



# Developments in lung transplantation over the past decade

Sophie C. van der Mark<sup>1,3</sup>, Rogier A.S. Hoek<sup>2,3</sup> and Merel E. Hellemons<sup>1,2</sup>

**Affiliations:** <sup>1</sup>Dept of Pulmonary Medicine, Division of Interstitial Lung Disease, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands. <sup>2</sup>Dept of Pulmonary Medicine, Division of Lung Transplantation, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands. <sup>3</sup>Authors contributed equally.

**Correspondence:** Merel E. Hellemons, Erasmus Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: m.hellemons@erasmusmc.nl

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**Many developments have taken place in lung transplantation over the last decade: indications have broadened, donor criteria expanded, allocations systems changed, and novel therapeutic interventions implemented, leading to improved long-term survival** <http://bit.ly/2vnpwc1>

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**ABSTRACT** With an improved median survival of 6.2 years, lung transplantation has become an increasingly acceptable treatment option for end-stage lung disease. Besides survival benefit, improvement of quality of life is achieved in the vast majority of patients. Many developments have taken place in the field of lung transplantation over the past decade. Broadened indication criteria and bridging techniques for patients awaiting lung transplantation have led to increased waiting lists and changes in allocation schemes worldwide. Moreover, the use of previously unacceptable donor lungs for lung transplantation has increased, with donations from donors after cardiac death, donors with increasing age and donors with positive smoking status extending the donor pool substantially. Use of *ex vivo* lung perfusion further increased the number of lungs suitable for lung transplantation. Nonetheless, the use of these previously unacceptable lungs did not have detrimental effects on survival and long-term graft outcomes, and has decreased waiting list mortality. To further improve long-term outcomes, strategies have been proposed to modify chronic lung allograft dysfunction progression and minimise toxic immunosuppressive effects. This review summarises the developments in clinical lung transplantation over the past decade.

## Introduction

Annually, over 4 600 lung transplantations (LTx) are performed worldwide, of which 55% are performed in North America and 36% in Europe. Approximately 80% are bilateral LTx [1]. In general, candidates for LTx should have advanced lung disease with a projected shortened life expectancy and compromised quality of life. Patients should be expected to have a survival benefit due to LTx [2]. Current median survival after LTx worldwide is 6.2 years, and if recipients survive the first year the median survival is 8.3 years. In the past decade, survival increased from a median of 4.3 years (1990–1998) to 6.5 years (2009–2016) [3]. Besides advantages in survival, LTx also, importantly, improves quality of life [4, 5]. These outcome data are estimated to represent approximately 80% of the world's LTx activity [6]. It should be noted that large differences exist between outcomes in various regions across the world as well as between centres. Approximately two-thirds of LTx are performed in high volume centres (>30 per year), and higher centre volume is known to be associated with superior survival [6, 7]. Several large centres currently report 1- and 5-year survival rates of 87–93% and 77–80%, respectively, in their most recent cohorts [8, 9]. Advances in optimising allocation and donor usage to reduce waiting list mortality, and

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advances in perioperative and late recipient management have all played an important role in improving outcomes. In this review article the developments in these fields during the past decade will be discussed.

## Waiting list and lung allocation

### *Lung allocation score*

Historically, most lung allocation systems were based on waiting time. In many countries lungs are allocated according to centre allocation within a region or on a national level [10, 11]. Many countries currently integrate the possibility of high emergency lung allocation for selected patients, mostly on top of regional allocation systems [11]. Criteria for high emergency listings vary, and rates of patients transplanted with high urgency status range from 8% to 28% [12, 13]. After introduction of the high emergency allocation system in France, high emergency LTx led to dramatic reduction in waiting list mortality, but also reduced survival in patients that were transplanted with high urgency [14]. Similar effects were reported within Scandiatransplant and in Spain [14, 15]. High emergency lung allocation is an effective strategy to reduce mortality on the waiting list, but causes a disruption of the list equilibrium that may have detrimental long-term effects in situations of significant organ scarcity [16]. Various countries have different high emergency criteria as well as varying donor rates, and the most effective allocation system varies between countries. Also, complex ethical questions and choices persist on the topic of effective allocation.

From the view that transplant allocation should be based on measures of medical urgency, while avoiding futile transplants, and should minimise the effect of waiting times, the so-called lung allocation score (LAS) was developed in the USA and approved in 2005 [17]. This lung allocation score replaced the waiting-time based system to an allocation system, based on maximising the benefit of the transplantation in terms of survival. In contrast to other allocation systems, such as the Model for End-Stage Liver disease score, the allocation is not based solely on likelihood of survival within the following year on the waiting list, but also takes into account the chances of survival after LTx in the next year to avoid futility of the transplant [18]. The LAS estimates these risks using a set of 17 patient-related variables, including age, body mass index (BMI), underlying diagnosis group, pulmonary function, presence of pulmonary hypertension, 6-min walk distance and renal function. After the LAS appeared to be successful in the USA, LAS-based allocation was adopted in Germany in December 2011, in the Netherlands from April 2014 and in Italy from March 2016, leading to currently >60% of LTx worldwide being allocated by the LAS [10, 13, 19]. In February 2015 a revised LAS model was introduced in the USA. Although the Eurotransplant LAS is not exactly the same as the revised USA-LAS score, both scores are approximately equivalent and do not affect median ranking position on the waiting list [20]. The main result of the introduction from the LAS score has been the significant reduction in waiting list mortality by 20–40% [13, 21]. Patients with idiopathic pulmonary fibrosis (IPF) and cystic fibrosis (CF), who have a rapid progressive course of disease with poor prognosis and who had high waiting list mortality rates prior to the introduction of the LAS, have significantly benefited from the introduction of this urgency-based system [13, 22, 23]. Within Eurotransplant countries, and also for countries without the LAS, the LAS is also used to balance organ exchange between participating countries, with a negative country balance resulting in donor lungs being allocated to this country to correct this balance.

The patients that are now transplanted under the LAS are, by definition, generally more ill than before the LAS was implemented. Nevertheless, 1-year survival after LTx is at least equivalent and has possibly even improved [13, 17]. Post-transplantation care costs increased after the introduction of the LAS, most likely as an effect of the transplantation of sicker patients, but these alterations may also be related to other developments in the field, such as the increased opportunities in bridging to LTx, which will be discussed later.

### *Disease-specific implications of the LAS*

The most common indications for LTx are COPD, interstitial lung disease (ILD), CF and pulmonary arterial hypertension (PAH). COPD remains the most common indication for LTx, but the distribution of primary diagnoses among transplant recipients has shifted away from obstructive and toward restrictive lung diseases in countries that have implemented the LAS system [13, 21]. This has resulted in considerably longer waiting times for patients with COPD *versus* shorter waiting times and reduced waiting list mortality for patients with IPF and other ILD.

Also, patients with CF were impacted by the introduction of the LAS. In the USA the risk of instantaneous death in patients with CF was reduced by 69% after introduction of the LAS [24]. This finding was corroborated in Germany, where more patients with CF were initially transplanted after the introduction of the LAS and waiting list mortality for CF decreased [25].

Whereas the LAS is able to predict waiting list mortality for PAH, it is less effective in discriminating between those patients in urgent need for LTx *versus* those who can wait [26]. The LAS does not include many of the factors known to be associated with poor outcomes in PAH patients [27]. Currently, the most critically ill PAH patients are not as likely to receive transplants because their risk is underestimated, whereas the healthier PAH patients may be slightly more likely to receive a transplant than would be warranted by a strictly accurate risk assessment. For this reason in the USA, the revised LAS (called LAS exemption) was introduced in February 2015 with the addition of more haemodynamic parameters, such as an increase in bilirubin and creatinine, central venous pressure and cardiac index. Within Eurotransplant, this was addressed by introducing the option of a specific LAS request, called exceptional LAS, for those patients with PAH in urgent need for a lung transplant who are underrepresented by their current LAS score.

## Recipient selection

### *COPD*

As COPD is generally a chronic disease that can be stable for a long period of time, not all patients with severe COPD benefit from LTx [28, 29]. Careful patient selection is therefore warranted, given the enormous shortage of donor organs. Endoscopic lung volume reduction is increasingly recognised as a treatment option in selected patients with COPD, and a few small studies have shown favourable effects on survival in these patients. Therefore, candidacy for endoscopic lung volume reduction should be considered prior to LTx as an option to improve outcome [2, 30].

Lung volume reduction surgery is also performed in selected patients prior to LTx. LTx after lung volume reduction surgery was associated with more complex surgery at the time of LTx with increased risk of postoperative bleeding and increased frequency of post-LTx dialysis, but noninferior long-term survival [31]. Another series reports longer LTx operative times and longer hospital stay, but otherwise noninferior results of LTx [32].

Those patients with the worse prognoses despite maximal treatment, as reflected by high BODE (BMI, airflow obstruction, dyspnoea, exercise capacity) index, forced expiratory volume in 1s ( $FEV_1$ ) <25%, frequent exacerbations, status after one severe (hypercapnic) exacerbation, or pulmonary hypertension, could benefit from LTx in terms of survival [2, 33].

### *CF*

Patients with CF are generally considered a candidate for LTx when patients develop more frequent exacerbations and have progressive worsening of  $FEV_1$ . Generally, a  $FEV_1$  <30% of predicted or higher in the presence of a comorbidity, such as rapidly worsening nutritional status, development of respiratory insufficiency, increasing resistance to antibiotics, poor clinical recovery, pneumothorax, persistent haemoptysis or pulmonary hypertension, should trigger referral to a transplant centre. Mortality is increased when a combination of these risk factors is present and could thus warrant listing for LTx [2, 33, 34].

In recent years, the availability of cystic fibrosis transmembrane conductance regulator modulator therapies have improved outcomes for patients with CF with reduction of exacerbation frequency and improvement of quality of life and prognosis [35–37]. The improved prognosis could be hypothesised to result in a fall in transplants for CF, although registry data available up to 2016 fail to show this effect [3]. However, infection with multi- or pan-resistant bacteria or fungal infections are associated with increased risk of death post-transplant. Nonetheless, with intensive antibiotic treatment and careful patient selection, equivalent survival rates can be achieved [38, 39].

### *Pulmonary hypertension*

Newer treatment options and changes in treatment strategies have made a significant impact on outcomes in patients with PAH [40]. Based on recent evidence, there has been a paradigm shift in the treatment of PAH, from step-up in cases of deterioration to more aggressive treatment strategies using treatment directly targeting two or even three pathways early in the course of disease. This more aggressive upfront combination therapy has led to better outcomes [41].

In fact, because of the better therapies, patients have even been removed from transplant lists, have had transplant evaluations deferred, or have not been offered transplant referrals. However, the need for transplant still exists and may actually increase as the number of surviving PAH patients increases. Referral should, thus, not be withheld for patients on parenteral prostanoid therapy, even if their New York Heart Association (NYHA) functional class is preserved. Despite the better therapeutic strategies, deterioration can be sudden and lead to urgent need for LTx, associated with more risks and complications. Currently, those patients who rapidly deteriorate under maximal therapy, have NYHA functional class  $\geq 3$ , 6-min

walk distance < 350 m, right atrial pressure >15 mmHg or cardiac index <2 L·min<sup>-1</sup>·m<sup>-2</sup>, progressive right heart failure, significant haemoptysis or pericardial effusion are recommended for listing [2].

#### *IPF and other forms of ILD*

IPF is a severe progressive lung disease with a median survival of 3.8 years from time of diagnosis [42]. Because of this poor and unpredictable course of disease with acute accelerations, as well as its prevalence, it is the most common indication for LTx amongst the ILDs [43]. Since the recent introduction of the antifibrotic drugs nintedanib and pirfenidone, it has been possible to slow the rate of lung function decline. Nevertheless, the usual clinical course of the condition remains progressive and unpredictable [44, 45].

Whereas the advice remains that patients with IPF should be referred at the time of diagnosis, the listing timing has become a challenge for transplant centres now that some patients stabilise for a long period of time under antifibrotic treatment. Also, the number of acute accelerations is decreased under antifibrotic therapy. Nonetheless, mortality remains high and acute exacerbations still occur unpredictably and are associated with an in-hospital mortality of >50%. Therefore, early referral remains the recommendation, but the timing of listing should be discussed with patients on an individual basis, as no new recommendations have been formulated on this point since the introduction of antifibrotic therapy. As patients with more advanced IPF are more susceptible to acute exacerbations, our centre tends to immediately list all patients with severely affected lung function or rapid decline, in contrast to those patients with relatively preserved lung function and clinical stability [46]. These patients are closely monitored and not immediately listed. As pulmonary hypertension is linearly correlated with greater mortality, this feature also warrants active listing [47].

For ILDs other than IPF, referral is recommended in patients with progressive disease despite optimal treatment, with decreased pulmonary function and associated functional limitation or dyspnoea or need for oxygen requirement. Listing is recommended if pulmonary function or 6-min walk distance declines substantially, secondary pulmonary hypertension develops or patients are hospitalised because of rapid decline [2]. Another new uncertainty is whether to continue antifibrotic therapy during listing for transplantation, and this topic becomes even more relevant now that the use of these drugs will potentially be expanded to other fibrotic lung diseases [48]. Pirfenidone could theoretically impair wound and anastomotic healing due to inhibition of multiple pro-fibrotic cytokines that are known to play a significant role in all stages of wound healing, such as transforming growth factor- $\beta$ , interleukin (IL)-4 and IL-13. Nintedanib is a tyrosine kinase inhibitor that inhibits vascular endothelial growth factor. Recent studies on this topic have so far shown no increased risk of either impaired wound healing or increased bleeding in patients undergoing LTx who had previously received antifibrotic therapy, so the current standard is to continue antifibrotics during listing for LTx [49].

#### *Effects of disease-specific novel treatment options on outcome*

The timing of the transplantation is crucial; transplanting too early shortens survival, while transplanting too late results in patients dying on the waiting list. Due to the novel treatment options in CF, PAH and IPF, transplantation is deferred as candidates more frequently go through a slowly progressing disease process rather than a shorter duration, more rapidly progressive lung disease. It could be argued that a slowly progressing disease may lead to increased frailty and could affect the function of other organs. It is currently unclear if and how this will affect LTx outcomes in the longer term, nor is much known on the relationship between time on the waiting list and outcome.

#### *Increasing comorbidity and LTx*

Over recent years there have been major changes in the general characteristics of LTx recipients, especially with respect to increasing acceptance of comorbidities and increasing age of the recipients. The number of LTx recipients aged  $\geq 60$  years increased worldwide from just over 20% in 2000 to >40% in 2012 [43]. This is in line with current guidelines that no longer recommend an upper age limit for LTx, although increased age at transplantation (>55 years) is associated with increased 10-year mortality [50]. A fixed upper age limit has been replaced by the notion that increasing age is generally associated with comorbidities that are either absolute or relative contraindications [2]. New strategies have been developed to identify risk factors for disability and death in candidates awaiting LTx, specifically focussing on frailty and biological age as opposed to calendar age [51, 52].

In the population as a whole, but also in potential LTx recipients, average weight is increasing and the prevalence of severe obesity is rising. Severe obesity (BMI  $\geq 35.0$  kg·m<sup>-2</sup>) is considered an absolute contraindication for LTx and BMI >30.0 kg·m<sup>-2</sup> is considered a relative contraindication [2]. Obesity is associated with early mortality after LTx, but also, in the longer term, increased risk of death [53, 54].

Therefore, lung transplant candidates should undergo nutritional assessment and counselling before and after LTx.

Previously, presence of coronary artery disease was considered an absolute contraindication for LTx in most centres. This is gradually shifting. Currently, uncorrected coronary artery disease (CAD) with end-organ ischaemia or dysfunction and/or CAD not amenable to revascularisation remains an absolute contraindication for LTx [2]. However, for people with mild-to-moderate CAD with preserved left ventricular ejection fraction and otherwise limited comorbidity, LTx is currently deemed acceptable with regards to outcomes [55].

Several centres perform concomitant cardiac surgery including coronary artery bypass grafting during LTx in patients with CAD and show comparable 5-year survival rates [56]. This procedure may be justified in selected recipients in experienced centres.

Another major change is that previously noncurable chronic extrapulmonary infections, such as chronic active viral hepatitis B, hepatitis C, and HIV, were considered to be absolute contraindications for LTx, but such patients can now be candidates under certain conditions [57, 58]. For patients infected with hepatitis B and/or C, a lung transplant can be considered in patients without significant clinical, radiologic or biochemical signs of cirrhosis or portal hypertension and who are stable on appropriate therapy. It remains advisable that in candidates with hepatitis B and/or C LTx should be performed in centres with experienced hepatology units [2, 33].

There is very limited experience to date with LTx in HIV-seropositive patients. With current antiretroviral therapy options, adequate viral suppression is possible with lengthy life expectancy and without important interactions with immunosuppressive medication. In a recent case series, 86% of patients experienced pulmonary bacterial infections, but there were also high rates of rejection within the first year (62%) [59]. The latter is probably related to the infrequent use of induction therapy as well as cautious use of immunosuppression due to the increased concern for infectious episodes. Despite the high rates of infection and rejection, survival in this small group was noninferior, but (renal) drug toxicity of the combination therapy was significant [59]. LTx in recipients with HIV as opposed to hepatitis B/C, therefore, remains challenging and controversial.

Overall, there has been a gradual shift in the comorbidities that are deemed acceptable in LTx recipients over the past decade. Although LTx is feasible in these patients, the patients that are currently transplanted are in general older and have more significant accumulation of comorbidities. This development is very likely to be related to the lack of significant improvement of long-term outcomes after LTx, despite important developments.

#### *Patients admitted to intensive care units*

Donor shortage has led to increasing waiting times and growing numbers of patients who experience substantial disease progression while on the waiting list with significant respiratory failure requiring admission to the intensive care unit (ICU) as a bridge to LTx. During the past decades, the number of patients supported in the ICU while being bridged to LTx by either mechanical ventilation or extracorporeal life support (ECLS) has increased. In 2003, 3.7% of patients in the USA were transplanted from the ICU, this increased to 14.1% in 2013 [60]. A similar trend is seen in the Eurotransplant region [25]. This is a result of the urgency-driven allocation systems (such as the LAS) that have been introduced in many countries, as well by substantial improvement in ECLS techniques and increased experience with bridging patients to LTx.

There are different ECLS techniques depending on the type and degree of respiratory failure. Veno-venous extracorporeal membrane oxygenation can be used in patients with severe hypoxaemia. Veno-arterial extracorporeal membrane oxygenation is used for patients with severe hypoxaemia and haemodynamic failure including pulmonary hypertension. Extracorporeal CO<sub>2</sub> removal devices are used in patients with hypercapnic respiratory acidosis. ECLS is complex and is associated with serious and potentially fatal complications, such as bleeding, infection and thromboembolism.

Due to the higher complication rate, the survival benefit of patients bridged to LTx remains under debate. Multiple series report inferior 1-year survival rates (between 57% and 58%), which are generally lower than nonbridged patients [61, 62]. Also, hospital stays were longer, and rejection was more prevalent in bridged patients.

However, there have been many improvements in techniques and experience over recent decades. Previously, patients requiring ECLS were sedated and kept on mechanical ventilation during bridging. Nowadays, patients can be bridged while awake with ECLS without mechanical ventilation and suffer fewer complications, such as ventilator-acquired pneumonia, critical illness polyneuropathy and extrapulmonary

organ failure. Undergoing transplantation after admission in the ICU, while being bridged awake on ECLS, has its benefits due to the ability of continuous active physiotherapy and mobilisation and resulted in improved 6 month outcomes after transplantation compared with bridging with mechanical ventilation [63, 64].

The more recent strategies for bridging show superior results; in the USA the success of bridging to LTx using ECLS has improved over the years, with 1-year survival after bridging improving from 47.1% in 2006–2008 to 74.4% % in 2009–2011, *versus* 85.7% in the nonbridged patients. Even more recently, mortality of bridging using ECLS in a large single centre cohort declined from 64% in 1998–2004 to 13% in 2010–2017, and significantly more patients were bridged awake on ECLS in the last 10 years [65, 66]. Thus, in these recent series ECLS-bridged patients have a noninferior prognosis compared with nonbridged patients regarding survival, despite being significantly more ill, when performed by experienced LTx centres. In addition, quality of life post-LTx is similar when compared with patients transplanted electively [67].

Although contraindications vary substantially between programmes, generally age remains a relative contraindication given a significantly lower survival rate of bridging in the elderly, along with limitations in vascular access, frailty, allosensitisation associated with expected prolonged waiting times, previous prolonged ventilatory support and deconditioning [68, 69]

The decision to initiate ECLS support in lung transplant candidates should be made after considering all relative contraindications and the potential of recovery. Accumulation of relative contraindications for LTx in general, and ECLS specifically, should be weighed up by a multidisciplinary team, and, in general, relative contraindications weigh more heavily in patients considered for ECLS support. ECLS should only be initiated if there is a chance for recovery or a chance to bridge to a successful LTx; initiating bridging should always be avoided if not there are no realistic chances of treatment success. These complex procedures should only be performed by experienced specialist teams in transplant centres. Currently, most centres only bridge patients to LTx who have previously been evaluated and listed. Urgent evaluation for LTx is performed occasionally in several centres but remains highly controversial as the evaluation potential in this situation is limited, obtaining adequate informed consent can be challenging and outcome data supporting this procedure are not available at this point.

### **Recipient allosensitisation**

The presence of anti-human leukocyte antigen (HLA) antibodies, especially donor specific anti-HLA antibodies, is associated with an increased frequency of rejection and graft loss [70, 71]. Recent advancements in antibody analysis by solid phase multiplex technologies have allowed for a more precise definition of the breadth and strength of HLA antibodies, and these techniques have replaced the traditional cell-based crossmatch. Unacceptable antigens can be identified, that can be used in a “virtual crossmatch” with a known donor HLA profile without adversely affecting outcomes [72].

These more sensitive solid phase techniques, however, have higher antibody detection rates, leading to more patients found to be highly sensitised. The clinical relevance of all anti-HLA antibodies that are detected is, nevertheless, not always fully clear. For these sensitised patients, however, finding a matching organ by can be troublesome and is associated with high waiting list mortality. Several centres have studied anti-HLA antibody depletion strategies prior to LTx for these patients; unfortunately, without convincingly improving outcomes compared with patients without antibody depletion. To date, the optimal strategy to manage these highly sensitised patients remains unknown [73, 74].

## **Donor selection**

### **Donor usage**

With increasing shortages of donor lungs and new indications for LTx in recent years, waiting list mortality is still substantial [75]. The number of patients awaiting LTx greatly exceeds the number of suitable lung donors. A standard criteria donor lung is generally from a donor aged <55 years who has an arterial oxygen tension >300 mmHg (on inspired oxygen fraction of 100% and positive end-expiratory pressure 5 cmH<sub>2</sub>O), smoking history of <20 pack-years, clear chest radiograph, no chest trauma, no aspiration, no purulent secretions and negative sputum gram stain or cultures. However, these ideal donor criteria were arbitrarily chosen and not based on evidence [76]. Of the total donor pool, only 15–25% of donors meet these ideal criteria [77]. Therefore, clinical judgement is usually of more importance than these “ideal” donor criteria, which are often not met.

During the past decade, various strategies have been employed to increase the donor pool, including the use of extended criteria donors, donors after donation after cardiac death and assessment and optimisation of previous unsuitable donor lungs using *ex vivo* lung perfusion (EVLP).

**Extended criteria donors**

LTx from donors outside the ideal or standard donor pool are called extended criteria donors (ECD). In the past decade, the donor pools have expanded substantially without detrimental effects on survival and development of chronic lung allograft dysfunction (CLAD) [78, 79].

When oxygenation of donor lungs falls below a standard criteria of 300 mmHg (on inspiratory oxygen fraction 100% and positive end-expiratory pressure 5 cmH<sub>2</sub>O), aggressive donor management with alveolar recruitment, ventilatory optimisation and diuretics can improve oxygenation. Even lungs used from donors with low oxygenation (*i.e.* arterial oxygen tension <300 mmHg) can be used for LTx without increased mortality or long-term graft failure, but increased incidence of primary graft dysfunction is reported [80].

Both short- and long-term outcomes of LTx are adversely affected with increasing number of pack-years (>20–30). Also, increased cancer risk is reported [81, 82]. While obvious features of smoking-related illness will be detected in donor history, radiological investigations or ventilatory settings and oxygenation status, less obvious features may be missed. In the UK, recipients of donor lungs from smokers had higher 3-year mortality and prolonged hospital stays compared with donor lungs from nonsmokers after adjusting for age and oxygenation. Contrasting data from the United Network of Organ Sharing database showed that 13% of LTx were performed with donor lungs from heavy smokers (>20 pack-years), with similar outcomes to LTx with lungs from nonsmoking donors [83]. Even if outcomes of LTx may be adversely affected by heavy smoking donor history, it is argued that it yields an overall survival benefit to use lungs from heavy smoking donors due to reduced waiting list mortality, which outweighs the potential inferior outcomes on an individual basis [81].

Lungs from donors aged >55 years are regarded as ECD. A notable increase in average donor age has occurred over the years and major differences in average donor age exist between regions [84]. A retrospective analysis of 8 860 recipients revealed no significant increase in 1-year graft failure among donors aged 55–64 years [85]. In smaller series, noninferior outcomes are even reported in lungs from donors aged >70 years [86]. Older donor lungs can thus be used for LTx with comparable early and midterm outcomes when used in stable recipients (without pulmonary hypertension or IPF), but survival was significantly impaired when they were allocated to critically ill recipients [50, 87]. Regarding long-term outcomes, the International Society for Heart and Lung transplantation (ISHLT) registry data show that increasing donor age is associated with increased 10-year mortality. A donor age of 60 years is associated with an approximately 10% increased risk of 10-year mortality compared with a donor age of 36 years. So, although short-term outcomes of older donors are noninferior in well-selected cases, in the longer term, the consequences of accepting lungs from older donors will become more apparent [50]. Moreover, little is known to date of the effects of increased donor age and the risk of transmission of donor-derived cancers, and on functional outcomes of older donor lungs.

Especially in restrictive lung disease with low intrathoracic lung volume and shrinking of the chest wall, size-reduction LTx or even lobar transplantation is an option when using oversized donor lungs with donor-recipient size mismatch. With this technique, excellent outcomes have been reported [88].

In a few centres worldwide, living-donor lobar lung transplantation (LDLLT) is performed in both adults and children. Japan in particular has considerable experience with LDLLT with acceptable reported 1- and 5-year survival rates of 70% and 45%, respectively. Nonetheless, even in this experienced centre, donor complications occur in 20–60% of donors, so LDLLT remains reserved for experienced centres with very long waiting times for deceased donor organs [89].

Infections are the second cause of mortality within 30 days after LTx [84]. Most centres use broad-spectrum antibiotics in the postoperative period after LTx [90]. In this light, the use of ECD lungs with culture positive non-multiresistant bacteria is feasible when antibiotics based on local susceptibility patterns are administered [91]. Using donor lungs from hepatitis B core positivity is feasible and with a low risk of transmission if viremia or surface antigen is absent [92]. Recently, successful use of hepatitis C positive donors has been reported [93].

Usage of donor lungs with fatal pulmonary arterial embolism has also been described. The retrograde flush in the pulmonary veins resulted in removal of residual thrombi. Without postoperative anticoagulation, transplantation of such lungs resulted in equivalent short and long-term results [94]. Another option is to assess such lungs with EVLP first, allowing further removal of thrombi if deemed necessary.

A history of cancer in the donor does not automatically preclude lung donation, but tumour transmission is reported and mortality in these cases is high [95]. When detailed donor history is present, donors with history of nonmelanoma skin cancer, as well as certain low-grade central nervous system tumours, can be used for LTx and are increasingly used [96]. Regarding other malignancies, the risk of transmission should be weighed up in individual cases.

As stated, in regions with lower donor availability and increased waiting list mortality, using ECD in LTx can safely increase transplantation rates. It seems to be safe when the number of ECD criteria is limited to one or two criteria [97]. However, when more marginal features are present, the risk of poor outcomes increases excessively. Also, it is important to consider the characteristics of the recipient when accepting such donors for transplantation, especially since use of ECD lungs in high-risk recipients is associated with decreased 1-year survival [98].

Identifying all potential donors is an essential step in identifying potential ECD lungs and optimising LTx rates [99]. Currently, use of ECD lungs has become common practice, with 56–99% of donor lungs having at least one marginal factor in some regions [78, 100].

Although the use of ECD is not without controversy and outcomes might be inferior compared with organs from standard criteria donors, this approach can be life-saving and increase quality of life for recipients who might otherwise remain on the waiting list.

#### ***Donation after circulatory death***

The implementation of donation after circulatory death (DCD) in some countries has substantially increased donation rates by 20–50% [101]. Controlled DCD (cDCD, or Maastricht category III DCD) entails the cessation of mechanical ventilation or life support in patients with an unfavourable prognosis in a controlled hospital setting. Uncontrolled DCD (uDCD, or Maastricht category II DCD) entails donation after unexpected out of hospital cardiac arrest.

Depending on national legislation and local protocols, cDCD can be performed with and without EVLP. Currently, 12% of cDCD cases are performed with EVLP with excellent results showing lower primary graft dysfunction scores and no difference in survival compared with donation after brain death LTx [102]. Whereas it has been shown that results with cDCD LTx without EVLP are equivalent to donation after brain death LTx with regard to primary graft dysfunction rates, survival and graft function, some protocols still prefer to use EVLP in cDCD [103, 104].

Only limited experience exists with LTx from uncontrolled DCD donors with 68% 1-year and 51% 5-year survival rates reported [105]. Because of prolonged warm ischaemia time *post mortem* and no ability for pre-procurement assessment of the donor lungs, usage of EVLP is recommended in uDCD LTx [106].

Of special notice is DCD organ donation after euthanasia (Maastricht category V). In countries where this has been legalised it has become an increasing source of organ donation (Belgium, the Netherlands and Canada) [107]. So far, no results have been published on outcomes after LTx, but the results seem equivalent (unpublished personal data).

#### ***EVLP***

Even with the measures discussed above, demand for donor lungs is still high with considerable discrepancy between waiting lists and transplants. EVLP is a relatively new technique of normothermic perfusion and ventilation of donor lungs which allows extended evaluation for quality and reconditioning [108, 109]. With this technique, lungs can be evaluated on quality between donation and transplantation. The lungs can be monitored on the device for development of pulmonary oedema by changes in compliance, airway pressure, pulmonary vascular resistance and perfusate oxygenation. In addition to providing a platform for evaluation, EVLP can allow treatments to be administered that can optimise graft function by adding antibiotics, immunomodulatory drugs and detection of biomarkers for poor outcomes after EVLP, all of which are currently under evaluation [110–112]. By using a solution with an optimised colloid osmotic pressure, fluid is drawn from the extracellular compartment, thereby improving gas exchange. This, together with the resetting of cold ischaemia time, allows for transplantation of lungs that would have previously been discarded to be used for LTx. Acceptance rates of previously discarded lungs after EVLP vary from 34% to 97% [113–115]. Outcomes of EVLP in donor lungs previously discarded for LTx are similar to LTx with standard criteria donor lungs, although in the Develop UK trial somewhat inferior survival results of LTx after EVLP were found [108, 115, 116]. As there were some methodological issues with the latter trial, trial results from ongoing trials with extend criteria donor lungs are eagerly awaited to establish the definitive role for EVLP in these marginal donor lungs (NOVEL, EXPAND and PERFUSIX trials).

In addition to EVLP in ECD lungs, two large trials have now been completed in which EVLP was evaluated in standard donors, to assess whether this would lead to improved outcomes. Both trials could not demonstrate a survival benefit of EVLP compared with standard cold storage in standard criteria donor lungs [117, 118]. However, it appeared feasible to safely increase preservation time. Also, extension of the preservation time beyond 12 h did not negatively affect LTx outcome, thus making it feasible to use EVLP for logistical purposes; for example, to schedule LTx surgery during the daytime [119]. Whereas this

seems an ideal scenario, high cost and personal demands preclude this from being standard of care at the moment in most centres.

With outcomes after EVLP, including long-term outcomes, that seem noninferior compared with normal cold storage LTx and high conversion rate to clinical LTx of previously discarded donor lungs, EVLP substantially expands the donor pool in LTx and has become standard of care in many centres over recent years and shows promise for future innovation [120, 121]. Nevertheless, at this point, it still remains unclear in which settings and subgroups of marginal donors EVLP has most value.

### *Donation rates*

Donation rates vary substantially between countries. Rates are determined by many factors, such as sociocultural attitudes, religion and legislation. Legislation is believed to play an important role in donation rates. Generally, two systems regarding organ donation exist: the presumed consent or opt-out system, and the informed consent or opt-in system. In the opt-out procurement system, people are considered donors if they have not registered an objection to be organ donors as the default option. In the opt-in system, however, people are considered donors if they registered or declared their wish to donate as the default option.

Various studies have demonstrated that in countries with opt-out systems deceased donor rates are higher [122, 123]. This has led countries with opt-in systems to alter their legislation, to boost organ donation rates. For example, the legislation has recently been modified in the Netherlands and the UK, where in 2020 an opt-out system will be implemented instead of the current opt-in system. However, a large recent analysis reveals no significant difference in donation rates between the two systems [124]. This suggests that the switch to the opt-out model may not provide the “quick fix” to improve donor rates that has been previously suggested. The effects of the recent alterations in legislation will be awaited.

## **Developments in immunosuppressive strategies**

### *Induction therapy*

In most patients induction therapy is given, but it is not universally applied and side-effects, such as major infection and malignancies, remain major fears. Currently, the ISHLT registry data show that 62% of lung transplant recipients received any induction therapy, and these numbers have increased over past years. Whereas it is not universally applied, the registry data suggest a survival benefit with induction [3].

Induction generally consists of an interleukin-2 receptor antagonist (daclizumab or basiliximab) and, less frequently, a lymphocyte depleting agent (ATG) or more recently monoclonal antibodies, such as alemtuzumab which is a CD52 antagonist, have been introduced. Induction agents are administered immediately following LTx to establish an acute immunosuppressive effect before other immunosuppressives take effect as standard immunosuppressive agents are introduced gradually and the dosing adjusted [125].

A recent large retrospective series comparing alemtuzumab to ATG and no induction showed significant benefits of induction therapy in terms of CLAD and survival, despite significantly lower calcineurin inhibitor (CNI) levels that were applied in the induction groups [8]. No additional adverse events were noted in terms of infection or malignancies. A major advantage to the lower CNI exposure is reduced toxicity, such as decreased prevalence of renal impairment. A recent systematic review of retrospective data also reported lower rates of acute rejection after alemtuzumab induction compared with conventional induction agents, but there are no prospective studies available confirming such results yet [126]. However, we can conclude that there is some evidence in favour of induction therapy and its application is increasing; however, it is not standard practice in all centres at this point.

### *Standard immunosuppressive schemes*

The goal of immunosuppression is to prevent both acute rejection as well as CLAD by inhibiting T- and B-cell proliferation and activation. CLAD remains a major problem after LTx precluding long-term survival. The incidence of CLAD is about 10% per year with a prevalence of 50% at 5 years, and CLAD represents the most important cause of late mortality after LTx [1].

Regarding the best immunosuppressive strategies, only a limited number of small randomised controlled trials have been performed in LTx. Most of the experience with immunosuppressive regimens came from experience from other fields of organ transplantation, as well as retrospective case series and expert opinion. This lack of a clear gold standard is also reflected by the broad diversity of strategies currently used worldwide [1]. Generally, the amount of immunosuppression needed after LTx is much higher due to increased susceptibility of the lungs to rejection compared with other solid organs, and significantly increases the risk of drug toxicity [127].

The current standard immunosuppressive regimens combine steroids with a CNI (cyclosporine or tacrolimus) and a cell cycle inhibitor (azathioprine or mycophenolate mofetil). Tacrolimus is currently used by most lung transplant centres as the preferred CNI mycophenolate mofetil due to the superiority of tacrolimus *versus* cyclosporine regarding CLAD incidence, lymphocytic bronchiolitis score, treatment withdrawal and arterial hypertension. However, a survival benefit has not been identified for tacrolimus *versus* cyclosporine, and a significantly decreased incidence of acute rejection episodes, infections, or other complications has yet to be shown [128]. Likewise, superiority of mycophenolate mofetil over azathioprine after LTx has never been demonstrated, despite its increased use.

#### *Evolving strategies to reduce risk of CNI toxicity*

In patients with long-term survival after LTx, renal toxicity, but also other CNI-related complications such as diabetes mellitus, hypertension and dyslipidaemia, become more prevalent and are associated with increased morbidity and decreased survival. Therefore, strategies to lower CNI have been employed. For example, mammalian target of rapamycin (mTOR) inhibitors have been added to schemes to lower CNI through levels, with similar efficacy with regards to acute rejection episodes, but with beneficial effects on renal function (NOCTET study) [129]. This effect was, however, negligible if patients were switched >5 years after LTx, and effects were not maintained in the longer term [130]. More recently, in the multicentre 4EVERLUNG study a quadruple immunosuppressive scheme with lowered CNI was demonstrated to be efficacious and safe, and early switch from a triple to a quadruple scheme with low CNI led to preserved renal function in the study population [131]. The highest benefit was shown in patients with the lowest glomerular filtration rates (<40 mL·min<sup>-1</sup>).

Belatacept, a novel selective T-cell costimulatory antagonist, has also been studied as a method to withdraw CNI therapy in patients with unacceptable CNI side-effects or with renal toxicity; in two small series, average renal function improved with belatacept, without increased incidence of acute cellular rejection [132, 133]. Currently, effectiveness and safety of belatacept to replace CNI in LTx is, however, not sufficiently established. In renal transplantation, a less immunogenic organ than the lung, there are important concerns regarding increased acute cellular rejection (ACR) in patients treated with belatacept [134]. Therefore, general use of belatacept is not justified at this point to replace CNI in LTx, and it should be reserved for those cases with unacceptable side-effects of CNI.

#### *ACR and antibody-mediated rejection after LTx*

ACR remains a feared phenomenon after LTx, occurring in ~30% of patients in the first year after LTx [84]. It is characterised by acute decline in pulmonary graft function without other cause. Diagnosis is preferably confirmed histologically using transbronchial biopsies and is based on the presence of perivascular and interstitial mononuclear cell infiltrates. It is graded in severity depending on the intensity of the cell infiltrates. In high-grade rejection there is severe endothelitis, necrosis, haemorrhage and pneumocyte damage. ACR episodes are a major contributor to the development of CLAD [135]. The cornerstone of ACR treatment is steroid pulse therapy, whereas therapy for persistent or refractory ACR is less well established. In cases of ongoing or refractory ACR, various strategies can be employed. Strategies include switching from cyclosporine to tacrolimus if applicable, adding mTOR in a quadruple immunosuppressive regime, ATG, alemtuzumab and extracorporeal photopheresis [136–139]. In the latter treatment, peripheral blood lymphocytes collected *via* apheresis are treated with 8-methoxypsoralen and ultraviolet to induce lymphocyte apoptosis and regulatory T-cells.

In recent years, antibody-mediated rejection (AMR) has been recognised as a separate entity leading to graft dysfunction [140]. In LTx, AMR diagnosis is based on presence of donor specific antibodies (DSA) directed towards donor HLAs. Histology can show neutrophil margination, neutrophil capillaritis, and arteritis and positive staining for C4d as marker of complement activation, but there can be overlap with features of ACR and infection [135, 141]. Diagnosis of AMR can be very challenging. The currently widely used new solid phase assays are more sensitive and have higher DSA detection rates, but the clinical correlation remains unclear. For example, DSA are also not specific for AMR, as AMR can occur without DSA and DSA can be present in recipients without any signs of graft dysfunction [142].

The current classification system recognises subclinical and clinical AMR and diagnosis is divided into definite, probable and possible AMR depending on how many of the diagnostic criteria (allograft dysfunction, DSA, congruent histology, C4d positivity) are present [141].

Apart from establishing a diagnosis of AMR, treatment is even more challenging. A large range of treatment schemes have been employed in different centres, commonly extrapolated from experience derived with other solid organ transplantations, despite major differences between AMR in different organs. Most strategies aim at depleting or modulating circulating DSA. Successful outcomes have been reported using plasmapheresis, intravenous immunoglobulin, rituximab, bortezomib, alemtuzumab and

eculuzimab [140, 143–145]. Nonetheless, there are more questions regarding AMR than answers and despite aggressive treatment strategies prognosis is generally grim with a reported 1-year survival of 47% [146].

### **Modifying CLAD**

CLAD is defined as a substantial and persistent decline ( $\geq 20\%$ ) in FEV<sub>1</sub> value from the baseline value. The baseline value is identified as the mean of the two best post-operative FEV<sub>1</sub> measurements taken at least 3 weeks apart, with or without change in the forced vital capacity, and can be staged by the CLAD staging (from CLAD 0 to 4). Secondary causes of lung function decline have to be excluded [147].

Allograft dysfunction can present in different phenotypes: a restrictive pattern (restrictive allograft syndrome), a predominantly obstructive ventilatory pattern (bronchiolitis obliterans syndrome), or a mixed pattern. CLAD is the leading cause of death after the first year, accounting for >20–30% of deaths, and the main obstacle to improving long-term survival after transplantation [1].

Regarding treatment or prevention of CLAD by using strategies other than intensifying immunosuppression or addressing known and potentially modifiable risk factors, some additional approaches may be beneficial. A small trial with prophylactic azithromycin, known for its immune-modulatory effects in chronic lung disease, improved pulmonary function and decreased prevalence of CLAD at 2 years after LTx transplantation [148]. Even in patients with established CLAD, azithromycin was shown to slow its progression in another randomised trial and improved pulmonary function after 12 weeks [149].

In addition to azithromycin, a randomised trial showed that montelukast had no additional beneficial effects on lung function decline [150]. In the subset of early CLAD patients it did, however, appear to be affective in slowing CLAD progression. This study was, unfortunately, hampered by small sample size (n=30). Later, a large retrospective analysis in the same centre showed that montelukast attenuated the course of FEV<sub>1</sub> in patients with CLAD across all stages, and this was most clear in patients with slowly progressive CLAD [150, 151].

(Subclinical) gastro-oesophageal reflux disease (GORD) is common after LTx (~70%) and is strongly associated with the development of CLAD [152, 153]. Factors that have been implicated in the increased prevalence of GORD after LTx are intraoperative vagal nerve damage, loss of cough reflex, impaired mucociliary clearance, and development of gastroparesis due to the immunosuppression [153]. While ambulatory pH testing is the most universally advocated, the optimal testing modality remains undefined [153]. It has been suggested that the prokinetic effect of azithromycin treatment decreased reflux and that this effect is more likely to prevent CLAD than its immune modulatory effects [154]. In most centres, standard proton-pump inhibition is prescribed; however, this does not reduce the number of reflux events, or markers of aspiration on bronchoscopy. Early fundoplication has been suggested as an option to prevent CLAD in patients with GORD, but data is limited to series of patients and this procedure is not standard practice in most centres [155, 156].

There is growing belief that certain pulmonary infections are risk factors for the development of CLAD. One of the most common pathogens isolated from respiratory secretions of lung transplant patients are *Aspergillus* species. There are data correlating *Aspergillus* colonisation with CLAD, although not all studies confirm this association [157, 158]. Most centres use some form of antifungal prophylaxis after LTx in all their patients to prevent invasive fungal infections [159]. Unfortunately, the effect of prophylaxis on CLAD development remains unclear.

Other options to modify CLAD are extracorporeal photopheresis combined with standard immunosuppressive regimens and total lymphoid irradiation, but additional clinical research is required to establish the efficacy [147, 160]. The trial data regarding modification of CLAD progression is mostly limited to small single centre trials, and the field is still awaiting confirmatory data from larger series. Several ongoing clinical trials in CLAD examine the role of pirfenidone (clinicaltrials.gov identifier NT02262299), extracorporeal photopheresis (clinicaltrials.gov identifier NCT02181257) and mesenchymal stromal cell therapy (clinicaltrials.gov identifier NCT02709343).

In advanced CLAD, re-transplantation can be considered. Better outcomes of re-transplantation are suggested in patients with obstructive rather than restrictive CLAD and for ambulatory patients waiting at home [161]. In well-selected patients, noninferior outcomes for retransplantation are reported [162].

### **Conclusion**

Developments in the field of LTx over the past decade have broadened the indications for LTx with the acceptance of increasing numbers of elderly transplant candidates and the increased availability of improved and novel bridging strategies that can be used in the ICU.

New allocation systems have been implemented in many countries and have led to both improved donor organ allocation and decreased waiting list mortality.

Although a major shortage of donor lungs persists, the use of DCD donors in many countries and the use of ECD lungs have substantially expanded the donor pool. Additionally, the development and clinical use of EVLP have allowed organs that may have been discarded to be used for transplant.

Current practices in LTx combined with novel therapeutic interventions and improved immunosuppressive strategies will hopefully lead to better outcomes and improved long-term survival for lung transplant recipients.

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