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Invited Review Article

Definition and diagnosis of asthma–COPD overlap (ACO)

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ACO, Asthma–COPD overlap; COPD, Chronic Obstructive Pulmonary disease;

FeNO, Fractional exhaled nitric oxide;

GINA, Global Initiative for Asthma;

GOLD, Global Initiative for Chronic

Obstructive Lung Disease; ICS, Inhaled

corticosteroids; LABA, Long-acting beta-2

agonists; LAMA, Long-acting muscarinic

antagonists

ABSTRACT

It is now widely recognized that asthma and COPD can coexist as asthma–COPD overlap (ACO), but the preliminary attempts at providing universal guidelines for the diagnosis of ACO still need to be improved. We believe that a case can be made for devising guidelines for the diagnosis of this increasingly common disease that are specific to Japan. In this paper, we present our consensus-based description of ACO which we believe is realistic for use in our country. In addition, we cite the scientific evidence for our own “objective” features used to develop the criteria for COPD and asthma diagnosis. We acknowledge that they will need to be validated and updated over time, but hope the results will encourage further research on the characteristics and treatment of this commonly encountered clinical problem.

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Introduction

Asthma and COPD are the pulmonary diseases most frequently encountered in clinical practice. Usually, each disease is caused by a different etiology and shows a different clinical picture and course. However, these two diseases sometime present within the same patient, and it is now recognized that asthma and COPD can coexist as asthma–COPD overlap (ACO),^{1–5} which is clinically important for several reasons. First, it is estimated that the number of patients with ACO will increase significantly together with the recent increase in numbers of patients with asthma and COPD. Secondly, patients with ACO are prone to experience more frequent and severe exacerbations. For example, patients who have asthma with a COPD component tend to present with severe hypoxia because of irreversible/fixed airway obstruction and impairment of the alveolar diffusion capacity by emphysematous changes. In contrast,

patients with COPD who have an asthma component not only have exertional dyspnea but also develop paroxysmal wheezing or dyspnea at night or in the early morning. Thirdly, evidence-based effective treatments for ACO have yet to be identified. There have been many clinical trials performed in patients with bronchial asthma and in those with COPD, but not in patients with ACO, mainly because no definitive inclusion criteria have been developed for patients with coexisting asthma and COPD. In this review, we describe ACO definitions and recommendations for the diagnosis in recent literature and introduce a part of new definitions and diagnostic criteria of ACO published by the Japanese Respiratory Society.⁶

Definition of ACO in recent literature

The Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) initially proposed guidelines for “asthma and COPD overlap syndrome (ACOS),”⁷ in which they recommended that the condition be defined in two steps (Table 1). Using these guidelines, the first step is the identification of a history of chronic airway disease, i.e., chronic or recurrent cough,

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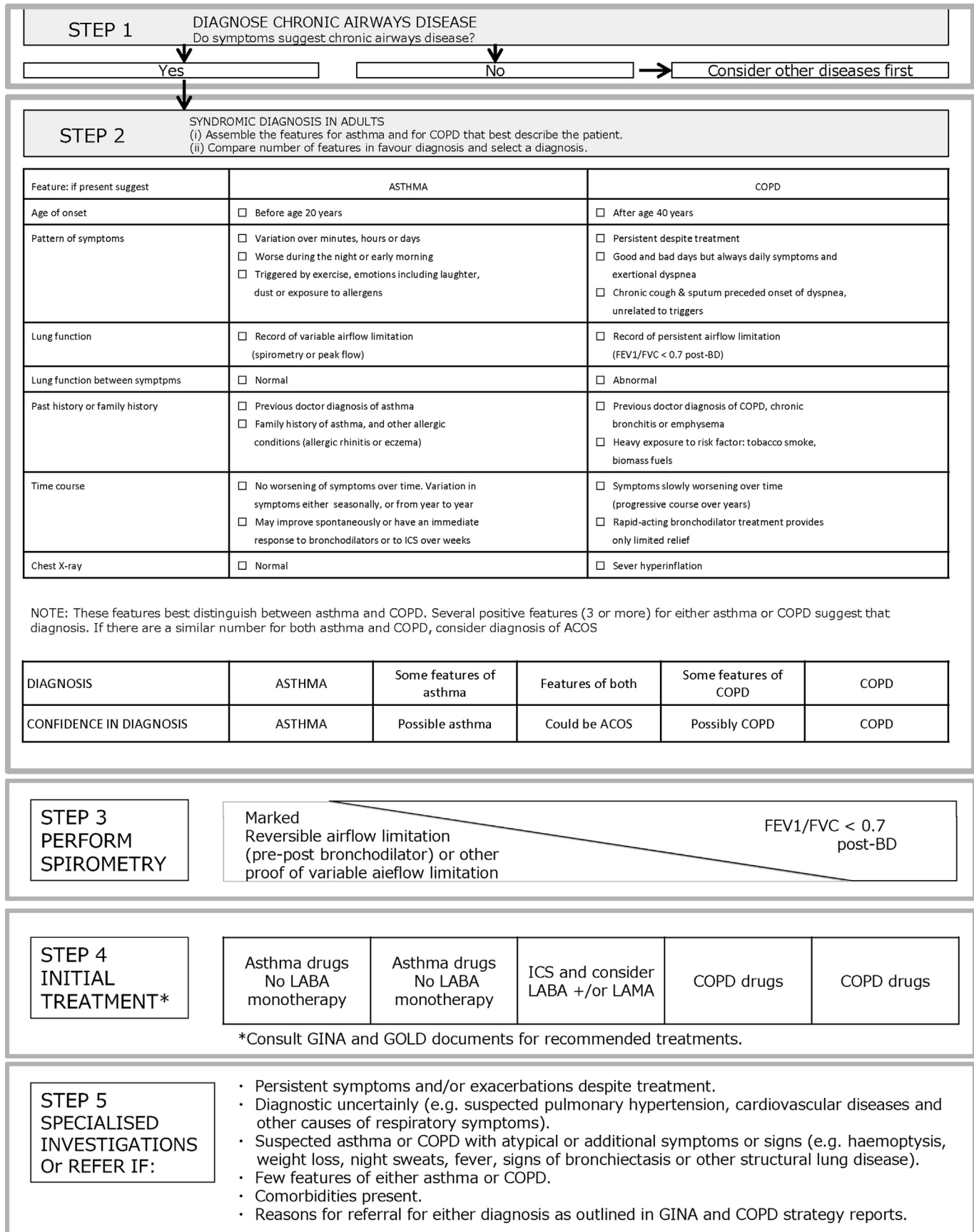
Table 1Summary of syndromic approach to diseases of chronic airway limitation.⁷

Table 2

Criteria for the diagnosis of asthma-chronic obstructive pulmonary disease overlap syndrome of chronic airway limitation.

Major
1. Persistent airflow limitation [post-bronchodilator FEV ₁ /FVC <0.70 or LLN] in individuals 40 years of age or older; LLN is preferred.
2. At least 10 pack-years of tobacco smoking
OR
equivalent indoor or outdoor air pollution exposure [e.g. biomass]
3. Documented history of asthma before 40 years of age
OR
BDR of >400 mL in FEV ₁
Minor
1. Documented history of atopy or allergic rhinitis
2. BDR of FEV ₁ ≥200 mL and 12% from baseline values on 2 or more visits
3. Peripheral blood eosinophil count of ≥300 cells μL

The committee recommends the presence of all three major criteria and at least one minor criterion for asthma-chronic obstructive pulmonary disease overlap syndrome. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; BDR, bronchodilator response using 400 μg of albuterol/salbutamol [or equivalent]; LLN, Lower limit of normal.

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sputum production, wheezing, or repeated acute lower respiratory tract infections. In the second step, the features of asthma and those of COPD that best describe the patient (i.e., age at onset, pattern of symptoms, results of pulmonary function tests, and findings on chest radiographs) are identified and compared, and the diagnosis is selected from the differentials of asthma, COPD, and ACOS. For example, variation in symptoms and airflow limitation (indicated by spirometry or peak flow readings) and an atopic disposition (indicated by a history of allergic disease) would favor the presence of asthma, whereas a smoking history and irreversible/fixed airway obstruction would favor the presence of COPD. The guidelines proposed by GINA/GOLD listed all features to be considered in a way that could be easily understood by general physicians, but has been criticized for not being sufficiently objective or quantitative.

In 2016, in an attempt to define ACO more precisely, Sin *et al.* proposed three major and three minor criteria⁸ (Table 2), and suggested that ACO could be diagnosed when the three major criteria and at least one minor criterion were satisfied.

In 2017, GINA formally recommended use of the term “ACO” rather than “ACOS”, to avoid giving the impression that this is a single disease.⁹ This stance seems reasonable, given that the term “syndrome” suggests a condition of unknown origin in which the clinical symptoms and/or laboratory findings indicate a common pathophysiologic mechanism. Further, both asthma and COPD have diverse phenotypes, so the term “syndrome” is not an appropriate description of ACO.

Definition of ACO by Japanese Respiratory Society⁶

Both the above-mentioned ACO definitions^{7,8} seem reasonable because they are consistent with the diagnostic procedure used in clinical practice whereby the asthma component and the COPD component are usually diagnosed separately and ACO is then defined as the coexistence of both components. They list in detail the characteristics of each disease component, and emphasize 1) atopic disposition and variation in symptoms or airflow limitation (on spirometry or peak flow) as asthmatic components and 2) a smoking history, irreversible/fixed airway obstruction, and pulmonary emphysematous change on chest radiographs as COPD components. However, there seem to be two problems with their

definition for ACO. First, the diagnosis of each disease component (asthma or COPD) is made on the basis of subjective symptoms that are easily influenced by background characteristics, such as patient age and disposition, rather than being objective and quantitative. Secondly, the laboratory tests that can be performed are limited to those that are universally accessible such as pulmonary function tests, chest radiographs, and peripheral blood eosinophil counts. Now we believe that ACO should be defined according to the domestic medical environment, where the health care, medical resources, and specialty services are distributed fairly uniformly throughout the country. For example, in Japan, the use of computed tomography (CT) is widespread and can be used for diagnostic purposes, and insurance coverage for measuring the fraction of exhaled nitric oxide (FeNO) means that this measuring is widely available in general medical wards,¹⁰ and data from our local epidemiologic and clinical studies would provide a strong basis for assessment of the pretest probability.^{11–14} Therefore, we have ready access to practical information for diagnosing ACO appropriately. Given this health care environment, it seems reasonable to devise guidelines specifically for use in Japan.

Therefore, the Japanese Respiratory Society defined ACO as follows⁶ (Table 3):

“Asthma and COPD overlap is defined as “the coexistence of asthma and COPD in patients with chronic airway obstruction”. The diagnosis of asthma and COPD is based on the Japanese Guidelines for Asthma¹⁰ and COPD,¹⁵ respectively.”

Diagnostic approach for ACO recommended by the Japanese Respiratory Society

Step 1

When individuals 40 years or older visit the office complaining of respiratory symptoms (cough, sputum, dyspnea) or with previously documented airflow limitation (FEV₁/FVC < 70%), a chest radiograph should be ordered to rule out other diseases that can

Table 3

Definition of asthma, COPD and Asthma–COPD overlap.

Asthma ¹⁰
Adult bronchial asthma (hereinafter, asthma) is characterized by chronic airway inflammation, clinically presenting variable airway narrowing (wheezes and dyspnea) and cough. Airway narrowing is reversible, and derives from airway inflammation and hyperresponsiveness. Pathological analyses in asthma demonstrate chronic airway inflammation accompanied by the infiltration of proinflammatory cells such as eosinophils, lymphocytes, mast cells, and others, and by the detachment of the airway epithelial cells. Long-standing inflammation will damage airways and induce airway remodeling, entailing subepithelial fibrosis under the basement membrane, smooth muscle hypertrophy, and submucosal gland hyperplasia. This results in intractable asthma, presenting irreversible airflow limitation and persistent airway hyperresponsiveness.
COPD ¹⁵
Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lung that is caused by long-term inhalation exposure to noxious substances such as tobacco smoke. COPD is characterized by irreversible airflow obstruction as demonstrated by pulmonary function tests. The airflow obstruction is progressive and attributable to the complex effects of the peripheral airway lesions and emphysematous lesions that contribute to the pathology in various ratios. Clinically, COPD is characterized by exertional dyspnea and chronic cough and sputum production whose onset and progression are gradual.
Asthma–COPD overlap ⁶
Asthma and COPD overlap (ACO) is defined as “the coexistence of asthma and chronic obstructive pulmonary disease in patients with chronic airway obstruction”.

cause airflow limitation, e.g., diffuse panbronchiolitis, congenital sinobronchial syndrome, obstructive bronchiolitis, bronchiectasis, pulmonary tuberculosis, pneumoconiosis, pulmonary lymphangiomyomatosis, congestive heart failure, interstitial lung disease, and lung cancer. The post-bronchodilator FEV₁/FVC should then be measured; if it is found to be <0.7, the patient potentially has ACO, so the clinician should proceed to Step 2.

Step 2

The features of COPD or asthma should be confirmed by history-taking and clinical investigations, including high-resolution CT, pulmonary function tests, measurement of FeNO, a peripheral blood eosinophil count, and measurement of the immunoglobulin E (IgE) level. COPD is likely to be present if any of the following criteria are satisfied: a smoking history or equivalent exposure to air pollution; emphysematous changes on high-resolution CT; and decreased gas exchange. Asthma is likely in the presence of the following: variable or paroxysmal clinical symptoms; a documented history of asthma before the age of 40 years; elevated FeNO; and a history of perennial allergic rhinitis, airway reactivity, elevation of peripheral blood eosinophils, or an elevated total or allergen-specific IgE level. A diagnosis of ACO (features of both asthma and COPD are present), asthma (only features of asthma are present), or COPD (only features of COPD are present) can then be made.

If the subject has a post-bronchodilator FEV₁/FVC >0.7 at Step 1, asthma (if features of asthma are present) or non-eosinophilic/non-atopic asthma (if features of asthma are not present) must be considered.

Features of COPD and asthma

We set our own objective criteria for the diagnosis of asthma and COPD, respectively, because subjective findings can often reflect the pathophysiology of each disease more precisely. For example, COPD can be assessed more accurately using D_{LCO} (carbon monoxide diffusion capacity) and CT because this variable and the results of this imaging method are strongly associated with the destruction of the alveolar wall. Likewise, atopic disposition and airway eosinophilic inflammation as suggested by elevated FeNO are each features that can be useful for the diagnosis of asthma. This is supported by epidemiological data showing that as many as 60% of asthmatic patients have allergic rhinitis.¹⁰ Importantly, subjects in Japan are easily able to access medical centers to undergo CT or FeNO testing. In this section, we cite the scientific evidence for each feature used to develop the criteria for the diagnosis of COPD and asthma.

Features of COPD

Emphysematous lesions: ill-defined low attenuation areas on high resolution computed tomography images

Emphysematous lesions are an important characteristic change in COPD and are detected as a low attenuation area (LAA) or low attenuation volume (LAV) in high resolution computed tomography (HRCT) images. Compared to healthy subjects, the ratio of LAA to lung parenchyma (LAA%) is known to increase in patients with COPD. In addition, LAA% is associated with impaired pulmonary function¹⁶ and is a useful prognostic marker of COPD¹⁷; therefore, LAA is an important feature for the diagnosis and assessment.

In contrast, alveolar destruction is unlikely in patients with asthma, and LAAs are usually not detected in asthmatic patients. Instead of LAAs, small airway lesions in asthmatic subjects may be detected by a change in the CT value between inspiratory and

expiratory conditions, known as “air-trapping”.¹⁸ The LAA% has been reported to be similar in cases with COPD and those with ACO.^{19,20} Additionally, air-trapping has been reported to be more severe in ACO than in COPD.²⁰

Decreased gas exchange

The single-breath carbon monoxide diffusion capacity (D_{LCO}) test is less stressful and is a useful index to assess carbon monoxide (CO) transfer from the alveolar space to the hemoglobin in the pulmonary microvasculature.²¹ By using a premixed gas (CO: 0.3%, He: 10%, O₂: 21%, N₂: 68.7%), we can measure both the rate constant of CO uptake from the alveolar gas (K_{CO}: the change in the concentration gradient of exhaled gas) and the accessible lung volume (V_A: alveolar volume determined by the dilution rate of He, which diffuses with CO). The D_{LCO} indicates the total volume of CO diffused, and the K_{CO} (D_{LCO}/V_A) represents CO transfer corrected for lung volume, which is regarded as the permeability capacity per alveolar unit. Because emphysematous changes, which are usually observed in COPD patients, cause alveolar and/or microvascular damage and destruction, the decrease in D_{LCO} and K_{CO} is an effective way to diagnose COPD.

In cases of asthma, D_{LCO} is known to exhibit normal or slightly increased values, possibly due to the better perfusion of the apices of the lungs.²²

Features of asthma

Elevated FeNO

FeNO is produced by nitric oxide synthase (NOS). There are two types of NOS: 1) the constitutive type (cNOS), which includes neuron-specific NOS (nNOS) and endothelial NOS (eNOS); and 2) the inducible type (iNOS), which is induced in the presence of inflammation. Although the airway contains both types of NOS, iNOS is thought to be the main source of FeNO both because cNOS has a superior capacity for NO production compared to iNOS and because cNOS is situated closer to the airway lumen than iNOS.

In patients with asthma, interleukin (IL)-4 or IL-13 induces iNOS through a STAT-6 mediated pathway.²³ In addition, both bronchial epithelial cells and inflammatory cells, including eosinophils or macrophages, express iNOS abundantly.²⁴ Therefore, the level of FeNO is higher in asthmatic patients than in healthy subjects.²⁵ Clinicians should take into account the various factors that might influence the FeNO levels. For example, corticosteroid use and current smoking²⁶ both reduce the FeNO levels. Further, atopic asthma patients show higher levels of FeNO compared to non-atopic asthma patients, and nasal allergies also contribute to the up-regulation of FeNO.²⁷ In asthma patients, FeNO has been shown to be positively correlated with the number of eosinophils in the sputum, bronchial wall, and alveolar spaces; therefore, it is a useful marker for eosinophilic airway inflammation. As expected, a reduction in the FeNO levels following inhaled corticosteroid (ICS) treatment is associated with decreased airflow obstruction and airway hypersensitivity.²⁸

Interestingly, the FeNO levels in stable COPD patients are known to range between the levels found in healthy subjects and those observed in asthmatic patients.²⁴ If an elevated FeNO level is observed in a subject with COPD, the possible co-existence of asthma (probably mediated by the IL-4/IL-13 pathway) should be determined using other asthmatic features in combination with the observed FeNO levels.¹² If co-existence of asthma is confirmed, ICS can be expected to improve the clinical symptoms and pulmonary function.²⁹

The American Thoracic Society/European Respiratory Society have published recommendations in which eosinophilic airway inflammation is categorized as low (FeNO < 25 ppb), intermediate

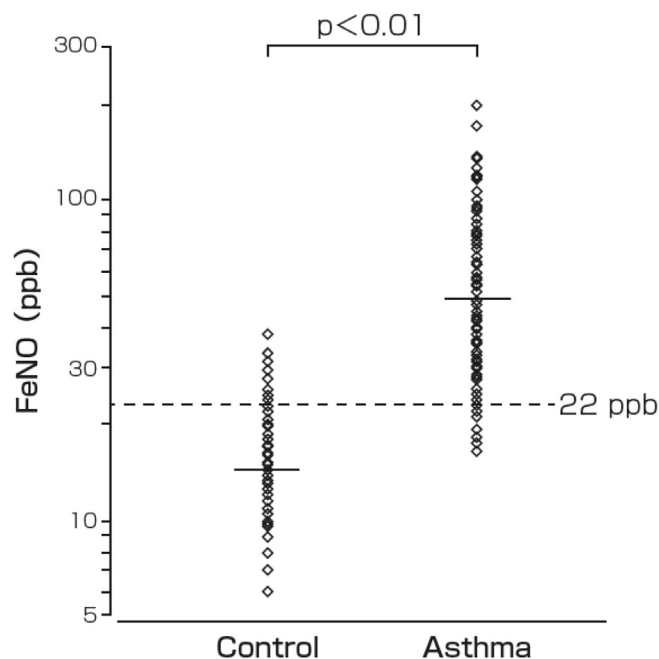


Fig. 1. Scatter plot of the exhaled nitric oxide fraction (FeNO) levels in control subjects and in steroid-naïve asthmatic patients.²⁷

(FeNO between 25 ppb and 50 ppb), or high (FeNO > 50 ppb).^{30,31} According to a recent study, the FeNO level observed in healthy Japanese subjects was less than 37 ppb (upper limit of normal < 37 ppb; Fig. 1).²⁷ We therefore included “FeNO > 35 ppb” as a feature of asthma.

Documented history of perennial allergic rhinitis

Asthma is known to be associated with a high incidence of rhinitis worldwide,^{32–34} and a large nation-wide study of rhinitis and asthma in Japan was first conducted in 2011 by Ohta *et al.*¹¹ The authors of this study applied the most widely-used questionnaires for both asthma³⁵ and rhinitis³² to assess the co-morbidity of rhinitis in terms of both prevalence and severity in subjects who had been diagnosed with asthma and who were already undergoing treatment. This study was the first to report the high incidence of rhinitis (68.5% and 66.2% of asthma patients with self-administered questionnaires or with physician-administered questionnaires, respectively) and its association with age. As expected, asthma control was impaired in patients with rhinitis, suggesting that the diagnosis of rhinitis in patients with asthma is crucial for effective treatment. Based on these epidemiological data from Japan, we included a history of rhinitis as a feature of asthma.

Bronchodilator response

Airway reversibility is a major feature of asthma and can be assessed by pulmonary function testing before and after the use of a short-acting beta-2 bronchodilator. As a general rule, it is necessary for the patient to refrain from any drugs that might influence airway reactivity prior to assessment, and the duration of activity for previously administered drugs should also be considered. Airway reversibility is diagnosed by a post-bronchodilator response of FEV₁ ≥200 mL and >12% from the baseline value.³⁶ Although airway reversibility is a well-known feature of asthma, it is sometimes diminished in subjects with a stable asthmatic condition or who have undergone airway remodeling; therefore, the absence of airway reversibility does not necessarily rule out the presence of asthma.

Presently, it is recognized that subjects with COPD also show airway reversibility to a varying degree. Although airway reversibility is not included in the diagnostic criteria of COPD, some patients with COPD show a post-bronchodilator response of FEV₁ ≥200 mL and >12% from the baseline values.³⁷ A post-bronchodilator response of FEV₁ ≥400 mL or 15% from the baseline in patients with COPD strongly suggests the co-existence of asthma and is therefore included as a major criteria for the diagnosis of ACO in multiple guidelines.^{8,38}

Peripheral blood eosinophil count

Eosinophils contain granules toxic to bronchial epithelial cells and have been considered to play a central role in the pathogenesis of asthma.¹⁰ Although the sputum eosinophil (SE) count is known to directly reflect the severity of airway inflammation, the peripheral blood eosinophil (PBE) count can be more conveniently measured and is known to be correlated with SE dynamics. In healthy subjects, the concentration of PBE ranges between 15 and 650/μL. This level has been reported to be increased in patients with asthma,³⁹ but at present there is no definite cut-off value for diagnosing asthma. In asthmatic subjects who are not being treated with ICS, an SE level of 2% has been reported to correspond to a PBE concentration of 220/μL.⁴⁰ Further, a previously published meta-analysis reported that a PBE level of 2% was comparable to an SE level of 210–414/μL, while a PBE level of 3% was comparable to an SE level 210–320/μL.⁴¹ PBE count is known to show significant associations with clinical symptoms, pulmonary dysfunction, airway hypersensitivity, and variability of peak flow,⁴² and a cut-off value of 400/μL is usually used for predicting exacerbations.

An increase in the PBE levels might be a useful asthmatic feature for exploring the possibility of ACO in patients who have already been diagnosed with COPD. In ICS-naïve COPD subjects, PBE has been shown to be correlated with the SE dynamics,⁴³ and a 2% PBE level has been reported to correspond to an SE level of 3%.⁴⁴ Indeed, 57–75% of COPD subjects are known to show a PBE level higher than 2%, and this level has been observed to be constantly elevated in 37.3% COPD subjects. In COPD, the PBE levels have been shown to be positively correlated with submucosal eosinophil counts and basement membrane thickness,⁴⁵ and a PBE concentration over 340/μL is reported as a risk factor for future exacerbations.^{46,47} Considering that corticosteroid treatment induces apoptosis in eosinophils, COPD subjects with peripheral blood eosinophilia are expected to show a better response to ICS treatment. There have been several large clinical studies that examined the effects of ICS on COPD patients. In 2015, Pascoe *et al.* reported a significant protective effect of ICS on COPD subjects with a PBE level higher than 2%.⁴⁸ In addition, the WISDOM study also showed that ICS treatment is associated with fewer exacerbations in COPD patients when the PBE counts are higher than 400/μL,⁴⁹ and this effect has been shown to be more pronounced in patients with a history of two or more exacerbation events per year.⁵⁰ Based on these reports, patients with ACO are expected to show a better response to ICS than those with COPD,⁵¹ and this may be a useful feature for identifying the subgroup of COPD patients who could be effectively treated by ICS.

Serum IgE elevation

Atopy involves a genetic tendency to produce IgE against environmental allergens. The presence of atopy is suggested if the documented history of a patient shows allergic disease (childhood asthma or atopic dermatitis) and the patient shows elevated levels of serum IgE (total or allergen-specific). These clinical findings are called “atopic disposition”. In subjects with chronic respiratory symptoms, such as cough, sputum, or wheezing, atopic disposition strongly suggests the presence of asthma.^{52,53} If atopic disposition

is detected in a subject with COPD, the co-existence of asthma, i.e. ACO, should be considered.

The serum total-IgE level has been shown to be associated with asthma symptoms and airway hypersensitivity.^{54–56} However, the diagnostic utility of serum total-IgE might be obscured in elderly subjects because total-IgE decreases with age.^{57,58} In contrast, smoking is known to elevate the serum total-IgE levels,^{59,60} and some reports have suggested that subjects with ACO show higher levels of total-IgE compared with COPD patients.^{13,61} The dynamics of the total-IgE levels have not yet been fully elucidated, but elevated serum total-IgE may suggest atopic disposition and may be a useful feature for defining asthma.

Allergen-specific IgE can be detected by various methods, such as skin tests (scratch-test, intradermal-test, and patch-test) and serological tests (semi-quantitative measurement of allergen-specific IgE or histamine release assay). Although a serological test is less stressful, the results of serological tests are not always correlated with clinically significant allergic reactions. As with serum total-IgE, serum allergen-specific IgE also decreases with age,⁶⁰ but its elevation strongly suggests the presence of asthma and provides important information for the management of asthma symptoms.

Conclusion

In this review, we describe ACO definitions and recommendations for the diagnosis in recent literature and introduce a part of new definitions and diagnostic criteria of ACO published by the Japanese Respiratory Society.⁶ Of course, the ACO definition and diagnosis criteria should be validated and updated, and we hope that it will encourage further research on the characteristics and treatment of this commonly encountered clinical problem.

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Conflict of interest

MI has received honoraria for speaking from AstraZeneca, Nippon Boehringer Ingelheim and Novartis Pharma. SY has no conflict of interest.

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