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INVITED REVIEW

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Bronchial thermoplasty: State of the art

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Abstract

Since the publication of a sham-controlled, randomized trial (AIR2) and subsequent marketing approval by the US Food and Drug Administration, we have significantly advanced our understanding of bronchial thermoplasty (BT)'s scientific basis, long-term safety, clinical efficacy and cost-effectiveness. In particular, the last 2 years have witnessed multiple research publications on several of these counts. In this review, we critically appraise our evolving understanding of BT's biologic underpinnings and clinical impact, offer an evidence-based patient workflow guide for the busy pulmonologist and highlight both current challenges as well as potential solutions for the researcher and the clinician.

KEYWORDS

bronchial thermoplasty, cost-effectiveness, efficacy, mechanism of action, safety, severe asthma

INTRODUCTION

It is estimated that worldwide, asthma affects over 250 million people and is responsible for over 20 million disability-adjusted life years.[1] In the United States, asthma affects 25 million people, 5%–10% of whom suffer from severe persistent symptoms and contribute to the majority of healthcare utilization associated with the disease; exacerbations requiring emergency management incur three to four times higher cost among patients with poorly controlled asthma.[2–4] In addition to social and behavioural interventions, various pharmacological therapies are currently available to help manage this disease, including biological therapies for patients with elevated markers of type 2 inflammation.[5] However, a significant portion of asthmatics continue to experience uncontrolled symptoms despite maximal pharmacological treatment, with poor inhaler technique (even among adults), poor affordability of asthma medications and refractory asthma (even in the face of multiple inhalers and biologic therapies) being surprisingly common.[6–10] Bronchial thermoplasty (BT) is a non-pharmacological treatment option for patients with severe refractory asthma. While initially considered a novel procedure with uncertain mechanism of action, high rate of postprocedural asthma exacerbation and questionable long-term benefit, the last few years have witnessed important research investigating the long-term efficacy and safety profile of BT. This state-of-the-art review provides a succinct overview of BT, including our understanding of its scientific basis and the most current data on its safety, efficacy and cost-effectiveness.

BT PROCEDURE AND ITS MECHANISM OF ACTION

BT is performed by direct application of radiofrequency (RF) energy to the mucosa of larger, endoscopically accessible airways distal to the mainstem bronchi (generally 3–10 mm in diameter). BT involves use of standard flexible bronchoscopy equipment and usual procedural sedation (i.e., either moderate sedation or general anaesthesia as per institutional preference).[11] The Alair™ Bronchial Thermoplasty System (Boston Scientific, Natick, MA, USA) consists of a flexible catheter with an expandable electrode array. This catheter is passed through the flexible bronchoscope's working channel and the electrode array, when expanded, is utilized for the delivery of RF energy via physical contact with airway walls (Figure 1).[12]

Each BT session comprises of a series of treatments (termed 'activations') targeting overlapping portions of each airway, beginning distally and moving proximally.[13] Three treatment sessions are scheduled roughly 3 weeks apart, each treating one out of the right lower lobe, left lower lobe and both upper lobes.[14] The right middle lobe (RML) was left untreated in clinical trials due to theoretical risk of obstruction and RML syndrome, but recent data have

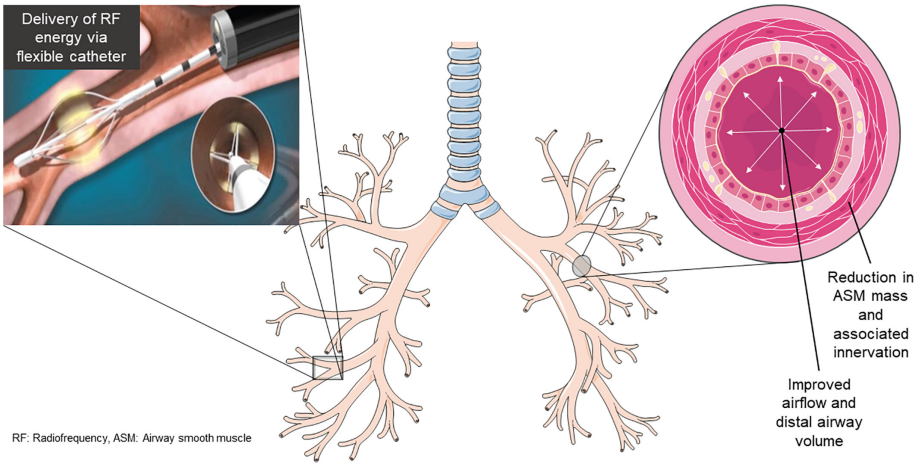

FIGURE 1 Bronchial thermoplasty: currently understood mechanisms of action involving ASM, associated innervation and distal airway volume. Reproduced with permission of the ©ERS 2022. European Respiratory Review 23 (134) 510–518; https://doi.org/10.1183/09059180.00005114 Published 1 December 2014. ASM, airway smooth muscle; RF, radiofrequency

suggested that it may be safe to treat it without clearly impacting either overall safety or overall efficacy.[15,16]

Structural changes in the airway wall

The mechanism of action by which BT exerts its effects appears to be complex and multipronged. Multiple studies have demonstrated significant reduction in airway smooth muscle (ASM) mass following BT.[17–19] BT has also been shown to decrease type 1 collagen deposition underneath the basement membrane.[20] However, the association of ASM mass reduction with clinical response as measured by improvement in Asthma Control Questionnaire (ACQ) scores is not well established.[17] Recent studies involving ex vivo human lung specimens have utilized computer-based simulation to demonstrate improvement in airflow through distal small airways brought about by a 75% reduction in larger airway ASM following BT.[21] Therefore, conceivably, the downstream effects of ASM reduction may better correlate with clinical outcomes than an absolute reduction in ASM mass.

Airway innervation, neuroendocrine apparatus and cytokine equilibrium

The parasympathetic nervous system plays an important role in controlling airway tone with stimulation of cholinergic nerves causing bronchoconstriction, bronchial vasodilation and mucus secretion.[22] One study involving 15 patients with severe asthma found significantly fewer autonomic nerve fibres in both bronchial submucosa and ASM bundles 3 months after BT.[18] Notably, this finding was significantly associated with a decrease in the number of severe exacerbations, suggesting that disruption of autonomic innervation post-BT may downregulate airway excitability and bring about clinical benefits. The same study demonstrated a 95% reduction in neuroendocrine epithelial cells at the 3-month mark post-BT, a finding that was also reported to corelate with an improved asthma control among those patients. Neuroendocrine cells were also decreased in the untreated middle lobe where the ASM area was unchanged—a finding that may offer further insights into the clinical significance of ASM reduction (or lack thereof). Other data, obtained via endobronchial biopsies and bronchoalveolar lavage from patients with severe asthma, point to modulation of key inflammatory cytokines such as transforming growth factor-beta following BT.[23]

Airway volumes and ventilation

In one study involving subjects with severe asthma, distal airway volumes measured using HRCT imaging at functional residual capacity (FRC) and total lung capacity (TLC) were noted to be significantly increased following BT, as early as at 1 month. These effects were sustained at 12 months. This increase in distal airway volume corelated well with a significant improvement in symptoms as assessed by the ACQ score.[24] Other studies involving adults with severe asthma have also demonstrated a significant improvement in ACQ scores post-BT, which have corelated with an increase in FRC and TLC coupled with decreased residual volume and airway resistance, with the greatest benefit observed in patients with more severe baseline obstructive lung disease.[25,26]

Hyperpolarized 129Xe MRI, which utilizes a gaseous contrast agent (Xenon-129) to provide direct visualization of lung airspaces in an MR image, has been used to quantify regional lung ventilation defects. This correlates well with spirometry, disease severity and risk of exacerbations in asthma.[27,28] Recent studies utilizing hyperpolarized MRI have demonstrated a decrease in the ventilation defect percentage and an increase in well-ventilated lung following BT—a finding that positively corelated with improved Asthma Control Test (ACT) scores. One randomized trial involving 30 subjects, published in 2020, demonstrated

equivalent clinical efficacy at 1 year and a greater than 50% reduction in short-term adverse events when limiting treatment to a single BT session targeting the six most involved airways (identified by hyperpolarized MRI as contributing most to ventilation defects) compared with the standard three-session BT therapy.[29]

Novel insights using optical coherence tomography

Optical coherence tomography, a non-ionizing and high-resolution imaging technique utilizing near-infrared light, has been used to assess airway wall changes following treatment with BT. Previous studies have demonstrated several changes immediately following BT including bronchial wall and peribronchial oedema as well as epithelial sloughing.[30–32] Some of these changes were noted in airways distal to the ones directly treated as well as in the untreated RML, again suggesting that the effects of BT are not limited to directly targeted airways.

Altogether, it appears that the clinical effect of BT may emanate from an improvement in small airways dysfunction—a multipronged process that is crucial to the pathophysiology of asthma.[33]

Relationship with the underlying endotype/phenotype

In a recent study published in 2021, endobronchial biopsies performed on 30 adults with severe asthma showed that BT's histologic effects varied considerably with the underlying endotype or phenotype.[34] Reduction in ASM was the most prominent among patients with type 2 high-inflammation (T2-high), and epithelial cell proliferation was the most pronounced in patients with non-allergic, non-eosinophilic and non-smoking related asthma, whereas expression of heat shock proteins appeared to vary with tobacco exposure. All patients demonstrated increased expression of epithelial cell glucocorticoid receptors. Notably, despite the seemingly different mechanisms of action of BT across different asthma endotypes/phenotypes, all subgroups in the study demonstrated similar degrees of clinical improvement as evidenced by mean change in ACT score (at 3 months post-BT) of >3 ($p < 0.001$). Other studies have demonstrated that certain biologic, genetic or clinical features may portend better clinical response to BT, including higher baseline serum eosinophil counts, higher serum IgE levels, higher mucosal eosinophil and IL-33-positive cell counts, atopic asthma, young age and more severe disease.[17,35–40]

MAJOR CLINICAL STUDIES

Major clinical studies are listed in Table 1.

AIR (published in 2007)

The AIR (Asthma Intervention Research) study was a clinical trial of 112 patients with moderate to severe asthma who were randomized to either BT or usual care.[41] At 1 year, exacerbations and improved ACQ and Asthma Quality of Life Questionnaire (AQLQ) scores were reported in the BT arm. Although there were no deaths, the BT arm had more early adverse events, mostly comprising a transient worsening of asthma symptoms soon after undergoing BT. A major limitation of this study was the lack of a sham control, making placebo effect a distinct possibility.

RISA (published in 2007)

RISA (Research in Severe Asthma) was a clinical trial of 32 adult patients with severe persistent asthma that was similar in design to the AIR study but involved patients with greater disease severity.[35] Once again, there was an uptick in asthma exacerbations during the 'treatment phase' (i.e., the first 6 weeks post-BT), although the rate of adverse events was similar between treatment and control groups during the ensuing 46 weeks. Treated patients reported several benefits post-BT including decreased use of short-acting beta-agonist inhalers and improvement in AQLQ and ACQ scores. Although the reported efficacy of BT was put in question by the absence of a sham control and a lack of blinding, this study did unequivocally demonstrate that BT could be performed in patients suffering from severe asthma with an acceptable safety profile.

AIR2 (published in 2010)

The AIR2 study was designed to address the potential for placebo effect in the preceding clinical trials.[5,36] This was a multicentre, double-blinded, sham-controlled trial including 288 adult patients with severe persistent asthma. Patients randomized to the control arm underwent bronchoscopy with deployment of the Alair catheter in the airways, but without the delivery of RF energy. While both arms trended towards improvement in AQLQ scores and the treatment group's scores were only modestly better (bringing into question the utility of AQLQ in the presence of a sham control), patients undergoing BT had much fewer severe exacerbations (32%), emergency department (ED) visits (84%) and days lost from work/school during the post-treatment period (weeks 7–52 following BT). As shown in previous studies, however, this study also showed a transient worsening of asthma symptoms during the 'treatment period' (i.e., first 6 weeks following BT).

While the AIR2 study unequivocally demonstrated impressive efficacy during the post-treatment period and avoided the placebo effect through use of double-blinding

TABLE 1 Summary of landmark trials

Trial, publication year, subjects included (*N*)	Design	Study groups	Duration followed	Subject characteristics	Asthma severity and baseline controller medications	Primary outcome	Results
AIR, 2007 $N = 112$	Multicentre, randomized trial	Usual medical management compared with BT	6–9-week treatment period, followed by 12-month follow-up with LABA withdrawn for 2-week periods at 3, 6 and 9 months	Age: 18–65, FEV1: 60%–85% predicted	Moderate to severe asthma (requiring ICS ≥ 200 μg/day beclomethasone equivalent and LABA ≥ 100 μg/day salmeterol equivalent)	Rate of mild exacerbation during periods of LABA abstinence compared with baseline	Reduced mean rate of mild exacerbations in the BT group
RISA, 2007 $N = 32$	Multicentre, randomized trial	Usual medical management compared with BT	6-week treatment period, followed by 46-week post-treatment period during which ICS and OCS dose weaned and stabilized as possible	Age: 18–65, FEV1 ≥ 50% predicted	Severe persistent asthma (requiring ICS > 750 μg/day fluticasone or equivalent and LABA ≥ 100 μg/day salmeterol or equivalent with or without oral prednisone ≤ 30 mg/day, LT modifiers or theophylline)	Difference in the rate of adverse events (pulmonary and non-pulmonary) between BT and comparator group	No difference in the rate of adverse events between BT and usual management group in post-treatment period
AIR2, 2010 $N = 288$	Multicentre, double-blind, randomized trial	Sham procedure group compared with BT	6-week treatment period followed by 46-week post-treatment period, assessed at 3, 6, 9 and 12 months	Age: 18–65, FEV1 ≥ 60% predicted	Severe asthma (requiring ICS > 1000 μg/day beclomethasone or equivalent and LABA > 100 μg/day salmeterol or equivalent). LT modifiers, omalizumab and OCS 10 mg/day or less allowed	Difference in AQLQ scores from baseline to average of 6, 9 and 12 months and proportion of groups with AQLQ score change of ≥0.5	Significantly greater change in average AQLQ score from baseline in BT arm; significantly higher proportion of subjects achieved AQLQ score change of ≥0.5 in the BT arm
PAS2, 2017 $N = 190$	Multicentre, prospective, observational study	First 190 subjects enrolled in PAS2 compared with 190 patients from AIR2 trial	Followed at 6 weeks following the completion of BT, annual visits up to 5 years after the therapy	Age: 18–65, FEV1 ≥ 60% predicted	Severe asthma (requiring ICS > 1000 μg/day beclomethasone or equivalent and LABA > 80 μg/day salmeterol or equivalent). LT modifiers, omalizumab and OCS 10 mg/day or less allowed	Proportion of subjects experiencing severe exacerbations during the subsequent 12-month period (years 2, 3, 4 and 5) compared to the first 12 months after BT	Significantly reduced proportion of patients experiencing severe exacerbation at 3 years of follow-up compared to prior to BT. Similar reduction compared to AIR2 cohort

(Continues)

TABLE 1 (Continued)

Trial, publication year, subjects included (*N*)	Design	Study groups	Duration followed	Subject characteristics	Asthma severity and baseline controller medications	Primary outcome	Results
BT10+, 2021 $N = 192$	International, multicentre follow-up study	Previous participants enrolled in AIR, RISA and AIR2 trials including control and sham arm subjects	Historical data from AIR, RISA and AIR2 used to follow outcomes during years 1–5, outpatient visit at 10 years following BT procedure	Mean age: 54 years. Mean FEV1 73% predicted	18/56 control/sham patients received BT after the initial trials concluded. Maintenance OCS use noted in 3%–5% of patients and 7%–8% received biologic medications	Proportion of participants with severe exacerbation at years 1 and 5 after BT compared to 12 months prior to 10-year follow-up visit. Safety endpoint regarding clinically significant imaging changes following BT	No significant difference in proportion experiencing severe exacerbations 12 months prior to BT10+ visit compared to years 1 and 5 after BT. 7% of AIR2 participants who underwent BT developed bronchiectasis but without clinical symptoms
TASMA, 2021 $N = 40$	Multicentre, randomized control trial	Immediate BT group compared to 6-month delayed treatment group	Followed 6 months after randomization to either arm and 6 months after BT treatment	Age: 18–65 years, FEV1 ≥ 50% predicted	Severe asthma utilizing WHO or IMI definition. OCS < 20 mg/day allowed	Absolute difference in ASM mass change following BT in immediate therapy group compared to pre-BT delayed therapy group	Significant decrease in ASM mass in immediate BT group compared to no change in delayed group following 6 months of standard care

Abbreviations: AIR, Asthma Intervention Research; AQLQ, Asthma Quality of Life Questionnaire; ASM, airway smooth muscle; BT, bronchial thermoplasty; FEV1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; IMI, Innovative Medicines Initiative; LABA, long-acting beta-agonist; LT, leukotriene; OCS, oral corticosteroid; PAS2, Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma; RISA, Research in Severe Asthma; TASMA, Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma; WHO, World Health Organization.

and a sham control, it begged the question of whether these gains would last beyond 1 year and therefore make the procedure (including the risk of transiently worsened asthma symptoms) truly worthwhile.

AIR2: 5-year follow-up (published in 2013)

This study exclusively followed up those patients in the AIR2 cohort, unblinded by now, who underwent BT either during or after the AIR2 study.[42] Compared to each subject's own baseline (defined as the year immediately preceding BT), rates of severe exacerbation, hospitalization and ED visits continued to be decreased up to 5 years following BT. An HRCT scan at 5 years post-BT demonstrated no clinically significant structural abnormalities following BT.

PAS2 (published in 2017 and in 2022)

In 2017, results of the post-market PAS2 (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma) study were published comparing the first 190 subjects enrolled in the PAS2 study at 3 years of follow-up with data on 190 subjects from the AIR2 trial at the same interval post-BT.[43] Of note, participants in the PAS2 study were on average older, had higher mean BMI, required higher doses of inhaled corticosteroids and reported higher rates of severe exacerbations and hospitalizations at baseline. While the initial 'treatment period' saw a higher rate of exacerbations and ED visits among the PAS2 cohort, no differences were noted in rates of respiratory-related adverse events in the subsequent follow-up period between the PAS2 and AIR2 cohorts. Moreover, compared to each PAS2 subject's own baseline, rates of severe exacerbation, ED visits and hospitalizations were lower (by 45%, 55% and 40%, respectively) at year 3 following BT. An extended follow-up of the PAS2 cohort demonstrated sustained reduction in these endpoints and significantly decreased proportion of subjects requiring maintenance oral corticosteroids at 5 years compared to baseline.[44,45]

BT10+ (published in 2021)

The safety and effectiveness of BT after 10 years in patients with persistent asthma (BT10+) study was published in 2021.[46] This was designed as an international, multicentre, follow-up study of participants originally enrolled in the AIR, RISA and AIR2 trials who ended up receiving BT (either as part of the study treatment group or as a crossover after the completion of the original study) and who had 10 or more years of follow-up since BT.

Participants were followed up for a median of 12.1 years. Improvements in mean AQLQ and ACQ scores after BT were sustained beyond 10 years. The healthcare utilization benefits of BT also continued, with ED visit rates and hospitalization rates significantly lower compared to each subject's own pre-BT baseline (defined as the 12-month period prior to undergoing BT). Among the AIR2 cohort, who had undergone HRCT imaging at enrolment, six patients (7%) had developed new bronchiectasis at the BT10+ follow-up visit. Importantly, clinical symptoms of bronchiectasis were not present in any of these patients, with one patient having moderate bronchiectasis and five patients having mild bronchiectasis based on computed tomography review.

TASMA (published in 2021)

The TASMA (Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma) study was an international, multicentre, randomized trial designed to assess the effect of BT on ASM mass in patients with severe asthma.[17] Investigators also analysed data for specific patient characteristics and biomarkers associated with positive response to BT. As the primary endpoint for this study was ASM mass, an objective metric, investigators chose not to include sham treatment protocol for the control group. However, blinding was used in outcome assessment.

At 6 months, the 'immediate treatment' group undergoing BT had 53% reduction in ASM mass and significantly improved AQLQ and ACQ scores compared to the 'delayed control' group that had received usual medical care thus far. Subsequently, the delayed control group also underwent BT and had similar improvements at 6 months. In a pooled analysis ($n = 35$), baseline ASM mass was not a predictor of improved ACQ scores at 6 months but baseline blood eosinophil and total IgE levels were.

The absence of sham treatment raises a question mark over the utility of patient-reported questionnaires as the primary marker for treatment success, as was done in this study. The absence of longer term follow-up should also be borne in mind when drawing conclusions from this study.

COST CONSIDERATIONS

In a budget impact analysis involving the addition of BT to standard care among severe persistent asthmatics and omalizumab non-responders, cumulative costs and cost per patient per year were projected to decrease despite an initial increase during the first year of treatment with BT.[47] According to a base case economic analysis, BT had an incremental cost-effectiveness ratio of $29,821/quality-adjusted life years at 10 years in patients with severe persistent asthma on high-dose combination inhaler therapy.[48] BT has also been studied in models specific to patients with moderate to severe allergic asthma and shown to be cost-effective relative to both omalizumab and standard therapy.[49]

Altogether, BT appears to be a cost-effective option if peri-procedural costs are outweighed by costs related to hospitalization and ED visits. Further studies are needed in larger populations of patients before a reliable comparison can be made. Such a 'real-world' economic comparison may allow both clinicians and policy makers to make informed decisions regarding the cost-effectiveness of treatment options for patients with severe persistent asthma.

PATIENT SELECTION INCLUDING SAFETY CONSIDERATIONS

Historically, clinical practice guidelines from various societies have offered divergent assessments of the evidence regarding BT and none to date have incorporated the more recent data published on this topic. After the 2014 European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines had recommended the use of BT in the context of a registry or a clinical study, the American College of Chest Physicians (ACCP) published a position statement to recognize the safety and efficacy of BT in appropriately selected patients, emphasizing that it should not be considered experimental nor withheld from patients pending additional research studies. The Global Initiative on Asthma (GINA) guidelines recommend considering BT as an add-on treatment option at step 5.[6]

Figure 2 illustrates an evidence-based general approach towards patient selection and subsequent management.[50]

All patients under consideration should be thoroughly evaluated to confirm a diagnosis of asthma along with relevant phenotyping.[51] An exclusion of alternate diagnoses should be performed to prove the existence of severe asthma despite optimal medical therapy.[52] The role of spirometry in patient selection is less clear. Although the AIR2 sham-controlled trial only enrolled patients with a forced expiratory volume in the first second (FEV1) ≥60% and the RISA trial demonstrated 1-year safety of BT among patients with FEV1 ≥ 50%, several recent observational studies have demonstrated largely comparable safety of BT among patients with FEV1 values as low as 30% along with similar improvements in ACQ scores.[18,53–55] A study of 77 consecutive patients included in the Australian Bronchial Thermoplasty Registry, of whom 19 had FEV1 ≤ 40%, showed significant clinical improvement and acceptable safety profile following BT despite including older patients (age > 65) and those with higher annual exacerbation rates compared with cohorts included in the North American studies. Of note, however, all patients underwent mandatory overnight hospitalization contrary to the conventional same-day surgery protocol.[55]

CURRENT CHALLENGES AND POTENTIAL NEXT STEPS

At present, several challenges remain in terms of our scientific understanding of BT and its provision to suitable patients

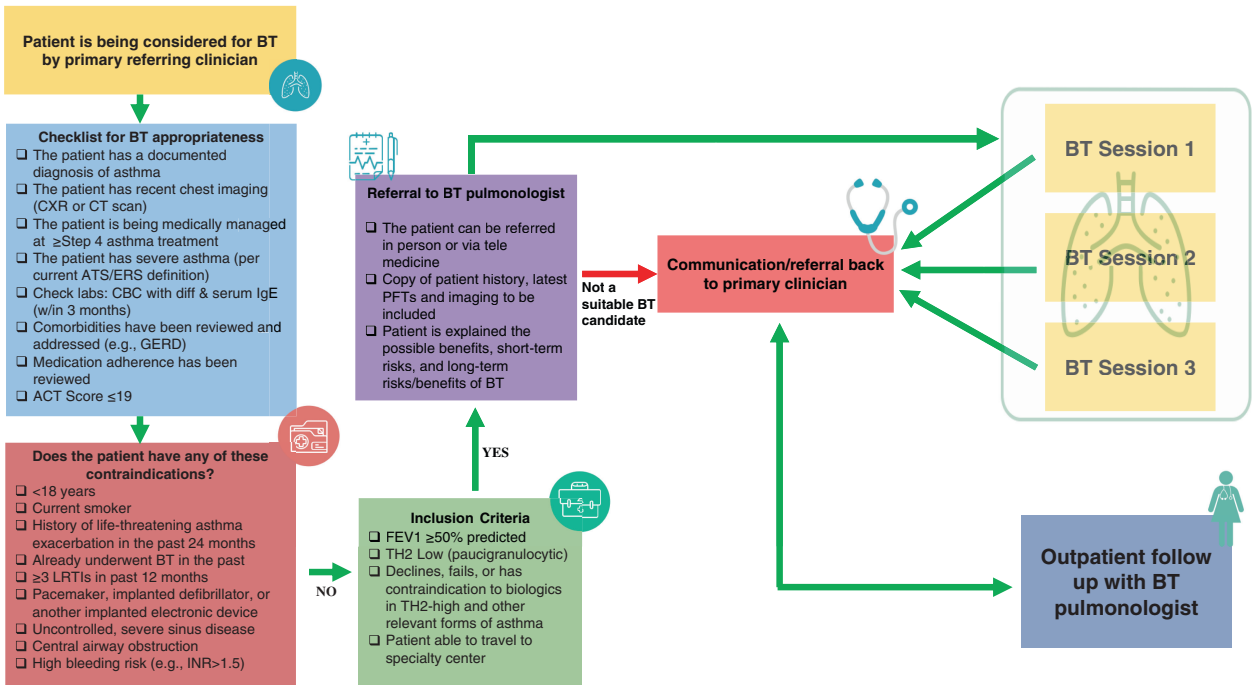

FIGURE 2 BT: an evidence-based general approach towards patient selection and subsequent management. ACT, Asthma Control Test; ATS, American Thoracic Society; BT, bronchial thermoplasty; CBC, complete blood count; CT, computed tomography; CXR, chest x-ray; ERS, European Respiratory Society; FEV1, forced expiratory volume in the first second; GERD, gastroesophageal reflux disease; INR, international normalized ratio; LRTI, lower respiratory tract infection; PFT, pulmonary function test

TABLE 2 Current challenges and potential next steps in the scientific understanding and clinical application of BT

Current challenge	Potential solutions(s)
Limited markers of treatment success[56]	• Ensure patient blinding (sham control) when using patient-reported symptom questionnaires • Measure impact on healthcare utilization (such as ED visits, hospitalization rates, etc.) • Consider functional imaging (CT and MRI) modalities[24,27,28,57] • Explore the role of unconventional markers of airflow obstruction (e.g., impulse oscillometry)
Lack of blinded long-term follow-up beyond 1 year	• Design a clinical trial along the lines of AIR2 with longer follow-up
Frequent worsening of asthma symptoms in the short term	• Investigate effective ways of reducing this occurrence, for example, a more effective peri-procedural steroid regimen (current convention is 5 days of oral steroids starting 3 days pre-BT) • Further explore targeted, single-session BT instead of the conventional, three-session BT[29]
Limited, although encouraging, cost-effectiveness data	• Perform additional economic analyses on a larger scale using real-world data
Limited, although increasing, understanding of the role of specific asthma endotypes/phenotypes[55]	• Perform additional studies on a larger scale to include extremes of ages, all endotypes/phenotypes and clinical variants such as cough-variant and exercise-induced asthma[58]
Difficulties with insurance coverage even when patients meet the conventional treatment criteria[59]	• Relevant professional societies should formulate updated evidence-based clinical practice guidelines to reflect the changing landscape of clinical evidence over the past few years since older guidelines had come out • Engage with insurance companies to educate them about our updated understanding of BT, including its safety, effectiveness and cost-effectiveness
Absence of direct comparison with novel biologic therapies[60]	• Performed randomized trials entailing head-to-head comparison of BT with novel biologics approved for T2-high asthma

Abbreviations: BT, bronchial thermoplasty; CT, computed tomography; ED, emergency department.

with severe, refractory asthma. These provide unique opportunities for impactful work in this area (Table 2).

CONCLUSION

Since the publication of the AIR2 sham-controlled, randomized trial in 2010 and subsequent approval of BT by the Food and Drug Administration (FDA) in the same year, additional data have made it more evident that BT is a useful option for patients suffering from severe persistent asthma despite optimization of medical therapy. Previous concerns regarding long-term safety have been largely put to rest by recently published data showing excellent safety over 10 or more years following BT, but the similarly excellent long-term effectiveness data are limited by a lack of patient blinding and control group comparisons beyond 1 year. The limited economic analyses thus far completed all point to excellent cost-effectiveness that rivals that of other step 5 therapy options including biologics, but more research is needed. Our scientific understanding of BT's mechanism(s) of action and the scope of its benefit across various asthma subgroups continues to increase, and thus far BT has emerged as a powerful, arguably underutilized, tool that can benefit a broad range of patients with severe asthma.

AUTHOR CONTRIBUTIONS

Asad Khan and Majid Shafiq were involved in study conception. Muhammad Daniyal Hashmi, Asad Khan, and Majid Shafiq participated in literature review, data synthesis, and manuscript writing.

CONFLICT OF INTEREST

None declared.

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