Referring a Patient for Lung Transplant

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Thirty-one years ago Dr. Joel Cooper and colleagues at Toronto General Hospital performed the first successful lung transplant. What began as an experimental treatment of last resort has evolved into a standard intervention for end stage lung disease. Over 3800 adult and pediatric lung transplants were performed worldwide in 2012\(^1\), including 194 performed in Canada\(^2\).

Lung transplants were initially performed on highly selected patients. With growing international experience it has become clear that older candidates and those with comorbidities can undergo successful lung transplantation and enjoy good long-term outcomes. This has resulted in incremental loosening of listing criteria to the point where general respirologists may be forgiven for feeling confused as to who is now an acceptable candidate. In this review I shall attempt to provide a contemporary perspective on candidacy for adult lung transplantation, with particular reference to policies of the Toronto Lung Transplant Program.

The International Society for Heart and Lung Transplantation (ISHLT) published guidelines for the selection of lung transplant recipients in 2006\(^3\) and an update to this document was published in 2015\(^4\). These documents offer detailed disease-specific criteria for assessment and listing, and they outline absolute and relative contraindications. They are intended to provide guidance and to reflect current international norms. However they should not be interpreted too dogmatically. When there is a question regarding suitability it is always best to speak with the Transplant Program directly.

When is transplant referral appropriate?

In general terms, lung transplant should be considered in patients suffering from incurable chronic lung disease with an expected survival of 2 years or less. It can also be considered in patients with a longer predicted survival but whose quality of life is intolerable due to refractory dyspnea or other respiratory symptoms.

The time from initial referral to transplantation often exceeds one year and this time frame needs to be taken into account when making a referral. Assessments can be expedited when necessary, but it is better to refer too early than too late.

Pulmonary Fibrosis
Pulmonary fibrosis has overtaken COPD as the leading indication for lung transplant. The ISHLT guideline suggests referral of patients with Idiopathic Pulmonary Fibrosis (IPF) or fibrosing Nonspecific Interstitial Pneumonia (NSIP) at the time of diagnosis, but in Ontario we do not believe it is necessary to routinely refer patients with early disease and mild physiologic impairment. IPF tends to be lethal and it is appropriate to refer patients with progressive disease (decline of >10% in FVC or >15% in DLco), moderate physiologic impairment (FVC < 70%, DLco < 50% of the predicted values), pulmonary hypertension, or desaturation below 88% on exertion. Whether the patient is receiving antifibrotic medication should not currently influence the timing of referral.

Other interstitial lung diseases tend to be less aggressive and more responsive to treatment. When deterioration is gradual referral can usually wait until patients have moderate to severe impairment (FVC < 60%, DLco < 40%) and require supplemental oxygen for exertion. However patients who show concerning disease progression in spite of treatment should be referred earlier.

**COPD**

Chronic Obstructive Pulmonary Disease (COPD) is the second commonest indication for lung transplant. Patients typically have an FEV1 < 25% of predicted, are on home oxygen and have important functional limitation. It is important to note that transplant does not necessarily offer a survival advantage for stable COPD patients\(^5\).

Therefore, in addition to FEV1 < 25% patients should have either 1) severe symptoms leading to an intolerable quality of life in spite of maximal medical treatment and pulmonary rehabilitation\(^6\) or 2) poor prognostic features such as a high BODE score (>7), recurrent exacerbations, an exacerbation requiring ICU admission, poor functional capacity or pulmonary hypertension. The possibility of lung volume reduction surgery should also be considered in appropriate patients, and this would not preclude subsequent transplant.

**Cystic Fibrosis**

Cystic fibrosis (CF) is the third leading indication for lung transplant. Referral is appropriate when the FEV1 is < 30 % of predicted, especially when accompanied by frequent exacerbations, requirement for supplemental oxygen, hypercapnia with PCO2 > 50 mm Hg, or pulmonary hypertension. Patients with a higher FEV1 may be referred if the lung function is declining rapidly (especially in females) or in the case of persistent pneumothorax or recurrent hemoptysis.

The decision to proceed to listing is generally made in conjunction with the referring CF team and the patient.

**Pulmonary Hypertension**
Patients with pulmonary arterial hypertension are typically referred by clinicians with specialized expertise in this area. Patients requiring parenteral therapy or those with New York Heart Association Class III-IV symptoms in spite of medical therapy should be assessed. The decision to list would usually be driven by persistent Class III-IV symptoms on full therapy and/or clinical and echocardiographic signs of right heart decompensation. Again the decision to list would be made in discussion with the patient and the pulmonary hypertension specialist.

Patients with other lung conditions including extensive adenocarcinoma in situ (but not invasive lung cancer) may be candidates for transplant. These less common scenarios would best be discussed with the transplant team prior to referral.

What are Contraindications?

General
Patients with non-pulmonary disease that is expected to limit survival to 5 years or less are generally not acceptable candidates. The Toronto program does not have an age cut-off, however only exceptional patients over age 75 are likely to be considered suitable.

Social Supports and Adherence
Lung transplant recipients must adhere to an extensive regimen of medications and follow-up. Because of this, patients with cognitive or memory impairment, patients with a strong history of non-adherence, or those without any “support person” to assist them through the transplant process are generally not acceptable candidates.

BMI
Obesity is a strong predictor of post lung transplant mortality and the Toronto Program will not assess patients whose BMI exceeds 35. Referrals for consultation are still accepted but full formal assessment would need to wait until the patient attains a BMI below 35. Patients are generally expected to decrease their BMI below 30 for listing, although there is some flexibility when listing is urgent. Low BMI is also a concern but would not preclude assessment.

Malignancy
Recent cancer is a major concern and patients with solid tumours should have a cancer-free interval of 2 to 5 years prior to assessment and a low risk of recurrence. Non-melanoma skin cancer is a concern but not a contraindication.

Major Organ Dysfunction
Patients with severe left ventricular dysfunction are not candidates for a lung transplant, although heart-lung transplant can be considered in patients younger than
approximately 60. Patients with ischemic heart disease need to be adequately revascularized prior to lung transplant. Bare metal stents are preferred over drug-eluting stents where feasible, to minimize the period during which the patient cannot be listed due to obligatory treatment with clopidogrel. Select patients may be candidates for bypass surgery or valve replacement during a lung transplant procedure.

 Decompensated cirrhosis is also an absolute contraindication to lung transplant, although some patients under age 60 can be considered for combined lung-liver transplant. Patients with compensated cirrhosis (i.e. normal hepatic synthetic function and no portal hypertension) may still be lung transplant candidates.

 The calcineurin inhibitors cyclosporine A and tacrolimus are nephrotoxic and eventually induce chronic kidney disease in many lung transplant recipients. Preexisting renal dysfunction is considered a relative contraindication to lung transplant. In older patients (>60) and those with multiple comorbidities chronic kidney disease (i.e. estimated GFR < 50 mL/minute) may preclude transplant, but can be evaluated case by case. In younger patients chronic kidney disease is generally acceptable, provided the patient accepts a substantial likelihood that they will require dialysis post transplant.

 **Infections**
 Poorly controlled active infection is a contraindication to transplant. Active TB would need to be fully treated prior to listing. Colonization with resistant organisms such as Burkholderia cenocepaia and Mycobacterium abscessus is a major concern, but not an absolute contraindication in the Toronto program. Hepatitis B infection is acceptable provided it is quiescent or suppressed with medication. Hepatitis C is not generally a contraindication but this depends on the extent of hepatitis activity and liver damage. Patients with HIV who are on treatment with undetectable viral load could be considered for lung transplant, however there is very limited experience in this area.

 **Smoking and Substance Abuse**
 Smoking is considered an absolute contraindication to lung transplant and patients must abstain completely from smoking for 3 months to be assessed and for 6 months to be placed on the waiting list. Patients are expected to limit themselves to minimal alcohol intake post transplant. Patients with a history of substance abuse or daily consumption of alcohol need to demonstrate abstinence prior to listing. Narcotic dependence is a major concern but would not preclude assessment.

 **Level of Function**
 Frailty and poor rehabilitation potential are important concerns but difficult to quantify. Patients who have been unable to walk 100m for a period of months are generally not transplant candidates. A young patient with this sort of limitation might still be considered. Frailty is recognized as an important predictor of post-
transplant outcome and attempts are being made to quantify it in a rigorous and consistent way. It is perhaps obvious that patients with limitation from frailty, cognitive dysfunction, neurologic disease or musculoskeletal problems will continue to have those limitations after a lung transplant. If the limitations are very significant then the appropriateness of lung transplant will need to be carefully considered.

Patients with ARDS are generally not suitable candidates for assessment, since in most cases they will either recover or succumb to their disease before a transplant could be done. Patients requiring long-term mechanical ventilation may be candidates for assessment if they are ambulatory and have minimal comorbidities.

**Musculoskeletal Conditions**
Patients whose mobility is severely affected by musculoskeletal problems would usually be considered poor candidates. Connective tissue diseases in themselves are not contraindications to transplant provided the patient is ambulatory and does not have other major organ dysfunction. Esophageal dysmotility in scleroderma (or other conditions leading to aspiration risk) will be evaluated carefully pre transplant, since aspiration may put the graft at risk. Severe osteoporosis is a relative contraindication to lung transplant.

**Pleura and Chest Wall Issues**
Previous chest surgery or pleurodesis are associated with a more complicated operation and higher bleeding risks but they are unlikely to be contraindications in themselves. Extensive previous chest procedures or chest wall deformity that will constrain function of the transplanted lung are important concerns that might preclude transplant.

**How do I refer?**

If referring to the Toronto Program please complete the referral form (found at http://www.uhn.ca/MOT/Health_Professionals/Referrals/Documents/MOT_PF_CC_LungREFERRAL.pdf). Please include:
- A letter summarizing the patient’s history
- Serial PFTs, 6 minute walk tests (if available) and radiology reports to give a sense of disease trajectory.
- Consultation notes and other documentation regarding co-morbidities.
- CDs with the patient’s CT scans and other relevant imaging.
- Patients over 50 or with a history of heart disease should have an echocardiogram and a stress test (persantine sestamibi or stress echocardiogram) done prior to referral.
If the patient’s suitability for assessment is doubtful or if the referral is highly urgent, a telephone discussion with the program can be very helpful. A Respirologist on call for the Toronto Lung Transplant Program can always be reached through locating at 416-340-3155.

**What should I tell my Patient about Lung Transplantation?**

Patients hope that a transplant will cure their lung disease, improve their quality of life and help them to live longer. It is important that these valid hopes be tempered with the reality that there are many risks and tribulations associated with undergoing a lung transplant. Patients may need to relocate far from friends and family for a year or longer, they will spend many hours in clinic and in rehabilitation sessions, and their life and health will depend on careful adherence to a lifelong follow-up regimen. They will face major surgery with a risk of death or a poor functional outcome afterward. And if all goes well they will still be vulnerable for the rest of their days to complications that can include medication side effects, renal failure, opportunistic infections and malignancy. Most lung transplant recipients will sooner or later develop chronic lung allograft dysfunction ("chronic rejection") that often leads to fatal complications such as infection or respiratory failure. The median survival after lung transplant is 6 to 7 years.

Lung Transplant can produce wonderful outcomes in otherwise hopeless situations. But it is important that patients have realistic expectations and an awareness of the risks.

**Summary**

Lung transplant can confer major survival and quality of life benefits for patients with advanced lung disease. Outcomes are optimized when patients are listed at the appropriate stage of their disease, and disease-specific referral criteria are outlined above. In general, it is best to refer early. If in doubt about a patient’s suitability it is often helpful to call the Program to discuss. Although contraindications to lung transplant have decreased over time, comorbidities are still major determinants of post-transplant outcome and are carefully considered in every patient.

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5Hosenpud JD et al. Effect of Diagnosis on Survival Benefit of Lung Transplantation for End-Stage Lung Disease. Lancet 1998 351 (9095); 24-27

6Eskander A et al. BODE Index and Quality of Life in Advanced Chronic Obstructive Pulmonary Disease Before and After Lung Transplantation. JHLT 2011 30(12) 1334-41

7Lederer D et al. Obesity and Underweight Are Associated with an Increased Risk of Death after Lung Transplantation. AJRCCM 2009 180(9) 887-95