REVIEW ARTICLE

Lung Transplantation: a Treatment Option in End-Stage Lung Disease

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SUMMARY

Background: Lung transplantation is the final treatment option in the end stage of certain lung diseases, once all possible conservative treatments have been exhausted. Depending on the indication for which lung transplantation is performed, it can improve the patient's quality of life (e.g., in emphysema) and/or prolong life expectancy (e.g., in cystic fibrosis, pulmonary fibrosis, and pulmonary arterial hypertension). The main selection criteria for transplant candidates, aside from the underlying pulmonary or cardiopulmonary disease, are age, degree of mobility, nutritional and muscular condition, and concurrent extrapulmonary disease. The pool of willing organ donors is shrinking, and every sixth candidate for lung transplantation now dies while on the waiting list.

Methods: We reviewed pertinent articles (up to October 2013) retrieved by a selective search in Medline and other German and international databases, including those of the International Society for Heart and Lung Transplantation (ISHLT), Eurotransplant, the German Institute for Applied Quality Promotion and Research in Health-Care *(Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen, AQUA-Institut),* and the German Foundation for Organ Transplantation *(Deutsche Stiftung Organtransplantation, DSO).*

Results: The short- and long-term results have markedly improved in recent years: the 1-year survival rate has risen from 70.9% to 82.9%, and the 5-year survival rate from 46.9% to 59.6%. The 90-day mortality is 10.0%. The postoperative complications include acute (3.4%) and chronic (29.0%) transplant rejection, infections (38.0%), transplant failure (24.7%), airway complications (15.0%), malignant tumors (15.0%), cardiovascular events (10.9%), and other secondary extrapulmonary diseases (29.8%). Bilateral lung transplantation is superior to unilateral transplantation (5-year survival rate 57.3% versus 47.4%).

Conclusion: Seamless integration of the various components of treatment will be essential for further improvements in outcome. In particular, the follow-up care of transplant recipients should always be provided in close cooperation with the transplant center.

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For patients with terminal lung conditions such chronic obstructive lung disease (COPD), lung transplantation (LuTx) offers treatment to improve quality of life and additionally, in those with certain other diseases—e.g., cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), and pulmonary arterial hypertension (PAH)—to prolong life (1, 2, e1). It is used at the point when, despite treatment by all available conservative methods, the patient's quality of life will be clearly impaired or life shortened if transplantation does not take place (3, 4, e2).

At present, there are four main surgical options when performing a lung transplantation (5, e3, e4). These are:

- Unilateral (single lung) transplantation (SLuTx)
- Bilateral (double lung) transplantation (DLuTx)
- Combined heart–lung transplantation (HLuTx)
- Transplantation of individual pulmonary lobes from living donors.

The last of these options is practiced in only a few centers in the world, and at present is burdened with the weight, not only of non-negligible risks for two healthy living donors, but also of an agglomeration of associated ethical difficulties, and for this reason it will not be discussed further in this article (e5).

Analysis of data from the relevant registries show that lung transplantations have been continually on the rise over the past 5 years, despite a reduction in numbers of willing donors. Worldwide, the increase is estimated at 30% (International Society for Heart and Lung Transplantation, ISHLT), while in Germany the figure is 19% (German Foundation for Organ Transplantation, DSO *[Deutsche Stiftung Organtransplantation]*). According to data from the ISHLT, 3519 lung transplantations were carried out worldwide in 2010, 298 of them in Germany (6, 7, e6). For 2012, the DSO recorded 357 organ transplantations (7). It is against the background of this positive development that the present article has been written to give an up-to-date overview of the topic of lung transplantation, and to answer questions on the key components of the therapy: recipient selection, contraindications, waiting lists, organ allocation procedures, surgical procedure, postoperative immune suppression, aftercare, early and late complications, rehabilitation, and recent long-term results (*eFigure*).

TABLE 1

Indications for lung transplantation in adults (international: ISHLT Registry 1995–2012 [6]; national (German): AQUA Institute 2008–2012)

	ISHLT Registry		
	SLuTx N = 14 197 n (%)	DLuTx N = 23 384 n (%)	Total N = 37 581 n (%)
COPD	6312 (44.5%)	6290 (26.9%)	12 602 (33.5%)
Idiopathic pulmonary fibrosis	4872 (34.3%)	4032 (17.2%)	8904 (23.7%)
Cystic fibrosis	229 (1.6%)	6002 (25.7%)	6231 (16.6%)
α1-Antitrypsin deficiency	753 (5.3%)	1429 (6.1%)	2182 (5.8%)
Idiopathic pulmonary arterial hypertension	87 (0.6%)	1073 (4.6%)	1164 (3.1%)
Sarcoidosis	265 (1.9%)	689 (2.9%)	954 (2.5%)
Bronchiectasis	59 (0.4%)	956 (4.1%)	1015 (2.7%)
Lymphangioleiomyomatosis	136 (1.0%)	255 (1.1%)	391 (1.0%)
Congenital heart defect (Eisenmenger syndrome)	56 (0.4%)	269 (1.2%)	325 (0.9%)
Re-transplantation (BOS)	276 (1.9%)	292 (1.2%)	568 (1.5%)
Re-transplantation (non-BOS)	182 (1.3%)	220 (0.9%)	402 (1.1%)
Other	970 (6.8%)	1877 (8.0%)	2843 (7.6%)
	AQUA Institute*		
	SLuTx N = 218 n (%)	DLuTx N = 1173 n (%)	Total N = 1391 n (%)
Obstructive lung disease (COPD, α1-antitrypsin deficiency, bronchiectasis)	88 (40.4%)	412 (35.1%)	500 (35.9%)
Restrictive lung disease (IPF)	96 (44.0%)	329 (28.0%)	425 (30.6%)
Pulmonary hypertension (PAH and Eisenmenger syndrome)	6 (2.8%)	53 (4.5%)	59 (4.2%)
Cystic fibrosis	7 (3.2%)	240 (20.5%)	247 (17.8%)
Other (incl. lymphangioleiomyomatosis, sarcoidosis and re-transplantations)	21 (9.6%)	139 (11.9%)	160 (11.5%)

ISHLT, International Society for Heart and Lung Transplantation; AQUA, Institute for Applied Quality Improvement and Research in Health Care (*Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen*);
SLuTx, single lung transplantation; DLuTx, double lung transplantation; COPD, chronic obstructive pulmonary disease; PAH, pulmonary arterial hypertension; BOS, bronchiolitis obliterans syndrome; IPF, idiopathic pulmonary fibrosis; N, total number of patients, n = subgroup.
*The data of the AQUA Institute relate to the disease groups lists; they are not coded into the individual disease entities (analogous to ISHLT)

Recipient selection

Lung transplantation is a highly complex treatment that carries considerable peri- and postoperative risks. It is a treatment option for patients whose pulmonary function, exercise capacity, and quality of life are drastically restricted and whose predicted 5-year survival is less than 50% (for indications and indication criteria, see *Table 1* and *Box 1*) (8, 9, e7–e14). Which form of lung transplantation is carried out depends on the underlying disease. In terms of 5-year survival, DLuTx is superior to SLuTx (57.3% versus 47.4%), so the number of DLuTx procedures has been continually rising since the mid-1990s while the number of SLuTx has remained relatively constant (6). The number of HLuTx procedures carried out worldwide has remained relatively constant at a mean of 70 to 90 procedures per year (6).

Older patients have a poorer survival rate after lung transplantation than do younger ones (*Figure 1a*) (6, e6, e15, e16). For this reason, the surgical indications for SLuTx in patients over the age of 60, DLuTx in patients over the age of 55, and HLuTx in patients over the age of 50 should be tested with a critical eye (*Figure 1b*) (8). However, a patient's actual age is not per se an exclusion criterion for transplantation (10, e17).

Evaluation of the patient's biological age has proved useful for guidance (among other things for determining risk factors for cardiovascular and metabolic disease, and evaluation of data on lifestyle and psychosocial environment) (e18, e19).

Contraindications

The selection of suitable candidates to receive a transplant is done at the transplantation center, taking account of disease-specific factors, analysis of risk factors, and any contraindications present (*Box 2*) (11–14, e7, e16, e20, e21). Poor physical status and severe organ dysfunction can be contraindications for transplantation in any age group. On the other hand, with intensive physiotherapeutic exercise and targeted rehabilitation, the condition even of patients with severe, advanced-stage chronic lung disease can be improved to the point at which they are ready to undergo transplantation (e22–e25).

Waiting list and organ allocation procedure

Early attendance at a transplantation center (there are 14 at present in Germany) is obligatory (*Case illustration*). The time at which a patient is placed on the waiting list is determined by the disease course and the expected waiting time until transplantation (Eurotransplant: <12 months for 74% of patients in 2012) (7, 15, e26–e29). A basic diagnostic program is followed by consultations between the patient and the transplantation team (*Table 2a*): based on symptoms, clinical findings, patient motivation, and the expected risk–benefit ratio between transplantation and the natural course of the disease, decisions are made about whether to carry out further investigations ("screening," *Table 2b*) (16, e7, e18). Direct statistical comparison between predicted survival in the natural course of the underlying disease and actual survival after lung transplantation is not possible, however (9). Once the patient has been placed on the waiting list, the waiting time until transplantation takes place should be used to correct over- or underweight, update the patient's immunization status, and carry out muscle strengthening exercise (17, 18, e25, e30, e31).

In December 2011, listing according to HU/U status ("highly urgent/urgent") was replaced by a "lung allocation score" (LAS). Like listing by HU/U status, listing by LAS reflects the urgency of the transplantation, but is more transparent, because the LAS is calculated by an internet program (optn.transplant.hrsa.gov; www.eurotransplant.org/cms/index.php?page= las_calculator) that is accessible to both the doctor and the patient. This program sets the mortality rate of patients on the waiting list and the risk associated with lung transplantation against the benefit the patient would receive from transplantation (19, e32). The values calculated in this way are standardized on a scale of 0 to 100 and this gives the individual LAS. The value of the LAS correlates with the urgency of transplantation (e33, e34). All patients on the waiting list undergo outpatient check-ups at frequent intervals to test and document the indications for surgery in order to update and, if appropriate, increase the LAS.

In Germany, there are many more potential lung recipients than donated organs: lungs are harvested from only about one in five multiorgan donors, because the donors do not fulfill the minimum criteria for lung

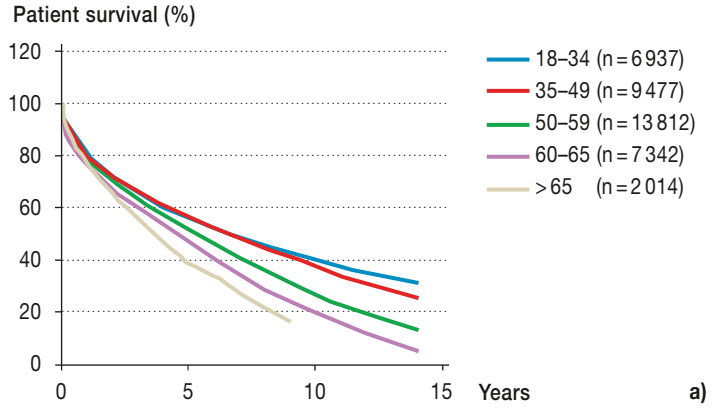
BOX 1

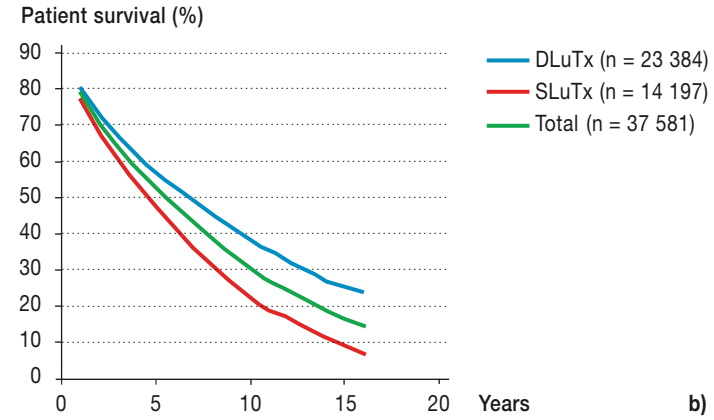
Indication criteria for isolated lung transplantation according to underlying disease

- **Chronic obstructive pulmonary disease (COPD)***
  - Documented abstinence from smoking for >6 months
  - BODE index >5
  - FEV_1 <20% of normal
  - D_{lco} 20% of normal
  - Long-term oxygen therapy with noninvasive ventilation
  - Pulmonary hypertension or cor pulmonale
  - Manifest ventilatory failure (hypercapnia, CO_2 partial pressure >50 mm Hg)
  - Progressive reduction of physical capacity
- **Fibrotic lung disease**
  - Respiratory failure at rest (initiation of oxygen therapy)
  - Pulmonary hypertension
  - (Dis)continuous deterioration of pulmonary function under standard medical treatment
  - FVC <60% of normal
  - Drop in FVC by ≥10% within 6 months
  - D_{lco} <39%
  - Drop in pulse oximetry by <88% (in 6MWT)
  - Honeycomb structure on high-resolution CT (fibrosis score >2)
- **Cystic fibrosis**
  - FEV_1 <30% of normal
  - Oxygen partial pressure <55 mm Hg
  - CO_2 partial pressure >50 mm Hg
  - Exacerbations requiring intensive care
  - Increasingly frequent infections requiring inpatient antibiotic therapy
  - Recurrent or refractory pneumothorax
  - Recurrent hemoptysis despite attempted embolization
  - Pulmonary hypertension
  - Progressive weight loss ("wasting") with BMI <18 kg/m^2
- **Pulmonary hypertension**
  - Ability to walk limited to <380 m (in 6MWT)
  - Maximum oxygen intake <10.4 mL/min/kg
  - NYHA functional stage IV
  - Signs of manifest right heart failure despite optimized medical treatment
  - Cardiac index <2 L/min/m^2
  - Right atrial pressure >15 mm Hg
  - Failure of intravenous epoprostenol therapy

* In COPD, to objectivize the decision criteria for LuTx, the BODE index is used, which is comprised of the following parameters: BMI = body mass index, FEV_1 = functional 1-second capacity, dyspnea severity on the MMRC (modified Medical Research Council) scale, and 6MWT = 6-minute walk test. D_{LCO} = diffusing capacity of the lung for carbon monoxide, FVC = forced vital capacity, NYHA = New York Heart Association

FIGURE 1





Patient survival

a) According to age group (transplantation period January 1990 to June 2011 [6])
b) According to surgical procedure (transplantation period January 1994 to June 2011 [6])
DLuTx, double lung transplantation; SLuTx, single lung transplantation

donation (*Table 2c*). Because of this relative lack of organs, about one in six German patients waiting for a lung transplant dies before receiving it (Eurotransplant 2012: 70 out of 459 patients, i.e., 15.3%). For this reason, at present a move is under way to extend the criteria for organ donation (e35–e38).

The conflicts over the practice of allocating abdominal organs, currently much discussed, raise the question of the status quo of organ allocation. Especially in regard to lung transplantation, it may be noted that, with the "multiple eye principle," together with the complex data collection included in LAS generation and the obligatory transplantation conferences held at the large centers, the required transparency has already been in place for a long time.

Surgical procedure

Operative time for a SLuTx is 2 to 3 hours; for a DLuTx it is about 4 to 6 hours. A cardiopulmonary bypass is used in about 20% of LuTx, if right heart failure and an excessive rise in pulmonary blood pressure occur during tentative clamping of the pulmonary artery, or if limited gas exchange occurs during one-lung ventilation (20, 21, e39). In addition to being technically simpler, not employing extracorporeal circulation has the advantage of resulting in less reperfusion injury to the allograft in the postoperative period (21). In isolated LuTx, the airway anastomosis on the main bronchi is carried out either end-to-end or using the so-called telescope technique; in HLuTx it is performed en bloc in the region of the distal trachea (e40, e41). The bronchial arterial supply is transected proximally and nonselectively anastomosed in LuTx, with the result that bronchial mucosal ischemia often occurs in the anastomotic region (e42–e45). Retrograde revascularization occurs over the course of several weeks (e46, e47). Minimally invasive procedures (anterolateral thoracotomy without sternotomy) have cosmetic advantages compared to classical thoracosternotomy, and reduce postoperative pain and wound healing disorders. They also leave important structural elements of the thorax intact (e17). Once transferred to the intensive care unit, many patients can be extubated after as little as 24 hours.

Postoperative immune suppression and aftercare

Since the lung has its own immunological competence, transports the entire cardiac output, and thus possesses a large immune-active interaction area, particularly intensive immune suppression is needed after lung transplantation (e48). Normally, immune suppression is achieved with the triple combination of a calcineurin inhibitor (CNI) (ciclosporin A, tacrolimus), a cell cycle inhibitor (azathioprine, mycophenolate mofetil), and prednisolone (22, 23, e49–e51). In recent years, the introduction of the mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) and of the anti-CD25 antibody (daclizumab, basiliximab—induction therapy only) has widened the range of combinations (24, 25, e52–e54). As to the incidence of chronic transplant rejection, randomized controlled studies have failed to indicate clear superiority of any of the above-named drug groups (26). Triple immune suppression is continued for the rest of life, unless severe adverse effects occur (23).

Infection prophylaxis is with valganciclovir in the case of cytomegalovirus (CMV) (or, where donor and recipient are CMV-negative, with aciclovir) (27, e55–e60), and with lifelong administration of cotrimoxazole in the case of *Pneumocystis jrovecii* pneumonia (28).

Follow-up care after lung transplantation includes monitoring of transplant function, assessment for known complications of transplantation by lung function tests, as well as clinical, radiological, chemical, and microbiological investigations (18, 29, e61–e65). For early identification of problems on the tightrope walk between chronic organ rejection (bronchiolitis obliterans syndrome [BOS], incidence 38.9% within 5

years) and infection, organ recipients carry out an outpatient lung function measurement at home every day of their lives (30, e66). Usually, lung function increases at first and reaches a relatively stable plateau after 3 to 6 months. If function deteriorates (drop in functional 1-second capacity, [FEV_1] by ≥10% of the baseline value), or newly developed cough, mucus, fever, or breathlessness occur, the transplantation center should be contacted immediately for further diagnostic investigation, which may be invasive (e8, e67). In addition to infection and rejection, recurrences of the underlying disease (e.g., sarcoidosis, pulmonary histiocytosis X, or lymphangioleiomyomatosis) may occur in the allograft after LuTx (30, e61, e68, e69), and these must be included in the differential diagnosis.

Early and late complications

The most serious complications during the first month after LuTx are primary graft dysfunction (PGD), donor-mediated pneumonia or pneumonia of other primary infectious origin, antibody-mediated hyperacute rejection (fairly rare), problems with the vascular and bronchial anastomoses, and periods of acute cellular rejection (31, e18, e70–e74) (*Table 3a*). Average 90-day mortality is 10% (6).

PGD is the most frequent cause of death in the first 30 days after LuTx (10% to 25%) (6, 31). The clinical features are similar to those of acute respiratory distress syndrome (ARDS), and mortality is between 50% and 73% (6, 31). Most cases of PGD are caused by ischemia–reperfusion injury. More rarely, infections and rejection reactions may act as triggers (31).

Rejection: clinical features and diagnosis

One-off or recurrent periods of rejection increase the probability of BOS, reduce graft function permanently, and hence endanger the patient's long-term survival (26, e75, e76). Since most acute rejections of lung allografts occur within the first 2 years after transplantation (33.9%), accurate diagnosis and staging of rejection are essential during this period in particular (e77–e81). Clinical signs of acute cellular rejection are nonspecific symptoms such as fatigue, raised body temperature, dyspnea, cough, increased mucus, hypoxemia, drop in FEV_1, interstitial infiltrates, and pleural effusions (32). Higher-grade rejection can be accompanied by acute breathlessness with dramatic symptoms (e82). Spirometry can indicate infections and rejection reactions (drop in FEV_1), but cannot distinguish between them (e83). Similarly, thoracic imaging can indicate nonspecific changes and hence the possibility of a rejection reaction, but only indirectly (e.g., by showing septal thickening, infiltrates, pleural effusions) (e61). For clinical follow-up after LuTx, bronchoscopy with bronchoalveolar lavage (eosinophilia, lymphocyte proliferation) and transbronchial biopsy (lymphocytic infiltration) have become established as standard techniques for rejection diagnosis, due to their high sensitivity and specificity (33, e84–e87).

BOX 2

Absolute and relative contraindications for isolated lung transplantation*

- **Absolute contraindications**
  - **Florid infection**
  - **Malignant tumor**

    (Not an absolute contraindication if:

    a) Disease-free for at least 2 years

    b) Disease-free for at least 5 years for
    - Renal cell carcinoma stage II
    - Breast cancer stage II
    - Colorectal cancer above Duke stage A
    - Melanoma Clark level II)
  - **Addictive behavior** (including tobacco consumption) during the past 6 months
- **Relative contraindications**
  - **General physical status**
    - Cachexia (approx. <70% of ideal weight), massively reduced muscle mass
    - Obesity (approx. >130% of ideal weight)
    - Mechanical ventilation (exception: non-invasive, intermittent self-ventilation)
  - **Concomitant disease**
    - HIV infection or infection by panresistant pathogens, pulmonary fungal infection
    - Renal failure (creatinine clearance <50% of normal)
    - Liver disease (chronic aggressive hepatitis B, hepatitis C, or liver cirrhosis with significantly impaired function)
    - Refractory coronary heart disease or significantly impaired left ventricular function
    - (Pronounced) diverticulosis
    - *Burkholderia cepacia* (type III)
    - Symptomatic osteoporosis with fractures
    - Neurological, neuromuscular, and psychiatric diseases (myopathy, seizure disorders, multiple sclerosis, cerebrovascular diseases, psychiatric illness, etc.)
    - Systemic disease with significant extrapulmonary manifestation (vasculitis, collagenosis)
  - **Psychosocial problems, poor compliance with treatment so far**

*Adapted from (e21)

Treatment of acute rejection is in accordance with the following parameters. The standard therapy is intravenous administration of 500 to 1000 mg methylprednisolone (15 mg/kg body weight per day) on each of 3 successive days (e88). In the case of steroid-refractory or early recurrent rejection, the immunosuppressive treatment is altered (e.g., change of CNI or exchange of CNI for mTOR inhibitors) (e89). Alternatively—although they are associated with

TABLE 2

Prerequisites for organ recipients and donors

a) Basic diagnostic criteria for attendance at transplantation center	
History	Diagnosis, disease course, any concomitant disease(s)
Current status	Height, weight, exercise capacity (6MWT), requirement for oxygen therapy, noninvasive ventilation, edema
Recent pulmonary function	Body plethysmography
Arterial blood gas analysis	Resting and – if possible – during exercise (alternatively, oxygen saturation after 6MWT)
Basic laboratory values	Complete blood count, differential blood count, coagulation, renal function (cystatin C, creatinine clearance), liver function, Quick test value, determination of blood group and HLA, cytotoxic antibodies (for recipients with auto-immunization), electrophoresis, immunglobulins
Recent echocardiography	To assess right ventricle (systolic right ventricular pressure)
Abdominal ultrasound	To assess abdominal organs
Recent chest CT (≤ 6 months)	High-resolution in patients with interstitial lung disease
Dental examination	To exclude focus of infection
ENT examination	To exclude focus of infection (especially in patients with bronchiectasis, cystic fibrosis)
Psychosocial status	Social environment, adherence with therapy so far
b) Further investigations as required by the transplantation center before acceptance onto waiting list	
Special laboratory tests	Immunglobulins, IgG subclasses, lymphocyte populations, viral serology (HIV, HBV, HCV)
Recent sputum culture	Bronchiectasis, necrotizing lung disease
Duplex sonography of extracranial arteries	>45 years (smokers: >40 years)
Gynecological and urological check-up	Irrespective of age
Peripheral capillary wedge pressure; duplex sonography of pelvic and leg arteries if required	>45 years (smokers: >40 years)
Ventilation–perfusion scintigraphy	Quantitative, separately for each side (only when SLuTx is planned)
Recent right heart catheter	RA, PAP, PCWP, PVR,CO (thermodilution)
Left heart catheter or coronary angiography	>45 years (smokers: >40 years) or risk factors for coronary heart disease, in patients in whom the presence of an unrecognized defect is suspected
Colonoscopy	In patients >50 years and those with diverticulosis
c) Basic prerequisites for organ donors	
Minimum criteria (selection)	Age <55 years; blood group compatibility; p_aO_2 >300 mm Hg with FiO_2 1.0 and PEEP 5 mm Hg; normal chest X-ray and bronchoscopy; exclusion criteria: malignant tumor, chest trauma, sepsis
Extended criteria (selection)	Age >55 years; radiological suspicion of infiltrates; suspected aspiration; abnormal bronchial secretion; chest trauma

Brain death leads to a series of hemodynamic and inflammatory changes (including a rise in interleukin-8 and increased neutrophil infiltration) that result in tissue damage and abnormal fluid balance. For this reason, organ donor management in the intensive care unit is extremely important. Because the donor criteria have been expanded, according to Eurotransplant data the percentage of lungs harvested has gone up from 16.7% in 2003 to 27.1% in 2012. Nonetheless, the majority of multiorgan donors do not meet the criteria and lung donation fails.
6MWT, 6-minute walk test; IgG, immunoglobulin G; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; SLuTx, single lung transplantation; RA, right atrium; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; CO, cardiac output; p_aO_2, arterial partial oxygen pressure; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure
Table adapted from [e18]

considerable early and late toxicity—monoclonal or polyclonal antibodies may be given.

Infections

Infections are the main cause of death in the first year after transplantation (ISHLT Registry: 38.0%; AQUA Institute: 35%) (e6). In addition to the medical immune suppression, the fact that the lung, unlike other transplantable solid organs, is permanently directly exposed to the environment means that there is an increased risk of infection (34, e90–e92). Furthermore, the lack of cough reflex in the transplant, together with simultaneous reduction of mucociliary clearance due to denervation and interruption of the lymphatics, also

TABELLE 3

Complications after lung transplantation (LuTx)

a) Main complications after LuTx[*1]	
Allograft	Primary transplant dysfunction, necrosis and obstruction of anastomotic region, acute rejection, BOS, drug-induced pneumonitis (sirolimus, everolimus)
Thoracic	Lesions of the phrenic nerve (diaphragm paralysis), recurrent nerve (vocal cord paralysis), vagus nerve (gastroparesis or delayed gastric emptying), and thoracic duct (chylothorax), pneumothorax, pleural effusion
Infections	Bacteria, fungi (esp. *Aspergillus spp.*), viruses (esp. CMV, HSV, RSV)
Cardiovascular	Air embolism, postoperative pericarditis, thromboembolism, supraventricular tachycardia, arterial hypertension
Gastrointestinal	Esophagitis (Candida or CMV), gastroparesis, gastroesophageal reflux with aspiration, diarrhea or pseudomembranous colitis due to C. difficile, diverticulitis, colon perforation, distal intestinal obstruction syndrome
Hepatobiliary	Hepatitis (CMV, EBV, HEV, HBV, HCV, drug-induced toxicity)
Renal	Acute renal failure, chronic renal failure (esp. calcineurin inhibitor–induced nephropathy)
Neurological	Tremor, seizures, posterior leukoncephalopathy, headache, paresthesias, peripheral neuropathy
Musculoskeletal	Steroid myopathy, rhabdomyolysis (combination of ciclosporin + HMG-CoA reductase inhibitor), osteoporosis, aseptic bone necrosis
Metabolic	Obesity, diabetes mellitus, hyperlipoproteinemia, hyperammonemia
Hematological	Anemia, leukopenia, thrombopenia, hypogammaglobulinemia, thrombotic microangiopathy
Oncological	Post-transplantation lymphoma, skin tumors, other malignant tumors

*[1] Adapted from [e18]

BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HSV, herpes simplex virus; RSV, respiratory syncytial virus

b) Incidence rates of important complications after LuTx[*2]	1 Year	5 Years	10 Years
Arterial hypertension	51.7%	82.4%	–
Renal failure	23.3%	55.4%	74.1%
Creatinine ≤ 2.5 mg/dL	16.2%	36.5%	40.3%
Creatinine >2.5 mg/dL	5.2%	15.0%	19.8%
Dialysis	1.7%	3.2%	8.7%
Kidney transplantation	0.1%	0.7%	5.3%
Hyperlipidemia	25.5%	58.4%	–
Diabetes mellitus	24.6%	40.5%	–
BOS	9.5%	39.7%	61.6%

*[2] Follow-up period April 1994 to June 2012 [6]. Because complications are not uniformly reported to the ISHLT Registry, the percentages cited are based on different numbers of patients, and therefore no absolute figures are given here.

BOS, bronchiolitis obliterans syndrome; ISHLT, International Society for Heart and Lung Transplantation

c) Incidence of cancer after LuTx[*3]	1 Year	5 Years	10 Years
No cancer	17 068 (96.4%)	5040 (84.6%)	883 (71.2%)
Cancer (all)	630 (3.6%)	920 (15.4%)	357 (28.8%)
Skin	199 (31.6%)	590 (64.1%)	226 (63.3%)
Lymphoma	243 (38.6%)	94 (10.2%)	38 (10.6%)
Other	164 (26.0%)	227 (24.7%)	93 (26.1%)
Not specified	24 (3.8%)	9 (1.0%)	–

*[3] Follow-up period April 1994 to June 2012 [6]. For skin tumors, exposure to sun plays an important role (occurrence varies regionally; registers contain no relevant data). Occurrence of lymphoma is related to Epstein–Barr virus infection and amount of lymph tissue transferred. "Other" cancers include cancer of the bladder, lung, breast, prostate, uterus, liver, and bowel

CASE ILLUSTRATION

A 58-year-old patient without significant concomitant disease had for years been under the care of a consultant pulmonologist for severe chronic obstructive pulmonary disease (COPD). Despite maximum medical therapy, he suffered progressive impairment of physical capacity (BODE index >5; spirometry: FEV_1 < 25% of normal; D_{lco} <20% of normal; global respiratory failure with long-term oxygen therapy: hypercapnia p_aCO_2 >50 mm Hg). No further therapeutic approaches were considered. By coincidence, the patient happened in his private life to meet a chest surgeon, who recommended an immediate appointment at a transplantation center. After appropriate assessment and once contraindications had been excluded, the patient was taken on to the Eurotransplant waiting list in Autumn 2005. About 7 months later, a double lung transplantation was carried out without complications. After an uncomplicated stay in hospital with optimization of the immune suppression, the patient was transferred barely 4 weeks after surgery to a specialized rehabilitation center. After completing inpatient rehabilitation at a specialized clinic, he returned to normal working and social life. To this day, he attends regularly at the outpatients department at the transplantation center; recently spirometry showed an FEV_1 of >70%. The consultant pulmonologist changed his views and now refers patients who might be candidates for lung transplantation for early evaluation at a transplantation center.

BODE index, body-mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease; D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, functional 1-second capacity; p_aCO_2, arterial partial CO_2 pressure

play a role (34, e93). Three out of four graft infections occur in the airways, either due to pathogen transfer from the donor or to pathogens descending from the upper airways in recipients who already have chronic bacterial colonization (e.g., those with bronchiectasia or cystic fibrosis) (34, e94–e96). Other predisposing factors are airway stenosis and postoperative ischemia, especially in the area of the anastomosis due to epithelial damage (e41–e43, e47, e97). The incidence of postoperative pneumonia is markedly higher after LuTx than, for example, after heart transplantation (6, e98). During hospitalization, gram-negative pathogens predominate, whereas during the outpatient phase, infections by pneumococci, *Hemophilus* species, and atypical pathogens prevail (34).

Airway complications

The prevalence of clinically significant airway complications is 10% to 15% (35, e99). Within the first 6 postoperative months, the interruption of the bronchial arterial supply to the donor lung can lead to ischemic necrosis at the bronchial anastomoses (e97). This may be expressed by obstructive granulation tissue (stricture, atelectasis), dehiscence, infections, or bronchomalacia (e100, e101). In addition to the extent of the ischemia in the area of the anastomosis, other risk factors are size disproportion between donor and recipient, and *Aspergillus spp.* colonization (e102–e104). Treatment options include bronchial stent implantation, bronchoscopic balloon dilation, intrabronchial disobliteration techniques (argon plasma coagulation, laser and cryotherapy) and surgical revision, among others (e104, e105).

Renal complications

Five years after LuTx, 37% of patients show chronic renal failure (glomerular filtration rate [GFR] <50% of the norm) (e106) (*Table 3b*). Five percent of transplanted patients require dialysis because of preexisting concomitant disease or CNI therapy.

Cardiovascular complications

Five years after transplantation, 82% of patients are suffering from arterial hypertension, 58% from hyperlipoproteinemia, and 41% from diabetes mellitus (6). However, cardiovascular diseases are the cause in only 5% of deaths (32). The reason for this is the younger average age of transplanted patients and their lower life expectancy compared to the normal population. For antihypertensive therapy, angiotensin converting enzyme (ACE) inhibitors and calcium antagonists are preferred; verapamil and diltiazem raise the concentration of immune suppressants. In the early postoperative period, atrial tachycardia often occurs, caused by electrolyte disturbances, hypoxemia, ischemia, or atrial reentry mechanisms. Pharmacologically, particular attention must be paid to drugs that prolong the Q–T interval (e107).

Malignant tumors

Within the first 5 years after transplantation, 15% of patients with lung transplants develop malignant tumors (*Table 3c*) (6, 36–38, e108, e109). For skin tumors, exposure to the sun plays an important role, so these tumors are variably distributed in different regions of the world. The incidence of lymphoma is related both to Epstein–Barr virus infection and to the amount of lymph tissue transferred (e110).

Rehabilitation

The patient's preoperative physical constitution, together with muscle status, transplant function, complications, immune suppression, and potential risks over the long term, necessitate a structured rehabilitation program (39). In addition to stamina, interval, and strength training, respiratory therapy and physiotherapy, psychological counseling, and nutritional advice are given, to educate the patient about the effects of immune suppression and possible concomitant diseases (diabetes mellitus, renal failure, over- or underweight), and to treat them (e111, e112).

After about 6 to 12 months, patients can gradually start to go back to work or retrain for an occupation involving light physical work, provided anti-infection measures are taken (e113).

Recent long-term results

Compared to the natural course (40, e114), increased survival rates among transplanted patients are reported particularly for the first postinterventional year. In the long term, mainly organ-specific problems occur (*eTable a* and *b*) (e6). Irrespective of survival time, what is most important to patients is the marked improvement in quality of life (2, e1, e115, e116). To further optimize long-term results, intensive pulmonological support and follow-up care in the transplantation centers and obligatory close collaboration with patients' resident practitioner and local hospitals are essential.

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Conflict of interest statement
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KEY MESSAGES

- Lung transplantation is a well-established treatment option for patients with end-stage congenital or acquired lung disease when all conservative treatment options have been exhausted. Depending on the underlying disease, it can improve both life expectancy and quality of life.
- Criteria for the selection of candidates, in addition to the causative lung disease, are: patient age, existing mobility, nutritional and muscle status, and concomitant extrapulmonary diseases.
- Once the indication for lung transplantation has been established, it is important to be in contact with a transplantation center as early as possible in order to minimize mortality during the wait for a transplant.
- The continuing development of surgical techniques has markedly reduced early mortality: within the past 25 years, 90-day mortality has reduced from 19.4% to 10.0%. In the postoperative period, acute (3.4%) or chronic transplant rejections (29.0%), infections (38.0%), graft failure (24.7%), airway complications (15%), malignant tumors (15.0%), and other extrapulmonary sequelae (29.8%) are to be expected. At the end of 5 years, survival rates of almost 60% are achieved.
- Ongoing collaboration between the transplantation center on the one hand and the patient's resident practioner and the hospital responsible for the patient's aftercare on the other will contribute to improving the long-term results.

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REVIEW ARTICLE

Lung Transplantation: a Treatment Option in End-Stage Lung Disease

Marc Hartert, Ömer Senbaklavaci, Bernhard Gohrbandt, Berthold M. Fischer, Roland Buhl, Christian-Friedrich Vahl

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eTABLE

Long-term results (international data: ISHLT Registry 1995–2012 [6]; national data [Germany]: AQUA Institute 2008–2012)

a) Recipient survival according to underlying disease

ISHLT Registry

		Survival rate (%)			
Diagnosis	**n**	**1 Year**	**3 Years**	**5 Years**	**10 Years**
COPD	12 914	82.1%	65.7%	52.4%	25.8%
Idiopathic pulmonary fibrosis	8528	74.7%	59.2%	46.9%	24.4%
Cystic fibrosis	6164	82.9%	69.3%	59.6%	43.5%
α1-Antitrypsin deficiency	2624	79.1%	65.4%	56.4%	34.5%
Idiopathic PAH	1400	70.9%	59.4%	50.9%	35.6%
Sarcoidosis	934	74.2%	60.0%	52.9%	31.2%

AQUA Institute

		Survival rate (%)			
Diagnosis	**n**	**1 Year**	**3 Years**	**5 Years**	**10 Years**
Obstructive lung disease (COPD, α1-antitrypsin deficiency, bronchiectasis)	400	79.8%	59.1%	–	–
Restrictive lung disease (idiopathic pulmonary fibrosis)	296	70.9%	60.3%	–	–
Pulmonary hypertension (PAH and Eisenmenger syndrome)	58	77.6%	57.9%	–	–
Cystic fibrosis	190	78.9%	57.6%	–	–
Other (incl. lymphangioleiomyomatosis, sarcoidosis and re-transplantations)	167	70.7%	56.6%	–	–

AQUA, Institute for Applied Quality Improvement and Research in Health Care (*Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen*);
COPD, chronic obstructive pulmonary disease; ISHLT, International Society for Heart and Lung Transplantation; PAH, pulmonary arterial hypertension; n, number of patients

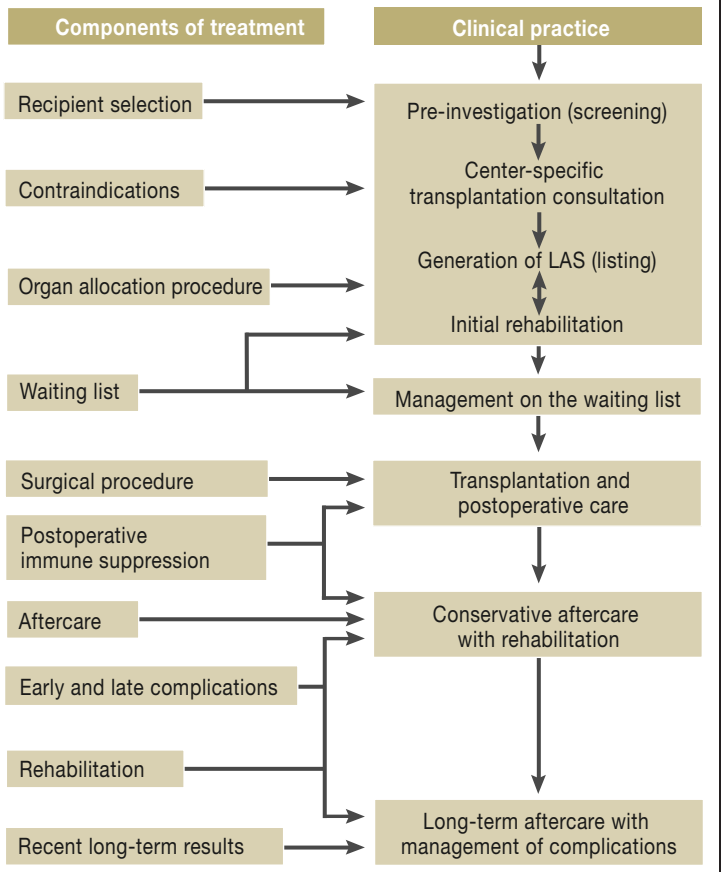
b) Causes of death after lung transplantation in adults

	0–30 Days	**31 Days–1 Year**	**1–3 Years**	**3–5 Years**	**5–10 Years**
ISHLT Registry	n = 2725	n = 4737	n = 4315	n = 2449	n = 2892
AQUA Institute	n = 125	n = 108	–	–	–
BOS	0.3%	4.6%	25.9%	29.0%	25.4%
	–	–	–	–	–
Acute rejection	3.4%	1.8%	1.5%	0.7%	0.6%
	1%	4%	–	–	–
Malignant tumors	0.2%	5.1%	9.4%	12.4%	15.0%
	–	–	–	–	–
Infection	19.6%	38.0%	23.5%	19.5%	18.2%
	14%	35%	–	–	–
Transplant failure	24.7%	16.7%	18.7%	18.0%	17.8%
	13%	4%	–	–	–
Cardiovascular	10.9%	4.8%	4.1%	4.9%	5.1%
	8%	1%	–	–	–
Technical	11.0%	3.4%	0.9%	0.6%	0.8%
	2%	6%	–	–	–
Other	29.8%	25.6%	16.0%	15.1%	17.0%
	36%	48%	–	–	–
Multiorgan failure	–	–	–	–	–
	26%	2%	–	–	–

ISHLT, International Society for Heart and Lung Transplantation; AQUA, Institute for Applied Quality Improvement and Research in Health Care (*Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen*); BOS, bronchiolitis obliterans syndrome; n, number of patients

At present, 45 centers report their data directly by entering data manually on the ISHLT's web-based data input system. In addition, the following organizations input information from 345 participating institutes into the ISHLT data system:
– United Network for Organ Sharing (United States of America)
– Eurotransplant (Germany, Austria, Belgium, Luxembourg, Netherlands, Slovenia)
– Organizacion Nacional de Trasplantes (Spain)
– Registro Español de Trasplante Cardíaco (Spain)
– UK Transplant (United Kingdom, Ireland)
– Scandia Transplant (Sweden, Norway, Denmark, Finland)
– Australia and New Zealand Cardiothoracic Organ Transplant Registry (Australia, New Zealand)
– Agence de la biomédecine (France)

eFIGURE



Interaction between components of treatment and current clinical practice in lung transplantation.
Once the candidate for lung transplantation has attended a qualified transplantation center, the decision about whether to place the patient on the waiting list is made taking account of the patient's individual disease-specific factors and any contraindications. To optimize long-term results, intensive pneumological support and aftercare in the transplantation centers and obligatory close collaboration with patients' doctors and local hospitals are essential. If the various elements of therapy interact successfully together, a new lung can mean a new quality of life.
(LAS, lung allocation score)