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Inside this issue: Lung Transplantation

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These 10 articles demonstrate the breadth of recent work in the field of lung transplantation, ranging from recipient management, through donor-recipient matching, donor pool expansion and finally post-transplant management. Regardless of the level of experience within your local lung transplant centre, we hope you will find the commentary below both interesting and relevant.

Weight loss prior to lung transplantation is associated with improved survival [1]

Obesity in lung transplant (LTx) recipients is associated with higher mortality. Current consensus guidelines list BMI ≥35 kg/m^2 as an absolute contraindication and 30-34.9 kg/m^2 as a relative contraindication to LTx. This is based on data demonstrating an association between recipient obesity and primary graft dysfunction and survival. This retrospective cohort study examines LTx recipients at two US centres over a ten-year period, in order to determine the impact of BMI on survival, duration of ventilation and ICU length of stay. At the time of transplantation, 43% of recipients had a normal BMI (18.5-24.9 kg/m^2), 42% were overweight (25-29.9 kg/m^2) and 9% were obese (≥30 kg/m^2). The mean decrease in BMI from initial review to LTx (median interval 272 days) was 0.6 kg/m^2, however for the obese group this was higher (2.9 kg/m^2). Weight loss had a significant impact on peri-operative morbidity; a 1-unit (1 kg/m^2) reduction in BMI was associated with a 4.4% decrease in median ICU days, 6.1% decrease in median ventilation days and 11% improvement in survival. This survival benefit was seen in those with BMI ≥25 kg/m^2, but not ≤24.9 kg/m^2. The survival impact also seemed to persist over time. No specific weight-loss regimen was described or instituted. In summary, this study highlights that a BMI ≥25 kg/m^2 is associated with worse outcomes and survival post-LTx, and that perhaps our current guidelines should recommend a lower BMI threshold as a contraindication for LTx.

Effects of Recipient Age and Diagnosis on Health-Related Quality of Life Benefit of Lung Transplantation [2]

As lung transplant recipients become increasingly older, it is prudent to look at outcomes in this evolving pool. The median age of transplant recipients has increased steadily to 58 years in 2014. According to the 2015 International Society of Heart and Lung Transplantation (ISHLT) report, recipients aged 66 years and over now make up almost 20% of all LTx. International guidelines (ISHLT 2014) no longer state advanced age as an absolute contraindication to LTx; rather, age should be taken into account together with frailty and comorbid conditions. Whilst survival is an important outcome, health-related quality of life (HR-QoL) is also a crucial measure when determining the benefit of LTx. This prospective longitudinal study demonstrates that HR-QoL improves for all patients post LTx, irrespective of age and underlying diagnosis. Not surprisingly, the largest improvement in HR-QoL was seen at the earliest measure (3-months post-LTx), when patients had stabilised in the post-surgical period. Long-term improve-

ments in HR-QoL were most pronounced in the COPD cohort. This data helps us recognise that lung transplantation in COPD patients who may not have a statistical survival advantage (not hypercapnic, nor with evidence of cor pulmonale) is worthwhile with the sole intention of improving QoL.

Influence of donor and recipient age in lung transplantation [3]

Both LTx donors and recipients are becoming steadily older as the population ages. The median ages of recipients and donors have increased from 43 and 26 years in 1990 to 56 and 41 years in 2013, respectively. This shift has meant more recipients > 65 years are receiving LTx (18% of total LTx recipients in 2014). With the age-old issue of supply not meeting demand, as well as growing waiting lists, appropriate donor allocation remains a contemporary issue. Lung allografts from older donors (>60 years) have been associated with reduced long-term survival in previous studies. This retrospective cohort study evaluates the impact of donor-recipient age matching from USA transplant databases; Organ Procurement and Transplant Network (OPTN) and United Network for Organ Sharing (UNOS). Looking at the entire LTx cohort, recipients had a lower probability of survival if they received lungs from an older donor (≥50 years). However, subgroup analysis demonstrated that older donor age was associated with increased risk of death in younger recipients (age <65 years), but not in older recipients (≥65 years). This supports the argument for donor-recipient age matching to allow fair utilisation of an already limited donor pool, without compromising graft survival.

Registry ISHLT Report 2015: Early Graft Failure [4]

This vast international registry (data collection from 1985 to June 30, 2014) describes both donor and recipient characteristics associated with early graft failure (EGF). EGF is a composite end-point of death or re-transplantation associated with graft failure within the first 30 days after lung transplantation (LTx). The most common causes of death within 30 days include non-CMV infection and “graft failure” (an umbrella term which includes allograft rejection), with cardiovascular and technical complications also highly represented. Overall rates of EGF were as follows: 2.2% for primary LTx, 4.4% for re-transplant and 6.8% for heart-lung transplant. In the period 2005 – 2013, 93% of recipients with EGF died, while 7% underwent re-transplantation. Independent categorical risk factors for EGF in primary LTx and re-transplantation included transplant indication (highest EGF rates with idiopathic pulmonary arterial hypertension), era post-transplant (higher rates in 2005-2008 compared with 2009-2013), non-identical ABO blood group, pre-transplant haemodialysis in the recipient, increased severity of pre-LTx illness in the recipient. Continuous independent risk factors for EGF were identified as increased donor age, lower transplant centre volume, lower recipient predicted FEV_1 and higher recipient weight. Many factors associated with EGF also confer an increased mortality risk. This paper highlights certain factors, most obvi-

ously BMI, which can be addressed prior to transplantation in an attempt to reduce the rate of EGF. Finally, although often challenging, we must be cognisant of timely wait listing as the severely unwell recipients have a higher risk of PGD.

Continued Utility of Single-Lung Transplantation in Select Populations: COPD [5]

While bilateral sequential lung transplantation (BSLTx) is the mainstay of LTx, single lung transplantation (SLTx) could allow more recipients to benefit from LTx by reducing both wait-list mortality and time on the list. Given the infective nature of bronchiectasis and cystic fibrosis, and the homogenous vascular abnormalities in pulmonary arterial hypertension, SLTx is inappropriate in these cohorts. However, in interstitial lung disease and COPD (excluding alpha-1 antitrypsin deficiency) without significant infective burden, there is a role for SLTx. This retrospective single-centre cohort study (1992-2012) from Denver, with a high proportion of SLTx (13%, n = 30) examines their BSLTx and SLTx comparative outcomes. They also benchmarked against national USA data (UNOS). Five-year survival was comparable between the two Denver cohorts (53.2% for SLTx and 56.7% for BSLTx). Denver's SLTx cohort had comparable five-year survival to the UNOS BSLTx cohort (53.2% vs 55.9%, p=0.539), and a trend to better survival compared to the UNOS SLTx cohort (53.2% vs 46.4%, p=0.053). Denver's BSLTx cohort also had comparable results to the UNOS BSLTx cohort. This data also describes a 4.2% reduction in wait-list mortality. Denver's experience with SLTx (including management of complications such as native lung hyperinflation) may have contributed to these excellent outcomes. From an ethical and societal standpoint, it can be asserted that survival outcomes from each set of donor lungs is greater when two recipients benefit (median total survival years is 10.3 for 2 x SLTx, compared with 4.7 in a single BSLTx recipient). Of note, it remains important to consider the risk of malignancy in the recipients' native lung, particularly COPD and ILD patients. Additionally, no quality of life measures were collected in this cohort, which is an important consideration in COPD patients who may be transplanted without a statistical survival advantage.

Survival in Sensitized Lung Transplant Recipients With Perioperative Desensitization [6]

Donor specific HLA antibodies (DSA) in the LTx recipient have an adverse effect on outcomes; increased episodes of acute rejection and chronic allograft dysfunction (CLAD), as well as worse survival. Panel reactive antibodies (PRAs) help identify the prevalence of HLA antigens in the community, expressed as a percentage, against which the transplant recipient's HLA antibodies target. Additionally, the quantity of a specific HLA antibody in the recipient can be is expressed as mean fluorescence intensity units (MFI). In this study, MFI was not available pre-transplant as prospective HLA-crossmatching was not performed; qualitative DSAs were determined virtually via HLA screening alone in both the recipient and donor. In an attempt to promote better access to LTx for highly sensitised patients, this group

conducted a prospective study to determine whether their desensitization strategy pre-transplant conferred outcomes equivalent to non-sensitised patients. The cohorts compared DSA-positive *(plus either PRA-positive[>30%] or PRA-negative[>30%]/medically urgent)* patients (N=53) with DSA-negative patients (N=194). The intended desentisation regimen for all DSA-positive patients included plasma exchange, intravenous immunoglobulins and baziliximab; plasma exchange was the only common treatment to all patients in the intention-to-treat analysis. Graft survival was equivalent between the 2 cohorts; 30-day survival (96 versus 96%) and 1-year survival (89 versus 86%). In summary, pre-transplant desensitisation has the ability to improve LTx access for highly sensitised individuals, without compromising graft function. This is at the expense of higher costs and longer length-of-stay. Moving forward, prospectively determining a pathological MFI threshold (eg >2000) as well as identifying which anti-HLA antibodies are themselves pathological (eg with C1q testing) may enable a more sophisticated approach in this complicated field.

Outcome of Extracorporeal Membrane Oxygenation as a Bridge To Lung Transplantation: An Institutional Experience and Literature Review [7]

Bridging patients to lung transplantation from Extracorporeal Life Support (ECLS) remains controversial. Early experiences were discouraging, with high rates of morbidity and mortality. In this paper, a Swiss group have published their retrospective single-centre analysis from 2007-2013, with one of the highest reported rates of ECLS as a bridge to lung transplantation in the world; 26/186 lung transplants (13.9%). Unadjusted survival data at 30 days, 1 year and 2 years were lower in the ECLS group compared with the non-ECLS group; 89 versus 96%, 68 versus 85%, 53 versus 79% respectively. Morbidity data were also of concern, with statistically longer ICU and intubation rates (p=0.001), more tracheostomies (p=0.001), haemothoracies (p=0.03), dialysis (p=0.001) and critical illness myopathies (p=0.001). Conversely, all patients bridged on awake ECLS (extubated, reduced sedation, avoidance of prolonged ventilation and some active rehabilitation) were still alive, with median follow-up of 10.8 months; complete long-term survival data was unfortunately not available for this cohort. In summary, despite advances in technology and expertise for bridging patients to lung transplant with ECLS, timing of transplantation remains paramount in all patients. Early referral and close monitoring can avoid the difficult decision regarding ECLS as a bridge to transplant.

International Society for Heart and Lung Transplantation Donation After Circulatory Death Registry Report [8]

The International Society for Heart and Lung Transplantation (ISHLT) Donation after Circulatory Death (DCD) registry is the largest of its kind. DCD donors have become more widely utilised since the first reported successful DCD lung transplant over 20 years ago, leading to the creation of an ISHLT DCD working group in 2011. This registry relies on centre-reported lung transplant events, and encompasses

10 centres across North America, Europe and Australia. This study retrospectively analysed all lung transplants reported to the registry from these 10 centres between 2003 and 2013; 306 DCD and 3992 DBD (Donation after Brain Death). This compares with approximately 20,000 total lung transplants throughout the world during the same period. There were no significant differences in survival at 30 days (96% versus 97%), 12 months (89% versus 88%) and 5 years (61% versus 61%) post-lung transplant in the DCD versus DBD groups. These data imply that DCD donors can extend the donor pool without compromising graft survival. It is important to note that ISHLT-affiliated transplantation centres included in the registry have well-established DCD protocols, tools and expertise, which may not be generalizable to a less familiar transplant unit.

Lung Transplantation With Donation After Circulatory Determination of Death Donors and the Impact of Ex Vivo Lung Perfusion [9]

To continue with the theme of identifying alternative strategies to expand the donor pool, this retrospective single-centre analysis looked at the impact of Ex-Vivo Lung Perfusion (EVLP) on survival of DCD lung transplantations, comparing with DCD alone and DBD. This Toronto group has one of the largest DCD/EVLP lung transplant programs in the world. Data were analysed from all lung transplants between 2007 and 2013; 27 DCD alone, 28 DCD+EVLP and 570 DBD (excluding all patients bridged to transplant from ECLS). Between February 2009 and January 2010, all DCD donor lungs utilised EVLP. Outside of this period, EVLP was utilized for marginal donors based on strict criteria. 1-year and 5-year survival were comparable between both DBD and DCD cohorts, as well as DCD and DCD+EVLP cohorts. This tells us that DCD with or without EVLP can safely expand the donor pool, and that EVLP does not cause harm. Interestingly, DCD+EVLP patients had significantly lower hospital length-of-stay when compared with the DCD group, possibly suggesting benefit from ex-vivo organ optimisation prior to implantation. In summary, it is felt that DCD should be utilised even if EVLP is not available, and that at present EVLP should be reserved for uncontrolled or controlled marginal DCD donors.

Nonspecific Immunoglobulin Replacement in Lung Transplantation Recipients With Hypogammaglobulinemia: A Cohort Study Taking Into Account Propensity Score and Immortal Time Bias [10]

Hypogammaglobulinaemia (IgG < 6 g/L) is commonly found in patients following lung transplantation, and has been shown to be associated with worse survival. This single-centre retrospective analysis compared outcomes between hypogammaglobulinaemic and non-hypogammaglobulinaemic LTx recipients between 1998 and 2010. Routine IgG levels were measured at frequent intervals within the first year post-transplant; if IgG was < 6 g/L then the patient received monthly intravenous immunoglobulin (IVIg) infusions, up until 2 consecutive IgG levels of > 7 g/L. All outcome data, which included 5-year survival, 5-year CLAD-survival, infection rates and episodes of acute cellular rejection, were not signifi-

cantly different between groups. Within the limitations of this study design, it appears that immunoglobulin replacement in IgG-deficient patients post-LTx confers similar outcomes to IgG-replete patients, and may also be protective when compared with historical hypogammaglobulinaemic cohorts.

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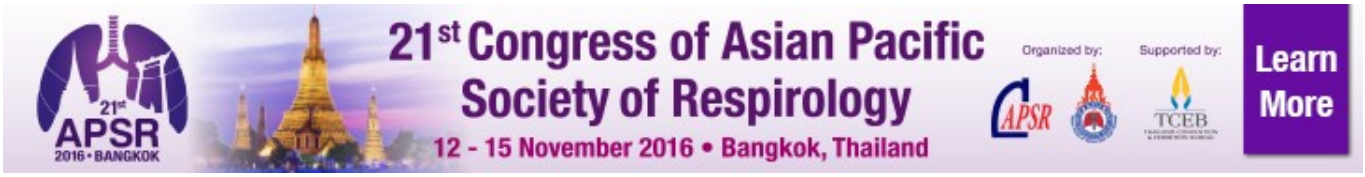

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