Lung allocation

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Abstract: Shortage of donor lungs in most western countries and broadening of indications for lung transplantation (LTx) has led increased waiting list mortality in the past. Usually donor lungs and recipients are matched by size as measured by total lung capacity and blood type in first order. In some countries regional allocation comes first, in other countries a national wait list exists and some nations are organized in supranational allocation systems. Organ distribution should respect the ethical principles of equity, justice, beneficence and utility. Generally, top priority on the list should be given to patients with the least amount of time to live but outcome is an important factor to consider to avoid futile transplantations. Installation of an urgency status will decrease mortality of the sickest candidates on the waitlist unless the proportion of patients on urgency status will be too high. Urgency can be determined by clinical judgment (so called center decision), an audit process or objectively by a score system. Among the 3,500 transplants performed worldwide annually, approximately 60% are allocated by lung allocation score (LAS) (US, Germany, the Netherlands). With the LAS a model for survival prediction after lung transplantation and wait list survival probability was created. Clinical experience in the US since 2005 and in Germany since 2011 favourable reports regarding effects on waiting list outflow, transplant activity and outcomes have been published. Future perspectives will focus on broader geographic sharing, updating and further development of the LAS.

Keywords: Lung transplantation; waiting list; lung allocation score (LAS); organ procurement; organ donation

Introduction

Currently, approximately 3,500 transplants are performed worldwide annually (1). Eligible patients are put on the waiting list at their local transplant centre. Unfortunately, a shortage of donor organs leads to considerable numbers of patients dying on the waiting list for lung transplantation (LTx) before suitable organs become available. Lung transplantation is nowadays an accepted therapy for end-stage thoracic disease, but major problems remain to be addressed. Transplantation is has a costly and risky therapy. Demand for donor lungs exceeds the supply by far. The discrepancy between supply of organs and demand for them as life-saving therapies has resulted in scrutiny of organ distribution policies, and raises ethical questions. In designing an allocation algorithm, a number of ethical principles should be considered including the four basic ethical principles:

(I)   Patient autonomy: a patient has the right to choose/refuse treatment;
(II) Beneficence: practitioner should act in the best interest of the patient;
(III) Non-maleficence: an obligation to not intentionally inflict harm to the patient;
(IV) Justice: concerns the distribution of scarce health resources ("Who gets what?").

Efficient donor organ allocation remains crucial in optimizing donor use, to reduce waitlist mortality and to improve transplant outcomes.

In some countries, there is national wait list and some countries are organized in supranational allocation systems (e.g., Eurotransplant). Available donor lungs will be assigned according to predetermined criteria. Usually lungs

Table 1 Comparison of different allocation models

Principle	Center decision	Waiting time plus urgency	Allocation score
Equity	(+)	+	++
Justice	(+)	+	(+)
Beneficence	(+)	(+)	++
Utility	(+)	(+)	++
Survival	(+)	+	++
Quality of life	(+)	−	−
Countries	UK, Italy, Belgium	Switzerland, France	US, Germany, the Netherlands

(+), variably influenced; +, influenced; ++, strongly influenced; −, not influenced.

are matched by size (total lung capacity) and blood type in first order. In case of several suitable candidates for a given organ offer, organs are distributed according further pre-specified rules. The entire process of organ distribution is called "organ allocation".

Allocation criteria after blood type and size matching may be based on clinical judgment (so called center decision), urgency (e.g., by audit process, individual decision, or objectively by a score system), or on waiting time, or a combination of several of these criteria. Currently, rules guiding allocation in most countries are based on urgency and transplant benefit, with survival benefit being the accepted primary goal. The ideal time for the transplant is not easy to determine and depends on the individual course of the underlying illness. Many pulmonary diseases experience a relatively slowly progressive course while other will develop a sudden acceleration with rapid deterioration of the patient's condition. Within a system of waiting time based allocation only up to 30% of patients will die before an organ becomes available (2). Installation of an urgency status will decrease mortality of critically ill candidates unless the proportion of patients on urgency status will be too high (3).

Most people agree that top priority should be given to patients with the least amount of time to live ('Rule of Rescue') and outcome is rated second by the majority. Existing registry data are often used to assist individual assessment of urgency and transplant benefit in conjunction with clinical judgment. Historically, lung allocation, in the US and in the Eurotransplant region, was mainly based on waiting time. In some European countries there is a national urgency list (France, Switzerland) and some European countries allocate donor lungs according center decision (UK). More than 60% of the worldwide lung transplant activity is allocated by the lung allocation score (LAS). Waiting time-based lung allocation and center-based allocation has been reported to be associated with high wait list mortality (2,4).

The pros and cons of the three most commonly used allocation models (center decision, waiting time plus urgency and an allocation score) are displayed in *Table 1*.

The LAS

The LAS is a numerical value used to assign relative priority in distributing donated lungs. The LAS evaluates several parameters of patient health to direct organ donation toward patients obtaining greatest benefit from lung transplantation (5).

More than a decade ago, the US Department of Health and Human Services issued the "Final Rule", intended to ensure that organs were allocated "based on medical criteria, not accidents of geography". In 1998, the Department of Health and Human Services of the US suggested that waiting time-based allocation should be replaced by medical urgency in the absence of unsuccessful transplants. Urgency was classified as more important than the prospect of success. A working group was set up to develop a corresponding system for lung allocation. Essential ethical aspects in the development were equality of all patients (blood group, ethnicity), justice (each patient is judged strictly according to objective criteria), benefit (principle: the benefit must outweigh the potential damage), and usefulness (benefit of a scarce resource).

To develop a statistical model, 3,104 American Lung Transplant-data recorded in the US Register OPTN were analysed from candidates of the years 1997 and 1998. Eighty percent of all listings were made according to four diagnostic groups [lung emphysema/chronic obstructive lung disease (COPD) including alpha1-

antitrypsin deficiency (n=1,461), cystic fibrosis (n=708), idiopathic pulmonary fibrosis (n=608) and idiopathic pulmonary arterial hypertension (n=327)].

Because of the relatively small number of patients with idiopathic pulmonary arterial hypertension, this group was enriched by patients from the years 1995 and 1996 so that in the end, 636 of these patients were available for evaluation. Approximately 30 parameters of lung transplant candidates were recorded in the US at that time on the wait list. These included age, height, weight, body mass index (BMI), pulmonary arterial pressure (PAP), cardiac index (CI), pulmonary capillary wedge pressure (PCWP), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV$_1$), functional status, etc.

In the four diagnosis groups mentioned above, multivariate Cox analysis was carried out, which resulted in disease-specific factors which had a significant influence on the wait list mortality.

The remaining 20% of the patients who were initially not covered by these groups were assigned to the four main groups on the basis of clinically similar symptoms and courses. This assignment was statistically verified by comparing the survival of the respective patients with the calculated survival of the group.

In addition, the results were adjusted by combining the parameters of all four groups into a total model. These factors were confirmed in their prognostic statement by separate analysis of the four disease categories. With the overall analysis of all patients, both the probable survival within a year on the wait list, as well as the 1-year survival after lung transplantation could be calculated using biometric and clinical data. Similarly, prognostic factors for 1-year survival after transplantation had been calculated in a multivariate regressive Cox analysis. The restriction to 1 year was made, since after this time the influence of factors, which determines the immediate success of transplantation, hardly could have any effect on the result.

The models for survival after lung transplantation and wait list survival probability were combined to form a model in which the actual benefit of the transplant was calculated as the difference between transplant survival and wait list survival. Double weighing of wait list survival corresponded to the original intention to take the urgency more into consideration than the success prospect. The LAS takes into account the estimated survival benefit offered by LTx by 1 year after surgery and medical urgency. Parameters included in the model are displayed in *Table 2*. LAS can be appointed a value between 0 and 100 and according to

this model rates the estimated survival advantage by LTx to 1 year. The aim of the system is to direct organs to recipients who are predicted to have the greatest potential transplantation survival benefit.

The LAS system was introduced in the US in May 2005 and has also been adopted in Germany in December 2011 for LTx candidates age 12 and older and in the Netherlands in April 2014. In the years following implementation in the US and Germany, numerous mainly favourable reports regarding effects on waiting list outflow, transplant activity and outcomes have been published. In the US and Germany constant reduction of mortality on the wait list was observed translated to approximately 8 lives saved on the waiting lists per 100 lung transplants performed (3,6).

Since its introduction as a tool for donor lung allocation in the US in 2005, the number of LTx for US CF patients has increased by 25%. Of note, 70% of wait-listed CF patients were transplanted after a waiting period of 1 year decreasing the 1-year waiting-list mortality from 15% to 10% (7).

Pulmonary hypertension accounts for approximately 5% of all lung transplant activity, with improvements in medical therapy leading to global declines in waiting list registrations and transplant activity. Existing US data on LAS performance for PH patients have revealed somewhat conflicting findings (8,9). Initial reports failed to demonstrate improved waiting list mortality among candidates with pulmonary hypertension, however, more recent analysis involving larger cohorts have contested this. The German data, whilst also limited by small sample size supports this latter report, showing clear reductions in waiting list mortality (3). Composition of transplant recipients changed, with fewer patients with obstructive lung diseases (e.g., COPD) and more recipients with restrictive lung diseases (e.g., idiopathic pulmonary fibrosis). Transplantation under invasive mechanical respiratory support increased in Germany from 9% to 13% (3).

In February 2015 a new LAS model was introduced in the US after the Thoracic Organ Transplantation Committee proposed a revision to the LAS system. This revision includes modifications to the covariates in the waiting list and post-transplant survival models, coefficients of the covariates, and baseline waiting list and post-transplant survival rates used in the LAS calculation. New parameters like increase in creatinine and bilirubin, central venous pressure (CVP), CI (if less than 2 L/min/m^2), 6-min-walk distance (if it is less than 1,200 feet), oxygen needed at rest were included in the 2015 LAS model, while others were abandoned. Results of performance of the new model are not

Table 2 Parameters of the 2010 LAS model

Age (years)
Height (cm)
Weight (kg)
Diagnosis of lung disease
Functional status (without support, mild support, full support)
Diabetes status (unknown, insulin-dependent, no diabetes, non-insulin-dependent)
Mechanical ventilation [none, continuous positive airway pressure (CPAP), bilevel Positive airway pressure (BiPAP), continuous invasive, intermittent invasive]
Oxygen treatment (none, at rest, only at night, only under stress)
Oxygen requirement at rest (L/min or %)
Forced vital capacity (% predicted)
Systolic pulmonary arterial pressure (mmHg)
Mean pulmonary arterial pressure (mmHg)
Mean pulmonary capillary closing pressure (mmHg)
Current carbon dioxide partial pressure (mmHg or kPa)
Rise in carbon dioxide partial pressure (%) in relation to minimal carbon dioxide partial pressure
6-min walking test (m)
Serum creatinine (µmol/L or mg/dL)

LAS, lung allocation score.

yet published. Germany has decided to continue with the 2010 model in 2017.

The LAS can be computed online (2010 model: http://www.eurotransplant.org/cms/index.php?page=las_calculator and 2015 model: https://optn.transplant.hrsa.gov/resources/allocation-calculators/las-calculator/). In the US, organ distribution is made locally first, while in Germany distribution is nationally in first step.

Broader geographic sharing may increase travel costs and ischemic time, but a more appropriate recipient might be identified closer to the donor in a neighboring donor service area. It could be demonstrated recently that 53% of the lungs in the US were transplanted locally (within 58 donor service areas). For each local allocation, a median of 6 recipients in a larger region (nationwide there are 11 regions) had higher LAS values in this retrospective analysis (10). There are practical limitations to transportation of donor lungs because increasing ischemic time and graft dysfunction is related to increasing donor age. Any lung organ distribution system needs to take into account the large size of this country, and a 'national' list is probably impractical for large countries.

The transplantation center is responsible for the correct

procurement and regular update of LAS (usually in intervals of 3 months, in critical patients every 2 weeks). It should be noted that LAS is not a suitable tool for identifying candidates. This must be performed via individual patient assessment by the transplant team.

No allocation system can eliminate death on the waiting list. Therefore distribution of donor lungs as a precious resource should be made wisely and fairly.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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