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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

Proceeding	91215699
Party	Plaintiff Boston Scientific Corporation, on behalf of itself and its subsidiaries, Asthmatx, Inc.
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD**

In the matter of Application Serial No.: 85/806,379
Filed: December 19, 2012
For the mark: HOLAIRA
Published in the Trademark Official Gazette on December 3, 2013

Boston Scientific Corp. and
Asthmatx, Inc.

Opposers,

v.

Opposition No. 91215699

Holaira, Inc.

Applicant.

OPPOSER'S REBUTTAL NOTICE OF RELIANCE

Boston Scientific Corp. and Asthmatx, Inc. ("Opposers") hereby make the following documents of record and notify Applicant of their reliance on the following:

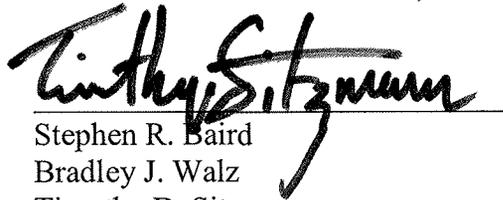
1. Pursuant to 37 C.F.R § 2.122(e); TBMP § 704.08(b), Opposers submit the following printouts from third-party websites. The relevance of these third-party website printouts is set forth below.

<u>Title</u>	<u>Relevance</u>	<u>Website</u>	<u>Date Printed</u>	<u>Ex.</u>
Asthma, COPD, and Asthma-COPD Overlap Syndrome (Summary)	Rebuttal to Dennis Wahr Testimony, evidence of overlap of asthma and COPD	http://www.goldcopd.org/asthma-copd-overlap.html	Aug. 10, 2015	68
Asthma, COPD, and Asthma-COPD Overlap Syndrome (Article)	Rebuttal to Dennis Wahr Testimony, evidence of overlap of asthma and COPD	www.goldcopd.org/uploads/users/files/AsthmaCOPDOverlap.pdf	Aug. 10, 2015	69
Diagnosing Asthma-COPD Overlap Syndrome	Rebuttal to Dennis Wahr Testimony, evidence of overlap of asthma and COPD and overlapping treatment for same	http://www.consultant360.com/articles/diagnosing-asthma-copd-overlap-syndrome	Aug. 10, 2015	70

<u>Title</u>	<u>Relevance</u>	<u>Website</u>	<u>Date Printed</u>	<u>Ex.</u>
Journal of Asian Pacific Society of Respiriology, Airway Vista 2015 Speakers	Rebuttal to Dennis Wahr Testimony, evidence of overlap of asthma and COPD and overlapping treatment for same	http://onlinelibrary.wiley.com/doi/10.1111/resp.12478/epdf	Aug. 10, 2015	71
“Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet	Rebuttal to Dennis Wahr Testimony, evidence of use of medical devices for non-indicated uses	http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm	Aug. 10, 2015	72
Bronchial Thermoplasty in Severe Asthma	Rebuttal to Dennis Wahr Testimony, evidence or overlap of asthma and COPD	http://www.consultant360.com/articles/bronchial-thermoplasty-severe-asthma	Aug. 12, 2015	77

Respectfully submitted,

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Date: August 12, 2015

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD**

Boston Scientific Corporation and Asthmatx, Inc.)	
)	
Opposers,)	
)	
v.)	
)	Opposition No. 91215699
Holaira, Inc.)	
)	
Applicants.)	
)	

CERTIFICATE OF SERVICE BY MAIL

STATE OF MINNESOTA)
) ss.
COUNTY OF HENNEPIN)

Jo Ellen Briley, of the City of Minneapolis, County of Hennepin, in the State of Minnesota, states that on the 12th day of August, 2015, she mailed by First Class mail, a true and correct copy of:

- 1) Opposers' Rebuttal Notice of Reliance; and
- 2) Second Affidavit of Timothy D. Sitzmann.

in the above-captioned action to the following last known address of record for Applicant, to-wit:

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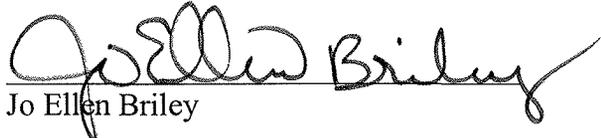

Jo Ellen Briley

Exhibit 68



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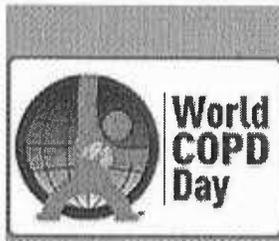
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2013: November 20

Documents

Asthma, COPD, and Asthma-COPD Overlap Syndrome

Updated April 2015



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A significant proportion of adult patients over age 40 who present with symptoms of a chronic airways disease have features of both asthma and COPD. Several diagnostic terms, most including the word 'overlap', have been applied to such patients, and the topic has been extensively reviewed. 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.

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 distinguishing between asthma, COPD and the overlap of asthma and COPD, for which the term Asthma COPD Overlap Syndrome (ACOS) is proposed. Rather than attempting a formal definition of ACOS, this document presents features that identify and characterize ACOS, ascribing equal weight to features of asthma and of COPD. A simple approach to initial treatment of ACOS is also included. 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. The primary objective of this approach is to inform clinical practice, based on current evidence.

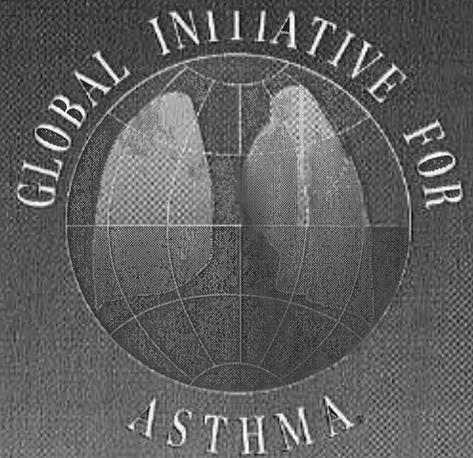
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Exhibit 69

Diagnosis of Diseases of
Chronic Airflow Limitation:

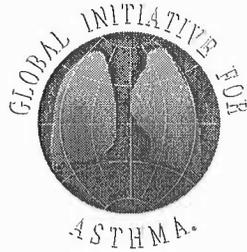
Asthma COPD and Asthma - COPD Overlap Syndrome (ACOS)



**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.**

2014

GLOBAL INITIATIVE FOR ASTHMA



GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE



**Diagnosis of Diseases of Chronic Airflow Limitation:
Asthma, COPD and Asthma-COPD Overlap Syndrome
(ACOS)**

GINA reports are available at <http://www.ginasthma.org>
GOLD reports are available at <http://www.goldcopd.org>

© Global Initiative for Asthma

Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS)

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Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS)

PREFACE

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 symptoms of a chronic airways disease have features of both asthma and COPD.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 resources¹⁴ 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 inclusion criteria used. However, prevalence rates between 15 and 55% have been reported, with variation by gender and age.^{8,13,15} 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 distinguishing between asthma, COPD and the overlap of asthma and COPD, for which the term Asthma COPD Overlap Syndrome (ACOS) is proposed¹⁰ Rather than attempting a formal definition of ACOS, this document presents features that identify and characterize ACOS, ascribing equal weight to features of asthma and of COPD. A simple approach to initial treatment of ACOS is also included. 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.¹⁸⁻²⁰ The primary objective of this approach is to inform clinical practice, based on current evidence.

Diagnosis Of Diseases Of Chronic Airflow Limitation: Asthma, COPD and Asthma–COPD Overlap Syndrome

A joint project of GINA and GOLD[#]

KEY POINTS

- Distinguishing asthma from COPD can be problematic, particularly in smokers and older adults
- ACOS is identified by the features that it shares with both asthma and COPD.
- A stepwise approach to diagnosis is advised, comprising recognition of the presence of a chronic airways disease, syndromic categorization as asthma, COPD or the overlap between asthma and COPD (the Asthma COPD Overlap Syndrome (ACOS)), confirmation 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.
- Initial treatment should be selected to ensure that:
 - Patients with features of asthma receive adequate controller therapy including inhaled corticosteroids, but not long-acting bronchodilators alone (as monotherapy), and
 - Patients with COPD receive appropriate symptomatic treatment with bronchodilators or combination therapy, but not inhaled corticosteroids alone (as monotherapy).
- The consensus-based description of the Asthma COPD Overlap Syndrome (ACOS) is intended to stimulate further study of the character and treatments for this common clinical problem.

OBJECTIVE

This consensus-based document aims to assist clinicians 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

[#] This chapter is excerpted from the Global Strategy for Asthma Management and Prevention, 2014. The full report can be viewed at <http://www.ginasthma.org>

DEFINITIONS

Table 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 2014]
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 2014] ²¹
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 by the features that it shares with both asthma and COPD.

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

STEP-WISE 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.^{3,22-24}

Clinical history

Features that should 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.²⁵⁻²⁷ 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.

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 (Table 2a), the approach proposed focuses on the features that are most helpful in distinguishing asthma and COPD (Table 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, the features favoring the diagnostic profile of asthma or of COPD can be assembled. The check boxes in Table 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.

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

From Table-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.²⁷ However, the absence of any of these 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 the absence of 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.

Table 2a. Usual features of asthma, COPD and ACOS				Table 2b. Features that favor asthma or COPD	
Feature	Asthma	COPD	ACOS	Favors Asthma	Favors COPD
<i>Age of onset</i>	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	<input type="checkbox"/> Onset before age 20 years	<input type="checkbox"/> Onset after age 40 years
<i>Pattern of respiratory symptoms</i>	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	<input type="checkbox"/> Variation in symptoms over minutes, hours or days <input type="checkbox"/> Symptoms worse during the night or early morning <input type="checkbox"/> Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	<input type="checkbox"/> Persistence of symptoms despite treatment <input type="checkbox"/> Good and bad days but always daily symptoms and exertional dyspnea <input type="checkbox"/> Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
<i>Lung function</i>	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	<input type="checkbox"/> Record of variable airflow limitation (spirometry, peak flow)	<input type="checkbox"/> Record of persistent airflow limitation (post-bronchodilator FEV ₁ /FVC < 0.7)
<i>Lung function between symptoms</i>	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitation	<input type="checkbox"/> Lung function normal between symptoms	<input type="checkbox"/> Lung function abnormal between symptoms
<i>Past history or family history</i>	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	<input type="checkbox"/> Previous doctor diagnosis of asthma <input type="checkbox"/> Family history of asthma, and other allergic condition	<input type="checkbox"/> Previous doctor diagnosis of COPD, chronic bronchitis or emphysema <input type="checkbox"/> Heavy exposure to a risk factor: tobacco smoke, biomass fuels
<i>Time course</i>	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	<input type="checkbox"/> No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year <input type="checkbox"/> May improve spontaneously or have an immediate response to BD or to ICS over weeks	<input type="checkbox"/> Symptoms slowly worsening over time (progressive course over years) <input type="checkbox"/> Rapid-acting bronchodilator treatment provides only limited relief.
<i>Chest X-ray</i>	Usually normal	Severe hyperinflation & other changes of COPD	Similar to COPD	<input type="checkbox"/> Normal	<input type="checkbox"/> Severe hyperinflation
<i>Exacerbations</i>	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	<p>*Syndromic diagnosis of airways disease: how to use Table 2b</p> <p>Shaded columns list features that, when present, best distinguish between 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, that diagnosis is suggested. If there are similar numbers of checked boxes in each column, the diagnosis of ACOS should be considered. See Step 2 for more details.</p>	
<i>Typical airway inflammation</i>	Eosinophils and/or neutrophils	Neutrophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum.		

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 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 (Table 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, 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.

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 Table 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. Inhaled corticosteroids 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.

STEP 4: Commence initial therapy

Faced with a differential diagnosis equally balanced between asthma and COPD (i.e. ACOS) the default position should be to start treatment accordingly for asthma (Table 4). This 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 attack¹⁰.

- If the syndromic assessment suggests asthma or ACOS, or there is significant uncertainty about the diagnosis of COPD, it is prudent to start treatment as for asthma until further investigation has been performed to confirm or refute this initial position.
 - o Treatments will include an ICS (in a low or moderate dose, depending on level of symptoms).
 - o A long-acting beta2-agonist (LABA) should also be continued (if already prescribed), or added. However, it is important that patients should not be treated with a LABA without an ICS (often called LABA monotherapy) if there are features of asthma.
- If the syndromic assessment suggests COPD, appropriate symptomatic treatment with bronchodilators or combination therapy should be commenced, but not ICS alone (as monotherapy).²¹
- Treatment of ACOS should also include advice about other therapeutic strategies¹⁶ including:
 - o Smoking cessation
 - o Pulmonary rehabilitation
 - o Vaccinations
 - o Treatment of comorbidities, as advised in the respective GINA and GOLD reports.

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.

Table 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, but ACOS should also be considered	Common and more likely when FEV ₁ is low, but ACOS should also be considered
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; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease.

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.

Table 5 summarizes specialized investigations that may be used to distinguish asthma and COPD.

Table 4. Summary of syndromic approach to diseases of chronic airflow limitation

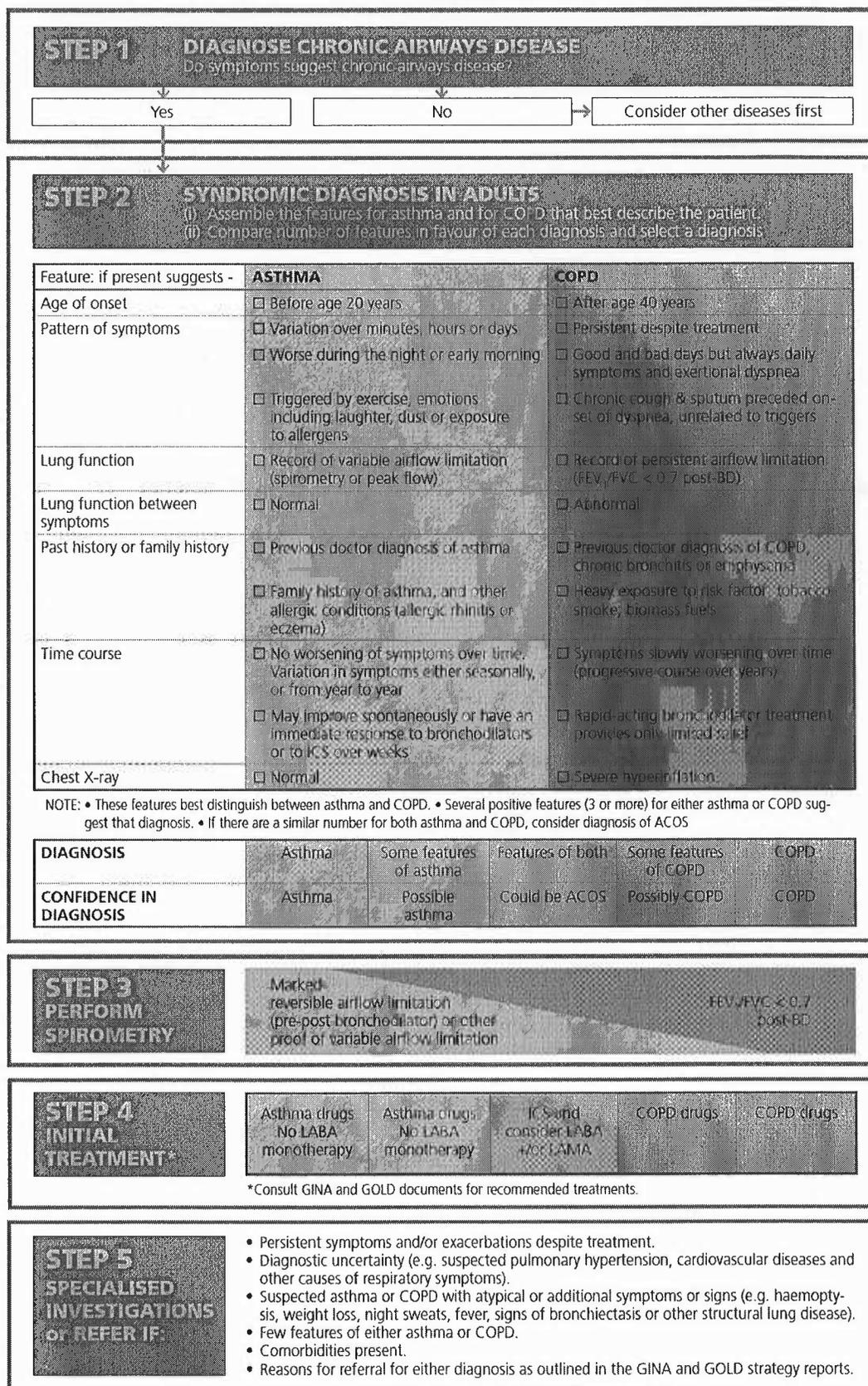


Table 5. Specialized investigations sometimes used in distinguishing asthma and COPD

	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 high 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	

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Visit the GINA website at www.ginasthma.org
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Visit the GOLD website at www.goldcopd.org
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URL: www.goldcopd.org/uploads/users/files/AsthmaCOPDOverlap.pdf Printed 10 August 2015

Exhibit 70



ALL-NEW REGIONAL MEETING SERIES ON
WOMEN'S HEALTH IN THE PRIMARY CARE SETTING

PEER-REVIEWED CONSULTATIONS IN PRIMARY CARE

Consultant

Diagnosing Asthma-COPD Overlap Syndrome

Wed, 08/06/14 - 13:11

Authors:

Amir A. Zeki, MD, MAS, and Samuel Louie, MD

Citation:

Consultant. 2014;54(8):845-849

A new patient with a history of hay fever and past cigarette use presents with wheezing, a productive cough, and dyspnea. Is the correct diagnosis asthma or COPD?

This question plagues clinicians daily because dogma dictates that a patient has either asthma or COPD—but not both. However, separating asthma from COPD in clinical practice is difficult due to the overlapping features common to both diseases. The pitfall is to presume that both conditions can not possibly exist in the same patient.

The Asthma-COPD Overlap Syndrome (ACOS) is a newly recognized diagnosis,¹⁻³ one that has long been neglected in part because clinical trials for decades have consistently excluded patients with overlapping asthma and COPD, using strict inclusion and exclusion criteria. These criteria routinely excluded asthma patients from COPD studies, and COPD patients from asthma studies (**Table 1**). As a result there are no evidenced-based guidelines for the diagnosis and treatment of ACOS that are based on actual clinical trials of subjects with ACOS.

Table 1. Definitions Related to ACOS³

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.⁶

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.

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 identified by the features that it shares with both asthma and COPD.

Definitions

A consensus ACOS description for clinical use has recently been published by both the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2014,³ however, a clear pharmacotherapeutic approach to these patients remains elusive. ACOS accounts for approximately 15% to 55% of patients with diseases of chronic airflow limitation.³ This syndrome represents an important population with worse outcomes than asthma or COPD alone.⁴

Patients with ACOS have the combined risk factors of smoking and atopy, and are generally younger than patients with COPD.^{1,4} ACOS patients have acute exacerbations with higher frequency and greater severity than lone COPD,⁴ manifest more air-trapping, and require more healthcare visits,⁵ despite a lower burden of cigarette smoking.

RELATED CONTENT

- FDA Approves Olodaterol Inhalation Spray for COPD
- Noncardioselective Beta-Blocker Use in Patients With Asthma

We have proposed a syndromic approach to recognize the considerable heterogeneity in obstructive airway diseases—ie, asthma [IgE or non-IgE mediated disease] and COPD should be considered as syndromes, and ACOS consists of similar phenotypes with characteristic, but nonspecific symptoms.^{2,3} COPD is a syndrome that includes patients with chronic bronchitis or patients with emphysema phenotypes that are united by the most common risk factor: tobacco cigarette smoking.

Based on our personal clinical experience in patients with overlapping features of asthma and COPD, ACOS can be defined as 1 of 2 clinical phenotypes.^{1,2}

1. Asthma with partially reversible airflow obstruction—ie, based on change in FEV1 with bronchodilators, with or without emphysema or reduced carbon monoxide diffusing capacity (carbon monoxide diffusion [DLCO], <80% predicted).
2. COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies (eg, elevated total IgE or eosinophils) or reduced DLCO.

Table 2 compares the 3 syndromes of obstructive airway diseases.^{3,6,7}

Syndrome	Asthma ⁶ (Severe)	Asthma-COPD Overlap Syndrome	COPD ⁷
Demographics	<ul style="list-style-type: none"> • > 40 years • Women > men • Nonsmoker or < 5 pack years • Obesity • Atopy typical • Rhinosinusitis • GERD • Frequent albuterol use • Exercise limited in between attacks • Dependence on prednisone • Hallmark problem: frequent exacerbations 	<ul style="list-style-type: none"> • > 40 years; 50 to 65 years • Past or current smoker • > 10 pack years • Atopy present • Rhinosinusitis • GERD • Exercise very limited • Hallmark problem: Very frequent exacerbations > COPD alone 	<ul style="list-style-type: none"> • ≥ 65 years, if not younger • Past or current smoker • > 10 pack years • No atopy • GERD • Multiple daily albuterol • Exercise very limited • Oxygen dependence • Hallmark problem: exacerbations and exercise intolerance
Pathophysiology	<ul style="list-style-type: none"> • Intermittent to chronic moderate to severe airflow obstruction 	<ul style="list-style-type: none"> • Intermittent to chronic moderate to severe airflow obstruction 	<ul style="list-style-type: none"> • Chronic airflow obstruction moderate to severe

	<ul style="list-style-type: none"> • FEV1/FVC < 0.70 • FEV1 < 68% predicted, ≥ 65% or < 65% after albuterol • SARP cluster 3, 4, or 5 • DLCO normal • FeNO > 50 ppb • ≥ 3% sputum eosinophils • Exacerbations > 3/yr 	<p>airway obstruction</p> <ul style="list-style-type: none"> • FEV1/FVC < 0.70 • FEV1 < 68% predicted, ≥ 65% or < 65% after albuterol • DLCO normal or < 80% predicted • FeNO > 25-50 ppb • Static hyperinflation • Exacerbations > 3-5/yr • Frequent nocturnal awakenings ≥ 4/wk 	<p>(GOLD II to IV)</p> <ul style="list-style-type: none"> • FEV1/FVC < 0.70 • DLCO < 80% predicted • FeNO < 25 ppb • Static and dynamic hyperinflation • Exacerbations > 2/yr after FEV1 < 50% • Infrequent nocturnal awakenings • Pulmonary hypertension late
First-line pharmacotherapy and treatments	<ul style="list-style-type: none"> • ICS • ICS + LABA* 	<ul style="list-style-type: none"> • ICS ± LAMA ± LABA • Smoking cessation • Pulmonary rehabilitation 	<ul style="list-style-type: none"> • Bronchodilators • LAMA or LABA or both • Smoking cessation • Pulmonary rehabilitation
Current add-on pharmacotherapy	<ul style="list-style-type: none"> • LABA, LAMA, LTRA, theophylline, omalizumab,^a or prednisone 	<ul style="list-style-type: none"> • LABA, LAMA, LTRA, roflumilast, theophylline, omalizumab,^a or prednisone 	<ul style="list-style-type: none"> • ICS, roflumilast, or theophylline
Emerging treatments	<ul style="list-style-type: none"> • Anti-IL-5, anti-IL-13 • ICS + LABA once daily • Azithromycin • Vaccines • Bronchial thermoplasty 	<ul style="list-style-type: none"> • Refer to asthma and COPD 'Emerging Treatments' • Consider using FeNO to endotype • Bronchial thermoplasty 	<ul style="list-style-type: none"> • LAMA + LABA once daily • Carbocysteine • Azithromycin • Anti-IL-3, p39 protein kinase inhibitors, or <i>H. influenzae</i> vaccine • Endobronchial valves • Lung transplantation
<p>^aFDA black box warning alert. ACOS: asthma-COPD overlap syndrome; COPD: chronic obstructive pulmonary disease; DLCO: carbon monoxide diffusing capacity; FeNO: fractional exhaled nitric oxide; GERD: gastroesophageal reflux disease; ICS: inhaled corticosteroids; IL: interleukin; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist.</p>			

Diagnosing ACOS

The approach proposed by GINA is simple and practical.³

1. Ask if the patient has chronic airways obstruction, which can only be confirmed by spirometry.
2. Correlate history (eg, hay fever or tobacco smoking history), physical examination (eg, sinusitis, wheezing, or rhonchi), spirometry (essential to confirm airways obstruction), chest x-ray, and screening questionnaires (eg, Asthma Control Test or COPD Assessment Test).
3. Use the GINA 5-step algorithm for diagnosis and initial treatment (Table 3). The GINA algorithm recommends assembling the clinical features that favor a diagnosis of asthma or COPD, followed by comparing the number of features in favor of asthma or COPD.
4. Evaluate the level of certainty around the diagnosis of asthma or COPD versus whether presenting features suggest ACOS as a diagnosis.

Table 3. Syndromic Approach to Chronic Airways Diseases³

STEP 1 **DIAGNOSE CHRONIC AIRWAYS DISEASE**
 Do 3 or more items suggest chronic airways disease?

Yes

No

Consider other diseases first

STEP 2 SYNDROMIC DIAGNOSIS IN ADULTS

(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis.

Feature: if present suggests -	ASTHMA	COPD
Age of onset	<input type="checkbox"/> Before age 20 years	<input type="checkbox"/> After age 40 years
Pattern of symptoms	<input type="checkbox"/> Variation over minutes, hours or days <input type="checkbox"/> Worse during the night or early morning <input type="checkbox"/> Triggered by exercise, emotions including laughter, dust or exposure to allergens	<input type="checkbox"/> Persistent despite treatment <input type="checkbox"/> Good and bad days but always daily symptoms and exertional dyspnea <input type="checkbox"/> Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	<input type="checkbox"/> Record of variable airflow limitation (spirometry or peak flow)	<input type="checkbox"/> Record of persistent airflow limitation (FEV ₁ /FVC < 0.7 post-BD)
Lung function between symptoms	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal
Past history or family history	<input type="checkbox"/> Previous doctor diagnosis of asthma <input type="checkbox"/> Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	<input type="checkbox"/> Previous doctor diagnosis of COPD, chronic bronchitis or emphysema <input type="checkbox"/> Heavy exposure to risk factor: tobacco smoke, biomass fuels
Time course	<input type="checkbox"/> No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year. <input type="checkbox"/> May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	<input type="checkbox"/> Symptoms slowly worsening over time (progressive course over years) <input type="checkbox"/> Rapid acting bronchodilator treatment provides only limited relief
Chest X-ray	<input type="checkbox"/> Normal	<input type="checkbox"/> Severe hyperinflation

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Possible asthma	Could be ACOS	Possibly COPD	COPD

STEP 3 PERFORM SPIROMETRY

Marked reversible airflow limitation (pre/post bronchodilator) or other proof of variable airflow limitation.

FEV₁/FVC < 0.7 post-BD

STEP 4 INITIAL TREATMENT*

Asthma drugs No LABA monotherapy	Asthma drugs No LABAs monotherapy	ICS and consider LABA or LAMA	COPD drugs	COPD drugs
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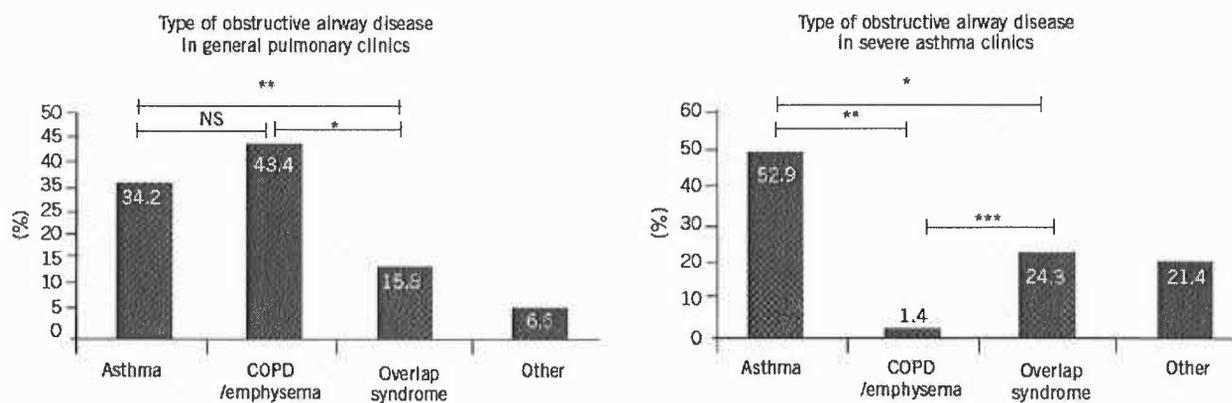
*Consult GINA and GOLD documents for recommended treatments.

STEP 5 SPECIALISED INVESTIGATIONS or REFER IF:

- Persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty (e.g. suspected pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms).
- Suspected asthma or COPD with atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease).
- Few features of either asthma or COPD.
- Comorbidities present.
- Reasons for referral for either diagnosis as outlined in the GINA and GOLD strategy reports.

GINA reports that the prevalence rates of ACOS are between 15% and 55%, with variation by gender and age.³ In our practice, we reported a prevalence between 15% and 25% (Figures 1 and 2).^{1,2}

Despite their relatively younger age and a lower burden of cigarette smoking, the healthcare costs for patients with ACOS is significantly greater than for COPD alone.^{2,3,5} Given the increasing costs of healthcare, our limited resources, and relatively high prevalence of ACOS, the time has come to better define this syndrome in order to pursue randomized clinical trials that are designed to evaluate targeted drug therapies.



Figures 1 and 2. Prevalence of obstructive airways disease in a general pulmonary clinic and in the UC Davis Medical Center severe asthma clinics.¹

Initial Therapy

The goals of treatment in all diseases of chronic airflow limitation (in lieu of a cure) are to control symptoms and prevent exacerbations, thereby reducing morbidity and mortality. Morbidity can result from coughing, wheezing, sputum production, and dyspnea on exertion. Mortality can result from frequent exacerbations and complications, including adverse drug reactions, and respiratory failure. Control is a valid concept in all diseases of chronic airflow obstruction and this is achieved through the reduction of risk and impairment (**Figure 3**).

The objectives or the steps needed to reduce risk and impairment, as well as prevent exacerbations, should be attainable (timeline of 3 months), measurable (eg, control questionnaire scores, FEV₁, or fractional exhaled nitric oxide [FeNO]), and cost-effective (eg, number needed to treat and acceptable risk of adverse drug effects).

Current drug treatments have been incorporated into clinical practice guidelines—the 2007 NAEPP-EPR3,⁶ 2014 GINA⁸ for asthma, and 2014 GOLD treatment guidelines for COPD⁷—all of which recognize the enduring risk of acute exacerbations. Knowledge of these treatment guidelines is important to help patients achieve basic control of their disease. The value of emerging peer-reviewed, large, randomized clinical trials and meta-analyses is that they add to current therapeutic strategies. Clinical trials that enroll patients from the real world instead of professional study subjects, are of greater value because they more closely reflect real clinical practice.

Current controller drugs for asthma action plans include inhaled corticosteroids (ICS); long-acting β_2 agonists (LABA), leukotriene receptor antagonists (LTRA); omalizumab; and theophylline. Of note, LABAs are contraindicated as monotherapy in the United States for the treatment of asthma. Current rescue drugs for asthma include short-acting β_2 agonists (SABA), short-acting muscarinic antagonists (SAMA), systemic corticosteroids, and in some cases, antibiotics.

Current maintenance or controller treatments for COPD action plans include tiotropium, a long-acting muscarinic antagonist (LAMA), LABA, LABA + ICS, LAMA + LABA, the phosphodiesterase-4 inhibitor roflumilast, theophylline, and “triple therapy” which combines LAMA + LABA + ICS. Current rescue drugs for COPD include SABA, SAMA, systemic corticosteroids, and antibiotics.

GINA recommends starting treatment for asthma first when faced with ACOS, which means the differential diagnosis is equally balanced between asthma and COPD. This recognizes the pivotal role ICS play in preventing acute

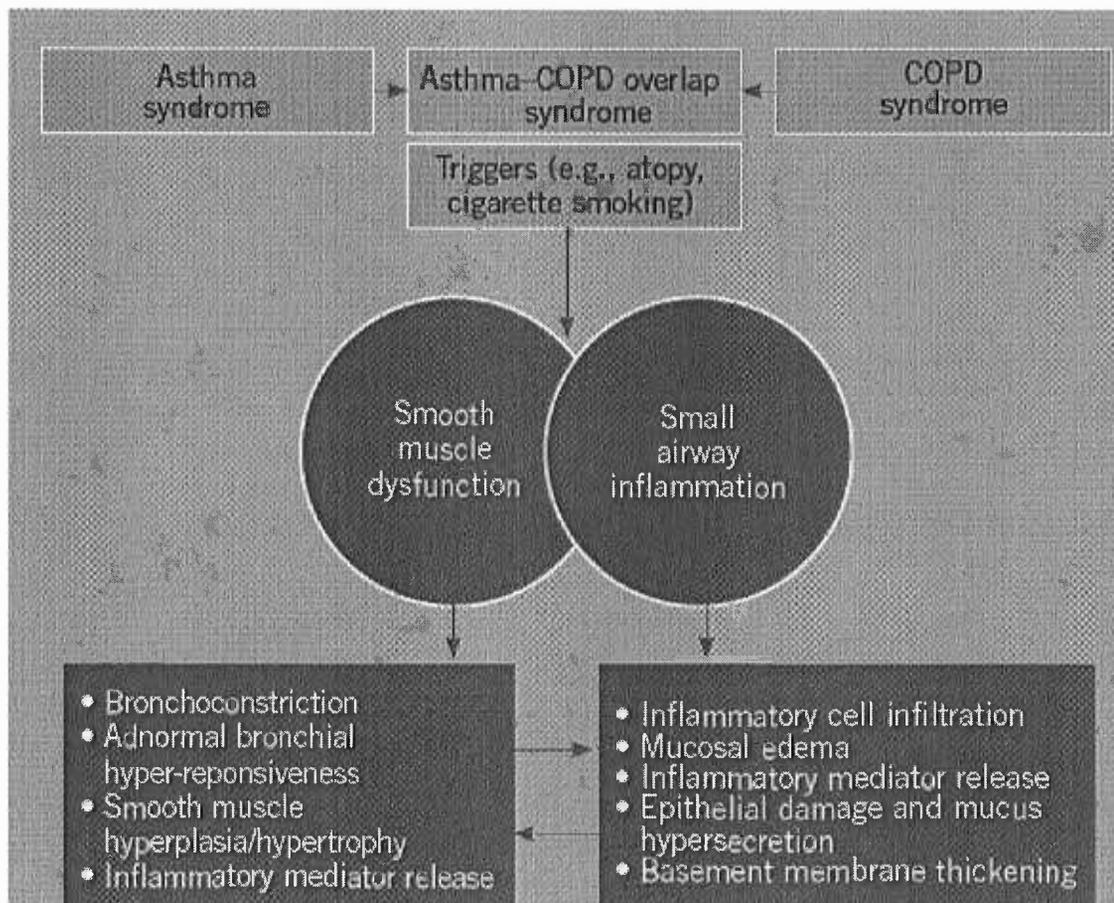
exacerbations in both asthma and COPD, and even death.^{2,3} ICS should be prescribed and patient response assessed in 2 to 6 weeks. Failure to improve lung function (FEV1 >5% over baseline spirometry) and symptoms should raise suspicion that the patient is a nonresponder to ICS.^{2,9} One can consider increasing the ICS dose and/or adding a LABA or LTRA to ICS treatment. Adding theophylline and/or omalizumab may also be an option for select patients. For instance, omalizumab can only be added if the asthma component is IgE-mediated and other anti-inflammatory drugs have failed to control symptoms and exacerbations.

A LABA remains the preferred add-on to ICS in asthma but is contraindicated as monotherapy in the United States per the FDA. Experience and expertise is required with other asthma treatments (eg, LTRA and omalizumab).

Bronchodilators, such as LAMA and LABA, are first-line therapies alone or in combination in COPD. A history of acute COPD exacerbation in the past 12 months should prompt the addition of a moderate dose ICS and/or roflumilast. ICS should not be prescribed alone in COPD or in ACOS if COPD features are very pronounced. The high doses of ICS typically used in asthma are associated with a higher incidence of pneumonia in patients with COPD.

A comprehensive program for all diseases of chronic airflow limitation must address, if relevant, the complex physiological and behavioral processes that contribute to nicotine addiction and relapse. It is a major pitfall to not offer smoking cessation education and pharmacological aides repeatedly to each patient. Concurrently, additional therapies—eg, personal hygiene education, vaccinations, pulmonary rehabilitation, and the recently-added bronchial thermoplasty procedure—should be employed to control symptoms and prevent acute exacerbations where appropriate. Immunotherapy against detected aeroallergens is considered adjunctive care by the NIH-NAEPP but may have utility in select difficult-to-control cases.²

Pharmacotherapeutic considerations in ACOS must currently rely on a combination of reasoned clinical experience and logical extrapolation from the existing literature in asthma and COPD. However, until clinical trials are accomplished specifically in patients with ACOS, it would be a serious pitfall not to conduct a clinical trial in every patient to tailor therapy, ie 1 drug therapy at a time to determine effective treatments while avoiding adverse effects.



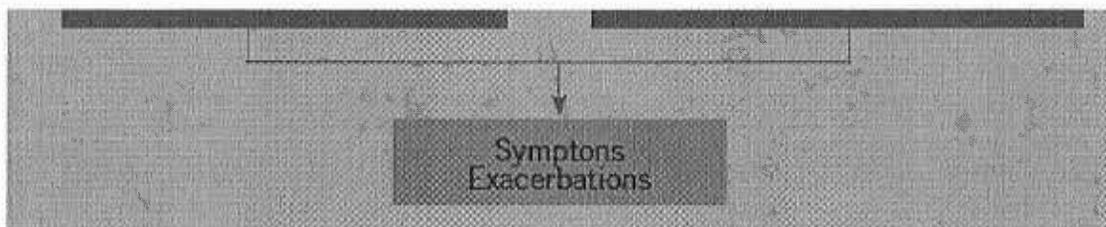


Figure 3. Pharmacotherapeutic targets in Asthma-COPD Overlap Syndrome.^{2,10}

To Avoid Pulmonary Pitfalls in ACOS:

Do not presume that features of asthma and COPD cannot exist in the same patient.

Remember advancing age, atopy, and tobacco smoking are risk factors for ACOS.

Confirm the presence of airflow limitation using spirometry in asthma and COPD patients. Spirometry is essential to diagnose and monitor response to treatment and management.

Offer smoking cessation education and pharmacological aides to every current smoker.

Conduct a clinical trial of 1 in every patient, using 1 drug therapy (or other intervention) at a time.

Treat the component of asthma first with ICSs and ascertain objectively if lung function and symptoms improve after 6 weeks. Then consider adding long-acting bronchodilators, such as a LAMA and/or LABA.

Alert patients of the FDA's black box warning assigned to the class of LABA in everyone, not just asthma patients. LABAs remain the preferred add-on drug to ICS.

Consider omalizumab and bronchial thermoplasty after 3 months of confirmed adherence to action plans without improvement in symptoms and/or the ability to control exacerbation risk.

Consider roflumilast early to reduce the risk of frequent acute exacerbations.

Offer pulmonary rehabilitation early to improve quality of life and reinforce patient education. ■

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Exhibit 71

AIRWAY VISTA 2015 SPEAKER ABSTRACTS

PHENOTYPING OF COPD FROM ASIAN PERSPECTIVE

S-D LEE

Asian Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and is associated with substantial socio-economic burdens which are increasing continuously in many countries. The situation seems particularly serious in Asia because of the high prevalence of tobacco smoking, exposure to outdoor and indoor air pollution related to the burning of wood and other biomass fuels, and exposure to occupational dust.

One of the main reasons for poor understanding of COPD is that the disease progresses slowly and is heterogeneous. Although chronic airflow limitation is one important characteristic of COPD, the disease shows heterogeneous features in terms of clinical presentation, physiology, imaging, response to therapy, decline in lung function, and survival, even in patients that show a similar degree of airflow limitation. This heterogeneity might arise from differences in environmental factors and/or the patient's genetic background. It follows, therefore, that long-term observational cohort studies should be performed in different countries, or regions in which patients of different genetic backgrounds may have been exposed to different disease etiologies to identify the pathogenesis of COPD heterogeneity.

Here we introduce two cohorts.

The Korean Obstructive Lung Disease (KOLD) Cohort Study is an ongoing prospective longitudinal study started in 2004. Analyses of the KOLD Cohort Study identified distinct phenotypes in patients with COPD, and predictors of therapeutic responses and exacerbations as well as the factors related to pulmonary hypertension in COPD. In addition, several genotypes were associated with radiological phenotypes and therapeutic responses among Korean COPD patients.

To understand the heterogeneity of COPD in Asian countries we organized Asian Network for Obstructive Lung Diseases (ANOLD) in 2008 and found subgroups of COPD patients with distinct phenotypes.

MAJOR CLINICAL TRIALS FOR COPD MANAGEMENT

RA WISE

Johns Hopkins University School of Medicine, Baltimore, MD, USA

This presentation will discuss the findings of major clinical trials that form the foundation of modern COPD management over the past several decades. Over this time period, clinical trials for COPD have become larger, and the clinical outcomes have included not only lung function, but also quality of life, mortality, exercise capacity, prevention of exacerbations, and cardiovascular safety. The mortality benefit of domiciliary oxygen therapy is based on the relatively small NOTT and MRC trials. Expansion of criteria for oxygen treatment is being tested in the LOTT trial with results next year. The role of smoking intervention for mild COPD has been supported by the Lung Health Study (LHS) in terms of lung function decline and mortality. The benefits of long-acting bronchodilator treatment with LABA or LAMA are based on the TORCH, UPLIFT and POET trials and confirmed by subsequent trials with other long-acting bronchodilators. The role of inhaled steroids remains controversial based on evidence from LHS2, EuroScop, TORCH and WISDOM. The use of prophylactic antibiotics for COPD exacerbations is based on the MACRO study, although implementation of the use of macrolides for preventing COPD exacerbations remains uncertain. The indications lung volume reduction surgery for emphysema has been better defined by the NETT trial and the use of endobronchial valves for non-invasive lung volume reduction was studied in the VENT trial. The safety of inhaled bronchodilators, particularly with respect to cardiovascular safety has been examined in the large-scale TIOSPIR trial. The SUMMIT and ASCENT trials in current progress are examining the role of ICS/LABA and LAMA therapies respectively for cardiovascular outcomes. Over the past two decades, our understanding of the risks and benefits of modern treatments for COPD have expanded and the nihilistic view of COPD therapy can no longer be sustained.

ASTHMA-COPD OVERLAP SYNDROME (ACOS): NEW INSIGHTS

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Although airway obstruction characterizes emphysema, chronic bronchitis and asthma, there exists considerable overlap in these syndromes. The recognition that significant numbers of patients are exposed to cigarette smoke complicates the definition of these common diseases. Evidence suggests that ACOS represents an overlap syndrome in which airway inflammation is typically corticosteroid insensitive, while reversible airway obstruction and hyperresponsiveness cannot discriminate these diseases. Further, pre-existing asthma may predispose patients to the development of COPD when exposed to tobacco smoke or biomass exhaust. The characterization of ACOS and the development of novel therapeutic approaches to improve outcomes are critical to decrease morbidity and mortality associated with this syndrome.

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COPD CLINICAL PHENOTYPES: THE PINK PUFFER, THE BLUE BLOATER, AND EVERYTHING IN BETWEEN

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Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in the United States behind heart disease, cancer, and cerebrovascular disease. It is a worldwide problem that is predicted to increase in the upcoming years. In 1990, COPD was ranked 12th in terms of worldwide burden of disease, but by 2020 it is projected to rank 5th. The face of COPD is changing; once considered a disease of the older white male, it is now known that COPD in women is on the rise, where the fatalities attributed to COPD in women has surpassed that in men. It has been further described in greater detail in the Asian and African American population. In addition, the recent description of other prominent environmental risk factors, such as biomass fuels, has increased recognition and diagnosis of COPD in other countries where these fuels are used for cooking.

The classic description of the COPD spectrum, with the emphysematous patient, or the "pink puffer," on one end and the chronic bronchitic patient, called the "blue bloater," on the other end is obsolete. Recent literature has advanced our understanding of COPD clinical phenotypes to include much more than what has been previously described. Newer phenotypes include the frequent exacerbator, the asthma/COPD overlap syndrome, the rapid decliner, and those with bronchodilator reversibility. There has also been increasing recognition of systemic comorbidities such as cardiovascular disease, osteoporosis, muscle weakness with impaired exercise tolerance, cachexia, and obstructive sleep apnoea.

This lecture aims to describe the spectrum of clinical phenotypes in COPD, with attention to the newly described phenotypes and associated comorbidities.

COPD AND PULMONARY VASCULAR DISEASE: IMPLICATIONS OF CT IMAGING

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Introduction: Pulmonary vascular disease is a risk factor for increased morbidity and mortality in subjects with patients with chronic obstructive pulmonary disease (COPD). Despite its impact, the incidence of pulmonary hypertension varies widely in COPD and diagnostic evaluation of these patients has been limited. There is increased interest in using non-invasive techniques including CT, cardiac MRI, and echocardiography compared to right-sided heart catheterization in this population. In fact, relative pulmonary artery enlargement by CT [pulmonary artery diameter to ascending aortic diameter (PA/A) > 1] is an important metric for identification of patients at highest risk for exacerbation and hospitalization. The technique is simple and reproducible across patient populations independent of imaging software available at different locations.

Methods: This session will summarize the epidemiology and identify factors associated with this phenotype and will discuss the importance of identifying these patients. There will be a review and discussion of invasive and non-invasive testing, including CT, cardiac MRI, echocardiography, and right heart catheterization in the diagnosis of this group of patients, highlighting findings of CT detected pulmonary artery enlargement and its value in predicting exacerbations. The session will close with discussion regarding management strategies for these patients.

Results and Conclusions: CT imaging provides robust information on the pulmonary vasculature and has implications for clinical practice and design of clinical trials.

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GENOMIC SIGNATURES OF TYPE-2 INFLAMMATION IN COPD

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Introduction/Aims: We have previously shown that asthma is heterogeneous and that one major subgroup of asthma is characterized by prominent type-2 inflammation. COPD is also heterogeneous at clinical and biological levels. One subgroup of biologically distinct COPD may be patients whose disease is driven by type-2 inflammation, similar to that found in asthma. Studying asthma-associated gene expression changes in COPD could add insight into COPD pathogenesis and reveal biomarkers that predict a favorable response to corticosteroids in COPD. Our aim in this study was to determine whether asthma-associated gene signatures are increased in COPD and associated with response to inhaled corticosteroids.

Methods: We compared disease-associated airway epithelial gene expression alterations in an asthma cohort (n = 105) and two COPD cohorts (n = 237 and 171). The Th2 signature ("T2S") score, a gene expression metric induced in Th2-high asthma, was evaluated in these COPD cohorts. The T2S score was correlated with inflammatory cell counts and response to corticosteroids in COPD in a randomized placebo-controlled trial (GLUCOLD, n = 89).

Results: The 200 genes most differentially expressed in asthma versus healthy controls were enriched among genes associated with more severe airflow obstruction in these COPD cohorts (p < 0.001), suggesting significant gene expression overlap. A higher T2S score was associated with decreased lung function (p < 0.001), but not with asthma history, in both COPD cohorts. Higher T2S scores correlated with higher airway wall eosinophil counts (p = 0.003), and greater improvements in hyperinflation following corticosteroid treatment (p = 0.019) in GLUCOLD.

Conclusions: These data identify airway gene expression alterations that can co-occur in asthma and COPD. The association of the Th2 signature with increased severity and "asthma-like" features (eosinophilia and a favorable corticosteroid response) in COPD suggests Th2 inflammation is important in a COPD subset that cannot be identified by clinical history of asthma.

RISK FACTORS AND DIAGNOSIS OF COPD

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Chronic obstructive pulmonary disease (COPD) is a chronic progressive disease of the airways and lung parenchyma that is associated with exposure to tobacco smoke and other environmental insults in genetically susceptible individuals.

The development of COPD is multifactorial, and the risk factors include both genetic and environmental factors.

Tobacco smoking is established as the most important risk factor associated with COPD. However, it was reported that between 25% and 45% of patients with COPD had never smoked. Exposure to smoke from biomass fuel, indoor and outdoor air pollutants, occupational exposure to dusts and fumes are considered as important risk factors related to the development of so called, 'non-smoker COPD'. Bronchial hyperresponsiveness and early childhood respiratory infection are thought to be important host factors for the development of COPD.

Efforts to identify the genetic determinants of COPD have found potential genes related to COPD, however, the individual risk contributed by most genetic variants has proven to be small. The combination of genome wide association study and carefully conducted candidate gene approaches with large stratified cohorts of well-phenotyped individuals will help to find responsible genes for the risk of COPD.

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the COPD. Spirometry is required to make the diagnosis in this clinical context, the presence of post-bronchodilator FEV₁/FVC < 0.7 confirms the presence of persistent airflow limitation and thus of COPD. Because there is no data to indicate that screening spirometry has beneficial outcomes in patients who have no significant symptoms, GOLD guideline advocates active case finding but not screening spirometry.

MANAGEMENT OF STABLE COPD AND CHOICE OF ADEQUATE INHALER

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The objective of management of stable COPD consists of reducing symptoms and also reducing risk. Therefore, identification and reduction of risk factor exposure are the first step in the management of COPD. FEV₁ for disease impact and MRC, CAT, or exacerbation frequency in the previous year for future risk of exacerbation are necessary for the individualized assessment of COPD.

Pharmacologic therapy mainly with appropriate inhaler could not only reduce patients' symptoms and frequency and severity of exacerbation, but also improve exercise tolerance and quality of life. For patients with significant symptoms, long-acting bronchodilators could be the first choice of treatment. Long term treatment of inhaled corticosteroids combined with long acting bronchodilators is recommended for exacerbation-prone patients. To select adequate inhaler for individual patient, patients' skill and preference to various inhaler and devices, co-morbidities and side effects should be considered in addition to the symptom severity and risk of exacerbation.

Recently, combination bronchodilators with different mechanisms and durations have been developed and shown to increase the degree of bronchodilation with similar or lesser side effects. And, combination inhaled corticosteroid and bronchodilator therapy especially with long acting beta2 agonists is more effective in improving lung function, quality of life and reducing exacerbations than each individual components. There are ongoing clinical trials with new inhaler therapy including new components or in various combinations (e.g. triple therapy with inhaled corticosteroid, beta2-agonist and anti-cholinergics or dual therapy with inhaled corticosteroid with anti-cholinergics). And, more individualized and optimized treatment with better efficacy and safety profile for stable COPD might possible in the near future.

PREVENTION AND TREATMENT OF COPD EXACERBATIONS

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Chronic obstructive pulmonary disease (COPD) is often associated with exacerbations described as an acute worsening of respiratory symptoms associated with a variable degree of physiological deterioration. Exacerbations of COPD are associated with poorer quality of life, accelerated decline of lung function and increased mortality. Prevention of COPD exacerbations are therefore a major goal of COPD treatment. Strategies that are currently being used to prevent COPD exacerbations include pharmacological interventions with long-acting bronchodilators alone or combined with inhaled corticosteroids, phosphodiesterase-4 inhibitors and mucolytics, long-term prophylactic macrolide, and non-pharmacological interventions such as smoking cessation, influenza vaccination and pulmonary rehabilitation. Pharmacological treatment for COPD exacerbation mainly used bronchodilators, corticosteroids, and antibiotics. Short acting inhaled β_2 agonists and anticholinergics are the main treatment modality for exacerbations. Systemic steroids can shorten recovery time, improve lung function and oxygenation, and reduce treatment failure and the risk of early relapse, and length of hospital stay in patients with COPD exacerbations. Although there are insufficient data about the optimal duration of corticosteroid therapy, recent GOLD guidelines recommend a dose of 40 mg prednisolone per day for 5 days. Antibiotics should be given to patients with three cardinal symptoms- increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is present; or require mechanical ventilation. The recommended length of antibiotic treatment is usually 5–10 days. Oxygen therapy and ventilator support are key components of hospital treatment of severe exacerbations. Patients with hypoxemia should receive supplemental oxygen with a target saturation 88–92%. Non-invasive mechanical ventilation (NIV) has been shown to reduce intubation rates, length of hospital stay and mortality. Thus, NIV is the preferred method of ventilator support in patients with COPD exacerbation. Invasive mechanical ventilation should be administered in patients unable to tolerate NIV or NIV failure.

MANAGEMENT OF COPD COMORBIDITIES

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Chronic obstructive pulmonary disease (COPD) is a complex disease with pulmonary and extra-pulmonary complications and comorbidities. In general, extra-pulmonary comorbidities such as cardiovascular disease, lung cancer, osteoporosis, anxiety and depression or diabetes have a significant impact on quality of life, health care utilization including hospitalization, and mortality in COPD patients. Since these comorbidities are often under-recognized and under-treated, the identification of comorbidities in COPD patients is one of key factors in assessment of COPD patients.

Cardiovascular disease is a major comorbidity and it is the most frequently seen in COPD patients. The management of cardiovascular disease should be treated according usual practice, and especially, treatment with selective beta₁-blocker is preferable to a non-selective beta-blocker in cardiovascular disease patients with COPD.¹ In management of COPD patients with lung cancer, a curative-intent standard resection and early intervention including inhalers and rehabilitation for COPD are necessary for better outcomes after surgery.² In treatment of osteoporosis, usual osteoporosis guidelines should be followed. Most importantly, risk factors including smoking cessation, increasing physical activity and minimizing use of systemic corticosteroids should be addressed. To reduce dyspnea, fatigue, anxiety and depression in COPD patients, pulmonary rehabilitation or relaxation therapy with cognitive behavioral therapy can be helpful. In other comorbidities including metabolic syndrome and diabetes, standard therapies according to local guidelines should be used.³

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PERSONALIZED MEDICINE USING NOVEL PHENOTYPING AND BIOMARKERS IN ASTHMA

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Asthma is an extremely heterogenous airway disease. The first step to personalized medicine in asthma is to define and categorize clinical phenotypes as well as endotypes in a concrete manner. To date, many researchers from in US, European, and Korean have focused on cluster analysis to classify phenotypes as an unbiased method in their asthmatic patients. These results contributed to understanding of various types of phenotypes and heterogeneity in asthma; however, the complexity and difficulty in practical application remains to be solved. In addition, most of the clusters were analysed cross-sectionally at a point of time, thus longitudinal validation of the analysis is also needed. Further, the comparison of clinical characteristics in asthma among different races across the world would be helpful in understanding of heterogeneity in asthma.

In terms of biomarkers in asthma, a number of biomarkers have been suggested to define asthma phenotype and treatment response to a specific drug. To overcome severe refractory asthma, many monoclonal antibodies are tried, which requires more specific biomarkers that can further assist in selecting the corresponding drug specific to the target. In addition to biologics, long-acting anti-muscarinic agents and bronchial thermoplasty are also emerging as new treatment modalities. Nevertheless, only a few biomarkers are found to be applicable to real practice in asthma.

In conclusion, more effort to define novel and practical asthma phenotypes, and to find useful biomarkers in real practice is needed for personalized medicine in asthma. Further, collaborative researches across large asthma research network in different countries can also be contributable to understanding and performing tailored medicine in asthma.

GENETIC HETEROGENEITY OF COPD

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Chronic obstructive pulmonary disease (COPD) is characterized by persistent and usually progressive airflow limitation. While COPD susceptibility is mainly attributable to cigarette smoking, not all heavy smokers develop COPD for reasons that are still unclear. Significant familial aggregation of COPD has been reported, suggesting an important role for genetic factors in COPD susceptibility and severity. Although chronic bronchitis (CB) and emphysema are two classic disease-related characteristics of COPD, many different COPD-related phenotypes have been suggested. The diagnosis of CB depends on subjective symptoms. However, many studies have demonstrated that CB is associated with frequent respiratory exacerbations, increased respiratory symptoms, poor quality of life, and even increased mortality. A meta-analysis of three genome-wide association studies (GWASs) suggested chromosome 11p15.5 as a novel genetic susceptibility locus associated with CB. On the other hand, pulmonary hypertension (PH) is one of the established complications of COPD, which is one of the most common forms of secondary PH. The ratio of the diameter of the pulmonary artery to the diameter of the aorta (PA/A) can be measured by computed tomography (CT), which correlates with pulmonary artery pressure gauged by right heart catheterization. A previous study demonstrated that pulmonary artery enlargement (PAE), defined as PA/A > 1, was associated with COPD exacerbation frequency. By using the same subjects as in the previous study, a meta-analysis of GWASs of PAE associated with COPD showed that genetic variants of iron-responsive element binding protein 2 (*IREB2*) and galactosylceramidase (*GALC*) are associated with susceptibility to PAE within COPD subjects. These studies support that clinically important subtypes of COPD are closely linked to genetic heterogeneity. Further studies including functional validation will provide insight into a new COPD classification and therapeutic implication.

TAILORED TREATMENT OF ASTHMA IN THE ELDERLY

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Asthma is present in about 6% of patients over the age of 75. Although it accounts for a minority of physician visits, the elderly account for an excess number of emergency department visits, asthma hospitalizations, and mortality. Asthma and COPD may be difficult to distinguish in elderly patients because they have less atopy, more neutrophilic lung inflammation and non-specific elevations of IgE. Older patients may have a past history of cigarette smoking which leads to asthma-COPD overlap syndrome. Elderly patients with long-standing asthma may also develop irreversible airflow limitation and emphysema without a history of cigarette exposure. In the elderly, asthma may be associated with other comorbid conditions such as gastroesophageal reflux, aspiration, cognitive impairment, arthritis, heart failure, or coronary artery disease that can exacerbate or be confused with asthma. Elderly patients with asthma are more prone to under-treatment because of failure to prescribe inhaled steroids, poor adherence with treatments, poor coordination with inhaler devices, or complex medical regimens. Tailoring treatment of asthma to elderly patients requires attention to treatment of co-morbid conditions, simplification of the medical programme, and engagement of social support.

GLYCANS, EOSINOPHILS AND ALLERGIC ASTHMA

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Allergic asthma is typically characterized by significant recruitment of eosinophils to the airways. Eosinophil adhesive interactions within inflamed blood vessels and subsequent activation and degranulation at sites of tissue inflammation are important contributors to the pathogenesis of allergic asthma. Identifying cellular factors and understanding the mechanisms by which they regulate eosinophil adhesive interactions and their recruitment to inflamed lungs is central to amelioration of allergic asthma. While the contribution of selectins, integrins, cytokines, chemokines and vascular adhesion molecules to eosinophil recruitment and pathogenesis of allergic asthma is recognized, recent studies have demonstrated an important role for glycans in regulating eosinophil activation and their recruitment to sites of inflammation. Heparan sulfates proteoglycans synthesized by key enzymes in endothelial cells appear to regulate the trafficking of eosinophils during allergic asthma. Likewise, cell surface-expressed N-glycans or O-glycans synthesized by specific enzymes have also been shown to play an important role in eosinophil trafficking and recruitment during inflammation by virtue of their ability to bind to selectins, siglecs and other adhesion molecules such as galectins to promote eosinophil trafficking and allergen-induced airway inflammation and remodeling. Studies related to the role of specific glycans, enzymes involved in processing of N-glycans and glycan-binding proteins in the context of allergic asthma will be reviewed in this presentation.

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UPDATE IN ASTHMA DIAGNOSIS (GINA 2014)

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New version of GINA report 2014 addresses several main issues regarding the diagnosis of asthma.

At first, asthma is defined to be a heterogeneous disease, characterized by chronic airway inflammation with variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and with variable expiratory airflow limitation.

Diagnosis is based on identifying both a typical pattern of symptoms and expiratory airflow limitation, characteristically varying over time in intensity. These variations are often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or viral respiratory infections. Variation in airflow limitation is generally assessed measuring FEV₁ or PEF. The diagnosis of asthma should be strongly considered, and effort should be made to demonstrate the reversibility of airflow obstruction with pulmonary function test, if symptom appears to be variable in nature. 'Reversibility' generally refers to rapid improvements in FEV₁ (or PEF), measured within minutes after inhalation of a rapid-acting bronchodilator such as 200–400 mcg salbutamol, or more sustained improvement over days or weeks after the introduction of effective controller treatment such as inhaled corticosteroid. If the symptoms suggest asthma but there is no evidence of airflow obstruction, bronchial provocation should be performed. If the bronchial challenge is positive, then once again the diagnosis of asthma should be strongly considered.

The last point is that, if possible, the evidence supporting a diagnosis of asthma should be documented when the patient first presents, as the features that are characteristic of asthma may improve spontaneously or with treatment; as a result, it is often more difficult to confirm a diagnosis of asthma once the patient has been started on controller treatment. Additional strategies may be needed to confirm the diagnosis of asthma in particular populations, including patients already on controller treatment, the elderly, and those in low-resource settings.

UPDATE IN ASTHMA TREATMENT

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Asthma is a chronic inflammatory disorder of the airways and inhaled corticosteroids (ICS) with or without long-acting β 2-adrenoceptor agonists (LABA) is the cornerstone of asthma management. In 2014, we had a major revision of the Global Initiative for Asthma (GINA) Strategy for Asthma Management and Prevention. The GINA 2014 report recommends therapeutic approach based not only on assessment of symptoms but also on risk factors for exacerbation, side effects of treatment and development of fixed airflow limitation. The GINA 2014 also suggests non-pharmacological therapies and strategies, and accepts the advantages of ICS plus LABA formoterol as maintenance and rescue treatment. Recent meta-analysis showed that combined ICS and LABA as maintenance and reliever treatment and combined ICS and LABA in a fixed daily dose equally effective and safe in preventing severe exacerbations of asthma.

New approach including changing physical characteristics or expanding the indications of existing drugs have been tried to control asthma more effectively. The involvement of the distal lung in the pathogenesis of asthma has been extensively investigated recently, and studies showed that treating the peripheral airways with smaller drug particle certainly achieve comparable efficacy, a reduction in the daily ICS dose, and greater asthma control. Studies confirmed the effectiveness of the use of inhaled long-acting anti-muscarinic agents (LAMA) as an add-on therapy in patients with asthma, who remain symptomatic despite guideline-based therapy with ICS with or without LABA, and LAMA was recently permitted to treat patients with asthma in medical insurance system in Korea.

Despite these treatments, current levels of asthma control remain poor in the considerable number of patients, especially in severe asthma. Heterogeneity of asthma phenotype, poor compliance for medication, and comorbidities may contribute to outcome of asthma treatment. Further studies for asthma phenotype will provide endotype-based and biomarker-driven approaches to asthma management, and even to personalized therapy.

SEVERE ASTHMA AND NEW DRUGS IN THE FUTURE

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Severe asthma refers to a minority of the asthmatics whose symptoms are not adequately controlled despite high dose inhaled corticosteroid plus additional medications. Severe asthma has become a major unmet need because these patients account for a large expenditure as asthma control is troubled or as patients have to endure adverse effects of corticosteroids in return for unsatisfactory control.¹

One reason we are faced with difficulty in overcoming severe asthma arises from its 'heterogeneity'.² Many recent researches have concentrated on classification of asthma into different phenotypes that many researchers believe to correspond with their pathophysiologic processes and development of therapeutics targeting the key disease modulating pathway for each phenotype.^{3,4} This is in other words 'personalized medicine' meaning application of different therapies for each different patient type.

Consequently, we have seen magnificent growth in the development of targeted biologics although the proposed pheno-endotypes of asthma are still challenging. Major inflammatory cells in asthmatic airways are notably eosinophils, mast cells, and lymphocytes; and intricate network of these cells, cytokines, chemokines, and structural cells contribute to the formation of difficult-to-control inflammation and structural remodeling. Along with the well-established role of IgE in allergic asthma and its target monoclonal antibody omalizumab, biologics are currently under different stages of development and clinical trials which direct against IL-5, IL-4, IL-13, GM-CSF, TNF- α , IL-17, and TSLP and still many more target molecules await investigation.⁵

The overall outcomes of new biologics for asthma have not been overwhelmingly dramatic so far and all comes down for us to realize again the heterogeneity of asthma and there is not one 'wonder drug' that works for all. Thus, we should further concentrate on discovering valuable targets for each endophenotype. On top of that, we should work on developing reliable biomarkers to facilitate firm selection of phenotypes who would respond to certain therapeutics.

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ASTHMA-COPD OVERLAP SYNDROME: AN EMERGING CONCEPT?

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There are a variety of chronic respiratory diseases showing chronic respiratory symptoms and chronic airflow limitation. Of these, asthma and chronic obstructive pulmonary disease (COPD) are the most frequent and serious diseases sharing much of the key characteristics: chronic inflammation, airway obstruction with variable degree of bronchodilator responses and airway hyperresponsiveness. Therefore, it is frequently hard to distinguish asthma from COPD and vice versa, especially in adults and elderly population. Now there is considerable agreement that ACOS could be accepted as new disease entity in spite of historical hypothesis that asthma and COPD has its own pathophysiological and clinical features.

In 2014, the Global Initiative for Asthma (GINA) and the Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD) collaborated to publish the paper on ACOS. In this report, ACOS is defined as a clinical condition, which is characterized by persistent airflow limitation and both features of asthma and COPD. While there has been attempt to build up diagnostic criteria for ACOS, it is still hard to identify which factors are critical and essential for discrimination of ACOS from asthma or COPD. Regarding the natural courses of ACOS, evidences are accumulating that ACOS is related with frequent exacerbation, poor quality of life, rapid decline of lung function and greater health care utilization compared with asthma or COPD alone. The poor outcomes for ACOS suggest that much attention should be paid on this clinical phenotype. However, there is lack of evidence about the treatment options for ACOS. Future studies are needed to evaluate the roles of inhaled corticosteroids, long acting beta2 agonists and/or muscarinic antagonists in the treatment of ACOS. Additionally, given the complexity of chronic airway diseases, the treatment should be personalized based on the phenotypes of each patient.

HOW CAN WE POPULARIZE SPIROMETRY AND CT IN THE DIAGNOSIS OF COPD?

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Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation. Spirometry is required to make the diagnosis of COPD; the presence of a post-bronchodilator FEV₁/FVC < 0.70 confirms the presence of persistent airflow limitation¹.

We had performed various educational campaigns throughout Shiga Prefecture in Japan in cooperation with the Shiga Medical Association; these included repeated educational lectures about the diagnosis and treatment of COPD, seminars about smoking cessation and practical training in the use of spirometers. Three surveys had been conducted over five years to evaluate the accomplishments of our campaigns. The survey, however, revealed that the usage of spirometers did not increase in the diagnosis of COPD in general practitioners (GPs).

In order to popularize spirometry and CT in COPD diagnosis, we started a clinical pathway in corporation with regional medical association. In this clinical pathway, GPs send the patients, who are suspected as having COPD, to the hospital. In hospital, patients underwent spirometry, chest computed tomography (CT), and so on. Using these data, respiratory specialists at the hospital make a diagnosis of COPD and recommend the standard therapy of COPD. Patients are then followed by the GPs. After 6 to 12 months at the GPs, patients again come to the hospital to undergo spirometry, chest CT, and others. Using this clinical pathway, we can diagnose and treat the COPD patients following the COPD guidelines.

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REGENERATION OF DESTRUCTED LUNG WITH STEM CELL TREATMENT IN ANIMAL MODELS OF EMPHYSEMA

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For the regeneration of destructed lung in emphysema patients, several treatment approaches may be considered: 1) lung transplantation, 2) artificial lung, 3) retinoic acid and growth factors, 4) stem cell treatment, and 5) others. Lung transplantation has been successfully performed in specialized centres despite the unsolved limitation of donor shortage. Artificial lung has been applied to an acute status of cardiac arrest or respiratory failure, but not to a chronic status of emphysema due to short durability and problems of anticoagulation. Retinoic acid and growth factors showed efficacy for the regeneration of emphysema in animal models; but, the efficacy of them was not proved to be effective in clinical trials yet. Stem cell treatment has been successful for the regeneration of emphysema in animal experiments but not in patients with emphysema or COPD. Although a clinical trial showed that the allogeneic stem cell treatment was safe in 62 COPD patients during the two years of follow-up, it failed to prove the efficacy.

For the emphysema treatment with stem cells, an unmet need is the improvement of efficacy of stem cells. So we performed some experiments to improve the efficacy of stem cells with two approaches: 1) intra-pleural injection of stem cells compared to intra-venous injection, and 2) intra-tracheal injection of artificial nano-vesicles originated from stem cells

We found the two approaches might improve the efficacy of stem cells for the regeneration of destructed lung in emphysema.

AIRWAY SMOOTH MUSCLE: A TARGET FOR NOVEL THERAPIES IN ASTHMA AND COPD

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Recent advances in airway smooth muscle (ASM) biology have fostered targeted approaches to improve bronchodilation and potentially reverse persistent airflow obstruction. Novel bronchodilators include Rho kinase inhibitors and G kinase inhibitors. Evidence suggests that glucocorticoids enhance β -agonist-mediated bronchodilation apart from increasing β 2-adrenergic receptor expression. ASM also orchestrates and perpetuates airway inflammation in asthma and COPD. The development of bronchial thermoplasty that decreases ASM mass may offer new approaches in mitigating ASM-dependent bronchial obstruction.

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SEVERAL ISSUES IN THE INTERPRETATION OF SPIROMETRY TESTING FOR AIRWAY DISEASES

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Spirometry testing is the standard diagnostic method for a case with chronic obstructive pulmonary disease (COPD) and asthma. Here, I briefly review several issues in the interpretation of spirometry testing. (1) *Fixed vs LLN criteria for airflow limitation:* Airflow limitation was defined as a low FEV1-to-VC ratio (FEV1/FVC). However, the cutoff defining obstruction has not been definitely determined. GOLD guideline defined COPD as a fixed postbronchodilator FEV1/VC < 0.7, while the ATS/ERS task force recommends the use of lower limit of normal (LLN) for the detection of airflow obstruction. Because FEV1/VC declines with ageing, there have been concerns that the applying a fixed ratio could lead to underestimation of obstruction in young people and overestimation in elderly.¹ However, elderly people with FEV1/VC \geq LLN also showed the higher risk of COPD-related hospitalization compared with normal population in a cohort study.¹ (2) *FEV6:* Recently, six-second FVC maneuvers have been proposed to make test less exhausting. FEV6 has been regarded as an acceptable surrogate for FVC, and its good diagnostic accuracy has been reported.² Long forced expiratory times were often associated with false negative discordant cases.³ (3) *Criteria for bronchodilator reversibility:* The use of different criteria for bronchodilator reversibility is another issue. For example, when ATS criteria is applied, 53.9% of participants in UPLIFT trial show bronchodilator reversibility. However, the criterion using FEV1 \geq 12% alone is applied 73% can be classified into responders. ERS criterion (absolute increase \geq 10% in FEV1%) minimizes the number of responders. (only 38.6% are responders) In conclusions, physicians should understand that there are some controversies and confusing issues in the interpretation of spirometry testings.

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PULMONARY REHAB IN KOREAN SITUATION

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Chronic obstructive pulmonary disease (COPD) is a major global health problem. Pharmacologic therapies of COPD are based on bronchodilators. Although bronchodilators can improve lung function and quality of life, the extent of improvement has limitation and most patients still have respiratory symptom despite of all available medications. Therefore, non-pharmacologic treatment should be also considered to make the life of COPD patients better.

Pulmonary rehabilitation is a multidisciplinary programme of care for patients with chronic respiratory impairment including exercise, education and physical therapy. Pulmonary rehabilitation leads to statistically significant and clinically meaningful improvements in health related quality of life, functional exercise capacity, and maximum exercise capacity in patients with COPD. Although its effects are evident, it is not easy to perform in real practice because of several problems such as reimbursement, facility, indifference and economic issues.

In Korea, pulmonary rehab programme is available only in several institutions. There are several reasons for this; First, national insurance does not cover pulmonary rehab and patients usually feel huge economic burden for the long term programme. Second, the institutions, where pulmonary rehab is available, are usually far from the patients' home, and it is not easy for patients with dyspnea to visit the institutions regularly without support of the family.

Home based rehabilitation and intensive rehab on admission are the alternatives to these difficulties. In this topic, we will cover the situation of pulmonary rehabilitation in Korea and possible solutions to activate the pulmonary rehab programmes.

CT OF COPD: EMPHYSEMA AND AIRWAY

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Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which vary from person to person¹. In order to assess the relative contribution of airways disease and emphysema, computed tomography (CT) of the chest has been widely used. Percentage of airway wall area (WA%) and percentage of low attenuation areas (LAA%) are the surrogate markers of airways disease and emphysema measured using CT. Although both WA% and LAA% correlated with measurements of lung function, it has been shown that the combination of airway and emphysema measurements improved the estimate of pulmonary function test abnormalities². These findings have led to the concept of phenotypes of COPD. Using both WA% and LAA%, COPD patients could be divided into four groups; normal phenotype, airways dominant phenotype, emphysema dominant phenotype and mixed phenotype³. With the advances in CT machines and computer science, we can now evaluate the lung in three dimensional fashion. Using these techniques, we should evaluate the COPD patients more precisely and treat the COPD patients more properly.

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CT OF COPD: FUNCTIONAL IMAGING

JB SEO

Department of Radiology, University of Ulsan College of Medicine, Asian Medical Center, Seoul ROK

In recent studies on COPD, CT has been accepted as one of important research tools in evaluating disease severity and characteristics. The extent of low attenuation area and bronchial wall thickening at segmental and distal level on volumetric CT scan acquired at suspended inspiration state are commonly used as useful markers for evaluating the severity of emphysema and airway wall inflammation, respectively. Many recently studies have proved that these potential imaging biomarkers are useful in subgrouping/phenotyping of patients, prediction of treatment response, frequency of exacerbation, prediction of disease progression and so on. Volumetric CT, however, with its high spatial and contrast resolution, has much additional potential to evaluate different aspects of COPD. Furthermore, dual energy CT has opened a way to the direct visualization of regional ventilation and perfusion of the lung. In this talk, I would like to introduce several new CT imaging techniques to visualize and quantify regional function of the lung.

They include:

- (1) Assessment of air trapping with combined inspiration and expiration CT via image co-registration technique
- (2) Direct visualization of regional ventilation with xenon-enhanced dual energy CT
- (3) Assessment of regional blood volume with iodine contrast-enhanced dual energy CT
- (4) Assessment of ventilation-perfusion mismatch with combined xenon-ventilation and iodine contrast dual energy CT imaging and image co-registration.

MRI OF COPDY Ohno^{1,2}*¹Division of Functional Imaging Research, Department of Radiology, Kobe University School of Medicine, and ²Advanced Biomedical Imaging Research Center, Kobe University Graduate School of Medicine*

Pulmonary magnetic resonance imaging (MRI) has been put forward as a new research and diagnostic tool mainly to overcome the limitations of CT and nuclear medicine study in various pulmonary diseases. However, pulmonary MRI has been difficult to use because of inherently low proton density, a multitude of air-tissue interfaces, which create significant magnetic field distortions and are commonly referred to as susceptibility artefacts, diminishing signal in the lung, and respiratory and/or cardiac motion artefacts. To overcome these drawbacks, various technical advances made during the last decade have been reported as useful for functional and morphological assessment of various pulmonary diseases.

Pulmonary MRI in COPD subjects currently provides not only morphology related, but also pulmonary function related information. It has the potential to replace nuclear medicine studies for the identification of regional pulmonary function and may perform a complementary role in various pulmonary disease assessments and patient managements instead of nuclear medicine study. In addition, pulmonary functional MRI can provide morphological and functional changes of lung structures, circulation, ventilation and oxygen diffusion using qualitative and quantitative assessments.

This lecture covers 1) state of the art pulmonary MR techniques for morphological and functional assessment, 2) its clinical applications in COPD and 3) future direction of pulmonary functional MR imaging. We believe that the findings of further basic studies as well as clinical applications of this new technique will validate the real significance of pulmonary MRI for the future of COPD assessment and its usefulness for diagnostic radiology and pulmonary medicine.

CHRONIC BRONCHITIS IN COPD: MUCUS IS THE NEW GOLIATH

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Chronic Bronchitis (CB) affects between 18 and 42 percent of patients with Chronic Obstructive Pulmonary Disease (COPD). CB affects approximately 10 million individuals in the United States, and the majority are between 44 and 65 years of age. CB has been associated with numerous adverse clinical outcomes. Exacerbation frequency has been shown to be greater in patients with COPD and CB in several studies. CB may increase all-cause mortality as well, independent of the level of airflow obstruction. Some but not all studies have shown CB to be an independent risk factor for death. CB has also been shown to hasten the rate of lung function decline and reduce health related quality of life. Recent large studies have shed greater light on its risk factors, the poor outcomes, and the clinical and radiographic phenotype of CB. Unlike the classic description of the "Blue Bloater," many subjects with CB are not obese or hypoxemic, and many subjects with emphysema describe chronic cough and mucus production. The major risk factor for CB remains cigarette smoking, but a greater body of literature has shown associations with occupational exposures and gastro-esophageal reflux disease with CB. CB is associated with greater quantitative airway wall thickening and gas trapping on CT. Not only is CB associated with lower airway symptoms of breathlessness, cough, and phlegm, but also with upper airway symptoms. What is becoming increasingly clear is that the CB phenotype is the new Goliath, a group that deserves the greatest attention and poses the greatest danger to those with COPD.

EXPLORATION OF A NOVEL PATHOLOGIC MECHANISM IN COPD COHORTS

JM WELLS

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Introduction: Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease often caused by cigarette smoke exposure and characterized by many distinct phenotypes and associated comorbidities. To date, there are numerous pathways and molecular targets described in COPD pathogenesis and progression. Despite these advances, there are no therapeutic options that specifically target the underlying pathobiological processes.

Methods: This session will highlight our experiences with the extracellular collagen fragment acetyl-proline-glycine-proline (AcPGRP), describe its function in chronic neutrophilic inflammation, and summarize its importance as a potential biomarker and therapeutic target in COPD. There will be a review and discussion of preclinical, observational, and clinical trials related to the AcPGRP pathway. This session will close with discussion on the topic of current gaps in knowledge and highlight opportunities for collaboration.

Results and Conclusions: Novel biologic mechanisms, including those focused on AcPGRP, may be central to the pathogenesis of COPD. Exploration of these pathways opens the prospects for multi-national collaboration in the basic, translational, and clinical research arenas.

Acknowledgements: The UAB Lung Health Center; and the ECLIPSE and SPIROMICS Investigators

COPD COHORT STUDY: HOW CAN WE COLLABORATE?

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A cohort study has been playing critical roles in characterizing COPD and exploring protein and genetic biomarkers as well as the clinical outcomes of COPD. As COPD is a heterogeneous and complex disorder, larger cohorts including various phenotypes of COPD may be necessary to achieve the goals of cohort study. Therefore, the collaboration among investigators is an important component in COPD cohort study. Based on personal experience in the collaborative works of the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), the COPDGene, and the TCGS (Transcontinental COPD Genetic Study) cohorts, I will discuss on how we can collaborate in COPD cohort study. Especially, in addition to the role of human networks and the importance of central laboratory and review boards, the necessity of systematic collaboration will be touched in the aspects of collecting samples and analyses of data from multiple cohorts.

CLINICAL IMPLICATIONS OF ENDOTYPING IN ASTHMA BASED ON DEGREE OF TYPE-2 INFLAMMATION

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Introduction/Aims: We have previously shown that asthma is heterogeneous and that one major subgroup of asthma is characterized by prominent type-2 inflammation. These studies identified periostin as a potential biomarker of Th2-high asthma. The clinical implications of asthma endotyping and periostin as an asthma biomarker are an area of active investigation.

Methods: We reviewed published studies of asthma endotyping and of periostin as a blood biomarker in asthma.

Results: Asthma endotypes that are based on degree of Th2-inflammation have been defined using measurement of sputum eosinophils, blood eosinophils, exhaled nitric oxide levels and serum periostin levels. In clinical trials of emerging biological therapies in asthma which target Th2-cytokines, favorable clinical responses have been identified after stratifying by sputum and blood eosinophils as well as serum periostin levels. Post-hoc analyses of these therapies have identified additional blood biomarkers of type-2 inflammation that are promising such as CCL13, CCL17, CCL26 and DPP4. In general, therapies that target IL-5 potentially reduce blood and sputum eosinophils but do not affect exhaled nitric oxide levels. Alternatively, therapies that target IL-3 and IL-4 reduce exhaled nitric oxide levels but do not reduce blood eosinophilia. Both approaches show clinical benefits.

Conclusions: Preferentially using biologics which target Th2 cytokines in patients with biomarkers of Th2-high asthma is likely to be a clinically valuable approach. The differential effects of biologics which target IL-5 versus IL-13/IL-4 on specific Th2 biomarkers likely reflects distinct modes of action with these two therapeutic approaches. Whether this will be reflected in distinct clinical effects, in the domains of bronchodilation versus exacerbation reduction, for example, is as yet unclear.

THE ROLE OF BACTERIA-DERIVED EXTRACELLULAR VESICLES ON THE PATHOGENESIS OF CHRONIC OBSTRUCTIVE AIRWAY DISEASE

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The role of infectious agents in the etiology of inflammatory diseases once believed to be non-infectious is increasingly being recognized. Many bacterial components in indoor dust can evoke inflammatory pulmonary diseases. Especially, we recently found that bacteria-derived EVs in indoor dust are pathophysiologically related to chronic inflammatory airway diseases which are characterized by neutrophilic inflammation. To elucidate pathogenic bacteria or bacteria-derived EVs, we performed metagenomic analysis of bacteria and bacteria-derived EVs in indoor dusts. Microbiota compositions in indoor dust revealed the presence of both gram-negative and gram-positive bacteria, with most sequences (>90%) related to just five genus: *Pseudomonas* (61.6%), *Enterobacter* (13.6%), *Acinetobacter* (7.0%), *Leclercia* (4.5%), and *Staphylococcus* (0.9%). *E. coli* is a model organism of gram-negative Enterobacteriaceae. We evaluated the role of *E. coli*-derived EVs on the development of lung pathology. To induce lung pathology, *E. coli* EVs were administered intranasally into the airways of 6 weeks-old mice six times on days 0, 1, 7, 8, 14 and 15. Pulmonary inflammation, emphysema, and immunologic parameters were evaluated 48 h after the final EVs administration. *E. coli*-derived EVs were present in indoor dust. Repeated inhalation of *E. coli*-derived EVs caused neutrophilic inflammation and emphysema in a dose-dependent manner. These phenotypes were accompanied by the production of both Th1 and Th17 cells. Additionally, emphysema induced by *E. coli*-derived EVs was partially eliminated by the absence of IFN-gamma or IL-17. Taken together, *E. coli*-derived EVs induce lung emphysema via both IFN-gamma and IL-17 dependent pathways, and EVs in indoor dust, especially derived from Gram-negative bacteria, appear to be an important causative agent in the pathogenesis of neutrophilic asthma and/or emphysema.

Exhibit 72

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The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required. However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

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- (iv) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
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- (vi) it does not intend to invoke 21 CFR 50.24.

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Exhibit 77

PEER-REVIEWED CONSULTATIONS IN PRIMARY CARE

Consultant

Bronchial Thermoplasty in Severe Asthma

Mon, 08/10/15 - 13:40

Authors:

Ken Y. Yoneda, MD, Nicholas J. Kenyon, MD, and Samuel Louie, MD

Severe adult asthmatics are defined partly by the need for high-dose inhaled corticosteroids (ICS) and inhaled bronchodilators¹ and their higher incidence of nonadherence. However, in some cases, the clinical severity may reflect the ineffectiveness of the drugs prescribed rather than the patient's adherence or severity of the underlying disease.² Infection treated with the wrong antibiotic is an analogous example.

Although the National Asthma Education and Prevention Program Expert Panel Report 3 Guidelines for Diagnosis and Management of Asthma³ recommended ICS as first-line therapy and the mainstay of daily anti-inflammatory treatment for persistent asthma, there is no discussion of future discontinuation. Instead, the recommendation is to keep patients on the lowest effective dose of ICS, which provides a difficult challenge in clinical practice. The majority of adults rely on bronchodilators, either short-acting or long-acting beta-2 agonists (LABA) everyday despite daily use of ICS.

Table 1. Confounding Conditions or Comorbidities in Patients with Apparent Severe Persistent Asthma

Allergic bronchopulmonary aspergillosis
Aspiration syndrome
Asthma-chronic obstructive pulmonary disease overlap syndrome
Cardiac asthma or heart failure
Chronic bronchiectasis
Churg Strauss syndrome
Chronic obstructive pulmonary disease
Cystic fibrosis
Gastroesophageal reflux disease
Obstructive sleep apnea
Vocal cord dysfunction

Pitfalls in Asthma Treatment

It is a common pitfall to think that ICS effectively controls symptoms and prevents the need for bronchodilators or exacerbations in all asthma patients. Recent studies suggest that 25% to 35% of patients with asthma may not improve lung function with ICS measured by quality of life (QOL) and exacerbation incidence. Patients who do not respond to ICS did just as well with placebo, whereas responders did very poorly with placebo with uncontrolled symptoms and exacerbations.⁴

Martin et al found that short-term response to ICS with regard to forced expiratory volume in 1 second (FEV₁) improvement >5% after 6 weeks predicted long-term asthma control. The decision to use long-term ICS could be based on a short-term trial, or a clinical trial of each drug individually.

Another common pitfall is to presume that the prescribed asthma controller drugs for an individual patient must be working effectively. It is essential to objectively assess asthma control at every clinic visit (eg, use the Asthma Control Test) and not to assume that the asthma is well-controlled. Uncontrolled patients need to be carefully evaluated prior to a step-up in pharmacotherapy from moderate- to high-dose ICS+LABA with add-on omalizumab or mepolizumab, or bronchial thermoplasty (BT). A confounding comorbidity should be searched for and treated (Table 1).⁵

Table 2. Indications, Contraindications, and Precautions for Bronchial Thermoplasty

Indications

- Age 18 years and older
- Severe persistent asthma not well-controlled despite adherence to ICS+LABA

Contraindications

- Active respiratory infection (eg, acute bronchitis)
- Acute asthma exacerbation or current use of prednisone for exacerbation in the preceding 14 days before bronchial thermoplasty procedure date
- Known sensitivity to required medications for bronchoscopy
- Presence of internal pacemaker or other implantable devices
- Inability to stop taking anticoagulants or antiplatelet drugs before procedure
- Anyone previously treated with bronchial thermoplasty

Precautions

- Post-bronchodilator FEV₁ <65% predicted
- Increased risk for adverse events associated with bronchoscopy or anesthesia (eg, pregnancy, coronary artery disease, acute or chronic renal failure, or uncontrolled hypertension)

Any of the following the past 12 months

- ≥4 lower respiratory tract infections in the past year
- ≥3 hospitalizations for respiratory symptoms
- ≥4 prednisone or methylprednisolone pulses for asthma exacerbations

*Asthma Control Test score <19.

Abbreviations: FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonists.

Another pitfall fraught with long-term safety concerns is to ascribe to the belief that asthma pharmacotherapy will eventually work even when annoying symptoms persist despite adhering to ICS+LABA for at least 3 to 6 months. LABA can improve lung function the first day of treatment but the effects of ICS may take 1 to 2 weeks if the patient is a responder. Leaving patients on ICS when it is ineffective can lead to unwanted oral thrush, viral infections, pneumonia, osteoporosis, and poor control of diabetes mellitus. The FDA notes that LABAs increase the risk of asthma-related deaths and must carry a black box warning. Note: LABAs are contraindicated for asthma, but not chronic obstructive pulmonary disease (COPD).

Pitfalls to Avoid in Severe Asthma

- To forget to confirm the diagnosis of asthma anew in difficult-to-control cases.
- To target treatment towards asthma severity instead of asthma control (eg, reducing impairment and risks from asthma, including acute exacerbations).
- To presume prescribed asthma controller drugs are working effectively, rather than objectively assessing asthma control at every clinic visit.
- To believe prescribed asthma pharmacotherapy will eventually work despite a good adherence to inhaled corticosteroids and long-acting beta-2 agonists for period of 3 to 6 months or longer.
- To presume patients have well-controlled asthma and are adherent to prescribed guideline-recommended pharmacotherapy in the absence of complaints, elicited, or volunteered. Inquire further.
- To leave asthma symptoms uncontrolled for longer than 3 to 6 months without considering alternative therapeutic options with omalizumab or mepolizumab and/or bronchial thermoplasty.
- To ignore confounding comorbidities (eg, gastroesophageal reflux, rhinosinits, vocal cord dysfunction, obstructive sleep apnea, allergic bronchopulmonary aspergillosis, and COPD in asthmatics) before declaring asthma is refractory to treatments.
- To maintain that bronchial thermoplasty is still experimental and its efficacy and safety not yet FDA approved.
- To employ bronchial thermoplasty without controlling confounding comorbidities first.

Bronchial Thermoplasty

Different therapeutic strategies would need to be established for nonresponders to ICS. BT is an important, new FDA-approved option in the battle to control asthma and should be considered for patients age 18 and older with severe persistent asthma who remain symptomatic and uncontrolled despite taking high doses of ICS+LABA.⁶ BT is now included in the Global Initiative for Asthma (GINA) guidelines as a preferred add-on therapy at step 5 before oral corticosteroids.⁷

The effectiveness and safety of BT—ie, the bronchoscopic circumferential application of radiofrequency energy (temperature of 65°F) to the bronchial airways—was demonstrated in 2010 in severe asthma, including refractory asthmatics.⁸ In 2010, the FDA Center for Devices and Radiological Health approved BT as the first medical device to treat severe and persistent asthma in certain adults.

The device is composed of a catheter with an electrode tip that delivers radiofrequency energy directly to the airways. A controller unit generates and controls the energy.

Inflammation causes the airways of patients who have asthma to swell and narrow, making breathing difficult by increasing the work of breathing. Bronchospasm from airway smooth muscle (ASM) contractions compound the problem, causing and difficulty breathing by further increasing airway resistance.

The radiofrequency energy reduces the thickness of ASM in the airways and can improve a patient's ability to breathe. However, to benefit, patients will require multiple sessions targeting different areas in the lungs—eg, BT is applied first to the right lower lobe bronchial airways (sparing the right middle by protocol), then the bronchial airways of the left lower lobe are treated 2 to 3 weeks later, and both upper lobes airways are treated 2 to 3 weeks after that.

AIR2 Study Results

The FDA based its approval largely on data from the AIR2 study, a randomized, double-blind, sham bronchoscopy-controlled clinical trial in 6 countries. The objectives were to evaluate the effectiveness and safety of BT versus a sham bronchoscopy procedure in subjects with severe asthma who remain symptomatic despite treatment with high-dose ICS+LABA.⁸

There were a total of 288 adult subjects (age 18 to 65) who required daily high-dose ICS+LABA—190 of which underwent BT bronchoscopies and 98 sham bronchoscopies in 3 procedures that were 3 weeks apart. The primary outcome was the difference in Asthma Quality of Life Questionnaire (AQLQ) scores from baseline to average at 6, 9, and 12 months. The secondary outcomes included rescue medication use, FEV1, morning peak expiratory flow rates, and the percentage of symptom-free days.

The results showed improvement from baseline in the integrated AQLQ score—79% of BT and 64% of sham subjects achieved changes in AQLQ of ≥ 0.5 . Note: 6% more BT subjects were hospitalized in the treatment period (up to 6 weeks post-BT).

In the post-treatment period (6 to 52 weeks after BT), the BT group experienced fewer severe exacerbations, emergency department (ED) visits, and days missed from work or school compared with the sham group. No device-related deaths or major adverse events, such as pneumothorax, need for mechanical ventilation, airway stenosis or focal narrowing, occurred with BT.

Possible side effects during the course of treatment may include asthma attacks, wheezing, chest tightness or pain, atelectasis, hemoptysis, anxiety, headaches, and nausea. The majority of these adverse effects occurred within 1 day of the procedure and resolved with the standard of care within 7 days.⁸

Long-Term Safety of BT

The FDA required a 5-year post-approval study of the BT device to study its long-term safety and effectiveness and the results were recently published. BT-treated subjects from the AIR2 study were evaluated annually for 5 years to assess the long-term safety of BT and the durability of its treatment effect through a review of adverse events, exacerbations, hospitalizations, spirometries, and high-resolution chest CT scans.⁹

The sham patients in the AIR2 study exited at the end of year 1 while the BT patients were followed for another 4 years, to give a total follow-up period of 5 years. Of the 50 sham patients from the AIR2 trial, 50% had undergone BT since exiting the AIR2 trial. These included patients that had participated in the industry-sponsored PAS2 study or had BT outside the clinical trial setting.⁹

Of the 190 BT-treated subjects from the AIR2 trial, 162 or 85.3% completed the 5 years of follow-up. There was a reduction in the proportion of subjects experiencing severe exacerbations as compared to the sham group at 1 year after BT that was maintained over the subsequent 4 years of follow-up. The proportion of subjects experiencing severe exacerbations and ED visits, and the rates of events in each of years 1 to 5, remained low and were less than those observed in the 12 months before BT treatment.⁹

There were no notable increases in hospitalizations, asthma symptoms, or respiratory adverse events that were observed over the course of 5 years after BT. The average 5-year reduction the proportion of subjects experiencing severe exacerbations and ED visits was reduced 44% and 78%, respectively. Respiratory adverse events and respiratory-related hospitalizations remained unchanged in years 2 through 5 compared with the first year after BT. Pre-bronchodilator FEV1 values remained stable between years 1 and 5 after BT, despite an 18% reduction in average daily ICS dose.

High-resolution CT scans from baseline to 5 years after BT showed no structural abnormalities that could be attributed to BT. There was no evidence of an increase in bronchiectasis, bronchiolitis obliterates, or pulmonary emphysema in any patient treated by BT.

This data demonstrate the 5-year durability of the benefits of BT with regard to both asthma control (based on maintained reduction in severe exacerbations and ED visits for respiratory symptoms) and safety.⁹

Another recent publication reported results in 10 patients who underwent endobronchial biopsies before and 12 weeks after BT (10 samples at each time point).¹¹ A decrease in smooth muscle (20.8% vs 10.6%) and subepithelial glands was found. Basement membrane thickness, epithelial metaplasia, goblet cells, lymphatic, and blood capillary vessels did not change.

The UC Davis Experience

Since April 2011, we have treated 22 adult asthma patients with BT (age 20 to 80), of which there were 10 women and 12 men. Follow-up has been varied: 4 years for 4 patients, 3 years for 1 patient, 2 years for 5 patients, 1 year for 2 patients, and <1 year for 10. No deaths occurred.

Three patients reported no improvement after BT while 18 who rated their outcomes as outstanding (n=13) and good (n=5). Two patients previously improved with omalizumab were able to discontinue this drug. Six patients met the criteria for asthma-COPD overlap syndrome; of which, 5 rated their result between outstanding (n=4) and good (n=1).

Our own patient experiences and the published literature have highlighted the need to identify predictors of BT response earlier in the management of asthma symptoms and exacerbations. Objective patient selection for BT is essential to assure patient safety, reduce risks, and position patients for the most favorable outcomes (Table 2).

Our position is that the European Respiratory Society/American Thoracic Society statement¹² stating that BT be performed only in the setting of a clinical study or independent registry, which cites the paucity of data regarding asthma phenotypes most likely to benefit or be harmed from BT, seemingly limits patient options and access to this FDA-approved therapy. That being said, we are indeed engaging patients in an International Review Board-approved protocol to evaluate gene expression changes in the airway epithelial cells of asthmatic patients undergoing BT.

In this regard, the more recent assessments of the data that included results from the 5-year follow-up have resulted in the inclusion of BT as a preferred add-on treatment option before oral corticosteroids in the treatment of severe asthmatics at step 5 of the GINA guidelines.⁷ Further support for BT has come from position statements by the American College of Asthma, Allergy and Immunology in 2015 and the American College of Chest Physicians and Interasma Global Asthma Association, both in 2014.

In a recent study funded by the National Institutes of Health, a number of predictors of response to BT were identified in 42 adults with severe persistent asthma.¹³ With a baseline post-bronchodilator FEV1 at 70% predicted, 80% required a burst of systemic corticosteroids the 12 months prior to BT or sham. Mean dosage of ICS was 2 mcg/d and average baseline AQLQ was 3.42.

Predictors of a clinically meaningful improvement in QOL as defined by at least a 0.5-point improvement in AQLQ score 1-year post-procedure included a shorter duration of asthma 19 years, as compared with an average of 45 years in nonresponders) and a greater number of severe exacerbations during the year prior to BT.

At least a 240 mcg/d dose reduction in inhaled corticosteroids or a 2.5 mg/d decrease in oral corticosteroids at 1-year post procedure is another yardstick of clinical improvement. Other predictors include age (55 years and older), a lower baseline AQLQ score (2.4 vs 4.0), and greater need for oral corticosteroids.

In addition, several quantitative metrics obtained through multi-detector CT scans of the chest showed promise as predictors of a corticosteroid dose reduction. Responders showed less baseline air trapping, with an average of 6.1% of the lung having a density below -850 Hounsfield units, compared with 12.1% in nonresponders. Responders also had less baseline emphysema-like lung, with 3.2% of the lung having a density below -950 Hounsfield units at total lung capacity, compared with 5.8% in nonresponders.

Patients with severe asthma represent only a minority of the total asthma population, but account for the majority of the mortality, morbidity, and healthcare-related cost of this chronic illness. The adherence rates are lower in the real world and adherence reduces asthma control to the point where uncontrolled asthma is more likely to be encountered than controlled asthma despite current pharmacotherapy with controller medications.

Patient Selection

BT is not a cure for asthma.⁶ BT should be recommended after 2 independent assessments (by a referring physician and an asthmato-logist) confirm that the indications for BT exist, precautions are recognized, and no contraindications are present. Appropriate patients for referral are those with uncontrolled symptoms despite adherence to their asthma action plan or those who are suffering serious adverse effects from their medications (eg, Cushing's syndrome, diabetes mellitus, and osteoporosis).

BT should not be recommended for asthma patients who are well-controlled on regularly scheduled ICS+LABA because of patient's wishes to avoid taking medications daily.

Not all patients with severe persistent asthma are good candidates for BT. Avoid referring patients if they are classified as the most severe of severe persistent asthma patients because of the higher risk of complications that can be expected to occur with BT. An experienced asthma team of pulmonologists, anesthesiologists, pulmonary nurse specialists, and/or registered respiratory therapists should be involved whenever BT is considered.

Patients who undergo BT should be on stable asthma medications and have stable asthma status without active pulmonary infection (viral or bacterial or both), asthma exacerbation, coagulopathy (eg, bleeding disorder, coumadin, novel oral anticoagulant; aspirin is considered safe for BT), or changing dosages of prednisone 2 weeks before the proposed BT procedure.

BT has not been studied for use in asthma patients with a pacemaker, internal defibrillator, or other implanted electronic device. Also, those patients with known sensitivities to lidocaine, atropine, benzodiazepines, or propofol should not undergo BT unless alternative medications can be used. BT has not been studied for success in retreatment of the same area of the lung.

Not all patients will be able to stop their daily medications after BT but a 20% reduction in ICS and oral corticosteroids can be expected after BT in addition to an improvement in their QOL and exacerbation frequency.

The final pitfall is to avoid thinking that BT is still experimental and not FDA approved. BT is currently performed at over 350 centers in the United States with over 3000 patients treated since approval of BT by the FDA. Transparent discussion of the evidence (or lack thereof) for BT and institutional experience with it continues in the published literature. Only through such open discourse can patients ultimately benefit from new, safe, and effective treatments.^{14,15}

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