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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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Date	08/13/2015
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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.

NON-CONFIDENTIAL SECOND AFFIDAVIT OF TIMOTHY D. SITZMANN

The undersigned, being hereby warned that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements and the like may jeopardize the validity of this document, declares that:

1. I am an attorney participating in the representation of Opposers Boston Scientific Corp. and Asthmatx, Inc. (“Opposers”) in the above-captioned matter (the “Opposition”).
2. The information contained in this Affidavit is based upon my personal knowledge.
3. Opposers and Holaira, Inc. (“Applicant”) entered into a stipulation regarding the submission of rebuttal testimony in the Opposition through the Declaration of Dr. Narinder Shargill (the “Stipulation”), which was executed by Opposers and Applicant on August 6, 2015 and July 30, 2015 respectively.
4. Attached as Exhibit 73 is a true and correct copy of the Stipulation.
5. Attached as Exhibit 74 is a true and correct copy of the Declaration of Dr. Narinder Shargill.

6. Attached as Exhibit 69 is a true and correct copy of a printed publication, namely an article titled "Asthma, COPD, and Asthma-COPD Overlap Syndrome" printed from the website url www.goldcopd.org/uploads/users/files/AsthmaCOPDOverlap.pdf.

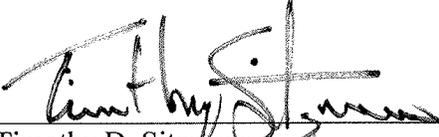
7. Attached as Exhibit 75 is a true and correct copy of an e-mail dated September 15, 2010, 08:42 AM.

8. Attached as Exhibit 76 is a true and correct copy of a Concept Submission Form for a research study submitted by [REDACTED].

9. Attached as Exhibit 77 is a true and correct copy of a printed publication, namely an article titled "Bronchial Thermoplasty in Severe Asthma" printed from the website URL www.consultant360.com.

FURTHER YOUR AFFIANT SAYETH NOT

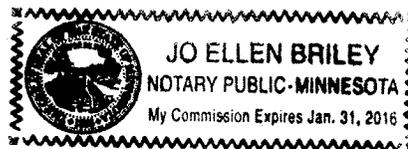
Date: August 13, 2015


Timothy D. Sitzmann

Subscribed and sworn to before me

This 13th day of August, 2015.


Notary Public



10728683v2

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

Boston Scientific Corporation and Asthmatx, Inc.)	
)	
Opposers,)	
)	
v.)	
)	
Holaira, Inc.)	Opposition No. 91215699
)	
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 13th day of August, 2015, she mailed by First Class mail, a true and correct copy of:

- 1) Non-Confidential Second Affidavit of Timothy D. Sitzmann; and
- 2) Confidential Second Affidavit of Timothy D. Sitzmann.

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

Barbara J. Grahn
OPPENHEIMER WOLFF & DONNELLY LLP
200 Campbell Mithun Tower
222 South Ninth Street
Minneapolis, MN 55402-3338


Jo Ellen Briley

Exhibit 73

**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
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Boston Scientific Corp. and
Asthmatx, Inc.

Opposers,

v.

Opposition No. 91215699

Holaira, Inc.

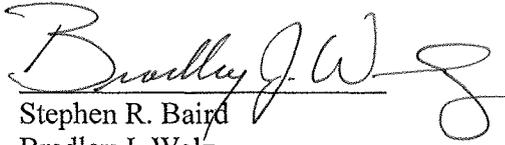
Applicant.

STIPULATION

Boston Scientific Corp. and Asthmatx, Inc. (collectively “Opposers”) and Holaira, Inc. (“Applicant”), by and through their respective counsel, hereby enter into the following stipulation:

- 1) Applicant agrees that Opposers may offer the testimony of Narinder Shargill through a declaration and the offered testimony will be treated the same as if Mr. Shargill had given oral testimony. Accordingly, Applicant waives its objection to the form of Mr. Shargill’s testimony through declaration.
- 2) Opposers agree that Applicant does not waive and specifically reserves any substantive or procedural objections to Mr. Shargill’s testimony and its admissibility for any purpose.
- 3) Applicant retains the right to cross-examine Mr. Shargill through oral testimony. If Applicant exercises its right to cross-examine Mr. Shargill, Applicant agrees that Opposers may re-direct Mr. Shargill.

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Stephen R. Baird
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*Attorneys for Opposers
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Dated: August 6, 2015

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*Attorneys for Applicant
Holaira, Inc.*

Dated: July 30, 2015

10673465v1

Exhibit 74

**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.

REBUTTAL TESTIMONY DECLARATION OF NARINDER SHARGILL

The undersigned, being hereby warned that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements and the like may jeopardize the validity of this document, declares that:

1. I am the Vice President of Clinical Strategy and Medical Affairs, Pulmonary Division at Boston Scientific Corp. I am the global subject matter expert on bronchial thermoplasty; responsible for design of our pulmonary clinical trials, data analysis, data review and dissemination of the data through publications etc., educating physicians on clinical studies and data; training physicians to perform bronchial thermoplasty, proctoring bronchial thermoplasty procedures; KOL development and relationships; and addressing medical affairs issues.

2. On pages 92 through 95 of Dr. Dennis Wahr's deposition testimony, Dr. Wahr testified that there would be no off-label use of the HOLAIRA device. He specifically testified that

bronchial thermoplasty is not an alternative therapy to targeted lung denervation because “bronchial thermoplasty is not indicated for . . . chronic bronchitis . . . “ and “no doctor in the world would tell an asthma patient that [targeted lung denervation] is an alternative therapy for [asthma].” He also testified that the HOLAIRA system is currently not commercially available, but will be in 2022.

3. Asthma and COPD are not mutually exclusive conditions. In fact, there are a subset of obstructive lung disease patients that exhibit symptoms of both Asthma and COPD. In 2014, the Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease jointly published a report about the subset of patients that exhibit symptoms of both asthma and COPD. Exhibit 69 is a true and correct copy of the paper titled Asthma, COPD, and Asthma-COPD Overlap Syndrome.

4. When the ALAIR[®] system was first commercially available following FDA approval in 2010, I received questions from physicians about whether the ALAIR[®] system could be used to treat other obstructive lung diseases such as chronic bronchitis. For example, on September 15, 2010, I received an e-mail from [REDACTED]

[REDACTED] Exhibit 75 is a true and correct copy of the e-mail correspondence I received from [REDACTED] dated September 15, 2010.

5. Indeed, Dr. Yoneda and colleagues at the University of California, Davis have treated COPD patients with the ALAIR[®] system as recently reported in an online article in Consultant360 entitled “Pulmonary Pitfalls: Bronchial Thermoplasty in Severe Asthma.” Exhibit 77 is a true and correct copy of this online publication that appeared in the August 2015 issue of Consultant360.

6. Because the FDA approved indication for the ALAIR[®] system is asthma, Boston Scientific does not and has not promoted the ALAIR[®] system as a treatment for any disease other than asthma such as chronic bronchitis. Nevertheless, physicians are permitted to exercise their independent medical judgment to use the ALAIR[®] system to treat any obstructive pulmonary disease including chronic bronchitis.

7. Indeed, Boston Scientific received a proposal from [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Exhibit 76 is a true and correct copy of the Concept Submission Form for a research study submitted by [REDACTED]

8. Currently, I routinely field questions from physicians about the differences between the ALAIR[®] system and the HOLAIRA system because the devices are virtually identical: both use a bronchoscope, catheter, and RF Controller and both use RF energy in the bronchial tubes. The only differences are the amount of energy used during the respective procedures and the location within the bronchial tubes where the energy is applied. I have learned about the HOLAIRA system through information on the Holaira website, recent publications of data from studies with the Holaira device, and presentations at scientific meetings; specifically, at the ERS annual meeting in 2014 that included a discussion with Dr. Marty Mayse of Holaira, Inc. FURTHER YOUR DECLARANT SAYETH NAUGHT.

Dated: August 12, 2015

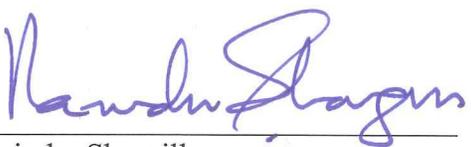
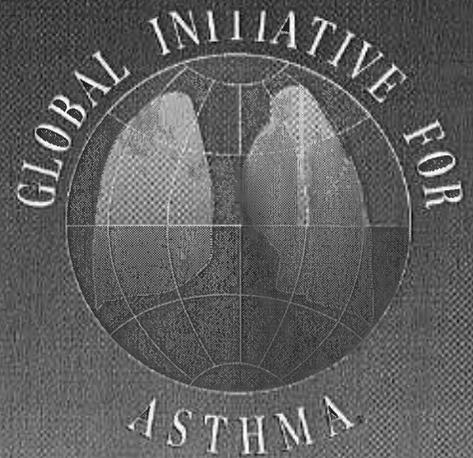

Narinder Shargill

Exhibit 69

Diagnosis of Diseases of
Chronic Airflow Limitation:

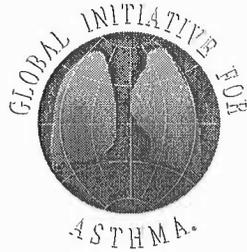
Asthma COPD and Asthma - COPD Overlap Syndrome (ACOS)



**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)

TABLE OF CONTENTS

PREFACE	2
KEY POINTS	3
OBJECTIVE	3
DEFINITIONS	4
Table 1. Current definitions of asthma and COPD, and clinical description of ACOS	4
STEP-WISE APPROACH TO DIAGNOSIS OF PATIENTS WITH RESPIRATORY SYMPTOMS	4
Step 1: Does the Patient Have Chronic Airways Disease?	4
<i>Clinical history</i>	
<i>Physical examination</i>	
<i>Radiology</i>	
<i>Screening questionnaires</i>	
Step 2: The Syndromic Diagnosis of Asthma, COPD and ACOS in an Adult Patient	5
<i>a. Assemble the features that favor a diagnosis of asthma or of COPD</i>	
<i>b. Compare the number of features in favor of a diagnosis of asthma or a diagnosis of COPD</i>	
<i>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</i>	
Table 2a. Usual features of asthma, COPD and ACOS	6
Table 2b. Features that favor asthma or COPD	6
Step 3: Spirometry	7
Step 4: Commence Initial Therapy	7
Table 3. Spirometric measures in asthma, COPD and ACOS	8
Step 5: Referral for Specialized Investigations (if necessary)	8
Table 4. Summary of syndromic approach to diseases of chronic airflow limitation	9
Table 5. Specialized investigations sometimes used in distinguishing asthma and COPD	10
REFERENCES	11

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.
 - Treatments will include an ICS (in a low or moderate dose, depending on level of symptoms).
 - 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:
 - Smoking cessation
 - Pulmonary rehabilitation
 - Vaccinations
 - 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

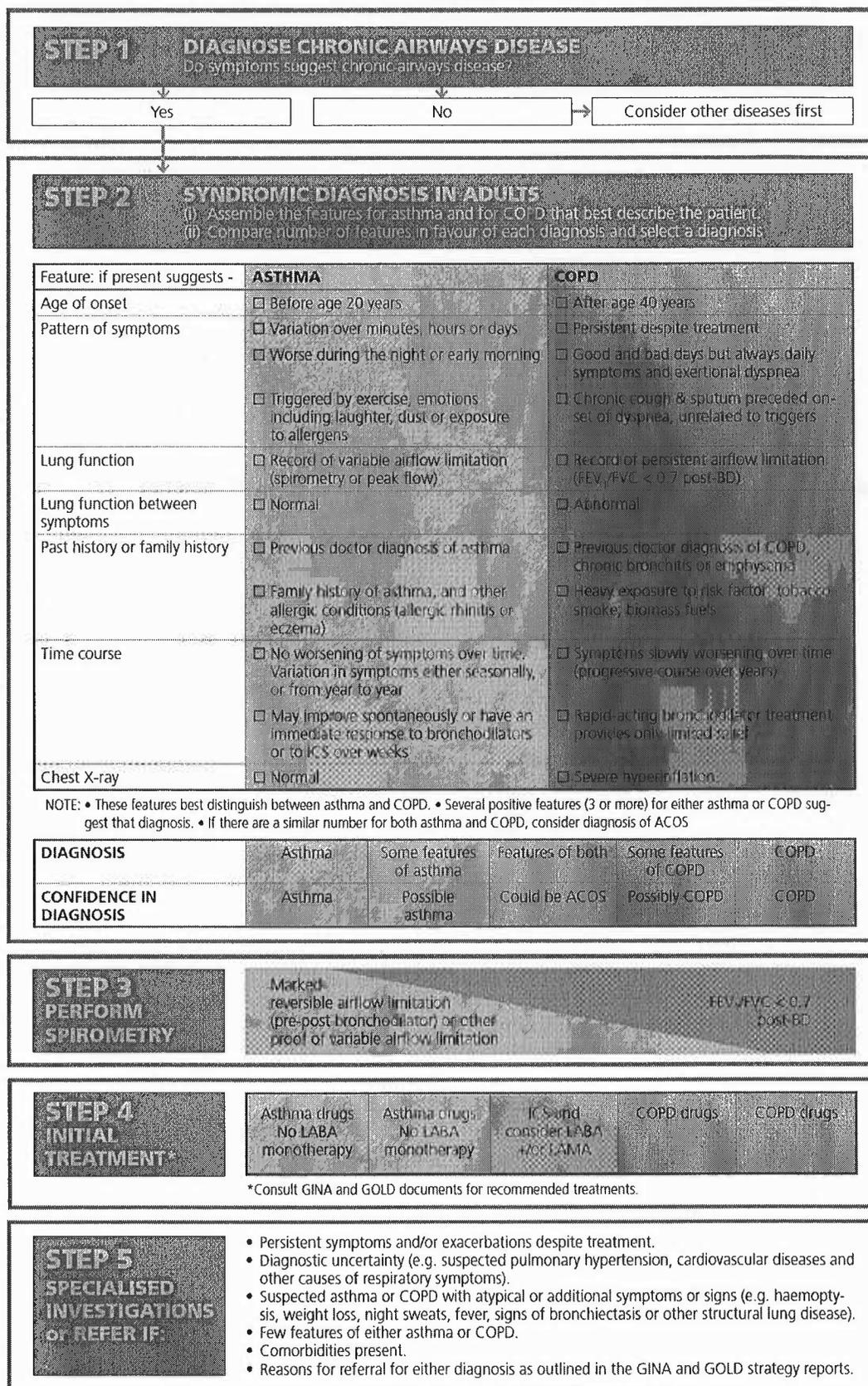


Table 5. Specialized investigations sometimes used in distinguishing asthma and COPD

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

Exhibit 75

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Exhibit 76

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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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