Diagnosis of Diseases of Chronic Airflow Limitation:

Asthma COPD and Asthma - COPD Overlap Syndrome (ACOS)

Based on the Global Strategy for Asthma Management and Prevention and the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease.

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Updated 2015

A joint project of GINA and GOLD

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This chapter is a joint project of GINA and GOLD. It has been excerpted from the Global Strategy for Asthma Management and Prevention, updated 2015. The full report can be viewed at www.ginasthma.org.

This report is intended as a general guide for health professionals and policy-makers. It is based, to the best of our knowledge, on current best evidence and medical knowledge and practice at the date of publication. When assessing and treating patients, health professionals are strongly advised to consult a variety of sources and to use their own professional judgment. GINA cannot be held liable or responsible for healthcare administered with the use of this document, including any use which is not in accordance with applicable local or national regulations or guidelines.

Key Points

- Distinguishing asthma from COPD can be problematic, particularly in smokers and older adults. Some patients may have clinical features of both asthma and COPD; this has been called the Asthma-COPD Overlap Syndrome (ACOS).
- ACOS is not a single disease. It includes patients with different forms of airways disease (phenotypes). It is likely that for ACOS, as for asthma and COPD, a range of different underlying mechanisms will be identified.
- Outside specialist centers, a stepwise approach to diagnosis is advised, with recognition of the presence of a chronic airways disease, syndromic categorization as characteristic asthma, characteristic COPD, or ACOS, confirmation of chronic airflow limitation by spirometry and, if necessary, referral for specialized investigations.
- Although initial recognition and treatment of ACOS may be made in primary care, referral for confirmatory investigations is encouraged, as outcomes for ACOS are often worse than for asthma or COPD alone.
- Recommendations for initial treatment, for clinical efficacy and safety, are:
    - For patients with features of asthma: prescribe adequate controller therapy including inhaled corticosteroids (ICS), but not long-acting bronchodilators alone (as monotherapy);
    - For patients with COPD: prescribe appropriate symptomatic treatment with bronchodilators or combination therapy, but not ICS alone (as monotherapy);
    - For ACOS, treat with ICS in a low or moderate dose (depending on level of symptoms); add-on treatment with LABA and/or LAMA is usually also necessary. If there are features of asthma, avoid LABA monotherapy;
    - All patients with chronic airflow limitation should receive appropriate treatment for other clinical problems, including advice about smoking cessation, physical activity, and treatment of comorbidities.
- This consensus-based description of ACOS is intended to provide interim advice to clinicians, while stimulating further study of the character, underlying mechanisms and treatments for this common clinical problem.

Objectives

The main aims of this consensus-based document are to assist clinicians, especially those in primary care or non-pulmonary specialties, to:

- *Identify* patients who have a disease of chronic airflow limitation
- *Distinguish* asthma from COPD and the Asthma-COPD Overlap Syndrome (ACOS)
- *Decide* on initial treatment and/or need for referral

It also aims to stimulate research into ACOS, by promoting:

- Study of characteristics and outcomes in broad populations of patients with chronic airflow limitation, rather than only in populations with diagnoses of asthma or COPD, and
- Research into underlying mechanisms contributing to ACOS, that might allow development of specific interventions for prevention and management of ACOS.

Background to diagnosing asthma, COPD and ACOS

In children and young adults, the differential diagnosis in patients with respiratory symptoms is different from that in older adults. Once infectious disease and non-pulmonary conditions (e.g. congenital heart disease, vocal cord dysfunction) have been excluded, the most likely chronic airway disease in children is asthma. This is often accompanied by allergic rhinitis. In adults (usually after the age of 40 years) COPD becomes more common, and distinguishing asthma with chronic airflow limitation from COPD becomes problematic.[1-4]

A significant proportion of patients who present with chronic respiratory symptoms, particularly older patients, have diagnoses and/or features of both asthma and COPD, and are found to have chronic airflow limitation (i.e. that is not

completely reversible after bronchodilatation).[5-9] Several diagnostic terms, most including the word 'overlap', have been applied to such patients, and the topic has been extensively reviewed.[4,6,10,11] However, there is no generally agreed term or defining features for this category of chronic airflow limitation, although a definition based upon consensus has been published for overlap in patients with existing COPD.[12]

In spite of these uncertainties, there is broad agreement that patients with features of both asthma and COPD experience frequent exacerbations,[6] have poor quality of life, a more rapid decline in lung function and high mortality,[6,13] and consume a disproportionate amount of healthcare resources[14] than asthma or COPD alone. In these reports, the proportion of patients with features of both asthma and COPD is unclear and will have been influenced by the initial inclusion criteria used for the studies from which the data were drawn. In epidemiological studies, reported prevalence rates for ACOS have ranged between 15 and 55%, with variation by gender and age;[8,13,15] the wide range reflects the different criteria that have been used by different investigators for diagnosing asthma and COPD. Concurrent doctor-diagnosed asthma and COPD has been reported in between 15 and 20% of patients.[7,10,16,17]

This document has been developed by the Science Committees of both GINA and GOLD, based on a detailed review of available literature and consensus. It provides an approach to identifying patients with asthma or COPD, and for distinguishing these from those with overlapping features of asthma and COPD, for which the term Asthma COPD Overlap Syndrome (ACOS) is proposed.[10]

Definitions

Box 5-1. Current definitions of asthma and COPD, and clinical description of ACOS

Asthma
Asthma is 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. [GINA 2015][18]
COPD
COPD is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. [GOLD 2015][19]
Asthma-COPD overlap syndrome (ACOS) – a description for clinical use
Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified in clinical practice by the features that it shares with both asthma and COPD. A specific definition for ACOS cannot be developed until more evidence is available about its clinical phenotypes and underlying mechanisms.

Just as asthma and COPD are heterogeneous diseases, each with a range of underlying mechanisms, ACOS also does not represent a single disease. However, few studies have included broad populations, so the mechanisms underlying ACOS are largely unknown, and a formal definition of ACOS cannot be provided at present. Instead, this document presents features that identify and characterize asthma, COPD and ACOS, ascribing equal weight to features of asthma and of COPD. It is acknowledged that within this description of ACOS will lie a number of phenotypes that may in due course be identified by more detailed characterization on the basis of clinical, pathophysiological and genetic identifiers.[20-22] The primary objective of this approach is, based on *current* evidence, to provide practical advice for clinicians,

particularly those in primary care and non-pulmonary specialties, about diagnosis, safe initial treatment, and referral where necessary,.

A summary of the key characteristics of typical asthma, typical COPD and ACOS is presented in Box 5-2a, showing the similarities and differences in history and investigations.

Stepwise approach to diagnosis of patients with respiratory symptoms

STEP 1: Does the patient have chronic airways disease?

A first step in diagnosing these conditions is to identify patients at risk of, or with significant likelihood of having chronic airways disease, and to exclude other potential causes of respiratory symptoms. This is based on a detailed medical history, physical examination, and other investigations.[3,23-25]

Clinical History

Features that prompt consideration of chronic airways disease include:

- History of chronic or recurrent cough, sputum production, dyspnea, or wheezing; or repeated acute lower respiratory tract infections
- Report of a previous doctor diagnosis of asthma or COPD
- History of prior treatment with inhaled medications
- History of smoking tobacco and/or other substances
- Exposure to environmental hazards, e.g. occupational or domestic exposures to airborne pollutants

Physical examination

- May be normal
- Evidence of hyperinflation and other features of chronic lung disease or respiratory insufficiency
- Abnormal auscultation (wheeze and/or crackles)

Radiology

- May be normal, particularly in early stages
- Abnormalities on chest X-ray or CT scan (performed for other reasons such as screening for lung cancer), including hyperinflation, airway wall thickening, air trapping, hyperlucency, bullae or other features of emphysema.
- May identify an alternative diagnosis, including bronchiectasis, evidence of lung infections such as tuberculosis, interstitial lung diseases or cardiac failure.

Screening questionnaires

Many screening questionnaires have been proposed to help the clinician identifying subjects at risk of chronic airways disease, based on the above risk factors and clinical features.[26-28] These questionnaires are usually context-specific, so they are not necessarily relevant to all countries (where risk factors and comorbid diseases differ), to all practice settings and uses (population screening *versus* primary or secondary care), or to all groups of patients (case-finding *versus* self-presenting with respiratory symptoms *versus* referred consultation). Examples of these questionnaires are provided on both the GINA and GOLD websites.

Box 5-2a. Usual features of asthma, COPD and ACOS

Feature	Asthma	COPD	ACOS
Age of onset	Usually childhood onset but can commence at any age.	Usually > 40 years of age	Usually age ≥40 years, but may have had symptoms in childhood or early adulthood
Pattern of respiratory symptoms	Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent but variability may be prominent
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV_1 may be improved by therapy, but post-BD $FEV_1/FVC < 0.7$ persists	Airflow limitation not fully reversible, but often with current or historical variability
Lung function between symptoms	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitation
Past history or family history	Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally, slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high
Chest X-ray	Usually normal	Severe hyperinflation & other changes of COPD	Similar to COPD
Exacerbations	Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment
Airway inflammation	Eosinophils and/or neutrophils	Neutrophils ± eosinophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum.

Box 5-2b. Features that if present favor asthma or COPD

More likely to be asthma if several of …*	More likely to be COPD if several of…*
☐ Onset before age 20 years	☐ Onset after age 40 years
☐ Variation in symptoms over minutes, hours or days ☐ Symptoms worse during the night or early morning ☐ Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	☐ Persistence of symptoms despite treatment ☐ Good and bad days but always daily symptoms and exertional dyspnea ☐ Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
☐ Record of variable airflow limitation (spirometry, peak flow)	☐ Record of persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.7$)
☐ Lung function normal between symptoms	☐ Lung function abnormal between symptoms
☐ Previous doctor diagnosis of asthma ☐ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	☐ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ☐ Heavy exposure to a risk factor: tobacco smoke, biomass fuels
☐ No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year ☐ May improve spontaneously or have an immediate response to BD or to ICS over weeks	☐ Symptoms slowly worsening over time (progressive course over years) ☐ Rapid-acting bronchodilator treatment provides only limited relief.
☐ Normal	☐ Severe hyperinflation

Syndromic diagnosis of airways disease: how to use Box 5-2b

Shaded columns list features that, <u>when present</u>, best identify patients with typical asthma and COPD. For a patient, count the number of check boxes in each column. If three or more boxes are checked for either asthma or COPD, the patient is likely to have that disease. If there are similar numbers of checked boxes in each column, the diagnosis of ACOS should be considered. See Step 2 for more details.

STEP 2. The syndromic diagnosis of asthma, COPD and ACOS in an adult patient

Given the extent of overlap between features of asthma and COPD (Box 5-2a), the approach proposed focuses on the features that are *most helpful* in identifying and distinguishing typical asthma and typical COPD (Box 5-2b).

a. Assemble the features that favor a diagnosis of asthma or of COPD

From a careful history that considers age, symptoms (in particular onset and progression, variability, seasonality or periodicity and persistence), past history, social and occupational risk factors including smoking history, previous diagnoses and treatment and response to treatment, together with lung function, the features favoring the diagnostic profile of asthma or of COPD can be assembled. The check boxes in Box 5-2b can be used to identify the features that are most consistent with asthma and/or COPD. Note that not all of the features of asthma and COPD are listed, but only those that *most easily distinguish between asthma and COPD in clinical practice*.

b. Compare the number of features in favor of a diagnosis of asthma or a diagnosis of COPD

From Box 5-2b, count the number of checked boxes in each column. Having several (three or more) of the features listed for either asthma or for COPD, in the absence of those for the alternative diagnosis, provides a strong likelihood of a correct diagnosis of asthma or of COPD.[28]

However, the absence of any of these typical features has less predictive value, and does not rule out the diagnosis of either disease. For example, a history of allergies increases the probability that respiratory symptoms are due to asthma, but is not essential for the diagnosis of asthma since non-allergic asthma is a well-recognized asthma phenotype; and atopy is common in the general population including in patients who develop COPD in later years. When a patient has similar numbers of features of both asthma and COPD, the diagnosis of ACOS should be considered.

c. Consider the level of certainty around the diagnosis of asthma or COPD, or whether there are features of both suggesting Asthma-COPD overlap syndrome

In clinical practice, when a condition has no pathognomonic features, clinicians recognize that diagnoses are made on the weight of evidence, provided there are no features that clearly make the diagnosis untenable. Clinicians are able to provide an estimate of their level of certainty and factor it into their decision to treat. Doing so consciously may assist in the selection of treatment and, where there is significant doubt, it may direct therapy towards the safest option - namely, treatment for the condition that should not be missed and left untreated. The higher the level of certainty about the diagnosis of asthma or COPD, the more attention needs to be paid to the safety and efficacy of the initial treatment choices (see Step 4, p8).

STEP 3. Spirometry

Spirometry is essential for the assessment of patients with suspected chronic disease of the airways. It must be performed at either the initial or a subsequent visit, if possible before and after a trial of treatment. Early confirmation or exclusion of the diagnosis of chronic airflow limitation may avoid needless trials of therapy, or delays in initiating other investigations. Spirometry confirms chronic airflow limitation but is of more limited value in distinguishing between asthma with fixed airflow obstruction, COPD and ACOS (Box 5-3).

Measurement of peak expiratory flow (PEF), although not an alternative to spirometry, if performed repeatedly on the same meter over a period of 1–2 weeks may help to confirm the diagnosis of asthma by demonstrating excessive variability (Box 1-2, p**Error! Bookmark not defined.**), but a normal PEF does not rule out either asthma or COPD. A high level of variability in lung function may also be found in ACOS.

Box 5-3. Spirometric measures in asthma, COPD and ACOS

Spirometric variable	Asthma	COPD	ACOS
Normal FEV_1/FVC pre- or post BD	Compatible with diagnosis	Not compatible with diagnosis	Not compatible unless other evidence of chronic airflow limitation
Post-BD FEV_1/FVC <0.7	Indicates airflow limitation but may improve spontaneously or on treatment	Required for diagnosis (GOLD)	Usually present
FEV_1 ≥80% predicted	Compatible with diagnosis (good asthma control or interval between symptoms)	Compatible with GOLD classification of mild airflow limitation (categories A or B) if post-BD FEV_1/FVC <0.7	Compatible with diagnosis of mild ACOS
FEV_1 <80% predicted	Compatible with diagnosis. Risk factor for asthma exacerbations	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and COPD exacerbations)	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and exacerbations)
Post-BD increase in FEV_1 ≥12% and 200 ml from baseline (reversible airflow limitation).	Usual at some time in course of asthma, but may not be present when well-controlled or on controllers	Common and more likely when FEV_1 is low	Common and more likely when FEV_1 is low
Post-BD increase in FEV_1 >12% and 400ml from baseline (marked reversibility)	High probability of asthma	Unusual in COPD. Consider ACOS	Compatible with diagnosis of ACOS

ACOS: asthma-COPD overlap syndrome; BD: bronchodilator; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease.

After the results of spirometry and other investigations are available, the provisional diagnosis from the syndrome-based assessment must be reviewed and, if necessary, revised. As shown in Box 5-3, spirometry at a single visit is not always confirmatory of a diagnosis, and results must be considered in the context of the clinical presentation, and whether treatment has been commenced. ICS and long-acting bronchodilators influence results, particularly if a long withhold period is not used prior to performing spirometry. Further tests might therefore be necessary either to confirm the diagnosis or to assess the response to initial and subsequent treatment (see Step 5).

STEP 4: Commence initial therapy

If the syndromic assessment favors asthma as a single diagnosis

Commence treatment as described in the GINA strategy report.[18] Pharmacotherapy is based on ICS, with add-on treatment if needed, e.g. add-on long-acting $beta_2$-agonist (LABA) and/or long-acting muscarinic antagonist (LAMA).

If the syndromic assessment favors COPD as a single disease

Commence treatment as in the current GOLD strategy report.[19] Pharmacotherapy starts with symptomatic treatment with bronchodilators (LABA and/or LAMA) or combination therapy, but not ICS alone (as monotherapy).

If the differential diagnosis is equally balanced between asthma and COPD (i.e. ACOS)

If the syndromic assessment suggests ACOS, the recommended default position is to start treatment for asthma (Box 5-4, p10) until further investigations have been performed. This approach recognizes the pivotal role of ICS in preventing

morbidity and even death in patients with uncontrolled asthma symptoms, for whom even seemingly 'mild' symptoms (compared to those of moderate or severe COPD) might indicate significant risk of a life-threatening attack[10].

- Pharmacotherapy for ACOS includes an ICS (in a low or moderate dose, depending on level of symptoms).
- Usually also add a LABA and/or LAMA, or continue these together with ICS if already prescribed.

However, if there are features of asthma, do not treat with a LABA without ICS (often called LABA monotherapy).

For all patients with chronic airflow limitation

Provide advice, as described in the GINA and GOLD reports, about:

- Treatment of modifiable risk factors including advice about smoking cessation
- Treatment of comorbidities
- Non-pharmacological strategies including physical activity, and, for COPD or ACOS, pulmonary rehabilitation and vaccinations
- Appropriate self-management strategies
- Regular follow-up

In a majority of patients, the initial management of asthma and COPD can be satisfactorily carried out at primary care level. However, both the GINA and GOLD strategy reports make provision for referral for further diagnostic procedures at relevant points in patient management (see Step 5). This may be particularly important for patients with suspected ACOS, given that it is associated with worse outcomes and greater health care utilization.

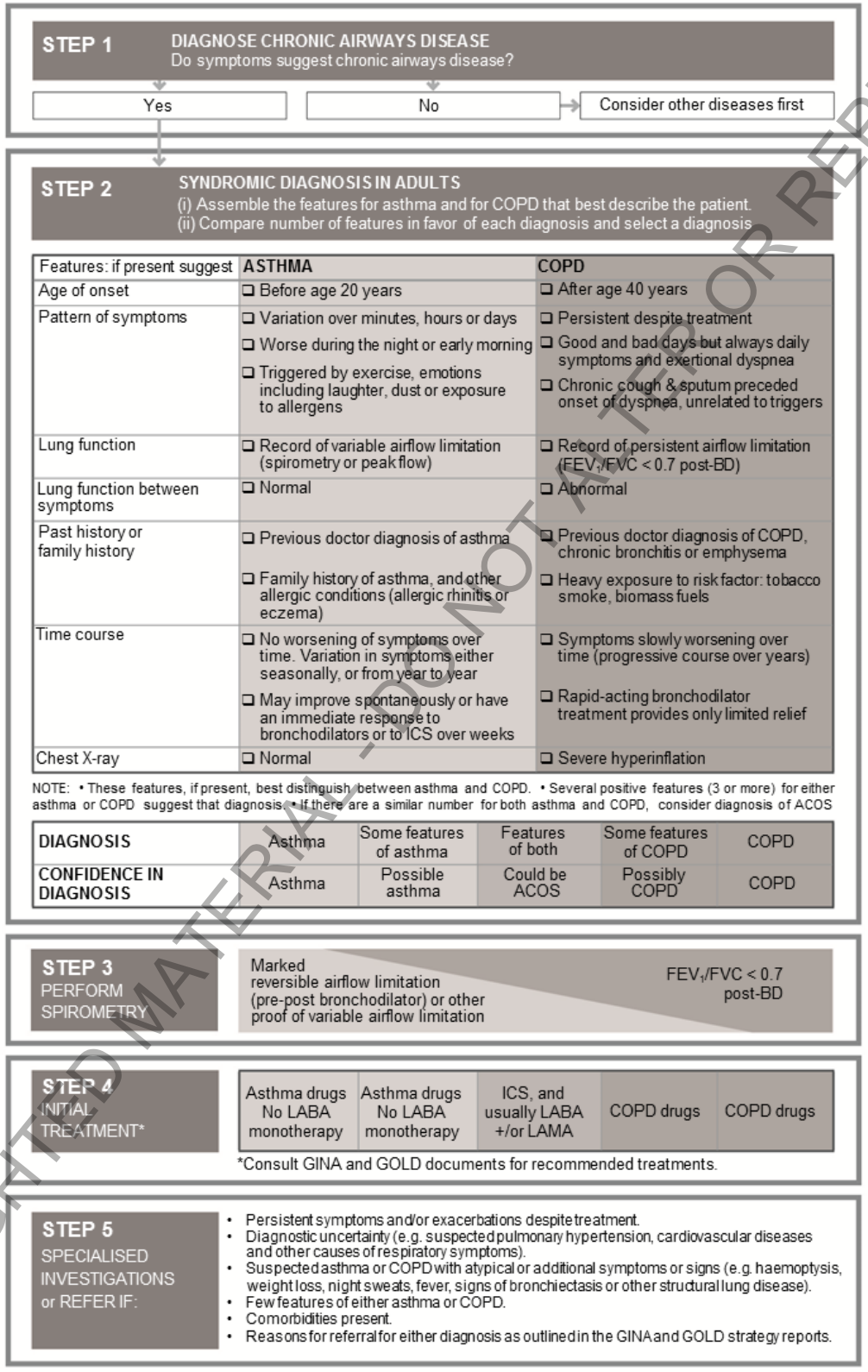
STEP 5: Referral for specialized investigations (if necessary)

Referral for expert advice and further diagnostic evaluation is necessary in the following contexts:

- Patients with persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty, especially if an alternative diagnosis (e.g. bronchiectasis, post-tuberculous scarring, bronchiolitis, pulmonary fibrosis, pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms) needs to be excluded.
- Patients with suspected asthma or COPD in whom atypical or additional symptoms or signs (e.g. haemoptysis, significant weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease) suggest an additional pulmonary diagnosis. This should prompt early referral, without necessarily waiting for a trial of treatment for asthma or COPD.
- When chronic airways disease is suspected but syndromic features of both asthma and COPD are few.
- Patients with comorbidities that may interfere with the assessment and management of their airways disease.
- Referral may also be appropriate for issues arising during on-going management of asthma, COPD or ACOS, as outlined in the GINA and GOLD strategy reports.

Box 5-5 (p11) summarizes specialized investigations that are sometimes used to distinguish asthma and COPD.

Box 5-4. Summary of syndromic approach to diseases of chronic airflow limitation



Box 5-5. Specialized investigations sometimes used in distinguishing asthma and COPD

	Asthma	COPD
Lung function tests		
DLCO	Normal (or slightly elevated).	Often reduced.
Arterial blood gases	Normal between exacerbations	May be chronically abnormal between exacerbations in more severe forms of COPD
Airway hyperresponsiveness (AHR)	Not useful on its own in distinguishing asthma from COPD, but higher levels of AHR favor asthma	
Imaging		
High resolution CT Scan	Usually normal but air trapping and increased bronchial wall thickness may be observed.	Low attenuation areas denoting either air trapping or emphysematous change can be quantitated; bronchial wall thickening and features of pulmonary hypertension may be seen.
Inflammatory biomarkers		
Test for atopy (specific IgE and/or skin prick tests)	Modestly increases probability of asthma; not essential for diagnosis	Conforms to background prevalence; does not rule out COPD
FENO	A high level (>50 ppb) in non-smokers supports a diagnosis of eosinophilic airway inflammation	Usually normal. Low in current smokers.
Blood eosinophilia	Supports asthma diagnosis	May be present during exacerbations
Sputum inflammatory cell analysis	Role in differential diagnosis is not established in large populations	

DLCO: diffusing capacity of the lungs for carbon monoxide; FENO: fractional concentration of exhaled nitric oxide; IgE: immunoglobulin E

Future research

Our understanding of ACOS is at a very preliminary stage, as most research has involved participants from existing studies which had specific inclusion and exclusion criteria (such as a physician diagnosis of asthma and/or COPD), a wide range of criteria have been used in existing studies for identifying ACOS, and patients who do not have 'classical' features of asthma or of COPD, or who have features of both, have generally been excluded from studies of most therapeutic interventions for airways disease.[29,30]

There is an urgent need for more research on this topic, in order to guide better recognition and appropriate treatment. This should include study of clinical and physiological characteristics, biomarkers, outcomes and underlying mechanisms, starting with broad populations of patients with respiratory symptoms or with chronic airflow limitation, rather than starting with populations with existing diagnoses of asthma or COPD. The present chapter provides interim advice, largely based on consensus, for the perspective of clinicians, particularly those in primary care and non-pulmonary specialties. Further research is needed to inform evidence-based definitions and a more detailed classification of patients who present overlapping features of asthma and COPD, and to encourage the development of specific interventions for clinical use.

References

1. Guerra S, Sherrill DL, Kurzius-Spencer M, et al. The course of persistent airflow limitation in subjects with and without asthma. Respir Med 2008;102:1473-82.
2. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. Chest 2004;126:59-65.
3. van Schayck CP, Levy ML, Chen JC, Isonaka S, Halbert RJ. Coordinated diagnostic approach for adult obstructive lung disease in primary care. Prim Care Respir J 2004;13:218-21.
4. Zeki AA, Schivo M, Chan A, Albertson TE, Louie S. The asthma-COPD overlap syndrome: a common clinical problem in the elderly. J Allergy 2011;2011:861926.
5. Abramson MJ, Schattner RL, Sulaiman ND, Del Colle EA, Aroni R, Thien F. Accuracy of asthma and COPD diagnosis in Australian general practice: a mixed methods study. Prim Care Respir J 2012;21:167-73.
6. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax 2009;64:728-35.
7. Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2000;160:1683-9.
8. Marsh SE, Travers J, Weatherall M, et al. Proportional classifications of COPD phenotypes. Thorax 2008;63:761-7.
9. Shirtcliffe P, Marsh S, Travers J, Weatherall M, Beasley R. Childhood asthma and GOLD-defined chronic obstructive pulmonary disease. Intern Med J 2012;42:83-8.
10. Louie S, Zeki AA, Schivo M, et al. The asthma-chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations. Expert Rev Clin Pharmacol 2013;6:197-219.
11. Miravitlles M, Soler-Cataluna JJ, Calle M, Soriano JB. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. Eur Respir J 2013;41:1252-6.
12. Soler-Cataluna JJ, Cosio B, Izquierdo JL, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. Arch Bronconeumol 2012;48:331-7.
13. Kauppi P, Kupiainen H, Lindqvist A, et al. Overlap syndrome of asthma and COPD predicts low quality of life. J Asthma 2011;48:279-85.
14. Andersen H, Lampela P, Nevanlinna A, Saynajakangas O, Keistinen T. High hospital burden in overlap syndrome of asthma and COPD. Clin Respir J 2013;7:342-6.
15. Weatherall M, Travers J, Shirtcliffe PM, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. Eur Respir J 2009;34:812-8.
16. McDonald VM, Simpson JL, Higgins I, Gibson PG. Multidimensional assessment of older people with asthma and COPD: clinical management and health status. Age Ageing 2011;40:42-9.
17. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. Chest 2003;124:474-81.
18. Global strategy for asthma management and prevention. 2015. (Accessed April 2015, at www.ginasthma.org.)
19. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management and Prevention of COPD. Available from www.goldcopd.org. 2015.
20. Carolan BJ, Sutherland ER. Clinical phenotypes of chronic obstructive pulmonary disease and asthma: recent advances. J Allergy Clin Immunol 2013;131:627-34.
21. Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. Respir Res 2011;12:127.
22. Wardlaw AJ, Silverman M, Siva R, Pavord ID, Green R. Multi-dimensional phenotyping: towards a new taxonomy for airway disease. Clin Exp Allergy 2005;35:1254-62.
23. Halbert RJ, Isonaka S. International Primary Care Respiratory Group (IPCRG) Guidelines: integrating diagnostic guidelines for managing chronic respiratory diseases in primary care. Prim Care Respir J 2006;15:13-9.
24. Levy ML, Fletcher M, Price DB, Hausen T, Halbert RJ, Yawn BP. International Primary Care Respiratory Group (IPCRG) Guidelines: diagnosis of respiratory diseases in primary care. Prim Care Respir J 2006;15:20-34.
25. Price DB, Tinkelman DG, Halbert RJ, et al. Symptom-based questionnaire for identifying COPD in smokers. Respiration 2006;73:285-95.
26. Thiadens HA, de Bock GH, Dekker FW, et al. Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. BMJ 1998;316:1286-90.
27. Tinkelman DG, Price DB, Nordyke RJ, et al. Symptom-based questionnaire for differentiating COPD and asthma. Respiration 2006;73:296-305.

28. Van Schayck CP, Loozen JM, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ 2002;324:1370.
29. Travers J, Marsh S, Caldwell B, et al. External validity of randomized controlled trials in COPD. Respir Med 2007;101:1313-20.
30. Travers J, Marsh S, Williams M, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? Thorax 2007;62:219-23.