

## Review

## Bronchial thermoplasty: a review of the evidence

Chelle Pope Wilhelm, MD<sup>\*</sup>; and Bradley E. Chipps, MD<sup>†</sup><sup>\*</sup> Division of Clinical Immunology and Allergy, Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi<sup>†</sup> Capital Allergy and Respiratory Disease Center, Sacramento, California

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## ABSTRACT

**Objective:** To provide a review of the literature regarding bronchial thermoplasty in the treatment of asthma.**Data Sources:** PubMed was searched without time limitations using the key term *bronchial thermoplasty* alone and in combination with the key terms *asthma* and *treatment of asthma*. Other key terms included *cost-effectiveness* and *bronchial thermoplasty*, *cost-effectiveness* and *omalizumab*, and *epidemiology* and *asthma*.**Study Selection:** Qualifying articles included clinical trials performed with bronchial thermoplasty and review articles outlining the procedure of bronchial thermoplasty.**Results:** Three predominant clinical trials investigated bronchial thermoplasty as a treatment of asthma, with only 1 of these being placebo-controlled with a sham procedure. Two of these clinical trials had follow-up data published 5 years after bronchial thermoplasty. The efficacy of bronchial thermoplasty is promising for patients with asthma whose symptoms are not controlled despite medical therapy; however, evidence from the 1 sham-controlled clinical trial has been met with some concerns because the long-term follow-up of the sham-treated group was not reported. This review of the literature indicates that the procedure is safe and effective at least 5 years after the procedure. The phenotype of asthma that can be expected to respond best to bronchial thermoplasty has not been determined.**Conclusion:** Bronchial thermoplasty could be a safe and effective option for patients with severe asthma, particularly when symptoms are uncontrolled despite medical therapy. Further investigation should be performed to determine which phenotypes of asthma would benefit from the procedure.

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## Introduction

Asthma has emerged as one of the most common chronic diseases, with more than 25 million people with the disease in the United States.<sup>1</sup> Severe and difficult-to-treat asthma is responsible for considerable morbidity and mortality and health care usage and costs.<sup>2</sup> Severe asthma is defined in the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines as asthma that requires treatment with a high-dose inhaled corticosteroid (ICS), a second controller medication, and/or systemic corticosteroids. It might or might not be controlled with these measures.<sup>3</sup> The prevalence of severe asthma in adults and children has been difficult to determine, but it is estimated to occur in 5% to 10% of the 23 million people with asthma in the United States.<sup>3,4</sup> Eighty percent of the \$56 billion dollars in health care costs attributed to asthma is a result of severe or poorly controlled asthma.<sup>5–7</sup> Most of these costs are from emergency department visits and hospitalizations.<sup>5,8</sup> A 3-year study, published in 2012,

evaluating more than 4,700 patients with asthma showed a significant burden of illness remained despite maximum guideline-based therapy; however, therapy at that time did not include omalizumab<sup>2</sup> (Figure 1).

Many factors can contribute to poor control of asthma symptoms. These include poor inhaler technique, persistent environmental exposures, and confounding comorbidities, such as psychological factors, rhinosinusitis, vocal cord dysfunction, obesity, gastroesophageal reflux disease, and smoking and smoking-related diseases.<sup>3</sup> Given the significant quality-of-life and social burdens that severe asthma has on health care, newer treatment options, such as bronchial thermoplasty (BT), might warrant consideration.

## Role of Bronchial Thermoplasty

Bronchial thermoplasty is a nonpharmacologic, device-based therapy that has been used to treat severe, uncontrolled asthma.<sup>9</sup> It was approved by the US Food and Drug Administration in 2010 for asthma in patients at least 18 years old when their symptoms are not controlled with conventional therapy.<sup>9</sup> In May 2014, the Global Initiative for Asthma (GINA) cited grade B evidence for BT in selected patients with uncontrolled asthma despite recommended

**Reprints:** Chelle Pope Wilhelm, MD, Division of Clinical Immunology and Allergy, Department of Medicine, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216; E-mail: CPope@umc.edu.

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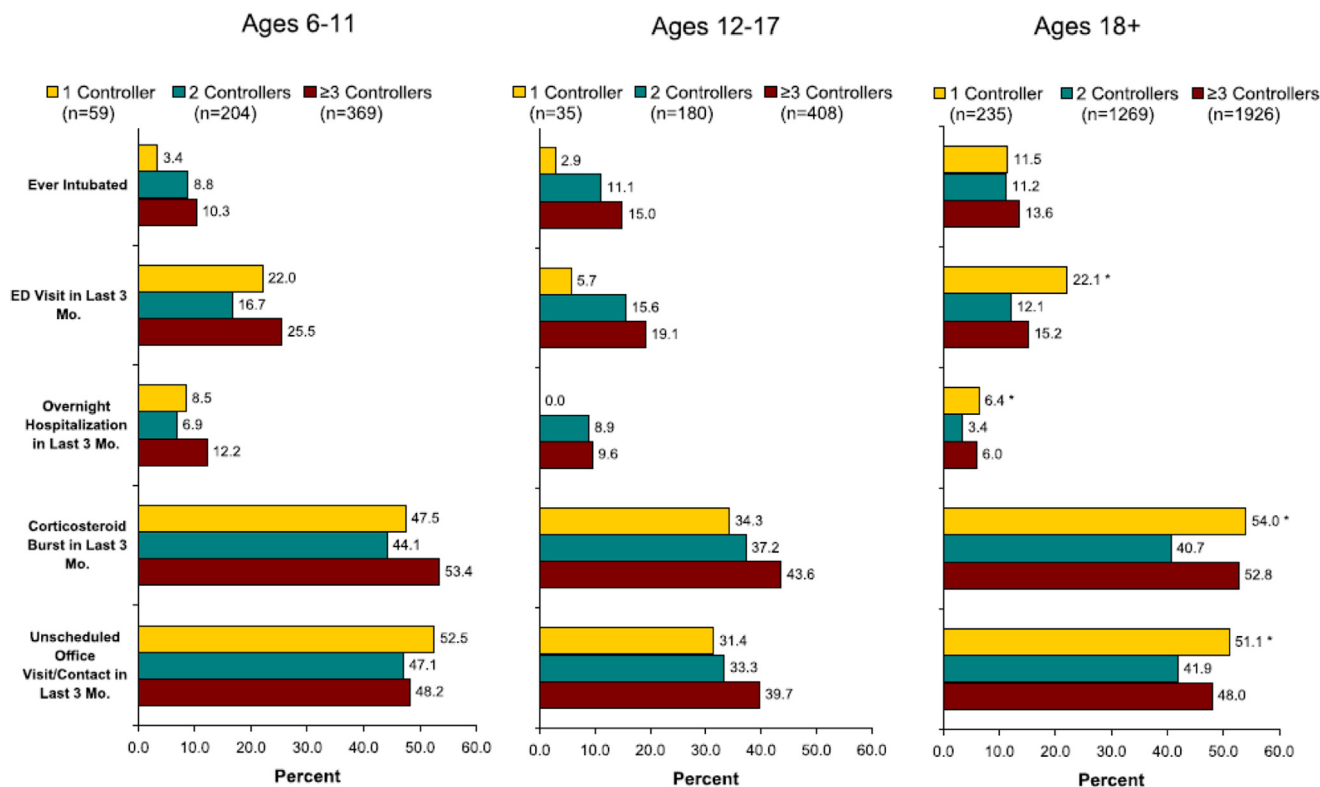


**Figure 1.** Outcomes for patients with asthma and lack of efficacy of standard treatment before the availability of omalizumab. ED, emergency department. Reprinted with permission from Elsevier from Chipps BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol*. 2012;130:332–342. \*  $P < .1$  for all health care use measures in adults, except history of intubation, which was not significant.

guideline-based therapy.<sup>10</sup> The international ERS/ATS guidelines on severe asthma from 2014 recommend that BT be performed in adults with severe asthma in the context of institutional review board–approved clinical studies.<sup>3</sup> They do comment that further research about asthma phenotype and long-term benefits and safety is likely to have an important impact on this recommendation.<sup>3</sup> The American College of Allergy, Asthma, and Immunology has encouraged insurance coverage for BT in carefully selected patients with severe, persistent asthma with persistent burden of disease, such as exacerbation, emergency department visits, and hospitalizations, despite maximum medical therapy.<sup>11</sup> The American College of Chest Physicians and INTERASMA, the Global Asthma Association published letters to encourage insurance coverage for appropriately applied BT.<sup>12,13</sup>

### Description of the Procedure

Unlike the anti-inflammatory targets of conventional asthma therapy, BT uses thermal energy to directly target the airway smooth muscle responsible for bronchoconstriction. In chronic, severe asthma, airway smooth muscle cells undergo cellular hypertrophy and hyperplasia.<sup>5,14</sup> They subsequently contribute to angiogenesis and extracellular matrix formation,<sup>5,15</sup> which result in dyspnea from airway narrowing and increased airway resistance. This pathophysiology provides the rationale for smooth muscle–targeted BT in asthma therapy. The first human BTs were performed in patients without asthma and with lung cancer scheduled for a lung resection. Miller et al<sup>16</sup> confirmed in their study that BT could decrease airway smooth muscle on histologic sections from the resected lung.<sup>5</sup>

Bronchial thermoplasty is performed using the Alair Bronchial Thermoplasty System (Boston Scientific, Marlborough,

Massachusetts). A radiofrequency catheter is inserted through the working channel of a bronchoscope and is used to deliver thermal energy (maximum 120 J) to airways 3 to 10 mm in diameter.<sup>5</sup> The procedure targets different regions of the lung performed in 3 separate treatment sessions at 3-week intervals. Typically the right lower lobe is targeted first, followed by the left lower lobe and upper lobes, respectively.<sup>5,9</sup> The right middle lobe is excluded based on the theoretical risk of development of right middle lobe syndrome.<sup>9</sup> Each bronchus is treated in its entire visible length, with each delivery of thermal energy targeting a 5-mm section of the bronchus, beginning distally and moving proximally along the bronchus.<sup>9</sup> During the bronchoscopy, the airway is visible to the subsegmental level, or the third to fourth generation of airway, which is proximal to the respiratory bronchiole level (approximately the 17th generation of airway), where gas exchange begins to occur. Each treatment session consists of 30 to 70 activations of thermal energy. The bronchoscopist must pay attention to ensure that each area is treated because failure to treat the bronchus completely could result in treatment failure. Each treatment session lasts 30 to 45 minutes. The procedure can be performed under moderate sedation or general anesthesia, depending on the facility and the comfort level of the proceduralist.<sup>9</sup> After the procedure, patients are given short-acting  $\beta_2$ -agonists and monitored until their post-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) is at least 80% of the preprocedural value.<sup>5</sup> Many patients will have increased symptoms during the first 24 to 72 hours after the procedure, but symptoms should return to baseline within a week of the procedure.<sup>5</sup>

### How Does Bronchial Thermoplasty Work?

The beneficial physiologic effects of BT are not completely understood. Several mechanisms have been suggested; however, no

one mechanism has been identified.<sup>9</sup> Airways of people with severe asthma have increased smooth muscle mass secondary to cellular hypertrophy and hyperplasia.<sup>17,18</sup> Because increased smooth muscle mass in severe asthma worsens airway hyperresponsiveness and ultimately causes permanent airflow obstruction,<sup>9,17</sup> it follows that patients might benefit from a decrease of airway smooth muscle mass. In a study of patients with severe asthma, a bronchoscopy with endobronchial biopsies was performed before and after BT. Airway smooth muscle area was assessed at biopsy examination by morphometry on  $\alpha$ -actin-stained sections and expressed as a percentage of airway smooth muscle area in the total biopsy area. The mean airway smooth muscle area decreased from 20.25% to 7.28%, with a decrease in the airway smooth muscle area seen even in the right middle lobe that was not treated by BT. This suggests that this procedure is effective in decreasing airway smooth muscle mass.<sup>19</sup> A decrease in airway hyperresponsiveness after a decrease of airway smooth muscle mass has not been consistently demonstrated in clinical studies.<sup>9,20</sup>

Another possible mechanism is the effect of BT on the contractile properties of the airway smooth muscle.<sup>9</sup> In bovines, airway smooth muscle contractile properties were altered at various temperatures, as would be seen with BT. It was demonstrated that acetylcholine-induced contraction of smooth muscle was inhibited at temperatures above 55°C. Relaxation from  $\beta_2$ -agonist was unaffected.<sup>9,21</sup> This effect was demonstrated in animal models only and has not been confirmed in human studies, although there is no reason to believe that bovine and human smooth muscle would differ in the sensitivity seen to temperature.

In addition, BT might affect the secretion of inflammatory mediators by the airway smooth muscle cells by changing the epithelium of the airways. These mechanisms have never been studied in humans.<sup>9</sup> Further studies on the mechanism of BT need to be performed for further understanding. The findings could help determine the asthma phenotype that would benefit most from the procedure.

### Clinical Trials of Bronchial Thermoplasty

The first nonrandomized feasibility study of BT in patients with asthma was performed in 16 patients with mild to moderate stable asthma to demonstrate the safety and feasibility of BT, not to detect efficacy outcomes. The patients had normal lung function but had substantial airway hyperresponsiveness to methacholine. The study found that after BT, the geometric mean of the provocation methacholine concentration that caused a decrease in FEV<sub>1</sub> of 20% of 0.92 mg/mL increased to 4.75 mg/mL at 12 weeks and 5.45 mg/mL at 1 year. It remained higher (3.40 mg/mL) than the pretreatment values at 2 years. Symptom-free days also increased from 50% to 73% after the procedure. The study demonstrated that the procedure was well tolerated, with side effects typical for after bronchoscopy and transient. The most common side effects included cough, dyspnea, wheezing, and bronchospasm. Most side effects were considered mild (84%), with the rest of the side effects being classified as moderate. There were no severe side effects, such as pneumothoraces, reported. All adverse effects resolved within 5 days of treatment, with 58% resolving spontaneously. Three percent required oral corticosteroids and 3% required supplemental oxygen for less than 6 hours after the procedure.<sup>5,22</sup>

The Asthma Intervention Research (AIR) trial was the first randomized controlled trial of BT and conventional therapy. It evaluated 112 patients with moderate to severe asthma. The patients who received BT in addition to conventional therapy compared with those who received conventional therapy alone had 50% fewer mild exacerbations at 12 months. Patients who received BT had more adverse respiratory events and hospitalizations immediately after the procedure, but by 6 weeks, there was no difference

between the 2 groups. At 1 year, the patients who received BT had statistically significant greater improvements in Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores, and this effect was seen at 3- and 6-month follow-up. At 3-month follow-up, patients in the BT group had a statistically significant increase in symptom-free days; however, this significance was lost at 1 year. Pre-bronchodilator FEV<sub>1</sub> percentage predicted in the BT group was  $75.2 \pm 13.9$  at 1 year compared with  $70.4 \pm 12.1$  at baseline, whereas the values for the control group were  $72.4 \pm 12.6$  and  $70.7 \pm 10.5$ , respectively; these changes were not statistically significant. Although airway hyperresponsiveness was decreased (increased provocation concentration that caused a decrease in FEV<sub>1</sub> of 20%) in the BT group, this was not statistically significant. During the treatment period, there were 407 adverse events in the BT group, with 69% of them being mild, 28% being moderate, and 3% being severe. The most common adverse events were dyspnea, wheezing, cough, and chest discomfort. Three of the 6 hospitalizations were for asthma exacerbation, 1 was for partial collapse of the left lower lobe, and 1 was for pleurisy. There were 106 adverse respiratory events seen in the control group, with 69% considered mild, 30% considered moderate, and 1% considered severe, with 2 patients each requiring 1 hospitalization.<sup>5,23</sup>

The Research in Severe Asthma (RISA) trial was an unblinded, randomized, controlled trial including 34 patients with symptomatic, severe asthma despite being on high-dose ICS and long-acting  $\beta$ -agonist therapy. The mean FEV<sub>1</sub> predicted was 63% in the BT group and 66% in the control group. At 22 weeks after the procedure, patients who underwent BT had a statistically significant (15%) improvement in pre-bronchodilator FEV<sub>1</sub> percentage predicted ( $14.9 \pm 17.4$ ) compared with the control group ( $-0.9 \pm 22.3$ ), but this difference was not found at 52 weeks. The BT group also had statistically significant improvements in AQLQ and ACQ scores compared with the control group, and this improvement also was seen at 52 weeks. Those receiving BT used rescue medications less frequently than those in the control group ( $-26.6 \pm 40.1$  vs  $-1.5 \pm 11.7$  puffs/7 days,  $P < .05$ ) at 22 weeks, and this improvement continued to be statistically significant at 52 weeks. Four of the 8 subjects in the BT group had been able to wean off oral corticosteroids and stay off at 52 weeks compared with only 1 of the 7 control subjects; however, this difference was not statistically significant. Similar to the AIR trial, patients who received BT were more likely to have transient worsening of asthma symptoms and be hospitalized during the treatment period. Ten percent of the 136 respiratory adverse events were considered severe, and most were related to asthma symptoms, such as wheezing, dyspnea, and cough, requiring nebulized bronchodilators and systemic corticosteroids. Two patients had a lower lobe collapse, with 1 resolving with chest physiotherapy and 1 requiring a repeat bronchoscopy to remove a mucus plug. One patient with respiratory failure required intubation and mechanical ventilation after the treatment period, but this patient was in the control group.<sup>5,24</sup>

The second AIR (AIR-2) trial was a sham-controlled, randomized, double-blinded clinical trial with 297 subjects. This study was designed to evaluate for improvement in quality of life and exacerbation rates after BT. These patients had symptomatic asthma despite high-dose ICS and long-acting  $\beta$ -agonist use, took oral corticosteroids at a dose lower than 10 mg/d, had documented airway hyperresponsiveness, and had a pre-bronchodilator FEV<sub>1</sub> of at least 60%. The patients in the control group received a sham procedure with every step of the BT procedure performed except the delivery of thermal energy.<sup>25</sup> The AIR-2 trial was a negative study, because it failed to reach the primary end point (significant difference in AQLQ scores) and the secondary end points, including improvement in FEV<sub>1</sub>, ACQ scores, total symptoms scores, morning peak expiratory flow, and rescue medication use.<sup>25,26</sup> In the study, patients who received BT did have 32% fewer severe exacerbations,

fewer days lost from work or school, fewer hospitalizations, and 84% fewer emergency department visits. There was no significant change in pre-bronchodilator FEV<sub>1</sub> percentage predicted values in either group. Patients who received the BT treatment did have an increase in asthma symptoms and a slight increased risk of hospitalization in the 24 to 48 hours after the procedure; this difference in risk resolved within 1 week. During the treatment period, there were 19 hospitalizations in 16 subjects, with most hospitalizations for worsening of asthma symptoms, 3 hospitalizations for segmental atelectasis, 1 for a lower respiratory tract infection, 1 for a low FEV<sub>1</sub>, 1 for hemoptysis, and 1 for an aspirated prosthetic tooth. No intubations or pneumothoraces were reported.<sup>5,25</sup> Another consideration in the 5-year follow-up study for the AIR-2 trial is that the information regarding outcomes in the sham group was not reported, which produces difficulty in interpreting the actual benefits of thermoplasty.<sup>27</sup>

One factor that makes the evaluation of the efficacy of BT in treating patients with asthma difficult is the lack of consistency throughout most of the clinical trials. Each clinical trial was performed with varying severities of asthma and exclusion criteria. There also were no consistent primary and secondary end points throughout the studies, with some measuring FEV<sub>1</sub> percentage predicted value and others measuring quality of life through asthma questionnaires.

### Five-Year Follow-up

The RISA and AIR-2 trials evaluated long-term safety data at 5 years in patients who underwent BT. The RISA investigators successfully followed 14 of the 15 patients who received BT treatment in the original trial. The respiratory adverse events were fewer after treatment compared with 1 year before treatment and were 1.4, 2.4, 1.7, and 2.4 per patient year for years 2 through 5, respectively. Five-year follow-up also showed a decrease in hospitalizations and emergency department visits in each of the years (1–5 years) compared with the year before treatment. Chest radiographs remained unremarkable at 5 years, and the mean pre-bronchodilator and post-bronchodilator FEV<sub>1</sub> percentage predicted values seen after 1 year after the procedure were unchanged, with a retained bronchodilator response, during the 5 years after BT.<sup>4,5</sup>

In the AIR-2 extension study, 162 of the original 190 patients receiving BT were available for assessment. The proportion of patients experiencing a severe exacerbation in years 1 through 5 after the procedure remained 21% to 30% compared with 51.6% 1 year before the procedure. Similarly, the rate of severe exacerbation was decreased 48% at 5 years compared with before treatment. The presence or absence of seasonal allergic disease had no effect on severe exacerbations. The BT group had 78% fewer emergency department visits at year 5 compared with the year before the procedure. Respiratory adverse events and respiratory-related hospitalizations remained unchanged in years 2 through 5 compared with the first year after BT (Figure 2). There were no incidences of pneumothorax, intubation with mechanical ventilation, cardiac arrhythmias, or death in the 5 years after BT. Pre-bronchodilator FEV<sub>1</sub> values remained stable from years 1 through 5. There was a 17% decrease in average daily ICS use, with 12% decreased bronchodilator use, 9% decreased ICS and bronchodilator use, and 7% no longer on any maintenance asthma medications. Of 93 high-resolution computed tomographic (HRCT) images of the chest available at 5 years, 82% showed no radiographic changes or an improvement from a baseline HRCT scan. Three patients (3%) were noted to have increased or new bronchiectasis, 1 with worsening of pre-existing bronchiectasis, 1 with mild bronchiectasis in 2 different lobes (including the right middle lobe that was not treated with BT), and 1 with new bronchiectasis. There was no evidence of

bronchial stricture, bronchiolitis obliterans, or new pulmonary emphysema seen at 5 years. These HRCT images were read by an independent pulmonary radiologist who was blinded to the time point of HRCT scanning. After completing the assessment, the radiologist was unblinded and assessed whether the findings were new, improved, or deteriorated from baseline HRCT images. Then, these images were provided to an independent pulmonologist who determined whether there was any clinical significance to the findings, based on information for each subject, including lung function, adverse events reported, and timing of adverse events.<sup>28</sup>

### Where Does Bronchial Thermoplasty Fit in the Treatment Regimen?

Exactly where BT fits into the treatment regimen of asthma has not been clearly defined. The studies on BT effectiveness evaluated different severities of asthma, ranging from mild to severe. Moreover, it is unclear what constitutes uncontrolled asthma despite medical therapy. For instance, is uncontrolled asthma determined by questionnaires such as the ACQ or the AQLQ alone? Should frequency of exacerbations, emergency department visits, or overall health care usage dictate control level and where BT fits into the treatment plan? Further studies will need to be performed to identify exactly when to implement BT in the treatment of difficult-to-control asthma.

Furthermore, it is not clear which asthma phenotypes would have the most benefit from BT. Patients with sputum eosinophilia have a lower FEV<sub>1</sub> and lower ratio of FEV<sub>1</sub> to forced vital capacity and greater bronchial hyperresponsiveness than patients with non-eosinophilic asthma. In addition, patients with concomitant systemic and bronchial eosinophilic inflammation have poor asthma control and quality of life and high bronchial hyperresponsiveness and exacerbation rates.<sup>29</sup> One might presume that BT would be most effective in patients with predominantly eosinophilic inflammation and significant airway hyperresponsiveness or in patients in whom smooth muscle contraction plays a large role in their disease. Thus far, there are no data to support this because several clinical trials did not measure bronchial hyperreactivity. There also are no data available regarding evaluation of airway inflammation, such as the measurement of peripheral or sputum eosinophilia or measurement of fractional exhaled nitric oxide, after BT. Bronchial thermoplasty might be of added benefit in patients with disease not driven by T-helper cell type 2, in which biologics are not helpful. Further studies are needed before any recommendations can be made as to the specific asthma phenotype that would most benefit from BT.

The GINA guidelines from 2014 recommend that BT be considered step 5 therapy in some adult patients with severe asthma that remains uncontrolled despite use of recommended therapeutic regimens (evidence level B). This falls into the same step of therapy as omalizumab (evidence level A) and tiotropium (evidence level B) for the treatment of asthma. No recommendations are made as to the order these interventions should be initiated.<sup>10</sup>

### Cost Effectiveness

Access to BT has been limited secondary to the high initial cost and lack of insurance coverage. Analyses of the cost effectiveness of BT are limited. One model-based analysis compared estimated cost effectiveness of standard therapy for severe persistent asthma with the cost effectiveness of BT in addition to standard therapy.<sup>1</sup> For each treatment option, the investigators projected a 5-year cost. This included the quality-adjusted life years, which incorporated the quantity and quality of life. They estimated the costs of physician office visits, emergency department visits, and hospitalizations and the costs of all controller medications. The costs of BT included physician costs and procedure costs. The cost effectiveness of BT

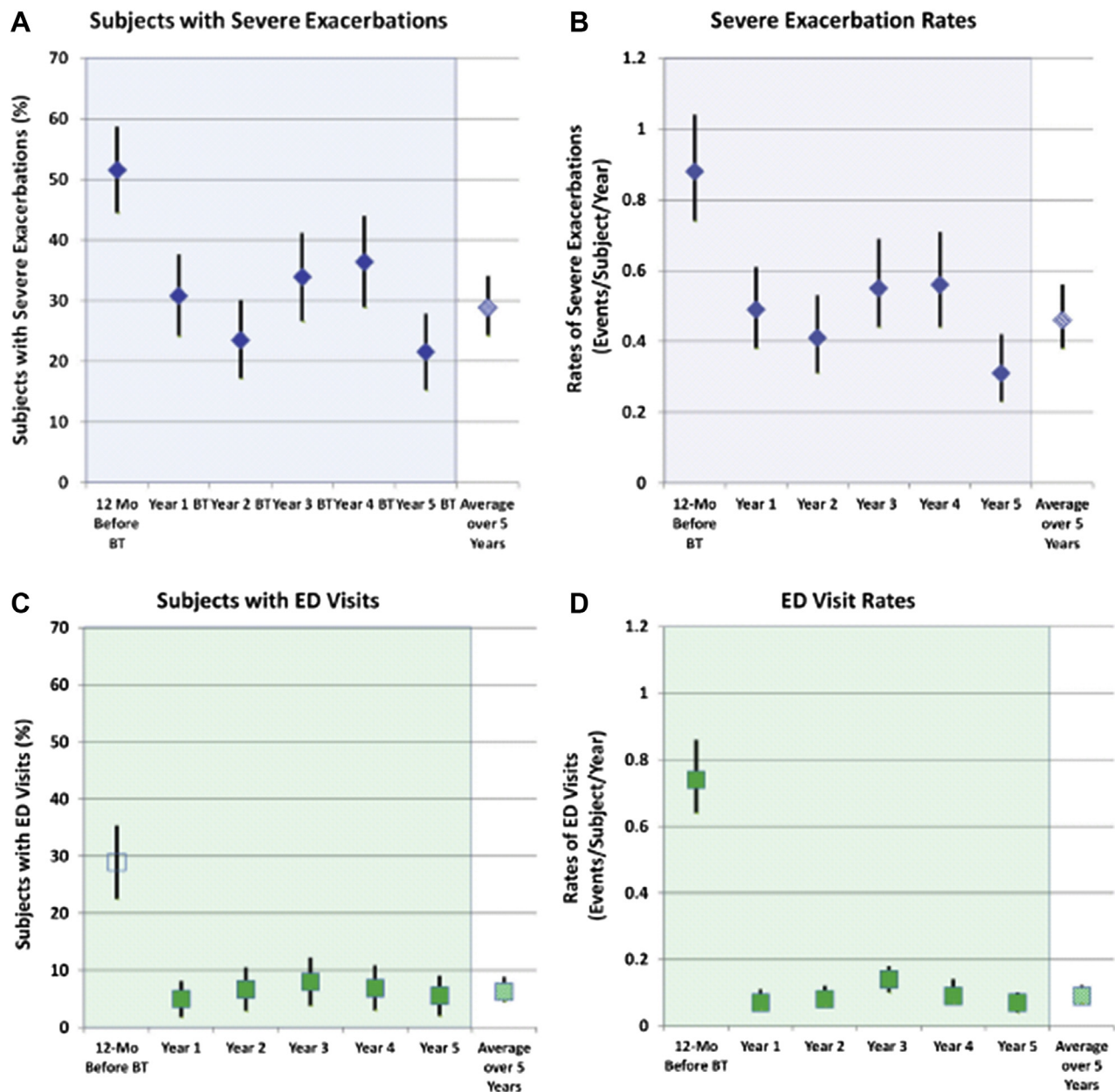


**Figure 2.** Severe asthma exacerbations and emergency department (ED) visits in years 1 through 5 after bronchial thermoplasty (BT). Reprinted with permission from Elsevier from Wechsler ME, Lavolette M, Rubin AS. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol*. 2013;132:1295–1302.

was US\$5,495 per quality-adjusted life year, indicating that BT is a cost-effective treatment option for patients with poorly controlled, severe, persistent asthma.<sup>1</sup> In a similar cost-effectiveness analysis of omalizumab performed during a 5-year period in people with moderate to severe persistent asthma, the cost-effectiveness ratio for omalizumab plus usual care compared with usual care alone was \$278,200 per quality-adjusted life year.<sup>30</sup>

### Concerns Surrounding Bronchial Thermoplasty

#### Selecting the Appropriate Patient

There are certain contraindications to having BT performed.<sup>18,31</sup> These contraindications include an age younger than 18 years; the presence of an internal defibrillator, pacemaker, or other implantable device; a sensitivity to a medication used during

bronchoscopy, such as lidocaine, atropine, and benzodiazepines; and previous treatment with BT. The procedure should be postponed if a patient has an active respiratory infection; an asthma exacerbation or a change in oral corticosteroid dosing in the previous 14 days; a known coagulopathy; or an inability to stop medications, such as anticoagulants, antiplatelet medications, and nonsteroidal anti-inflammatory drugs. There is no defined severity of measured lung function provided that precludes BT from being performed.<sup>18,31</sup> The authors recommend that providers ensure that the patient understands the risks and benefits of the procedure, because patients with lower lung function might be more likely to develop complications from the bronchoscopy in general. However, they argue that severity of measured lung function should not be used as an indication of whether or not BT can be performed, because the procedure is recommended only in patients who have

symptoms that are uncontrolled despite aggressive medical therapy, and these patients are likely to have poor measured lung function in general.

Clinical studies of BT have been performed in patients with various severities of asthma. One common factor in these studies has been an inadequate control of asthma with evidence of airway obstruction. The exact dose of maintenance asthma medications and the FEV<sub>1</sub> and level of hyperresponsiveness have varied in these studies.<sup>9</sup> The different factors in these clinical studies might make it difficult to determine exactly which patients should be offered BT. The authors recommend that the guidelines, as set by GINA, be followed and that medical therapy should be maximized before offering BT.

The AIR-2 trial excluded patients with at least 3 hospitalizations or at least 4 oral corticosteroid courses in a single year and those who were using short-acting bronchodilators frequently (>4 puffs in 1 day). Data on the effects of BT on this population are not available; although it stands to reason that this population might very well benefit from this procedure. Currently, some predominant precautions and exclusions to BT include chronic obstructive pulmonary disease, recurrent respiratory infections, bronchiectasis, or any other uncontrolled respiratory disease.<sup>9</sup>

The predominant location of airway obstruction is important when considering BT as a treatment option. BT is effective in more central airway obstruction as seen in patients with asthma. This is different from the peripheral airway obstruction seen with chronic obstructive pulmonary disease and bronchiolitis. Chronic obstructive pulmonary disease is characterized by peripheral, small airway, and alveolar involvement. It is important to note that these airways are not reached by BT. HRCT imaging can be a useful tool in identifying any underlying pulmonary parenchymal abnormalities and small airway disease (as seen by gas trapping on HRCT scan).<sup>5</sup> This could help with identifying patients who are unlikely to benefit from BT. Patients with small airway disease are unlikely to have any improvement in AQLQ scores compared with patients with predominantly large airway disease.<sup>5</sup>

Another uncertainty is when to consider BT as a treatment option over biologic medical therapies, such as omalizumab. The GINA guidelines place BT as a treatment option in step 5 of asthma therapy, in addition to omalizumab; however, there are no clear guidelines of when to consider one option over the other.<sup>10</sup> The ERS/ATS guidelines on severe asthma suggest a trial of omalizumab in patients with severe allergic asthma. The guidelines suggest that patients (≥6 years old) with severe asthma, confirmed IgE-dependent allergic asthma uncontrolled despite maximum therapy, and a total serum IgE level of 30 to 700 IU/mL be given a trial of omalizumab therapy. The guidelines also remark that if a patient has not responded within 4 months of treatment, then further administration is unlikely to be beneficial.<sup>3</sup> The ERS/ATS guidelines also consider more recent experimental biologic therapies, such as anti-interleukin-5 and anti-interleukin-13 antibodies; however, these are not currently available for clinical use.<sup>3</sup> These and other biologic therapies are likely to play a role in the future for options of treatment for severe asthma.

#### Overall Danger of Procedure

As discussed from clinical trials, patients experienced very few complications from the procedure. The complications were typically mild and did not require any invasive therapy, such as intubation with mechanical ventilation or chest tube thoracostomy, and these complications have not been reported with the procedure in clinical use. The adverse events that were seen during the clinical trials included worsening of baseline symptoms initially, such as worsening of dyspnea, wheezing, and cough, and reported upper respiratory tract infections, discolored

sputum, and bronchial irritation, all of which can occur after a routine bronchoscopy.

One potential problem with BT involves the overall risk of bronchoscopy in general. Of course, there are several complications that can occur secondary to sedation, including those from under-sedation, over-sedation, and idiosyncratic responses to therapeutic levels of sedation. When a patient is under-sedated during bronchoscopy, the procedure can be difficult to perform secondary to excessive movement and coughing from the patient. Also, there is a risk of the patient developing delirium and pain from the procedure if under-sedated. Most sedatives act as myocardial depressants and/or vasodilators, which can lower blood pressure. Sedatives also tend to work as respiratory depressants. Complications, such as hemodynamic collapse and/or respiratory depression leading to apnea, can occur if a patient is over-sedated, particularly secondary to the additive effects of multiple medications used for sedation. Even when an appropriate, therapeutic level of sedation is used, patients can develop allergic reactions to the medications, rigidity, or laryngospasm.<sup>32</sup>

There also are risks to consider from the bronchoscopy procedure itself. Flexible bronchoscopy is a relatively safe and well-tolerated procedure; however, like all procedures, it is not without possible complications. Occasionally, patients might develop airway problems, such as increased airway resistance and exacerbation of obstructive airway disease.<sup>33</sup> In the clinical trials of BT, patients did have increased asthma symptoms during the week after the procedure, but no mention was made of increased airway resistance during the procedure itself. It stands to reason that patients with severe asthma might be at an increased risk of this particular complication. In addition, bronchoscopy in general carries a risk of epistaxis, hemoptysis, infection, and pneumothorax.<sup>33</sup> Major complications, such as bleeding, respiratory depression, and pneumothorax, occur in fewer than 1% of cases. Mortality with bronchoscopy is rare, with a reported death rate of 0% to 0.04%.<sup>33,34</sup>

Critics suggest parenchymal damage from BT could result in an interstitial lung disease pattern with pulmonary restriction. In the various clinical studies, no indication of this was found with follow-up imaging (chest radiography and HRCT imaging) and spirometry. The FEV<sub>1</sub> in the AIR-2 and RISA trials remained stable during the 5-year follow-up. There was no mention of full pulmonary function studies with regard to other values, such as total lung capacity, in these studies. However, it is not likely that BT would induce a restrictive lung disease from parenchymal damage because it is limited to central airways and not performed on the lung parenchyma or alveolar units. Restrictive lung disease can result from infiltrative interstitial processes, neuromuscular disease, thoracic cage abnormalities, and chronic pleural disease. Concern for interstitial lung disease is minimal because BT targets airways with a diameter of at least 3 mm, essentially the more central, larger airways and proximal to the interstitium.

#### Conclusion

Severe, uncontrolled asthma has a major impact on the economy and on the individual patient's quality of life. All too often, asthma is uncontrolled despite maximum medical therapy, including oral corticosteroids. BT is becoming more widely accepted as a safe treatment option for these patients. Currently, clinical studies indicate an improvement in quality of life and a decrease in overall health care usage. More research needs to be done to determine the asthma phenotype that can be expected to respond best to this procedure.

#### References

- [1] Cangelosi MJ, Ortendahl JD, Meckley LM, et al. Cost-effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma. *Expert Rev Pharmacoecon Outcomes Res.* 2015;15:357–364.

- [2] Chipps BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol*. 2012;130:332–342.
- [3] Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation, and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373.
- [4] Pavord ID, Thomson NC, Niven RM, et al. Safety of bronchial thermoplasty in patients with severe refractory asthma. *Ann Allergy Asthma Immunol*. 2013;111:402–407.
- [5] Sheshadri A, McKenzie M, Castrol M. Critical review of bronchial thermoplasty: where should it fit into asthma therapy? *Curr Allergy Asthma Rep*. 2014;14:470.
- [6] Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. *J Allergy Clin Immunol*. 2011;127:145–152.
- [7] Smith DH, Malone DC, Lawson KA, et al. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med*. 1997;156:787–793.
- [8] Cisternas MG, Blanc PD, Yen IH, et al. A comprehensive study of the direct and indirect costs of adult asthma. *J Allergy Clin Immunol*. 2003;111:1212–1218.
- [9] Dombret MC, Alagha K, Boulet LP, et al. Bronchial thermoplasty: a new therapeutic option for the treatment of severe, uncontrolled asthma in adults. *Eur Respir Rev*. 2014;23:510–518.
- [10] Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention: updated 2015. <http://www.ginaasthma.org>. Accessed November 11, 2015.
- [11] American College of Allergy, Asthma, and Immunology—statement on bronchial thermoplasty. [http://college.acaai.org/pages/statement\\_on\\_bronchial\\_thermoplasty.aspx](http://college.acaai.org/pages/statement_on_bronchial_thermoplasty.aspx). Accessed October 10, 2015.
- [12] American College of Chest Physicians. Coverage and payment for bronchial thermoplasty for severe persistent asthma. Letter. MS. Glenview, Illinois. 2014. <http://www.chestnet.org/News/CHEST-News/2014/05/Position-Statement-for-Coverage-and-Payment-for-Bronchial-Thermoplasty>. Accessed November 19, 2015.
- [13] INTERASMA: Global Asthma Association. Bronchial thermoplasty: an additional option for managing patients with severe asthma. Letter. <http://www.btforasthma.com/physicians/society-support#interasma>. Accessed November 19, 2015.
- [14] James AL, Elliot JG, Jones RL. Airway smooth muscle hypertrophy and hyperplasia in asthma. *Am J Respir Crit Care Med*. 2012;185:1058–1064.
- [15] Panettieri RA Jr, Kotlikoff MI, Gerthoffer WT, et al. Airway smooth muscle in bronchial tone, inflammation, and remodeling: basic knowledge to clinical relevance. *Am J Respir Crit Care Med*. 2008;177:248–252.
- [16] Miller JD, Cox G, Vincic L, et al. A prospective feasibility study of bronchial thermoplasty in the human airway. *Chest*. 2005;127:1999–2006.
- [17] Benayoun L, Druilhe A, Dombret MC, et al. Airway structural alterations selectively associated with severe asthma. *Am J Respir Crit Care Med*. 2003;167:1360–1368.
- [18] Dunn R, Wechsler ME. Reducing asthma attacks in patients with severe asthma: the role of bronchial thermoplasty. *Allergy Asthma Proc*. 2015;36:242–250.
- [19] Pretolani M, Dombret MC, Knap D, et al. Letter to the editor: reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. *Am J Respir Crit Care Med*. 2014;190:1452–1454.
- [20] Castro M, Rubin A, Laviolette M, et al. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. *Ann Allergy Asthma Immunol*. 2011;107:65–70.
- [21] Dyrda P, Tazzeo T, DoHarris L, et al. Acute response of airway muscle to extreme temperature includes disruption of actin–myosin interaction. *Am J Respir Cell Mol Biol*. 2011;44:213–221.
- [22] Cox G, Miller JD, McWilliams A, et al. Bronchial thermoplasty for asthma. *Am J Respir Crit Care Med*. 2006;173:965–969.
- [23] Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med*. 2007;356:1327–1337.
- [24] Pavord ID, Cox G, Thomson NC, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med*. 2007;176:1185–1191.
- [25] Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med*. 2010;181:116–124.
- [26] Iyer VN, Lim KG. Bronchial thermoplasty: where there is smoke, there is fire. *Allergy Asthma Proc*. 2015;36:251–255.
- [27] Iyer VN, Lim KG. Bronchial thermoplasty: reappraising the evidence (or lack thereof). *Chest*. 2014;146:17–21.
- [28] Wechsler ME, Laviolette M, Rubin AS. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol*. 2013;132:1295–1302.
- [29] Schleich FN, Chevremont A, Paulus V, et al. Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. *Eur Respir J*. 2014;44:97–108.
- [30] Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy*. 2010;65:1141–1148.
- [31] Boston Scientific Corporation. Bronchial thermoplasty. <https://btforasthma.com/how-it-works>. Accessed August 13, 2015.
- [32] Pratt S. Anesthesia for bronchoscopy. In: Ernst A, ed. *Introduction to Bronchoscopy*. New York: Cambridge University Press; 2009:59–60.
- [33] Waxman A. Flexible bronchoscopy: indications, contraindications, and consent. In: Ernst A, ed. *Introduction to Bronchoscopy*. New York: Cambridge University Press; 2009:82.
- [34] De Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. *Eur Respir J*. 2002;20:1271–1276.