18. Transplantation

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1. INTRODUCTION

- Lung transplantation for end-stage CF has been performed for more than two decades.
- In very well selected CF patients, lung transplantation provides a net survival benefit and an improved quality of life, superior to all other patients with underlying diagnoses other than CF.
- In CF, liver transplantation for end-stage CF-liver disease is performed less frequently.
- In rare cases, combined liver-lung transplantation has been carried out in selected CF patients successfully.
- Experience is very limited with transplantation of the pancreas or pancreatic islets in patients with CF-related diabetes.

2. LUNG TRANSPLANTATION

2.1. Indications for referral and listing

- **Mean waiting times on transplantation list have increased over recent years in Switzerland. Currently, the mean waiting time for a blood group A lung transplant recipient is approximately 200 days and for a blood group O recipient approximately 400 days.**
- In general, recipients with CF are not prioritized on the waiting list unless a recipient is younger than 40 years of age, in which case an organ of a donor less than 40 years of age is preferentially allocated. Thus, waiting times for CF lung transplant candidates are rather similar to patients with COPD, and longer compared to some other countries (USA, France). Therefore, **early referral of patients with advanced CF-lung disease for transplant assessment is vital**.
- In 2014, the Pulmonary Council of the International Society for Heart and Lung Transplantation (ISHLT) updated the consensus document for the selection of lung transplant candidates including for CF. Details that are given below.
- In general, lung transplantation should be considered for patients with end-stage CF-lung disease meeting all of the following general criteria:
  - >50% risk of death due to CF lung disease within 2 years without lung transplantation
  - >80% likelihood of surviving at least 3-months post-transplant
  - >80% likelihood of 5-year post-transplant survival if graft function is sustained
- In addition to a survival benefit, another desired goal of lung transplantation is a substantial symptomatic benefit and improvement of quality of life.
- The criteria for referral are summarized in **Table 1**.

Table 1: Referral criteria for lung transplantation in CF (adapted from[1])

$FEV_1 \leq 30\%$ predicted or a patient with advanced disease with a rapidly falling FEV_1 despite optimal therapy (particularly young female patients, NTM-pulmonary disease*, *B. cepacia* complex infection* and/or diabetes mellitus)
A 6-minute walk distance <400 m
Development of pulmonary hypertension in the absence of a hypoxic exacerbation
Clinical decline characterized by increasing frequency of exacerbations associated with any of the below: – An episode of acute respiratory failure requiring non-invasive ventilation – Increasing antibiotic resistance and poor clinical recovery from exacerbations – Worsening nutritional status despite supplementation – Recurrent pneumothorax – Life threatening hemoptysis despite bronchial embolization

* See section 2.4, *Specific considerations*

2.2. Contraindications

- Contraindications (in particular relative contraindications) are often center-specific. These issues should be discussed with the transplant center well in advance. Generally, the following applies **(Table 2)**.

Table 2: Contraindications to lung transplantation in CF (adapted from[1])

Absolute contraindications

– Recent history of malignancy:
  - In most cases, a 5-year disease-free interval is required
  - In cases with a low predicted risk of recurrence after lung transplantation, e.g. non-melanoma localized skin cancer that has been treated appropriately, a 2-year disease-free interval may be acceptable.
  - In cases with a high risk of recurrence, even a 5-year disease-free interval may not be sufficient.

– Untreatable significant dysfunction of another major organ system (i.e. heart, liver, kidney) unless combined transplantation is performed
– Uncorrected atherosclerotic disease with suspected or confirmed end-organ ischemia, not amenable to revascularization
– Acute medical instability (e.g. acute sepsis, myocardial infarction, liver failure)
– Uncorrectable bleeding disorder
– Chronic infection with highly virulent and/or resistant microbes, including M. tuberculosis
– Significant chest wall or spinal deformity
– Class II or III obesity (BMI > 35.0 kg/m^2)
– Non-adherence to medical therapy

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– Psychiatric or psychological conditions associated with the inability to cooperate with the medical/allied health care team and/or adhere with complex medical therapy
– Substance abuse (e.g. alcohol, tobacco, marijuana) within the last 6 months

Relative contraindications

– Class I obesity (BMI 30.0 to 34.9 kg/m^2)
– Progressive or severe malnutrition
– Severe, symptomatic osteoporosis
– Extensive prior chest surgery with lung resection
– Mechanical ventilation and/or extracorporeal life support. However, carefully selected patients without other acute or chronic organ dysfunction may be successfully bridged to transplantation
– Chronic infection with highly resistant or highly virulent bacteria, fungi, mycobacteria or viruses (e.g. chronic extra-pulmonary infection expected to worsen after transplantation, including hepatitis B, hepatitis C, and HIV)
– Other medical conditions that have not resulted in end-stage organ damage, such as poorly treated diabetes mellitus, systemic hypertension, important atherosclerotic disease, epilepsy, peptic ulcer disease, or poorly controlled gastro-esophageal reflux

2.3. Specific considerations

- **Non-tuberculous mycobacteria (NTM) (see also Chapter "*Non-tuberculous mycobacteria*")**
  - Patients with NTM disease who are being evaluated for transplantation should have the organism confirmed according to microbiology guidelines and commence therapy before transplant listing.
  - Patients with persistent *M. abscessus* or *M. avium* infection despite optimal therapy may be referred for consideration of transplantation. Decisions regarding suitability will be made on an individual basis according to risk stratification. *M. abscessus* or *M. abscessus* subsp. *massiliense* should be identified at a subspecies level by accurate molecular methods in a reference laboratory.
  - Progressive pulmonary or extra-pulmonary disease due to NTM (despite optimal therapy or due to inability of the patient to tolerate the therapy) is usually a contraindication for transplant listing.
- ***Burkholderia cepacia* complex (BCC) (see also Chapter "*B. cepacia complex*")**
  - Patients with *B. cenocepacia* have an increased risk of mortality due to recurrent disease after transplantation.
  - Patients with species other than *B. cenocepacia* do not have an increased risk for mortality after transplantation and can be listed providing other criteria are met.
  - At the time of writing, the Zurich Lung Transplant Team considered infection with *B. cenocepacia* an absolute contraindication for lung transplantation. At CURT (Centre Universitaire Romand de Transplantation), the inclusion in the waiting list for lung transplantation of a CF patient colonized by *B. cenocepacia* is discussed on a case by case basis.

2.4. Pre-transplant evaluation

- Evaluation for lung transplantation is center-specific, but generally the following applies:
  - Outpatient clinic appointments.
  - Contact with lung transplant recipients for "first-hand experience".
  - Inpatient assessment prior to decision for listing.
  - Patient education and teaching regarding transplantation (information relative to the follow-up while on list and preparation for the post-transplant period).
  - **Table 3** outlines the general evaluation during the pre-transplant assessment.

Table 3: Exams that are considered during the pre-transplant assessment

Extensive laboratory tests including – Serology (e.g. for CMV, EBV, HBV, HCV, HIV) – Blood group – HLA typing and anti-HLA antibodies
Microbiology – Complete sputum culture (bacteriology, fungus, mycobacteria) – Screening for MRSA – Urine and stool culture – ENT culture (in selected cases)
Vaccination status and completion of vaccination if necessary*
PFTs (spirometry, body plethysmography, diffusion capacity) 6-minute walk test Blood gas analysis and/or oxymetry and/or capno-oxymetry
Imaging studies – Chest CT scan (if not performed within the last 6 months) – Ventilation/perfusion scan – Abdominal ultrasound (or abdominal CT in selected cases) – Imaging of the sinuses – DEXA bone density scan – Duplex ultrasound of central venous access
ECG Echocardiography (right heart catheter in selected cases) Coronary angiography in patients >50 years of age
Colonoscopy for patients >40 years of age Gastroscopy and colonoscopy for patients >50 years of age

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Diverse specialized reviews by:
- Thoracic surgeon
- Anesthesiologist
- Infectious diseases specialist
- Psychiatrist
- Nutritionist
- Dentist
- Gynecologist
- ENT Specialist (in selected cases)
- Opthalmologist (in selected cases)
- Social worker

*See also Chapter *"Vaccination"*

2.5. Post-transplant outcomes and main complications

- **In very well selected CF patients, lung transplantation provides a net survival benefit and an improved quality of life.**
  - According to the 2017 ISHLT Registry Report, the median survival of adult CF patients receiving lung transplantation is 9.2 years, which is superior to the survival of LT patients with other diagnoses and also to the survival of transplanted pediatric CF patients (5.2 years).
  - Some clinical prediction tools have been developed to estimate the risk of mortality before or after lung transplantation in CF. Although these scores may provide information on patient risk stratification, scores have important limitations and cannot incorporate all the components of the multidisciplinary assessment of the individual transplant candidate. Currently, these scores are not widely used in clinical practice.
- **CF does not recur in the transplanted lungs,** however, patients may develop other pulmonary complications the frequency of which depends on the time-point after transplantation:
  - primary graft dysfunction may develop during the immediate post-operative period
  - infectious complications and acute cellular rejections are more frequent during the first months after transplantation, whereas
  - chronic lung allograft dysfunction (CLAD) is the main cause of long-term mortality and develops in approximately 50% of the patients within 5-years of follow-up. The severity and clinical course of CLAD varies and in cases of important lung function deterioration re-transplantation may be considered.
- Lung transplantation does not address extra-pulmonary CF manifestations, some of which may complicate the clinical course after lung transplantation (e.g. DIOS during the perioperative period, diabetes etc.), whereas new comorbidities may develop over-time as a result of the immunosuppressive treatment **(Table 4)**.

Table 4: Examples of long-term medical complications after lung transplantation in CF

System	Complication	Main contributing factors
Gastrointestinal	Gastroesophageal reflux Gastroparesis	It is common before transplantation in CF but the frequency increases further after transplantation. Possibly due to surgery-induced vagal nerve and esophageal dysfunction
Renal	Renal dysfunction	Calcineurin inhibitors Diabetes Hypertension
Endocrine	Diabetes mellitus	Corticosteroids Calcineurin inhibitors mTOR inhibitors
	Osteoporosis	Corticosteroids Calcineurin inhibitors (cyclosporine, possibly tacrolimus)
Cardiovascular	Hypertension	Calcineurin inhibitors Corticosteroids to a less extent
	Dyslipidemia	Corticosteroids Calcineurin inhibitors (cyclosporine, to a less extend tacrolimus) mTOR inhibitors
Malignancy	PTLD Skin Digestive, other	Epstein-Barr virus (EBV) for PTLD Sun exposure for skin cancer Immunosuppression for all types of cancer

EBV: Epstein-Barr virus, mTOR: mammalian target-of-rapamycin, PTLD: post-transplant lymphoproliferative disease

3. LIVER TRANSPLANTATION

3.1. Indications

- Seven per cent of CF patients, mostly children and young adults, develop multi-lobular biliary cirrhosis and may need liver transplantation **(see also Chapter "*Hepatobiliary diseases*")**.
- A score used for referral to liver transplant assessment is presented in **Table 5**. This score has been used mostly in children with CF liver disease and does not include lung function parameters.
- In practice, other indices, such as declining lung function, poor nutritional status or presence of encephalopathy are also considered. Patients with an FEV1 <60% of predicted value, are most likely to benefit from liver transplantation.
- Indications for liver transplantation in CF are summarized in **Table 6**.

Table 5: Score indicating the need for liver transplant assessment, NB score (adapted from[3])

Indication		Score	
Portal hypertension	*Splenomegaly must be present*		
	– Varices present	4	Score only one
	– Bleed with 1-2 transfusions	8	
	– Variceal bleed >twice or a single life threatening bleed	10	
	Ascites	6	
Hepatocellular function	Albumin <30 g/l	2	
	PT>19 sec	2	
Hypersplenism	WBC<4 G/L	2	
	PLT<100.000/μL	2	
Nutrition	BMI<16th percentile	6	
	Mid-arm circumference <5th percentile	6	

NB: score>10 indicates the need for liver transplant assessment.
In practice, other parameters are also considered:
1) declining lung function
2) poor nutritional status
3) encephalopathy

Table 6: Indications for liver transplantation in CF (adapted from[4])

Progressive hepatic dysfunction – declining serum albumin (<30 g/l) – increasing coagulopathy not corrected by vitamin K
Development of ascites and jaundice
Intractable variceal bleeding, not controlled by conventional treatment
Hepatopulmonary syndrome and portopulmonary hypertension
Severe malnutrition, unresponsive to intensive nutritional support
Deteriorating quality of life related to liver disease
Deteriorating pulmonary function

3.2. *Contraindications*

- Contraindications (in particular relative contraindications) are often center-specific. These issues should be discussed with the transplant center well in advance. Generally, the following applies **(Table 7)**.

Table 7: Absolute contraindications for liver transplantation in CF (adapted from[5])

– Severe multi-organ dysfunction unless multi-organ transplantation can be considered
– Malignancy (non-hepatobiliary) or metastatic hepatobiliary malignancy
– Active alcohol/substance abuse
– Uncontrolled sepsis
– Psychiatric or psychological conditions associated with the inability to cooperate with the medical/allied health care team and/or adhere with complex medical therapy

Note: prior abdominal surgery or surgery for portal hypertension should be considered during risk assessment

3.3. *Specific considerations*

- Pulmonary and nutritional status should be optimized before liver transplantation.
- Peri-operative antibiotics should be adapted to microbiology results and continually re-assessed while the patient is on the waiting list.
- Biliary-enteric anastomosis is prefered to end-to-end choledochal anastomosis owing to the presence of abnormal epithelium in the recipient bile duct.
- A portosystemic shunt may be considered to delay liver transplantation in patients with well-preserved synthetic liver function but the benefits of delaying liver transplantation must be weighted against the potential risks of portosystemic shunting (encephalopathy, hepatopulmonary syndrome, portopulmonary hypertension).

3.4. *Pre-transplant evaluation*

- A system-based pre-transplant evaluation, similar to the one performed for lung transplantation is used for liver transplant candidates.
- In addition to the exams described in **Table 4**, the following are performed for patients assessed for liver transplantation:
  - Serology for HEV
  - Abdominal angio CT scan
  - Head MRI (evaluation for signs of encephalopathy)
  - Specialized reviews by:
    - liver transplant surgeon
    - neurologist
    - neuropsychologist (in selected cases to assess for minimal hepatic encephalopathy)

3.5. Post-transplant outcomes and main complications

- Post liver transplant life expectancy is greater in patients younger than 18 years of age than older adults.
- Although based on older data, analysis of the European liver transplant registry (ELTR) and Scientific registry of transplant recipients (SRTR) showed a 3 and 5-year patient survival of approximately 80%. It is possible that with improved current management, survival may also have improved.
- In regard to the impact of liver transplantation on other outcomes
  - Lung function: in one study CF patients having received isolated liver transplant improved their FEV_1 by 5.9%.
  - Comorbidities: increased prevalence of diabetes mellitus. For other comorbidities induced by immunosuppresion see **Table 5**.
  - Nutritional status: a slight improvement of nutritional status has been reported.
- In very well selected CF patients, liver transplantation provides a net survival benefit and an improved quality of life. Although post liver transplant survival in adult CF patients has been shown to be less compared to adults having a liver transplant for other indications, this discrepancy was not related to graft failure but most likely to the presence of comorbidities.

4. COMBINED LIVER-LUNG TRANSPLANTATION (CLL-TX)

4.1. Indications

- Patients with severe lung disease and liver cirrhosis are at high risk for mortality and morbidity after lung transplantation due to liver failure. For these patients combined liver-lung transplantation (CLL-Tx) is usually warranted.
- Although not stated clearly in the literature, it is generally accepted that CLL-Tx is indicated when the chance of survival with a single organ transplantation is estimated $<50\%$.
- Patients <18 years old have better survival rates than adults. Thus in severe two-system disease, combined transplant should be considered during adolescence or early adulthood.

4.2. Pre-transplant evaluation

- Evaluation for liver and lung transplant as mentioned above.
- Additionally:
  - Pulmonary changes associated with portal hypertension are an important consideration. Transplanting the lung in the presence of porto-systemic shunting secondary to portal hypertension could impair graft function or compromise clinical outcomes due to hypoxemia.
  - Careful anesthesia planning is essential to determine which lung will be transplanted first and to plan circulatory bypass.
  - Ascertaining the extent of vascular access or compromise is essential.
  - Adequate nutrition is essential in the pretransplant period to ensure that the patient is anabolic at the time of transplant. Total parenteral nutrition (TPN) may be required as enteral nutrition is often poorly tolerated in advanced portal hypertension.
- A detailed pre-, peri-, and post- transplant protocol is essential.

4.3. Outcomes

- Unfortunately, data on outcomes are scarce.
- In a study of the UNOS database, looking at 11 patients, survival of CLL-Tx was equal to isolated liver or isolated double lung transplantation.
- In a more recent study examining older adults with CLL-Tx due to various diagnoses (not CF only), 30-day, 90-day, and 1 year survival was 87.5%, 75.0% and 71.4% respectively.
- Subsequent studies have confirmed these findings and suggested that younger patients fare slightly better.

5. TRANSPLANTATION OF THE PANCREAS OR PANCREATIC ISLETS

- **Transplantation of the pancreas**
  - Currently, data are very limited concerning pancreas transplantation in CF: a recent analysis of the United Network for Organ Sharing (UNOS) database showed that among the 4600 CF patients transplanted between 1987 and 2014, only 28 received a pancreas transplant (in most cases combined with liver transplants).
  - The procedure is underused because it is not considered life-saving and, in cases of combined transplantation, it increases the complexity of the operation and the probability of complications.
- **Transplantation of pancreatic islets**
  - It is a less invasive option than pancreatic transplantation. It consists of the isolation and culture of donor pancreatic islet cells and their transplantation by catheterization of the portal vein or the transverse colic vein. Elevation of plasma C-peptide is measured as an indicator of islet allograft recovery.
  - There are no studies on the long-term efficacy and safety of this procedure in CF.
  - Only case reports for simultaneous or sequential lung - pancreatic islet transplantation in cases of brittle diabetes (poor glycemic control with numerous hypoglycemic episodes) in an attempt to improve glucose stability, decrease insulin requirements and eliminate hypoglycemic events.

6. REFERENCES

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