Bronchoscopic Lung Volume Reduction Therapy Approved for Severe Emphysema

Results of the National Emphysema Treatment Trial (NETT), published in New England Journal of Medicine in 2003, convincingly demonstrated improvement in lung function and symptomatic relief of patients with severe emphysema with lung volume reduction surgery (LVRS). This benefit was evident only when LVRS was performed on selected patients with upper lobe predominant emphysema and a low baseline exercise capacity. While effective, the LVRS procedure helps only a select patient population with severe emphysema and is associated with a high cost, the potential for postoperative surgical complications and related lengthy hospital stays, and other surgical risks.

Recognition of the benefits and risks associated with LVRS prompted further evaluation and investigation of less invasive techniques to achieve lung volume reduction. Bronchoscopic lung volume reduction has emerged as a potential alternative to LVRS, and a less invasive method by which to achieve lung volume reduction in patients with emphysema and hyperinflation. Studies assessing bronchoscopic therapies aimed at reducing lung volumes have evaluated the use of various one-way valves that cause distal atelectasis, lung volume reduction coils that mechanically reduce lung volume, and thermal ablation. Initial studies had mixed results, though both endobronchial coils and one-way valves are commercially available for the treatment of emphysema in many countries worldwide outside the United States.

Bronchoscopy treatment for emphysema

In June 2018, the FDA approved Zephyr endobronchial valves (Figure), manufactured by Pulmonx, as the first bronchoscopic treatment for emphysema in the United States for patients with hyperinflation and minimal collateral ventilation. The role of these endobronchial valves in the management of emphysema was evaluated in the LIBERATE study published in American Journal of Respiratory and Critical Care Medicine in 2018. LIBERATE included 160 patients and randomized 128 to treatment with endobronchial valves and compared them with 62 patients treated by standard of care (optimized bronchodilator therapy and pulmonary rehabilitation).

LIBERATE included patients who were former smokers between the ages of 40 and 75 with a post-bronchodilator forced expiratory volume in one second (FEV1) between 15 and 45 percent, and with hyperinflation as evidenced by a residual volume ≥ 175 percent predicted. They also had a diffusing capacity of the lungs for carbon monoxide ≥ 20 percent and a six-minute walk distance of 100 to 500 m. A CT had to reveal heterogeneous emphysema.

Eligible patients then underwent bronchoscopy using the Chartis system to identify collateral ventilation. At 12 months, 47.7 percent of valve recipients and 16.8 percent of the control arm had an increase in FEV1 ≥ 15 percent (p < 0.001). Further, valve recipients had significant improvements in their six-minute walk distances (+ 39.31 m; p = 0.002) and improvements in dyspnea as measured by the St. George’s Respiratory Questionnaire (-7.05 points; p = 0.004). The major side effect with endobronchial valve placement was a pneumothorax, occurring in 27 percent of recipients, with 85 percent occurring within the first five days.

Similar to LVRS, this procedure will likely benefit only a subset of patients with emphy-
For this trial, 909 patients gave consent. Only 160 met the full inclusion trial. Of those patients who did not meet the inclusion criteria:
• 40 percent were excluded due to imaging characteristics predictive of suboptimal responses
• 22 percent were excluded for lung volumes
• 9 percent were excluded for collateral ventilation found on bronchoscopy after passing the noninvasive criteria

Despite inclusion criteria limitations, there may still be a sizable population of patients with emphysema who may benefit from this therapy. As one of the early trial centers studying bronchoscopic lung volume reduction, Mayo Clinic will offer this technology to appropriate candidates in the near future.

For more information


Cone-Beam CT for Enhanced Bronchoscopic Access to Pulmonary Nodules

Peripheral pulmonary nodules are a common abnormality seen by pulmonologists. In some cases, nodules are best managed by serial imaging to assess for interval growth. Alternatively, if the pretest probability of malignancy exceeds 70 percent, a lung nodule or mass may be surgically resected without biopsy. However, there are many lesions of indeterminate probability for lung cancer or metastasis that require biopsy for treatment decisions. CT-guided biopsies are the gold standard for nonsurgical biopsy technique with a diagnostic rate around 90 percent. The drawback is the high rate of pneumothoraces, often quoted as high as 15 percent.

A preoperative intervention also may be required to help the thoracic surgeon localize the nodule while in the operating room to minimize the extent of normal parenchymal resection. A CT-guided transthoracic needle approach is often used for placement of localizing coils or injection of a radionucleotide tracer. These types of procedures usually take place in a separate room in a different part of the hospital.

Because of these limits of CT-guided transthoracic procedures, there have been substantial efforts to find a bronchoscopic technique that rivals CT-guided procedures without the drawbacks. Over the past 10 years there have been many new developments in navigational bronchoscopy, including electromagnetic navigation bronchoscopy, radial probe endobronchial ultrasound (EBUS) and other hybrid techniques. Many of these modalities use virtual-guidance-based planning derived from a breath-hold CT scan, which potentially puts nodules in a different location within the chest than does bronchoscopy performed with sedation. The virtual nature of some of these bronchoscopic guidance technologies might partially explain diagnostic rates that are disappointingly low in the 60 to 70 percent range. However, the use of cone-beam CT (CBCT) for real-time bronchoscopic navigation has received increasing interest in the past year.

CBCT scanning technology is not new. It has been available for over 20 years and has been used by oral surgeons, orthopedic surgeons, vascular surgeons and interventional radiologists, among others. CBCT scanning essentially utilizes a fluoroscopy C-arm that rotates around the patient and provides a real-time CT image. The quality is not as high as that of a standard multidetector CT scan (Figure 1), but CBCT image quality is sufficient for localizing pulmonary nodules, with the added benefit of real-time 3D guidance to confirm a lesion has been accessed. A CBCT scan can also be fused with fluoroscopy (Figure 2) to allow precise localization (Figure 3).

A study published in the Journal of Bronchology & Interventional Pulmonology in 2018 described the first large patient series using CBCT with augmented fluoroscopy combined with more conventional navigational bronchoscopy techniques to biopsy 93 lesions with a median size of 16.0 mm in 75 consecutive patients. The overall diagnostic yield was about 84 percent, approach-
ing yields found with a CT-guided transthoracic needle approach.

At Mayo, interventional pulmonologists and thoracic surgeons are exploring the use of CBCT during bronchoscopy, in the hope that CBCT will allow improvements over existing navigational bronchoscopy techniques. In the near future, the use of this technology may allow bronchoscopic therapeutics for malignant lesions in the lungs.

For more information

Anti-Interleukin-5 Therapy for Severe Asthma: A New Therapeutic Option

For patients with severe eosinophilic asthma — practically defined as patients with the need for frequent or continuous oral corticosteroid therapy or patients with inadequate asthma control despite maximal inhaler therapy — there is a new treatment option in the form of anti-interleukin-5 (IL-5) therapy. There are currently three FDA-approved anti-IL-5 therapy agents on the market: benralizumab, mepolizumab and reslizumab (Table). Results of clinical trials for these agents were published in The Medical Letter on Drugs and Therapeutics and New England Journal of Medicine between 2014 and 2018.

Both benralizumab and mepolizumab are approved for patients age 12 years and older, whereas reslizumab is approved for patients age 18 years and older. These agents appear to have excellent safety and efficacy profiles with a major beneficial impact on reduction of asthma exacerbations and associated health care utilization.

Selection of patients for anti-IL-5 therapy
It is essential that patients be carefully chosen for this step-up therapy. Anti-IL-5 therapy is approved for patients with refractory asthmaph with an eosinophilic phenotype. The eosinophilic phenotype is defined slightly differently for each agent. For the purposes of mepolizumab drug approval, eosinophilia is defined by the presence of 150 or more eosinophils per microliter in the peripheral blood at the time of the clinic visit or 300 or more cells per microliter at any time during the previous year. Patients who benefit most from anti-IL-5 therapy are those who continue to have inadequate asthma control or exacerbations despite high-dose inhaled corticosteroids, frequent oral corticosteroid use, or both.

Practice points when considering anti-IL-5 therapy
The new anti-IL-5 therapy agents have now helped to improve asthma care for many patients with severe eosinophilic asthma. The 2018 Global Initiative for Asthma (GINA) guideline recommends these therapies for severe asthma despite optimal inhaler therapy. It is important to remember that these agents are best initiated after a thorough evaluation by physicians and centers comfortable with managing patients with severe asthma.

Very rapid taper of oral corticosteroids soon after initiating anti-IL-5 therapy is not advised due to risk of an asthma flare. Patients should be advised regarding the absolute need to continue existing controller therapies for asthma, including inhaled corticosteroids, long-acting beta agonists, long-acting musca-
Table. FDA-approved anti–IL-5 therapy agents on the market include benralizumab, mepolizumab and reslizumab. Based on The Medical Letter on Drugs and Therapeutics. 2018;60:33.

<table>
<thead>
<tr>
<th></th>
<th>Benralizumab (Fasenra)</th>
<th>Mepolizumab (Nucala)</th>
<th>Reslizumab (Cinqair)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>IL-5 receptor blocker</td>
<td>IL-5 antagonist</td>
<td>IL-5 antagonist</td>
</tr>
<tr>
<td>Ages approved for</td>
<td>≥ 12 years</td>
<td>≥ 12 years</td>
<td>≥ 18 years</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Dose/frequency</td>
<td>30 mg every 4 weeks for 3 doses, then every 8 weeks</td>
<td>100 mg every 4 weeks</td>
<td>3 mg/kg every 4 weeks</td>
</tr>
<tr>
<td>Eosinophilic phenotype criteria</td>
<td>≥ 150 eosinophils/µL at time of visit/within the previous 6–12 weeks of visit or ≥ 300 eosinophils/µL at any point in the past 12 months</td>
<td>≥ 150 eosinophils/µL at time of visit/within the previous 6–12 weeks of visit or ≥ 300 eosinophils/µL at any point in the past 12 months</td>
<td>≥ 400 eosinophils/µL within 4 weeks of initiating therapy</td>
</tr>
<tr>
<td>Anaphylaxis rate</td>
<td>&lt; 1 percent</td>
<td>&lt; 1 percent</td>
<td>&lt; 1 percent</td>
</tr>
<tr>
<td>Cost</td>
<td>$4,752</td>
<td>$2,868</td>
<td>$2,580</td>
</tr>
</tbody>
</table>

For more information
Benralizumab (Fasenra) for severe eosinophilic asthma. The Medical Letter on Drugs and Therapeutics. 2018;60:33.


Mepolizumab (Nucala) for severe eosinophilic asthma. The Medical Letter on Drugs and Therapeutics. 2016;58:11.

Reslizumab (Cinqair) for severe eosinophilic asthma. The Medical Letter on Drugs and Therapeutics. 2016;58:81.

Update in Pleural Disease

Pleural diseases remain a common and challenging clinical problem. With an estimated 1.5 million new pleural effusions diagnosed annually in the United States, the incidence approaches that of diabetes (1.8 million new diagnoses annually) and eclipses that of congestive heart failure (400,000 new diagnoses annually). Spontaneous and iatrogenic pneumothoraces affect an additional 40,000. Yet in spite of pleural diseases’ high prevalence and standardized diagnostic approaches, the etiology of up to one-quarter of effusions remains unknown even after an exhaustive investigation. Almost 75 percent of effusions are ultimately due to congestive heart failure, malignancy or infection, and with an aging population, the incidence of all three continues to rise worldwide. This update addresses some of the latest understanding and approaches to management of malignant pleural disease and pleural space infection.

Malignant pleural disease
In 2010, the British Thoracic Society (BTS)...
published its comprehensive approach to pleural diseases. Included in these guidelines was a well-written and logical approach to the management of malignant pleural disease. Recognizing that malignant pleural effusions remain just one of a multitude of explanations for dyspnea, cough and chest pain in the setting of underlying cancer, BTS proposed in algorithmic form an approach to treating symptomatic malignant pleural effusions. Options discussed included to do nothing, perform serial thoracentesis, or progress on to chemical pleurodesis or tunneled pleural catheter placement.

Since the overwhelming majority of malignant pleural effusions recur and require treatment within 30 days of diagnosis, BTS’ recommendation for serial thoracentesis was that it be reserved primarily for patients with highly responsive malignancies or very brief life expectancy, or patients who decline other options. Life expectancy in the setting of malignant pleural effusions has been challenging to estimate, however, with performance scores the only reasonable, albeit marginally accurate, predictor.

Results of a multicenter prospective study published in Thorax in 2014 greatly advanced the ability to predict life expectancy in this group of patients. Investigators from the United Kingdom prospectively analyzed mortality in patients with malignant pleural effusions and developed and validated a scoring system conveniently named the LENT prognostic score. This four-part score assigned relative values to measurements of pleural fluid lactate dehydrogenase (L), ECOG performance score (E), serum neutrophil-to-lymphocyte ratio (N) and tumor type (T).

In the study, patients with low composite scores (0-1) were shown to have median survivals of 319 days, those with moderate scores (2-4) showed survivals of 130 days, and those with high scores (5-7) showed survivals of 44 days. For patients with high scores, more conservative management such as serial thoracentesis or tunneled pleural catheter placement may be most appropriate, whereas patients with low and moderate scores likely can be treated with any one or a combination of approaches.

For patients with low to moderate LENT prognostic scores, the 2010 BTS recommendation is to proceed to chemical pleurodesis and reserve the use of tunneled pleural catheters to those patients with unexpandable lung or failed pleurodesis.

Much has changed since the BTS guidelines were published in 2010. Of particular importance is the 2012 TIME2 trial published in JAMA. In this randomized prospective trial, patients were randomized to either undergo chemical pleurodesis with talc or placement of a tunneled pleural catheter for management of their malignant pleural effusion. The primary outcome measured was a visual analog score for dyspnea at 42 days after the intervention, which did not differ between the chemical pleurodesis and pleural catheter arms, although the dyspnea score favored the pleural catheter at six months. Other key findings were a statistically shorter initial hospital length of stay and the need for fewer additional procedures, both favoring the pleural catheter. There were, however, more adverse events in the pleural catheter arm relative to the pleurodesis arm, although most of the adverse events were considered nonserious. This study has in many ways altered the primary approach in the management of malignant pleural effusions away from chemical pleurodesis and in favor of tunneled pleural catheters.

A subsequent retrospective review of the TIME2 data set, published in Chest in 2014, determined that up to six months there was no difference in cost between patients treated with chemical pleurodesis and those treated with tunneled pleural catheter; however, for patients with less than 14 weeks estimated survival, tunneled pleural catheters are the less costly option by a mean cost difference of about $1,700. Certainly the cost can be further reduced in those patients who achieve a spontaneous pleurodesis from the catheter itself. This outcome is known to occur in approximately 40 percent within 50 days of catheter placement and is facilitated by daily drainage.

A randomized controlled study performed in the United Kingdom and published in The American Journal of Respiratory and Critical Care Medicine in 2017 compared patients who received talc administration via the pleural catheter with those receiving placebo. The study was performed to investigate the possible role of talc pleurodesis via the tunneled catheter administered in the outpatient setting. Although the incidence of pleurodesis in the talc-plus-pleural catheter arm (43 percent) was similar to that reported in prior studies that did not employ talc along with a pleural catheter, it significantly exceeded that in the placebo-plus-pleural catheter arm (32 percent). Participants who received talc also reported better quality of life and symptoms scores than those receiving placebo.

Pleural space infection

Pleural space infections, whether parapneumonic effusion or frank empyema, are the most common cause of exudative pleural effusions.
worldwide. The incidence of and mortality from pneumonia and parapneumonic effusions continue to rise. The cornerstone of treating parapneumonic effusions and empyema remains appropriate antibiotic selection based on local microbiology and resistance patterns and establishing early drainage. Delayed drainage often results in fibrinous septation of the pleural space, which makes subsequent drainage more difficult or even impossible.

Traditionally, surgery has been needed to address undrained pockets of infected pleural fluid. However, more recently intrapleural thrombolysis has been employed with good results. The MIST2 trial results, published in the *New England Journal of Medicine* in 2011, demonstrated a 77 percent reduction in surgery for those patients receiving three days of twice daily intrapleural tissue plasminogen activator (TPA) and DNase. Those patients receiving this treatment also had a shorter hospital stay. However, no mortality benefit could be demonstrated based on the study design.

The study treatment included 10 mg of TPA administered into the pleural space and then allowed to dwell for one hour before drainage and subsequent administration of 5 mg of DNase. This treatment was administered twice daily for three days. Although the two medicines were administered separately for the purposes of the MIST2 trial, subsequent smaller reports published in *Journal of Bronchology & Interventional Pulmonology* in 2018 indicate that co-administration is likely as effective and certainly easier. This therapy is expensive (approximately $7,000 for the complete three-day treatment), and questions remain about which patients are most likely to benefit from it relative to a surgical intervention.

To help clarify this issue, the MIST2 investigators performed a retrospective review of the MIST1 and MIST2 databases and developed a multistep scoring system to better predict prognosis in those patients who present with pleural space infections. The RAPID score assigns points to various clinical measures such as renal function (R), age (A), pleural fluid purulence (P), infectious source (I) and dietary factors as reflected in serum albumin (D). By calculating this score, patients can be stratified into those at low risk (score 0-2), moderate risk (score 3-4), and high risk (score 5-7) for mortality within the subsequent three months. The study was published in *Chest* in 2014.

On the basis of the calculated score, those in the low-risk category were shown to have a 1 to 3 percent chance of dying within three months, whereas those in the moderate-risk group were shown to have a 9 to 12 percent chance, and those in the high-risk group, a 31 to 51 percent chance. By assessing this mortality risk, investigators believe that patients can be more appropriately stratified toward a more aggressive, early surgery arm vs. a less aggressive approach that may include intrapleural thrombolytic therapy.

**For more information**


Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis comprises three different syndromes — granulomatosis with polyangiitis (GPA, also known as Wegener’s granulomatosis); microscopic polyangiitis (MPA); and eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss syndrome) — all with frequent respiratory manifestations.

Diffuse alveolar hemorrhage (DAH) caused by capillaritis occurs in about 25 percent of patients with GPA and MPA, either at presentation or during a disease relapse, whereas DAH is extremely rare in EGPA. Patients with DAH usually have detectable ANCAs, either targeting proteinase 3 (PR3) or myeloperoxidase (MPO). Lung nodules, masses or cavities are disease-defining consequences of necrotizing granulomatous inflammation in GPA. Tracheobronchial involvement also is a feature predominantly of GPA, rarely found in MPA but not in EGPA. Asthma and eosinophilic pneumonia are disease-defining features of EGPA when they occur in patients with features of small vessel vasculitis.

**Cyclophosphamide and rituximab**
Recent studies have shown that ANCA specificity (PR3 versus MPO) is more important for prognosis, relapse risk, response to therapy and outcomes than the specific diagnosis (GPA versus MPA). Specifically, the presence of PR3-ANCA (rather than MPO-ANCA) portends a better response to rituximab than to cyclophosphamide, but also a much higher relapse risk, and hence the need for ongoing maintenance therapy. For patients with EGPA, the presence of ANCA (usually MPO-ANCA) conveys a vasculitic disease phenotype, and glomerulonephritis or DAH is very unusual in the absence of ANCA.

For management purposes, GPA and MPA are considered together because of significant clinical overlap at presentation and similar treatment response. By contrast, asthma and specific disease manifestations caused by eosinophilic inflammation define the treatment needs of patients with EGPA.

Rituximab has been found superior to cyclophosphamide for patients positive for PR3-ANCA and for patients with relapsing GPA or MPA and therefore has essentially replaced the use of cyclophosphamide. This outcome is also true for patients with DAH requiring mechanical ventilation, as confirmed in research published in *Arthritis & Rheumatology* in 2016.

For patients with MPA or MPO-ANCA-associated vasculitis, cyclophosphamide remains an option for remission induction because these patients respond equally well to cyclophosphamide or rituximab, and they have a much lower relapse risk than those with PR3-ANCA or GPA. However, for patients with MPA or MPO-ANCA-associated vasculitis who experience a disease relapse, or for whom fertility preservation or compliance is of concern, rituximab is preferable to cyclophosphamide.

Rituximab is also emerging as an effective and safe remission maintenance agent. A randomized controlled trial has documented that rituximab given at a dose of 500 mg intravenously every six months following remission induction with glucocorticoids and cyclophosphamide in newly diagnosed patients is superior to daily oral azathioprine for maintenance of remission.

This trial also showed rituximab to be cost-effective because higher drug costs were offset by increased cost of care arising from relapses and subsequent end-stage renal disease occurring at a higher frequency when azathioprine was used for remission maintenance. Trial results were published in the *New England Journal of Medicine* in 2014.

Prompted by a better understanding of the short-term and long-term risks associated with glucocorticoid use, the focus of clinical research in ANCA-associated vasculitis has shifted toward minimizing glucocorticoid use. To date, high-dose glucocorticoids remain necessary for remission induction, regardless of whether rituximab or cyclophosphamide is used. Yet the improvements in overall outcomes have not substantially altered the early (within three to six months after diagnosis) mortality of about 10 percent, more than half of which is related to sepsis and other severe infections. Uncontrolled underlying vasculitis disease activity accounts for less than 20 percent. Therefore, new drugs that can safely control the acute inflammatory response of the innate immune system as well as glucocorticoids are under investigation.

A double-blind, double-placebo-controlled, multicenter phase III trial in 300 patients with GPA or MPA has recently completed enrollment. In this trial, a small molecule (oral agent) inhibitor of the receptor for activated complement factor 5, avacopan, is being compared head-to-head with standard glucocorticoid dosing for remission induction. Results of this trial will be available next year.
Another landmark randomized controlled trial conducted in 700 patients with GPA or MPA was designed to evaluate the efficacy of adjunct plasma exchange and to compare standard glucocorticoid dosing with an accelerated glucocorticoid tapering regimen. Headline results of this trial were presented in June 2018 as showing no efficacy of plasma exchange in the entire cohort or any clinical subset (severe renal disease or DAH), while the accelerated glucocorticoid tapering regimen was as effective but safer (lower infection rate) than the standard glucocorticoid dosing.

Reducing the cumulative glucocorticoid dosing is also a major issue in EGPA, as patients often require significant ongoing use of systemic glucocorticoids to control severe asthma, rhinosinusitis and nasal polyposis, long after the vasculitic disease manifestations have been well-controlled. The recently completed randomized, placebo-controlled, phase III trial of mepolizumab (300 mg subcutaneously once a month) has shown superiority to the standard of care for all primary and secondary endpoints of the trial, leading to FDA approval of mepolizumab for use in EGPA, and its availability as a welcome option for patients who cannot sustainably reduce their systemic glucocorticoid usage below a level of about 7.5 mg of prednisone daily. Trial results were published in the New England Journal of Medicine in 2017.

For more information


Longitudinal Protocol for Granulomatosis With Polyangiitis (Wegener’s) and Microscopic Polyangiitis. Mayo Clinic.