Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

ORIGINAL ARTICLE

OPEN ACCESS

Effect of budesonide formoterol combined with tiotropium bromide on pulmonary function and inflammatory factors in patients with asthma-COPD overlap syndrome

Ting Jiang[a]*, Pengfei Li[a], Yang Wang[b]

[a]*Department of Respiratory and Critical Care Medicine, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, Jiangsu, China*
[b]*Department of Respiratory and Critical Care Medicine, The Affiliated Yixing People's Hospital of Jiangsu University, Wuxi, Jiangsu, China*

Received 22 March 2023; Accepted 23 May 2023
Available online 1 July 2023

KEYWORDS
AOCS;
budesonide formoterol;
endothelial function;
immune function;
lung function;
tiotropium bromide

Abstract
Objective: To investigate the clinical efficacy of combining budesonide formoterol with tiotropium bromide for treating asthma-chronic obstructive pulmonary disease overlap syndrome (AOCS).
Methods: The data of 104 patients with AOCS admitted to our hospital from December 2019 to December 2020 were assessed, randomly and divided into an experimental group (comprising 52 patients, receiving drug combination therapy) and a conventional group (comprising 52 patients, receiving drug therapy alone). Patients' clinical efficacy, pulmonary function, fractioned exhaled nitric oxide (FeNO), immune function, endothelial function, serum lipid peroxidation injury indexes, adverse reactions, and quality of life scores were compared.
Results: Prior to treatment, no significant differences were observed in various pulmonary function indicators, FeNO, immune function, endothelial function, and lipid peroxidation injury indexes between the two groups ($P > 0.05$). However, after treatment, all observation indexes in both groups improved to different levels, with the experimental group demonstrating significantly superior improvement, compared to the conventional group ($P < 0.05$). We also observed that adverse reactions in the experimental group were significantly lower than in the conventional group ($P < 0.05$).
Conclusion: The combination of budesonide formoterol to tiotropium bromide in treating asthma-COPD overlap syndrome may significantly improve pulmonary function, endothelial function, and immune status of patients and encourage the recovery of serum lipid peroxidation injury; therefore, this may deserve widespread adoption and application.

***Corresponding author:** Ting Jiang, Department of Respiratory and Critical Care Medicine, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Zhouxian Lane, Tianning District, Changzhou, Jiangsu 213003, China. *Email address*: jiang_tt0323@163.com

https://doi.org/10.15586/aei.v51i4.876

Introduction

Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (AOCS) is characterized by the coexistence of COPD and asthma, with the patients presenting the characteristics of both diseases.[1] The clinical manifestations of asthma–COPD overlap syndrome mainly comprise airflow limitation accompanied by shortness of breath, dyspnea, recurrent cough, and wheezing. Typically, asthma–COPD overlap syndrome affects individuals aged more than 40 years and is rare in adolescents.[2] Several clinical researchers have reported that its pathogenesis might be closely related to inflammation, hyperreactivity, and remodeling in airways as well as potentially other underlying factors.[3,4] Environmental factors and aging population have also contributed to an increased incidence of the disease in recent years.

Currently, the clinical management of asthma–COPD overlap syndrome is primarily based on drug therapy whereas targeted physical rehabilitation also could be considered as an essential alternative to adjuvant therapy. Regarding medical treatment, glucocorticoids and long-acting bronchodilators are the preferred options, as they can efficiently control airway inflammation, relieve airway obstruction, and decrease clinical manifestations, thereby promoting clinical efficacy.[5,6] Tiotropium bromide, a long-acting anticholinergic drug, exhibits significantly long-acting bronchodilatory effects and specificity and has demonstrated notable competence in promoting the relaxation of airway smooth muscles. Budesonide formoterol, an anti-inflammatory glucocorticoid, has demonstrated effective ability in improving the clinical management of bronchial asthma and chronic asthmatic bronchitis. In addition, the combination of these two drugs has been been effective in inhibiting progression of asthma–COPD overlap syndrome.[7] However, there have been few studies on the combination of these two drugs in treating asthma-COPD overlap syndrome.

Based on the active summaries of clinicians' experience and clinical studies, our hospital observed that the combination of drugs for treating asthma–COPD overlap syndrome can improve the control of related clinical manifestations and the quality of life because of the resulting improvement in airway obstruction, reduced airway inflammation as well as relieve of complications. Therefore, to further investigate the clinical efficacy of budesonide formoterol combined with tiotropium bromide in treating asthma-COPD overlap syndrome, data of the patients of this syndrome, clinically admitted at our hospital from December 2019 to December 2020, were retrieved and assessed.

Materials and Methods

General data

The data of 104 patients treated at our hospital from December 2019 to December 2020 were assessed and randomly divided into an experimental group (52 patients that received drug combination therapy) and a conventional group (52 patients that received budesonide formoterol alone). Their baseline data are shown in Table 1. The inclusion criteria for the study were: (1) meeting the global strategy for the diagnosis, management, and prevention of COPD (www.goldcopd.org; updated 2014 version); (2) patients aged >18 years; (3) patients providing signed informed consent; and (4) patients that cooperated with the prescribed treatment. The exclusion criteria were: (1) presence of dyspnea, cough and asthma because of other reasons; (2) lactating or pregnant women; and (3) patients with severe liver and kidney dysfunction. The study protocol was approved by the Ethics Committee of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University (Approval No. 2018-043).

Method

After admission, patients in both groups were immediately given conventional treatment. Patients in the experimental group were also given two doses of inhalation therapy with tiotropium bromide (Lianyungang Runzhong Pharmaceutical Co. Ltd.; State Medical Permit No. H20060690), at a dose of 18 ug/time, once in the morning and the other in the evening. It was combined with budesonide formoterol inhalation, at a dose of 320 ug/time, once in the morning and the other in the evening.

Patients in the conventional group were given budesonide formoterol (CF PharmTech. Inc.; State Medical

Table 1 Comparison of general data between the study groups.

Indicator		Experimental group (n = 52)	Conventional group (n = 52)	t/χ^2 value	P-value
Gender (n, %)	Female	26, 50%	27, 51.92%	0.0385	0.8445
	Male	26, 50%	25, 48.08%		
Age (year)		43.54 ± 4.12	43.63 ± 4.31	0.1088	0.9135
Height (cm)		170.83 ± 14.32	170.65 ± 14.54	0.0636	0.9494
Weight (kg)		59.62 ± 5.23	59.71 ± 5.38	0.0865	0.9312
Disease severity (n, %)	Severe	16, 30.77%	17, 32.69%	0.0606	0.9702
	Moderate	17, 32.69%	16, 30.77%		
	Mild	19, 36.54%	19, 36.54%		
Smoking (n, %)	Yes	15, 28.85%	17, 32.69%	0.1806	0.6709
	No	37, 71.15%	35, 67.31%		
Allergic history (n, %)	Yes	16, 30.77%	17, 32.69%	0.0420	0.8377
	No	36, 69.23%	35, 67.31%	0.0444	0.8331

Permit No. H20213357) inhalation, 320 ug/time, twice a day (BID). Patients in both groups were treated for approximately 6 months. All procedures involving human participants were conducted following the standards of the Ethics Committee of our hospital and the Declaration of Helsinki 1964 and related later amendments.

Outcome measures

1. *Clinical efficacy*
   Treatment response was graded as marked response (patients whose pulmonary function indexes returned to normal, with the disappearance of symptoms, such as asthma, dyspnea, and others), moderate response (patients that indicated significant improvement in pulmonary function indexes and experienced noticeable relief in asthma and breathing difficulties, although they did not return to normal), no response (patients not achieving marked or moderate response). The overall response was calculated as the sum of marked response rate and moderate response rate.
2. *Fractioned exhaled nitric oxide (FeNO)*
   Prior to and following the treatment, the pulmonary function indexes of the patients were measured using the NIOX FeNO measurement system (Swedish). The equipment was configured with the following settings: an expiratory flow rate of 50 mL/s. During the test, the patients were asked to maintain a sedentary position while exhaling as deeply as possible with a disposable filter in their mouth. When patients exhaled to the residual volume, they inhaled deeply for 3–5 s, then exhaled steadily for 10 s. The relevant data were recorded for analysis.
3. *Immune function indexes*
   Venous blood samples of the patients were collected in the morning prior to and following the treatment. A volume of 100 μL of blood was drawn using a micropipette and added to the bottom of a tube in a flow cytometer. Distilled water was used as a blank control. Then, 20 μL of monoclonal antibody was added to the machine tube and incubated at 37°C for 20 min, following which 500 μL of erythrocyte lysate was added. Following incubation at 37°C for 20 min with continuous shaking, 500-μL phosphate-buffered saline (PBS) solution was added. The parameter was set at 500 g/min, and centrifugation was performed for 10 min. Then the precipitate was removed, and the collected supernatant was tested. T cell subsets with fluorescently labeled CD3 + antibody, CD4 + T cells, and CD8 + T cells were differentiated with CD8 + antibody. Th1 and Th2 cells were distinguished using interleukin (IL)-4 antibody and interferon gamma (IFN-γ) antibody. Finally, the Th1/Th2 value was calculated using the obtained data.
4. *Pulmonary function indexes*
   Prior to and following the treatment, forced expiratory volume in 1 s (FEV1), inspiratory fraction/total lung capacity (IC/TLC), and ratio of residual volume to total lung capacity (RV/TLC) were measured using a Mastercreen spirometer (Jaeger, Germany).
5. *Endothelial function*
   Prior to and after the treatment, ET-1 (endothelin-1) and sICAM-1 (soluble intercellular adhesion molecule-1) were measured using enzyme-linked immunosorbent serological assay (ELISA) kit (Shanghai Jining Industrial Co. Ltd, China) by following the manufacturer's instructions.
6. *Lipid peroxidation injury indexes*
   BeforePrior to and after the treatment, venous blood samples were drawn from patients in the morning to measure the patients' malondialdehyde (MDA) and superoxide dismutase (SOD) levels by using an automatic biochemical analyzer (Shanghai Shangbao Biological Technology Co. Ltd, China) based on the manufacturer's instructions.

Finally, adverse reactions, such as dry mouth, constipation, etc., were observed.

Statistical analysis

The SPSS v21.0 statistical software was used for data processing. Measurement data were expressed as $\bar{x} \pm s$, and *t*-test was performed. Enumeration data were expressed as relative numbers, and the Chi-square (χ^2) test was used. $P < 0.05$ was used to indicate significant differences.

Results

Therapeutic efficacy

Our results showed that the overall response rate in the experimental group was 92.31%, which was significantly higher than 73.08% that of the conventional group ($P < 0.05$). The detailed results are shown in Table 2.

Pulmonary function indexes and FeNO

Prior to the treatment, no significant difference was observed in pulmonary function and FeNO indexes of both groups ($P > 0.05$). However, after the treatment, all pulmonary function and FeNO indexes in both groups were found

Table 2 Comparison of therapeutic efficacy (n [%]).

Group	n	No response	Moderate response	Marked response	Overall response rate
Experimental group	52	4 (7.69)	28 (53.85)	20 (38.46)	48 (92.31)
Conventional group	52	15 (28.85)	17 (32.69)	20 (38.46)	38 (73.08)
X^2 value	-				6.7183
P-value	-				0.0095

to improve substantially, with the experimental group demonstrating significantly superior improvement, compared to the conventional group ($P < 0.05$). The results are shown in Table 3.

Immune function indexes

Prior to the treatment, no significant differences were observed in various immune function indexes of both groups ($P > 0.05$). However, after treatment, various immune function indexes in both groups improved notably, with amelioration being significantly greater in the experimental group, compared to the conventional group ($P < 0.05$). The detailed results are shown in Table 4.

Endothelial function

Prior to treatment, the values of various endothelial function indexes in both groups were similar ($P > 0.05$); however, after treatment, we observed that the experimental group had significantly better endothelial function indexes, compared to the conventional group ($P < 0.05$) (Table 5).

Indexes of serum lipid peroxidation injury

Prior to treatment, no significant differences were observed in all indexes of lipid peroxidation injury in both groups ($P > 0.05$); however, after treatment, they improved significantly in both groups, with the experimental group demonstrating superior improvement, compared to the conventional group ($P < 0.05$) (Table 6).

Adverse reactions

The incidence of adverse reactions in the experimental group was lower than in the conventional group, and the difference was statistically significant ($P < 0.05$). Detailed results are presented in Table 7.

Discussion

The asthma-COPD overlap syndrome is a complex condition, with patients exhibiting features of both asthma and COPD. The underlying pathogenesis of this syndrome is believed to be closely related to inflammation, hyperreactivity, and remodeling of airways. In terms of airway inflammation, mast cells, eosinophils, and CD4 + T lymphocytes are reported to be the primary cells promoting airway inflammation in asthmatic patients, while macrophages, neutrophils, and CD8 + T lymphocytes are found to be the primary cells promoting airway inflammation in patients with simple COPD.[8] As an inflammatory mediator generated by eosinophils and mast cells, cysteinyl leukotrienes (CysLTs) could exacerbate airway inflammation and promote bronchial contraction in asthmatic patients.[9-11] However, the impact of cysteinyl leukotrienes has been shown to be insignificant in patients with simple COPD.[12-14] Comparatively, as the level of eosinophils remains high in

Table 3 Comparison of pulmonary function indexes and FeNO ($\bar{x} \pm s$).

Group	n	FEV1 (L)				IC/TLC (%)				RV/TLC (%)				FeNO (μg/L)			
		Pre-treatment	Post-treatment	*t*-value	P-value	Pre-treatment	Post-treatment	*t*-value	P-value	Pre-treatment	Post-treatment	*t*-value	P-value	Pre-treatment	Post-treatment	*t*-value	P-value
Experimental group	52	1.25 ± 0.12	1.94 ± 0.16	24.8783	0.0000	40.14 ± 3.31	54.15 ± 5.16	16.4798	0.0000	47.24 ± 4.16	30.84 ± 2.86	23.4262	0.0000	29.74 ± 2.16	17.85 ± 1.36	33.5907	0.0000
Conventional group	52	1.22 ± 0.11	1.34 ± 0.13	5.0814	0.0000	40.24 ± 3.65	46.24 ± 3.13	8.9984	0.0000	47.66 ± 4.20	41.13 ± 3.30	8.8158	0.0000	30.75 ± 3.20	26.12 ± 2.30	8.4722	0.0000
t-value		1.3289	20.9874	-	-	0.1463	9.4513	-	-	0.5123	16.9921	-	-	1.8865	22.3188	-	-
P-value		0.1868	0.0000	-	-	0.8839	0.0000	-	-	0.6095	0.0000	-	-	0.0621	0.0000	-	-

FEV1: forced expiratory volume in 1 second; IC/TLC: inspiratory fraction; RV/TLC: ratio of residual volume to total lung capacity; FeNO: fractional exhaled nitric oxide.

Table 4 Comparison of immune function indexes ($\bar{x}$ ± s).

Group	n	TH1 (%)				TH2 (%)				TH1/TH2			
		Pre-treatment	Post-treatment	*t*-value	*P*-value	Pre-treatment	Post-treatment	*t*-value	*P*-value	Pre-treatment	Post-treatment	*t*-value	*P*-value
Experimental group	52	10.21 ± 0.11	34.34 ± 3.13	55.4889	0.0000	2.24 ± 0.15	1.68 ± 0.13	20.3442	0.0000	4.59 ± 0.30	20.63 ± 2.51	45.7564	0.0000
Conventional group	52	10.24 ± 0.10	21.94 ± 2.16	39.0183	0.0000	2.23 ± 0.21	1.89 ± 0.16	9.2868	0.0000	4.63 ± 0.42	11.77 ± 1.79	28.0033	0.0000
t-value	-	1.4552	23.5127	-	-	0.2794	6.2962	-	-	0.5588	20.7242	-	-
P-value	-	0.1487	0.0000	-	-	0.7805	0.0000	-	-	0.5775	0.0000	-	-

Note: TH1: T-helper 1; TH2: T-helper 2.

Table 5 Comparison of endothelial function ($\bar{x}$ ± s).

Group	n	ET-1 (ng/L)				SICAM-1 (mg/mL)			
		Pre-treatment	Post-treatment	*t*-value	P-value	Pre-treatment	Post-treatment	*t*-value	P-value
Experimental group	52	3.21 ± 0.21	2.45 ± 0.23	17.5966	0.0000	637.24 ± 59.15	428.23 ± 40.23	21.0695	0.0000
Conventional group	52	3.24 ± 0.20	3.15 ± 0.26	1.9785	0.0506	648.25 ± 60.21	632.54 ± 60.16	1.331	0.1862
t-value	-	0.746	14.5414	-	-	0.9406	20.3574	-	-
P-value	-	0.4574	0.0000	-	-	0.3491	0.0000	-	-

Note: ET-1: endothelin-1; SICAM-1: human intercellular adhesion molecule-1.

Table 6 Indexes of serum lipid peroxidation injury ($\bar{x}$ ±s).

Group	n	MDA (nmol/L)				SOD (U/mL)			
		Pre-treatment	Post-treatment	*t*-value	P-value	Pre-treatment	Post-treatment	*t*-value	P-value
Experimental group	52	7.21 ± 0.61	4.45 ± 0.42	26.8734	0.0000	43.25 ± 4.15	68.24 ± 6.23	24.0734	0.0000
Conventional group	52	7.24 ± 0.60	6.35 ± 0.56	7.8197	0.0000	43.28 ± 4.21	56.54 ± 5.16	14.3582	0.0000
t-value	-	0.2528	19.573	-	-	0.0366	10.4297	-	-
P-value	-	0.8009	0.0000	-	-	0.9709	0.0000	-	-

Note: MDA: malondialdehyde; SOD: superoxide dismutase.

Table 7 Comparison of adverse reactions (n [%]).

Group	n	Candida infection	Dry mouth	Constipation	Palpitation	Dysuria	Overall incidence
Experimental group	52	1 (1.92)	0 (0.00)	1 (1.92)	1 (1.92)	1 (1.92)	4 (7.7)
Conventional group	52	3 (5.77)	2 (3.85)	1 (1.92)	5 (9.62)	4 (7.69)	15 (28.85)
X^2 value	-			-			7.7920
P-value	-			-			0.0052

airway inflammatory cells in the asthma–COPD overlap syndrome patients, it could be reasonable to assume that the levels of leukotrienes also remain relatively high in these patients.

Airway hyperresponsiveness is a notable characteristic of asthma–COPD overlap syndrome, resulting from reversible changes in airways formed during the course of COPD. In patients with airway inflammation, airway hyperresponsiveness refers to airway narrowing triggered by various stimuli, such as dust, pollen, tobacco, smell, cold air, etc. Although airway hyperresponsiveness could be encountered in both asthmatic and COPD patients, it

is more commonly observed in asthmatic patients. Airway hyperresponsiveness contributes to increased clinical manifestations and a significant decrease in FEV1. Consequently, the targeted management of airway hyperresponsiveness is one of the essential principles of the clinical treatment of asthma–COPD overlap syndrome.

Airway remodeling is also an important characteristic of asthma–COPD overlap syndrome, mainly characterized by an increase in airway smooth muscle mass, goblet cell hyperplasia, vascular proliferation, airway edema, epithelial detachment, and shorter distance between epithelial cells and smooth muscle cells. This changes lead to inflammatory reactions, mucosal edema, massive mucus secretion, and mucus plugs,[15,16] and are commonly observed in patients with asthma–COPD overlap syndrome and those with airway-obstructive diseases.[17,18] Structural changes in airways increase airway hyperresponsiveness, thereby exacerbating patient's clinical manifestations. For patients with asthma–COPD overlap syndrome, remodeling in small airways is the main cause of reduced lung function. Based on this, relevant clinical studies have confirmed that bronchodilators, glucocorticoids, and leukotriene receptor antagonists are the main drugs for treating asthma–COPD overlap syndrome.

Tiotropium bromide is a clinical anticholinergic drug and a common selective bronchodilator recommended as an optimal therapy for the clinical maintenance treatment of COPD. It can interact with M1 and M3 receptors to effectively inhibit the process of airway inflammatory response, thereby improving clinical efficacy. Budesonide formoterol, as a glucocorticoid, is the drug of choice for the clinical treatment of airway inflammation.[19,20] It also acts as a β2 receptor agonist to bind to eosinophils-related inflammatory cells, thereby inhibiting the effect of inflammatory cells and attenuating the contraction of smooth muscles. Studies have shown that the combination of these two drugs in treating asthma–COPD overlap syndrome has synergistic effects, resulting in significant improvement in overall clinical efficacy.[21] FeNO is a biomarker used widely in clinical practice to reflect the level of respiratory inflammation and changes in eosinophil levels and is applied to monitor the diseased condition. Restoration of lung function is one of the main objectives of treating asthma, and parameters such as FEV1, IC/TLC, RV/TLC, and FeNO (ug/L) are the commonly used lung function indexes.[22]

The present study revealed that the investigated combination drug therapy had a better effect on improving these pulmonary function parameters, possibly because the integration of both drugs could improve lung function and airway inflammation by ameliorating bronchial smooth muscle functions.

Studies have demonstrated that airway hyperresponsiveness is closely related to immune function, with the Th1/Th2 ratio serving as an immune function index.[23,24] Airway hyperresponsiveness is associated with an imbalance of Th1/Th2 cytokine ratio, which is characterized by decreased Th1 expression and increased Th2 expression. This results in decreased Th1/Th2 ratio, which has been confirmed in asthmatic patients. In this study, patients in the experimental group demonstrated increased Th1 expression, decreased Th2 expression, and increased Th1/Th2 ratio after treatment, which was better than that observed in the patients of conventional group. This demonstrated that the combined drug treatment could better regulate the imbalance of Th1/Th2 cytokine ratio and promote the recovery of Th1 and Th2 cytokine structure, thereby effectively promoting the recovery of immune function and patient's immunity.

sICAM-1 promotes endothelial cell and leukocyte adhesion by binding to ligands, and its downregulation improves endothelial functions. Enhanced endothelial function can promote the secretion of ET-1, which helps to regulate systemic vascular tension and reduce the proliferation of smooth muscle cells. Serum lipid peroxidation injury indexes, including MDA and SOD, are used for evaluating oxidative processes *in vivo*. MDA can degrade fatty acid peroxides and reflect the degree of lipid peroxidation and oxygen-free radical damage. SOD can effectively scavenge oxygen-free radicals and resist free radical damage.[25]

In the present study, improvement of the above-mentioned indexes in the experimental group was significantly better than that in the conventional group after treatment, suggesting that the combination regimen could improve endothelial functioning of patients, regulate vascular tension, and effectively protect against serum lipid peroxidation injury, consistent with similar reports in the literature.[26-28] Meanwhile, regarding adverse reactions, this study observed no serious adverse reactions in patients treated with combination regimen, thereby demonstrating its potential clinical safety.

This study has certain limitations pertaining to hospital conditions. The range of discovery and observation indicators used may not be comprehensive enough. This indicates the necessity to further expand the scope of observation indicators in the future research to assess more comprehensively the clinical effects of combination regimen of budesonide formoterol and tiotropium bromide in treating asthma–COPD overlap syndrome.

Conclusion

Asthma–COPD overlap syndrome is a common respiratory disease characterized not only by airflow limitation but also by clinical manifestations such as shortness of breath, dyspnea and wheezing. The disease is closely associated with airway inflammation. Combined therapy is used in its clinical treatment, which has shown promising efficacy in lessening airway obstruction, reducing airway inflammation, controlling clinical manifestations, and improving quality of life. Tiotropium bromide, commonly used for treating COPD, softens smooth muscles. Budesonide has a significant anti-inflammatory effect and is applied to treat asthma and bronchitis. Combined drug therapy prescribed to patients with asthma–COPD overlap syndrome improves pulmonary and vascular endothelial functioning, reduces adverse reactions, and enhances immune functioning, thereby supporting this treatment approach.

Funding

This work was supported by the Municipal Science and Technology Plan (Guidance) Project of Nantong City of 2014 (Grant No. HS149147).

Availability of Data and Material

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed are available from the corresponding author on making a reasonable request.

Competing interests

The authors stated that there was no conflict of interest to disclose.

Author Contributions

Ting Jiang designed the study, completed the experiment, and supervised data collection. Pengfei Li analyzed and interpreted the data. Yang Wang prepared and reviewed the draft of the manuscript for publication. All authors read and approved the final manuscript.

References

1. Shin S, Bai L, Burnett RT, Kwong JC, Hystad P, van Donkelaar A, et al. Air pollution as a risk factor for incident chronic obstructive pulmonary disease and asthma. A 15-year population-based cohort study. Am J Resp Crit Care Med. 2021;203(9):1138–48. https://doi.org/10.1164/rccm.201909-1744OC
2. Eklöf J, Alispahic IA, Sivapalan P, Wilcke T, Seersholm N, Armbruster K, et al. Targeted antibiotics for chronic pulmonary diseases (TARGET ABC): Can targeted antibiotic therapy improve the prognosis of pseudomonas aeruginosa-infected patients with chronic pulmonary obstructive disease, non-cystic fibrosis bronchiectasis, and asthma? A multicenter, randomized, controlled, open-label trial. Trials. 2022;23(1):817. https://doi.org/10.1186/s13063-022-06720-z
3. Gemicioglu B, Uzun H, Borekci S, Karaali R, Kurugoglu S, Atukeren P, et al. Focusing on asthma and chronic obstructive pulmonary disease with COVID-19. J Infect Develop Countries. 2021;15(10):1415–25. https://doi.org/10.3855/jidc.14611
4. Boulet LP, Hanania NA. When asthma and chronic obstructive pulmonary disease overlap; current knowledge and unmet needs. Immunol Allergy Clin North Am. 2022;42(3):499–505. https://doi.org/10.1016/j.iac.2022.05.001
5. Adrish M, Anand MP, Hanania NA. Phenotypes of asthma-chronic obstructive pulmonary disease overlap. Immunol Allergy Clin North Am. 2022;42(3):645–55. https://doi.org/10.1016/j.iac.2022.04.009
6. Liang Y, Mak JCW. Inhaled therapies for asthma and chronic obstructive pulmonary disease. Curr Pharm Des. 2021;27(12):1469–81. https://doi.org/10.2174/1389201021666201126144057
7. Ismaila AS, Haeussler K, Czira A, Youn JH, Malmenäs M, Risebrough NA, et al. Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy compared with other therapies for the treatment of COPD: A network meta-analysis. Adv Ther. 2022;39(9):3957–78. https://doi.org/10.1007/s12325-022-02231-0
8. Li A, Chan HP, Gan PXL, Liew MF, Wong WSF, Lim HF. Eosinophilic endotype of chronic obstructive pulmonary disease: Similarities and differences from asthma. Korean J Int Med. 2021;36(6):1305–19. https://doi.org/10.3904/kjim.2021.180
9. Shao KM, Bernstein JA. Asthma-chronic obstructive pulmonary disease overlap: The role for allergy. Immunol Allergy Clin North Am. 2022;42(3):591–600. https://doi.org/10.1016/j.iac.2022.04.002
10. Hudler A, Holguin F, Sharma S. Pathophysiology of asthma-chronic obstructive pulmonary disease overlap. Immunol Allergy Clin North Am. 2022;42(3):521–32. https://doi.org/10.1016/j.iac.2022.04.008
11. Sharma S, Khurana S, Federman AD, Wisnivesky J, Holguin F. Asthma-chronic obstructive pulmonary disease overlap. Immunol Allergy Clin North Am. 2020;40(4):565–73. https://doi.org/10.1016/j.iac.2020.07.002
12. Kaminsky DA, Irvin CG. The physiology of asthma-chronic obstructive pulmonary disease overlap. Immunol Allergy Clin North Am. 2022;42(3):575–89. https://doi.org/10.1016/j.iac.2022.04.001
13. Dumitrache MD, Jieanu AS, Scheau C, Badarau IA, Popescu GDA, Caruntu A, et al. Comparative effects of capsaicin in chronic obstructive pulmonary disease and asthma (review). Exp Ther Med. 2021;22(3):917. https://doi.org/10.3892/etm.2021.10349
14. Sahu A, Swaroop S, Kant S, Banerjee M. Signatures for chronic obstructive pulmonary disease (COPD) and asthma: A comparative genetic analysis. Br J Biomed Sci. 2021;78(4):177–83. https://doi.org/10.1080/09674845.2021.1905988
15. Hanania NA, Miravitlles M. Pharmacologic management strategies of asthma-chronic obstructive pulmonary disease overlap. Immunol Allergy Clin North Am. 2022;42(3):657–69. https://doi.org/10.1016/j.iac.2022.05.002
16. Schultze A, Walker AJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: An observational cohort study using the OpenSAFELY platform. Lancet Respir Med. 2020;8(11):1106–20. https://doi.org/10.1016/S2213-2600(20)30415-X
17. D'Urzo AD, Price D, Kardos P, Maleki-Yazdi MR. Importance of distinguishing between asthma and chronic obstructive pulmonary disease in primary care. Can Fam Phys (Medecin de Famille Canadien). 2021;67(9):661–7. https://doi.org/10.46747/cfp.6709661
18. Long B, Rezaie SR. Evaluation and management of asthma and chronic obstructive pulmonary disease exacerbation in the emergency department. Emerg Med Clin North Am. 2022;40(3):539–63. https://doi.org/10.1016/j.emc.2022.05.007
19. Diver S, Brightling CE, Greening NJ. Novel therapeutic strategies in asthma-chronic obstructive pulmonary disease overlap. Immunol Allergy Clin North Am. 2022;42(3):671–90. https://doi.org/10.1016/j.iac.2022.04.005
20. Huang K, Chung KF. Clinical assessment and utility of biomarkers in asthma-chronic obstructive pulmonary disease overlap. Immunol Allergy Clin North Am. 2022;42(3):631–43. https://doi.org/10.1016/j.iac.2022.04.004
21. Zhou XL, Zhao LY. Comparison of clinical features and outcomes for asthma-COPD overlap syndrome vs. COPD patients: A systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25(3):1495–510. https://doi.org/10.26355/eurrev_202102_24857
22. Halpin DMG. What is asthma chronic obstructive pulmonary disease overlap? Clin Chest Med. 2020;41(3):395–403. https://doi.org/10.1016/j.ccm.2020.06.006
23. Gaffney AW. Disparities in disease burden and treatment of patients asthma and chronic obstructive pulmonary disease. Med Clin North Am. 2022;106(6):1027–39. https://doi.org/10.1016/j.mcna.2022.08.005
24. Hahn DL. Does the asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) exist? A narrative review

from epidemiology and practice. Allergol Immunopathol. 2022;50(6):100–6. https://doi.org/10.15586/aei.v50i6.678
25. Jo YS, Rhee CK, Yoon HK, Park CK, Lim JU, An TJ, et al. Evaluation of asthma-chronic obstructive pulmonary disease overlap using a mouse model of pulmonary disease. J Inflam (Lond Engl). 2022;19(1):25. https://doi.org/10.1186/s12950-022-00322-x
26. Boulet LP. Early features of chronic obstructive pulmonary disease in patients with asthma: Is there ACO before ACO? Immunol Allergy Clin North Am. 2022;42(3):549–58. https://doi.org/10.1016/j.iac.2022.03.002
27. See KC, Ng J. Management of acute severe asthma and chronic obstructive pulmonary disease. Singapore Med J. 2022;63(9):535–41. https://doi.org/10.4103/SINGAPOREMEDJ.SMJ-2022-015
28. Li JT. Asthma chronic obstructive pulmonary disease and lower respiratory disorders. Ann Allergy Asthma Immunol. 2023;130(2):131. https://doi.org/10.1016/j.anai.2022.09.015