure, the length of hospitalization and improve lung functions and breathlessness.^{14–17} Our data showed that glucocorticoids were widely used to treat AECOPD in hospitals in China (90.17%). From the data, we observed a

high proportion (40.51%) of combination use of glucocorticoids that reflected clinicians' preference of combining systemic and nebulized glucocorticoids for AECOPD treatment. The adverse effects resulting from the use of glucocorticoids has been an important concern, especially because COPD patients are generally elderly and immobilized.¹⁸ Cumulative dose (total dose in a lifetime) is the most essential factor to affect adverse effects using glucocorticoids.¹⁸ It has been shown that older patients persistently using nebulized inhaled corticosteroids (ICSs) are associated with fewer emergency department visits and the use of systemic corticosteroid.¹⁹ The cumulative doses of systemic corticosteroids can be reduced while prescribing ICS.²⁰ Physicians may prescribe lower doses of systemic glucocorticoids combined with higher doses of nebulized glucocorticoids in order to reduce systemic corticosteroid use and the adverse effects.

A total of 38% of patients were prescribed nebulized glucocorticoids in which nebulized budesonide was the most commonly used (69.35%). It is consistent with a national survey in China by Zhu and colleagues which showed that nebulized therapy was extensively utilized for respiratory diseases in the hospitals.²¹ This is likely due to the recommendation of nebulized budesonide being an alternative of systemic glucocorticoids in the Chinese expert consensus on AECOPD and the GOLD guideline.^{1,10} In a review by Gunen and colleagues, the positive role of high-dose nebulized budesonide in AECOPD was established, thus suggesting its use as an alternative to systemic corticosteroids.²² Nebulizers are easier for older people to use and physicians at tertiary hospitals are knowledgeable about nebulized therapy and have better accessibility to nebulizer equipment for inpatients.^{19,21} Frequent use of high-dose nebulized budesonide is relatively safe and adverse effects of the systemic corticosteroids are an important concern during the treatment of AECOPD.¹⁸ In addition, ICSs have higher topical anti-inflammatory activity and lower systemic activity leading to fewer systemic side effects compared with systemic glucocorticoids.^{23,24} A better side effect profile with nebulized budesonide was demonstrated in a randomized, controlled multicenter trial conducted in 10 hospitals in China when compared with systemic methylprednisolone. Efficacy was found to be similar between the two drugs (except for significant improvement in partial pressure of oxygen with systemic

Table 3. Most commonly prescribed glucocorticoid in different routes of administration ($n = 5067$).

Route of administration	Most commonly prescribed	Number of patients (%)	Mean daily dose \pm SD (mg)	Mean duration \pm SD (d)
nebulized	budesonide	3514 (69.35)	3.5 \pm 1.69	9.31 \pm 5.40
intravenous	methylprednisolone sodium succinate	2296 (45.31)	45.15 \pm 18.39	6.37 \pm 4.14
oral	prednisone acetate	603 (11.90)	18.43 \pm 6.94	6.25 \pm 3.84
inhaled (other than nebulized)	fluticasone propionate	990 (19.54)	0.80 \pm 0.26	8.20 \pm 5.88

methylprednisolone).¹² Our data showed the majority of patients received low-dose (most common daily dose 2 mg, followed by 4 mg) nebulized glucocorticoids. The daily dose of nebulized budesonide used in various studies ranged from 4 to 8 mg, slightly higher than the mean dose of 3.5 mg in our study.^{18,25–27} However, the optimal dose and duration of nebulized corticosteroid therapy has not been well established.

Systemic corticosteroids reduce recovery time and treatment failures in the treatment of acute exacerbations.¹ In our study, patients receiving glucocorticoids *via* the parenteral route was three times as much as those who received the drug *via* the oral route (48.65% *versus* 15.31%). This is likely due to the reason that high use of intravenous infusions/injections is very prevalent in China and many clinicians assume that the intravenous route of corticosteroid administration leads to faster onset of action and better results.^{28–30} Some clinicians may believe that onset of action of intravenous glucocorticoids is faster than that of oral glucocorticoids, especially in the acute exacerbation phase. Although current evidence indicates that the efficacy of oral glucocorticoids and intravenous glucocorticoids is comparable, the choice of route of administration of glucocorticoids was as per the discretion of the admitting physicians. Furthermore, the mean daily dose of systemic glucocorticoids was 18.43 mg (oral) and 45.15 mg (intravenous). A daily dose of 40 mg prednisone for 5 days is recommended for acute exacerbations in the GOLD guidelines.¹ However, there is no definite dose recommendation for a variety of glucocorticoids.

Our study showed an average glucocorticoid treatment of 6.25–9.31 days which lay between older guidelines recommendations (a 10 to

14-day course, GOLD 2013) and the current guideline recommendations (a 5-day course).^{1,10,31} Thus, the treatment duration of glucocorticoids seemed reasonable. In-hospital mortality in our study (1.24%) was lower than rates observed in other similar studies (ranging from 2.2% to 7.2%) and one study reported a relatively high mortality rate of 14.8%.^{11,14–16} The mean or median length of hospitalization was comparable or lower (12.2 and 11 days, respectively) when compared with other studies (ranging from 11.38 to 20.7 days), except one study with a median duration of 6 days.^{32–34} The present study was not designed to evaluate the effects of glucocorticoid therapy on the outcomes of COPD exacerbations. As a result, further research is warranted to assess the implications of these data associated with the use of glucocorticoid treatment.

Limitations of the study

There are several limitations in the study. Firstly, the majority of these hospitals were tertiary hospitals in large cities and the findings may not reflect the status of smaller hospitals in rural areas. Secondly, due to the nature of retrospective and observational design of the study, there were missing data, lack of complete evaluations of pulmonary function tests such as FEV1 and the assessment of severity of COPD, and not all pertinent risk factors were recorded. Additionally, specific comorbidities and drug therapies prior to admission have not been included.

Future directions

A post-hoc analysis is currently underway to determine the efficacy of glucocorticoids on hospitalized AECOPD patients. Further carefully designed randomized controlled trials are

warranted to evaluate the effects of the dosage or route of administration of glucocorticoids on the outcomes of the exacerbations and clarify the appropriate glucocorticoids strategy for the better management of AECOPD.

Conclusions

In conclusion, the present study was the first to provide insights into the prescribing pattern of glucocorticoids and could help understand the current practice in AECOPD management in China. The results of this study indicated that glucocorticoids were extensively used in the treatment of AECOPD in China. Nebulized corticosteroids were the most commonly used route for administering glucocorticoids either used alone or in combination with a systemic route. However, the glucocorticoid treatment related to clinical outcomes remains unknown. Therefore, further studies are needed in order to determine the optimal route of administration, dose, and duration of glucocorticoids to achieve better management of AECOPD. This study also points out the gap between guideline recommendations and real-world clinical practice in terms of the corticosteroid dosage used in AECOPD. The findings should prompt physicians and hospital administrators to closely implement guideline recommendations for better clinical outcomes.

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Conflict of interest statement

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