

Challenges in lung transplantation

Thorsten Krueger^{a*}, Carine Berutto^{b*}, John-David Aubert^c

^a Service de Chirurgie Thoracique et Vasculaire, CHUV, Lausanne, Switzerland

^b Centre de Transplantation d'Organes, CHUV, Lausanne, Switzerland

^c Unité de Transplantation Pulmonaire, Service de Pneumologie, CHUV, Lausanne, Switzerland

* Contributed equally

Summary

Lung transplantation is an established therapy for end-stage pulmonary disorders in selected patients without significant comorbidities. The particular constraints associated with organ transplantation from deceased donors involve specific allocation rules in order to optimise the medical efficacy of the procedure. Comparison of different policies adopted by national transplant agencies reveals that an optimal and unique allocation system is an elusive goal, and that practical, geographical and logistic parameters must be taken into account.

A solution to attenuate the imbalance between the number of lung transplant candidates and the limited availability of organs is to consider marginal donors. In particular, assessment and restoration of gas exchange capacity *ex vivo* in explanted lungs is a new and promising approach that some lung transplant programmes have started to apply in clinical practice.

Chronic lung allograft dysfunction, and especially bronchiolitis obliterans, remains the major medium- and long-term problem in lung transplantation with a major impact on survival. Although there is to date no cure for established bronchiolitis obliterans, new preventive strategies have the potential to limit the burden of this feared complication. Unfortunately, randomised prospective studies are infrequent in the field of lung transplantation, and data obtained from larger studies involving kidney or liver recipients are not always relevant for this purpose.

Key words: lung transplantation

Introduction

With more than 32 000 procedures performed worldwide in the last three decades, lung transplantation has become the

Abbreviations:

LAS	Lung Allocation Score
SOAS	Swiss Organ Allocation System
EVLP	Ex vivo lung perfusion
BO(S)	Bronchiolitis obliterans (syndrome)
DSA	Donor specific antibody

standard of care for selected patients with advanced lung diseases. However, short- and long-term survival are inferior to those in other solid organ transplantation. Specific challenges include higher perioperative mortality, a higher rate of acute and chronic rejection, and infections of the transplanted graft which is in direct contact with open air. In this review we focus on three issues that have a profound impact on lung transplantation programmes around the world: the system of lung allocation, new procedures to evaluate suboptimal organs, and the challenge of chronic lung allograft dysfunction.

Lung allocation

Legal and ethical perspective

Organ transplantation from deceased donors is a treatment associated with specific constraints, there being a universal shortage of donors compared to recipient candidates on the waiting list. It is therefore a unique situation involving explicit rationing of therapy. To deal with this situation most countries have developed a legal framework for allocation of organs from deceased donors, with a specific set of rules for each organ (table 1). The allocation systems that have been implemented throughout the world are always a compromise between two antagonistic demands: patient's equity and medical efficacy. The patient's equity principle implies that no one should be discriminated against in organ allocation because of age, gender, ethnicity and socioeconomic status, physical or psychic characteristics. The medical efficacy principle means that organ transplantation should be offered to the recipient who will derive maximum improvement of survival compared with conventional standard care. A classical illustration of this dilemma encountered in the daily life of lung transplantation teams is the "competition" between a young patient with cystic fibrosis and a 60-year-old ex-smoker with end-stage COPD. Which of them will receive transplant of the lungs from a 55-year-old donor?

Practical solutions

Several allocation systems have been devised to solve this transplantation dilemma [1–3]: historically most trans-

plantation centres have started their programme with locally based allocation: it was the surgeon who made the choice, in the middle of the night, of the most befitting recipients on the local waiting list. Although considered the most simple and efficient method of resource allocation by many, this method is no longer accepted by the health authorities in some countries (e.g. Switzerland) because of the lack of transparency and a theoretical proneness to non-medical bias. Next, the easiest way to choose the right recipient is chronological, that is, time spent on the waiting list. This rule was applied in the USA until 2005 [1], and is still in use in the Swiss Organ Allocation System (SOAS), with some exceptions [3] (cf below): The major drawback of chronological allocation is that the risk of death on the waiting list differs according to lung diseases, being highest for idiopathic lung fibrosis and lowest for COPD. Strict enforcement of the chronological rule would therefore run counter to the equity principle, since most patients with lung fibrosis will die on the waiting list before receiving a transplant. For these reasons, several lung transplantation agencies have implemented, on top of chronological allocation, some rules of priority, usually labelled as urgent or super-urgent status (table 2). Urgent status is usually defined by the severity of the disease or the amount of care, but not by a specific diagnosis [4]. Although mechanical ventilation in the ICU is the usual criterion for urgent status, the other criteria differ significantly within countries: for example, COPD and retransplantation are exclusion criteria for urgency status in France, but not in Eurotransplant or in the SOAS. Another consequence of chronologically-based allocation is preemptive listing of the patient and, therefore, a longer waiting time on the list (table 1). The Swiss SOAS is basically a modified chronological system: a high priority urgent status is assigned to patients treated with invasive mechanical ventilation in the ICU. A second and third order of priority is assigned to patients with pulmonary arterial hypertension (PAH) and then idiopathic lung fibrosis. Finally, at the lowest order of pri-

ority before chronological order, lungs from donors aged below 40 are allocated preferentially to recipients <40. According to this system, the lungs from a 25-year-old donor will be allocated first to a 60-year-old recipient with PAH, then to a 30-year-old patient with cystic fibrosis.

Is a comparison between systems possible?

It is scientifically highly challenging to decide objectively which is the best system. Every lung transplantation team throughout the world will acknowledge some frustration in the daily life of lung allocation in the context of a continuously growing waiting list. Furthermore, objective comparison between systems is a difficult task: data are not reported or even calculated in the same manner between registries, and epidemiological together with geographical considerations prevent side-to-side comparison. Local, surgeon-based allocation, while allowing the greatest flexibility, has the weakness of relying on a single individual's judgment. A strict chronological rule is unethical for patients with rapidly evolving disease. A chronological system modified by some exceptions is always a compromise within inherent rigidity, especially for less common lung disorders. Theoretically, allocation based on medical efficacy and not on waiting time appears to be more appealing. This is the objective of the lung allocation score (LAS) implemented in the USA since 2005 [5–7]. Based on data continuously recorded and analysed from the UNOS registry, a score based on mortality risk on the waiting list, combined with survival in the first year after transplantation, allows the adult future recipient to be ranked on a scale from 0 to 100. Clinical parameters, haemodynamics and laboratory data are used to calculate the LAS. The immediate impact of such a system is to dramatically decrease waiting time, there being no need to list the patient preemptively to allow him a reasonable chance of receiving a transplant. One may consider this change merely artifactual, but for the patient it may be of clinical significance since his quality of life may be affected by a des-

Table 1: Lung allocation systems in 4 different areas.

Allocation system	LAS	Eurotransplant	Agence de la Biomédecine	SOAS
Web page	www.unos.org	www.eurotransplant.org	www.agence-biomedecine.fr	www.swisstransplant.org
Country	USA	AU; GE; NL; BE; LU	France	Switzerland
References	[6]	[4]	[52]	[3]
Year of introduction	2005	NA	2007	2007
Main allocation rule	Severity score	High urgency and urgency status	Local allocation	Chronological; exceptions: ICU, IPF, PAH
Urgent status	Yes; review board	Yes; predefined	Yes, with expert panel	Yes; predefined
Median waiting time (days)	148	195	135	208
% deaths on the waiting list	6.5 (yr 2008)	15.5 (yr 2009)	10.3 (yr 2009)	10.0 (2007–2009)
Number of lung tx/million / yr	4.5	6.1 (Germany) 7.2 (Belgium)	3.6	5.0
% lungs accepted	21	56	17	42

NA: not available; IPF: idiopathic pulmonary fibrosis; PAH: pulmonary arterial hypertension.

Table 2: Comparison of 3 European urgency statuses for lung transplantation.

Urgency criteria	Eurotransplant	Agence de la Biomédecine	SOAS
Mechanical ventilation in the ICU	Yes	Yes	Yes
COPD included	Yes	No	Yes
Re-Tx included	Yes	No	Yes
% of total candidates	40	17	10

SOAS: Swiss Organ Allocation System; Re-Tx: re-transplantation.

perately long wait for an organ. On the other hand, while the prediction of survival for lung candidates could be evaluated with reasonable accuracy, pre-transplantation prediction of survival after transplantation is very poor [8–10]. Thus the LAS is essentially a pretransplant severity score. This means that the most severely affected patients are transplanted first, with the potential for higher perioperative morbidity and mortality due to these high-risk recipients. This has indeed been observed for recipients with the highest quartile of the LAS score [9].

Despite these difficulties, what are the critical parameters to consider for the evaluation of a lung transplantation programme at the national level? In our opinion these should include at least the number of transplants per million inhabitants per year, the percentage of lung grafts transplanted compared to identified donors, the percentage of deaths on the waiting list and early and late post-transplant survival. Periodic analysis of these data is of utmost importance in devising policies of organ allocation.

Ex-vivo lung perfusion: a new tool for donor organ assessment and reconditioning before lung transplantation

The lack of donor organs is a well-known major obstacle to the treatment of benign end-stage lung disease by lung transplantation. Two different approaches are currently being explored to enlarge the pool of donors: use of extended criteria for selection of donor lungs [11] and lung procurement from donors after cardiac death [12]. These new strategies will hopefully increase the number of organs for lung transplantation in the future, and both may change the way potential donor lungs are managed before transplantation.

The donor organ is classically selected on the basis of donor history, physical examination, bronchoscopy, blood gas analysis and chest x-ray. An ideal donor lung is defined by age below 55 years, a PaO₂/FiO₂ ratio >300 mm Hg, no history of smoking or less than 20 pack-years, a clear chest x-ray and no purulent tracheal secretions [13]. Assessment of the potential donor lung is completed during procurement surgery. To avoid harmful effects of brain death on the lung, such as neurogenic oedema formation, potential donor lungs are resuscitated by appropriate medical donor management before organ retrieval [14]. Many transplantation centres do not restrict lung procurement to ideal donors, but have extended these criteria to so-called “marginal” lungs. Uncertainties remain, however, as to the extent to which these criteria can be widened. Nevertheless, even with the most aggressive approach, more than 50% of donors are considered unsuitable for lung donation (table 1). New concepts have been developed to enlarge the donor pool:

Marginal grafts not fulfilling the standard criteria for lung transplantation may undergo a so-called “pretransplant reconditioning” to render them suitable for transplantation. As a result, graft assessment should take initial lung function into account, but should also judge the possible suitability of the organ for transplantation after reconditioning.

In this context, ex vivo lung perfusion (EVLV) is set to evolve as a promising strategy: it may be applied (1.) to assessing graft function after procurement and before implantation, (2.) to preserving the graft after harvesting over long time intervals, and (3.) to repairing potential grafts which are initially considered inappropriate for transplantation.

This new technique has been developed on the basis of pioneer work by Steen et al. [15–18], in which explanted lungs are perfused and ventilated in a closed ex-vivo circuit (Ex-Vivo Lung Perfusion, EVLP; XVIVO[®], Vitrolife, Sweden). The lungs are perfused at a constant pressure below 20 mm Hg with a buffered extracellular normothermic solution at an optimal colloid osmotic pressure (Steen solution[®], Vitrolife, Sweden), and are simultaneously ventilated at low volume and pressure to avoid ventilation-induced lung injury. During perfusion, several aerodynamic (airway pressure, lung compliance) and haemodynamic (pulmonary vascular resistance) measurements are done, together with repeated blood gas analysis in the effluent of the circuit. As a result, lungs can be properly evaluated to determine their suitability for subsequent transplantation [18].

Next to precise assessment of lung function, by ex vivo perfusion of the explanted lung it is possible to protect the donor organ from systemic effects of brain death. Recent technical developments allow successful ex-vivo perfusion for up to 12 hours without deterioration of the explanted lungs' physiological parameters [19, 20]. Interestingly, it has been shown in experimental and clinical studies that the functional status of marginal donor lungs can be improved by EVLP to render them suitable for subsequent transplantation, a process for which the term “reconditioning” has been coined [15, 21]. Lung oedema can be eliminated during the process of EVLP thanks to the hyperoncotic perfusate, while atelectatic lung regions can be re-expanded by the application of positive end-expiratory pressure in the ventilation circuit. Pharmacological interventions are possible while the lung is perfused and ventilated in the EVLP system, either by intravascular or endobronchial administration of drugs: experimental studies indicate that inhaled nitric oxide may reduce ischaemia-reperfusion injury [22], and endobronchial application of surfactant was found to reduce lung damage after acid aspiration [23]. Pulmonary embolism was successfully treated by fibrinolytics [24] and antibiotics may be added to the perfusion solution to treat lung infection. Another experimental approach is transbronchial ex-vivo gene therapy by EVLP: EVLP was used to transfect lungs with an adenovirus encoding the anti-inflammatory interleukin-10 [25]. EVLP was also applied to clean the donor lung from pro-inflammatory cytokines by inserting an adsorbing membrane in the circuit. In conclusion, these different experimental studies show that EVLP may at some point offer a specific graft repair opportunity, depending on the type of donor lung injury, such as aspiration, infection, atelectasis or oedema. A limited number of human lung transplantations after EVLP have been reported to date [15, 21, 26, 27]. The largest and most recent one was published by the Toronto group, reporting on 20 such procedures from marginal donors. The authors concluded that lung transplantations from high risk donors, with lungs

exhibiting ex-vivo stability for 4 hours, have a similar outcome to those obtained with conventionally selected lungs [26]. These pilot studies are promising since they provide first evidence that initially discarded human donor lungs can be reconditioned to acceptable function and used for transplantation with a satisfactory outcome.

In conclusion, ex vivo lung perfusion is a new technique for functional assessment of donor organs, and may be applied in the future for specific repair of graft injury before lung transplantation. EVLP can be used to recondition not only marginal lungs from brain-dead donors, but also has the potential for evaluation of lungs obtained from donors after cardiac death. This may increase the number of available donor organs for lung transplantation in the future. Further clinical studies are needed to establish the feasibility of this procedure.

Prevention and treatment of bronchiolitis obliterans (BO) / bronchiolitis obliterans syndrome (BOS)

Definition and epidemiology

Bronchiolitis obliterans (BO) is the most prevalent form of chronic lung allograft dysfunction (CLAD) and is the leading cause of late mortality following lung transplantation [28]. BO is a progressive fibro-obliterative occlusion process of the small airways triggered by lymphocytic infiltration of the submucosa resulting in epithelial cell necrosis, mucosal ulcerations and formation of granulation tissue. Because BO is difficult to document histologically, in 1993 a committee sponsored by the International Society for Heart and Lung Transplantation proposed a clinical description of BO termed bronchiolitis obliterans syndrome (BOS). These criteria were updated in 2001 and are now defined by a sustained decrease in pulmonary function parameters of $\geq 20\%$ for FEV₁ or FEF₂₅₋₇₅ [29]. Radiographic features suggestive of BOS include air trapping and bronchiectasis, but are not highly sensitive. Currently the incidence of BOS according to the ISHLT database is 49% at 5 years and 75% at 10 years [28].

The risk factors are immunological (acute graft rejection, donor antigen-specific reactivity) and non-immunological (viral-bacterial or fungal infections, primary graft dysfunction, gastroesophageal reflux with aspiration, air pollution) [30, 31].

Recent research is directed at finding early markers of BOS. Most of the markers identified to date are related to chronic neutrophilic inflammation, such as exhaled nitric oxide (eNO), chemokines and cytokines (IL-6, IL-8, IL-10, IL-15, KL-6 [28], RANTES) [32]. However, none of these molecules has evidenced enough specificity to distinguish infection from rejection.

Impact of the standard immunosuppressive regimen on BOS prevalence

A few randomised controlled trials have been conducted to compare the efficacy and adverse effects of cyclosporine versus tacrolimus. In a meta-analysis conducted by Fan et al., tacrolimus was found to be superior to cyclosporine for the prevention of acute allograft rejection episodes [33]. However, the impact on BOS prevalence and survival was not statistically significant.

In a monocentric prospective observational study, Speich et al. found that mycophenolate mofetil compared to azathioprine started from the first post-operative days significantly decreased the incidence, severity and recurrence of acute rejection episodes [34]. The incidence of graft loss due to BO was reduced, although the incidence of BOS and overall mortality was unchanged. A multicentric study comparing the same immunosuppressants failed to show a significant difference, although a higher rate of switches or dropouts in the azathioprine arm was observed [35].

Rapamycin, also known as sirolimus, because of its anti-fibroproliferative effect, may improve and/or stabilise the decline of FEV₁ but must be frequently withdrawn because of adverse effects [36, 37].

Recently Vos et al. conducted an interesting prospective randomised study by using the macrolide azithromycin to prevent BOS after lung transplantation [38]. The rationale for this trial was the known therapeutic effect of azithromycin in neutrophilic BOS (cf. below). They demonstrated a significant improvement of BOS-free survival among patients receiving azithromycin. The overall survival did not differ between groups, but the follow-up may have been too short to test this endpoint. On the basis of a single monocentric study it is probably premature to introduce azithromycin systematically to the regimen of every new lung transplant recipient, but further reports involving this strategy are awaited by the lung transplant community.

On the whole, very few randomised prospective studies have been conducted and published with the incidence of BOS as a specific aim (table 3).

Table 3: Randomised prospective trials for the prevention of BOS in lung transplantation.

Authors (ref.)	Therapeutic action	Endpoint	Main results
Vos [38]	Azithromycin	BOS and survival at 2 yr	Positive for BOS, negative for survival
Iacono [48]	Inhaled CsA	AR, survival	Negative on acute rejection rate, but improvement in survival
Palmer [53]	MMF versus aza	AR, survival at 6 months	Negative
McNeil [35]	MMF versus aza	BOS at 3 yr	Negative
Hachem [54]	Tac versus CsA	AR, BOS	Positive in favour of Tac for AR, negative for BOS
Zuckermann [55]	Tac versus CsA A	AR, BOS, survival at 2 yr	Negative
Bhorade [37]	Sirolimus versus aza	AR, BOS, survival at 1 yr	Negative
Snell [56]	Everolimus versus aza	AR, BOS, survival at 1 and 2 yr	Positive in favour of Everolimus at 1 yr, negative at 2 yr

CsA: cyclosporine A; Aza: azathioprine; MMF: mycophenolate mofetil; Tac: tacrolimus; AR: acute rejection.

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Therapeutic strategies for established BOS

A few studies have described stabilisation of the decline in FEV₁ after conversion from cyclosporine to tacrolimus [39–41]. Methotrexate has been used in a few patients with recurrent acute rejection or BOS, and showed diminution of the decline in pulmonary function; however, it is now rarely used because of severe side effects and toxicity [42]. Attempts in the early years of lung transplantation to reverse BOS by increasing the dosage of the immunosuppressive regimen have systematically failed and were plagued by severe infectious complications.

In 2003 Gerhard et al. used the macrolide azithromycin for the first time 3 times a week in a pilot study against BOS. In five of their six patients FEV₁ of 17.1% improved [43]. This study raised new hope for the control of BOS. Subsequent non-randomised studies have suggested that azithromycin can alter the decline of FEV₁ in about 35% of patients, particularly those with neutrophilia of $\geq 15\%$ in the bronchoalveolar lavage [44, 45].

In addition to a significant anti-inflammatory effect by lowering the inflammatory mediators such as IL-17, IL-8, IL-1 β , TNF- α , RANTES, azithromycin also inhibits the formation of *Pseudomonas aeruginosa* biofilm, flagellin expression and adherence to the tracheal epithelium, and may diminish gastroesophageal reflux (GER) by enhancing oesophageal motility and favouring gastric emptying [45]. Although azithromycin is now widely used for patients with BOS in lung transplantation centres, controlled prospective studies are awaited to strengthen the scientific rationale for this.

Vanaudenaerde et al. proposed two clinical phenotypes of BOS based on neutrophilic airway inflammation, clinical status, time of onset, rapid progression, histology, and radiology [45]. The immunological mechanism underlying the development of these two phenotypes appears to be entirely different. The NARD (neutrophilic reversible allograft dysfunction) is triggered by repetitive mild injuries such as infection, colonisation, GER and air pollution, and will respond to azithromycin. The fBOS (fibroproliferative BOS) is initiated by direct active fibrosis without inflammation and without clearly identified triggers, and does not respond to azithromycin. This dichotomy in the clinical spectrum of BOS needs to be confirmed by other clinical investigators.

If in recent years azithromycin has shown some potential for prophylaxis and treatment of neutrophilic BOS, the challenge remains: what kind of treatment can be proposed for non-responders with fBOS?

Based on the concept that montelukast, a leukotriene receptor antagonist in animal models, is able to inhibit pulmonary as well as hepatic fibrosis, Verleden et al. tested this agent in 11 patients with BOS without BAL neutrophilia [46]. With the addition of montelukast they observed significant attenuation of the decline of FEV₁ compared to placebo, but this strategy now needs to be confirmed by a larger placebo-controlled randomised study.

Intravenous immunoglobulins (IVIG) are administered as an immunomodulatory agent for desensitisation protocols in kidney transplant recipients. Hachem et al. used it in a prospective study as preemptive antibody-directed therapy after lung transplantation [47], and showed that IVIG ad-

ministered in combination with rituximab were more efficient in depleting donor specific antibody (DSA) than IVIG alone.

Aerosolised therapy with corticosteroid was used without success in BOS. In a prospective randomised trial Iacono et al. describe how inhaled cyclosporine did not improve the rate of acute rejection but did improve survival and extended periods of chronic rejection-free survival [48].

Non-pharmacological therapy

Total lymphoid irradiation (TLI) is a non-pharmacological immunomodulatory approach that has been first applied with success in renal transplantation. A few observational studies have reported TLI of 8 Gy (10 sessions) in patients with BOS unresponsive to azithromycin. They observed a slowdown in the decline of FEV₁ but this manoeuvre was only a bridge to retransplantation [49].

Extracorporeal photopheresis was first used in acute graft rejection. It is thought to induce immunological tolerance by increasing the level of regulatory T cells rather than inducing overall immunosuppression. Morrell et al. showed a significant reduction in the rate of decline in lung function but photopheresis was used as a third-line therapy in addition to modifications of the maintenance immunosuppressive regimen, initiation of azithromycin and lymphocyte-depleting therapies [50]. The Zurich team has reported the most extensive experience with photopheresis in lung transplantation to date [51]. Photopheresis has not yet gained widespread acceptance due to the burden of this therapy for the ambulatory patient and the cost with inconsistent health insurance coverage.

Clearly the treatment of established BOS, with irreversible airway fibrosis, is not satisfactory. It is the reason why new strategies must focus on the prevention of risk factors (immune and non-immune), as well as identification of early and specific markers of BOS, before pulmonary function tests have started to decrease.

Conclusion

Lung transplantation is no longer an experimental procedure for a few desperate patients. It remains, however, a complex therapy with specific challenges starting prior to surgery and expanding far beyond the first year of survival. Improvement in the management of these patients will result from well-designed prospective and controlled studies, together with data-mining from large scale registries.

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Correspondence: John-David Aubert, MD, Unité de Transplantation Pulmonaire, Service de Pneumologie, CHUV BH-10.658, CH-1011 Lausanne, Switzerland, john-david.aubert@chuv.ch

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