Original Article

The efficacy and safety of antibiotics and glucocorticoids in the treatment of elderly patients with chronic obstructive emphysema: systematic review and meta-analysis

Yanqing Mao[1,2], Ting Fu[2], Ling Wang[1], Chunjie Wang[2]

[1]Department of General Practice, The First Affiliated Hospital of Soochow University, Suzhou, China; [2]Department of General Practice, Dushu Lake Hospital Affiliated to Soochow University, Suzhou, China

Contributions: (I) Conception and design: Y Mao; (II) Administrative support: L Wang; (III) Provision of study materials or patients: C Wang; (IV) Collection and assembly of data: T Fu; (V) Data analysis and interpretation: T Fu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Chunjie Wang. Dushu Lake Hospital Affiliated to Soochow University, No. 8, Chongwen Road, Industrial Park, Suzhou 215000, China. Email: wangchunjie_suzhou@163.com.

Background: To systematically evaluate the efficacy and safety of inhaled corticosteroids (ICS) combined with antibiotics in the treatment of elderly chronic obstructive pulmonary disease (COPD) patients, and to provide some reference for the optimization of clinical treatment regimen for elderly COPD patients.

Methods: Combination of perfect search and keywords from the Chinese and foreign language databases, and the Cochrane Collaboration Center provided Review Manger 5.2 software [Cochrane Information Management System (IMS)] for statistical analysis, and the risk ratio (RR) of dichotic variables was adopted. RR and 95% confidence interval (95% CI) were used as efficacy and side effects analysis statistics in meta analysis.

Results: After independent screening by two researchers, 18 studies were included into the meta-analysis. After data analysis and statistics, the results of meta-analysis showed that the observation group (glucocorticoid combined with antibiotic treatment) and the control group (glucocorticoid therapy) first second forced expiratory volume (FEV1%) expected value (OR =1.21; 95% CI: 0.11–2.32; P=0.03), and 6-min walking distances (6-MWDs) (OR =12.92; 95% CI: 4.61–21.22; P=0.002), the COPD Assessment Test (CAT) score (OR =3.08; 95% CI: 2.58–3.57; P<0.00001) the improvement was statistically significant; incidence of adverse reactions (OR =1.24; 95% CI: 0.58–2.67; P=0.58), the incidence of acute exacerbation (OR =0.65; 95% CI: 0.39–1.08; P=0.10), FEV1 (OR =0.07; 95% CI: 0.01–0.15; P=0.09). There was no statistical difference.

Discussion: The combination of glucocorticoids and antibiotics in elderly patients with stable COPD can significantly improve their lung function and exercise ability with minimal adverse reactions.

Keywords: Antibiotics; glucocorticoids; chronic obstructive pulmonary disease (COPD); meta-analysis; systematic review

Submitted Dec 07, 2021. Accepted for publication Mar 04, 2022.

doi: 10.21037/atm-22-239

View this article at: https://dx.doi.org/10.21037/atm-22-239

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable chronic inflammatory disease of the airways characterized by airflow restriction (1). In the course of COPD, patients often have lower respiratory tract infection and other acute exacerbation of the disease. Frequent exacerbations can reduce the quality of life or patients, aggravate airway inflammation, further deteriorate lung function, and increase the hospitalization rate and mortality. Although studies (2,3) have demonstrated the presence of bacterial colonization (primarily haemophilus influenzae) in the airway of patients with stable COPD, antibiotic prophylaxis in patients with stable COPD is associated with acute exacerbation. There is consensus that antibiotic prophylaxis is not recommended for patients with stable COPD. The need for antibiotic treatment in acute exacerbation of COPD (AECOPD) has been controversial. However, the results of studies in the past 10 years have shown that infection is the main cause of AECOPD. Bacterial and atypical pathogen infection play an important role in the pathogenesis of AECOPD. In AECOPD patients with antimicrobial indications, aggressive and highly effective antibiotic treatment can rapidly relieve clinical symptoms, shorten the course of acute exacerbations, reduce the bacterial load in the airway, and delay acute exacerbations. During the course of AECOPD, the patient's cough, expectoration, shortness of breath, and wheezing are aggravated in the short term, the expectoration volume is increased, and the sputum is purulent or mucus purulent. These symptoms can be accompanied by fever and other inflammatory manifestations that are significantly aggravated. However, there is no unified definition and criteria for AECOPD. AECOPD was defined by the American Thoracic Society/European Respiratory Society in 2020 as dyspnea, cough, and/or expectoration beyond the usual variation in COPD patients requiring modifications to existing treatment. At present, the main symptoms of acute exacerbation and their categorization have been proposed by Canadian scholar. Of the symptoms identified, patients with three main symptoms are classified as type I; patients with only two major symptoms are classified as type II; and patients are classified as type III if they only have one major symptom and one of the following secondary symptoms: (I) respiratory infection within the past 5 days; (II) fever of unknown cause; (III) severe wheezing; (IV) cough aggravation; or (V) an increase in the respiratory rate or heart rate by 20% or more than usual. In general, AECOPD can be considered when COPD patients present with two of the above symptoms (at least one of which is the main symptom) for ≥2 days. The doctor will evaluate the elderly COPD patient's condition comprehensively according to the degree of dyspnea, the degree of impaired lung function, the number of acute attacks in the year before the visit and whether there are complications, and formulate the corresponding treatment plan. Drugs included short-acting bronchodilators, short-acting β2 agonists, short-acting anticholinergic agents and aminophylline; long-acting bronchodilators are long-acting β2 agonists, long-acting anticholinergic agents and sustained-release theophylline. Inhaled corticosteroids and phosphodiesterase 4 inhibitors; expectorant such as ambroxol hydrochloride, acetylcysteine, carbocylsteine, etc. Antioxidants such as carboxymethylstan and N-acetylcysteine can reduce the number of acute exacerbations of disease. Bronchodilators are important treatment drugs to control COPD symptoms, and inhalation is the first choice.

The Global Initiative Guidelines for Chronic Obstructive Pulmonary Disease (GOLD) recommend inhaled glucocorticoids (ICS) in combination with long acting β2 somatic agonists LABA as maintenance therapy for moderate to severe COPD during stabilization. To a large extent, medical regimens have not achieved satisfactory results in the control of COPD progression. Recent studies (4,5) have shown that glucocorticoid therapy for respiratory diseases such as asthma and COPD has drug resistance in the human body, which is due to the decreased sensitivity of drugs for airway receptors. Increasing the dose may ameliorate the situation, but at the same time cause adverse effects and an increased economic burden as the dose increases, especially in developing countries. Appropriate antibiotic treatment can reduce the airway inflammation of patients with COPD, and is also beneficial to improve the lung function of COPD patients, reduce the role of acute exacerbation, and significantly reduce the adverse reactions. The main innovations of this study are as follows: (I) in addition to analyzing glucocorticoid combined with antibiotics in the treatment of COPD, we also further analyzed the mechanism of action of its treatment; (II) the literatures included in our study are the latest clinical trial data, and the statistical methods are more rigorous; (III) the criteria of the included studies are more strict, and the bias and heterogeneity analysis of the included literatures are strictly controlled.

Clinical trials have explored the efficacy of glucocorticoids

and antibiotics, but there are controversies. Therefore, based on the existing literature, this study conducted a systematic and comprehensive evaluation of glucocorticoid combined with antibiotics in the treatment of elderly patients with COPD. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-239/rc).

Methods

Inclusion criteria

Studies were included in the meta-analysis if they contained all of the following:

Subject investigated: the patient was in moderate and severe COPD stability (according to the GOLD grade), 40 years of age, did not have a history of acute exacerbation within 2 weeks before enrollment, and did not regularly use theophylline medication.

Intervention study: the observation group was treated with glucocorticoid combined with antibiotics, while the control group was treated with glucocorticoid alone. Patients received topical administration of the ICS compound and oral administration of antibiotics.

Outcomes: one or more of the first second forced expiratory volume (FEV1), FEV1 as a percentage of expected value (FEV1%, FEV1% expected, FEV), adverse reactions (palpitation, palpitation, arrhythmia, nausea, vomiting), acute exacerbation (acute deterioration of respiratory symptoms requiring additional treatment), 6-min walking distance (6MWD), COPD Assessment Test (CAT) score.

Study type: randomized, controlled, and parallel clinical studies (RCT).

Exclusion criteria

Studies were excluded from the meta-analysis if they included any of the following: (I) patients with bronchial asthma, bronchiectasis, cardiovascular disease, liver and renal function impairment, active tuberculosis, digestive disease, severe hypertension, hyperglycemia, systemic disease with serious harm, or uncontrolled mental illness; (II) cohort studies, recall reports, individual case reports, or reviews; or (III) repeat reporting of literature or literature with higher similarity.

Search strategy

The Cochrane databases were searched through PubMed, Embase, The Cochrane Library, CNKI database, Wanfang Database, VIP database, China Biomedical Literature Service System, and other databases. In addition to retrieving relevant authoritative databases, this study also performs retrieval and statistical analysis on some relevant data of Registers or Websites. The retrieval time limit was until October 2021. In order to improve the retrieval strategy, we browsed the necessary references to improve the retrieval method. English keywords were searched by superposition and mixture and were the following: antibiotics, chronic obstructive pulmonary disease, glucocorticoid, and budesonide.

Literature screening and data extraction

Through perfecting the system of evaluation in advance into the exclusion standard and data extraction, and made the corresponding form in the table is made after training learning related content, in the process of screening literature, extract data is expected to appear special circumstances, after discussion decision criterion, finally by two to participate in the system evaluation personnel is based on the literature retrieval model for independent early screening. Through preliminary reading literature title and abstract to qualify in this system by perfecting the system of evaluation in advance into the exclusion standard and data extraction, and made the corresponding form in the table is made after training learning related content, in the process of screening literature, extract data is expected to appear special circumstances, after discussion decision criterion. Finally, two participants in the system evaluation conducted an independent preliminary screening of the literature obtained according to the retrieval formula, and screened the literature titles and abstracts through preliminary reading.

Bias risk assessment

Studies included in the meta-analysis were reviewed by a third person using the complete RCTs bias evaluation system from the Cochrane 5.1.0 system evaluation manual. The bias risk assessment examined the following components of each study: whether the method was random, the allocation scheme, blindness, lost visit and exit, whether the study contained selective reports of study

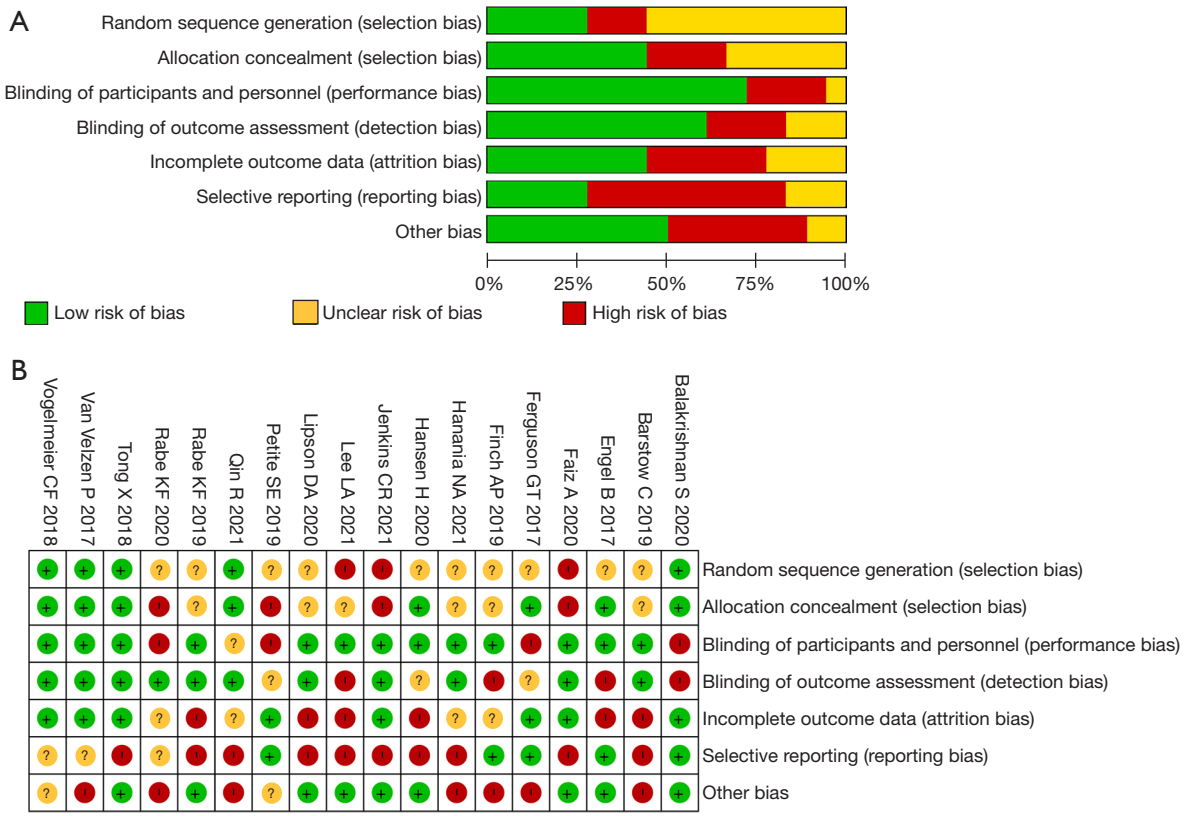

Figure 1 Literature quality evaluation chart. (A) Risk of bias graph; (B) risk of bias summary.

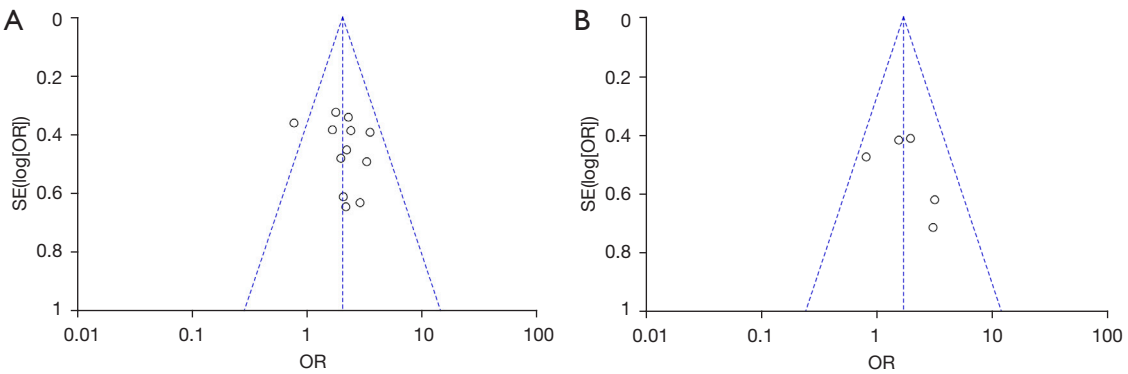

Figure 2 Funnel plot showing the literature publication bias. (A) Funnel plot of FEV1; (B) funnel plot of FEV1%. SE, standard error; OR, odds ratio; FEV1, the first second forced expiratory volume.

results, and another six risk evaluation criteria (*Figures 1*,*2*).

Data processing

There were differences in units of measurement in different documents. To overcome this, the units were unified into an international general form according to the conversion method, and then the corresponding change values were calculated by extracting the FEV1, FEV1% expected value, 6MWD, and CAT score treatment.

Statistical analysis

The Cochrane Collaboration Center provided Review

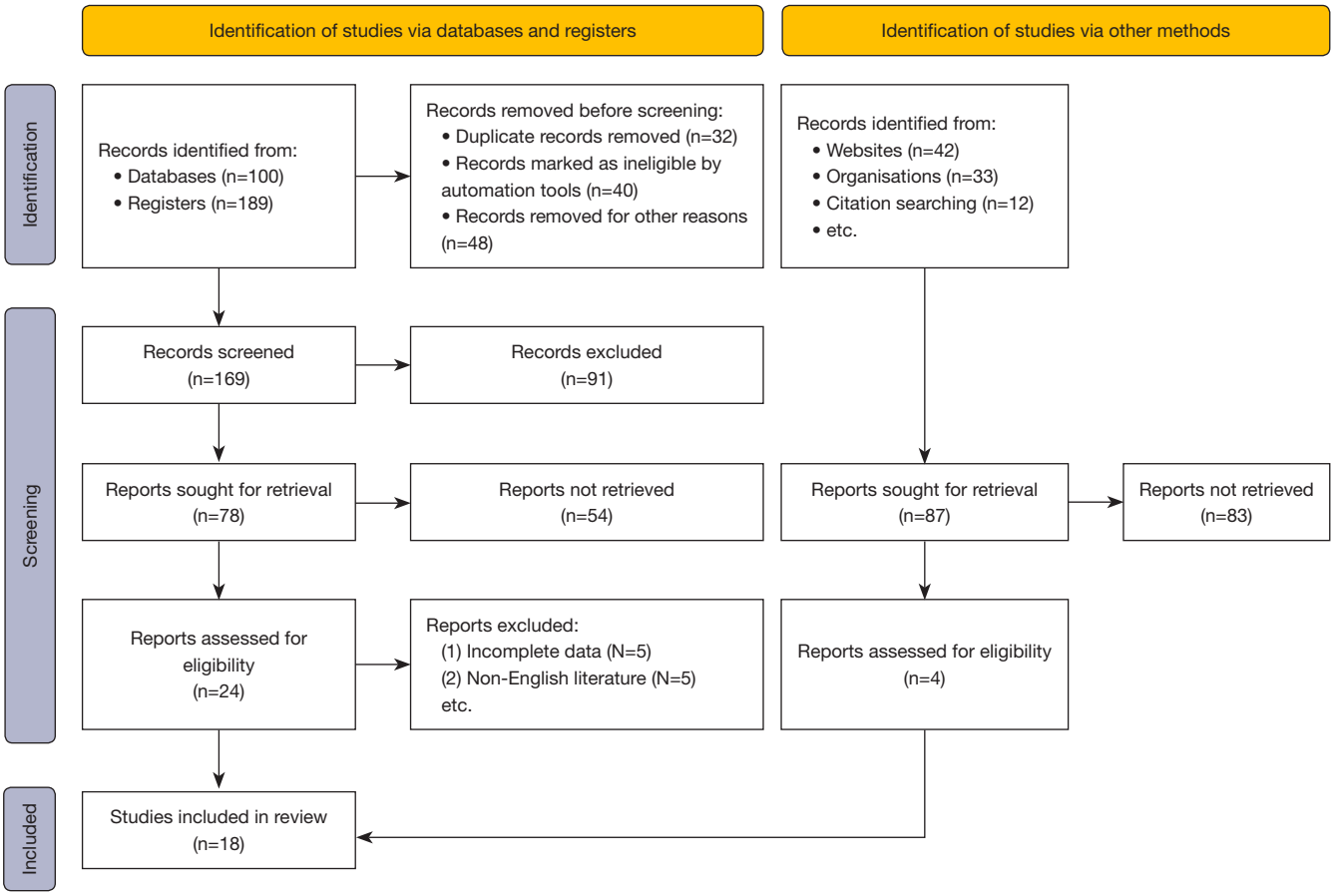

Figure 3 Flow chart of the literature screening.

Manger 5.2 software [Cochrane Information Management System (IMS)] for statistical analysis, and the Risk ratio of dichotic variables was adopted. RR and 95% confidence interval (95% CI) were used as efficacy and side effects analysis statistics in meta analysis. The included studies were analyzed by chi-square tests, and the heterogeneity size was determined based on the size of the I^2 values. I^2<50% indicated that heterogeneity should be a fixed effect mode. When I^2 was 50%, the heterogeneity was large. The source of heterogeneity was explored through sensitivity analysis. If there was statistical heterogeneity between studies without clinical heterogeneity, random effect models were used. Descriptive analysis was used when the heterogeneity between the two groups was too large or the sources of heterogeneity could not be found. When more than ten studies were included, we drew funnel plot to evaluate the publication bias.

Results

Results of literature

A total of 289 documents were obtained for the preliminary examination, and 120 relevant documents were imported into NoteExpress. All 169 articles were read, and from these 91 were excluded because they examined unstable COPD, had inconsistent administration, were non-prospective studies, or used unrelated outcome indicators (*Figure 3*). Finally, 18 studies (6-23) contained 1,636 patients (*Table 1*). No significant publication bias was found in the literature included in this study (*Figures 1,2*).

FEV1% predicted value

A total of 12 of the included studies contained data on FEV1% predicted value. Due to the small degree

Table 1 Basic clinical features of the 18 articles that were included in our study

Study	Cases (n)	Age	COPD classification	Intervention		Outcome	Treatment (months)
				Experimental group	Control group		
Tong 2018	180	68.31±3.41	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; FEV1 (%)	6
Vogelmeier 2018	120	61.60±8.59	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; FEV1 (%)	12
Barstow C 2019	70	67.96±8.79	IV	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; FEV1 (%)	5
Petite SE 2019	50	66.14±9.24	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; FEV1 (%)	6
Balakrishnan 2020	120	68.03±4.53	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; FEV1 (%)	6
Ferguson GT 2017	140	65.80±8.07	IV	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; FEV1 (%)	12
Van Velzen 2017	99	62.51±6.51	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%)	3
Engel B 2017	68	65.12±5.22	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%)	3
Finch AP 2019	78	64.05±3.71	IV	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%)	2
Rabe KF 2019	50	61.15±7.65	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%)	2
Lipson DA 2020	45	63.25±2.65	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%); 6MWD	12
Rabe KF 2020	78	62.22±4.15	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%); 6MWD	3
Hansen H 2020	56	61.35±5.65	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%); 6MWD	5
Faiz A 2020	68	68.15±5.61	III	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%); 6MWD	12
Lee LA 2021	110	68.23±2.53	IV	Glucocorticoid + antibiotics	Glucocorticoid	FEV1 (%); 6MWD	6
Jenkins CR 2021	60	67.22±4.15	IV	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; CAT	1
Hanania NA 2021	40	64.03±1.55	IV	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; CAT	1
Qin R 2021	70	645.03±3.78	IV	Glucocorticoid + antibiotics	Glucocorticoid	FEV1; CAT	4

COPD, chronic obstructive pulmonary disease; FEV1, first second forced expiratory volume; 6MWD, 6-min walking distance; CAT, COPD Assessment Test.

of heterogeneity (I^2=0%), the fixed-effect model was applied. Results showed that FEV1% predicted value in the glucocorticoid combined treatment group was better than that in the control group, and the difference was statistically significant (OR =2.00; 95% CI: 1.58–2.54; P<0.00001) (*Figure 4*).

FEV1

FEV1 was reported in 5 studies with low heterogeneity (I^2=8%). After undertaking a sensitivity analysis, two highly heterogeneous literatures were excluded and the fixed effect model was used. Meta-analysis results showed that the improvement of FEV1 in the glucocorticoid and antibiotic combined treatment group was better than that in the control group. The difference was statistically significant (OR =1.68; 95% CI: 1.10–2.57; P=0.02) (*Figure 5*).

Incidence of acute aggravation

A total of 8 studies were included, all of which lasted for 3 months or more. Due to the acceptable heterogeneity (I^2=26%), the fixed-effect model was applied. Results showed that the incidence of acute exacerbations in the glucocorticoid combined with antibiotic treatment group was lower than that in the control group. The difference was statistically significant (OR =0.68; 95% CI: 0.52–0.90; P=0.007) (*Figure 6*).

Adverse reactions

A total of 4 studies reported adverse events related to glucocorticoid combined with antibiotic therapy, including palpitations and nausea. Due to the small degree of heterogeneity (I^2=0%), the fixed-effect model was applied. Results showed that the incidence of

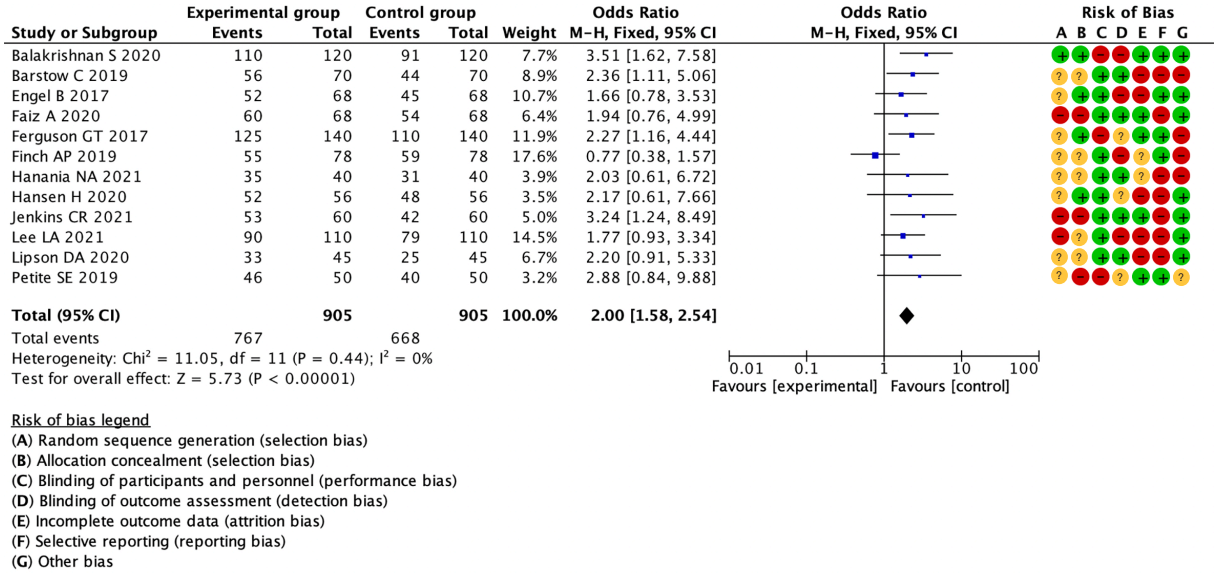

Figure 4 Meta-analysis of FEV1% predicted value. FEV1, first second forced expiratory volume.

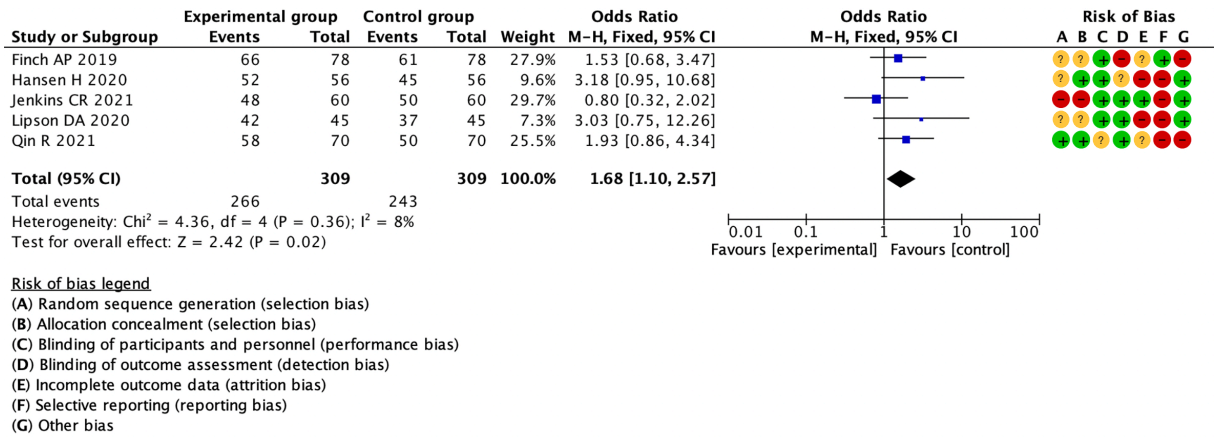

Figure 5 Meta-analysis of FEV1. FEV1, first second forced expiratory volume.

adverse reactions was statistically different between the glucocorticoid and antibiotic combination group and the control group (OR =0.51; 95% CI: 0.30–0.84; P=0.009) (*Figure 7*).

6MWD

A total of 6 included studies contained data about 6MWD. Due to acceptable heterogeneity (I^2=9%), the fixed effect model was used for analysis. Results showed that the improvement of 6MWD in patients treated with glucocorticoid combined with antibiotics was better than that in the control group, with a statistically significant difference (OR =1.52; 95% CI: 1.19–1.94; P=0.0007) (*Figure 8*).

CAT score

A total of 6 studies were included, and the heterogeneity (I^2=74%) was analyzed using fixed effect model. The improvement of the CAT score in the glucocorticoid combined with antibiotic treatment group was better than that in the control group, and the difference was statistically significant (OR =1.53; 95% CI: 1.13–2.07; P=0.006) (*Figure 9*).

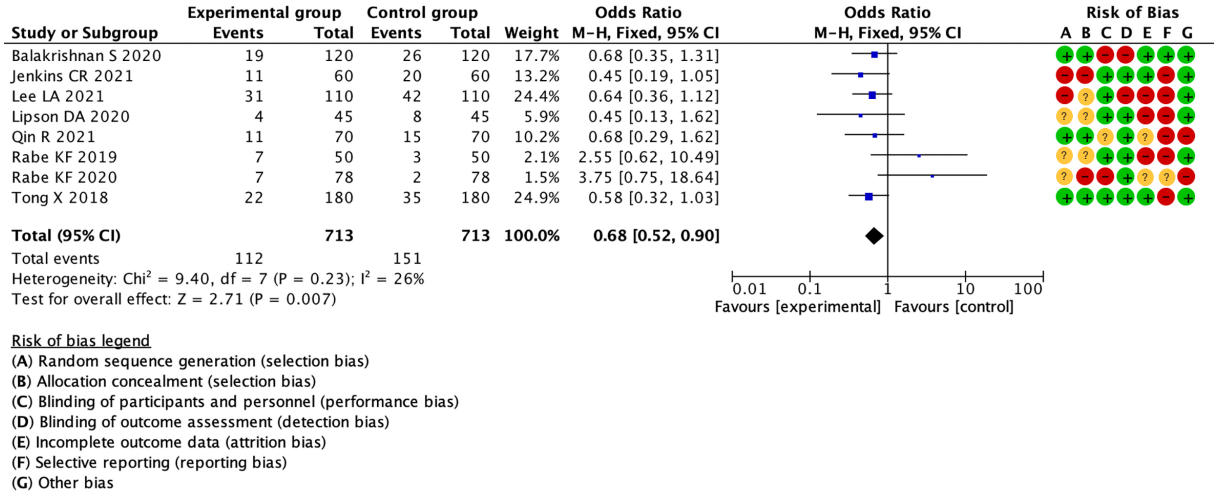

Figure 6 Meta-analysis of incidence of acute aggravation.

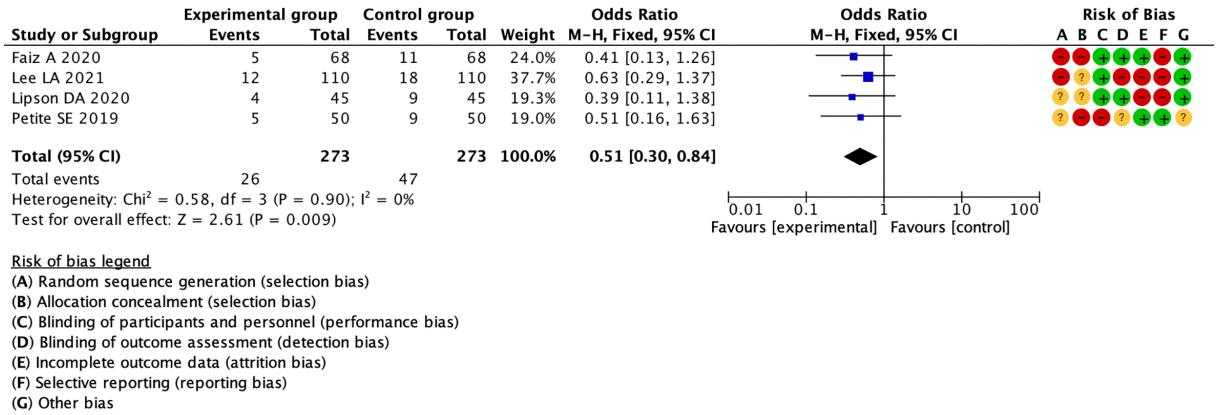

Figure 7 Meta-analysis of adverse reactions.

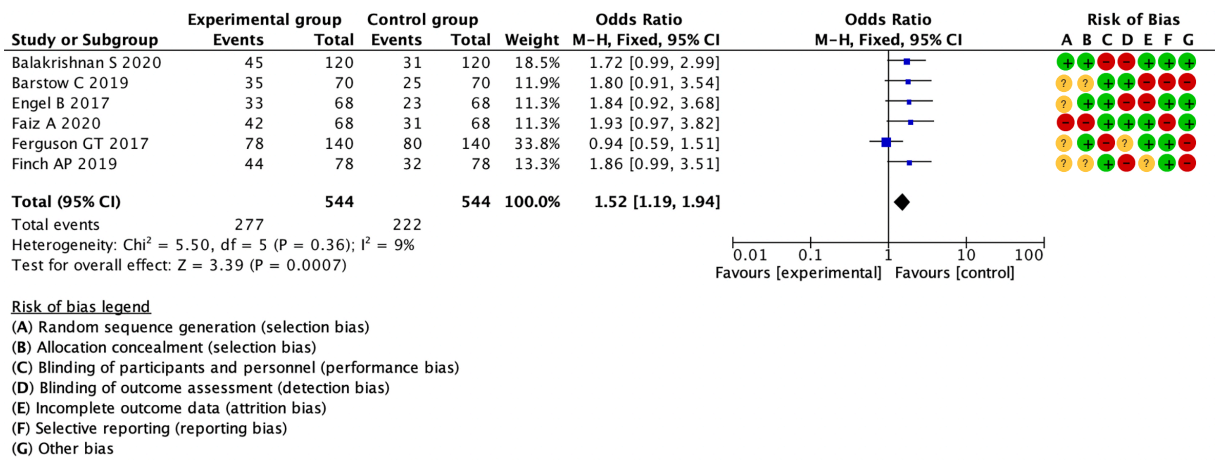

Figure 8 Meta-analysis of 6MWD. 6MWD, 6-min walking distance.

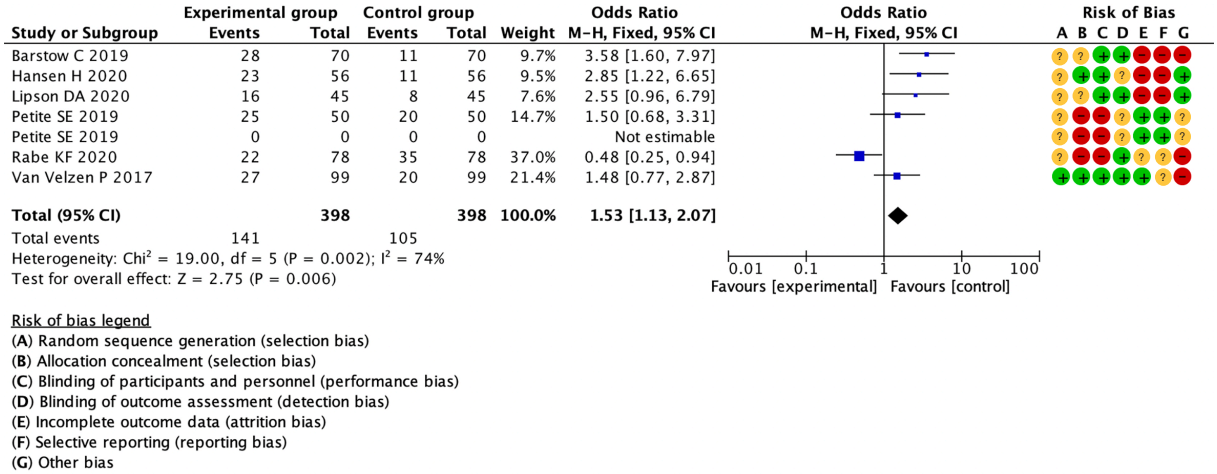

Figure 9 Meta-analysis of CAT score. CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease.

Discussion

The pathogenesis of COPD gradually evolves from acute inflammation to chronic inflammation and to tissue remodeling, resulting in irreversible airflow obstruction (24). COPD has attracted worldwide interest because of its high prevalence, morbidity, and mortality, which pose great challenges to the healthcare system and the economy. Although there are still many controversial issues surrounding the treatment regimen of COPD, the current treatment direction is mainly to combat airway inflammation and diastolic bronchial delayed airflow limitations (25-28).

A large proportion of elderly patients have COPD and also have more difficulty during treatment. For such patients, more conservative drug treatment will be carried out (29). Effectively controlling the infection is a key part of treatment in elderly patients because they have reduced body function, poor immune ability, and are often more prone to infections (30). Antibiotics have a wide clinical application rate (31). They are also commonly used in the treatment of COPD. Antibiotic drugs can inhibit synthesis of the bacterial cell wall, which kills bacteria. However, bacteria can develop different degrees of resistance to antibiotics, so antibiotics may not always be effective and the assistance of other drugs is needed (32). Clinical antibiotics and glucocorticoids are often used. Glucosides inhibit steroid hormones, which can effectively inhibit the body's immune response, have anti-toxicity and anti-inflammatory properties, and are mostly used in the clinical treatment of diseases for which there are insufficient antibiotics and anti-inflammatory drugs (33-35).

COPD is an abnormal inflammatory reaction mainly characterized by airway airflow restriction (36). Treatment often fails repeatedly, and patients with COPD can have a long disease course, especially in elderly patients who have other co-morbidities. In the process of COPD treatment, the application of antibiotics is the main measure to eliminate pathogenic bacteria and reduce symptoms. However, most patients have varying degrees of resistance to antibiotics. In view of this, this study observed that, on the application of antibiotics, methylprednisolone was added on the basis of sodium succinate, which is a glucocorticoid and has a strong anti-inflammatory and anti-shock effects, and inhibits immune response (37). In the diagnosis and treatment of COPD, glucocorticoid can reduce airway reactivity and relieve clinical symptoms by inhibiting the production and release of inflammatory cytokines (38). Our results also showed that the overall efficacy and lung function improvement in the observed group were significantly better than in the control group (39,40). Moreover, there were no serious adverse reactions, which further confirmed that treating COPD in elderly patients with a combination of glucocorticoids and antibiotics can better improve the lung function of patients (41). As medical professionals, we must recognize that the same disease affects younger and older people differently, and we must address this perceived impact and tailor and optimize treatment for each patient. Younger patients more frequently reported that COPD was extremely affecting their ability to perform tasks outside the home (37% *vs.* 22%) and to travel long distances (38% *vs.* 18%), and the

effect of glucocorticoid combined with antibiotics in the treatment of young COPD patients is better than that of elderly COPD patients, the bronchial mucosa of young COPD patients is more sensitive to drugs, and the effect of bronchial smooth muscle relaxation is more obvious, the specific clinical manifestations are shorter medication cycle, higher symptom relief rate, fewer complications.

Limitations of this study were as follows: (I) literature inclusion had geographical limitations; (II) some studies did not employ randomized hidden assignment, blinded not described, could generate selection and operational bias; (III) most of the included RCT did not report specific randomized methods for inclusion into their studies; and (IV) some indicators showed publication bias.

Conclusions

In this study, the combined group was treated with antibiotics and glucocorticoids, and the levels of FEV1, FEV%, 6MWD, and CAT score in the combined group were better than those in the control group. The total clinical effective rate in the combination group was significantly higher than that in control group, with a statistically significant difference ($P<0.05$). Our meta-analysis showed that the combination of antibiotics and glucocorticoids in the treatment of elderly patients with COPD can improve the lung function of patients, effectively control infection, and ensure the best effect of available drugs.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-239/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-239/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Vermeersch K, Gabrovska M, Aumann J, et al. Azithromycin during Acute Chronic Obstructive Pulmonary Disease Exacerbations Requiring Hospitalization (BACE). A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial. Am J Respir Crit Care Med 2019;200:857-68.
2. Walters JA, Tan DJ, White CJ, et al. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2018;3:CD006897.
3. Fawzy A, Putcha N, Aaron CP, et al. Aspirin Use and Respiratory Morbidity in COPD: A Propensity Score-Matched Analysis in Subpopulations and Intermediate Outcome Measures in COPD Study. Chest 2019;155:519-27.
4. Zhang R, Zhu J, Liu Y, et al. Optimization of Nebulized Budesonide in the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis 2020;15:409-15.
5. Petite SE, Murphy JA. Impact of the implementation of a pharmacist-driven chronic obstructive pulmonary disease exacerbation orderset in an inpatient setting. Am J Health Syst Pharm 2020;77:1128-34.
6. Tong X, Cheng A, Xu H, et al. Aspergillus fumigatus during COPD exacerbation: a pair-matched retrospective study. BMC Pulm Med 2018;18:55.
7. Vogelmeier CF, Chapman KR, Miravitlles M, et al. Exacerbation heterogeneity in COPD: subgroup analyses from the FLAME study. Int J Chron Obstruct Pulmon Dis 2018;13:1125-34.
8. Barstow C, Forbes D. Respiratory Conditions: Chronic Obstructive Pulmonary Disease. FP Essent 2019;486:26-32.
9. Petite SE, Murphy JA. Systemic Corticosteroid and

Antibiotic Use in Hospitalized Patients With Chronic Obstructive Pulmonary Disease Exacerbation. Ann Pharmacother 2019;53:144-50.
10. Balakrishnan S, Rakesh PS, Jayasankar S, et al. Lung Health Care pilot project trims patient pill load and antibiotic prescription in primary health care settings in Kerala, India. Indian J Tuberc 2020;67:202-7.
11. Ferguson GT, Tashkin DP, Skärby T, et al. Effect of budesonide/formoterol pressurized metered-dose inhaler on exacerbations versus formoterol in chronic obstructive pulmonary disease: The 6-month, randomized RISE (Revealing the Impact of Symbicort in reducing Exacerbations in COPD) study. Respir Med 2017;132:31-41.
12. van Velzen P, Ter Riet G, Bresser P, et al. Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind placebo-controlled trial. Lancet Respir Med 2017;5:492-9.
13. Engel B, Schindler C, Leuppi JD, et al. Predictors of re-exacerbation after an index exacerbation of chronic obstructive pulmonary disease in the REDUCE randomised clinical trial. Swiss Med Wkly 2017;147:w14439.
14. Finch AP, van Velzen P, Ter Riet G, et al. Doxycycline Added to Prednisolone in Outpatient-Treated Acute Exacerbations of COPD: A Cost-Effectiveness Analysis Alongside a Randomised Controlled Trial. Pharmacoeconomics 2019;37:689-99.
15. Rabe KF, Martinez FJ, Ferguson GT, et al. A phase III study of triple therapy with budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler 320/18/9.6 μg and 160/18/9.6 μg using co-suspension delivery technology in moderate-to-very severe COPD: The ETHOS study protocol. Respir Med 2019;158:59-66.
16. Lipson DA, Crim C, Criner GJ, et al. Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2020;201:1508-16.
17. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. N Engl J Med 2020;383:35-48.
18. Hansen H, Bieler T, Beyer N, et al. Supervised pulmonary tele-rehabilitation versus pulmonary rehabilitation in severe COPD: a randomised multicentre trial. Thorax 2020;75:413-21.
19. Faiz A, Imkamp K, van der Wiel E, et al. Identifying a nasal gene expression signature associated with hyperinflation and treatment response in severe COPD. Sci Rep 2020;10:17415.
20. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. Lancet Respir Med 2021;9:69-84.
21. Jenkins CR, Wen FQ, Martin A, et al. The effect of low-dose corticosteroids and theophylline on the risk of acute exacerbations of COPD: the TASCS randomised controlled trial. Eur Respir J 2021;57:2003338.
22. Hanania NA, Mannino DM, Criner GJ, et al. Effect of Age on the Efficacy and Safety of Once-Daily Single-Inhaler Triple-Therapy Fluticasone Furoate/Umeclidinium/Vilanterol in Patients With COPD: A Post Hoc Analysis of the Informing the Pathway of COPD Treatment Trial. Chest 2021;159:985-95.
23. Qin R, Liu Z, Zhou X, et al. Adherence and Efficacy of Smoking Cessation Treatment Among Patients with COPD in China. Int J Chron Obstruct Pulmon Dis 2021;16:1203-14.
24. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:228-37.
25. Daniels JM, Snijders D, de Graaff CS, et al. Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;181:150-7.
26. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med 2012;186:48-55.
27. Rabe KF, Fabbri LM, Israel E, et al. Effect of ADRB2 polymorphisms on the efficacy of salmeterol and tiotropium in preventing COPD exacerbations: a prespecified substudy of the POET-COPD trial. Lancet Respir Med 2014;2:44-53.
28. Rennard SI, Martinez FJ, Rabe KF, et al. Effects of roflumilast in COPD patients receiving inhaled corticosteroid/long-acting β2-agonist fixed-dose combination: RE(2)SPOND rationale and study design. Int J Chron Obstruct Pulmon Dis 2016;11:1921-8.
29. Sánchez-Nieto JM, Andújar-Espinosa R, Bernabeu-Mora R, et al. Efficacy of a self-management plan in exacerbations for patients with advanced COPD. Int J Chron Obstruct Pulmon Dis 2016;11:1939-47.
30. Rohde GG, Koch A, Welte T, et al. Randomized double blind placebo-controlled study to demonstrate that

antibiotics are not needed in moderate acute exacerbations of COPD--the ABACOPD study. BMC Pulm Med 2015;15:5.
31. Fan VS, Gaziano JM, Lew R, et al. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. Ann Intern Med 2012;156:673-83.
32. Kern DM, Davis J, Williams SA, et al. Comparative effectiveness of budesonide/formoterol combination and fluticasone/salmeterol combination among chronic obstructive pulmonary disease patients new to controller treatment: a US administrative claims database study. Respir Res 2015;16:52.
33. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest 2008;133:756-66.
34. Roberts M, Mapel D, Petersen H, et al. Comparative effectiveness of budesonide/formoterol and fluticasone/salmeterol for COPD management. J Med Econ 2011;14:769-76.
35. Perrone V, Sangiorgi D, Buda S, et al. Comparative analysis of budesonide/formoterol and fluticasone/salmeterol combinations in COPD patients: findings from a real-world analysis in an Italian setting. Int J Chron Obstruct Pulmon Dis 2016;11:2749-55.
36. Walters JA, Gibson PG, Wood-Baker R, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2009;(1):CD001288.
37. Perren A, Cerutti B, Lepori M, et al. Influence of steroids on procalcitonin and C-reactive protein in patients with COPD and community-acquired pneumonia. Infection 2008;36:163-6.
38. Calverley P, Vlies B. New Pharmacotherapeutic Approaches for Chronic Obstructive Pulmonary Disease. Semin Respir Crit Care Med 2015;36:523-42.
39. Bourbeau J, Sedeno MF, Metz K, et al. Early COPD Exacerbation Treatment with Combination of ICS and LABA for Patients Presenting with Mild-to-Moderate Worsening of Dyspnea. COPD 2016;13:439-47.
40. Beaulieu-Genest L, Chrétien D, Maltais F, et al. Self-administered prescriptions of oral steroids and antibiotics in chronic obstructive pulmonary disease: are we doing more harm than good? Chron Respir Dis 2007;4:143-7.
41. Stefan MS, Rothberg MB, Shieh MS, et al. Association between antibiotic treatment and outcomes in patients hospitalized with acute exacerbation of COPD treated with systemic steroids. Chest 2013;143:82-90.

(English Language Editor: C. Mullens)

Cite this article as: Mao Y, Fu T, Wang L, Wang C. The efficacy and safety of antibiotics and glucocorticoids in the treatment of elderly patients with chronic obstructive emphysema: systematic review and meta-analysis. Ann Transl Med 2022;10(6):287. doi: 10.21037/atm-22-239