General Perspective

Bronchial Thermoplasty for Severe Asthma: A Position Statement of the Indian Chest Society

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ABSTRACT

Bronchial thermoplasty (BT) is an interventional bronchoscopic treatment for severe asthma. There is a need to define patient selection criteria to guide clinicians in offering the appropriate treatment options to patients with severe asthma. Methodology: An expert group formed this statement under the aegis of the Indian Chest Society. We performed a systematic search of the MEDLINE and EMBASE databases to extract evidence on patient selection and the technical performance of BT. Results: The experts agreed that the appropriate selection of patients is crucial and proposed identification of the asthma phenotype, a screening algorithm, and inclusion/exclusion criteria for BT. In the presence of atypical clinical or chest radiograph features, there should be a low threshold for obtaining a thoracic computed tomography scan before BT. The patient should not have had an asthma exacerbation in the preceding two weeks from

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Received: 09-09-2019 **Accepted:** 26-10-2019 **Published:** 31-12-2019

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_418_19

How to cite this article: Madan K, Mittal S, Suri TM, Jain A, Mohan A, Hadda V, *et al*. Bronchial thermoplasty for severe asthma: A position statement of the Indian chest society. Lung India 2020;37:86-96.

the day of the procedure. A 5-day course of glucocorticoid should be administered, beginning three days before the procedure day, and continued until the day following the procedure. General Anesthesia (total intravenous anesthesia with a neuromuscular blocker) provides ideal conditions for performing BT. A thin bronchoscope with a 2.0 mm working channel is preferable. An attempt should be made to deliver the maximum radiofrequency activations. Middle lobe treatment is not recommended. Following the procedure, overnight observation in the hospital, and a follow-up visit, a week following each treatment session, is desirable. Conclusion: This position statement provides practical guidance regarding patient selection and the technical performance of BT for severe asthma.

KEY WORDS: Anesthesia, bronchial asthma, bronchial thermoplasty, prednisolone

SUMMARY OF RECOMMENDATIONS

- Patients being considered as possible candidates for bronchial thermoplasty (BT) should be screened for modifiable and reversible factors for poor asthma control and should be treated with adequate dosage and combination of controller treatments, Usual Practice Point (UPP)
- A comprehensive inclusion and exclusion criteria checklist should be used to select possible BT candidates from among those who pass the pre-BT screening phase (UPP)
- In the presence of atypical clinical or chest radiograph features, there should be a low threshold for performing a thoracic computed tomography scan to rule out alternative diagnoses in patients of severe asthma being considered for BT (UPP)
- BT should be performed when the patient is in a state of relative clinical stability (without any exacerbation or respiratory infection for two weeks preceding the day of procedure). Also, the following should be ensured on the day of the procedure (UPP): Spirometry (procedure day or the day before) - forced expiratory volume in one second should be >80% of patient's baseline value, SpO2 on room air: >90%, no active respiratory infection, written informed consent has been obtained, ensure premedication dose of oral corticosteroid, nebulization with short-acting bronchodilator just before procedure initiation, and a recent chest radiograph within the previous three days is available and reviewed
- General anesthesia (total intravenous anesthesia using propofol with a neuromuscular blocking agent administration) along with shorter-acting opioid (e.g. fentanyl) is preferable for BT (3A)
- Either a supraglottic airway device or an endotracheal tube may be used for airway management to provide ventilation during the procedure (UPP)
- Other considerations regarding anesthesia during BT include: (1) intraoperative monitoring should include noninvasive blood pressure, five lead electrocardiography with heart rate and pulse oximetry (SpO2), (2) during general anesthesia, ventilator strategy should target the respiratory rate (8–10/min), tidal volume (5–8 ml/kg), and inspiratory: expiratory ratio of 1:3–1:4 to prevent auto-positive end-expiratory pressure, (3) inspired oxygen fraction should be kept <40% to prevent airway ignition using oxygen air mixture (nitrous oxide should be avoided), and (4) when using GA, target control infusion with bispectral index monitoring is ideal
- Two dedicated assistants, one to control the radiofrequency (RF) catheter and the other to note down the treated segments should be available in addition to other bronchoscopy and anesthesia personnel (UPP)
- Middle lobe treatment should not be routinely performed during BT unless a part of an IRB approved research protocol (UPP)
- It is preferable to use the thinnest available bronchoscope with a 2.0 mm working channel to perform BT (3A)
- An attempt should be made to treat all the bronchoscopically visible segments and deliver the maximum number of activations technically feasible. A thin bronchoscope is ideal for delivering more RF activations (3A)
- A systematic bronchoscopic approach should be followed during the session for treatment of various segments (UPP)
- Consideration should be given to postponing RF treatment if the bronchoscopic examination shows extensive mucosal abnormality and active infection should be ruled out and appropriately treated (UPP)
- A postprocedure chest radiograph should be obtained if clinically indicated. Routine postprocedure spirometry is not required (UPP)
- It may be preferable to keep the patient overnight for observation in the hospital following BT. Decision to discharge should be based on clinical stability (UPP)
- Following discharge from the hospital, patients should be kept under regular telephonic contact for a week. Further follow-up visits following the treatment session completion may be done at 1–3 monthly intervals for assessment of asthma control (UPP).

INTRODUCTION

Bronchial asthma is a significant public health concern in India and across the globe. According to the Global Burden of Disease Study, there were 37.9 million (35.7–40.2 million) patients with asthma in India in 2016.[1] Furthermore, the INSEARCH study (a nationwide population prevalence study) estimated the prevalence of asthma among Indian

adults (>15 years) around 2.05%.[2] Severe asthma includes a subset that represents about 5%–10% of asthma patients, yet this group contributes to the bulk of morbidity, healthcare resource utilization, and healthcare costs related to asthma.[3] These patients often require repeated hospitalizations and have an impaired quality of life despite maximal/optimal medical therapy. Though the prevalence in India has not been systematically studied, an estimated 1–2 million adults in India likely have severe asthma.

The burden of severe asthma necessitates exploration of newer modalities for this group of patients. Biological therapies and bronchial thermoplasty (BT) are two such newer modalities.[4] Two biological therapies (anti-immunoglobulin E: omalizumab and anti-interleukin-5: mepolizumab) are currently available in India. BT was introduced in India in 2018. The United States of America Food and Drug Administration (FDA) approved BT in the year 2010, and the procedure has been performed in over 6000 patients globally according to recent data. The procedure involves the delivery of radiofrequency (RF) energy to the larger airways (3–10 mm) using a flexible catheter passed through the working channel of a flexible bronchoscope to ablate the airway smooth muscle, thereby improving asthma control.[5]

As with any newer procedure, there is a need to define the patient selection criteria and procedural aspects clearly. In the context of BT particularly, guidelines in this regard are lacking and patients recruited in clinical trials may be very different from those encountered in clinical practice. Therefore, a need was perceived to frame a position paper based on a systematic review of the available literature to define the patient selection criteria and guide clinicians regarding the technical aspects of the procedure.

METHODOLOGY

This document is an expert consensus-based position statement on the following aspects of BT:

- Patient selection
- The technical performance and follow up of patients undergoing BT.

Four authors (KM, TMS, AJ, and SM) performed a systematic search of the MEDLINE and EMBASE databases using the search term "bronchial thermoplasty." We limited our search to articles published in the English language. The articles were classified into the relevant subsections (randomized controlled trials, systematic review/meta-analysis, narrative reviews, expert consensus statements, case series, case reports, and long-term follow up studies). Relevant sections of existing severe asthma guidelines were also reviewed. Following internal deliberations among the group, a set of questions were finalized to be addressed as part of the consensus paper. Subsequently, an expert group meeting was convened at the All India Institute of Medical Sciences, New Delhi under the aegis of the Indian Chest Society (ICS) to finalize the content of the document. The expert group panel included interventional pulmonologists already performing BT, anesthesiologists and pulmonary physicians from various centers across India. The evidence on each question was presented and deliberated. Recommendations were formulated and graded according to the current level of evidence and the strength of the recommendation [Table 1].[6] In situations where there was a lack of adequate evidence, the recommendations were framed by expert consensus. It was decided that the recommendations may be revised after five years or even earlier, keeping in mind the emerging evidence on the subject.

Bronchial thermoplasty (an overview)

BT is an interventional bronchoscopic treatment option for severe asthma which involves the delivery of controlled RF energy to the airways to ablate airway smooth muscle.[7] The procedure involves the use of the Alair™ BT system which consists of an RF energy generator, an earthing plate, and a single-use flexible RF delivery basket catheter that is activated using a footswitch [Figure 1].[8] The flexible catheter can be introduced through the working channel of a flexible bronchoscope (at least 2.0 mm working channel) wherein the operator uses a footswitch to trigger delivery of RF energy activations (10 s per activation) to the airways at 5 mm intervals. The catheter probe delivers

Table 1: Quality of evidence levels and strength of recommendations

Quality of evidence	Level
Evidence from ≥1 good quality and well-conducted randomized control trial (s) or meta-analysis of RCT's	1
Evidence from at least 1 RCT of moderate quality, or well-designed clinical trial without randomization; or from cohort or case-controlled studies	2
Evidence from descriptive studies, or reports of expert committees, or opinion of respected authorities based on clinical experience	3
Not backed by enough evidence; however, a consensus reached by the working group, based on clinical experience and expertise	UPP
Strength of recommendation	**Grade**
Strong recommendation to do (or not to do) where the benefits outweigh the risk (or vice versa) for most, if not all patients	A
Weak recommendation, where benefits and risk are more closely balanced or are more uncertain	B

UPP: Useful practice point, RCT: Randomized controlled trials

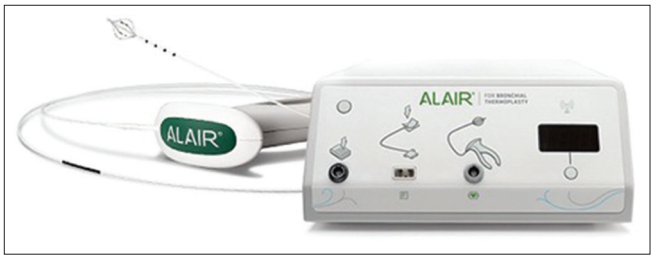

Figure 1: Figure showing the Alair bronchial thermoplasty controller and the flexible basket catheter

a series of RF bursts to heat the targeted airways to 65°C. This procedure is employed in a distal-to-proximal or a medial-to-lateral fashion. The aim is to prevent duplicate treatment or omission of any segmental bronchus.

BT is performed in three separate sessions, three weeks apart: one session each for the two lower lobes (right lower lobe followed by left lower lobe) and third session for both the upper lobes.[9] Each session usually lasts between thirty to 60 min. By convention, the middle lobe is not treated to avoid the possible risk of middle lobe syndrome.[5]

Section A: PATIENT SELECTION FOR BRONCHIAL THERMOPLASTY

The most crucial step in performing BT is choosing the right patient who might benefit from this procedure. Concerns have been raised regarding the real-life utility of BT as patients recruited in the randomized clinical trials (RCTs) of BT are possibly different from the severe asthmatics in real-life practice. In clinical practice, poor control of asthma may be secondary to multiple modifiable factors. Therefore, a systematic approach to patient selection for BT is of utmost importance.

Randomized controlled trials of bronchial thermoplasty

Till date, three randomized controlled trials have been performed which have examined the safety and efficacy of BT in the management of severe asthma.

Asthma Intervention Research trial (2007)

The Asthma Intervention Research (AIR) study recruited 112 patients with moderate or severe persistent asthma and demonstrated a reduction in the mild exacerbation rate with an enhanced asthma-related quality of life with BT. There were also improvements in the Asthma Control Questionnaire (ACQ) score, morning peak expiratory flow and symptom scores.[10]

Research in Severe Asthma trial (2007)

The Research in Severe Asthma (RISA) study was primarily a safety trial. In this study, despite a transient increase in asthma symptoms during the treatment, there was excellent long-term safety and improved asthma control in patients undergoing BT.[11]

Asthma Intervention Research 2 trial (2010)

The pivotal study, the AIR2 trial was the first and only RCT till date to include a sham-procedure control arm. Two hundred ninety-seven patients were randomized in a 2:1 ratio to undergo either BT or an identical bronchoscopic procedure without the delivery of RF energy. Improvements were found in the Asthma Quality of Life Questionnaire (AQLQ) scores in both the intervention and control arms with superior improvements in the intervention arm.[12] Furthermore, there was a reduction in severe exacerbations, emergency department visits, and days missed from school/work in the BT group. A comparison of the inclusion criteria of the three RCTs is presented in Table 2.

All trials included adult patients aged 18–65 years. Compared with the AIR trial, the RISA and AIR2 trials included patients who were receiving higher doses of inhaled steroids at baseline. Furthermore, patients with more severe airway obstruction were enrolled in the RISA trial (baseline prebronchodilator forced expiratory volume in one second (FEV_1) >50% in RISA, and >60% in AIR and AIR2 trials). Notably, each of the trials had a measure of poor asthma control in the inclusion criteria to ensure that only patients with uncontrolled asthma were enrolled [Table 2]. Patients from each of these randomized controlled trials were enrolled in extension studies, which followed them for five years. These extension studies have demonstrated the long-term safety of BT with the stability of the FEV_1 on follow-up.[13-15] The AIR2 extension study has shown durable improvements in exacerbation rates and emergency department visits until 5 years after BT.[15]

Case Series

The United States FDA approved BT in 2010, subject to the performance of a postmarketing study.[16] The PAS-2 study is the FDA mandated prospective observational "real-life" ongoing study designed to resemble the AIR2 trial in its patient population and outcomes.[17] However, unlike AIR2, the patients in PAS2 were not required to demonstrate airway hyper-responsiveness by a methacholine challenge test. Furthermore, the less stringent PAS2 study criteria excluded fewer patients as compared to the AIR2 trial to resemble "real-life" clinical practice [Table 3]. The interim results of the first 190 patients enrolled over a 3-year period were compared with the results of the AIR2 trial and published in 2017. The patients enrolled in the

Table 2: A summary of the inclusion criteria of the bronchial thermoplasty randomized controlled trials

Trial	Ag (years)	ICS dose	OCS dose	Other medications	Stable Asthma duration (weeks)	Baseline AQLQ score	Baseline Pre-BD FEV_1	Measure of poor control
AIR	18-65	≥200 µg/d beclomethasone	-	-	6 weeks	-	60%-85%	Worsening asthma control on LABA abstinence
RISA	18-65	>750 µg/d fluticasone	≤30 mg/d	LTRA, theophylline	-	-	≥50%	Rescue medications on ≥8 out of 14 days Daytime symptoms on ≥10 out of 14 days
AIR-2	18-65	≥1000 µg/d beclomethasone	≤10 mg/d	LTRA, omalizumab	4 weeks	≤6.25	>60%	>2 days of asthma symptoms during a 4 weeks baseline period

ICS: Inhaled corticosteroid, OCS: Oral corticosteroid, AQLQ: Asthma Quality of Life Questionnaire, BD: Bronchodilator, LABA: Long acting beta2 agonist, LTRA: Leukotriene receptor antagonist, FEV_1: Forced expiratory volume 1 s, AIR: Asthma Intervention Research, RISA: Research in Severe Asthma

PAS2 study had more severe asthma with higher doses of inhaled corticosteroids at baseline and higher rates of hospitalizations and exacerbations in the 12 months before the BT. Despite this, the patients experienced similar benefits as the AIR2 trial in terms of reductions in exacerbations and hospitalizations.[17]

Numerous case series have been published that possibly represent the real-world performance of BT.[18-24] Invariably, patients in these reports have more severe asthma than the ones enrolled in the RCT's. The key outcomes of these trials are summarized in Table 4. Bicknell *et al*. compared the performance of BT in ten "real-life" patients versus fifteen patients enrolled in the context of a clinical trial at the same site. It was observed that despite the baseline severity being greater in "real-life" patients, the rate of adverse effects was similar. Clinical improvement (reduction in exacerbation or hospitalization rates, reduction in corticosteroid dose or, improved ACQ or AQLQ score) was seen in 50% of "real-life" patients and 73% of trial patients.[25] Reports of BT being used in patients who would be deemed too "severe" to fit the inclusion criteria of the trials are also available. Tolla *et al*. reported the safe performance of BT in a 75-year-old obese male smoker with multiple comorbidities, including obstructive sleep apnea (OSA). The patient was weaned off oral steroids, had fewer exacerbations, reduced rescue inhaler use, and reduced CPAP pressures following BT.[26] Han *et al*. reported a 60-year-old man with very severe airflow obstruction (FEV1 of 20.4% predicted) who underwent BT. Although the patient developed a viral respiratory infection after the second session requiring mechanical ventilation, he went on to complete his therapy. He had an improved quality of life following BT.[27]

Table 3: Differences in the exclusion criteria of Asthma Intervention Research 2 trial and PAS2 study

AIR2	PAS2
Hypersensitivity to methacholine	Not an exclusion
Use of immunosuppressants, beta blockers, and anticoagulants	Not an exclusion
Comorbidities: Insulin-dependent diabetes, obstructive sleep apnea, ILD, chronic sinus disease, uncontrolled GERD, epilepsy	Not an exclusion
Remaining exclusion criteria similar between AIR2 and PAS2 to enable comparability of outcomes	

ILD: Interstitial lung disease, GERD: Gastroesophageal reflux disease, AIR2: Asthma Intervention Research 2, PAS2: Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma study

Complications following bronchial thermoplasty

BT is associated with increased short-term morbidity, particularly during the treatment period. In the AIR2 trial, there were 6% additional hospitalizations in the treatment arm as compared to the sham arm during the treatment period (up to 6 weeks following BT). The most common adverse event was worsening asthma. Other early posttreatment complications included lower respiratory tract infection, segmental atelectasis, and hemoptysis. However, most complications were short-lasting and resolved with conservative management. There were no significant long-term complications. In fact, during the posttreatment period, there were fewer adverse respiratory events in the treatment arm as compared to the sham arm.[12] Similar findings were reported in the RISA trial with transient worsening of asthma during the treatment

Table 4: Case Series of Bronchial Thermoplasty in Severe Asthma

Author, year	*n*	Country	Patient characteristics	Key outcomes	Complications
Doeing *et al*., 2013[18]	8	USA	Mean FEV_1, 51.8%; 4 on OCS; 2 on omalizumab; hospitalizations, 2.88/patient/year; mean IgE, 155 IU/mL; mean eNO 55 ppb	Safety trial	No unexpected severe adverse events; no significant decline in FEV_1
Watchorn *et al*., 2014[19]	7	Ireland	Mean age, 55.6 years; 5 on OCS; 6 on Omalizumab; mean hospitalization, 5/year	Improvement in ACT score, reduced hospitalization	4 patients had exacerbation within 24 h. of procedure, 1 pneumonia <48 h. of procedure
Arrigo *et al*., 2016[20]	7	Italy	Age, 35-69 years; FEV_1, 61%-80%; severe exacerbation, 2-12 in past year	AQLQ and ACQ improved; reduced severe exacerbations; OCS use and SABA use	Atelectasis in 1 case
Burn *et al*., 2016[21]	59	United Kingdom	Mean age, 42.7 years; mean FEV_1, 70.2%	Safety trial	46.1% postprocedural ICU stay; 11.8% emergency readmission
Langton *et al*., 2016[22]	20	Australia	All patients fulfilled ATS/ERS criteria for severe asthma; mean FEV_1, 62.8% (33%-95%); FEV_1<50% in 4 patients; 10 on OCS; 6 on Omalizumab; mean exacerbations, 4.5/year; mean ACQ, 3.5	Improved ACQ score; SABA use reduced from 8 to 0.25 puffs/day; severe exacerbations reduced; 50% stopped OCS; in patients with FEV_1<60%, significantly improved FEV_1	Only 2 procedures required hospitalization >1 day; no deaths, pneumothorax, pneumonia, bronchiectasis or invasive ventilation
Fernández-Bussy *et al*., 2016[23]	4	Chile	All patients on high dose ICS; OCS use, 10-40 mg/d; FEV_1, 53.2%-70.1%; exacerbation, 5-8 in past year	2 discontinued OCS; 2 halved doses of OCS; all had reduced exacerbation rates	All 4 patients had exacerbations/hospitalization after session 3; one patient required NIV for 3 days
Iikura *et al*., 2018[24]	12	Japan	75% patients were on GINA step 5 treatment; Mean FEV_1, 70.5%; 5 had FEV_1<60%; 5 on OCS; 6 on Omalizumab; mean exacerbations 5.8/year	Improved AQLQ and ACQ scores; improved FEV_1 at 1 and 12 months; exacerbations reduced from 5.8 to 2/year	No deaths/mechanical ventilation; Cough or wheeze (97%); atelectasis (16.7%); pneumonia (8.3%); fungal infection (5.6%); hemoptysis (5.6%)

OCS: Oral corticosteroid, ACT: Asthma Control Test, AQLQ: Asthma Quality of Life Questionnaire, ACQ: Asthma Control Questionnaire, SABA: short acting beta2 agonist, FEV_1: Forced expiratory volume (1 s), ICS: Inhaled corticosteroid, NIV: Noninvasive ventilation, GINA: Global Initiative of Asthma

period. Four out of fifteen patients undergoing BT required seven hospitalizations out of which five were within 3 days of the procedure. Two patients had segmental atelectasis of the treated lobe, one requiring bronchoscopic suctioning.[11] However, most patients with severe asthma were able to tolerate the procedure well.

As the experience with BT increased and has expanded, other uncommon adverse effects have been reported [Table 5]. Hemothorax and mediastinal hematoma secondary to a bronchial artery pseudoaneurysm, hemoptysis due to thermal necrosis of bronchiectatic segments, and development of bronchiectasis have been reported.[12,28-30]

Bronchoscopic re-examination of the previously treated lobe during subsequent BT sessions may be warranted. Matsubayashi *et al*. reported the observation of a whitish ulcerated lesion in the previously treated lobe during the second session (1 month after the first session). Microbiological investigations established diagnosis of *Aspergillus fumigatus* and *Nocardia*. The patient was successfully treated with cotrimoxazole and voriconazole.[31] The occurrence of a lung abscess three days following a BT treatment session has also been reported.[32] Clinicians should remain alert to the possibility of infectious complications, especially in patients previously receiving immunosuppressant medications.

Other reported complications include the development of a self-resolving inflammatory endobronchial polyp, development of pulmonary cyst, and pneumothorax following BT.[33,34] Tissue fragility due to steroid use coupled with thermal energy application has been implicated in the latter.

Position of existing severe asthma guidelines on bronchial thermoplasty

ATS/ERS Guidelines for severe asthma (2014)

The ATS/ERS guidelines define severe asthma as one that requires treatment with high dose inhaled corticosteroids plus a second controller for the previous year and/or systemic corticosteroids (>50% of the previous year) to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy.[35] Herein, asthma is referred to as "uncontrolled" in one of the following situations:

a. Poor symptom control
b. Frequent severe exacerbations (>2 bursts of systemic corticosteroids in the past 1 year)
c. Serious exacerbations (>one exacerbation requiring hospitalization, intensive care unit stay or mechanical ventilation in the past one year)
d. Airflow limitation (FEV_1 <80% with FEV_1/forced vital capacity below the lower limit of normal after withholding bronchodilators).

Poor symptom control may further be determined by questionnaires, i.e., Asthma Control Test (ACT) score <20 or ACQ score >1.5.[36,37] It may also be defined as "not well-controlled" by the global initiative of asthma (GINA) symptom control tool [Table 6].[38]

Although the ATS/ERS criteria for severe asthma requires the use of a high-dose inhaled glucocorticoid plus a second controller, which is commonly a LABA, the expert group agreed that in the clinical setting, treatment should be attempted with at least a high dose glucocorticoid, a LABA and a third controller, i.e., a LAMA, before consideration is given to BT or biological therapy for severe asthma.

The ATS/ERS recommendation for BT in severe asthma is as follows: The ATS/ERS Guidelines "recommend that BT be performed in adults with severe asthma only in the context of an Institutional Review Board approved independent systematic registry or a clinical study" (Strength of recommendation– Strong and Quality of evidence – Very low).

Global initiative of asthma guidelines on difficult-to-treat and severe asthma (2019)

The GINA has specified the following key definitions:

a. Uncontrolled asthma: includes either one or both of following: poor symptom control (see above), and frequent or serious exacerbations (i.e., >2 requiring oral corticosteroid or >1 requiring hospitalization)
b. Difficult-to-treat asthma requires GINA step 4 or step 5 treatment (i.e., medium or high-dose inhaled corticosteroid with an additional controller or maintenance oral corticosteroid) to maintain asthma control or uncontrolled despite the above therapy. Asthma may be difficult-to-control due to modifiable factors including poor adherence, improper inhaler technique, unaddressed

Table 5: Complications reported following bronchial thermoplasty

Reported adverse events after bronchial thermoplasty
Asthma exacerbations
Segmental atelectasis
Infective complications (lower respiratory tract infection, lung abscess, Aspergillosis and Nocardiosis)
Bleeding complications (hemoptysis, hemothorax, mediastinal hematoma)
Pulmonary cyst and pneumothorax
Endobronchial inflammatory polyp
Bronchiectasis

Table 6: Global initiative for asthma symptom control tool global initiative for asthma

In the past 4 weeks has the patient had	Well controlled	Partly controlled	Uncontrolled
Daytime asthma more than twice a week Any nighttime waking due to asthma Reliever needed for symptoms more than twice a week Any activity limitation due to asthma	None of these	1 or 2 of these	3 or 4 of these

comorbid conditions, coexistent smoking, or incorrect diagnosis

c. Severe asthma is a subset of difficult-to-treat asthma which is uncontrolled despite adherence to maximally optimized therapy and treatment of comorbid conditions or which becomes uncontrolled when maximal therapy is decreased.

The GINA has outlined the treatment algorithm for severe asthma. The GINA recommendation for BT in severe asthma is as follows:[39] GINA recommends that add-on treatment with BT (Step 5) may be considered for some adult patients with severe asthma (Evidence B).

The critical component in patient selection for BT is therefore a comprehensive screening phase wherein the modifiable factors potentially responsible for poor asthma control are addressed and adherence to adequate doses and combinations of controller medications are ensured for a reasonable duration so that it is the correct subset of severe asthmatics who are offered the next line of treatment. Despite the repeated emphasis in various guidelines on prescribing the most suitable inhaler device to patients and ensuring correct inhaler technique, it is not uncommon to notice that this is often neglected in clinical practice. These aspects were deliberated in detail by the expert group given the increasing availability of newer add on therapies in severe asthma. We recommended a thorough screen of patients (Pre BT screen comprising of three Cs [checklist, criteria, and course]), being considered for BT to take care of modifiable and reversible factors [Figure 2]. The primary aim of the screening phase is to exclude patients who have difficult to control asthma due to modifiable factors. In the groups' experience, the majority of these patients improve following a phase of treatment optimization. The remaining may be considered for BT provided they meet the inclusion criteria and the risk-benefit profile has been discussed with the patient [Table 7].

The treatment options for severe asthma include a choice between biological therapies and BT. The available biologics in India currently include Omalizumab and Mepolizumab, which are both subcutaneously administered. Omalizumab is an anti-IgE therapy that reduces the rate of exacerbations by 25% among patients with severe allergic asthma.[40] Mepolizumab is an anti-IL 5 therapy that has been found to reduce the risk of exacerbation by about 50%.[41] It has also been shown to improve symptom control and reduce the need for oral glucocorticoids for maintaining asthma control.[42]

Phenotyping of asthma before BT was not a component of any of the major trials examining the safety and efficacy of BT, thereby leading one to the conclusion that BT may plausibly be efficacious in asthma patients irrespective of their inflammatory phenotype.[10-12] Taking into consideration the available evidence supporting the use of noninvasive biological therapies in the context of specific phenotypes, the patient having such phenotypes maybe initially offered a biologic therapy. However, the experts felt that specific pertinent issues were affecting Indian patients. Firstly, many Indian patients tend to prefer one-time or short-term therapies wherein BT has an advantage over biological therapy. Second, the cumulative costs of long-term biologic therapy may exceed the cost of BT. Hence, the guidelines group suggests a judicious choice between biologic therapy and BT in Indian patients who are eligible for either therapy, taking into consideration the local resources, the patient, and physician preference.

Recommendation

- Patients being considered as possible candidates for BT should be screened for modifiable and reversible factors for poor asthma control and should be treated with adequate dosage and combination of controller treatments (UPP)
- A comprehensive inclusion and exclusion criteria checklist should be used to select possible BT candidates from among those who pass the pre-BT screening phase.(UPP).

Section B: TECHNICAL/PROCEDURAL ASPECTS OF BRONCHIAL THERMOPLASTY

Should a computed tomography scan of the thorax be performed prior to bronchial thermoplasty?

In adult patients with severe asthma, a computed tomography (CT) scan of the thorax is not obtained routinely for the evaluation of asthma unless the clinical presentation is atypical based on history, examination, or disease progression. Although ATS/ERS guidelines do not recommend routine CT scans in the evaluation

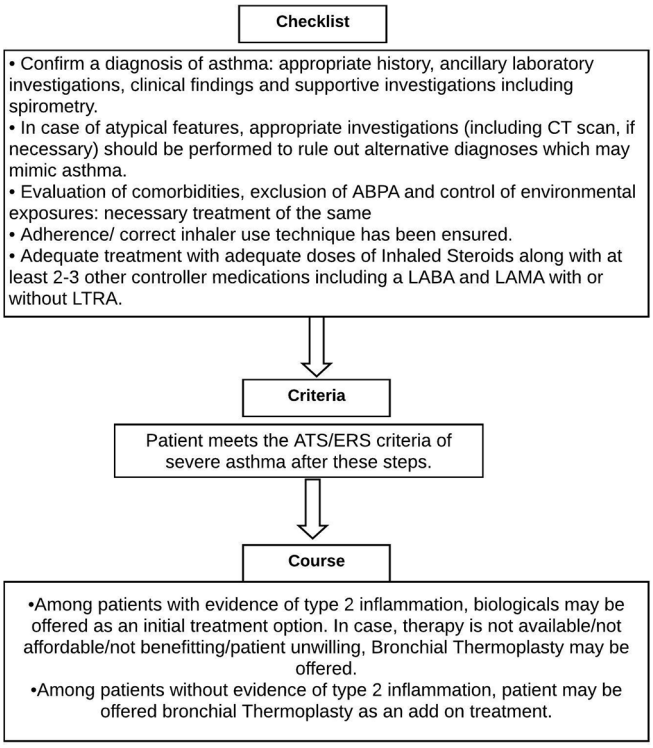

Figure 2: Figure summarizing the screening and approach to patient selection for bronchial thermoplasty

Table 7: Inclusion and exclusion criteria for bronchial thermoplasty

BT inclusion criteria	
Definite inclusion criteria	**Conditional criteria**
Diagnosis of severe asthma according to the ATS/ERS criteria Age 18-65 years Pre-bronchodilator FEV_1 ≥60% Oral prednisolone dose ≤10 mg/day Stable asthma maintenance medications for 4 weeks Poor symptom control: Patient not "Well controlled" as assessed using the GINA symptom control tool (or ACQ >1.5) Written informed consent Nonsmoker for >1 year	Patients meeting the following criteria may be considered for BT after detailed discussion with the patient regarding possible risks/benefits and BT be performed at a centre with facilities to manage potential complications Age >65 years Oral prednisolone dose >10 mg/day Prebronchodilator FEV_1% predicted <60%
BT exclusion criteria	
Absolute contraindications	**Relative contraindications**
Current asthma exacerbation Implanted electrical stimulation device Contraindications to flexible bronchoscopy Other major respiratory diseases Any significant radiographic abnormality in recent chest imaging including consolidation, collapse or pneumothorax Unstable cardiovascular disease, aortic aneurysm or any other significant comorbid illness like active cancer or any organ failure Pregnancy Coagulopathy, platelet count <50,000/μL, known bleeding diathesis	History of life-threatening asthma (requiring invasive mechanical ventilation) in the preceding 2 years ≥4 lower respiratory tract infections in the last 1 year Previous treatment with BT Inadequately controlled coexistent comorbidities

The performance of BT in patients with progressively lower FEV_1 below 60% may be associated with increased risk of complications, hence caution should be exercised in this group of patients. BT: Bronchial Thermoplasty, FEV_1: Forced expiratory volume 1 s, ACQ: Asthma Control Questionnaire, GINA: Global Initiative of Asthma

and management of severe asthma, it may be prudent to perform the same prior to BT as it is an invasive procedure requiring RF application to airways and complications possibly related to underlying structural lung disease have been reported. Before considering these patients for BT, it is advisable to rule out other important clinical conditions which may mimic or lead to poor control of asthma.[43]

Recommendation

- In the presence of atypical clinical or chest radiograph features, there should be a low threshold for performing a thoracic CT scan to rule out alternative diagnoses in patients of severe asthma being considered for BT (UPP).

Preprocedure assessment and preparation

Before the procedure, the patient should be in a stable state on optimized medical treatment without any exacerbation or respiratory infection in at least the two preceding weeks. Spirometry should be obtained during the period of clinical stability which will serve as a baseline for future reference. The patient should be administered 30–50 mg prednisolone or equivalent (oral or parenteral) steroid for three days prior, the day of the procedure and on the day following the procedure.[43] In previous RCTs examining safety and efficacy of BT (AIR, AIR2, RISA), patients were administered this corticosteroid regimen with an aim to reduce the local edema and airway damage caused by BT and to prevent postprocedure exacerbations.[10-12]

Recommendation

- BT should be performed when the patient is in a state of relative clinical stability (without any exacerbation or respiratory infection for two weeks preceding the day of procedure). Also, the following should be ensured on the day of the procedure (UPP):
- Spirometry (procedure day or the day before): FEV1 should be >80% of patient's baseline value.
- SpO2 on room air: >90%
- No active respiratory infection
- Written informed consent has been obtained
- Ensure premedication dose of oral corticosteroid
- Nebulization with short-acting bronchodilator just before procedure initiation
- A recent chest radiograph within the previous three days is available and reviewed.

Anesthesia

In the RCTs (AIR, AIR2, RISA), BT has been performed under both general anesthesia (GA) and moderate sedation. BT is a relatively long duration procedure in which each session usually lasts for 30–60 min with considerable airway foreign body contact (by the expandable basket catheter) and requires 5 mm spacing catheter deployment and RF application to all the airways of the lobe/lobes being treated during the session. Also, it is essential to avoid reapplication of RF energy to the same site to prevent airway damage therefore accurate catheter control and minimization of cough and respiratory excursions is important.

Case series have reported that BT may be safely performed under moderate or deep sedation with good acceptability by the patients and the operator. However, there may be a higher number of events of oxygen desaturation.[44,45] There is no head-to-head comparative data available between GA and various sedation strategies. General anesthesia remains

the most commonly utilized and suggested technique of sedation/anesthesia for the performance of BT.[46]

Recommendation

- General anesthesia (total Intravenous anesthesia using propofol) with a neuromuscular blocking agent administration) along with short-acting opioid (e.g. fentanyl) is preferable for BT (3A).
- Either a supraglottic airway device or an endotracheal tube may be used for airway management to provide ventilation during the procedure (UPP).

Other considerations regarding anesthesia during BT include the following:

- Intraoperative monitoring should include – noninvasive blood pressure, five lead electrocardiography with heart rate, and pulse oximetry (SpO_2)
- During general anesthesia, ventilator strategy should target the respiratory rate (8–10/min), tidal volume (5–8 ml/kg), and inspiratory: expiratory ratio of 1:3–1:4 to prevent auto-positive end-expiratory pressure
- Inspired oxygen fraction should be kept < 40% to prevent airway ignition using oxygen air mixture (nitrous oxide should be avoided)
- When using General Anesthesia (GA), target control infusion with Bispectral index monitoring is ideal.

Personnel requirement

For performing BT, it is necessary to have a skilled operator who has previously attended, assisted, or performed BT procedures and undertaken equipment training from the manufacturer. Two dedicated assistants are required apart from the routine bronchoscopy personnel: one to note the treated segments on a BT map (provided by the manufacturer), and the other to control the flexible RF array catheter during the procedure. Other members of the BT team may vary depending upon bronchoscopy procedure requirements and anesthesia strategy.

Recommendation

- Two dedicated assistants, one to control the RF catheter and the other to note down the treated segments should be available in addition to other bronchoscopy and anesthesia personnel (UPP).

Middle lobe treatment during bronchial thermoplasty

The middle lobe has not been treated traditionally because of the theoretical risk of middle lobe syndrome.[47] The risk of RML syndrome has not been studied systematically to date. However, various centers have treated the middle lobe without reporting middle lobe syndrome.[5] More long-term safety data are required before recommending treatment of the middle lobe.

Recommendation

- Middle lobe treatment should not be routinely performed during BT unless a part of an IRB approved research protocol (UPP).

Bronchoscope specifications and number of radiofrequency activations

BT is usually performed using a bronchoscope with an outer diameter of 4.8 mm or more with a working channel of at least 2.0 mm to allow easy passage of the flexible RF catheter. Langton *et al*. evaluated the use of a thinner bronchoscope with an outer diameter of 4.2 mm versus the standard 4.8 mm bronchoscope in 27 patients with severe asthma undergoing BT. The use of a thinner bronchoscope led to better access to the bronchial tree along with the delivery of more RF activations.[48]

BT is performed in three separate sessions. Conventionally, the right lower lobe is treated in the first session followed by the left lower lobe. Both upper lobes are treated together in the third session. Usually 40–70 activations are delivered in each lower lobe and 50–100 activations are delivered in the upper lobes. The number of activations given is important for a successful clinical outcome. Langton *et al*. report a series of 24 patients of severe asthma who underwent BT. The total number of activations delivered (139 ± 11 vs. to 221 ± 45) was the only variable which could differentiate between responders and nonresponders (ACQ-5 improvement >0.5).[49] Hence, an attempt should be made to treat all the bronchoscopically visible segments during the procedure in order to ensure the greatest number of activations technically feasible.

Recommendation

- It is preferable to use the thinnest available bronchoscope with a 2.0 mm working channel to perform BT (3A)
- An attempt should be made to treat all the bronchoscopically visible segments and deliver the maximum number of activations technically feasible. A thin bronchoscope is ideal for delivering more RF activations (3A).

Airway examination and radiofrequency treatment

A systematic approach should be followed during the procedure. Before each BT session, a careful bronchoscopic inspection of the airways should be done to look for any anatomical abnormalities, excessive or purulent secretions, mucosal abnormalities, or delayed healing of previously treated lobe. In the case of anatomical or mucosal abnormalities, RF application may be avoided in the affected segment. If an extensive mucosal abnormality of the previously treated lobe is noted, consideration should be given to postponing the procedure to a later date, and secondary infection should be ruled out by necessary investigations.

Activation sequence should be planned before the procedure, and a dedicated assistant should note the activated segments during the procedure on a BT map. This may help avoid both omission and retreatment of a given sub-segmental bronchus. A systematic approach should be followed during the procedure from distal to the proximal bronchus and from medial to the lateral segment.

Recommendation

- A systematic bronchoscopic approach should be followed during the session for treatment of various segments (UPP)
- Consideration should be given to postponing RF treatment if the bronchoscopic examination shows extensive mucosal abnormality and active infection should be ruled out and appropriately treated (UPP).

Postprocedure monitoring

Patients should be closely monitored for a minimum of 4 hours following each procedure, which includes clinical examination and pulse oximetry. Transient radiological abnormalities are common following BT. A routine postprocedure chest radiograph may not be required. A chest radiograph may be performed following BT only if clinically indicated. However, a chest radiograph should be available before a BT session. The patient should continue other background asthma treatment as before, along with the postprocedure day steroid dose, which was started before the procedure. The patient may develop sore throat, cough, or streaky hemoptysis postprocedure which may resolve within 2–3 days. Immediate posttreatment spirometry is not routinely required. Many patients might not be able to perform adequate spirometry following the procedure.

Recommendation

- A postprocedure chest radiograph should be obtained if clinically indicated. Routine postprocedure spirometry is not required (UPP).

Discharge

Most BT-related complications occur in the immediate postprocedure period and resolve within a week.[10,11] Langton *et al*. described a series of twenty patients who were routinely hospitalized on the day of the procedure.[22] In contrast, Burn *et al*., in their series of 59 patients, reported that 46.1% of patients required postprocedural hospitalization for at least one day.[21] The patient should be counseled at the time of discharge regarding the asthma management plan at home.

Recommendation

- It may be preferable to keep the patient overnight for observation in the hospital following BT. Decision to discharge should be based on clinical stability (UPP).

Follow-up of patients with bronchial thermoplasty

As BT-related complications such as worsening of asthma symptoms, postprocedure discomfort, and lower respiratory tract infections are common in the 1st week following the procedure, close follow-up following BT is essential. The patient should be kept under regular telephonic contact during the initial week following a BT session. Further monitoring of patients should be done on a 1–3 monthly basis for the first six months, depending on the patient's clinical condition. At each follow-up visit, the patient should be clinically evaluated, and asthma control should be ascertained (using ACQ/GINA control assessment tool). The patient should be followed up as per the current asthma treatment guidelines.

Recommendation

- Following discharge from the hospital, patients should be kept under regular telephonic contact for a week. Further follow-up visits following the treatment session completion may be done at 1–3 monthly intervals for assessment of asthma control (UPP).

CONCLUSION

This document is a consensus paper on various aspects relevant to patient selection and the performance of BT. The expert group also recognized that centers performing BT should maintain a log of patient characteristics, procedural outcomes, and exacerbation rates following BT. A national BT registry will enable an assessment of the "real-life" performance of this newer interventional pulmonary modality in the Indian setting.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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