NCPD 2.0 CONTACT HOURS
Rx 1.0 CONTACT HOUR

sumroeng chinnapan

Asthma-COPD overlap: The NP's role in diagnosis and management

Abstract: Asthma-COPD overlap (ACO) presents in persons, especially adults, with persistent airflow limitation along with clinical symptoms reflective of both asthma and chronic obstructive pulmonary disease (COPD). It includes multiple clinical phenotypes with different underlying pathophysiology. Patients with ACO typically have a worse clinical course than those with asthma or COPD alone. This article provides an overview of diagnosis and management of this underrecognized condition.

By Lynda Jarrell, DNP, APRN, FNP-BC

Asthma-COPD overlap (ACO) presents in persons (primarily adults) with persistent airflow limitation along with clinical symptoms reflective of both asthma and chronic obstructive pulmonary disease (COPD). This is a term that encompasses many clinical phenotypes with disparate underlying pathophysiology. Patients with ACO have various clinical symptoms and pathways, which embody a heterogenous, composite inflammatory process that is poorly understood.[1] A 2021 systematic review and meta-analysis concluded that patients with ACO have a higher number of exacerbations per year than

Keywords: asthma, asthma-COPD overlap, COPD, inhaled corticosteroids (ICS), long-acting beta-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), spirometry

patients with COPD alone.[2] ACO is correlated with worsened lung function values, more frequent exacerbations, and poor quality of life with a variation of clinical symptoms.[2] A meta-analysis approximated that 2% of the general population globally is afflicted with ACO.[3] A study of patients in primary care settings in the United Kingdom found that 20% of patients with asthma, COPD, or both have ACO.[4] Patients with ACO are seen frequently in general practice and are often misdiagnosed and given inappropriate care.[4,5] It is essential that primary care NPs diagnose ACO early, initially manage, and refer when appropriate to ensure positive patient outcomes.

Definition and diagnostic criteria for ACO

The Global Initiative for Asthma (GINA) defines asthma as "a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation."[6] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as "a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development."[7]

ACO does not indicate a single disease but rather several different phenotypes and multiple underlying mechanisms.

Though recognized as a clinical syndrome, currently there is no prevailing definition for ACO. ACO does not indicate a single disease but rather several different phenotypes and multiple underlying mechanisms.[6] Prevalence is dependent on diagnostic criteria, which are not clearly defined.[8]

The GINA/GOLD first reported clinical characteristics suggestive of ACO in 2015.[9] These include patients older than 35-40 years of age with evidence of airflow obstruction on spirometry that is at least partly reversible with bronchodilator challenge along with presence of other clinical findings consistent with asthma. These findings may include eosinophilia in the blood or sputum, in conjunction with clinical features consistent with COPD.[1,9] In 2016, an expert panel developed a definition that is based on clinical criteria. ACO is diagnosed for patients meeting all three major and at least one minor diagnostic criteria.[10] Major criteria include persistent airflow limitation in people age 40 or older, smoking history of 10 or more pack-years or equivalent indoor or outdoor air pollution exposure, and asthma history or bronchodilator response of greater than 400 mL in forced expiratory volume in 1 second (FEV_1). Minor criteria include documented history of atopy or allergic rhinitis; bronchodilator response of FEV_1 at least 200 mL and 12% from baseline values on two or more visits; and peripheral blood eosinophilia count of at least 300 cells/mcL.[1-3,8,10] ACO was suggested as an interim clinical label by a joint American Thoracic Society/National Heart, Lung, and Blood Institute workshop report in 2017, but the group decided against developing a single, universal definition.[1,11]

Spirometry interpretation

Spirometry interpretation is paramount in the diagnosis of asthma, COPD, and ACO (see *Normal spirometry results*). Principal metrics for a diagnosis of asthma include reduced FEV_1/forced vital capacity (FVC) ratio (less than 0.75-0.80 in adults) and postbronchodilator increase in FEV_1 of more than 12% and more than 200 mL. Diagnosis of COPD is determined by postbronchodilator FEV_1/FVC less than 0.7, and FEV_1 is used to qualify severity. FEV_1 less than 80% increases exacerbation and mortality risk. ACO diagnosis is dependent on a postbronchodilator result of FEV_1/FVC less than 0.7 and postbronchodilator increase in FEV_1 of greater than or equal to 200 mL and 12% from baseline.[6]

Investigational diagnostic testing

Ongoing studies are showing promise in utilizing other inflammatory markers specific to ACO to aid in diagnosis. Fractional exhaled nitrous oxide (FeNO) of greater than 50 parts per billion (ppb) in patients who do not smoke is a marker for eosinophilic airway inflammation and may assist with diagnosis of ACO in some patients; however, no specific values are established for identification of patients with ACO.[5,10] Studies regarding FeNO for diagnosing ACO are incongruent, and more research is needed.[12]

Blood eosinophils along with immunoglobulin E (IgE) are elements of the T helper 2-mediated response.[12] Elevated blood eosinophil levels are indicative of eosinophilic airway inflammation; levels of 300 cells/mcL or greater combined with elevated serum interleukin (IL)-4 are associated with ACO. Like other biomarkers, there are no clearly defined levels in patients with ACO.[7] IgE is indicative of allergic asthma and does not rule out COPD.[5] Elevated IgE levels play an important role in guiding treatment with IgE-specific therapy in certain patients with ACO.[12]

In a large multicenter observational study, evidence of sputum eosinophilia was reported to be more accurate than blood eosinophil concentration in identifying patients with more severe disease and more frequent exacerbations.[13] Sputum eosinophilia may prove to be a reliable test for diagnosing different phenotypes of chronic airway diseases; however, there is a lack of available testing, and specialized training is required for dependable testing.[12,13]

A 2019 study reported elevated periostin levels in both asthma and ACO but not in COPD. Serum chitinase-3-like protein 1 (YKL-40) was shown to be elevated in both COPD and ACO but not asthma. Serum periostin levels were comparable between asthma and ACO. YKL-40 was comparable between ACO and COPD, concluding that both markers may be beneficial in identifying ACO.[14]

Histidine is an essential amino acid associated with inflammation. Urinary L-histidine levels were found to be much higher in patients with ACO than in those with either asthma or COPD alone. Urinary L-histidine is promising as a biomarker for ACO.[12,15]

Vascular endothelial growth factor (VEGF) is a glycosylated peptide component found in tissues with increased blood supply including lung tissue. VEGF is involved in airway remodeling. A 2020 study by Ding et al. found serum levels of IL-9 as well as levels of VEGFA (part of the VEGF family) significantly elevated in patients with ACO compared with those without ACO. Levels of IL-8 and IL-17A were significantly lower in patients with ACO compared with the non-ACO group. Also, reported VEGFA was negatively correlated with FEV_1/FVC and IL-8 and IL-17A were positively correlated with FEV_1/FVC. The conclusion was that IL-8 was highly sensitive and VEGFA was highly specific, potentially aiding in the diagnosis of ACO.[16]

Elevated IgE levels play an important role in guiding treatment with IgE-specific therapy in certain patients with ACO.

Prostaglandin D2 (PG-D2) is an inflammatory marker. In a 2020 study, FEV_1/FVC levels were found to be negatively correlated with PG-D2 levels in patients with ACO. It was determined that PG-D2 may be used as a diagnostic biomarker to differentiate asthma and ACO from COPD (see *Investigational testing for ACO*).[17]

Pharmacologic management of ACO

GINA recommends a four-step approach to diagnose and manage ACO. The first step is history and clinical assessment to establish respiratory symptoms, history of asthma diagnosis, and exposure to risk factors for COPD.

Normal spirometry results[27]

Test	Parameters Measured	Normal Results
Tidal Volume (TV)	Normal volume of air inhaled or exhaled in a resting subject	500 mL
Inspiratory reserve volume (IRV)	Additional amount of air inhaled over and above the TV	2.1-3 L
Expiratory reserve volume (ERV)	Volume of air exhaled from the resting position (after exhalation of TV)	800-1,100 mL
Forced vital capacity (FVC)	Total amount one can exhale after deep inspiration (sum of TV, ERV, and IRV)	3.88-5.0 L
Forced expiratory volume in one second (FEV_1)	Volume of the FVC exhaled in the first second	3.12-3.96 L
FEV_1/FVC ratio	Detects early obstruction	≥80% predicted

Investigational testing for ACO[7,12-17]

Test	Role
FeNO	Values >50 ppb in patients who do not smoke indicate eosinophilic inflammation Specific values not established for ACO
Blood eosinophils, IL-4	Values of ≥300 cells/mcL combined with elevated IL-4 are associated with ACO
IgE	May help to guide treatment of ACO
Sputum eosinophils	More accurate than blood eosinophils Lack of available testing Specialized training required
Periostin, YKL-40	May be beneficial to diagnose ACO More research needed
Urinary L-histidine	Higher in patients with ACO than in those with asthma or COPD alone
IL-8, VEGFA	IL-8 is highly sensitive and VEGFA is highly specific in the diagnosis of ACO
PG-D2	May be used to differentiate asthma and ACO from COPD

Abbreviations: FeNO, fractional exhaled nitrous oxide; IL-4, interleukin-4; ppb, parts per billion; PG-D2, prostaglandin D2; VEGFA, vascular endothelial growth factor A; YKL-40, chitinase-3-like protein 1

Detailed history and assessment can help providers distinguish asthma from COPD (see *Approach to initial treatment in patients with asthma and/or COPD*).

The second step is spirometry for confirmation of persistent airflow limitation and variable expiratory airflow limitation. Spirometry should be performed with the patient's first visit prior to starting any medications to prevent skewed results. This will corroborate airflow limitation and reversibility.

The third is selecting initial treatment. Pharmacotherapy for asthma should include inhaled corticosteroid (ICS) to prevent episodes of exacerbations, improve symptoms, and prevent death. Long-acting beta-agonists (LABAs) and/or long-acting muscarinic antagonists (LAMAs) should be added as needed. LABA and/or LAMA therapy should not be administered without ICS. ICS-formoterol may be used as the reliever for mild asthma and as both reliever and maintenance therapy for moderate-severe asthma.[6]

Pharmacotherapy for COPD should include short-acting beta-agonist (SABA) as needed and LABA or LAMA or both. ICS is added only with hospitalizations, two or more exacerbations/year requiring oral corticosteroids (OCS), or blood eosinophils of 300/mcL or greater. High doses of ICS should be avoided due to risk of pneumonia in patients with features of COPD.[7]

GINA recommends initially treating ACO as asthma, which consists of low- or medium-dose ICS based on symptoms and risk of adverse effects, including pneumonia. These patients will usually also require LABA and/or LAMA, which should not be administered without ICS.

The last step is referral for specialized evaluation if indicated. Patients requiring referral are those not responding to treatment; those with frequent exacerbations; those in whom an alternative diagnosis needs to be explored; those with atypical or additional symptoms; patients with additional comorbidities that might hinder or affect assessment or management of asthma and/or COPD; and those who have issues with ongoing ACO management.[6]

Nonpharmacologic management and patient education

Patients with ACO require frequent follow-up. Appropriate inhaler technique increases medication efficiency and therefore decreases usage, dosage, and adverse reactions. Inhaler technique should be addressed at each visit.[6,7]

Smoking cessation should also be discussed at each visit. Cessation of smoking, including vaping and marijuana use, is vital in the nonpharmacologic treatment of ACO.[6,18] A 2021 study reported that ACO was twice as likely among adults who used e-cigarettes compared with adults who did not smoke cigarettes or e-cigarettes.[19] Pharmacotherapy and nicotine replacement increase long-term success.[7]

The combination of pharmacotherapy and behavioral support improves outcomes. GOLD guidelines recommend the five As approach: ask, advise, assess, assist, and arrange.[7]

Recommended vaccines for patients with asthma, COPD, and ACO include influenza (annually); tetanus, diphtheria, and pertussis (Tdap); Zoster; and pneumococcal vaccines. Both pneumococcal vaccines (PCV13 and PPSV23) are recommended for patients age 65 or older, and PPSV23 is recommended for younger patients with COPD and/or asthma.[6,18,20] COVID-19 vaccines should be given to patients with ACO. These should be given in a healthcare setting where anaphylaxis may be treated if necessary. These patients should also continue wearing masks and avoiding close contact when out in public.[6]

The World Health Organization recommends that all patients diagnosed with COPD be screened for alpha-1 antitrypsin deficiency (AATD) at least once. A low concentration (less than 20% of normal) is highly predictive of AATD and requires referral to a specialist.[7]

Active lifestyle and exercise are important in patients with ACO.[6,7] Pulmonary rehabilitation is defined as "a comprehensive intervention based on thorough patient assessment, followed by patient-tailored therapies that include, but are not limited to, exercise training, education, self-management intervention aiming at behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors."[7,21] Pulmonary

Pulmonary rehabilitation has proven to be the most effective therapy to improve symptoms, overall health, and exercise tolerance.

Approach to initial treatment in patients with asthma and/or COPD

CLINICAL PHENOTYPE - ADULTS WITH CHRONIC RESPIRATORY SYMPTOMS (dyspnea, cough, chest tightness, wheeze)

HIGHLY LIKELY TO BE ASTHMA if several of the following features TREAT AS ASTHMA	FEATURES OF BOTH ASTHMA + COPD TREAT AS ASTHMA	LIKELY TO BE COPD if several of the following features TREAT AS COPD
HISTORY • Symptoms vary over time and in intensity - Triggers may include laughter, exercise, allergens, seasonal - Onset before age 40 years - Symptoms improve spontaneously or with bronchodilators (minutes) or ICS (days to weeks) • Current asthma diagnosis, or asthma diagnosis in childhood **LUNG FUNCTION** • Variable expiratory airflow limitation • Persistent airflow limitation may be present	**HISTORY** • Symptoms intermittent or episodic - May have started before or after age 40 • May have a history of smoking and/or other toxic exposures, or history of low birth weight or respiratory illness such as tuberculosis • Any of asthma features at left (e.g. common triggers; symptoms improve spontaneously or with bronchodilators or ICS; current asthma diagnosis or asthma diagnosis in childhood) **LUNG FUNCTION** • Persistent expiratory airflow limitation • With or without bronchodilator reversibility	**HISTORY** • Dyspnea persistent (most days) - Onset after age 40 years - Limitation of physical activity - May have been preceded by cough/sputum - Bronchodilator provides only limited relief • History of smoking and/or other toxic exposure, or history of low birth weight or respiratory illness such as tuberculosis • No past or current diagnosis of asthma **LUNG FUNCTION** • Persistent expiratory airflow limitation • With or without bronchodilator reversibility

INITIAL PHARMACOLOGICAL TREATMENT (as well as treating comorbidities and risk factors. See Box 3-5A)

• **ICS-CONTAINING TREATMENT IS ESSENTIAL to reduce risk of severe exacerbations and death.** See Box 3-5A - As-needed low dose ICS-formoterol may be used as reliever. See Box 3-5A • **DO NOT GIVE LABA and/or LAMA without ICS** • Avoid maintenance OCS	• **ICS-CONTAINING TREATMENT IS ESSENTIAL to reduce risk of severe exacerbations and death.** See Box 3-5A • Add-on LABA and/or LAMA usually also needed • Additional COPD treatments as per GOLD • **DO NOT GIVE LABA and/or LAMA without ICS** • Avoid maintenance OCS	• **TREAT AS COPD (see GOLD report)** - Initially LAMA and/or LABA - Add ICS as per GOLD for patients with hospitalizations, ≥2 exacerbations/year requiring OCS, or blood eosinophils ≥300/µl • Avoid high dose ICS, avoid maintenance OCS • Reliever containing ICS is not recommended

REVIEW PATIENT AFTER 2-3 MONTHS. REFER FOR EXPERT ADVICE IF DIAGNOSTIC UNCERTAINTY OR INADEQUATE RESPONSE

GOLD: Global Initiative for Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist

rehabilitation has proven to be the most effective therapy to improve symptoms, overall health, and exercise tolerance.[7] A small 2020 randomized controlled trial of a short-term pulmonary rehabilitation program in patients with ACO resulted in improved functional capacity and quality of life, but did not change pulmonary function.[22]

Investigational drugs

Immunotherapy targets various neurohormonal pathways in asthma and may play a role in patients with ACO and severe allergic asthma who do not respond to bronchodilator therapy. A study by Maltby et al. established that omalizumab therapy improved asthma symptoms and quality of life in patients with severe allergic asthma and overlapping COPD.[23]

Mepolizumab and benralizumab have also been studied in patients with COPD and eosinophilic asthma. Mepolizumab was found to reduce the annual rate of exacerbations in patients with COPD and an eosinophilic phenotype and in patients with severe eosinophilic asthma.[12,24] No reduction of exacerbations was associated with benralizumab for patients with COPD and eosinophilic inflammation.[12,25]

Another medication that shows potential in the treatment of ACO includes metformin. Metformin is normally used in the treatment of type 2 diabetes. Metformin has also shown to be effective in decreasing allergic airway inflammation and asthma exacerbations. Metformin's mechanism of action is inhibition of smooth muscle proliferation through cytokine proliferation, and it decreases airway inflammation in allergic asthma. Wu et al. concluded that metformin use produced fewer respiratory exacerbations and improved quality of life in persons with ACO but not COPD alone. Further research to answer these questions is needed.[26]

Conclusion

ACO presents in persons with persistent airflow limitation along with clinical symptoms reflective of both asthma and COPD, especially in adults. Patients with ACO have worsened lung function values, frequent exacerbations, and poor quality of life, and present with a variety of clinical symptoms.[2] Of patients who present to primary care with asthma, COPD, or both, 20% have ACO.[4] In general practice, patients with ACO are often misdiagnosed and given inappropriate care.[4,5]

GINA and GOLD guidelines recommend a stepwise clinical approach for evaluation and management of ACO. Mainstay medications currently are ICS, LABAs, and LAMAs. LABA and LAMA cannot be given without ICS in patients with asthma or ACO because of increased risk for death. Appropriate diagnosis is critical for the safety of these patients. Several new therapies show promising results in the treatment of ACO including monoclonal antibodies and metformin. Also, many new biomarkers, which may be specific to an ACO diagnosis, are being investigated, and may offer options for tailored treatment.

Further research is needed to determine more comprehensive definitions and classification of patients with ACO. Future studies should include characteristics, biomarkers, outcomes, underlying mechanisms, and treatments of this patient population.[6]

NPs have the skills to diagnose and initially manage patients with ACO by ordering and evaluating appropriate diagnostic tests and introducing pharmacologic and nonpharmacologic therapy to improve clinical outcomes. NP

REFERENCES

1. Mart MF, Peebles RS Jr. Asthma-chronic obstructive pulmonary disease overlap syndrome. *Curr Opin Immunol*. 2020;66:161-166. doi:10.1016/j.coi.2020.10.006.
2. Zhou X-L, Zhao L-Y. 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):1495-1510. doi:10.26355/eurrev_202102_24857.
3. Hosseini M, Almasi-Hashiani A, Sepidarkish M, Maroufizadeh S. Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. *Respir Res*. 2019;20(1):229. doi:10.1186/s12931-019-1198-4.
4. Krishnan JA, Nibber A, Chisholm A, et al. Prevalence and characteristics of asthma-chronic obstructive pulmonary disease overlap in routine primary care practices. *Ann Am Thorac Soc*. 2019;16(9):1143-1150. doi:10.1513/AnnalsATS.201809-607OC.
5. Moore C. Implementing an asthma and COPD overlap protocol in general practice. *Nurs Times*. 2020;116(4):31-34.
6. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2021 [Internet]. www.ginasthma.org.
7. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for diagnosis, management, and prevention of COPD: 2021 report [Internet]. http://goldcopd.org.
8. Sharma S, Khurana S, Federman AD, Wisnivesky J, Holguin F. Asthma-chronic obstructive pulmonary disease overlap. *Immunol Allergy Clin North Am*. 2020;40(4):565-573. doi:10.1016/j.iac.2020.07.002.
9. Global Strategy for Asthma Management and Prevention and the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Diagnosis of diseases of chronic airflow limitation: asthma, COPD, and asthma-COPD overlap syndrome (ACOS) [Internet]. 2015. www.ginathma.org.
10. Sin DD, Miravitlles M, Mannino DM, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. *Eur Respir J*. 2016;48(3):664-673. doi:10.1183/13993003.00436-2016.
11. Woodruff PG, van den Berge M, Boucher RC, et al. American Thoracic Society/National Heart, Lung, and Blood Institute Asthma-Chronic Obstructive Pulmonary Disease Overlap workshop report. *Am J Respir Crit Care Med*. 2017;196(3):375-381. doi:10.1164/rccm.201705-0973WS.
12. Venkata AN. Asthma-COPD overlap: review of diagnosis and management. *Curr Opin Pulm Med*. 2020;26(2):155-161. doi:10.1097/MCP.0000000000000649.

13. Hastie AT, Martinez FJ, Curtis JL, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. *Lancet Respir Med*. 2017;5(12):956-967. doi:10.1016/S2213-2600(17)30432-0.

14. Shirai T, Hirai K, Gon Y, et al. Combined assessment of serum periostin and YKL-40 may identify asthma-COPD overlap. *J Allergy Clin Immunol Pract*. 2019;7(1):134-145. doi:10.1016/j.jaip.2018.06.015.

15. Oh JY, Lee YS, Min KH, et al. Increased urinary L-histidine in patients with asthma-COPD overlap: a pilot study. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1809-1818. doi:10.2147/COPD.S163189.

16. Ding Q, Sun S, Zhang Y, et al. Serum IL-8 and VEGFA are two promising diagnostic biomarkers of asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis*. 2020;15:357-365. doi:10.2147/COPD.S233461.

17. Uzan GC, Borekci S, Doventas YE, Koldas M, Gemicioglu B. The relationship between inflammatory markers and spirometric parameters in ACOS, asthma, and COPD. *J Asthma*. 2020;57(12):1273-1279. doi:10.1080/02770903.2019.1652644.

18. Albertson TE, Chenoweth JA, Pearson SJ, Murin S. The pharmacological management of asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS). *Expert Opin Pharmacother*. 2020;21(2):213-231. doi:10.1080/14656566.2019.1701656.

19. Bircan E, Bezirhan U, Porter A, Fagan P, Orloff MS. Electronic cigarette use and its association with asthma, chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap syndrome among never cigarette smokers. *Tob Induc Dis*. 2021;19:23. doi:10.18332/tid/132833.

20. Centers for Disease Control and Prevention. Recommended adult immunization schedule for ages 19 years or older, United States, 2021. Immunization Schedules. February 12, 2021. www.cdc.gov/vaccines/schedules/hcp/imz/adult.html.

21. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation [published correction appears in *Am J Respir Crit Care Med*. 2014;189(12):1570]. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64.

22. Orooj M, Moiz JA, Mujaddadi A, Ali MS, Talwar D. Effect of pulmonary rehabilitation in patients with asthma copd overlap syndrome: a randomized control trial. *Oman Med J*. 2020;35(3):e136. doi:10.5001/omj.2020.54.

23. Maltby S, Gibson PG, Powell H, McDonald VM. Omalizumab treatment response in a population with severe allergic asthma and overlapping COPD [Erratum in: *Chest*. 2017;151(3):730]. *Chest*. 2017;151(1):78-89. doi:10.1016/j.chest.2016.09.035.

24. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377(17):1613-1629. doi:10.1056/NEJMoa1708208.

25. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the prevention of COPD exacerbations. *N Engl J Med*. 2019;381(11):1023-1034. doi:10.1056/NEJMoa1905248.

26. Wu TD, Fawzy A, Kinney GL, et al. Metformin use and respiratory outcomes in asthma-COPD overlap. *Respir Res*. 2021;22(1):70. doi:10.1186/s12931-021-01658-3.

27. McCarthy K, Kamangar N. Pulmonary function testing. Medscape. May 14, 2020. Emedicine.medscape.com/article/303239-overview.

Lynda Jarrell is a clinical assistant professor at the University of Texas at Arlington, Fort Worth, Tex.

The author and planners have disclosed no potential conflicts of interest, financial or otherwise.

DOI-10.1097/01.NPR.0000806392.71827.cc