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Outcomes of various transplant procedures (single, sparing, inverted) in living-donor lobar lung transplantation.

Date H, et al.

J Thorac Cardiovasc Surg. 2017 Feb;153(2):479-486. doi: 10.1016/j.jtcvs.2016.10.017

<http://www.sciencedirect.com/science/article/pii/S0022522316313927?via%3Dihub>

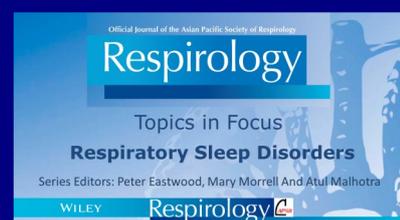
Date et al published the Kyoto series of 65 cases of living donor lobar lung transplant (LDLLT) performed between 2008 to 2016. They outlined their approach with functional size matching and anatomical size matching, and discussed their strategies when faced with size mismatch. For over-sized mismatch single lobar transplant or down-sizing transplant was performed, and for under-sized mismatch, native upper lobe sparing transplant or right-left inverted transplant was performed.

In their series, 29 patients (44.6%) underwent non-standard LDLLT, including 12 single lobe lung transplant (LTx), 7 native upper lobe sparing LTx, 6 right-to left inverted LT, 2 sparing plus inverted LTx, and two others. The remaining patients underwent standard LDLLT. The need for postoperative ECLS support, tracheostomy and mechanical ventilation was similar between the two groups. The three- and five-year survival rates were similar between the patients who received non-standard and standard LDLLT (89.1% and 76.6% for non-standard LDLLT, vs 78% and 71.1% for standard LDLLT). The authors concluded that in cases where ideal size matching is not available for LDLLT, various transplant procedures are feasible options with satisfactory outcomes.

The Kyoto team has one of the most extensive experience with LDLLT in the world, owing to the historical and cultural factors specific to Japan, where the option of brain dead cadaveric donors was not available before the year 2000, and even after that, the number of brain dead donors has been significantly fewer than western countries. This is the first paper to report on a series of non-standard LDLLT, and the outcomes of the Kyoto team are indeed impressive for both standard and non-standard LDLLT. The reader should be cognizant of the fact that this is a reflection of the very selective process of listing of patients for lung transplantation, careful preoperative planning, excellent surgical technique and meticulous peri- and postoperative management. The innovative surgical techniques used by the Kyoto team to overcome issues is yet another important contribution by the Kyoto team the field of LDLLT

New Topics in Focus issue!

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Lung lavage and surfactant replacement during ex vivo lung perfusion for treatment of gastric acid aspiration-induced donor lung injury.

Nakajima D, et al.

J Heart Lung Transplant. 2017 May;36(5):577-585. doi: 10.1016/j.healun.2016.11.010.

<http://www.sciencedirect.com/science/article/pii/S1053249816304399?via%3Dihub>

Nakajima et al from Toronto addressed the role of EVLP in a pig model of gastric acid aspiration. After cold preservation for 10 hours, pig lungs damaged by gastric acid were placed on EVLP for 6 hours, during which time these lungs underwent: (1) no treatment, (2) lung lavage, (3) surfactant administration, and (4) lung lavage followed by surfactant. These lungs were then transplanted (single left lung Tx) and evaluated after four hours of perfusion.

They found that physiologic function significantly improved after adding surfactant during EVLP. The levels of IL-1B, IL-6, IL-8 (all closely related to 30 day mortality in clinical lung transplant) and secretory phospholipase A2 in the EVLP perfusate were significantly lower in the lavage + surfactant group. Total phosphatidylcholine was increased, and minimum surface tension recovered to normal levels in the bronchoalveolar fluid after adding surfactant. Surfactant dysfunction is thought to be caused by the conversion of the active surfactant phosphatidylcholine to the inactive form lysophosphatidylcholine by phospholipase A2. Lysophosphatidylcholine in the bronchoalveolar fluid was found to be significantly lower in the lavage + surfactant group. Post-transplant lung function was significantly better in the lavage+ surfactant group, compared to all other groups.

This study addresses an important clinical concern regarding gastric acid aspiration which is common in patients with neurological injury, and using donor lungs with this injury may lead to severe primary graft dysfunction. This results in a very high rate of decline of such donor lungs. The Toronto group has been working on the use of EVLP not only as a way to evaluate marginal donor lungs, but also has been active in exploring the use of EVLP as a platform for injury-specific therapeutic interventions. Although the use of lung lavage and surfactant administration have been previously described for gastric aspiration, in the clinical setting where a potential donor shows deteriorating lung function, this has practical limitations. In this acute pig lung transplant model, the use of lung lavage and surfactant during EVLP is associated with reduction of key inflammatory mediators, and is shown to result in superior post-transplant lung physiologic function. This study demonstrates the versatility of EVLP as a platform for repair as well as organ evaluation, and shows promise that it may be possible to recondition donor lungs injured by gastric acid aspiration for clinical lung transplantation in the future.

Standard donor lung procurement with normothermic ex vivo lung perfusion: A prospective randomized clinical trial.

Slama A, et al.

J Heart Lung Transplant. 2017 Jul;36(7):744-753. doi: 10.1016/j.healun.2017.02.011.

<http://www.sciencedirect.com/science/article/pii/S1053249817316200?via%3Dihub>

Ex Vivo Lung Perfusion was originally developed to evaluate marginal donor lungs, and by using objective physiologic parameters after explantation from the donor, clinicians are given a further opportunity to assess these organs in order to make a decision whether to proceed to lung transplantation. The use of EVLP has been shown to increase the number of useable donor lungs, and in centers such as Toronto, the use of EVLP has increased the clinical lung transplant volume by more than 20%.

In this single-center prospective randomized controlled trial from the Vienna group, EVLP has been taken one step further. Between 2013 to 2015, lungs from cadaveric donors which met the standard criteria for clinical lung transplantation were randomized to either (1) an EVLP group using the Toronto protocol with a four hour perfusion time, followed by transplantation (n=39), or (2) a control group which underwent the standard cold preservation followed by transplantation (n=41). All transplants were performed with routine intraoperative veno-arterial ECMO support.

Four of the lungs in the EVLP group were rejected after perfusion. The total cold ischemic time was significantly longer for the EVLP group (defined as aortic cross clamp to reperfusion minus EVLP duration) for both implanted lungs compared to control group (first side 372 min vs 291 min $p<0.001$; second side 437 min vs 370 min $p=0.001$). There was no difference in duration of the surgery between the groups. Median P/F ratio at T24 was 516 in the EVLP group vs 491 in the control group. Incidence of PGD >1 was lower in the EVLP group at all time points compared with control. There was no difference in short term clinical outcomes in the recipients in both groups in terms of duration of intubation, ICU stay and hospital stay and 30-day survival.

This paper established the non-inferiority of EVLP against standard cold preservation for cadaveric donor lungs that met standard criteria for clinical transplantation. Moreover, the significantly longer cold ischemic time in the EVLP group did not result in any difference in the clinical outcomes. This has important implications because under conventional thinking, clinicians may be concerned about the use of donor lungs because of an anticipated long ischemic time, for example because of the distance between donor hospital and the transplant center. With the use of EVLP, the concept of extended cold ischemic time needs to be revisited, and this may also

have important implications in terms of the scheduling of lung transplant operations, making it a potentially semi-elective procedure, as opposed to the 'middle of the night affair' that it is in most places. These issues may in turn have important cost impact on the provision of lung transplant service.

The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups.

Gall H, et al.

J Heart Lung Transplant. 2017 Sep;36(9):957-967. doi: 10.1016/j.healun.2017.02.016.

<http://www.sciencedirect.com/science/article/pii/S105324981731625X?via%3Dihub>

This is a single center prospective registry from Giessen, Germany, and aims to understand the long term transplant-free survival and its determinants in patients with pulmonary hypertension (PH) diagnosed by right heart catheterization.

The registry was started in 1993, and from 2008 onwards all patients needed a right heart cath to be eligible for inclusion in the registry. Out of a total of 2067 patients with PH, 33.1% were pulmonary arterial hypertension (PAH), 14.9% were pulmonary venous hypertension, 26.4% were PH secondary to lung diseases (LD-PH), mainly interstitial lung diseases and COPD, 22.2% were due to chronic thromboembolic pulmonary hypertension, and 3.4% were PH due to unknown causes.

At a median follow-up of 37 months, they found highly significant differences in transplant free survival between the different subgroups. For example, for PAH, survival at 1yr, 3 yr and 5 yr were 88.2%, 72.2, and 59.4%, compared to LD-PH group: 79.5%, 52.7% and 38.1%. They also found that the patient's age, gender and 6 minute walk distance correlated well with survival across all PH subtypes, but not the New York Heart Association functional class.

This is the largest single center registry on PH to be published. Moreover, most published series focused on the PAH subgroup of PH, whereas the Giessen series encompasses all subgroups. The fact that all included patients had a right heart catheter since 2008 also meant that the case mix of this tertiary referral center would be different from those seen in the community. Whilst significant progress has been made in the management of PAH subgroup, the Giessen data show that in the non-PAH subgroups there is a significantly worse transplant-free survival. This reflects the lack of evidence-based management of non-PAH patients with PH (which in the Giessen registry accounts for 67% of cases), and highlights an important area where further work is needed.

Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation.

Snell GI et al.

J Heart Lung Transplant. 2017 Oct;36(10):1097-1103. doi: 10.1016/j.healun.2017.07.021.

<http://www.sciencedirect.com/science/article/pii/S105324981731923X?via%3Dihub>

In 2005 the ISHLT published the consensus-based standardised definition and grading system for Primary Graft Dysfunction (PGD). The current publication is the first ISHLT Consensus statement since 2005. In explaining the rationale for this Consensus Statement, the authors acknowledged that while many papers have validated the PGD system proposed in 2005, many questions have arisen since then regarding the terminology, sub-phenotypes, optimal timing of measurement, and range of the grading scale. Moreover the 2012 Berlin definition of the grading of Adult Respiratory Distress Syndrome (ARDS) have raised issues relevant to PGD grading. Furthermore, there have been novel organ preservation technologies and other therapies where PGD is used as a clinical outcome.

The authors start by referencing eight epidemiologic studies published since the 2005 ISHLT PGD Consensus Statement that validated the PGD definition by confirming the predictive validity of PGD for clinical outcomes.

Next, the authors addressed the issue of differential grading of PGD according to selected key potential PGD risk factors. The authors acknowledged the observation that recipients of single lung transplantation may have a higher incidence of PGD than bilateral lung transplant recipients, and that they recommend to consider separate reporting for bilateral and single lung transplants. However there is insufficient evidence to routinely change the PGD grading system within each transplant type. Furthermore, there is insufficient evidence to routinely exclude lobar, size-reduced or significantly undersized allografts from pooled analyses of PGD. In a similar vein, they also concluded that there is insufficient evidence to separately analyse PGD grading according to the presence or absence of specific recipient complications or confounding issues.

Regarding the timing of measurement, the authors clarified that PGD timing starts at the point of reperfusion of the second lung recipient pulmonary arterial cross-clamp. Based on the current literature on the timing of grading, the authors recommend that no changes be made to the grading time points of T0, T24, T48 and T72. It was also pointed out that PGD 3 present at T48

and /or T72 seems to be most suited for use as an outcome in clinical trials because of its clinical impact.

The 2012 revised Berlin definition of ARDS gave rise to the possibility of additional severity thresholds for PGD, and although an extra grade for P/F ration less than 100 was considered, the 2016 Consensus concluded that the current literature does not support the addition of this category.

The 2005 Consensus was unclear regarding those patients with PF ratio less than 300 but who do not have diffuse pulmonary edema on chest X-ray. The 2016 Consensus clarifies that 'any' PF ratio is to be considered PGD grade 0 in the absence of diffuse pulmonary edema on chest X ray. The authors also reaffirmed that it is prudent to maintain the current PGD grading cutoffs at this time.

The grading of extubated patients was not addressed in 2005. The 2016 Consensus recommends that non-invasive ventilation strategies and other forms of support such as high-flow nasal cannula delivery systems should be graded using the same method as for mechanically ventilated patients, and noted that extubated patients with FiO₂ >40% should not be graded differently than those needing non-invasive ventilation. For patients needing less than FiO₂ 40%, they should not be graded as PGD 3. For practical purpose, if there is insufficient data to calculate PF ratio (such as missing arterial blood gas measurement), then the oxygen saturation/ FiO₂ ratio should be calculated and the 200 and 300 PGD cutoffs should be adjusted to 235 and 315 when arterial blood gas measures are not available.

The use of ECLS post LTx has been historically considered equivalent to PGD 3. The 2016 Consensus recommends continued use of PGD 3 for patients with consistent abnormalities on chest x-ray in whom the indication of ECLS is hypoxemia. In cases where the chest x-ray is clear and /or the indication of ECLS is not for primarily hypoxemia, then the Consensus recommends these patients be viewed as ungradable. The use of ECLS should be explicitly recorded and accounted for in reporting and analyses of clinical outcome. In patients who receive nitric oxide and/or aerosolized epoprostenol, they should be graded the same way as those patients who are not given these agents.

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Waiting list outcomes in pediatric lung transplantation: Poor results for children listed in adult transplant programs.

Scully BB, et al.

J Heart Lung Transplant 2017.

<http://www.sciencedirect.com/science/article/pii/S1053249817317539?via%3Dihub>

The Texas group looked at the OPNT/UNOS database to analyse the waiting list outcomes among pediatric lung transplant (LTx) centers in the USA (1). Between 2002 and 2014, there were 1139 pediatric candidates listed for lung transplant. Out of these 720 patients (63,2%) underwent LTx. The authors subdivided the candidates according to the level of clinical activity of the transplant center: high-volume pediatric (4 or more cases per year), low-volume center (fewer than four cases per year), and adult centers (ie transplant volume predominantly in adults). They found that 58% of the pediatric candidates were listed in adult centers, and the resultant transplant rate was low: 42% of the pediatric candidates listed in adult centers received a transplant, compared to 93% of candidates who were listed in pediatric centers. The risk factors for pediatric candidates dying while on the transplant waiting list were: for pediatric candidates listed in an adult program (hazard ratio 15.6, which is the most important risk factor by far), listing in a low volume pediatric transplant center (hazard ratio 5.4), need for inotropic support, and a previous transplant.

Previous work suggest that low case volume in pediatric lung transplant is linked to inferior post-transplant outcomes (2). This paper shows that the pre-transplant outcomes are also influenced by the type and level of activity of the center where a pediatric patient is listed. As observed by the authors, in the USA 58% of pediatric candidates were listed in adult centers, and 16% were listed in low volume centers. The transplant rate and waiting list mortality are parameters that should be scrutinized to evaluate the performance of a transplant program.

In the editorial which accompanies the Scully paper, Sweet postulated the following which may influence the pediatric LTx waitlist outcomes (3).

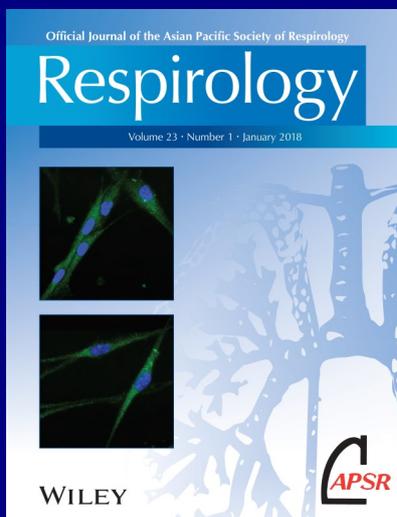
- 1) Geographical variation in donor availability: Texas and Missouri were the two centers with a relatively higher rate of pediatric LTx compared to the rest of the country, suggesting they have a higher ratio of available pediatric donors to candidates in these areas.
- 2) Competition from adult candidates listed in the same (or nearby) transplant center, where the competition from LAS Group D adult candidates would be greatest (eg patients with idiopathic pulmonary fibrosis).

- 3) The socioeconomic status and health care access may limit the ability of pediatric candidates to the high volume pediatric lung transplant centers.

This year the OPTN/UNOS changed their policy which might significantly increase the sharing of donor lungs from adolescent donors to pediatric lung transplant candidates. Previously, adolescent donor lungs not accepted by pediatric centers in the same area will be offered to adult candidates in the same area first, before they are offered to pediatric centers elsewhere. Under the new rule, adolescent donor lungs are offered to children, then adolescents within a 1000 mile radius, before they are offered to adults (4). In time, it will be interesting to see how the waitlist mortality observed in the Scully study will be affected by this new policy.

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1. Scully BB, Goss M, Liu H, et al. Waiting list outcomes in pediatric lung transplantation: poor results for children listed in adult transplant programs. *J Heart Lung Transplant* 2017.
2. Valapour M, Skeans MA, Smith JM, et al. OPTN/SRTR 2015 annual data report: lung. *Am J Transplant* 2017;17(Suppl 1):357-424.
3. Sweet SC: Assessing the impact of program volume and composition on waiting list outcomes in pediatric lung transplantation. *J Heart Lung Transplant*. 2017 Nov;36(11):1180-1182. doi: 10.1016/j.healun.2017.06.006. Epub 2017 Jun 21.
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Outcomes of adolescent recipients after lung transplantation: An analysis of the International Society for Heart and Lung Transplantation Registry.

Paraskeva MA et al.

J Heart Lung Transplant. 2017 Feb 17. pii: S1053-2498(17)31626-1. doi: 10.1016/j.healun.2017.02.017. [Epub ahead of print]

<http://www.sciencedirect.com/science/article/pii/S1053249817316261?via%3Dihub>

The authors of this paper interrogated the ISHLT database for the outcomes of recipients aged between 10 to 24 years, transplanted between 2005 to 2013. They further subdivided the patients into tertiles by age: 10 to 14 years, 15 to 19 years, and 20 to 24 years. Out of a total of 24730 lung transplants done in that period, 2319 or 9% were for adolescents (defined as 10-24 years of age). Kaplan-Meier survival estimates at three years post-transplant showed lower survival for adolescents (65%) when compared with young children (73%) and adults 25 to 34 years (75%) and 35 to 49 years (71%), and without significant difference compared with older adults 50 to 65 years.

When examined by tertiles, 15-19 year old recipients had the poorest outcomes with reduced 1 year survival (82%) compared to 10 to 14 year olds (88%), and reduced three year survival (59%) compared to those 10 to 14 (73%) and 20 to 24 years (66%).

This study is notable because not only does it confirm lower survival in adolescents compared to adults, as reported by other groups, but also the fact that the 15-19 year old tertile had the poorest outcomes. This is despite the fact that in the 10-14 year tertile, they had the highest hospitalized/ ICU patients compared to the 15-19 year tertile. Boyer¹, in the editorial which accompanied this paper, suggested there may be factors particular to the 15-19 year group which made them especially at risk, including difficulties to emotionally process their experiences, the sense of loss of their old identity (often focused on disability and illness) after transplant, poor adherence and difficulty practicing independence, issues with socialization, and the transition from pediatric to an adult transplant program. The Paraskeva paper highlights the need to better understand issues related to this 15-19 year age group of recipients, in order to develop appropriate interventions to better support them.

Reference:

1. Boyer D. Poor outcomes in adolescent lung transplant patients: Why the gap? J Heart Lung Transplant. 2017 May 4. pii: S1053-2498(17)31779-5. doi: 10.1016/j.healun.2017.05.003. [Epub ahead of print]

Airway microbiota signals anabolic and catabolic remodeling in the transplanted lung.

Mouraux S et al.

J Allergy Clin Immunol. 2017 Jul 18. pii: S0091-6749(17)31102-8. doi: 10.1016/j.jaci.2017.06.022. [Epub ahead of print]

<http://www.sciencedirect.com/science/article/pii/S0091674917311028?via%3Dihub>

The SysCLAD consortium took 203 bronchoalveolar lavage (BAL) samples from 112 post lung transplant (LTx) patients, and isolated microbiota DNA and host total RNA. They showed that the characteristics of the pulmonary microbiota aligned with distinct innate cell gene expression profiles. Specifically, they identified four host gene expression profiles which could be classified into catabolic remodelling (high expression of metalloproteinase-7,9 and -12) and anabolic remodelling (linked to maximal thrombospondin and platelet-derived growth factor D expression). The authors observed that catabolic remodeling gene expression was aligned with a microbiota dominated by pro-inflammatory bacteria (namely Staphylococcus, Pseudomonas, and Corynebacterium), whereas anabolic remodeling gene expression was linked to typical members of the healthy state microbiota (namely Prevotella, Streptococcus, and Veillonella). Furthermore, mechanistic assays showed that the bacteria can impact host macrophage-fibroblast activation and matrix deposition.

The SysCLAD consortium previously reported that the airway microbiota composition varies according to the BAL cell gene expression post LTx, and that a balanced bacterial microbiota was aligned to a neutral gene expression profile. In this study the authors further showed that the expression of anabolic vs catabolic gene expression of the host post LTx can be linked to the different airway microbiota, and raises the possibility that the extracellular matrix turnover may be differentially affected by the constituents of the local bacterial communities.

In recent years the airway microbiota in lung diseases such as COPD and idiopathic pulmonary fibrosis has been shown to be different from those of healthy subjects. This study shows that the typical bacterial pathogens that occasionally bloom in the first months after LTx appear to promote the degradation of the extracellular matrix, while bacteria belonging to a healthy steady-state microbiota permit fibroblast to myofibroblast differentiation and matrix deposition. These findings provide another mechanism into the remodeling of the post transplant lung, which may affect the long term outcome of the graft, and potentially open up new therapeutic opportunities to improve long term post LTx outcomes.

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lung. *J Allergy Clin Immunol*. 2017 Jul 18. pii: S0091-6749(17)31102-8. doi: 10.1016/j.jaci.2017.06.022. [Epub ahead of print]

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Mechanical ventilation and extracorporeal membrane oxygenation as a bridging strategy to lung transplantation: Significant gains in survival.

Hayanga A, Du A, Joubert K et al.

Am J Transplant. 2017 Jul 11. doi: 10.1111/ajt.14422. [Epub ahead of print]

<http://onlinelibrary.wiley.com/doi/10.1111/ajt.14422/abstract>

This is a single centre retrospective series from Pittsburgh, comprising of 826 lung transplants (LTx) performed between 2008 and 2015, which studied the impact of using mechanical ventilation (MV), with or without ECMO, as a bridge to LTx (BTT), on survival after transplantation. In this series, 48 patients required MV, and 49 patients required MV + ECMO. The authors did not find a difference in overall survival between the MV and MV+ECMO groups. However, the MV+ECMO group had significantly higher survival conditioned on surviving to one year, although these recipients were more likely to require ECMO after transplant. There were no differences in duration of postoperative MV, hospital stay, or airway complications. The authors concluded in this contemporary series, MV and ECMO are viable bridging strategies to LTx.

The thinking regarding mechanical BTT has undergone significant evolution. The use of ECMO as BTT was first attempted in 1975 but poor outcomes discouraged widespread application (2). The introduction of the Lung Allocation Score in 2005 gave priority to sicker patients, and consequently there was an increase in demand for BTT.

In 2015 the same Pittsburgh group showed that the 1-year survival for patients bridged with ECMO, compared to those without BTT, progressively increased over time (3). This improvement is likely the result of improved technology in terms of hollow-fibre polymethylpentene oxygenators, improved levitated centrifugal pumps, heparin-bonded circuits, and equally important,

better patient/ donor selection. However it has not been easy to delineate the efficacy of ECMO as BTT in addition to MV, or as an alternative to MV. The current paper by Hayanga et al suggests that once medical therapy has failed, an early aggressive approach regarding the initiation of ECMO may lead to improved survival post LTx.

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1. Hayanga A, Du A, Joubert K et al. Mechanical Ventilation and Extracorporeal Membrane Oxygenation as a Bridging Strategy to Lung Transplantation: Significant Gains in Survival. *Am J Transplant*. 2017 Jul 11. doi: 10.1111/ajt.14422.
2. Veith FJ: Lung transplantation. *Transplant Proc* 1977, 9:203–208.
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Voriconazole and squamous cell carcinoma after lung transplantation: A multicentre study.

Hamandi B et al.

Am J Transplant. 2017;00:1–12. <https://doi.org/10.1111/ajt.14500>
<http://onlinelibrary.wiley.com/doi/10.1111/ajt.14500/abstract>

This is a multicenter retrospective study which looked at adult patients who underwent lung transplant (LTx) between 2005-2008, and the authors try to evaluate the independent contribution of voriconazole to the development of squamous cell carcinoma in lung transplant recipients (1).

In this cohort of 900 lung transplant recipients and a median follow-up time of 3.51 yrs, the authors showed that voriconazole exposure increases the risk of squamous cell carcinoma in LTx recipients, which is independent of immunosuppression and sunlight exposure. On univariate analysis, increasing age, sunlight exposure, malignancy before LTx, and exposure to alemtuzumab, tacrolimus/ mycophenolate, or cyclosporine/ azathioprine were significantly associated with increased risk of SCC. On multivariate analysis, exposure to voriconazole was still significant, and was dose-dependent. It was most significant when exposure was more than 180 days, and when used as prophylaxis rather than targeted treatment. Exposure to voriconazole alone gave a hazard ratio of 2.39 for developing squamous cell carcinoma, and exposure to voriconazole plus other azoles, the hazard ratio was 3.45, compared to those unexposed to voriconazole, after controlling for confounders including immunosuppression. The study concluded that the use of voriconazole should be weighed carefully against the po-

tential risk of squamous cell carcinoma.

Although the FDA has linked the use of voriconazole to SCC in LTx recipients, previous studies have not controlled for confounding factors such as comorbidities. The Hamadi study presents strong evidence for the association of voriconazole and SCC independent of immunosuppression and sunlight exposure.

Kulkarni and Witt (2) in the accompanying editorial highlighted the following issues: whether targeted treatment (ie when there is proof of *Aspergillus* infection) should be used in favour of universal prophylaxis, and when voriconazole is used, the appropriate duration and the dose need to be defined. Finally, other alternative drugs should be considered, eg posaconazole and isavuconazole.

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1. Voriconazole and squamous cell carcinoma after lung transplantation: A multicenter study. Hamadi B, Fegbeutel C, Silveira FP, Verschuuren EA, Younus M, Mo J, Yan J, Ussetti P, Chin-Hong PV, Solé A, Holmes-Liew CL, Billaud EM, Grossi PA, Manuel O, Levine DJ, Barbers RG, Hadjiliadis D, Aram J, Singer LG, Husain S. *Am J Transplant*. 2017 Sep 12. doi: 10.1111/ajt.14500. [Epub ahead of print]
2. Voriconazole in lung transplant recipients - how worried should we be? Kulkarni HS, Witt CA. *Am J Transplant*. 2017 Sep 23. doi: 10.1111/ajt.14517. [Epub ahead of print]



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