Balancing fairness and efficacy in lung allocation for transplantation: unfinished business

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While the field of lung transplantation has evolved considerably since the first lung transplant with long-term success was performed in 1983,[1] the need for donated lungs to help patients with progressive end-stage lung diseases that do not respond to non-transplant therapies continues to outstrip the availability of lungs from organ donors.[2] Many patients with certain types of lung disease or other characteristics such as short stature or ABO blood type O may be less likely to receive an organ offer than those with different profiles and are, therefore, more at risk to die while waitlisted and awaiting lung transplantation.[3 4] Organ allocation systems need to evolve (along with improvements in technical and medical aspects of lung transplantation) to optimally balance fairness and efficacy in donor lung allocation while also attempting to minimise the risk of death without transplant for waitlisted patients, optimise post-transplant survival and quality of life and avoid unsustainable resource utilisation.

In this issue of the journal, Kourliouros et al[5] examined outcomes emanating from the donor lung allocation system used in the UK by examining National Health Service UK Transplant Registry data for a patient cohort (n=2213) comprised of all adult patients (≥16 years old) registered for lung transplantation between January 2004 and March 2014. Donor lung allocation to listed patients during this period of time was at the discretion of the specific transplant centre (there are five designated centres in the UK for adult lung transplantation) at which candidates were listed for transplantation, and decisions for which patient to transplant with available organs were based on clinical assessments that would often take into account both waiting times and the degree of acuity for a specific patient. Statistical analyses of the available data showed that disease-specific and key patient-specific factors had a

significant impact on length of time from listing to transplantation and waiting list mortality rate, and disparity was observed among major disease indications for transplantation with 78% of patients with chronic obstructive pulmonary disease (COPD) receiving a transplant by 3 years postregistration versus 61% of those with cystic fibrosis (CF), 48% of those with pulmonary fibrosis (PF) and 59% of patients with other lung pathologies. Other discrepancies that were identified included a significantly reduced likelihood of receiving a transplant for short stature candidates with PF, patients with COPD having the greatest opportunity for transplant despite having the lowest waiting list mortality compared with patients with PF and CF, and candidates with blood group O having reduced opportunity to receive a transplant (especially those with a diagnosis of PF or CF) due to transplantation of many group O donor lungs into ABO compatible recipients. Review of these data has led to revision of the UK lung allocation scheme such that ABO identical recipients take priority for organ offers before ABO compatible recipients and candidates are prioritised for urgency and height,[6] but the revised policy still does not control for lung disease type or use a composite risk profile derived from a combination of variables.

Over the past two decades, organ allocation schemes in the USA, UK and other countries have evolved from being based on ABO blood compatibility and time on the waiting list to more sophisticated systems that focus on fairness and efficacy for lung transplant candidates with a variety of disease indications for transplant and other patient-specific factors. As the authors point out in their report, the longest running lung allocation system that is based on the ethical principles of equity of access, justice, beneficence and utility is the use of the Lung Allocation Score (LAS) that was developed in the USA.[7 8] The Organ Procurement and Transplantation Network (OPTN) policy issued in 1990 allocated lungs on the basis of waitlist time and ABO matching with geography-based organ offers, and in 1995 the system was changed to allow patients with a diagnosis

of idiopathic PF (IPF) to have an extra 90 days of waiting time credit due to this group's high mortality while on the waitlist.[8] It became clear, however, that many patients would be placed on the waitlist before they became sick enough to require a transplant, which gradually increased median time to transplantation and was accompanied by a steadily increased risk of death for waitlisted patients, and many patients with advanced disease were not even listed for transplant. The LAS was created to take an array of disease-specific and patient-specific variables into account and attempt to balance the urgency for transplanting waitlisted patients with the likelihood of post-transplant survival (net transplant benefit).

With implementation of the LAS in 2005, the number of active waitlisted candidates was more than halved by 2007 as compared with 2004 (from 2163 to 1005), and the median waitlist time declined from 762 days for those listed in 2004 to 141 days in 2007.[9] However, although the number of patient deaths on the waitlist from 2005 to 2007 declined, the death rate did not change as more urgent patients were listed.[9] Nonetheless, when Egan and Edwards[10] examined the OPTN database (years 2001–2011) and compared both pre-LAS and post-LAS death rates (5 years prior and 6 years after LAS implementation), the annual waiting list death rate had declined from 500 to 300 per year. This was accompanied by an increase in the number of patients transplanted for the indication of PF, but the transplant rate for COPD did not increase. Despite the trend of listing and transplanting older and sicker patients post-LAS, survival at 1-year post-transplant appeared to increase significantly. Nonetheless, certain subgroups, such as patients with idiopathic pulmonary arterial hypertension, remained at a disadvantage as compared with relative transplant rates for patients with IPF or CF, and for this reason, the LAS was modified in February 2015.[11] Current allocation policy initially identifies donor organ geographical location and age to match to compatible waitlisted patients, and then the LAS value, ABO blood type, thoracic cavity size and immunological compatibilities are used to ultimately select a match.

How do we modify current donor lung allocation systems that prioritise clinical acuity to equitably allocate donated organs yet maximise the number of transplants to reduce the waiting list mortality rate? Different countries (eg, Australia, Canada, France, Spain, UK, USA) or the multicountry Eurotransplant Consortium

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Box 1   Potential remedies to improve donor organ availability

► Increased supply of donor lungs
- Increased donation rates (eg, opt-out donation policies).
- Increased use of donation after cardiac death donors.
- Use of increased risk donors.
- Favour single lung transplantation if not contraindicated.
- Use of extended donor criteria.
- Rehabilitation of marginal donor lungs via ex vivo lung perfusion.

► Improved geographical organ sharing.

► Improved desensitisation techniques to overcome immunological compatibility issues.

► Reduced lung size for short stature recipients
- Donor lung size reduction.
- Lobar transplantation.
- Living donor transplant.

► Xenotransplantation (pig to human).

► Tissue engineering (creation of de novo humanised lung).

(which has adopted a LAS system) have systems that have evolved over time that attempt to address these issues, but disparities continue to exist that can hopefully be refined by evaluating and tweaking allocation policies while also developing new technologies that can increase donor organ availability, reduce deaths on the transplant waitlist and increase the total number of patients transplanted. One partial solution can be broader geographical sharing of donor organs, as candidates waitlisted in the US system in areas with low rates of local donor lung availability between 2006 and 2015 were shown to have worse waitlist outcomes.[12] A recent US OPTN policy modification was implemented on 24 November 2017, that replaced the donor service area as the first level of distribution with a 250 mile nautical circle around the donor hospital as the first level of distribution to better accommodate urgent transplant candidates.[13]

Many other potential remedies exist or are evolving that can further optimise lung transplant rates (box 1). These include strategies to increase the supply of donor organs, increase donor organ allocation efficiency and decrease the demand for donor organs by developing more effective therapies for various forms of advanced lung disease.[4 14] An evolving strategy using ex vivo lung perfusion to rehabilitate marginal donor lungs shows considerable promise to increase donor organ availability.[15] Such an approach can allow improvements in donor-recipient immunological matching, expand geographical distances for donor organ matching with potential recipients, allow organ resuscitation and even repair, and lessen time constraints between donor lung explantation and recipient implantation by significantly prolonging preservation times. As the number of new patients listed for lung transplant increases due to waitlisting of more patients advanced in age and with an increasing number of patients bridged to transplant via use of mechanical ventilation or extracorporeal life support systems, patients who may have been too old or too ill to await lung transplant may be evaluated and waitlisted. Periodic examination of outcomes data is needed, and the impact of patient-specific factors (eg, frailty, body composition) that may affect post-transplant outcomes significantly but are not used in the current LAS system need further evaluation.[16 17]

Clearly, allocation systems should not work against candidates with PF or CF, who may achieve better post-transplant survival outcomes than patients with other indications such as COPD,[18] and improvements in donor organ retrieval and allocation policies can increase the likelihood that waitlisted patients can survive to transplantation. Kourliouros *et al*[5] are to be lauded for uncovering discrepancies between risk profile and probability of lung transplantation that led to changes in the UK system that attempt to remedy these issues. Optimising donor lung allocation practices remains an unfinished task for all allocation systems.

Contributors This is a commissioned editorial with unique text and a unique table that have not been published in any journal or book.

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