Lung transplantation: a review of the optimal strategies for referral and patient selection

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Abstract: One of the great challenges of lung transplantation is to bridge the dichotomy between supply and demand of donor organs so that the maximum number of potential recipients achieve a meaningful benefit in improvements in survival and quality of life. To achieve this laudable goal is predicated on choosing candidates who are sufficiently unwell, in fact possessing a terminal respiratory illness, but otherwise fit and able to undergo major surgery and a prolonged recuperation and rehabilitation stage combined with ongoing adherence to complex medical therapies. The choice of potential candidate and the timing of that referral is at times perhaps more art than science, but there are a number of solid guidelines for specific illnesses to assist the interested clinician. In this regard, the relationship between the referring clinician and the lung transplant unit is a critical one. It is an ongoing and dynamic process of education and two way communication, which is a marker of the professionalism of a highly performing unit. Lung transplantation is ultimately a team effort where the recipient is the key player. That principle has been enshrined in the three consensus position statements regarding selection criteria for lung and heart-lung transplantation promulgated by the International Society for Heart and Lung Transplantation over the last two decades. During this period, the number of indications for lung transplantation have broadened and the number of contraindications reduced. Risk management is paramount in the pre- and perioperative period to effect early successful outcomes. While it is not the province of this review to reiterate the detailed listing of those factors, an overview position will be developed that describes the rationale and evidence for selected criteria where that exists. Importantly, the authors will attempt to provide an historical and experiential basis for making these important and life-determining decisions.

The reviews of this paper are available via the supplementary material section.

Keywords: COPD, cystic fibrosis, idiopathic pulmonary fibrosis, LAS, lung transplantation, referral, selection

Introduction

Historical overview
The focus of this review is to discuss optimal strategies for the referral and active listing of patients for lung transplantation with appropriate selection of the best candidate from the waiting list to match a specific donor. Hence, this document will have a slightly different perspective to the authoritative Consensus statements from the International Society for Heart and Lung Transplantation (ISHLT), which have largely evolved over the last two decades to describe whom may be suitable for lung transplantation (LTx) and when might be appropriate to refer and list.[1–3] The differences in real world experience are subtle but important. Indeed, the ISHLT statements have undergone three iterations, commencing with the initial 'guidelines' document supported by the ISHLT, the American Thoracic Society (ATS), the American Society of Transplant Physicians (ASTP) and the European Respiratory Society (ERS).[1] The term

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'guidelines' is used advisedly as the process employed at the time did not meet strict GRADE criteria (Grading of Recommendations Assessment, Development and Evaluation), as these were introduced some years later.[4] Nor did later Consensus statements, wherein it was specifically recognized that the pronouncements were based on 'expert' opinion, in the absence of sufficient high level evidence to allow a GRADE determination.[2,3] Evaluating successive Consensus documents reveals changes in approach, with a gradual softening of the conservative statements of the original manifesto. In the beginning, the overview position was to find the 'ideal' potential candidate who met or exceeded the rigorous physical, psychological, social and age criteria save for end stage lung (or heart and lung) disease that was refractory to medical therapies but amenable to transplant surgery. There were more 'absolute contraindications', which included age over 45 years for one (see commentary below for the impact of age on outcomes, for which we now have some compelling data), overweight and obesity and, paradoxically, lack of fitness, which was used as a surrogate for formal frailty testing, which is now available.[5,6] The picture becomes clear that candidates accepted and selected were younger, fitter, socially well supported and predominantly had single system dysfunction. At this stage, admittedly, there were few active units and relatively few transplants performed worldwide, but a number of recipients are still alive and well today, 25–30 years later, a testament to the enduring benefits that can be achieved when the right recipient is matched with the right donor, given excellence in surgical and intensive care unit (ICU) management and dedicated longterm medical follow up. There is perhaps a salient message here regarding how to achieve the 'best' results.

Current status

On that historical basis, and building on the accumulating experience of first hundreds, then thousands, of LTx worldwide, a new paradigm has been developed that boldly aims to offer LTx to almost all patients with incurable terminal lung diseases such as idiopathic pulmonary fibrosis (IPF), now the dominant indication, and where the formal ATS Guidelines using the GRADE format specifically recommend referral to a LTx centre upon diagnosis unless there are compelling reasons to demur.[7,8] No longer is the question 'What excludes this patient from LTx?', rather 'How can we fit this patient for LTx and achieve a meaningful individual improvement in duration and quality of life?' The iconoclastic change from a 'time accrued' system on the active waiting list, which saw many patients perish while waiting, to a more nuanced lung allocation score (LAS), initially in the USA but subsequently also in Europe, has made a dramatic change in both the composition of indications for LTx and the acuity of patients transplanted.[9–11] Despite these worthwhile changes, the recent Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) report documents, in the USA, the need for organs continues to outpace available donors.[12] Despite an increase of 126 donors in 2017, 1360 candidates remained on the waiting list at the end of the year, and 326 patients died or became too sick to undergo LTx.

The tide has turned worldwide and the evidence is slowly beginning to offer various insights into levels of risk for selected comorbidities, some of which will be described in detail below. The overriding caveat here is the level of experience of the individual unit, which comprises both volume and time components. Simply put, a well-resourced unit performing more than 50–100 LTx per annum over a period of years will most likely perform more successful transplants and, arguably, be more inclined to adjust their selection criteria to manage isolated complex cases with greater facility, including bridge to transplant with extracorporeal membrane oxygenation (ECMO), *ex vivo* lung perfusion and ventilation (EVLP) and the use of donation after circulatory death donors (DCD), both of which may expand the donor pool.[13–19] Moreover, larger units, in broad-based transplant-focused hospitals may well be able to develop mutually beneficial relationships with other key service providers so that cutting edge work can be undertaken, particularly where expertise in conditions such as human immunodeficiency virus (HIV) infection and Hepatitis C is required to secure optimum results, let alone multi-organ transplant procedures such as lung–kidney or more commonly, (heart) lung–liver transplants.[20–23]

Referral strategies

The relationship between the referring clinician and the lung transplant unit is a dynamic one where there needs to be a continual updating of

information and evidence to secure timely and appropriate referral of patients who might benefit from LTx. It is oft said that many are called but few are chosen, and the road to transplant is littered with obstacles for the patient, who needs resilience and support to negotiate the pathway. This understanding is critical to provide a basis for an ongoing therapeutic alliance. Intellectual support for LTx within the broad thoracic medicine community is variable, and may be swayed by personal experiences with individual patients either positive or less so. The engaged LTx unit recognizes the importance of building a strong working relationship with referring clinicians and especially with high volume referring units such as interstitial lung disease (ILD) and cystic fibrosis (CF) centres of excellence. Ongoing education and excellent communication remain the cornerstones of this strategy, so that the referring clinician feels able to make appropriate referrals in a timely fashion. Late referral is sometimes inevitable in cases of catastrophic deterioration or new onset disease, but, in the main, is a marker of lack of planning and forethought, perhaps engendered by denial or an unrealistic faith in medical therapies. For this reason, the ATS guidelines for the management of IPF recommend referral for LTx evaluation at diagnosis. While this may not always occur, it would obviate the need for urgent work-up and listing of critically ill IPF patients in a number of cases, and, just as importantly, permit a thorough evaluation in a less stressful environment to facilitate the development of trust in the new caregiving team. In one sense, repeated late referral with the inevitable suboptimal outcomes becomes a self-fulfilling prophecy, and is fair to neither the patient nor the LTx team trying to provide care. Intervention to interrupt this cycle is indicated. The mechanics of the referral relationship remain critical for success.

Current ISHLT guidelines have clear recommendations for the appropriate time to refer patients for transplant. These differ based on underlying disease process, but these documents are now available for general pulmonologists to guide their decision-making process in managing patients with end stage lung disease.[3] Many years of experience worldwide provide the basis for optimal time to refer patients for LTx, to allow sufficient time for a full psychosocial and physical workup as mentioned earlier, while still accounting for the fact that many of these patients will continue to deteriorate while being worked up and while on the waiting list.[24] Further education, and closer working relationships with referring physicians may be an important step in improving this process.

However, recent literature suggests that many factors that were considered important in when to refer patients for transplant may be mitigated as our processes and understanding continue to improve. Furthermore, targeted therapies for diseases such as IPF and PAH have led to improved outcomes for these patients and a greater period of progression-free survival that have delayed and, in some cases, negated the need for LTx.[25,26] New procedural options are becoming available for chronic obstructive pulmonary disease (COPD) that aim to minimize the impact of emphysematous areas of the lung, such as endobronchial lung volume reduction (ELVR) or bronchial thermal vapour ablation (BTVA), whereby inflammation and atelectasis is induced to reduce the volume of the most severely affected lobes of the lung and increase perfusion to less diseased areas. These advances have led to increased quality of life for COPD patients,[27] and may offer an alternative treatment options prior to referral for transplantation. Strategies must be dynamic and continuously updating, in order to provide best care for patients.

Candidate listing

Who to list?

The work up process is rigorous, time-consuming and energy intensive for many patients; however, it remains an important step in ensuring fitness for transplantation and in predicting longer term outcomes. Based on many years of experience, a greater range of patients, including those who are older and with other comorbidities, are now achieving successful transplant outcomes,[28] and indeed, the median survival post-LTx continues to improve, despite lagging behind many other solid organ transplants.[8] Additionally, favourable transplant outcomes have been demonstrated with older donors, thus allowing an increase in size of the potential donor pool. A recent analysis by Hall and colleagues determined that the interplay between donor and recipient age alone was not an independent predictor of survival, particularly in older recipients, and that use of organs from older donors should be considered, taking into account total donor demographics.[29] A further study by Whited and colleagues demonstrated similar findings, in that reasonable transplant outcomes were

achieved across all recipient age groups with the use of donors aged over 60 years.[30]

In contrast to this, there are still some absolute contraindications to listing patients for transplant that take into consideration potential survival benefit for the individual patient, as well as allocation of a scare resource. Patients who have had recent malignancy (within 2 years), untreatable significant dysfunction of another organ system, other acute medical instability, chronic resistant infection, significant chest wall deformities, class II or III obesity, substance abuse or demonstrated inability to cope and comply with medical therapy post-transplant, are considered unsuitable for transplant.[31] There are a range of other relative contraindications; however, the importance of these will depend on the transplant centre and respective experience in management. These include older age with low functional status, class I obesity, severe malnutrition or osteoporosis, mechanical ventilation or ECMO and certain infections. It is also important that treatment for comorbid conditions, particularly atherosclerotic disease, diabetes mellitus and gastro-oesophageal reflux disease (GORD), are optimized prior to transplantation.[3]

Much research is now focused on the management of frailty and improving functional status prior to transplantation. Factors include accurate evaluation of frailty in the patient with end-stage organ failure and early identification of patients at risk of deteriorating functional status.[32] Rozenberg and colleagues have recently assessed the use of different frailty indices in the evaluation of frailty of LTx patients and relevance to postoperative outcomes. They determined that the construct variability and agreement between indices was sufficient. Furthermore, this study showed that patients with a higher frailty index prior to transplant did not have worse early outcomes compared with less frail recipients, and derived a larger improvement in St George's Respiratory Questionnaire and 6 min walk distance.[33] Conversely, Singer and colleagues found that, in their cohort, frailty scores assessed by the Short Physical Performance Battery (SPPB) or Fried Frailty Phenotype (FFP) predicted an increased risk of death, particularly within the 1st year post-transplantation.[6] As new developments arise in the early identification of patients at risk of becoming particularly frail, and better management strategies are put in place, impact of frailty on when to list and when to transplant these patients may be altered.

When to transplant?

Many countries, in the last few years, have introduced new lung transplant allocation systems that aim to ensure that the most unwell patients have priority access to available organs, over those who still have remaining physiological reserve. These systems consider a range of patient factors to attempt to achieve fair allocation of a scare resource, while minimizing waitlist mortality. The LAS is being used successfully in countries such as the US, Germany and the Netherlands, and now accounts for approximately 60% of lung allocation worldwide.[34] There has been success with this approach, with analyses from the US showing a significant decrease in waitlist mortality, while also increasing the number of lung transplants. Furthermore, the predominant indications for lung transplant changed, with a substantial increase in the number of transplants for fibrotic lung disease.[35] However, as many years have now passed since implementation of the LAS, problems with this approach are starting to arise, and recent publications have begun to address some of the factors that may need revision going forward.

A large study analyzed cystic fibrosis-related variables that impacted waitlist mortality and post-transplant survival with the aim of improving the LAS models for patients awaiting transplant with CF. This group suggests addition of modelled CF-specific variables to improve the predictive accuracy of the LAS, particularly in terms of waitlist mortality. These variables included a relative decline in FEV_1 of >30% in the 12 months preceding listing/transplant, presence of *Burkholderia* species, between 29 and 42 days spent in hospital in the 12 months preceding listing/transplant and massive hemoptysis. Analyses also indicated that including a drop in FEV_1 as a variable in LAS calculations improved waitlist mortality for COPD, while not adversely affecting access to transplant for the other groups.[36]

A recent study by Tague and colleagues denoted that another important consideration is allosensitisation of patients while on the waitlist. It was shown that, as calculated panel reactive antibody (CPRA) values increased, so did time spent on the waiting list and the risk of mortality during this period.[37] This suggests that allosensitisation, and particularly higher CPRA values, could be taken into consideration as part of priority calculations in organ allocation schemes.

Body mass index (BMI) is taken into consideration in most current LAS calculations; however, the current categories may not accurately reflect the pattern of risk. BMI has been shown to be an independent predictor of mortality at 90 days and 1 year post-transplantation, with a BMI of 20 (OR, 1.18; 95% CI, 1.02–1.36) and a BMI of 28 (OR, 1.07; 95% CI, 1.02–1.13) being significantly associated with an increased risk of mortality at 90 days. At 90 days, a BMI of 25 had the lowest predicted probability of death; therefore, the authors demonstrate that each individual BMI unit is associated with a distinct risk for post-transplant mortality, and thus suggest that the LAS should consider BMI units independently and not as part of a larger category where risk is assumed to be constant across the category.[38]

Retransplantation

Retransplantation of the lung raises a number of ethical and equity issues regarding the distribution of a scarce resource.[39] Nevertheless, much progress has been made in our understanding of whom may benefit from retransplantation and when it may be appropriate.[40] Early retransplantation, as a heroic rescue gesture for primary graft failure, is now recognized, in the main, to carry an unacceptable risk-benefit ratio, particularly in children, whereas judicious retransplantation after a period of stability post LTx can be associated with outcomes equivalent to primary LTx, especially where less invasive modalities are employed (in adults) off pump.[41,42] There is no defined time interval but generally so called 'late' retransplantation implies at least 2 years postprimary LTx.[43] There are a number of theoretical reasons supporting this time interval. It allows the patient familiarization with the post LTx management routine, and the LTx team adequate time to assess the compliance of the potential redo recipient as well as time to fully manage any acute cellular rejection (ACR) or antibody mediated rejection (AMR), which are thought to be the principal risk factors for developing chronic lung allograft dysfunction (CLAD), the major indication for redo LTx. Moreover, many potential redo candidates are highly allosensitized, so it may take longer to match a suitable graft, unless novel induction therapies to reduce antibody load are employed in the perioperative period.[44] The prospective redo candidate should meet all traditional criteria for LTx suitability, as outlined above, but it is understood that they will be immunesuppressed and often carry the legacy of a higher corticosteroid burden, perhaps related to therapy for ACR or AMR.[3] The potential for opportunistic infection, both overt and covert, therefore should not be understated and a careful assessment should be undertaken, including of the allograft where possible, if bronchoscopy with bronchoalveolar lavage (BAL) is deemed safe. As might be expected, older candidates have inferior outcomes.[43] One clinical situation that bears particular mention is retransplantation after therapy for post-transplant lymphoproliferative disease (PTLD), often in the context of primary Epstein Barr virus (EBV) infection of an EBV naïve recipient. The almost obligatory reduction in immune suppression employed as a major plinth of the therapy for PTLD is often associated with the development of ACR, if not ABM, with the resultant loss of graft function associated with CLAD. In this situation, retransplantation is not absolutely contraindicated, as enduring benefits may be achieved; however, the caveats mentioned above must be understood. The phenotype of CLAD does appear to be important. A recent four-centre retrospective analysis reported outcomes of 143 LTx recipients who underwent re-LTx for CLAD (BOS:RAS = 94:49) 2003–2013.[45] Unadjusted and adjusted survival after re-LTx for RAS was worse compared with BOS (HR = 2.60, 1.59–4.24; $p < 0.0001$ and HR = 2.61, 1.51–4.51; $p = 0.0006$, respectively). Additionally, patients waiting at home prior to re-LTx experienced better survival compared with hospitalized patients (HR 0.40; 0.23–0.72; $p = 0.0022$). The authors advised that re-LTx for RAS should be critically discussed, particularly when additional perioperative risk factors were present.

Which transplant modality?

The choice of transplant modality is no longer an arbitrary one. Experience is a hard teacher and the risk-benefit ratios of individual LTx modalities for specific conditions are well understood. As is often the case in therapeutic endeavours where resource limitation (in this case donor availability) is a major factor, the clinical balance is how best to achieve the optimum result for the largest number of potential recipients.[46] The LAS works to maximize survival benefit but does not address modality specifically. Once the dominant form of LTx, heart-lung transplantation (HLTx) is now virtually reserved for congenital heart disease (CHD) refractory to medical and

surgical therapies and, in truth, is now rarely performed outside major high-volume centres. It is, of course, resource intensive, using three organs that could service three separate patients in the one recipient. Potentially, two recipients might miss out and, given the persistent mortality rate on the active waiting list, the consequences may be dire. In the past, the technique of performing a 'domino transplant' whereby the recipient's heart is transplanted into another heart transplant recipient was used to ameliorate this risk. The majority of potential recipients with nonsuppurative lung disease can be serviced with either single lung transplantation (SLTx) or bilateral sequential single lung transplantation (BSSLTx). BSSLTx is definitely preferred for bullous emphysema, especially due to alpha-1 antitrypsin deficiency, where there is a perioperative risk of pendelluft due to different dynamics of regional inflation and deflation between the native compliant lung and the transplanted, less compliant, lung. A serious long-term complication devolving from the same physiology is native lung hyperinflation syndrome, which can be difficult to differentiate from CLAD due either to bronchiolitis obliterans syndrome (BOS) or restrictive allograft syndrome (RAS).[47–49]

The argument regarding the utility of SLTx *versus* BSSLTx for other forms of nonsuppurative lung disease, especially IPF, is a complex one.[50] Sometimes, only one donor lung may be available to the transplanting team so the decision rests on whom to transplant. More commonly, both lungs are on offer and a judicious decision needs to be made. The mechanics differ from unit to unit and particularly from country to country, with the allocation algorithm being somewhat proscriptive at times.[24] Now that more sophisticated outcome data are available to help answer the question of single *versus* bilateral, it is clear that survival outcomes for the older recipient in particular are equivalent, if not superior, after SLTx, which is reversed in the case of BSSLTx for younger recipients with COPD.[51]

Lung transplantation for success

Resource allocation

As mentioned, LTx is a resource-limited field. No donors, no transplants, as simple as that and, despite the original fears expressed by some health care economists, there is no realistic expectation that LTx will so dominate the health care budget as to consume vast financial resources. Despite admirable and successful global attempts to improve organ donation rates through the development of in hospital networks and trained donation specialists, as well as the use of donation after circulatory death (DCD) donors and EVLP, there remains a surfeit of demand over supply.[12] This has led quite rightly to a careful appraisal of donor suitability, with the recognition that many 'extended criteria' donors (including smokers of nicotine and cannabis, donors with an initial low PaO2/FiO2 ratio) that were previously discarded may be used safely, although some emerging evidence provides a note of caution.

If the stated aim of LTx is to prolong life and improve quality of life of patients afflicted with terminal lung disorders, decisions regarding resource utilization must balance the needs of the individual patient with the needs of the community.[46] This ethical dilemma underscores many of the discussions regarding the use of SLTx *versus* BSSLTx, the use of extended criteria donors and recipient age criteria as well as the vexed question of retransplantation.[52] At extremes of age in particular, and, given the ravages of chronic diseases, it is important to consider actuarial survival as a factor when making decisions regarding suitability, allowing that ageism should not dictate behaviour.

Ultimately, the weight of evidence supports the proposition that younger recipients with single system disorders who receive ideal donors and undergo BSSLTx will likely have superior outcomes, the vagaries of immunological matching and treatment adherence notwithstanding. There are exceptions and some frail recipients may achieve significant benefits although sarcopenia of the psoas muscles appears to be associated with inferior outcomes.[33,53] In fact, transplanting for success is predicated on long-standing compliance with medical therapies, diligence in healthcare monitoring and dedicated medical follow up. Exactly this is the key to securing better uses of resources, of valuing the organ donor gift and the community support for organ transplantation as a normal consideration in end-of-life discussions. Too often, the focus is front loaded, when enduring success, year after year, which depends on compliance, is underplayed. Perhaps it is not as exciting as the initial transplant period, but in time, is just as important.

Quality and quantity

Aspects of quality have been alluded to above, but how best do we measure quality? What makes a 'good' lung transplant? Is it survival, which of course is necessary to compute other variables over time, or quality of life, as measured by physical and psychological variables? Or is it a subjective patient sensation that can be quantitated, if not adequately described, by various visual analogue scales? Ultimately, the beneficiary of these services is the patient, so it behoves all who work in the field to be cognizant of quality as understood by the patient. Part of quality service delivery embraces an orderly and understood pathway to LTx and thereafter, so, once again, communication and education are keys to quality. Including caregivers and the family is vital in this process as it is they who usually will outlive the LTx recipient and will have the most vivid recollections of the care their loved one received from the LTx team. Psychological support for all involved in this most stressful domain, patients, caregivers and staff, is a *sine qua none*.

The argument prevails as to whether large volume centres do better than small volume centres, and the turning point appears to be about 20 LTx per annum. The bulk of evidence suggests they do, with some notable exceptions. Some smaller centres have excellent results that are equivalent, if not superior to, those of larger centres. On closer inspection, the team in those units often comprises very experienced staff with years of practice in this most difficult domain. Attention to detail in candidate selection, preoperative care, surgery and ongoing management is the hallmark of those smaller units. Of interest, the literature has not, to date, analyzed these factors *versus* outcomes, especially experience and decision making.

Conclusion

How to optimize outcomes in the current era

The global volume of LTx procedures performed each year now exceeds 4500, and large data repositories such as the ISHLT Registry and OPTN database facilitate risk assessment to determine optimal candidacy characteristics that have been well described above and in a recent consensus statement from the ISHLT.[3] As ever, the balance is the risk *versus* the benefit, and the LAS appears to be a powerful and informative tool to assist in achieving that goal by computing

the likelihood of life days gained for an individual recipient, but the process begins with the referring clinician who takes primary responsibility for timely referral of a potential candidate.[54] A close working relationship between the LTx unit and the referring source will help optimize outcomes.

Future prospects

Selection criteria for LTx have continued to evolve over nearly four decades and will continue to do so as the target population changes with the development of new therapeutic modalities for specific conditions. Ongoing robust data analysis of large data sets will drive change in the approach taken towards both selection and listing, but it may well be sentinel unit behaviour that expands the pool of potential recipients. Witness the experience with Hepatitis C and HIV, which are no longer absolute contraindications in units with the experience and resources to manage any pharmaceutical issues that might arise. It seems that where there is a will, there is a way, and that is part of the grand attraction of the LTx field .

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

The reviews of this paper are available via the supplementary material section.

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