COPD Part III:
LVRS, BiPAP, and Transplantation

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Educational Objectives:

1. Review selection criteria for and outcomes of lung volume reduction surgery and bronchoscopic lung volume reduction
2. Review indications for and outcomes of non-invasive nocturnal ventilation
3. Outline when to consider lung transplantation for COPD

Scenario One:
Mr. S is a 62 yo male with severe COPD (FEV_1 of 38% predicted). You have been following him for several years and have treated him with fluticasone/salmeterol 250/50 1 puff twice daily, tiotropium 18 mcg 1 capsule inhaled daily, and albuterol 2 puffs or a nebulizer treatment every 6 hours as needed. About a year ago, you prescribed roflumilast 500 mcg oral daily due to a history of several exacerbations in the preceding year and ongoing chronic bronchitic symptoms. He says he initially had some loss of appetite and lost 6 pounds, but he feels better now and denies ongoing side effects. He thinks it may be helping a little bit but he still struggles with severe dyspnea despite regular aerobic exercise. A friend told him to ask about lung volume reduction surgery and he wonders if he is a candidate.

<u>Question 1</u>: What patient characteristics are favorable for lung volume reduction surgery (LVRS)? What are the potential risks and benefits?

LVRS involves surgical resection of severely emphysematous lung tissue from one or both upper lung zones. The resection is non-anatomic (i.e. not a lobectomy or segmentectomy). Up to a third of lung tissue may be removed from each lung, and the surgeon will attempt to balance removal of non-functional tissue with preservation of as much functional tissue as possible. Techniques for lung tissue removal include median sternotomy, VATS, and thoracotomy.

- **Mechanism:** There are several postulated mechanisms of benefit:
  - First, as the remaining lung stretches to fill the evacuated space in the chest, elastic recoil is increased, thereby increasing stenting forces holding open

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small airways and reducing small airways resistance allowing for improved expiratory airflow.
  - Second, the reduction in overall volume of the chest brings the diaphragm up and chest wall back in toward a more normal resting position, restoring some mechanical advantage.
  - Third, the resection of dead space in the lung may improve V/Q matching, leading to better gas exchange despite the decrease in overall surface area.

- **Patient selection:** All patients should have severe dyspnea despite aggressive treatment with bronchodilators, oxygen as necessary, and exercise training (preferably pulmonary rehabilitation). Testing should include full pulmonary function tests with plethysmographic lung volumes (gas dilution methods may significantly underestimate volumes), high-resolution chest CT without contrast to assess severity and distribution of emphysema, arterial blood gas to exclude significant hypercapnia, and echocardiogram to exclude significant pulmonary hypertension. V/Q scanning with quantitative regional perfusion is helpful to corroborate apical lung destruction (demonstrated by apical hypoperfusion on posterior projections). Cardiopulmonary exercise testing by cycle ergometry on 30% oxygen is not strictly necessary except to distinguish whether a patient may derive a mortality benefit from the procedure. See Table 1.

Table 1: Selection criteria for lung volume reduction surgery

Favorable characteristics	Unfavorable characteristics
• Severe, apical predominant emphysema • Severe obstruction (FEV_1 ≤45% pred) • Severe air trapping (ideally RV >200% pred, TLC >100%) • Apical hypoperfusion on V/Q (<10% perfusion to upper lung thirds) • Apical air trapping on V/Q (long tracer half life in upper lung thirds) • Low exercise capacity after rehab (<25 W on cycle ergometry for women, <40 for men) • Single organ disease	• Airways disease phenotype (i.e. severe obstruction but only mild emphysema) • Homogenous or basilar predominant emphysema* • Insufficient obstruction (FEV_1 >45% pred) • Insufficient air trapping (RV <150%) • Preserved apical perfusion on V/Q (≥20% perfusion to upper lung thirds) • FEV_1 and DLCO both <20% predicted * • Severe comorbid illness • pCO_2 >60 • PASP >45 (or mean PA >35)

**Higher risk of early mortality (<90 days post-procedure) based on the NETT Trial (see below)*

National Emphysema Treatment Trial (NETT) (NEJM 2003)
Study design: Unblinded randomized control trial randomizing 1218 subjects with severe COPD to LVRS or continued maximal medical management. Baseline assessments and eligibility were determined after completing pulmonary rehab to exclude the effect of exercise conditioning.

Inclusion criteria: COPD with FEV_1 ≤45% predicted, bilateral emphysema, TLC ≥100% pred, RV ≥150% pred, pCO_2 ≤60, pO_2 ≥45, BMI ≤31.1 (males) or ≤32.3 (females), nonsmoker for ≥4 mos.

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Exclusion criteria: FEV1 ≤20% predicted and either homogeneous disease or DLCO ≤20% predicted (criterion added at interim analysis due to increased mortality), inability to perform valid DLCO maneuver (also added at interim), previous sternotomy or lobectomy, giant bulla, pulmonary nodule requiring surgery, MI within 6 mos of baseline, CHF (EF <45%), uncontrolled HTN (SBP >200, DBP>110), pulmonary hypertension (Cath PASP ≥45 or mean PA ≥35), clinically significant bronchiectasis, daily use of >20 mg prednisone, O_2 requirement >6 L/min, history of recurrent infections with clinically significant daily sputum production, six minute walk distance <140 m after rehab, comorbid disease expected to compromise survival over the course of the study.

Intervention: LVRS by either VATS or median sternotomy vs. medical management alone

Primary Outcomes: Survival and maximal exercise capacity.

Results: At an interim analysis, the subgroup with FEV1 ≤20% predicted and either homogeneous disease or DLCO ≤20% predicted was found to have significantly higher mortality with LVRS and were subsequently excluded from the trial.

Overall mortality was not different between treatment groups, even after excluding these high-risk subjects. The LVRS group had a greater chance of a 10 W improvement in exercise capacity (16% vs. 3%, p<0.001).

Among the subgroup of subjects (at least partially conceived *a priori*) with predominantly upper lobe emphysema and a lower exercise capacity (max workload <25 W for women, <40 W for men), mortality was lower in the LVRS group (risk ratio for death 0.47, p=0.005). In contrast, those with non-upper lobe predominant emphysema and a higher exercise capacity had a higher mortality with LVRS (risk ratio for death 2.06, p=0.02).

Adverse events: Overall mortality 5% in LVRS group. Other adverse events included re-intubation (22%), air-leak >7 days (~40%), arrhythmias (19%), pneumonia (18%), and failure to wean (trach required in 8%). MI (1%) and stroke (<1%) were rare.

Table 3. Improvement in Exercise Capacity and Health-Related Quality of Life at 24 Months.*

Patients	Improvement in Exercise Capacity				Improvement in Health-Related Quality of Life			
	Surgery Group	Medical-Therapy Group	Odds Ratio	P Value	Surgery Group	Medical-Therapy Group	Odds Ratio	P Value
	no./total no. (%)				*no./total no. (%)*			
All patients	54/371 (15)	10/378 (3)	6.27	<0.001	121/371 (33)	34/378 (9)	4.90	<0.001
High-risk†	4/58 (7)	1/48 (2)	3.48	0.37	6/58 (10)	0/48	—	0.03
Other	50/313 (16)	9/330 (3)	6.78	<0.001	115/313 (37)	34/330 (10)	5.06	<0.001
Subgroups†								
Predominantly upper-lobe emphysema								
Low exercise capacity	25/84 (30)	0/92	—	<0.001	40/84 (48)	9/92 (10)	8.38	<0.001
High exercise capacity	17/115 (15)	4/138 (3)	5.81	0.001	47/115 (41)	15/138 (11)	5.67	<0.001
Predominantly non–upper-lobe emphysema								
Low exercise capacity	6/49 (12)	3/41 (7)	1.77	0.50	18/49 (37)	3/41 (7)	7.35	0.001
High exercise capacity	2/65 (3)	2/59 (3)	0.90	1.00	10/65 (15)	7/59 (12)	1.35	0.61

Figure 1. Improvement in exercise capacity and health-related quality of life at 24 months. above and below from the National Emphysema Treatment Trial (NEJM 2003).

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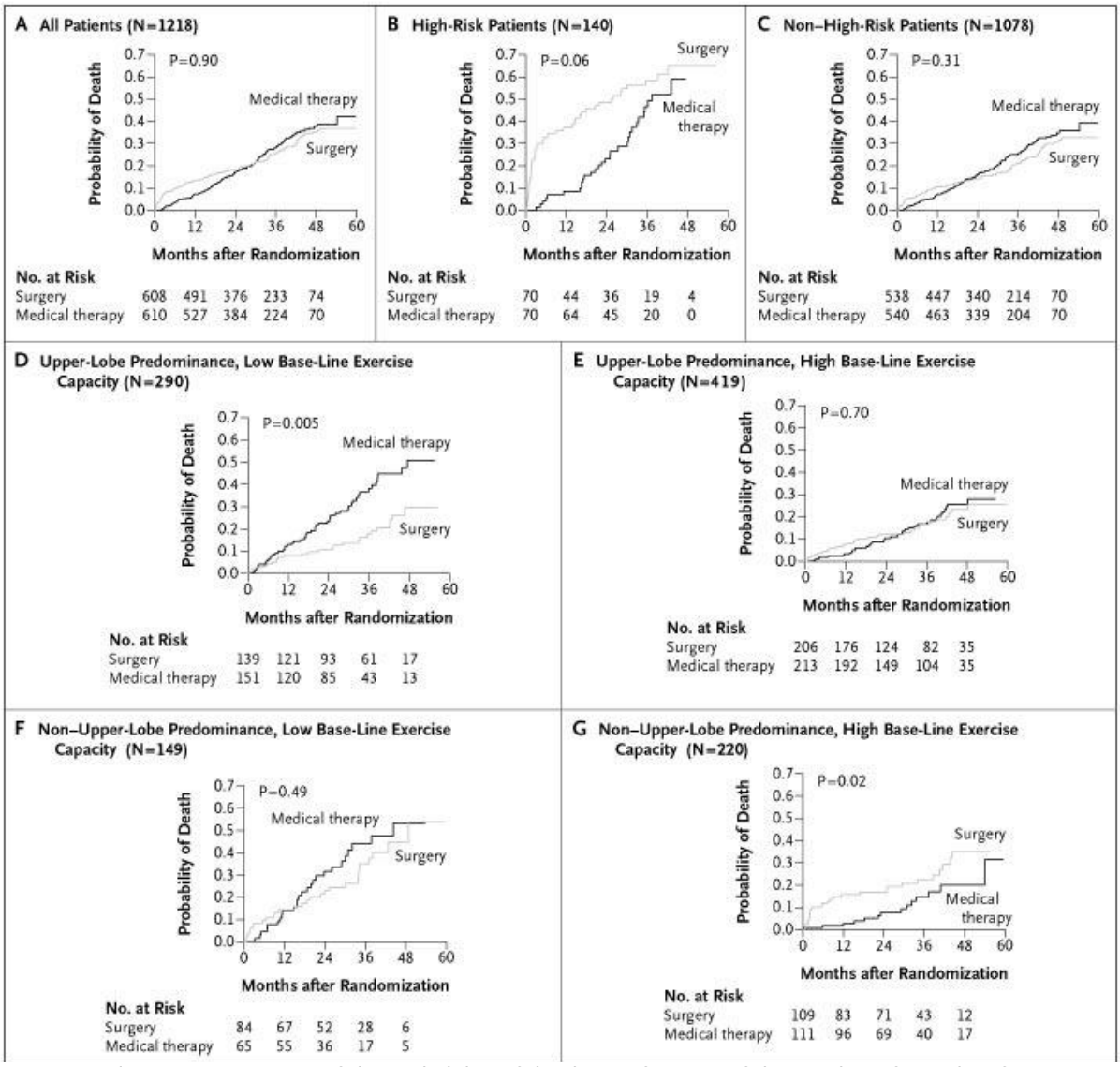

Figure 2. Kaplan-Meier estimates of the probability of death as a function of the number of months after randomization. High risk patients were defined as having an FEV1 <20% predicted and either homogenous emphysema or a DLCO <20% predicted from National Emphysema Treatment Trial (NEJM 2003).

Summary: Surgical LVRS can help with removal of lung tissue in severe emphysema to enable improvement of physiologic status; leading to improved exercise tolerance and mortality. **There was an early risk of death in the first three months for those who underwent LVRS**, however, long-term outcomes (>36 months) show a benefit of surgery over medical therapy for appropriately chosen candidates. Improvements in lung function, quality of life and exercise capacity were also seen **Candidates who may garner the most benefit from LVRS are those with apical predominant emphysema and low exercise capacity.** Interestingly, although early mortality (<90 d) was increased in the entire homogeneous or basilar predominant group after exclusion of the high risk (FEV1 ≤20% predicted and either homogeneous disease or DLCO ≤20% predicted) phenotype, those with homogeneous disease and a low exercise capacity ultimately did not have higher long-term mortality compared with medical therapy (the survival curves crossed, indicating an early mortality in the surgery group followed by a late survival benefit, such that the overall difference was statistically insignificant, with the surgery group technically having

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the numerically lower mortality). In fact, Medicare approved the procedure for the homogeneous low exercise group, although not all centers recommend LVRS for this group.

Scenario one continued:
On evaluation, Mr. S has an FEV_1 of 38% pred, TLC 110% pred, RV 145% predicted, and DLCO 32% pred. His CT shows severe, relatively homogeneous emphysema. His ABG on room air is 7.32/65/54. Echocardiogram shows normal LV size/fxn, normal RV size/fxn, and an estimated PASP of 44 mm Hg. You explain that he is not a candidate for LVRS due to homogeneous emphysema, insufficient air-trapping, and significant hypercapnia.

Question 2: What other options for lung volume reduction might be considered for Mr. S?

Bronchoscopic lung volume reduction (BLVR) has been demonstrated to be a non-surgical alternative to LVRS for symptomatic patients with heterogenous emphysema and significant hyperinflation. While several methods for achieving BLVR are under investigation, the best studied (and only FDA-approved) method is endobronchial valve placement. In these procedures, one-way valves are placed in the airways leading to areas of hyperinflated and emphysematous lung. These valves allow for expiration of air, but close during inspiration and prevent air from passing into an area of lung. This results in collapse of the distal lobe, thereby improving hyperinflation. As mentioned in the previous section, dyspnea improves due to improved diaphragm and chest wall mechanics, improved recoil, and in some cases re-expansion of less affected regions of lung.

BLVR carries a high risk of pneumothorax. As the target lobe collapses, the ipsilateral untreated lobe expands and stretches. As this part of the lung is also typically affected with emphysema as well to some degree, lung defects (blebs, bullae, etc.) may rupture during rapid expansion, resulting in the development of pneumothorax. Pneumothorax complicates up to 34% of BLVR procedures. A number of factors associated with pneumothorax and poor outcomes following valve placement are listed in the table below (van Dijk M et al. 2021). In addition, mortality following valve placement is approximately 3%. Consequently, appropriate patient selection is very important (Fernandez-Bussy et al. 2018, Herth F. et al. 2017).

Table 2: Selection criteria for bronchoscopic lung volume reduction

Favorable characteristics	Unfavorable characteristics
• Severe, heterogenous emphysema • Severe obstruction (FEV_1 ≤45% pred) • Severe air trapping (RV >175% pred) • Resting hyperinflation (TLC >100% pred) • 6MWD of less than 500 m • BMI < 33 • No tobacco use in last 4 months • No evidence of collateral lobar ventilation (Chartis® negative) • Completed pulmonary rehab program within 6 months • mMRC of at least 2 • On maximal inhaler therapy	• Homogenous emphysema • Insufficient obstruction (FEV_1 >45% pred) • Insufficient residual FEV1 (<15% pred) • Insufficient air trapping (RV <175% pred) • Insufficient diffusion (DLCO <20% pred) • Significant cardiac disease (Reduced EF, recent MI, persistent bradycardia, etc) • pCO_2 >50 • PASP >45 (or mean PA >35) • 6MWD of less than 100m • Giant bullae involving >30% of either lung • Daily prednisone of 20mg or more

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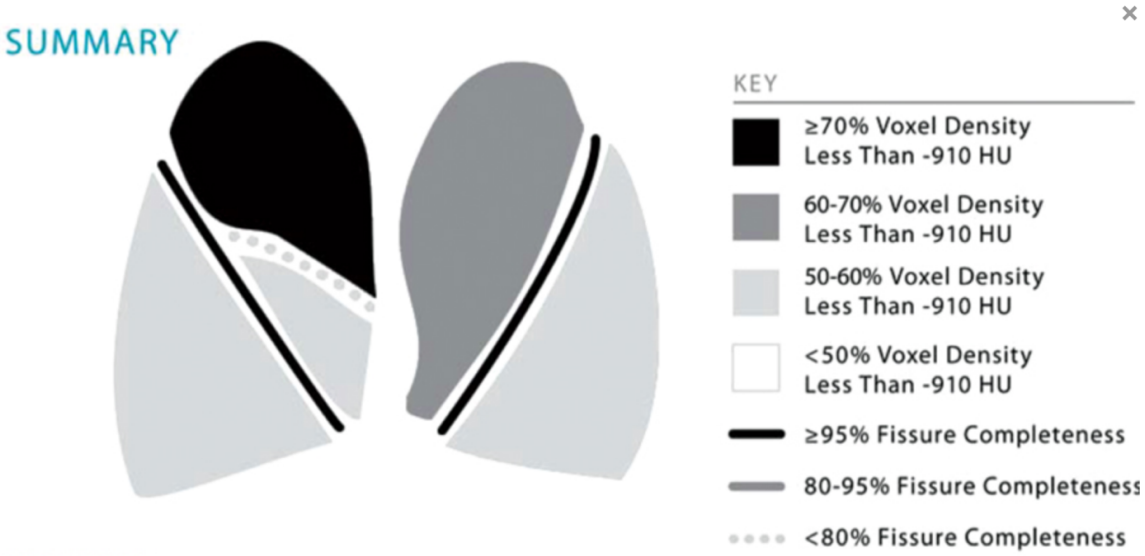
A significant number of patients fail BLVR secondary to the presence of collateral ventilation in the selected airways, leading to airflow from adjacent lobe(s) preventing lobar collapse. Fissure completeness should be at least 80% for endobronchial valves to be successful (Fernandez-Bussy et al. 2018).

With Zephyr® valves, a StratX® report is often obtained (Figure 3). This gives a quantitative measure of fissure completeness, and utilizes CT densitometry to estimate lobar emphysema involvement. A higher percentage of <-910 Hounsfield units (HU) indicates more extensive emphysematous destruction.



RESULTS

	RIGHT LUNG				LEFT LUNG	
	RUL	RUL+RML	RML	RLL	LUL	LLL
% Fissure Completeness	89.8	100.0	88.7	100.0	98.1	98.1
% Voxel Density Less Than -910 HU	74	69	50	56	69	57
% Voxel Density Less Than -950 HU	58	50	20	39	51	38
Inspiratory Volume (ml)	1736	2228	492	1655	2259	2044

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Figure 3. A StratX® report assessing fissure completeness (https://pulmonx.com/stratx/).

For suitable patients, outcomes after BLVR are favorable. In a randomized controlled trial of 190 patients, 56% of patients had an increase of at least 12% in FEV1 at 1 year, with improvements in a significant proportion of patients in RV, SGRQ, mMRC and BODE at 1 year as well (Figure 4). There is inadequate evidence for BLVS related to mortality, however, there has been an observed survival benefit in those who experience lobar atelectasis following intervention compared to those who do not (Gompelmann D et al. 2019).

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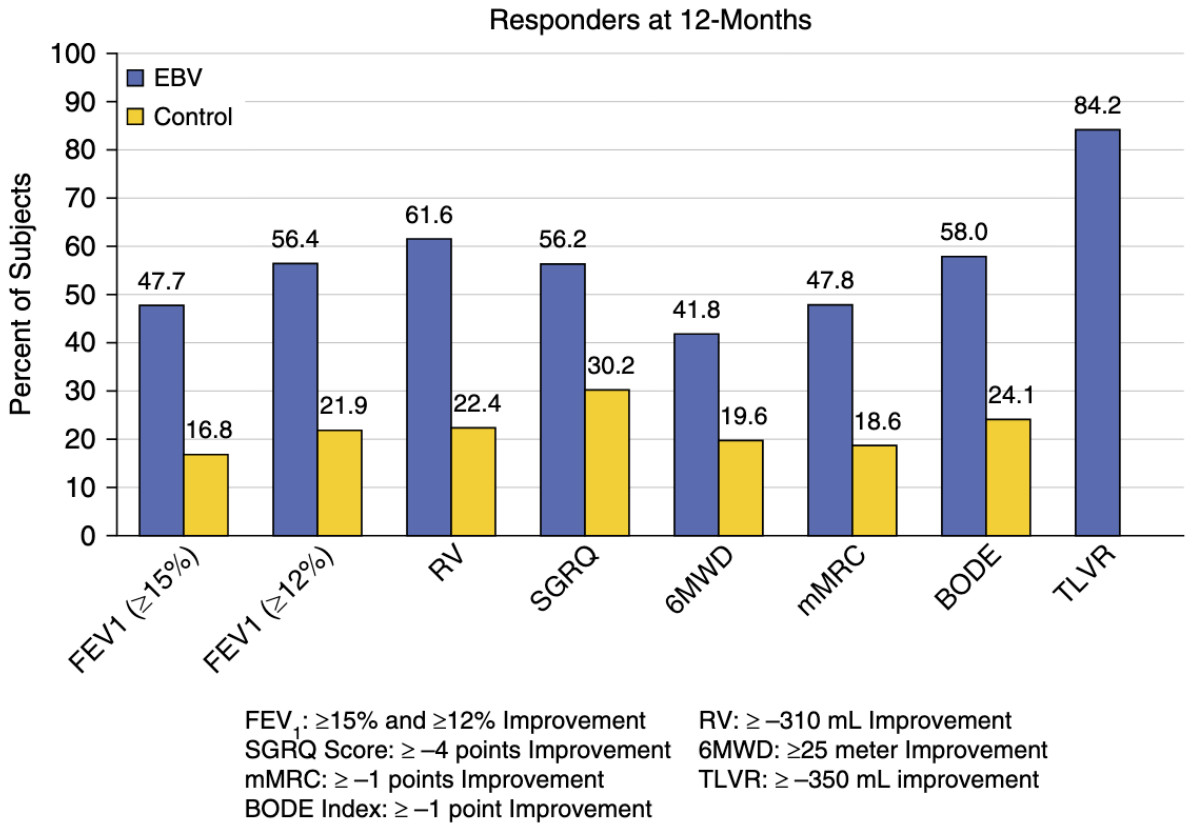

Figure 4. Summary of responders based on minimal clinically important difference for variables assessed in the LIBERATE study of Zephyr EBV (AJRCCM 2018)[6].

Scenario one continued:
Mr. S has insufficient air trapping to be a good candidate for BLVR with an RV of 145%. His homogenous emphysema and resting PaCO2 of 65 also portend a high risk of a poor outcome. You inform Mr. S that he is not a candidate for bronchoscopic lung volume reduction either due to these factors.

<u>Question 3</u>: Would Mr. S benefit from non-invasive positive pressure ventilation at night?

Non-invasive positive pressure ventilation (NIPPV, e.g. BiPAP) is an established, proven therapy for severe acute exacerbations of COPD, reducing mortality and subsequent intubation. Similarly, the data for NIPPV in patients with an overlap of COPD and sleep disordered breathing show consistent benefit. There is growing evidence to support the use of NIPPV in patients with stable COPD. There have been several older RCTs (Casanova et al. 2000, Clini et al. 2002), however which have not supported these conclusions.

A meta-analysis (JAMA, 2020) of 15 RCTs and 6 observational studies has recently shown significant support for the use of home NIPPV in COPD patients. A review of BiPAP compared to no device showed a lower risk of mortality (OR 0.66 (96% CI:0.51-0.87), p=0.003), as well as a reduction in all-cause hospital admissions and a reduced need for intubation. Of note, there was no significant improvement found in quality of life.

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ATS Guidelines (Macrea et al. 2020) support the above findings with their recommendations that nocturnal NIPPV can be considered in patients with chronic stable hypercapnia, in whom OSA has been excluded. Initiation of NIPPV during an admission is for an acute-on-chronic hypercapneic respiratory failure episode is not explicitly recommended, rather this should be re-assessed in 2-4 weeks. Though not well studied at present, carefully selected hospitalized patients could be initiated inpatient on chronic nocturnal therapy, particularly those with a high risk of readmission.

To qualify a stable COPD patient for home NIPPV, insurance criteria (Medicare guidelines) generally require that the patient have:

- **chronic hypercapnia (arterial pCO_2 ≥52)**
- **nocturnal hypoxia (SaO_2 ≤88% for ≥5 min out of at least 2 hours of nocturnal recording time on 2 L/min or patients baseline O_2 dose, whichever is higher)**
- **exclusion of OSA**

Scenario one continued:
Mr. S undergoes a sleep study, which demonstrates sleep related hypoventilation with an oxygen saturation nadir of 84% on oxygen at 2 L/min. There are no significant obstructive apneas. During the study, he spends 57 minutes with an oxygen saturation of 88% or less. You obtain authorization for BiPAP and Mr. S begins using it every night. He feels it helps him rest more comfortably but over the next 2 years his dyspnea and lung function impairment continue to progress. He asks you if he may be a candidate for lung transplantation.

<u>Question 4</u>: What factors determine when it is appropriate to refer for lung transplant?

Timing of referral and listing vary among centers but many use these consensus guidelines to aid in their decision making (see Table 3).

Table 3: Selection Criteria for Referral and Listing for Lung Transplantation in COPD

Timing of Referral	Timing of Listing
• BODE score of 5-6 with additional risk factor(s) suggestive of increased morality: 1. Frequent exacerbations, 2. Increase in BODE Score of >1 over the past month 3. Pulmonary artery: aorta diameter >1 on CT scan, 4. FEV1 20-25% • Clinical deterioration despite maximal medical therapy, pulmonary rehabilitation, oxygen and nocturnal NIPPV (if indicated) • Poor quality of life unacceptable to patient • For a candidate appropriate for bronchoscopic or surgical LVRS; simultaneous referral to lung transplant is appropriate	• BODE score of 7-10 • Additional factors which may prompt listing: 1. FEV1 of <20% 2. Presence of moderate to severe pulmonary hypertension 3. History of severe exacerbations 4. Chronic hypercapnia

(Ref: Leard et al Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation,
The Journal of Heart and Lung Transplantation,2021. https://doi.org/10.1016/j.healun.2021.07.005).

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There are many risk factors for a potentially poor lung transplant outcome. These may change over the time. Below you will find a brief list of absolute contraindications to transplant and may make a transplant most likely harmful for a patient (see ISHLT reference above):

- Lack of patient willingness or acceptance of transplant
- Malignancy with high risk of recurrence or death related to cancer
- Glomerular filtration rate <40mL/min/1.73m2 unless being considered for multi-organ transplant
- Acute coronary syndrome or myocardial infarction within 30 days (excluding demand ischemia)
- Stroke within 30 days
- Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant
- Acute liver failure
- Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery
- Septic shock
- Active extrapulmonary or disseminated infection
- Active tuberculosis infection
- HIV with detectable viral load
- Limited functional status (e.g. non-ambulatory) with poor potential for post-transplant rehabilitation
- Progressive cognitive impairment
- Repeated episodes of non-adherence without evidence of improvement (not applicable for pediatric patients)
- Active substance use or dependence including current tobacco use, vaping, marijuana smoking or IV drug use
- Other severe uncontrolled medical condition expected to limit survival after transplant

Patients with COPD may be listed for either single or bilateral lung transplantation. The presence of significant pulmonary hypertension is a relative contraindication, and severe suppurative airways disease is an absolute contraindication to single lung transplantation. Whether to list a COPD patient for single lung transplantation is somewhat controversial. Post single-lung transplant, native lung hyperinflation (enlargement of bullous emphysema of the native lung) can occur, but this does not appear to affect clinical outcomes.

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