Bronchial Thermoplasty

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DESCRIPTION

Asthma, a chronic lung disease, affects approximately 8% of adults and 7% of children in the United States. In 2018, asthma accounted for 1.6 million emergency department visits and in 2020 4,145 deaths were related to asthma. Asthma symptoms include episodic shortness of breath that is generally associated with other symptoms such as wheezing, chest tightness and coughing. Objective clinical features include bronchial hyper-responsiveness, airway inflammation, and reversible airflow obstruction (at least 12% improvement in forced expiratory volume in 1-second post-bronchodilator, with a minimum of 200 mL improvement). However, there is substantial heterogeneity in the inflammatory features of patients diagnosed with asthma, and this biologic diversity is responsible, at least in part, for the variable response to treatment in the asthma population.

Management of asthma consists of environmental control, patient education, management of comorbidities, and regular follow up for all affected patients, as well as a stepped approach to medication treatment.

Guidelines from the National Heart, Lung and Blood Institute in 2020 have defined six pharmacologic steps: step 1 for intermittent asthma and steps 2 through 6 for persistent asthma. The preferred daily medications:

- Step 1: short-acting b-agonists as-needed and at the start of RTI add a short course of daily inhaled corticosteroids (ICS)
- Step 2: daily low-dose inhaled corticosteroids (ICS) and as needed short-acting b-agonists;
- Step 3: Daily inhaled corticosteroids (ICS) and as needed short-acting b-agonists;
- Step 4: Daily medium-dose inhaled corticosteroids (ICS) – long-acting b-agonists (LABA) and as needed short-acting b-agonists;
- Step 5: Daily high-dose inhaled corticosteroids (ICS) – long-acting b-agonists (LABA) and as needed short-acting b-agonists;
- Step 6: Daily high-dose inhaled corticosteroids (ICS) – long acting b-agonists (LABA) and oral systemic corticosteroid and as needed short-acting b-agonists;

In 2021, guidelines from Global Initiative for Asthma (GINA) for difficult to treat and severe asthma in adolescents and adults has the following 8 step approach for the management of these patients:

- Step 1: Confirm the diagnosis (asthma/differential diagnosis);
- Step 2: Look for factors contributing to symptoms, exacerbations and poor quality of life;
- Step 3: Optimize management: asthma education; optimize treatment (e.g., check and correct inhaler technique and adherence, switch to ICS-formoterol maintenance and reliever therapy if available); treat comorbidities and modifiable risk factors; consider non-biologic add on therapy e.g. LABA, tiotropium, LM/LTRA if not used; consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination); consider trial of high dose ICS if not used;
- Step 4: Review response after 3-6 months;
- Step 5: Asses the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations;
- Step 6a: Consider non-biologic treatments;
- Step 6b: Consider add on biologic Type-2 targeted treatments;
- Step 7: Review response;
- Step 8: Continue to optimize management as in Step 3 including inhaler technique, adherence, comorbidity management, patients social/emotional needs and two-way communication with GP for ongoing care.

Despite these multidimensional approaches, many patients continue to experience considerable morbidity. In addition to ongoing efforts to optimally implement standard approaches to asthma treatment, new therapies are being developed.

Bronchial thermoplasty is a potential treatment option for patients with severe persistent asthma, it is a controlled delivery of radiofrequency energy to heat tissues in the distal

airways. Bronchial thermoplasty is based on the premise that patients with asthma have an increased amount of airway smooth muscle (ASM) and the contraction of this airway smooth muscle (ASM) is a major cause of airway constriction. The thermal energy delivered via bronchial thermoplasty aims to reduce the amount of airway smooth muscle (ASM) and thereby decrease muscle mediated bronchoconstriction with the ultimate goal of reducing asthma-related morbidity. Bronchial thermoplasty is intended as a supplemental treatment for patients with severe persistent asthma (i.e., steps 5 and 5 in the stepwise approach to care according to the guidelines from the National Heart, Lung and Blood Institute).

During the procedure, a standard flexible bronchoscope is placed through the patient's mouth or nose into the distal targeted airway and a catheter is inserted into the working channel of the bronchoscope. After placement, the electrode array in the top of the catheter is expanded, and radiofrequency energy is delivered from a proprietary controller used to heat tissue to 65 degrees Celsius over a 5 mm area. The positioning of the catheter and application of thermal energy is repeated several times in contiguous areas along the accessible length of the airway. At the end of the treatment session, the catheter and bronchoscope are removed.

After the first treatment session, previously treated airways are evaluated by bronchoscopy before proceeding with further treatment. A course of treatment consists of 3 separate procedures in different regions of the lung scheduled about 3 weeks apart (the first two sessions target the right lower lobe and left lower lobe separately while the final session targets the bilateral upper lobes). The procedure is performed on an outpatient basis with conscious sedation and requires approximately 1 hour to complete.

Clinical Context and Therapy Purpose
The purpose of bronchial thermoplasty in patients who have asthma refractory to standard treatment is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Patients
The relevant population of interest are individuals with treatment refractory asthma. Asthma symptoms can vary between individuals but may include bronchial hyperresponsiveness, airway inflammation and reversible airflow obstruction. For adults with persistent and severe asthma whose symptoms are not adequately controlled with low-dose inhaled corticosteroids and long-active B-agonists (LABAs), bronchial thermoplasty may be an add-on treatment.

Interventions
The therapy being considered is bronchial thermoplasty as an add-on treatment in patients whose asthma is not adequately controlled with medical management.

Bronchial thermoplasty delivers thermal energy to tissue in the distal airways in an attempt to reduce excess smooth muscle, which causes airway constriction in

active disease. Radiofrequency energy is applied through a catheter and a flexible bronchoscope. A typical full course of treatment consists of three, one-hour sessions, given three weeks apart under moderate sedation. All accessible airways distal to the main stem bronchus that are 3 to 10 mm in diameter are treated once, except those in the right middle lobe; the lower lobes are treated first followed by the upper lung.

Comparators
Currently, clinical response to continued medical management is being used to make decisions about the use of bronchial thermoplasty for treatment-refractory asthma. Continued medical management of asthma consists of environmental control, patient education, management of comorbidities, and regular follow-up for affected patients, as well as a stepped approach to medication treatment.

Outcomes
Beneficial outcomes are symptom relief, improvement in quality of life (QOL), reductions in medication adverse events and hospitalizations, and treatment-related morbidity. Instruments such as the Asthma Quality of Life Questionnaire (AQLQ) score may be used to assess improvements in asthma symptoms.

Potential harms include periprocedural risk and risk for exacerbation of asthma during the treatment phase.

Short-term results are evaluated from weeks post-treatment to 12 months. Long-term follow-up studies have evaluated patients receiving bronchial thermoplasty up to five years post-treatment.

Randomized Controlled Trials
There are three industry sponsored randomized controlled trials (RCTs) that have evaluated the efficacy and safety of bronchial thermoplasty for the treatment of asthma (AIR, RISA, AIR2). The largest RCT with the most rigorous methodology was the AIR2 trial. This was the only published trial that was double blinded, and sham controlled, and also the only published RTC with sites in the United States.

(2021) Chaudhuri et al. reported 10-year safety and efficacy results for patients enrolled in the AIR, RISA, and AIR2 trials, including 136 (52%) patients who had received bronchial thermoplasty and 56 (33%) sham or control patients. Eighteen patients in the sham/control group received bronchial thermoplasty after participation in the original trials. Median patient follow-up was 12.1 years post-treatment (range, 10.8 to 15.6 years). The primary study effectiveness endpoint was the durability of treatment effect, described as the proportion of participants with severe exacerbations during years 1 and 5 compared to the proportion of patients who experienced severe exacerbations in the 12 months preceding the 10+ year visit. No formal hypothesis testing was planned. Severe exacerbations were defined as a self-reported worsening of symptoms requiring the use of systemic corticosteroids or increased dose of systemic corticosteroids. The primary safety endpoint was the absence of clinically significant respiratory changes, including

bronchiectasis or bronchial, as confirmed by CT imaging. In the year preceding the 10+ year visit, 34/136 (24%, 95% CI, 18.0 to 33.1) patients treated with bronchial thermoplasty experienced severe exacerbations, which were similar to the year 5 (22%, 95% CI, 14.8 to 29.6) and year 1 (24%, 95% CI, 17.5 to 32.6) proportions. The number of severe exacerbations per patient were significantly higher compared to year 5 (p =.044), but not significantly different compared to year 1 (p =.43). In the year preceding the 10+ year visit, severe exacerbations were experienced in 14/38 (37%, 95% CI, 21.8 to 54.0) sham or control patients compared to 12/38 (32%, 95% CI, 17.5 to 48.7) in year 1. There was no change in the rate of severe exacerbations over time in the 24 sham participants from the AIR2 trial who had baseline, 1 year, and 10-year data. Both treated and non-treated groups experienced a reduction in emergency department visits. Six (7%) AIR2 patients treated with bronchial thermoplasty developed new cases of asymptomatic bronchiectasis compared to 0 cases in the sham group at the 10-year visit. Improvements in AQLQ and ACQ scores were sustained in patients treated with bronchial thermoplasty. However, these scores were not reported for sham/control patients. Interpretation of study results is limited by recall bias and low enrollment of sham-treated patients. While bronchial thermoplasty is only recommended for use in patients with severe asthma, 26% of participants did not fulfill these criteria. Additionally, the long-term effects of treatment on clinically significant respiratory changes requires further elucidation.

AIR2 was an RCT evaluating the efficacy of bronchial thermoplasty at 30 sites in 6 countries (including the United States); findings were published in 2010 by Castro et al. Unlike the other 2 RCTs, the control condition was a sham intervention, and the trial was double-blind. Eligibility criteria were similar to those in the AIR trial; key differences were that a higher initial dose of ICSs was required (equivalent to at least 1000 μg beclomethasone), and patients were required to have experienced at least 2 days of asthma symptoms during the 4-week baseline period and have a baseline score on the Asthma Quality of Life Questionnaire (AQLQ) of no more than 6.25. (The possible range of the AQLQ score is 1 to 7, with a higher number representing a better QOL.) Also different from the AIR trial, patients were not required to experience symptom worsening during a period of abstinence from LABAs. Patients were stable on their asthma medication and continued their regimens during the study. The primary outcome was the difference between groups in the change from baseline in the AQLQ score, with scores from the 6-, 9-, and 12-month follow-ups averaged (integrated AQLQ score). A related outcome was the proportion of patients who achieved a change in their AQLQ score of 0.5 or greater, generally considered the minimally important difference for this scale. Bayesian analysis was used. The target posterior probability of superiority (PPS) of bronchial thermoplasty over sham was 95%, except for the primary AQLQ end point; there the target was 96.4% to adjust for 2 interim looks at the data.

A total of 297 patients were randomized, 196 to a bronchial thermoplasty group and 101 to a sham control group. The intervention for all participants consisted of 3 bronchoscopy procedures, performed 3 weeks apart. Participants and outcome assessment was blinded, but the intervention team was unblinded. The sham intervention was identical to the active treatment, except that no radiofrequency energy was delivered. Nine participants

withdrew consent before beginning treatment, and 288 underwent bronchoscopy and were included in the intention-to-treat (ITT) population. One hundred eighty-five participants in the treatment group and 97 in the sham control group underwent the second bronchoscopy, and the same numbers of patients had the third bronchoscopy (it is not clear whether they were exactly the same patients). A total of 278 (94%) of the 297 enrolled patients completed the 12-month visit, 181 in the treatment group and 97 in the sham control group.

The superiority of bronchial thermoplasty was not achieved in the ITT population for the primary effectiveness outcome, mean change in the integrated AQLQ score. Mean (SD) change was 1.35 (1.10) in the bronchial thermoplasty group and 1.16 (1.23) in the sham control group. Using Bayesian analysis, the PPS was 96%. This did not surpass the target PPS of 96.4%. However, superiority of bronchial thermoplasty on a related outcome was achieved. In the ITT population, the percentage of patients achieving an AQLQ score change of 0.5 or greater (i.e., at least the minimally important difference) was 79% in the bronchial thermoplasty group and 64% in the control group. The PPS at 99.6% surpassed the target probability for secondary outcomes of 95%. Additional analysis of data from the active treatment group suggested that responders (defined as a change in AQLQ score of at least 0.5) were more likely to have a lower baseline score than non-responders (mean, 4.1 vs 5.1, respectively).

Several secondary outcomes favored bronchial thermoplasty over the sham control group. They include a reduction in the proportion of patients reporting asthma worsening during follow-up (27.3% vs 42.9%, respectively; PPS=99.7%) and a reduction in the number of emergency department visits (0.07 vs 0.43 visits per person per year, respectively; PPS=99.9%). Moreover, there was a reduction in severe exacerbations of 0.47 per person per year in the bronchial thermoplasty group compared with 0.70 per person per year in the control group (PPS=95.5%). There were no significant differences between groups in other secondary efficacy outcomes, including morning peak expiratory flow, number of symptom-free days, symptom score, and rescue medication use.

For safety outcomes, during the treatment phase, there was a higher rate of respiratory adverse events in the active treatment group (85% of participants; mean, 1.0 events per bronchoscopy) compared with the sham group (76% of participants; mean, 0.7 events per bronchoscopy). A total of 16 (8.4%) patients in the active treatment group required 19 hospitalizations for respiratory symptoms during the treatment phase compared with 2 (2%) patients in the sham group, who required 1 hospitalization each. However, during the posttreatment period, 70% of patients in the bronchial thermoplasty group and 80% of patients in the sham group reported adverse respiratory events. During this phase of the trial, 5 (2.6%) patients in the bronchial thermoplasty group had a total of 6 hospitalizations for respiratory symptoms, and 4 (4.1%) patients in the sham group had 12 hospitalizations (1 patient had 9 hospitalizations).

In the AIR2 trial, the sham group had a relatively high rate of response (eg, 64% experienced a clinically significant increase in the AQLQ score). Blinding appeared to be

initially successful and remained so for the sham group. Participants in both groups were unable to correctly guess their treatment group after the first bronchoscopy. During subsequent assessments, this continued among patients in the sham group, whereas in the bronchial thermoplasty group, a larger proportion guessed correctly.

Two- and 5-year follow-up data on patients in the treatment group of the AIR2 trial have been published. In 2011, Castro et al reported 2-year data on 166 (87%) of 190 patients randomized to the bronchial thermoplasty group. In the second year after treatment, the proportion of participants who experienced severe exacerbations was 23.0% (95% confidence interval [CI], 16.6% to 29.5%). This compares with a 30.9% (95% CI, 24.2% to 37.7%) rate of exacerbations during year 1. The proportion who experienced asthma adverse events were 28.7% (95% CI, 22.1% to 35.3%) in year 1 and 26.5% (95% CI, 19.8 to 33.2) in year 2. In 2013, Wechsler et al reported 5-year data on 162 patients in the AIR2 trial (85% of those randomized to the treatment group).10 In a matched-pair analysis including the 162 study completers and the same group in previous years, the rate of severe exacerbations in years 1, 2, 3, 4, and 5 were 30.9%, 23.5%, 34.0%, 36.4%, and 21.6%, respectively. The proportion of patients experiencing severe exacerbations in years 2, 3, 4, and 5 did not differ significantly from the number of exacerbations in year 1. The proportion of patients who experienced asthma adverse events (at least $\geq$ 2 asthma symptoms occurring at the same time) were 28.7%, 27.9%, 29.6%, 31.4%, and 24.7%, respectively. The proportion of patients with at least 1 hospitalization for respiratory adverse events these same years was 3.3%, 4.2%, 6.2%, 5.7%, and 1.9%, respectively. In the 12 months before bronchial thermoplasty, the rate of hospitalization for respiratory symptoms in this group was 4.2%. These follow-up studies are limited in that follow-up data were not collected on patients randomized to the sham group, and therefore outcomes (eg, rate of exacerbations, rate of hospitalizations) cannot be compared in patients who did and did not receive bronchial thermoplasty.

The results of the AIR-2 trial have generated enormous interest, controversy, and confusion regarding the true efficacy of bronchial thermoplasty for severe asthma. The FDA approved bronchial thermoplasty for the treatment of adults with severe asthma and this approval was based on the results of the AIR-2 trial. Current marketing of bronchial thermoplasty highlights its use for adult patients with severe and persistent asthma, which is interpreted by most clinicians as meaning oral corticosteroid dependence, frequent exacerbations, or a significantly reduced FEV_1 with poor quality of life (QOL). However, these types of patients were specifically excluded from the AIR-2 trial which raises questions about the efficacy of bronchial thermoplasty.

Systematic Reviews

(2021) Perotin and associates completed a review on "Bronchoscopic management of asthma, COPD and emphysema", and stated "International recommendations do not recommend bronchial thermoplasty as routine management of severe asthma. The European Respiratory Society/American Thoracic Society guidelines of severe asthma management do recommend that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent

systematic registry or a clinical study. The 2020 Global Initiative for Asthma guidelines specify that bronchial thermoplasty is a potential treatment option at Step 5 in some countries for adult patients whose asthma remains uncontrolled despite optimization of asthma therapy and referral to a severe asthma specialty center (Evidence B) and should be performed in adults with severe asthma only in the context of an independent Institutional Review Board-approved systematic registry or a clinical study. Both international guidelines base these recommendations on the limited evidence for bronchial thermoplasty efficacy and long-term safety in severe asthma".

(2021) Vijayan and colleagues stated that BT is a therapeutic bronchoscopic procedure in which controlled thermal energy is applied to the airway wall to reduce smooth muscle mass. Immediate complications of BT include acute exacerbation of bronchial asthma, upper and lower respiratory tract infection, hemoptysis, among others. These researchers examined these immediate AEs and the changes in FEV1% measured 4 hours after each procedure from baseline. They also examined the number of activations during each cycle of treatment and its correlation to the corresponding change in FEV1% from baseline. This study was a case-series analysis of 17 patients who underwent BT between 2014 and 2019. Demographic, clinical characteristics, including pre- and post-BT FEV1% measures, and the number of activations were obtained. Acute exacerbation of asthma was the commonest complication accounting for 33 %, 57 %, and 75 % after BT1, BT2, and BT3, respectively. There was deterioration in FEV1% following each treatment phase, the most significant being in BT3. There was no correlation between the number of heat activations with the change in FEV1% from baseline. The authors concluded that the number of activations in BT did not correlate with the immediate deterioration in FEV1%, although exacerbation of asthma was the commonest complication post-BT.

(2020) A clinical evidence assessment by ECRI was completed by searching PubMed, EMBASE, and selected web-based resources for clinical studies published between January 1, 2008, and May 12, 2020, and reporting on BT with the Alair in patients with severe asthma. This assessment identified and reviewed full text of two systematic reviews (SRs) and one nonrandomized comparison study published after the SRs. The SRs overlap with one RCT that was in both SRs.

- 1 SR (12 studies including 3 RCTs; n = 487) compared symptoms, exacerbations, hospitalizations, ED visits, QOL, rescue medications use, and AEs at 1-year follow-up in patients with moderate to severe asthma treated as usual, with or without BT, or a sham procedure. (1) Authors also reported on five-year outcomes after BT. The SR included 3 RCTs (AIR, AIR2, and RISA), 1 nonrandomized comparison study, 2 case series, and 6 case reports.
- 1 SR (Niven et al. 2018) used meta-analysis to make indirect comparisons between Alair and immunotherapy. The review included 3 RCTs (AIR2 Alair study, n = 288; and INNOVATE and EXTRA placebo-controlled RCTS on omalizumab immunotherapy n = 1,267) and reported on severe asthma exacerbations, hospitalizations, ED visits, and QOL up to 1-year follow-up in patients with severe asthma. (2)

- 1 prospective, single-center, nonrandomized study (n = 91) compared symptoms, exacerbations, rescue medication use, and hospital readmissions in patients with severe asthma despite medications who underwent BT with Alair (n = 44) or immunotherapy with mepolizumab (n = 47).

The available evidence is inconclusive because of major limitations to interpretation. The SR comparing bronchial thermoplasty (BT) to immunotherapy provides only indirect evidence because no head-to-head randomized controlled trials (RCTs) are available that make direct comparisons. Also, studies in both SRs are at risk of bias from two or more of the following: small sample size, lack of randomization, lack of blinding, and differences in follow-up times (i.e., 7 to 12 months). Studies reported between-group differences of unclear significance because results were imprecise for some outcomes (e.g., exacerbations, rescue medication use, QOL). Findings may not be generalizable because of differences in patient characteristics across studies (e.g., age, asthma severity, asthma scores, QOL, inhaled corticosteroids use). The nonrandomized comparison study is at high risk of bias from small sample size, single-center focus, and lack of randomization.

Larger, multicenter RCTs that compare BT with the Alair system to sham therapy, immunotherapy, and other devices for asthma control are needed in patients with severe asthma. Additional RCTs reporting longer (e.g., > 5 years) follow-up would also be useful.

No healthcare product alerts were identified. Identified 36 MAUDE reports (35 injuries, 1 malfunction). The 25 most recent injury reports include asthma hospitalizations (6), peribronchiolitis (6), dyspnea (3), lower tract respiratory infection (2), pneumonia (2), and one case each of the following: peripheral capillary oxygen saturation decrease, bronchial aspergillosis, bronchonocardiosis, bronchial pruritus, hemoptysis, and asthma exacerbation. The malfunction report involved a broken device but did not include additional details.

(2018) Nasim et al. completed a review of the literature providing an update review of bronchial thermoplasty (BT) and its role (if any) in the management of severe asthma patients, especially given the availability of multiple new monoclonal antibody (mAb) based therapies with excellent safety and efficacy in specific asthma phenotypes. Bronchial thermoplasty involves the delivery of radiofrequency (RF) energy through bronchoscopy to all visible airways (except the right middle lobe) to selectively ablate airway smooth muscles (ASM).

In the analysis of the trials, to date none of the BT trials have shown a statistically significant improvement in airway hyperresponsiveness or forced expiratory volume-1 (FEV1). An explanation of this might lie in the small airways which are untreated in BT and which are considered to be the source of considerable airflow resistance, mucous production, and inflammation in asthma patients. The small airways are not only difficult to reach by standard inhaled medications but also remain untreated in BT which only

treat large airways visible through bronchoscope. It is also a crucial point that the AIR-2 trial is the only sham-controlled trial of BT ever published. Recent reports have also highlighted adverse outcomes associated with BT. A recent report is alarming because it shows a high incidence of acute postoperative inflammation and pulmonary consolidations, extending far beyond the treated airways. One study reported CT abnormalities extending beyond the BT treated zone with the involvement of the adjacent untreated lung lobe in one-third of cases. Reports of reversible complete lobar collapse, asthma exacerbations, pulmonary abscess, pulmonary pseudoaneurysm, and massive hemoptysis requiring embolization have also been reported. Thus, the long-term implications of this significant BT associated lung injury are uncertain but definitely raise significant concerns about the long-term safety of this procedure.

Asthma is now recognized as a heterogenous disease with varying phenotypes. With the advent of targeted therapies, asthma is becoming an increasingly phenotyped disease with potential for personalized medicine approaches. In recent years, two new anti-interleukin 5 (anti-IL-5) mAb medicines have been approved for the eosinophilic phenotype of asthma. Numerous other targeted therapies for asthma are on the horizon. To date, bronchial thermoplasty has not been compared head-to-head to its biologic pharmacological counterparts approved for treatment of severe asthma. Another shortcoming of the AIR-2 trial is the phenotyping of asthma patients was not performed. Given the excellent safety and efficacy data of the IL-5 inhibitors in eosinophilic asthma, they are the preferred agent for refractory or severe eosinophilic asthma cases in our practice. The role of BT (if any) in the management of other asthma phenotypes is unclear and requires further study.

The authors concluded, bronchial thermoplasty (BT) is the only FDA approved nonpharmacological treatment available for severe asthma patients. The only sham-controlled trial of BT (the AIR-2 trial) failed to achieve its primary endpoint and has left many unanswered questions about the results reported in that trial. As a result, major societies including the American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommend that BT be performed in the context of an IRB approved study protocol. The safety of BT is also in question with recent reports of significant pulmonary parenchymal injury beyond treated airways. BT may be an effective treatment option in selected asthma phenotypes, but further sham-controlled studies are necessary to test those hypotheses. In the meantime, a growing number of targeted therapies with good efficacy are becoming available for specific asthma phenotypes.

(2017) Chupp et al. compared outcomes in bronchial thermoplasty subjects with 3 years of follow-up from the ongoing, post-market PAS2 (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma) study with those from the AIR2 trial. Bronchial thermoplasty is an endoscopic therapy for severe asthma. The previously reported, randomized sham controlled AIR2 (Asthma Intervention Research 2) trial showed a significant reduction in severe asthma exacerbations, emergency department visits, and hospitalizations after bronchial thermoplasty. More “real world” clinical outcome data is needed. 279 subjects were treated with bronchial thermoplasty in

the PAS2 study. The reviewers compared the first 190 PAS2 subjects with the 190 bronchial thermoplasty treated subjects in the AIR2 trial at 3 years follow-up. The PAS2 subjects were older (mean age 45.9 versus 40.7 years) and more obese (mean body mass index 32.5 versus 29.3 kg m2 and took higher doses of corticosteroids (mean dose 2301 versus 1961 ug/day). More PAS2 subjects had experienced severe exacerbations (74% versus 52%) and hospitalizations (15.3% versus 4.2%) in the 12 months prior to bronchial thermoplasty. At year 3 after bronchial thermoplasty, the percentage of PAS2 subjects with severe exacerbations, emergency department visits and hospitalizations significantly decreased by 45%, 55% and 40%, respectively, echoing the AIR2 results. The authors concluded The PAS2 study subjects described in this article appear to be slightly sicker than the subjects in the AIR2 trial based on baseline characteristics. The PAS2 study shows, similar to the AIR2 trial, that bronchial thermoplasty is safe and that subjects have markedly lower rates of steroid exacerbations, hospitalizations and emergency department visits at 3 years after bronchial thermoplasty compared with the 12 months prior to bronchial thermoplasty treatment, and that the treatment effect is consistent and durable. The study subjects also sustainably reduced their asthma medication, including complete discontinuation of maintenance OCSs for a significant number of subjects. Notably the PAS2 study is a prospective nonrandomized clinical study, comparing its results to a randomized controlled trial is challenging due to potential for exogenous bias and confounding factors outside those baseline demographics and clinical characteristics measured. Notwithstanding these caveats, this study offers useful results to clinicians convinced of the efficacy of bronchial thermoplasty within the confines of a randomized controlled trial, but who questioned its "real world" clinical benefits. Although the prospectively enrolled PAS2 study population in this article is described as "real world", the study eligibility criteria mean that the most severe subjects often seen in clinical practice were not included. Nevertheless, the 3-year results from this subset of subjects in the PAS2 study inspire confidence, because they suggest that the "real world" results obtained after bronchial thermoplasty in the PAS2 study echo those observed in the AIR2 randomized controlled trial.

(2017) Agency for Healthcare Research and Quality (AHRQ) issued a comparative effectiveness review on the effectiveness and safety of bronchial thermoplasty in the management of adults with asthma. Data sources included five bibliographic databases, MEDLINE, Embase, PubMed, CINAHL, and Cochrane Library, through April 20, 2017. Eligible studies included systematic reviews, meta-analyses, randomized controlled trials (RCTs), and nonrandomized interventional studies with concurrent controls. Case reports and case series were also considered for describing adverse events. Fifteen studies, including three RCTs with 5-year single arm follow-up in bronchial thermoplasty (BT) treated patients (n=432 for the RCTs), examined the impact of BT in addition to standard care (continued medical management) on patients with asthma. BT and standard of care improved asthma control (defined by the Asthma Control Questionnaire (ACQ) change from baseline to 12 months) and Asthma Quality of Life Questionnaire (AQLQ) scores more than standard care alone to a degree that was statistically significant but not clinically important (low strength of evidence). However, BT and standard care,

compared with a sham bronchoscopic procedure and standard care, did not improve asthma control (defined as ACQ change from baseline to 12 months), hospitalizations for respiratory symptoms, use of rescue medications, pulmonary physiology measures, or AQLQ scores (in the intention to treat analysis), low strength of evidence. In the sham-controlled trial, BT reduced severe exacerbations after the 12-week treatment period to a statistically but not clinically important degree (low strength of evidence), and patients undergoing BT had fewer emergency department visits than patients who had the sham bronchoscopic procedure (moderate strength of evidence). In the RCTs comparing BT and standard care alone, evidence was insufficient to assess if BT reduced rates of severe exacerbations. Common adverse events following BT during the 12-week treatment period in the RCTs included bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing. Hospitalizations were more common in patients undergoing BT than with either standard care alone or sham bronchoscopy during the 12-week treatment period as were upper respiratory tract infections, wheezing, dyspnea, lower respiratory tract infections, anxiety, and segmental atelectasis, but the events were to infrequent to achieve statistical significance. Severe adverse events (including post-procedure segmental atelectasis due to mucus plugging, hemoptysis, chest infections requiring hospitalization, and bronchial artery pseudoaneurysm) were also reported in six case reports and two small case series. Following the 12-week treatment period, rates of respiratory related hospitalizations were not significantly different between groups for up to 5 years of follow-up. No deaths were attributed to BT. The authors concluded while asthma control and quality of life measures modestly improved in patients undergoing BT compared to medical management alone in two controlled but non-blinded studies, these measures did not improve in the sham-controlled study. The sham-controlled, blinded study found modest improvements in severe exacerbations and significantly fewer emergency department visits following BT compared to the sham bronchoscopic procedure, but serious adverse events and post-procedure hospitalization were common during the 12-week treatment period in patients undergoing BT than in patients undergoing sham treatment. The available body of literature on BT is small and uncertainty remains about appropriate patient selection criteria and the effects of the treatment beyond 5 years.

Several pooled analyses of the 3 published RCTs were identified. Most recently, in 2016, Zhou et al published a systematic review of the published RCTs and extension studies, focusing on the durability and long-term responses for treated patients. Reviewers pooled data on long-term effects in bronchial thermoplasty treated patients only (i.e., not in comparison groups). In an analysis of 216 patients with 5 years of follow-up, there was no significant decline in spirometry-detected prebronchodilator FEV1 (percent predicted) compared with 1-year findings (weighted mean difference [WMD], 0.75; 95% CI, -3.36 to 1.85; p=0.57; I2=0%). Similarly, there was no significant decline in postbronchodilator FEV1 (WMD=0.62; 95% CI, -3.32 to 2.08; p=0.65; I2=0%). In terms of adverse events over time, the rates of respiratory adverse events, emergency department visits for adverse events, and hospitalizations did not differ significantly after the 1- and 5-year follow-ups.

(2014) A Cochrane review of RCTs was published by Torrego et. al. reviewers included the 3 RCTs. Potential trial limitations identified by reviewers were lack of blinding in 2 of the 3 trials and lack of a sham control in 2 trials. Pooled analyses were not conducted for asthma exacerbation outcomes. A meta-analysis of the 3 trials found significantly greater improvement in AQLQ scores at 12 months in the bronchial thermoplasty groups than in the control groups (mean difference [MD], 0.28; 95% CI, 0.07 to 0.40). However, at 12 months, the proportion of patients using rescue medication did not differ significantly between groups (MD = -0.68; 95% CI, -3.63 to 2.28). In terms of adverse events, a significantly higher number of patients were admitted to the hospital for respiratory events during the treatment period (relative risk [RR], 3.50; 95% CI, 1.26 to 9.68). There was no significant difference between groups in the proportion of patients admitted to the hospital for respiratory events in the posttreatment period (RR=1.12; 95% CI, 0.44 to 2.85).

(2014) A Blue Cross Blue Shield Association TEC Assessment was published on bronchial thermoplasty for treatment of inadequately controlled severe persistent asthma. The Assessment included the 3 published RCTs (AIR, RISA, AIR2) and concluded, "the evidence is insufficient to determine whether potential improvements in some outcomes, but not others defining the net health outcome, outweigh the potential harms" and that the technology did not meet TEC criteria.

Case Series

After publication of the 3 RCTs (AIR, RISA, AIR2), several case series have described outcomes in clinical practice. They generally had small sample sizes (eg, N=7,14 N=10,15 and N=2016). In addition, a rigorous U.K. registry study was published by Burn et al (2016), which focused on safety outcomes. The study combined data from 2 sources, the U.K. Difficult Asthma Registry and the Hospital Episode Statistics warehouse, and included patients treated with bronchial thermoplasty in the U.K. between June 2011 and January 2015. Eighty-three patients were identified in the Difficult Asthma Registry and 85 in the Hospital Episode Statistics database. For 59 patients, data in the 2 databases could be matched. Most patients had a course of 3 bronchial thermoplasty treatment sessions. Data from the matched cohort were used to calculate event rates for 4 binary safety outcomes. Procedural complications were reported in 17 (11%) of 152 procedures in 13 (22%) patients; emergency department readmissions within 30 days of the initial hospitalization were reported for 15 (11.8%) patients; and accident and emergency visits (i.e., emergency department) visits for any reason were reported for 13 (8.6%) patients. For the fourth binary outcome (post-procedure overnight stay), 70 (46.1%) of 152 procedures were followed by an overnight stay. In total, 20.4% of procedures in the matched cohort were associated with at least 1 of the 4 safety issues. The authors noted that the relatively high rate of safety events might be related to older patients with more severe disease being treated in clinical practice compared with patients included in clinical trials.

Registries
Report from the U.K. Severe Registry (UKSAR). All U.K. Centers performing bronchial thermoplasty provide data to the registry.

(2019) Burn et al. completed prospective, longitudinal, cohort, multicenter registry study and the main aim of this study was to assess the long-term efficacy for bronchial thermoplasty (BT) in UK clinical practice. Secondary aims were to use experience from clinical practice to identify the characteristics of those patients most likely to benefit from BT, and to update safety evidence reported previously. It used data collected in UKSAR and was one of the largest 'real-world' observational studies of BT to date, with all UK centers performing BT contributing data. Eligible patients were those selected to receive BT in the UK between 01/06/2011 and 03/09/2016 with data in UKSAR (n=133). Efficacy data were available for 86 patients with a BT baseline and at least one follow-up record. Safety data were available for 131 patients with at least one BT procedure record. The efficacy outcomes considered were AQLQ, ACQ, EQ-5D-3L (descriptive index), HADS anxiety and HADS depression scores, FEV_1 (% predicted), rescue steroid courses, unscheduled healthcare visits (A&E/Asthma clinic/GP), hospital admissions and days lost from work/school. Safety outcomes included peri-procedural events, device problems and any other safety-related findings. Responder analysis: differences in baseline characteristics of responders ($\geq$0.5 increase in AQLQ at 12 months) and non-responders. Following Bonferroni correction for paired comparisons, mean improvement in AQLQ at 12 months follow-up compared with BT baseline was statistically and clinically significant (0.75, n=28, p=0.0003). Median reduction in hospital admissions/year after 24 months follow-up was also significant (−1.0, n=26, p<0.0001). No deterioration in FEV_1 was observed. From 28 patients with AQLQ data at BTBL and 12-month follow-up, there was some evidence that lower age may predict AQLQ improvement. 18.9% (70/370) of procedures and 44.5% (57/128) of patients were affected by an adverse event; only a minority were considered serious. The authors concluded the mean improvement in AQLQ at 12 months compared with BTBL is consistent with similar findings from clinical trials. No deterioration in FEV_1 (% predicted) was observed following BT and there was a significant reduction in hospital admissions at 24-month follow-up. However, improvements were not seen in all patients and an exploration of the characteristics of responders to BT could only identify age as a possible predictor of outcome. Current and future studies looking into factors which determine those who respond well to BT will be crucial to informing patient selection. Continued data collection would also help to understand whether the improvement in AQLQ observed for some patients is maintained over a longer period. Of the adverse events recorded, only a minority were considered significant by the treating clinician. It appears that BT is being carried out safely in the UK; however, long-term safety should continue to be monitored and the decision to select a patient for BT should continue to lie with a multidisciplinary team who can assess their history and suitability for the procedure.

Summary of Evidence
For individuals who have asthma refractory to standard treatment who receive bronchial thermoplasty (BT), the evidence includes 3 randomized controlled trials (RTCs). The

Asthma Intervention Research (AIR) trial was a randomized controlled trial (RCT) published in 2007. It was neither blinded nor sham controlled. Individuals were randomized 1:1 to either BT or the control arm. The AIR trial demonstrated feasibility and safety of BT in human individuals. The Research in Severe Asthma (RISA) trial was also published in 2007. This was a much smaller study of only 15 patients in the BT arm and 17 in control arm. This was also an open, 1:1 randomized control trial with no sham component. The 3rd trial (AIR-2) published in 2010 was the pivotal trial and the primary evidence base for the FDA approval of BT. The AIR-2 trial was a multicenter (multinational) double-blind, sham-controlled, randomized clinical trial (RCT). Participants with severe asthma were randomized on a 2:1 basis to receive either BT or sham thermoplasty.

Patients enrolled in AIR-2 were aged 18–65 years and needed to be on stable doses of inhaled corticosteroids (>1,000 mg/d of beclomethasone or equivalent and >100 mg/d of salmeterol or equivalent) for at least 4 weeks. The AIR-2 trial did not achieve its primary endpoint or achieve any meaningful secondary endpoint. What about the supposed reduction in asthma exacerbations, emergency room (ER) visits, hospitalizations, and days lost from work in the BT arm of the AIR-2 trial? These analyses were done *post hoc* and were not part of the declared primary or secondary endpoints of the AIR-2 trial. Another very important fact to also point out is that AIR-2 trial specifically excluded patients with frequent asthma exacerbations. Patients needing >10 mg of prednisone per day; having a history of three or more hospitalizations/lower respiratory tract infections or reporting four or more oral corticosteroids courses within the past year were excluded from the trial. Thus, the AIR-2 trial specifically excluded "frequent exacerbators" who are the very group of patients for whom BT is often considered in clinical practice. In addition, in the long-term follow-up trials after BT published so far, there has been no follow-up published on the sham arm at all. The long-term safety or efficacy of BT cannot be determined when there is no long-term information available about the sham (control) arm of the AIR-2 trial.

Furthermore, given that BT reduces airway smooth muscle (ASM) mass by radiofrequency ablation (RF) ablation; one would expect to see decreased bronchial hyper-responsiveness and/or improvement in airway obstruction. However, none of the BT trials to date have shown a statistically significant improvement in airway hyperresponsiveness or forced expiratory volume-1 (FEV1). An explanation for this might lie in the small airways which are untreated in BT and are considered to be the source of considerable airflow resistance, mucous production, and inflammation in asthma patients. The small airways are not only difficult to reach by standard inhaled medications but also remain untreated in BT which only treat large airways visible through the bronchoscope.

Recent reports have also highlighted adverse outcomes associated with BT. A recent report is alarming because it shows a high incidence of acute postoperative inflammation and pulmonary consolidations, extending far beyond the treated airways. One study reported computed tomography abnormalities extending beyond the BT-treated zones

with involvement of the adjacent untreated lung lobe in one-third of cases. Reports of reversible complete lobar collapse, asthma exacerbations, pulmonary abscess, pulmonary pseudoaneurysm, and massive hemoptysis requiring embolization have also been reported. Thus, the long-term implications of this significant BT associated lung injury are uncertain but definitely raise significant concerns about the long-term safety of this procedure.

Asthma is now recognized as a heterogeneous disease with varying phenotypes. With the advent of targeted therapies, asthma is becoming an increasingly phenotyped disease with potential for personalized medicine approaches. Omalizumab was the first anti-immunoglobulin E to be approved for the treatment of asthma. An indirect comparison of the BT posttreatment period to ongoing treatment with Omalizumab showed no significant differences in the risk for severe exacerbations. In recent years, two new anti-interleukin 5 (anti-IL-5) mAb medicines have been approved for the eosinophilic phenotype of asthma. Numerous other targeted therapies for asthma are on the horizon. To date, BT has not been compared head-to-head to its biologic pharmacological counterparts approved for treatment of severe asthma. Another shortcoming of the AIR-2 trial is that phenotyping of asthma patients was not performed. Given the excellent safety and efficacy data of the IL-5 inhibitors in eosinophilic asthma, they are the preferred agent for refractory or severe eosinophilic asthma cases in our practice. The role of BT (if any) in the management of other asthma phenotypes is unclear and requires further study.

BT is the only FDA approved nonpharmacological treatment available for severe asthma patients. The only sham-controlled trial of BT (the AIR-2 trial) failed to achieve its primary endpoint and has left many unanswered questions about the results reported in that trial. As a result, major societies including the American Thoracic Society (ATS) and the European Respiratory Society (ERS) joint Task Force recommends that BT in asthma be performed in the context of an IRB approved study protocol. In a clinical evidence assessment in 2020 by ECRI the available evidence is inconclusive due to too few data. The safety of BT is also in question with reports of significant pulmonary parenchymal injury beyond treated airways. While BT may show promise in the treatment of adult patients with severe asthma with asthma control and quality of life (QOL) measures compared to medical management alone, further research is needed as uncertainty remains about appropriate patient selection criteria and the effects of the treatment beyond 5 years. Larger, multicenter RCTs that compare BT with the Alair system to sham therapy, immunotherapy and other devices for asthma control are needed in patients with severe asthma. Also, additional RCTs reporting longer (e.g., > 5 years) follow-up would also be useful as the long-term effects of bronchial thermoplasty beyond five years following treatment are not known. In the meantime, a growing number of targeted therapies with good efficacy are becoming available for specific asthma phenotypes. The evidence is insufficient to determine the effects of bronchial thermoplasty on net health outcomes.

Practice Guidelines and Position Statements

American College of Allergy, Asthma and Immunology (ACAAI)

(2015) In a statement on bronchial thermoplasty the ACAAI notes: "Bronchial thermoplasty is a well-studied treatment for patients with very severe asthma who continue to be symptomatic despite maximal medical treatment including steroids, long-acting beta agonists (LABAs), long-acting muscarinic agents (LAMAs), leukotriene antagonists and biologics. The device to deliver this therapy is FDA approved. The scientific literature supports bronchial thermoplasty as a therapeutic consideration for some carefully chosen patients with severe asthma. Carefully selected patients with severe persistent asthma who have persistent burden of disease, asthma exacerbations, emergency department visits or hospitalizations despite maximal medical treatment may benefit from this procedure. Therefore, ACAAI recommends that insurers provide coverage for bronchial thermoplasty for those adult patients who meet the stringent requirements." (*Accessed February 2022*)

American College of Chest Physicians (ACCP)

(May 2014) The ACCP posted a position statement on Coverage and Payment for Bronchial Thermoplasty for Severe Persistent Asthma. The document states in part,

- "CHEST believes that based on the strength of the clinical evidence, bronchial thermoplasty offers and important treatment option for adult patients with severe asthma who continue to be symptomatic despite maximal medical treatment and, therefore should not be considered experimental. Randomized controlled trails of bronchial thermoplasty for severe asthma have shown a reduction in the rate of severe exacerbations, emergency department visits, and days lost from school or work. Additionally, data published in December 2013 demonstrates the persistence of reduction in asthma symptoms achieved by bronchial thermoplasty for at least 5 years…" (*Accessed February 2022*)

British Thoracic Society and Scottish Intercollegiate Guidelines Network

(2019) The British Thoracic Society and the Scottish Intercollegiate Guidelines Network updated the national guideline on management of asthma. The guideline states:

- The aim of bronchial thermoplasty is to reduce bronchial smooth muscle mass, thus reducing the capacity for bronchoconstriction. Currently only a few UK centres offer this treatment which has considerable cost and resource implications. A systematic review of three RCTs (n=429) looking at the use of bronchial thermoplasty for moderate or severe persistent asthma in adults (aged 18 and over) showed a significantly lower rate of severe asthma exacerbations at 12 months in those treated with bronchial thermoplasty in one trial that included a sham intervention in the control group. A second trial, with no sham intervention in the control group, showed a decrease in severe exacerbations in both the intervention and control groups. There were no significant differences in asthma control, lung function, changes in doses of regular medication or use of rescue medication between the intervention and control groups. A small, but statistically significant improvement in quality-of-life scores (measured using AQLQ) with

bronchial thermoplasty compared with control groups was seen only in the two studies without a sham intervention. In the study with a sham intervention, QoL scores improved in both groups.

Bronchial thermoplasty is an invasive procedure and is associated with an increased rate of adverse respiratory events in the short term. Significantly more patients receiving bronchial thermoplasty than controls were admitted to hospital because of respiratory adverse events within the first 12 weeks following treatment (8 per 100 *v* 2 per 100; risk ratio (RR) 3.5, 95% CI 1.26 to 9.68). By 12 months following treatment, there was no difference between groups.

A systematic review looking at the long-term efficacy and safety of bronchial thermoplasty, including the same three RCTs, reported a significant reduction in respiratory adverse events in patients after five years compared to one year following treatment, although these results were not compared to a control group who had not received bronchial thermoplasty. There was no difference in the number of ED visits or hospitalizations for respiratory adverse events between one and five years of follow up in those treated with bronchial thermoplasty. The longer-term effects of bronchial thermoplasty, beyond five years following treatment, are not known.

Further research is needed to identify which patients with asthma might benefit from bronchial thermoplasty. However, it is likely that patients who remain uncontrolled despite optimal medical treatment and who have been considered for biological treatments and are either unsuitable for or fail a trial of such a treatment may be an appropriate group, as other treatment options for these patients are elusive. There are no trials comparing the efficacy of bronchial thermoplasty with biological treatments for people with asthma.

Bronchial thermoplasty may be considered for the treatment of adult patients (aged 18 and over) with severe asthma who have poorly controlled asthma despite optimal medical therapy.

- Patients being considered for bronchial thermoplasty should be assessed to confirm the diagnosis of asthma, that uncontrolled asthma is the cause of their ongoing symptoms, and that they are adherent with current treatment.
- An asthma specialist with expertise in bronchial thermoplasty should assess patients prior to undergoing treatment, and treatment should take place in a specialist center with the appropriate resources and training, including access to an intensive care unit.
- Patients undergoing bronchial thermoplasty should have their details entered onto the UK Severe Asthma Registry.

Recommendations for Research

- Which patients with asthma might benefit most from bronchial thermoplasty and what are the long-term outcomes and safety of this treatment?

- What is the place of bronchial thermoplasty in the management of severe asthma compared with other options such as biological treatments?
- What is the relative clinical effectiveness and safety of bronchial thermoplasty compared with monoclonal antibody treatments?

(*Accessed February 2022)*

European Respiratory Society (ERS) and American Thoracic Society (ATS):
(2014) We recommend that bronchial thermoplasty (BT) is performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent systematic registry of a clinical study." The authors remarked: "This is a strong recommendation, because of the very low confidence in the available estimates of effects of BT in patients with severe asthma."

- "Both potential benefits and harms may be large and the long-term consequences of this new approach to asthma therapy utilizing an invasive physical intervention are unknown."
- "Specifically designed studies are needed to define its effects on relevant objective primary outcomes such as exacerbation rates, and on long term effects on lung function."
- "Studies are also needed to better understand the phenotypes or responding patients, its effects on patients with severe obstruction asthma (FEV_1 <60% of predicted value) or in whom systemic corticosteroids are used, and its long-term benefits and safety."
- "Further research is likely to have an important impact on this recommendation."

(*Accessed February 2022*)

Global Initiative for Asthma (GINA)

(2021) GINA is an international network of organizations and professional with expertise in asthma. The group has been updating a report entitled Global Strategy for Asthma Management and Prevention annually since 2002, the most recent update was issued in 2021. GINA recommends the following stepped care for the preferred treatment of asthma.

- Step 1 includes low dose combination ICS-formoterol taken as-needed for relief of symptoms
- Step 2 includes low dose ICS-formoterol, taken as-needed for relief for symptoms and, if needed before exercise.
- Step 3 includes low dose ICS-formoterol maintenance and reliever therapy
- Step 4 includes medium dose ICS-formoterol maintenance and reliever
- Step 5 refer for expert assessment, phenotyping and add-on therapy

According to the GINA document, options for add-on treatment include bronchial thermoplasty for some adults with severe asthma (Evidence B), evidence is limited and in selected patients. The long-term effects compared with control patients including for lung function, are not known. The document also notes the following:

- Bronchial Thermoplasty is a potential treatment option at Step 5 in some countries for adult patients whose asthma remains uncontrolled despite

optimized therapeutic regimens and referral to an asthma specialty center (Evidence B). Bronchial Thermoplasty involves treatment of the airways during three separate bronchoscopies with a localized radiofrequency pulse. The treatment is associated with a large placebo effect. In patients taking high dose ICS-LABA, bronchial thermoplasty was associated with an increase in asthma exacerbations during the 3-month treatment period, and a subsequent decrease in exacerbations, but no beneficial effect on lung function or asthma symptoms compared with sham-controlled patients. Extended follow up of some treated patients reported a sustained reduction in exacerbations compared with pre-treatment. However, longer-term follow up of larger cohorts comparing effectiveness and safety, including for lung function, in both active and sham treated patients is needed.

Advice

- For adult patients whose asthma remains uncontrolled despite optimization of asthma therapy and referral to a severe asthma specialty center, bronchial thermoplasty is a potential treatment option at Step 5 in some countries (Evidence B).
- Caution should be used in selection patients for this procedure. The number of studies is small, people with chronic sinus disease, frequent chest infections or FEV1 <60% predicted were excluded from the pivotal sham-controlled study, and patients did not have their asthma treatment optimized before bronchial thermoplasty was performed.
- Bronchial thermoplasty should be performed in adults with severe asthma only in the context of an independent Institutional Review Board – approved systematic registry or a clinical study, so that further evidence about effectiveness and safety of the procedure can be accumulated.

6A. If There is no Evidence of Type 2 Inflammation

If the patient has no evidence of persistent Type 2 inflammation

- Consider bronchial thermoplasty with registry enrollment. However, the evidence for efficacy and long- term safety is limited.

(*Accessed February 2022*)

National Asthma Education and Prevention Program

(2020) The National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Expert Panel Working Group published focused updates to the National Heart, Lung, and Blood Institute's guidelines for the diagnosis and management of asthma. This update was based on prior systematic reviews of the evidence published by the Agency for Healthcare Research and Quality.

The following conditional recommendation based on low certainty evidence on the use of bronchial thermoplasty was issued:

- "In individuals ages 18 years and older with persistent asthma, the Expert Panel conditionally recommends against bronchial thermoplasty.

- Individuals ages 18 years and older with persistent asthma who place a low value on harms (short-term worsening symptoms and unknown long term side effects) and a high value on potential benefits (improvement in quality of life, a small reduction in exacerbations) might consider bronchial thermoplasty."

For patients who opt to choose this intervention via shared decision-making, the panel recommends that clinicians offer the procedure in the setting of a clinical trial or registry study to facilitate the collection of long-term outcomes. (*Accessed February 2022*)

National Institute of Health and Clinical Excellence (NICE)
(2018) The National Institute of Health and Clinical Excellence (NICE) issued an updated interventional procedure guidance regarding bronchial thermoplasty for the treatment of severe asthma. The recommendation states the following:

- "The current evidence on the safety and efficacy of bronchial thermoplasty for severe asthma is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit. The procedure should only be done by a multidisciplinary team in specialist centers with on-site access to intensive care. It should be done by clinicians with training in the procedure and experience in managing severe asthma. Further research should report details of patient selection and long-term safety and efficacy outcomes.

(*Accessed February 2022*)

Regulatory Status
In April 2010, the Alair® Bronchial Thermoplasty System (Asthmatx, Inc. Sunnyvale, CA, now part of Boston Scientific Corp.) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval (PMA) process for the use in adults with severe and persistent asthma whose symptoms are not adequately controlled with inhaled corticosteroids and long-acting beta agonists. The labeling also lists the following contraindications:

Patients with the following conditions should not be treated:

- Presence of a pacemaker, internal defibrillator, or other implantable electronic devices
- Known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines
- Patients previously treated with the Alair System should not be retreated in the same area(s). No clinical data are available studying the safety and/or effectiveness of repeat treatments.

Patients should not be treated while the following conditions are present:

- Active respiratory infection
- Asthma exacerbation or changing dose of systemic corticosteroids for asthma (up or down) in the past 14 days
- Known coagulopathy

- As with other bronchoscopic procedures, patients should stop taking anticoagulants, antiplatelet agents, aspirin and NSAIDS before the procedure with physician guidance.

PRIOR APPROVAL

Not applicable.

POLICY

Bronchial thermoplasty is considered **investigational** for all indications, including but not limited to the treatment of asthma.

Although the U.S. Food and Drug Administration (FDA) has approved the bronchial thermoplasty system, there is insufficient and low-quality evidence regarding the use of bronchial thermoplasty in patients with severe asthma who are resistant to standard therapies. The only sham-controlled trial of bronchial thermoplasty (the AIR-2 trial) failed to achieve its primary endpoint and has left many unanswered questions about the results reported in that trial. As a result, major societies including the American Thoracic Society (ATS) and the European Respiratory Society (ERS) joint Task Force recommend that bronchial thermoplasty be performed in the context of an institutional review board (IRB) approved study protocol. In a clinical evidence assessment in 2020 by ECRI the available evidence is inconclusive due to too few data. The safety of bronchial thermoplasty is also in question with reports of significant pulmonary parenchymal injury beyond treated airways. While bronchial therapy may show promise in the treatment of adult patients with severe asthma with asthma control and quality of life (QOL) measures compared to medical management alone, further research is needed as uncertainty remains about appropriate patient selection criteria and the effects of the treatment beyond 5 years. Larger, multicenter randomized controlled trials that compare bronchial thermoplasty with the Alair system to sham therapy, immunotherapy and other devices for asthma control are needed in patients with severe asthma. Also, additional randomized controlled trials reporting longer (e.g., > 5 years) follow-up would also be useful as the long-term effects of bronchial thermoplasty beyond five years following treatment are not known. In the meantime, a growing number of targeted therapies with good efficacy are becoming available for specific asthma phenotypes. The evidence is insufficient to determine the effects of bronchial thermoplasty on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 31660 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed: with bronchial thermoplasty, 1 lobe
- 31661 Bronchoscopy, rigid or flexible, including fluoroscopic guidance when performed; with bronchial thermoplasty, 2 or more lobes

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POLICY HISTORY

Date	Reason	Action
February 2022	Annual Review	Policy Renewed
February 2021	Annual Review	Policy Revised
February 2020	Annual Review	Policy Revised
February 2019	Annual Review	Policy Renewed
May 2018	Interim Review	Policy Revised
February 2018	Annual Review	Policy Revised
November 2017	Interim Review	Policy Revised
February 2017	Annual Review	Policy Renewed
February 2016	Annual Review	Policy Revised
March 2015	Annual Review	Policy Renewed
April 2014	Annual Review	Policy Renewed
May 2013	Annual Review	Policy Renewed
May 2012	Annual Review	Policy Renewed
July 2011	Evidence Review	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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