APSR RESPIRATORY UPDATES

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APSR EDUCATION PUBLICATION

Inside this issue: Lung transplantation

Dear APSR Colleagues,

Over the course of the last year, the field of lung transplantation has been reshaped by new developments in the diagnosis of rejection, microbial characterization and organ reconditioning. New light has been shed on the effect of donor smoking and recipient age on transplant outcomes as well as access to transplantation services and quality of life post lung transplantation. An increasing proportion of the international literature involves the use of the lung allocation Score (LAS) from which, although not universally accepted in the Asia-Pacific region, many lessons can still be learnt. Great steps have been taken, but there is still much more to be achieved to improve outcomes in lung transplantation.

Your colleagues,

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Experience with the first 50 *ex vivo* lung perfusions in clinical transplantation

Authors: Cypel M et al.

Reference: J Thorac Cardiovasc Surg. 2012; 144:1200-6

URL: http://www.jtcvsonline.org/article/S0022-5223(12)00957-9/abstract

Comment: In the setting of organ donor shortages, the rate of utilisation of donor lungs has been disappointing. Donor lungs are vulnerable in the dying process. *Ex vivo* lung perfusion (EVLP) technology was devised to recondition and assess high-risk donor organs with the aim of increasing organ utilisation. This technology involves resuscitating and reconditioning organs once they are re-warmed to normothermia while being ventilated and perfused outside the body.

From the Toronto group, world leaders in EVLP technology, this retrospective analysis of 317 transplants included 50 EVLP transplants from marginal brain dead donors (PaO2 /FIO2 <300mmHg, chest X-ray/clinical findings of pulmonary oedema) or donation after circulatory death donors. These 50 donor organs were subjected to a 4-6 hour, EVLP run prior to lung transplantation. These were compared with standard non-EVLP controls from the same period. Those organs that achieved a PaO2/FIO2 >400mmHg with acceptable compliance and vascular physiology were used. Encouragingly, the rate of utilization was high (50/58, 86%). The primary end point revealed a trend towards a reduced incidence of grade 3 primary graft dysfunction (PGD) at 72 hrs when compared with controls (2% vs. 8.5%, p= 0.14). 30-day mortality, one-year survival, proportion of patients requiring ECMO support, median time to extubation, intensive care unit stay, and hospital length of stay, were similar between the two arms.

This paper is important in declaring that EVLP technology has arrived, is safe and helps clinicians maximize donor utilisation.

Lung transplantation in patients 70 years old or older: Have outcomes changed after implementation of the lung allocation score?

Authors: Kilic A et al.

Reference: J Thorac Cardiovasc Surg. 2012;144:1133-8.

URL: http://www.jtcvsonline.org/article/S0022-5223(12)00927-0/abstract

Comment: Few transplant centres in the Asia-Pacific region would transplant recipients >70 years of age even if relatively co-morbidity free. In this registry study from the Johns Hopkins University, the pre and post lung allocation score (LAS) era 1-year survival of 4634 subjects in the 60-69 yr age group were compared with 225 subjects in the ≥ 70 year age group. The ≥

70 year age group made up a greater proportion of patients in the post LAS era group (3.1% vs. 0.3%, P<0.001). Cox analysis suggested that age ≥ 70 years was a risk factor for 1-year survival in the pre LAS era (HR 2.00; 95% CI, 1.10-3.62, P = 0 .02) but not in post LAS era (HR 1.02; 95% CI, 0.71-1.46; P = 0.92). The authors concluded that age ≥ 70 yrs has similar outcomes in the post LAS era to the 60-69yr age group and that age ≥ 70 yrs should not be an absolute contraindication to lung transplant in the post LAS era.

Although not directly applicable in the Asia-Pacific region, as most centres do not employ the LAS, this study does provides evidence that carefully selected older recipients can achieve reasonable outcomes post lung transplantation, challenging us to expand our horizons.

Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry

Authors: Bonser RS et al.

Reference: Lancet. 2012; 380:747-55

URL: http://www.sciencedirect.com/science/article/pii/S0140673612601603

Comment: With high cardiovascular risk, smokers make up nearly 40% of the donor pool. In an attempt to maximize utilization of donor organs, this group from Birmingham explores the impact of donor smoking on 3 yr survival and compares survival of subjects who receive organs from smoking donors with the survival of those remaining on the waiting list. In this registry study of 1295 lung transplant recipients, between 1999 and 2010, 39% of subjects received organs from smokers. Of the 2181 subjects on the active transplant list, 37% died or were removed from the list. Those who received organs from donors with positive smoking histories had reduced 3 yr survival compared with recipients of organs from non-smokers (Adjusted HR 1.36, 95% CI 1.11–1.67). However, transplantation, whether from a smoking or non-smoking donor was still associated with a markedly reduced risk of death compared to remaining on the waiting list (HR 0.79, 95% CI 0.70–0.91). Recipients with interstitial lung disease benefited the most (adjusted HR 0.39, CI 0.28–0.55).

The authors concluded that although using organs from donors with a smoking history reduces outcomes post transplant, it improves overall survival for those on the waiting list. In the Asia-Pacific region, donors are frequently turned down due to smoking history. Of these, it is difficult to tell to what degree organs are affected by smoking, apart from pack-year history and chest X-ray appearances. Despite this, the greater good for those patients on the waiting list lies in using organs from donors with a smoking history.

Cryoprobe transbronchial lung biopsy in patients after lung transplantation

Authors: Yarmus L et al.

Reference: Chest. 2013; 143:621-6.

URL: http://journal.publications.chestnet.org/article.aspx?articleid=1654280

Comment: In order to diagnose lung allograft rejection from transbronchial lung biopsies at least 5 pieces of alveolated lung are required. As standard biopsy specimens are small and often contain crush artifact, a large number of biopsies are frequently required in order to obtain a satisfactory number of specimens, thereby increasing the risk of bleeding and pneumothorax.

In this article from the Johns Hopkins and Pennsylvania State Universities, 21 procedures were performed on 17 Lung transplant recipients using standard biopsy forceps as well as cryoprobe (CPBx). Cryoprobe biopsies are taken with the probe tip cooled to approximately -89°C through the effect of compressed gas. Those patients with coagulopathy, FEV 1 < 0.8 L, diffuse bullous disease, hemodynamic instability, and severe hypoxemia (PaO_2 < 55 mm Hg or SpO_2 , 92% on room air) were excluded. 10 Procedures were performed via rigid bronchoscopy with 11 via flexible bronchoscopy. Specimen size and percentage of alveolated lung were found to be greater in the CPBx group (P <0.05). All patients were assessed for bleeding and screened for pneumothorax with image intensifier. No clinically significant complications were recorded with either technique.

The authors concluded that cryoprobe is safe and provides an alternative to standard biopsy forceps. Larger studies will be required, to determine if cryoprobe reduces complication rates or increases diagnostic yield thereby reducing the number of required biopsies and time in the bronchoscopy suite.

New Impact factor and ranking for Respirology released June 2013

Edited By: Peter Eastwood

Impact Factor: 2.781

ISI Journal Citation Reports ©

Ranking: 2012: **18/50** (Respiratory System)

Online ISSN: 1440-1843

Survival benefit of lung transplant for cystic fibrosis since lung allocation score implementation.

Authors: Thabut G et al.

Reference: Am J Respir Crit Care Med. 2013;187:1335-40

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201303-0429OC

Comment: This study of 704 registry subjects from 60 American centres with Cystic Fibrosis (CF) used Cox analysis to model the survival of patients on the waiting list and compared this with post transplant survival. The LAS was used as a surrogate marker of disease severity with transplantation status incorporated as a time-dependent covariate. At 3 months, 39% (95% CI, 35.6–42.9%) of patients were transplanted with 8.5% (6.4–10.6%) of patients dying on the waiting list. At 12 months, 64% (61.0–68.4%) of patients were transplanted compared with 12.9% (10.3–15.5%) dying on the waiting list. There was a reduced risk of death 69% (51–80%) with lung transplantation. There was an association between a higher LAS and survival benefit post transplant (P<0.001).

The authors concluded that for adult CF patients there is a survival benefit with lung transplantation in the LAS era. This article is of interest as it is contrary to the findings of previous studies including that of Liou et al who found no survival benefit for cystic fibrosis children post lung transplantation.[1]

1.Liou TG, Adler FR, Cox DR, Cahill BC. Lung transplantation and survival in children with cystic fibrosis. N Engl J Med 2007;357:2143-52.

Association of large-airway lymphocytic bronchitis with bronchiolitis obliterans syndrome

Authors: Greenland JR et al

Reference: Am J Respir Crit Care Med. 2013;187 :417-23

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201206-1025OC

Comment: The inherent risk of bleeding and pneumothorax associated with transbronchial lung biopsies (TBLBx) has stimulated great interest in devising a less invasive test that can become an alternative marker of rejection.

In this prospective study of 298 subjects in the first 90 days post lung transplantation, this Californian group compared surveillance endobronchial biopsies (EBBx) with concomitant TBLBx to assess large airway lymphocytic bronchitis and its relation to BOS and survival. Samples with concurrent infection were excluded. They devised an E score (0-2) grading system for

lymphocytic bronchitis analogous to the BR grading system. These were compared with standard A and BR scores from TBLBx specimens. E scores were not adequately concordant with A and BR scores to facilitated substitution of large airway biopsies for standard TBLBx. Large airway lymphocytic bronchitis was associated with BOS grades 1-3 and a previously described grade 0p which has been suggested as a precursor to developing BOS. With the addition of E scores to their modeling, the ability to predict BOS was improved (P<0.01) with the higher the E score the higher the BOS grade (adjusted HR, 1.76; 95% CI, 1.11– 2.78; P = 0.02). The maximum E score within the first 90 days post transplant correlated with the development of BOS (P < 0.01) particularly those with E2 scores.

Better tools to predict graft outcome are urgently needed not only to improve individual survival but also to facilitate the timely conduct of clinical trials in transplantation. EBBx may prove to be one such tool.

Disparities in access to lung transplantation for patients with cystic fibrosis by socioeconomic status

Authors: Quon BS et al.

Reference: Am J Respir Crit Care Med. 2012 Nov 15;186(10):1008-13

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201205-0949OC

Comment: Socioeconomic status (SES) has been described as a barrier to accessing health care. This study from the Seattle group attempted to answer the question of whether or not there is differential access to lung transplantation based on socioeconomic status. They assessed 2167 adult registry subjects. The main socioeconomic indicator was Medicaid membership, a health program for those with low income and resources. It conveyed an adjusted 1.56-fold increased risk (95% CI, 1.27–1.92) of being declined for transplantation after initial assessment. This figure was independent of race, educational status, regional household income and driving time from a transplant centre (OR = 1.37; 95% CI, 1.10–1.72). Those who failed to leave school (OR=2.37; 95% CI, 1.49–3.79) or lived in the poorest regions (OR = 1.39; 95% CI, 1.01–1.93) were also more likely to be declined transplantation.

The authors concluded that there are multiple indicators of low SES associated with higher odds of being declined a lung transplant. Those with lower SES are more likely to burdened with medical comorbidities, have higher rates of psychiatric disease and fewer social supports, which may affect suitability for transplantation. Processes need to be put in place to ensure those with lower SES have improved access to lung transplantation with acceptable outcomes.

ISHLT SUMMARY STATMENT
Pathology of pulmonary antibody-mediated rejection: 2012 update from the Pathology Council of the ISHLT

Authors: Berry G et al.

Reference: J Heart Lung Transplant 2012;32:14-21.

URL: http://www.jhltonline.org/article/S1053-2498(12)01393-9/fulltext

Comment : Antibody mediated rejection (AMR) is an established entity in kidney and heart allografts. It is also thought to be an important factor in chronic lung allograft dysfunction (CLAD) / bronchiolitis oblitorans syndrome (BOS), however accepted diagnostic criteria to this point have been lacking. This paper is important for defining the histologic, serology and clinical features required for making a diagnosis of pulmonary AMR. It stresses the importance of the "triple test," namely; clinical allograft dysfunction, circulating donor-specific antibodies (DSA) and suggestive pathologic findings. The authors characterise a range of histopathology findings, including neutrophilic capillaritis and septal margination, which should trigger further evaluation with immunopathology stains. While acknowledging the non-specific nature of complement split product C4d staining, this paper declares C4d staining $\geq$ 50% of interstitial capillaries as being "suggestive of AMR."

The authors encourage frequent surveillance with C4d staining of biopsy specimens and DSA monitoring in order to develop protocols to diagnose pulmonary AMR and assess the risk for chronic allograft rejection.

Impact of lung transplantation on recipient quality of life - A serial, prospective, multicenter analysis through the first posttransplant year

Authors: Finlen Copeland CA et al.

Reference: Chest. 2013;143:744-50.

URL: http://journal.publications.chestnet.org/article.aspx?articleid=1363289

Comment: These investigators from Durham and North Carolina assessed whether lung transplantation results improves physical and psychological quality of life (QOL) at 1 year. They analysed data previously collected from a CMV prevention study, which used the Medical Outcomes Study 36-Item Short-Form Health Survey version 2 (SF-36). They found the physical component score improved an average 10.9 points (P<0.0001) which approached normal values for the general population. A benefit was seen across all native diseases but did not vary by sex, age or type of transplant. The mental component score failed to improve from baseline (P=0.36) persisting below that of the normal population.

The authors concluded that despite the high cost, transplantation can improve QOL related to physical functioning in the first year post transplantation, however impaired psychological well being persisted.

Reestablishment of recipient-associated microbiota in the lung allograft is linked to reduced risk of bronchiolitis obliterans syndrome.

Authors: Willner DL et al.

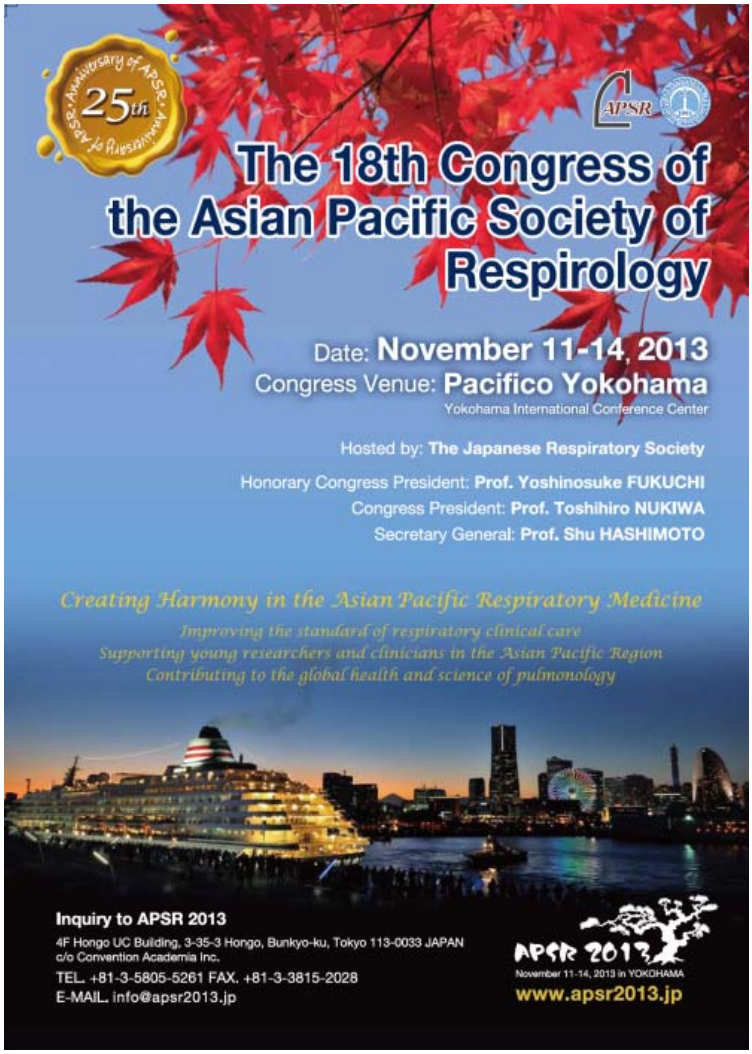
Reference: Am J Respir Crit Care Med. 2013;187:640-7.

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201209-1680OC

Comment: The principle management challenge in the lung transplant recipient is the treatment of, and balance between, infection and rejection. Traditionally, our understanding of the recipient microbiome has been based on microscopy and simple cultures. Now, high throughput genetic sequencing is transforming the field of microbiology.

In this study, from the Queensland group, BAL samples were collected from 57 lung transplant recipients, up to 10 years post transplant, and eight health controls. 17 had a diagnosis of BOS and 50.9% were transplanted for cystic fibrosis (CF). Microbial communities were determined using 454 genetic pyrosequencing of the 16S RNA gene. Communities were dominated either by Pseudomonas or Streptococcus and Veillonella. Surprisingly, the odds ratio of BOS was reduced in patients with Pseudomonas dominated communities. Aspergillus was only isolated from the Streptococcus/Veillonella type communities and was associated with BOS in CF patients ($P < 0.01$). Concordance between pre and post transplant communities was associated with freedom from BOS ($P < 0.01$). In 16 of the CF subjects (six with BOS) up to six additional BAL samples were collected and compared over time. Again, an abundance of Pseudomonas decreased the odds of BOS (OR = 0.25 [0.09, 0.65]; $P = 0.01$) as did pre and post transplant microbial concordance. A significant decrease in the overall diversity over time was also associated with BOS ($P = 0.04$).

The authors concluded that the re-establishment of pre transplant microbial communities in the lung allograft appears protective against BOS and acquisition of new populations may increase the risk of BOS. This study highlights that basic microbial culture is really just the tip of the iceberg when assessing graft microbial communities. It emphasises how antibiotic therapy may impact microbial balance and survival.



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