Health technology assessment of proposal
to establish paediatric lung and paediatric
heart-lung transplantation procedures as a
Nationally Funded Centre

NSW Department of Health on behalf of the Nationally
Funded Centres Reference Group
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1 Executive summary

This report presents the findings of a health technology assessment for paediatric lung and heart-lung transplantation to determine whether the procedure meets the criteria for inclusion on the Nationally Funded Centres (NFC) Program. This assessment was conducted in response to a submission made by the Victorian Department of Health following a proposal from the Alfred Hospital Melbourne (AHM) and was undertaken in accordance with the criteria established for the NFC Program.

The target population for the NFC Program should be children and adolescents aged 6-15 years, who typically weigh 20-40 kilograms. However, some flexibility will be required to allow for referral to the NFC Program of older adolescents who present with small size, low weight or complex paediatric issues. In addition, some children aged less than 16 years may be of an appropriate size to be managed in an adult centre.

Lung and heart-lung transplantation are established treatment options for paediatric patients with a wide variety of end-stage lung and pulmonary vascular diseases. The clinical indications for both transplant types are similar. Bilateral sequential lung transplantation is more commonly performed than heart-lung transplantation.

Lung transplantation is currently undertaken in Australia at the AHM, St Vincent’s Hospital Sydney (SVHS), Royal Perth Hospital and Prince Charles Hospital Brisbane and in Auckland, New Zealand. All of these services offer transplants to older adolescents aged 17 and 18 years. Some adolescents aged 15 and 16 years have received lung transplants at SVHS but to date the majority of procedures on children and young people aged less than 16 years have been performed at the AHM. SVHS and Children’s Hospital Westmead (CHW) have indicated an intention to offer a paediatric lung and heart-lung transplantation service to younger children and adolescents.

Currently two to four lung and heart-lung transplants are performed each year in Australia and New Zealand in patients aged less than 16 years. Most surgical centres worldwide perform fewer than five lung and heart-lung transplants annually.

Demand for donor organs exceeds supply. Most donor lungs are acquired from donors after brain death. Donation after cardiac death and the use of ‘marginal’ donors are alternative sources of lung allografts. Living donor lobar lung transplantation (LDLLT) is also an accepted source of donor lungs.

Selection criteria for lung and heart-lung transplantation have been established and contraindications to transplantation proposed. Different treatment centres apply different acceptance criteria and contraindications. Timing of transplantation is critical to ensure maximal survival benefit is achieved. Timing needs to balance the need to not transplant too early (before the natural history of the underlying clinical condition warrants intervention) or too late (which increases the risk of the patient dying whilst on the waiting list).

Preoperative assessment is comprehensive and patients require ongoing maximal preoperative medical therapy to treat their underlying condition, supplemented by medical and / or surgical management to optimise their health prior to transplantation being performed.

Surgical management is complex. Research is largely insufficient to provide definitive recommendations regarding the evidence-based intra-operative patient care or guide specific protocol development. As a result, specific protocols regarding intra-operative management vary between treatment centres.
Post-operative monitoring and management also vary between treatment centres. The mainstay of post-operative care is the regular, frequent monitoring of the patient for the emergence of complications, including regular bronchoscopy and trans-bronchial biopsy, intensive rehabilitation and education and ongoing pharmacological management, including the use of combination immunosuppressive therapy.

Complications can occur immediately after surgery or be delayed for several years. The significant complications associated with heart-lung transplantation and lung transplantation are similar and predominantly relate to the lung allograft.

In appropriately selected patients paediatric lung and heart-lung transplantation prolong life. The five year survival after paediatric lung transplantation is comparable to that of heart-lung transplantation and survival in paediatric patients is comparable to that achieved in adult patients. The five year mortality is approximately 50%. In contrast, 50% mortality following heart, kidney and liver transplants occurs at approximately 10 years.

Internationally, the number of paediatric lung transplants is modest at approximately 65 per year, and has decreased from its peak in the mid 1990s. The number of paediatric heart-lung transplants performed internationally is smaller than the number of lung transplants, with between eight and 17 procedures performed worldwide each year since 2002. Numbers have also decreased from the peak in the 1990s. Numbers of paediatric LDLLT have declined to an average of one per year worldwide between 2005 and 2007, a decrease from the peak of 14 procedures per year in the late 1990s.

An association between transplant centre annual caseload and mortality has been demonstrated for both adult and paediatric lung transplantation. Centres performing fewer than five paediatric procedures per year experience a higher mortality at one year than those performing greater than five procedures, but at five years post-transplant the difference is not significant. Worldwide, numbers of procedures are insufficient for associations between higher centre volumes and mortality, or heart-lung transplant centre volume and mortality to be assessed. However, studies in adult transplant patients demonstrate lower mortality in centres performing more than 20 lung transplant procedures a year.

Outcomes between adult and paediatric transplant centres have not been extensively studied. Available data suggest the outcomes of adolescent lung transplantation performed in paediatric centres may be superior to those of adult centres.

There are numerous ethical issues that influence the provision of paediatric lung and heart-lung transplantation services. Many of these have not been resolved and account for some of the variability in service delivery and models of care between different countries worldwide, and between surgical centres within the same country.

In considering the optimal service system configuration for low volume, high complexity surgery, equity of access and demonstrated volume/quality relationships are both important considerations. Currently, there appears to be good geographic access to paediatric lung and heart-lung transplantation, with referrals received from all states and with transplants being performed on residents from five states in the last four years. It is also necessary to ensure that expertise in managing paediatric patients post-transplant is developed in referring transplant units.

Where the family of the affected patient does not live in close proximity to the treating centre, relocation of family members to the treatment centre is usually required from the time the patient is placed on the waiting list for transplantation. This results in significant financial and social impacts on families. Services such as accommodation, meals, transport, counselling and
pastoral care are currently perceived by many affected parents as insufficient to meet the needs of families.

Based on the model of care at AHM the estimated cost of lung and heart-lung transplantation when subjected to analysis and review is $190,907. In this analysis no distinction was made for the type of transplant.
2 Recommendations

Recommendation 1
That paediatric lung and heart-lung transplantation meet the relevant criteria for inclusion in the NFC Program.

Recommendation 2
That the current and expected caseload indicates there should be one NFC site for paediatric lung and heart-lung transplantation, with a target population of children and adolescents aged 6-15 years and weighing 20-40 kilograms, but with the opportunity to manage older adolescents who are smaller or of low weight or who have complex paediatric issues.

Recommendation 3
That the paediatric lung and heart-lung transplantation service could be:

- integrated with an adult lung transplantation service in an adult centre, with attention to the special infrastructure and service needs of paediatric patients; or
- integrated with a paediatric cardiac transplantation service in a paediatric centre;

noting, however, that:

- the most common configuration nationally and internationally is integration with an adult lung transplantation service;
- previous Australian experience with a service based in a children's hospital was not successful; and
- international experience of integrating paediatric lung and heart-lung transplantation services with paediatric cardiac transplantation services is limited.

Recommendation 4
That in order to foster innovation and improve quality of service delivery, the small numbers of patients treated annually necessitates maintenance and development of:

- clinical protocols and acceptance criteria, drawing on best practice in the linked adult program and the best international paediatric programs;
- training and succession planning of specialist clinicians including medical practitioners, nurses and allied health clinicians in disciplines including but not limited to respiratory medicine, cardiothoracic surgery, intensive care and anaesthetics;
- outcome evaluation including mortality and morbidity, against international benchmarks;
- research programs;
- program monitoring and development; and
- transition protocols for ongoing paediatric care and then adult care in the home state.
Recommendation 5
That a set of key clinical performance indicators specific to mortality, morbidity and quality of life outcomes are developed for paediatric lung and heart-lung transplantation which:
• draw from international key clinical performance indicators;
• enable close monitoring of access by jurisdiction of residence; and
• enable monitoring of long-term outcomes following discharge from the transplant unit.

Recommendation 6
That should paediatric lung and heart-lung transplant be included in the NFC Program, the funding of the episode of care should, as defined within the NFC Guidance Document (January 2010), encompass the time from acceptance on the waiting list until three months after discharge.

Recommendation 7
That the financial modelling based on the unit costs of the AHM proposal is noted and that it provides guidance for future comprehensive evaluation of the costs of models of care.

Recommendation 8
That applicants for selection as an NFC for paediatric lung and heart-lung transplant should be asked to include in their proposal:
• historical and projected ICU and ward length of stays;
• the component costs of ICU and ward overheads; and
• a breakdown of specialist staffing (medical, nursing, allied health) costs so that direct comparisons between submissions can be made.

Recommendation 9
That should paediatric lung and heart-lung transplant be included in the NFC Program, the following criteria should be used to guide centre selection:
• the integration and/or collaboration of the transplant service with a paediatric cardiothoracic service and the capacity, throughput and specific expertise of that service;
• the ability of the centre to provide paediatric intensive care;
• the integration and/or collaboration of the transplant service with paediatric respiratory, paediatric cardiology, general paediatric, paediatric allied health and paediatric counselling services;
• the ability of the centre to provide a service 24 hours a day, 365 days a year, taking into account staff leave requirements and the need to maintain clinical and practical skills with a relatively low caseload;
• the ability of the centre to support staff delivering services in a high-stress speciality;
• the level of maturity of the model of care and the clinical pathways;
• the level of experience of the institution, cardiothoracic surgeons and other specialists with regard to number of paediatric lung and heart-lung transplants; the clinical outcomes achieved; and the number of suitably experienced specialists across relevant disciplines;
• the ability of the centre to provide adequate support services, including accommodation and psychosocial support services for families who need to relocate for extended periods;

• whether services are provided in a paediatric or adult facility; and if in an adult facility, the mechanisms that will ensure the needs of paediatric patients are met;

• an established research and development program including established systems for monitoring and ongoing data collection; and

• the capacity of the institution to ensure equitable access to transplant care for patients from all States and Territories.

**Recommendation 10**

That should paediatric lung and heart-lung transplant be included in the NFC Program, the NFC should be supported by each jurisdiction to develop its communication efforts with specialist clinicians involved in the counselling of families whose children may benefit from lung and heart-lung transplantation.
3 Terms and abbreviations used in this report

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABO</td>
<td>ABO blood-type system</td>
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<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
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<td>AHMAC</td>
<td>Australian Health Ministers’ Advisory Council</td>
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<td>AHMC</td>
<td>Australian Health Ministers’ Conference</td>
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<td>AHM</td>
<td>Alfred Hospital, Melbourne</td>
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<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
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<tr>
<td>ANZCOTR</td>
<td>Australia and New Zealand Cardiothoracic Organ Transplant Registry</td>
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<td>ANZOD</td>
<td>Australia and New Zealand Organ Donation Registry</td>
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<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
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<td>ATGAM</td>
<td>Equine antithymocyte globulin</td>
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<td>BAL</td>
<td>Bronchoalveolar lavage</td>
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<td>BiPAP</td>
<td>Bilevel positive airway pressure ventilation</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>BO</td>
<td>Bronchiolitis obliterans</td>
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<td>BOS</td>
<td>Bronchiolitis obliterans syndrome</td>
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<tr>
<td>BSLT</td>
<td>Bilateral sequential lung transplant</td>
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<td>CF</td>
<td>Cystic fibrosis</td>
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<td>CHW</td>
<td>Children’s Hospital Westmead</td>
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<tr>
<td>CINAHL</td>
<td>Cumulative Index of Nursing and Allied Health Literature</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
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<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
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<td>CPR</td>
<td>Cardiopulmonary resuscitation</td>
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<tr>
<td>CT</td>
<td>Computerised tomography</td>
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<tr>
<td>CTEPC</td>
<td>Clinical, Technical and Ethical Principal Committee of AHMAC</td>
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<tr>
<td>DCD</td>
<td>Donors after cardiac death</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>DoH</td>
<td>Department of Health (Victoria)</td>
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<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
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<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
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<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in 1 second</td>
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<tr>
<td>FiO₂</td>
<td>Fractional inspired oxygen</td>
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<td>FVC</td>
<td>Forced vital capacity</td>
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<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>GM-CSF</td>
<td>Granulocyte-macrophage colony stimulating factor</td>
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<td>HLA</td>
<td>Human leukocyte antigen</td>
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<td>HLT</td>
<td>Heart-lung transplant</td>
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<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>IL2</td>
<td>Interleukin 2</td>
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<tr>
<td>ILD</td>
<td>Interstitial lung disease</td>
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<tr>
<td>IPAH</td>
<td>Idiopathic pulmonary arterial hypertension</td>
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<td>ISHLT</td>
<td>International Society for Heart and Lung Transplantation</td>
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<td>IVC</td>
<td>Inferior vena cava</td>
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<tr>
<td>LAS</td>
<td>Lung allocation score</td>
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<td>LDLLT</td>
<td>Living-donor lobar lung transplantation</td>
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<tr>
<td>MMF</td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>OKT3</td>
<td>Muromonab-CD3</td>
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<tr>
<td>PaO₂</td>
<td>Partial pressure of arterial oxygen</td>
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<tr>
<td>PRA</td>
<td>Panel reactive antibody</td>
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<td>PT</td>
<td>Prothrombin time</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PTLD</td>
<td>Post-transplant lymphoproliferative disease</td>
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<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>RAD</td>
<td>40-0-[2-hydroxyethyl]-rapamycin</td>
</tr>
<tr>
<td>RATG</td>
<td>Rabbit antithymocyte globulin</td>
</tr>
<tr>
<td>RCHM</td>
<td>Royal Children’s Hospital Melbourne</td>
</tr>
<tr>
<td>SLCH</td>
<td>St Louis Children’s Hospital</td>
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<tr>
<td>SVC</td>
<td>Superior vena cava</td>
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<tr>
<td>SVHS</td>
<td>St Vincent’s Hospital Sydney</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TSANZ</td>
<td>Transplantation Society of Australia and New Zealand</td>
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<tr>
<td>UNOS</td>
<td>United Network for Organ Sharing</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>WIES</td>
<td>Weighted inlier equivalent separation</td>
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4 Nationally Funded Centres Program

Background

At the June 1990 Australian Health Ministers’ Conference (AHMC), Ministers endorsed a national policy for public sector provision of high cost, highly specialised clinical practices and technologies with limited demand – the Nationally Funded Centres Program.

Nationally Funded Centres (NFCs) are established to provide Australians with access to certain high cost, low demand, new and emerging technologies in a manner which optimises equitable access. They are approved by the Australian Health Ministers’ Advisory Council (AHMAC) and funded by the jurisdictions. The NFC Reference Group, which has representatives from the Australian Government and each State and Territory, is responsible for planning and managing the NFC Program, the assessment of new submissions and the commissioning of reviews of existing programs. The NFC Reference Group reports to AHMAC through the Clinical, Technical and Ethical Principal Committee (CTEPC).

The objectives of the NFC Program are to ensure that:

• there is optimal access to certain high cost, low demand, new and emerging technologies regardless of geographic location, in the context of workforce and resource availability;
• these technologies are provided efficiently and effectively;
• requirements for high quality and safe introduction and ongoing provision of these technologies have been defined and implemented; and
• health and cost outcomes of these technologies are monitored and evaluated.

For a technology to be considered for provision through an NFC, it must be an established clinical practice requiring a national population base for efficient and effective service provision. Technologies eligible for consideration for provision through an NFC include devices, prostheses, techniques, skills or expertise (or personnel with skills or expertise) and/or procedures, or combinations of these.

NFCs for a particular technology may be established in one or more sites and service delivery is intended to be restricted to these sites.

Funding for NFCs is provided by the jurisdictions according to a weighted population-based formula. There is an agreed level of funding for each procedure.

Assessments of proposals for the establishment of NFCs are commissioned when required by the NFC Reference Group. The basis of the assessment of proposals is set out in Nationally Funded Centres Guidance for Governance, Management, Funding, Establishment, Review (the NFC Guidance Document). This assessment for paediatric lung and heart-lung transplantation was largely undertaken using the May 2007 NFC Guidance Document, but also included reference to the definition of the episode of care as set out in the January 2010 NFC Guidance Document.

Appendix 7 of the Guidance Document sets out the criteria by which NFC Programs are to be assessed, which include:

• nature of the technology and clinical need:
  • description and classification of new technology;
• clinical indication/disease/condition(s) for treatment by proposed new technology/clinical practice;
• patient population(s) and projected demand for proposed new technology;
• health outcomes for new technology;
• use of new technology;
• comparison with existing approach(es) to clinical intervention; and
• ethical issues;

• safety and clinical effectiveness:
  • regulatory approval for the new technology;
  • evidence of safety of new technology;
  • evidence of clinical effectiveness;

• model of care and service delivery;
• financial implications:
  • cost effectiveness;
  • cost estimates;

• synthesis of evidence and information supporting service concentration:
  • national demand;
  • workforce;
  • clinical infrastructure;
  • quality and safety;
  • facilities;
  • cost;

• implementation and establishment:
  • site determination;
  • number of sites;
  • service delivery; and
  • monitoring and evaluation.

The assessment results in a report to the NFC Reference Group which in turn provides a report to AHMAC through the CTEPC. The possible recommendations from an assessment include:
• establish or not establish an NFC for the procedure or condition proposed;
• if a NFC is established to:
  • propose the number of NFCs that should be established;
  • propose a level of service activity for a defined period with a regular review period specified (no longer than every three to five years).
Decisions regarding the number of NFC providers are made according to assessment of:

- the threshold at which satisfactory health and cost-effectiveness outcomes can be achieved;
- service arrangements required to meet the needs of the Australian population for the foreseeable future;
- the combined national and international demand justify establishment;
- the cost effectiveness of an additional centre or centres is similar to that of the first centre;
- establishment of an additional centre or centres will not adversely affect the health outcomes; and
- establishment of an additional centre or centres will not adversely affect equity of access.

At some point in the decision-making process regarding provision of a specific NFC Program, agreement may be reached by AHMAC that NFC status is not appropriate. This point may be reached when:

- there is no need for an NFC as technology or services are provided in the majority of jurisdictions; or
- the technology has been superseded by another practice.
This assessment

This report is the outcome of a comprehensive assessment of a proposal to include, in the NFC Program, paediatric lung and paediatric heart-lung transplantation for Australian children and adolescents with medical conditions for which these treatments are clinically indicated.

The assessment was undertaken DLA Phillips Fox (Consultants: Dr Heather Wellington, Dr Paul Woodhouse, Dr Kelly Shaw) who were appointed following a competitive tender process. Clinical advice was provided by Dr Barry Duffy OAM (Paediatric Intensivist and former Director of Paediatric Intensive Care, Sydney Children’s Hospital, Randwick). Expert comment on the draft report was provided by Dr Paul Aurora, Consultant in Paediatric Respiratory Medicine and Lung Transplantation at Great Ormond Street Hospital for Children, London.

The assessment was conducted in accordance with the criteria set out in the May 2007 NFC Guidance Document. This Report follows the structure established in Appendix 7 of that document. A Project Management Group was established by the NFC Reference Group to oversee and guide the assessment.

The process for the assessment incorporated:

- a literature review;
- a site visit was undertaken at AHM on 1 December 2009, with key staff from AHM and Royal Children’s Hospital Melbourne (RCHM) in attendance;
- face-to-face interviews with Dr Phillip Spratt and Professor Alan Glanville (SVHS) and Mr David Winlaw (Children’s Hospital Westmead) on 24 November 2009;
- interviews with patients and carers identified by SVHS and AHM;
- a survey of referring units in all jurisdictions;
- interviews with Victorian Department of Health officers;
- an interview with Professor Chris Kimber and Professor Jill Sewell, co-chairs of the Victorian Paediatric Clinical Network;
- review of information provided by AHM/RCHM including:
  - the initial application made to the NFC Secretariat; and
  - the presentations provided to the assessment team at the visit to AHM;
- Annual Reports from Australia and New Zealand Cardiothoracic Transplant Registry (ANZCOTR) and Australia and New Zealand Organ Donation Registry (ANZOD);
- more detailed data from ANZCOTR; and
- Australian Bureau of Statistics (ABS) and Australian Institute of Health and Welfare (AIHW) births and deaths data.
5 Paediatric lung and heart-lung transplantation

History

Lung and heart-lung transplantation are treatment options for selected paediatric patients with advanced lung disease and cardio-respiratory conditions that have failed to respond to standard medical and surgical therapy.\(^1\)

There are various definitions of the term ‘paediatric’. Commonly-used age end-points include the 17\(^{th}\), 18\(^{th}\) and 19\(^{th}\) birthday. Variations in age end-points reported in the literature are reflected in this report. The majority of paediatric lung transplant recipients are in the adolescent age group. For the purposes of this report's recommendations, we have selected an age range of six years to 15 years inclusive, recognising, however, that:

- some patients at the upper end of this age group are physically and psychologically mature and should be treated in adult services;
- some patients older than 15 who are small or are of low weight or have complex paediatric problems should also be eligible for treatment at a paediatric service; and
- as transplantation services develop and build capacity, it is likely that families and paediatricians will seek transplantation for children younger than six years old.

Although significant gains have been made in improving lung function and survival in children affected by chronic respiratory conditions, ultimately respiratory failure is the leading cause of mortality in many children affected by severe chronic respiratory and cardio-respiratory disease.\(^2\) In some of these children, lung or heart-lung transplantation may prolong survival and improve quality of life.

Outcomes after transplantation were poor until the early 1980s, when the development of immunosuppressive agents such as cyclosporine resulted in reduced complications and longer-term survival. As a result, although lung and heart-lung transplantation had been performed experimentally since the 1960s, the first long-term successful lung and heart-lung transplants were not performed until the 1980s.\(^3\) The first successful isolated lung transplantation was performed in 1983 in an adult with pulmonary fibrosis. This was followed by the first successful paediatric lung transplantation in 1987, performed on a 16-year old female patient with pulmonary fibrosis.\(^4\) Successful paediatric heart-lung transplants were reported from the end of the 1980s.

Lung and heart-lung transplantation have not been compared with medical therapy in published randomised controlled trials. Investigators have most commonly reported the outcomes associated with transplantation from retrospective cohort studies and analyses of registry data and administrative datasets. As a result, comparative quantitative estimates of the improvements in life expectancy and quality of life obtained between transplantation and

\(^3\) Woo M. Overview of lung transplantation. Clinical Reviews in Allergy and Immunology 2008;35:154-63.
medical management in paediatric patients are unavailable. Numerous studies have demonstrated that lung transplantation increases life expectancy in the majority of recipients.

Clinical indications

Introduction

According to the registry of the International Society for Heart and Lung Transplantation (ISHLT), there were 1207 lung transplantations performed worldwide in persons aged less than 18 years between January 1990 and June 2008. Approximately 65% were performed in children aged 12 to 17 years. It should be noted that not all countries with a transplant program report data to the ISHLT. Therefore, registry data are likely to underestimate true numbers of lung transplants being performed worldwide.

The clinical indications for paediatric lung transplantation vary according to age group (Table 1). In children aged less than one year, congenital heart disease and primary pulmonary hypertension are the leading indications and account for approximately half of all lung transplant procedures. In children aged between one and five years, primary pulmonary hypertension is the most common condition. In children aged six years and above, cystic fibrosis (CF) is the most common diagnosis.

Between January 2000 and June 2008 there were 443 paediatric lung transplants performed in North America, 181 performed in Europe, and 35 performed in other countries.

Over this period the majority of paediatric lung transplants internationally were performed in adolescents (66%), with the most common clinical indication for transplantation being CF (60%). In North America, proportionally fewer lung transplant procedures are performed in adolescents and fewer are performed for CF compared with other countries:

- in North America, 64% of paediatric lung transplants are performed in adolescents, compared with 80% in Europe and 85% in other countries;
- in North America, 56% of transplants are performed for CF, compared with 65% in Europe and 68% in other countries; and

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• between January 2000 and June 2008 there were approximately 70 lung transplants reported in recipients aged five years or less in North America and 12 procedures reported elsewhere in the world in this period. This may be in part because outside North America there are few reported donors aged six years or less.

LDLLT has become a rare operation internationally. Worldwide, numbers have fallen from a peak of 14 in both 1998 and 1999 to three between January 2005 and December 2007\textsuperscript{15}. With the exception of Japan, most countries in the world do not currently perform LDLLT\textsuperscript{16,17}.

Table 1: Age specific indications for lung transplantation 1990-2008 (Worldwide)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age &lt; 1 year</th>
<th>Age 1 – 5 years</th>
<th>Age 6 – 11 years</th>
<th>Age 12 – 17 years</th>
<th>Total</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>2</td>
<td>5</td>
<td>124</td>
<td>547</td>
<td>678</td>
<td>56</td>
</tr>
<tr>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>11</td>
<td>22</td>
<td>25</td>
<td>60</td>
<td>118</td>
<td>10</td>
</tr>
<tr>
<td>Re-transplantation or graft failure</td>
<td>3</td>
<td>8</td>
<td>15</td>
<td>43</td>
<td>69</td>
<td>6</td>
</tr>
<tr>
<td>Interstitial lung diseases (ILD)</td>
<td>5</td>
<td>9</td>
<td>17</td>
<td>37</td>
<td>68</td>
<td>6</td>
</tr>
<tr>
<td>Bronchiolitis obliterans (BO) (not re-transplant)</td>
<td>0</td>
<td>9</td>
<td>10</td>
<td>29</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>21</td>
<td>8</td>
<td>4</td>
<td>10</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>5</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary vascular disease</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Eisenmenger’s syndrome</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
<td>17</td>
<td>26</td>
<td>54</td>
<td>122</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>82</strong></td>
<td><strong>99</strong></td>
<td><strong>234</strong></td>
<td><strong>792</strong></td>
<td><strong>1207</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Paediatric heart-lung transplants are performed far less frequently than paediatric lung transplantations and numbers of transplants performed each year are declining. Between eight and 17 paediatric heart-lung transplantation a year have been performed worldwide since 2002. Approximately 60% of these are performed in adolescents\textsuperscript{18}.

\textsuperscript{15} Ibid


\textsuperscript{17} Date H. Improved survival after living-donor lobar lung transplantation. Journal of Thoracic and Cardiovascular Surgery 2004;128:933-40.

\textsuperscript{18} Ibid
The clinical indications for paediatric heart-lung transplantation are similar to those for lung transplantation, with the principal diagnoses in persons aged less than 18 years being IPAH (26%), CF (22%) and congenital heart disease (22%) (Figure 1).

**Figure 1: Primary diagnosis of paediatric heart-lung transplant recipients (1986 to 2007)**

In Australia and New Zealand the diagnoses leading to lung and heart-lung transplant in patients aged less than 18 years are set out in Table 2.

**Table 2: Primary diagnosis of heart-lung and lung transplant patients aged <16 years in period 2003-2009 (Australia & New Zealand)**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>8</td>
<td>53%</td>
</tr>
<tr>
<td>Miscellaneous lung condition (includes post-viral illness)</td>
<td>4</td>
<td>26%</td>
</tr>
<tr>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>1</td>
<td>7%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1</td>
<td>7%</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>1</td>
<td>7%</td>
</tr>
</tbody>
</table>

Source: ANZCOTR 2009, AHM 2010

**Cystic fibrosis**

Cystic fibrosis (CF) is the most common terminal hereditary disease in the Caucasian population, affecting one in every 2500 births. In 2001 there were approximately 2300 people in Australia living with CF, two-thirds of whom were children and adolescents.

CF is a recessive genetic disorder affecting the CF transmembrane regulator protein which is present on all cell surfaces. The condition affects many organs in the body, but primarily the

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lungs, pancreas, liver and reproductive systems. The most serious impacts are on the lungs and pancreas\textsuperscript{21}.

Major advances in the diagnosis and treatment of cystic fibrosis have prolonged life expectancy into adulthood. Although the overall median survival rate for CF is approximately 32 years, life expectancy has improved dramatically in recent years. The median estimated survival for children with CF born in the year 2000 is now approximately 50 years\textsuperscript{22}. The reasons for improved survival are thought to include earlier diagnosis of CF due to neonatal screening, improved nutrition and management of respiratory infections, and management in tertiary CF centres, where it is recommended children visit at least quarterly for multidisciplinary assessment and care\textsuperscript{23}. This improved life expectancy requires strict adherence to intensive and time-consuming treatment regimes\textsuperscript{24,25}.

There is currently no cure for CF and treatment aims to slow the progression of the condition through early screening and better management. Management of CF can create a significant burden on the patient and family. Daily treatment regimens are time-consuming and include physiotherapy, high-calorie meals and routine medications. Additionally, chronic lung infections result in repeated hospitalisations, which can adversely affect study and employment\textsuperscript{26}. These factors have a substantial impact on the quality of life of those with CF and their families\textsuperscript{27}.

Each year in Australia there are approximately ten deaths due to CF recorded in ABS mortality data in children and adolescents aged less than 18 years\textsuperscript{28}. Factors that have been associated with a greater risk of death include a predicted forced expiratory volume in 1 second (FEV\textsubscript{1}) of less than 30\%, elevated pCO\textsubscript{2} and decreased pO\textsubscript{2} on arterial blood gases, female gender, younger age and poor nutritional status. Other factors predictive of increased mortality include increased frequency of hospitalisations, increased need for intravenous antibiotics, height / weight centile, reduced oxygen uptake during exercise, resting heart rate, haemoptysis and greater than 30\% disparity in perfusion difference between lungs\textsuperscript{29}.

**Pulmonary vascular disease**

Pulmonary vascular disease occurs in a number of forms including IPAH, congenital heart disease in association with pulmonary hypertension, obstructive pulmonary venous disease, thromboembolic disorders leading to pulmonary hypertension, arteriovenous fistulae of

\begin{thebibliography}{99}
\bibitem{26} Burker E. Psychological and educational factors. . Pediatric Pulmonology 2004; 38:413–8.
\bibitem{28} ABS Mortality Database. Lung mortality due to cystic fibrosis in persons aged 0-18 years (1999-2006).
\end{thebibliography}
pulmonary vessels, aneurysms of the pulmonary artery, kyphoscoliotic heart disease and pulmonary hypertension associated with parenchymal lung disease\textsuperscript{30}.

The frequency of pulmonary vascular disorders in children, in particular pulmonary arterial hypertension, remains unknown. Each year in Australia there are approximately nine deaths due to pulmonary vascular diseases recorded in ABS mortality data in children and adolescents aged less than 18 years\textsuperscript{31}.

Treatment for pulmonary vascular disease has improved significantly in the past 15 years, largely due to the development of more effective pharmacological agents and the use of surgical techniques such as atrial septostomy to relieve pulmonary hypertension, however this procedure is rarely performed in Australia. Patients who are receiving maximal medical therapy but who have increasing central venous pressure with declining cardiac index on serial cardiac catheterisations have a poor prognosis and may require transplantation to improve life expectancy and quality of life\textsuperscript{32}.

**Pulmonary arterial hypertension**

Pulmonary arterial hypertension is a serious progressive condition with a poor prognosis if not identified and treated\textsuperscript{33}. The prognosis is worse in children than in adults. Pulmonary arterial hypertension is subcategorised into idiopathic pulmonary arterial hypertension and associated pulmonary arterial hypertension\textsuperscript{34}. Sustained pulmonary arterial hypertension is associated with the development of intractable pulmonary vascular disease, which when advanced leads to right heart failure and death\textsuperscript{35}.

The annual incidence of pulmonary arterial hypertension is estimated to range from one to two new cases per million people in the general population\textsuperscript{36}. Although rare, increasingly frequent reports of confirmed cases suggest that more patients have pulmonary arterial hypertension than was previously recognised. The sex incidence in children is approximately 1.8:1 female to male ratio, with no significant difference in younger children compared with older children\textsuperscript{37}.

Until recently, the diagnosis of IPAH was associated with a mean survival of 10 months in children\textsuperscript{38}. However, with earlier diagnosis, more definitive assessment of disease severity and more effective treatment, prognosis has improved and survival has increased\textsuperscript{39}. At specialist overseas treatment centres survival of 85-94\% at one year, and 57-72\% at five years have been achieved, with between 10 and 21\% of children progressing to transplantation\textsuperscript{40 41}.

\textsuperscript{31} ABS Mortality Database. Lung mortality due to cystic fibrosis in persons aged 0-18 years (1999-2006).
\textsuperscript{32} Haworth S. The management of pulmonary hypertension in children. Archives of Disease in Childhood 2008; 93:620-5.
\textsuperscript{34} Ibid
\textsuperscript{39} Haworth S. Treatment and survival in children with pulmonary arterial hypertension. Heart 2009;95:312-7.
\textsuperscript{40} Ibid
\textsuperscript{41} Ibid
Interstitial lung diseases

In children, interstitial lung diseases (ILDs) comprise a heterogeneous group of rare, mostly idiopathic disorders characterised by diffuse lung infiltrates, restrictive functional respiratory defects and disordered respiratory gas exchange\(^{42}\). Each year in Australia there are approximately four deaths due to ILD recorded in ABS mortality data in children aged less than 18 years\(^{43}\).

ILD is most frequently diagnosed in the first year of life, with a predominance of paediatric entities such as pulmonary interstitial glycogenosis, neuroendocrine cell hyperplasia of infancy and genetic disorders of surfactant metabolism. In older children the pathogenesis is similar to adults\(^{44}\).

The relative frequencies of these disorders are quite different in children compared with adults, and the overall prevalence is lower in children than adults. The precise annual incidence is not known but has been estimated at between 13 and 20 cases per 100 000 population, and increases with age\(^{45}\).

There are few empiric data available to guide the evidence-based management of ILD in children. Most current treatment regimens for children are based on experience gained in small numbers of patients within individual centres, and extrapolated from information provided by adult studies\(^{46,47}\).

The mainstay of treatment is supportive care, including the use of oxygen for chronic hypoxia, maintaining adequate nutrition, annual immunisation for influenza, aggressive treatment of intercurrent infections, strict avoidance of tobacco smoke and air pollutants and the selective use of bronchodilators\(^{48}\).

Pharmacological management includes the use of immunosuppressive, anti-inflammatory (including corticosteroid) and antifibrotic drugs. Patients with underlying systemic disorders require primary treatment for that disorder. For example, this includes chemotherapy for malignancy, gamma globulin for hypogammaglobulinaemia, anti-infective treatments for chronic infections and granulocyte-macrophage colony-stimulating factor (GM-CSF) and/or interferon-alpha for alveolar proteinoses where indicated\(^{49,50}\).

Children with ILD may require lung or heart-lung transplantation as forced vital capacity on pulmonary function tests drops below 40% of predicted values and other signs of clinical

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\(^{43}\) ABS Mortality Database. Lung mortality due to cystic fibrosis in persons aged 0-18 years (1999-2006).


deterioration are present. Lung and heart-lung transplantation outcomes are similar to those achieved with other clinical conditions. However, transplantation for ILD has been associated with the recurrence of the ILD in the transplanted lungs.

**Bronchiolitis obliterans**

BO is a pathologic process leading to the obstruction and/or obliteration of smaller airways. The histology seen in BO suggests that BO is a ‘final common pathway’ of response to airway epithelial injury from a number of agents and/or mechanisms. The aetiology remains elusive in spite of a growing body of basic science and clinical research.

The diagnosis is relatively rare in the general paediatric population. Although the exact incidence is unknown it is estimated to occur in less than 1 in 100 000 children in the general population.

There are multiple pathological forms of BO, each with varying clinical associations. BO can be considered according to two separate patient groups; BO occurring in the general population, and BO in patients who have received lung or stem cell transplants. In the general paediatric population BO is usually preceded by respiratory tract infection caused by adenovirus, influenza or measles, or by recurrent aspiration. In some patients, collagen vascular diseases (e.g. rheumatoid arthritis), toxic inhalation of gases such as oxides of nitrogen or metal fumes or ingestion of substances such as alkaloids may precede BO development.

In contrast to the general population, the diagnosis of BO in recipients of bone marrow or lung transplants is common. It is estimated that 10% of all bone marrow transplant recipients and 35% to 60% of lung transplant recipients will develop BO. Further, BO is the most common cause of death after lung transplantation, accounting for over 40% of deaths that occur beyond one year after lung transplant.

BO is diagnosed histologically but biopsy is an insensitive tool for detection as the pathology occurs focally throughout the lungs. Instead, clinical surrogates are used to indicate the presence of BO, including a decline in FEV1 and FVC. The clinical surrogates are referred to as Bronchiolitis Obliterans Syndrome (BOS) and are applied to the detection of BO in patients post-transplant rather than to cases of BO that occur in the general population.

There is no consistently effective treatment strategy for BO. The approaches used include immunosuppression, photopheresis and total lymphoid irradiation. All have shown benefit in some patients but none are uniformly beneficial. Other potential options include the use of

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55 Ibid
57 Ibid
antimicrobials or statins (a cholesterol-lowering medication that also influences systemic fibrotic activity)\(^{60}\). Re-transplantation is an option in select individuals. However, re-transplantation is a risk factor for death within the first year post-transplant\(^{61}\).

**Congenital heart diseases**

Congenital heart diseases are a heterogeneous group of conditions that may lead to a requirement for heart-lung or lung transplantation when other surgical treatment options and/or when maximal medical therapy fails\(^{62}\). Approximately 36% of heart-lung and 6% of lung transplants are performed for children and adolescents with congenital heart abnormalities, including Eisenmenger syndrome\(^{63}\).

The prevalence of congenital cardiac disease where heart-lung or lung transplantation are indicated is low, and estimated as less than one in 1 million population\(^{64}\).

Current indications for heart-lung or lung transplantation in this patient group include severe pulmonary hypertension with right ventricular failure, pulmonary atresia with diminutive pulmonary arteries and congenital cardiac conditions that have led to irreversible bilateral pulmonary vascular disease\(^{65}\).

If not corrected, congenital cardiac defects such as ventricular septal defects, atrial septal defects and patent ductus arteriosus may lead to chronic increased flow from the left to right side of the circulation. Over time, this increases pulmonary vascular resistance, leading to a reversal of the shunt from right to left, resulting in the development of cyanosis and progressive functional disability. This is referred to as Eisenmenger syndrome\(^{66}\).

Once irreversible changes of pulmonary hypertension are established, there is no longer a role for isolated cardiac surgical repair. Heart-lung transplantation is indicated as the treatments of choice if pulmonary hypertension with an irreparable cardiac defect is present. In patients with pulmonary hypertension and a repairable cardiac defect, the choice of surgical therapy is more complex and may include heart-lung transplantation (the majority of patients), bilateral lung transplantation or single lung transplantation with cardiac repair. Clinical trials comparing the outcomes of these options have not been performed\(^{67}\).

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\(^{64}\) Crossland D. Heart and heart-lung transplant. Paediatrics and Child Health 2007;17:6-10.

\(^{65}\) Ibid


\(^{67}\) Ibid
6 Activity and demand

International clinical activity

The number of centres internationally reporting paediatric lung transplant procedures to the ISHLT has risen over time. According to the most recent ISHLT data, there were 32 centres reporting paediatric transplants to the ISHLT registry in 2006 and 36 in 2007.\textsuperscript{68,69}

In 2007, centre volumes were as follows:

- 89% of centres reported performing fewer than five paediatric lung transplants per year;
- 8% (three centres) performed between five and nine transplants; and
- 3% (one centre) performed between 10 and 19 transplants.

The number of centres reporting heart-lung transplantation in children and adolescents has decreased since the 1990s. Between 2002 and 2008 the number of centres worldwide reporting heart-lung transplants each year varied between seven and 11, and all of these reported fewer than five transplants a year (Figure 2).

Figure 2: Number of centres reporting paediatric heart-lung transplants by centre volume (1984 to 2008)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Number of centres reporting paediatric heart-lung transplants by centre volume (1984 to 2008)}
\end{figure}


National clinical activity and centre volumes\textsuperscript{70 71 72 73}

In Australia and New Zealand, all lung transplantation services are based in adult institutions. All adult units (Sydney, Melbourne, Brisbane, Perth and Auckland) accept referrals of adolescent patients aged 16 to 18 years. Some adolescents aged 15 years have received lung transplants at SVHS. Smaller and/or younger patients may be referred to the AHM. The youngest patient to receive a lung transplant in Australia to date was nine years of age at the time of transplantation\textsuperscript{74 75}.

It is understood that some Australian families with younger children may have sought care overseas. Funding may be provided by an act of grace payment in such circumstances, however to our knowledge this has occurred just once in a 13 month old infant in 1997\textsuperscript{76}.

ANZCOTR contains information on all heart, heart-lung and lung transplants performed across the six Australian and New Zealand cardiothoracic transplant centres. An annual report is produced by June each year providing statistical information on numbers of adult and paediatric transplants performed, waiting list activity and survival outcomes. The registry also contributes its Australian de-identified information to the ISHLT on an annual basis. The clinical activity of all centres is described in Table 3. Internationally, 25\% of centres perform more than 30 adult and paediatric lung and heart-lung transplants each year and only 10\% transplant more than 40 transplants. The combined adult and paediatric lung and heart-lung transplant caseload of SVHS and AHM places them in a high volume category of transplant activity. In 2009, SVHS undertook 40 transplant procedures and the AHM undertook 56 transplant procedures.

Table 3: Clinical activity by surgical centre, all age groups (2001 to 2009)\textsuperscript{77}

<table>
<thead>
<tr>
<th>Centre</th>
<th>Heart-lung transplant</th>
<th>Single lung transplant</th>
<th>Bilateral lung transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVHS</td>
<td>12</td>
<td>24</td>
<td>278</td>
</tr>
<tr>
<td>AHM</td>
<td>13</td>
<td>89</td>
<td>280</td>
</tr>
<tr>
<td>Royal Perth Hospital</td>
<td>3</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Auckland</td>
<td>0</td>
<td>12</td>
<td>77</td>
</tr>
<tr>
<td>Prince Charles Brisbane</td>
<td>16</td>
<td>12</td>
<td>99</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44</strong></td>
<td><strong>151</strong></td>
<td><strong>756</strong></td>
</tr>
</tbody>
</table>

\textsuperscript{70} Morton J. Successful lung transplantation for adolescents at a hospital for adults. Medical Journal of Australia 2007; 278-82.


\textsuperscript{74} ANZCOTR Thirteenth Annual Report. 2009.


\textsuperscript{76} Robotin M Successful lung transplantation for adolescents at a hospital for adults. Medical Journal of Australia 2008; 188:430.

\textsuperscript{77} ANZCOTR Fourteenth Annual Report. 2010.
On request ANZCOTR provided activity and patient data for Australian and New Zealand hospitals. Only two centres, SVHS and AHM, operated on patients under 16 years of age and only one, AHM, transplanted a patient less than 10 years old. Table 4 summarises the data for SVHS.

**Table 4: Lung and heart lung transplant activity at SVHS in patients aged <16 years (2003-2009)**

<table>
<thead>
<tr>
<th>Year</th>
<th>No. patients</th>
<th>Operation type</th>
<th>Mean age</th>
<th>Age range</th>
<th>Place of residence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>2 BSLT(2)</td>
<td>15.5</td>
<td>15.4-15.5</td>
<td>NSW(2)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>1 BLST(1)</td>
<td>15.2</td>
<td>15.2</td>
<td>NSW(1)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>1 HLT(1)</td>
<td>15.8</td>
<td>15.8</td>
<td>NSW(1)</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>1 BLST(1)</td>
<td>15.1</td>
<td>15.1</td>
<td>NSW(1)</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5</td>
<td>-</td>
<td>15.4</td>
<td>15.1-15.8</td>
<td>NSW(5)</td>
</tr>
</tbody>
</table>

Source: ANZCOTR 2009

The data indicate that since 2004 all patients transplanted at SVHS aged less than 16 years were at least 15 years old and lived in New South Wales. Table 5 summarises the comparable data for AHM. The then Victorian Department of Human Services funded the establishment of the Victorian Paediatric Lung Transplant program at AHM, working in collaboration with the Royal Children’s Hospital Melbourne, in 2005.

**Table 5: Lung and heart lung transplant activity at AHM in patients aged <16 years (2003-2009)**

<table>
<thead>
<tr>
<th>Year</th>
<th>No. patients</th>
<th>Operation type</th>
<th>Mean age</th>
<th>Age range</th>
<th>Place of residence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>1 HLT</td>
<td>12.6</td>
<td>12.6</td>
<td>Vic(1)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>2 HLT(2)</td>
<td>11.6</td>
<td>9.5-13.7</td>
<td>Vic(2)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>2 Cutdown(2)</td>
<td>11.4</td>
<td>9.2-13.6</td>
<td>Qld(2)</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>1 Cutdown(1)</td>
<td>15.8</td>
<td>15.8</td>
<td>Qld(1)</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>4 BLST(3)</td>
<td>12.8</td>
<td>11-14</td>
<td>SA(2), WA(1), NSW(1)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10</td>
<td>-</td>
<td>12.5</td>
<td>9.2-15.8</td>
<td>Vic(3), Qld(3) SA(2), WA(1), NSW(1)</td>
</tr>
</tbody>
</table>

Source: ANZCOTR 2009, AHM 2010

The patient cohort transplanted at AHM is generally younger than at SVHS, with residents from four states other than Victoria treated there.

**Projected future demand in Australia**

Availability of paediatric lung transplantation in Australia depends upon the clinical indications, caseload and access to appropriate donor organs. As outlined above, whilst the clinical indications are well established estimation of actual demand is less precise, although it is likely to remain low with no expected change in the prevalence of precursor diseases.
Fundamentally, caseload depends upon availability of donor organs. The demand for paediatric lung and heart-lung transplantation exceeds the availability of donor organs, both within Australia and worldwide. Review of the ANZOD registry data for the period between 1998 and 2007 demonstrates that in Australia, of 605 lung retrievals and 47 heart-lung retrievals there were 28 lung donors and seven heart-lung donors younger than 14 years of age. Despite some use of ‘extended’ donor organs (e.g. from older donors), only 30% to 50% of available lungs are actually suitable for transplantation. National waiting list mortality rate data are limited, but estimates of 20% have been reported. It is anticipated that due to joint Australian and State and Territory initiatives to increase rates of organ donation, organ availability may increase and lead to increased numbers of paediatric lung and heart-lung transplants able to be performed.

AHM has developed protocols for lung retrieval from donors after cardiac death (DCD), to increase the donor pool by adding to the traditional ‘donation after brain death’ pool. DCD is being utilised to acquire adult lungs for transplantation and is planned to be extended to paediatric lung donation. Lung transplant centres can also increase organ availability by utilising extended donor lungs (e.g. where there are secretions or an abnormal chest X-ray) or LDLT where adult donor lungs are cut down to fit a paediatric patient, which increases the potential donor pool for children and adolescents. The LDLT involves transplanting one lobe from each of two adults to make a bi-lobar transplant for a child or smaller adolescent.

Each year in Australia there are approximately ten paediatric deaths from CF, nine from pulmonary vascular diseases and four from ILDs recorded in ABS mortality data in persons aged less than 18 years. Together these diagnoses represent 85% of the primary disease in paediatric transplants in Australia (Table 2). Therefore, there are approximately 28 paediatric deaths annually from diseases for which lung and heart-lung transplantation might be indicated as a treatment option.

The proposal from AHM estimates that based on adult transplantation rates, paediatric transplant rates would be in the order of four to six each year. In 2007 there were 114 adult lung and heart-lung transplants in Australia and 2620 worldwide. This represents 4.4% of the total international caseload being performed in Australia. Based on this ratio, the Australian pro rata paediatric caseload for lung and heart-lung transplantation would be expected to be three to six cases each year.

However, expert advice from transplant physicians and surgeons consulted in this assessment is that a paediatric lung and heart-lung transplantation caseload of 15 to 20 procedures a year would be indicated if suitable donor organs were available.

Therefore, it is estimated that four to eight lung and heart-lung transplants will be performed each year in Australia in paediatric patients. Based on these numbers, at the end of five years there will be 15 to 25 long-term survivors who would eventually transition to an adult transplant program for on-going follow-up. After five years the number of paediatric patients entering the program will approximate the number of patients exiting the program.

7 Clinical decision-making

Referral for assessment

Indications for lung transplantation in children have expanded and referral to a transplant centre can be considered in virtually any child with limited life expectancy because of lung disease. However, exactly when lung transplantation should be considered during the specific disease process requires detailed attention to not only the trajectory of the underlying illness but also to psychosocial factors, such as the readiness of the patient to cope emotionally with the demands of daily therapy and the likelihood of frequent procedures.\(^{82}\)

Lung transplantation is a procedure of last resort and, when performed, should ideally provide the patient an improved likelihood of survival and an improved quality of life. There are no strict guidelines regarding the appropriate time to refer patients for assessment of suitability for lung or heart-lung transplant. Early referral is preferred by most treatment centres as it allows the patient, family and treatment team to establish a therapeutic relationship, which facilitates adherence to therapeutic interventions in the long-term.\(^{83}\)

The Transplantation Society of Australia and New Zealand (TSANZ) has recently reviewed its Lung protocol for organ transplantation: eligibility and allocation criteria. The TSANZ Standing Committees have submitted a Consensus Statement on Organ Transplantation from Deceased Donors – Eligibility Criteria and Allocation Protocols, to the Australian Organ and Tissue Authority for consideration and consultation, which is still being undertaken. The protocol stipulates that within Australia and New Zealand assessment, listing and transplantation can only occur after careful evaluation by a recognised multidisciplinary Australian or New Zealand Lung Transplant Unit. In addition, recent international guidelines that were formulated with Australian input, and which Australian and New Zealand units broadly follow with local interpretations, form the basis for the evaluation process.\(^{84}\)

The best time for referral of paediatric patients for heart-lung transplantation is difficult to estimate with certainty because of the heterogeneity of patients in this group and the sometimes very long waiting times before donor organs become available. With respect to Eisenmenger syndrome, some surgical centres follow guidelines for IPAH proposed by the ISHLT, whereas other centres only refer patients with advanced symptoms consistent with the New York Heart Association (NYHA) functional class IV. For other congenital cardiac conditions, some centres recommend referral of patients with any cardiac anomaly where there is persistent NYHA class III or IV symptoms despite maximal medical therapy, low or declining 6-minute walking distance, cardiac index of less than 2 litres/minute/m\(^2\), or right arterial pressure exceeding 15mmHg.\(^{85}\)

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\(^{85}\) Date H. Lung and heart-lung transplantation. Cardiology in the Young 2009;19:45-8.
Selection criteria for listing for transplantation

Lung or heart-lung transplantation are considered in selected children with end stage or progressive lung disease or life-threatening pulmonary vascular disease for which there is no other medical or surgical therapy. Usually, this means candidates are on full medical therapy, and in spite of full medical therapy the predicted life expectancy for the child is poor (i.e. have less than 50% chance of surviving two years without transplant intervention)\textsuperscript{86,87}. Each transplant centre has slightly different selection criteria, based on their experience and local preferences.

Irrespective of underlying diagnosis, all candidates should possess\textsuperscript{88,89,90}:

- a clear diagnosis or adequately delineated trajectory of illness despite optimal medical therapy that puts the individual child at risk of dying without a lung transplant;
- adequate family support;
- adequate access to transplant services and medications after transplantation; and
- adequate evidence of willingness and ability on the part of patient and parent to adhere to the rigorous therapy, daily monitoring and re-evaluation schedule after transplant.

General selection guidelines have been published for some conditions only. For other clinical conditions there are no strict selection criteria\textsuperscript{91,92}. Condition specific guidelines include:

**Cystic fibrosis**

- baseline FEV\textsubscript{1}<30% predicted;
- hypoxia at rest (PaO\textsubscript{2}<55mmHg);
- hypercapnia (PaCO\textsubscript{2}>50mmHg);
- rapid clinical decline; or
- greater than two pulmonary exacerbations per year requiring hospital admission or home IV antibiotic therapy.

**Idiopathic pulmonary arterial hypertension**

- New York Heart Association functional class III or IV;
- unresponsive to medical management;

\textsuperscript{87} Doherty G, Aurora P. Update on paediatric lung transplantation. Paediatric Respiratory Review 2010; 11:54-61.
\textsuperscript{91} Woo M. Overview of lung transplantation. Clinical Reviews in Allergy and Immunology 2008;35:154-63.
• mean right atrial pressure >10mmHg;
• mean pulmonary arterial pressure >50mmHg; or
• cardiac index <2 l/min/m².

Alternative treatment options

Lung transplantation is only considered when both medical and surgical management have already been fully optimised and cannot significantly improve lung function. There is no randomised controlled trial or systematic review of any form of lung transplantation.

The management of severe lung disease by experienced teams, including appropriate use of newer therapies such as bi-level positive airway pressure (BiPAP), dornase alpha and azithromycin in patients with CF, may lead to a successful ‘bridge-to-transplant’. Similarly, intravenous prostacyclin, oral bosentan and sildenafil may bridge patients of all ages with severe pulmonary hypertension. These interventions are, however, ongoing, associated with risk and costly.

Contraindications to transplantation

Contraindications to lung and heart-lung transplantation include anatomical, surgical, medical and psychological factors. However, there is a high degree of variability between treatment centres regarding relative and absolute contraindications for transplantation. Those most commonly agreed upon include⁹³ ⁹⁴ ⁹⁵ ⁹⁶ ⁹⁷:

**Absolute**

• marked chest wall abnormalities (including severe scoliosis and severe tracheal abnormalities);
• active malignancy;
• sepsis;
• active tuberculosis;
• severe neuromuscular disease;
• documented, refractory non-adherence with clinical management;
• multiple organ dysfunction; or
• hepatitis C with histological liver disease.

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⁹⁴ Wells A. Special considerations in pediatric lung transplantation. Seminars in Respiratory and Critical Care Medicine 2006;27:552-60.
Relative

- pleurodesis;
- renal insufficiency;
- markedly abnormal body mass index (BMI);
- mechanical ventilation;
- scoliosis;
- poorly controlled diabetes mellitus;
- osteoporosis;
- chronic airway infection with multiply resistant organisms;
- fungal infection / colonisation; or
- hepatitis B surface antigen positive.

Talc pleurodesis is a contraindication in some surgical centres but not others. Formerly, history of pneumonectomy was also considered a strong contraindication due to altered thoracic anatomy. However recent success has been demonstrated in performing transplantation in carefully selected cases where anatomy permits lung transplant\textsuperscript{98}.

Renal insufficiency (creatinine clearance less than 50 mL /1.73 m\textsuperscript{2}), hepatic insufficiency and left ventricular dysfunction are contraindications for isolated lung transplantation\textsuperscript{99}. However, transplantation is considered if combined with transplantation of the second failing organ. Heart-lung and lung-liver transplantation are established surgical clinical treatments for combined organ failure whereas simultaneous lung-kidney transplantation is rarely performed worldwide\textsuperscript{100}.

Adult patients with high BMI are at increased risk for early death following lung transplantation. Those with low BMI are not particularly at risk, unless the patient has cachexia which is associated with increased risk of waiting list death\textsuperscript{101}. The association between BMI and mortality following lung transplantation is less defined.

Children with cancer generally have to be in remission for one to five years, depending on the cancer type, prior to being listed for lung or heart-lung transplantation\textsuperscript{102}.

Virulent antibiotic resistant bacteria such as *Mycobacterium abscessus* and *Burkholderia cenocepacia* in patients with CF is considered an absolute contraindication in the majority of transplant centres. The presence of *Burkholderia cenocepacia* in particular is associated with


\textsuperscript{100} Dishop M. Pediatric lung transplantation. Pediatric and Developmental Pathology 2008;11:85-105.


early death and poor survival rates after lung transplantation. The presence of multi-resistant
Pseudomonas aeruginosa is also an absolute contraindication in some transplant centres103 104.

Psychosocial and financial factors are generally assessed in overseas centres prior to listing for
lung transplantation105.

Child psychologists and paediatric social workers assess children and their families as a routine
component of pre-transplantation evaluation in order to determine whether families and children
are likely to be able to comply with the rigorous requirements of management post-surgery.
Uncontrolled psychiatric or behavioural disorders are a contraindication to lung transplantation
in most treatment centres106.

A history of poor compliance with medical care is a relative contraindication in most centres,
and is an important consideration for some families. In one study of heart and heart-lung
recipients, 9% of children and adolescents were not compliant with their medication regimen
and one third demonstrated non-adherence to the overall treatment regimen. This results in
increased risk of graft failure. Lung and heart-lung transplantation usually require relocation of
the child and parent to the treatment centre from the time of listing. For some families this
financial and emotional commitment is not possible107.

**Preoperative assessment**108 109 110

In order to list the patient for transplant, a thorough preoperative assessment is required. This
usually involves hospital admission for a number of days, and assessment involving a team of
transplant coordinators, surgeons, physicians, nursing staff, social workers, psychologists,
anaesthetists and intensive care staff. The diagnosis of and alternatives to transplantation are
taken into consideration, along with social and psychological factors important to the wellbeing
of the child and likelihood of long-term successful outcomes post-transplant111.

**Laboratory studies**

- full blood count and differential: to establish baseline values and screen for underlying
  immunodeficiency;

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103 Williams G. Anesthesia considerations for pediatric thoracic solid organ transplant. Anesthesiology Clinics of

104 De Soyza A. Lung transplantation and the Burkholderia cepacia complex. Journal of Heart and Lung

105 Serrano-Ikkos E. Incomplete adherence after pediatric heart and heart-lung transplantation. Journal of Heart
and Lung Transplantation 998;17:1177-83.

106 Orens J. International guidelines for the selection of lung transplant candidates. Journal of Heart and Lung

107 Orens J. General overview of lung transplantation and review of organ allocation. Proceedings of the

108 Trulock E. Lung transplantation. American Journal of Respiratory and Critical Care Medicine 1997;155:789-
818.

109 Wells A. Special considerations in pediatric lung transplantation. Seminars in Respiratory and Critical Care
Medicine 2006;27:552-60.


• prothrombin time (PT) and/or activated partial thromboplastin time (aPTT): to detect abnormalities of blood coagulation that may complicate surgery;
• blood typing and screening to match the donor and recipient;
• renal function: for baseline monitoring before immunosuppression and antimicrobials are commenced;
• liver function and blood borne virus screening: to assess for contraindications to transplantation;
• preformed reactive antibody panel: to assess the risk of development of hyperacute rejection;
• lipid profile: for baseline monitoring before immunosuppression is commenced;
• serologic tests for rubella, herpes viruses and Epstein-Barr virus (EBV), varicella, toxoplasmosis, and cytomegalovirus (CMV): to screen for previous exposure and the need for vaccination;
• sputum microscopy, culture and sensitivities: to direct the choice of antimicrobial agents after transplantation;
• autoantibodies: ongoing monitoring of patients with autoimmune disease;
• arterial blood gases: to provide a measure of lung function; and
• thyroid function: prior to commencement of immunosuppression medications.

**Imaging studies**
• chest radiography and computerised tomography (CT) scanning: to evaluate the extent of disease and to determine the size of the thorax and vessels;
• ventilation-perfusion scanning: to assist in determining the function of both lungs and, in a bilateral sequential procedure, to determine which lung should be replaced first;
• echocardiography: to evaluate cardiac function and assess for pulmonary hypertension;
• sinus CT scanning: performed in some centres to determine the need for surgical intervention in patients with CF before transplantation (because the sinuses contain organisms that may reinfect the lower respiratory tract after transplantation); and
• bone densitometry: performed in some centres to assess risk for fractures in patients with end-stage lung disease as patients often have a history of steroid use.

**Other tests**
• pulmonary function testing: to help determine the degree of impairment, timing of lung transplantation and provide baseline data for postoperative comparison;
• six-minute walk test: to help determine the timing of lung transplantation;
• tuberculin skin test: performed in patients from endemic areas of TB infection in order to rule out active tuberculosis (an absolute contraindication to lung transplantation);
• electrocardiography: to assess for right ventricular hypertrophy or other cardiac dysfunction; and
• cardiac catheterisation: if indicated, to measure degree of pulmonary hypertension or to assess benefits of vasodilator therapy.
**Diagnostic procedures**

- Bronchoscopy with bronchoalveolar lavage may be indicated to isolate pathogens from the lower airways or to document clearance of atypical mycobacteria.

**Timing of transplantation**

The goals of lung and heart-lung transplantation are to prolong life and to improve quality of life. Careful patient selection and timing of transplantation are critical to achieving these goals. Re-analysis of data published by Liou et al. (2007) highlighted the importance of timing for surgery as a factor that significantly influences the survival benefit achieved through transplantation \(^{112}\).

A thorough understanding of the course of the disease in the prospective recipient is necessary in order to time transplantation as late as possible to achieve the maximal survival benefit, whilst timing transplantation early enough to minimise the risk of dying on the waiting list \(^{113},^{114}\). Further, in order to achieve the best survival benefit, systems for allocation of donor organs and selection of appropriate patients for transplantation need to be supported by policies and protocols that enable good decision-making regarding timing of the surgery \(^{115},^{116}\).

Criteria regarding donor organ allocation vary between countries. In some countries, time accrued on the waiting list is used as the criterion for allocation. In the case of lung transplantation, the practice of early listing is a problem with this approach, as is the risk that transplantation will be performed too early in the disease course for a survival benefit to be gained, whilst others with a more urgent need for transplantation, and in whom survival benefit could be obtained, die on the waiting list \(^{117}\). In contrast, listing for heart-lung transplantation needs to be relatively early as there may be a longer wait compared with lung transplantation (up to several years) \(^{118}\).

Other countries use urgency of need as the principal criterion for transplantation. Centres in Australia and the UK prioritise sicker patients for transplantation \(^{119}\). Difficulties with this system arise due to the fluctuating clinical course many patients may follow, and difficulties empirically determining who the most urgent cases are \(^{120},^{121}\). In Australia and New Zealand the average waiting time for all 125 lung transplant patients in 2009 was 234 days, with the median time
being 125 days\textsuperscript{122}, whereas AHM advised in 2009 that the average wait for paediatric and adolescent patients was 121 days.

In the US, the United Network for Organ Sharing (UNOS) revised lung allocation scoring (LAS) system (2006) is used to determine waiting list priority for transplantation by attempting to balance urgency and outcome. This system preferentially allocates lungs from paediatric donors to paediatric patients. A lung allocation score is calculated for each patient 12 years of age and older on the waiting list while donor lungs for children aged less than 12 years of age continue to be allocated by time accrued on the waiting list. ABO blood type and distance between the donor and transplant centres are also considered in allocating donor organs\textsuperscript{123}.

**Ethical issues**

Paediatric lung and heart-lung transplantation are complex and demanding forms of treatment that require intensive and invasive ongoing surveillance and management for the life of the patient. The emotional impacts associated with paediatric lung and heart-lung transplantation are significant and commence before transplanted organs are received. Recipient candidates negotiate the medical system whilst significantly physically disabled and experience an unknown period of waiting for donor organs, the possibility they may die on the waiting list before donor organs are received and the specific emotional impacts associated with receipt of deceased donor organs\textsuperscript{124}. Transplantation places significant demands on the patient, family and caregivers of the recipient. It is therefore essential to ensure the patient and family are completely and realistically informed of the transplantation process prior to their decision, including patient selection and indications, donor criteria, surgical technique, long-term follow-up, outcomes, survival rates and living-related lobe donations, if applicable. In addition, patients and families need to gain a realistic understanding of the social and financial disruption associated with a potentially long period away from their places of residence and work.

Before paediatric lung and heart-lung transplantation were available, palliative care was the focus of therapeutic care for patients whose anticipated survival was less than two years. Concerns have been raised that placement on a waiting list for transplantation may complicate palliative care, as an expectation that life-extending therapy may become available is created but not necessarily achieved. Deaths on the waiting list are common and there is a chance that successful transplantation will not occur\textsuperscript{125}. It may be difficult for patients, families and carers to undergo a process of transition towards acceptance of death in these circumstances.

The Australian Health Ethics Committee of the National Health and Medical Research Council has published guidance documents regarding broad ethical and social issues associated with organ transplantation. These include consent issues, organ procurement, resource allocation and living donor-associated issues\textsuperscript{126}. Guidance is not specific to paediatric lung or heart-lung transplantation.

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\textsuperscript{122} ANZCOTR Fourteenth Annual Report. 2010


\textsuperscript{126} http://www.nhmrc.gov.au/publications/synopses/e70_1_4_5syn.htm
A range of ethical issues associated more broadly with transplantation have been debated in the literature. Few definitive positions have been reached on these issues. Issues include:

- distributive justice – what is fair with respect to the allocation of donor organs when demand exceeds supply?
- re-transplantation - is it fair to provide a patient with a second organ when there are patients on waiting lists that have not received their first?
- live organ donation - is it fair to risk one person’s life to possibly save another?

In addition, both the source and method of obtaining the organ to transplant are major ethical issues in the international context. “Transplantation tourism” is a documented practice that has the potential to violate human rights or exploit the poor, to have unintended health consequences, and to provide unequal access to services, all of which ultimately may cause harm. Some consider the practice a violation of basic human rights according to Articles 3 and 4 of the Universal Declaration of Human Rights.

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8 Service delivery

Preoperative management

Treatment varies depending on the primary diagnosis. The goal of therapy for patients on the transplant waiting list is to optimise their medical care in preparation for the upcoming surgery and to correct deficiencies discovered during the evaluation. This is specific to the clinical conditions for which transplantation is indicated but also includes improving the patient's nutritional status, providing pulmonary rehabilitation and trying to decrease the number of preoperative pulmonary exacerbations for which intravenous antibiotics are needed\textsuperscript{131}.

Perioperative management

\textit{Donor organs}

Lung allografts can be obtained from:

- deceased (i.e. brain dead) donors;
- non-heart beating (i.e. deceased cardiac) donors; or
- lobes obtained from live donors who are ABO compatible and who are an appropriate match for lung lobe size (LDLLT)\textsuperscript{132}.

The criteria for acceptability for lung donors have been derived from experience rather than from clinical trials. The ideal lung donor should be a non-smoker of the appropriate body size and blood type with no significant lung disease. The ischaemic time should be minimal, gas exchange should be normal and there should be no pulmonary trauma or infections. A comprehensive review of factors that influence allograft survival for lung transplantation in general was completed by the Pulmonary Council of the ISHLT\textsuperscript{133}. However, specific criteria for paediatric patients have not been established. Contraindications to lung donation include active malignancy, positive HIV status, hepatitis B or C antibodies, sepsis and significant tobacco use. Other factors leading to the unsuitability of lungs for transplantation include pulmonary contusion, fat embolism, pulmonary emboli, trauma to the lung and airways, pneumonia, aspiration, atelectasis, pulmonary oedema and systemic inflammatory response.

The donor is usually screened with a chest radiograph and $\text{PaO}_2$ whilst receiving mechanical ventilation to ensure the chest radiograph is free of infiltrates, atelectasis and pulmonary oedema and that $\text{PaO}_2$ meets specific criteria that are determined by ventilator settings\textsuperscript{134}.

Further evaluation of the donor by flexible bronchoscopy and gross examination of the lungs with the chest open are usually performed. Bronchoscopy is used to detect erythematous

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airways suggestive or gastric aspiration and purulent secretions that do not clear with suctioning. Gross examination may reveal abnormalities not detectable on chest radiograph.\textsuperscript{135}

Minimising damage from ischaemic-reperfusion injury is important. Antegrade and retrograde flush using ice-cold saline or crystalloid flush solutions, inflation using 100\% oxygen and maintenance of hypothermia are all employed to reduce the allograft metabolic demands and decrease cellular injury.\textsuperscript{136}

Marginal donors have been used with varying success in selected cases. Marginal may be defined as a donor with an infiltrate/atelectasis, lower PaO\textsubscript{2}, older age or smoking history (particularly when greater than 20 pack years). Because of the limited data available on the use of marginal donors in children no specific recommendations have been developed regarding their use in paediatric populations.\textsuperscript{137, 138}

Management of the patient

Antibiotic therapy is usually initiated empirically at the time of transplant according to the child's history of airway organisms.\textsuperscript{139}

Whether the patient also receives the first doses of immunosuppressive medications and/or induction therapy before the surgical procedure is program specific. The use of an induction agent to either eliminate T lymphocytes or inhibit T cell function is somewhat controversial primarily due to concerns regarding the increased risk of infection associated with the use of these agents.\textsuperscript{140} Approximately 45\% of paediatric lung transplant recipients receive induction therapy with either interleukin-2 receptor antagonists or cytolytics.\textsuperscript{141}

Transplant surgery

Very few paediatric single-lung transplants are performed. Most children undergo bilateral sequential lung transplantation for a number of reasons: two lungs are typically available from paediatric donors, two lungs of similar size promote symmetrical thoracic growth and patients with CF require bilateral lungs to prevent risk of infection from a diseased native lung to a single transplanted lung.\textsuperscript{142}

The surgical approach in paediatric patients depends on the type of transplant to be performed, the patient's primary diagnosis and the surgeon's experience and preference, but is generally via a bilateral anterolateral clamshell thoracotomy.\textsuperscript{143}

\begin{thebibliography}{99}
\bibitem{136} Woo M. Overview of lung transplantation. Clinical Reviews of Allergy and Immunology 2008;35:154-63.
\bibitem{142} Bishop M. Pediatric lung transplantation. Pediatric and Developmental Pathology 2008;11:85-105.
\bibitem{143} Mallory G. Pediatric lung transplantation. European Respiratory Journal 2004;24:839-45.
\end{thebibliography}
Bilateral sequential lung transplantation involves transplanting one lung while the patient is supported on their remaining lung. The patient is then supported by their new transplanted lung, allowing the transplantation of the second lung. The transplantation is performed with or without cardiopulmonary bypass (CPB), depending on the preference of the treatment centre\textsuperscript{144}. CPB allows the native lungs to be deflated, thereby facilitating their surgical removal, may reduce the donor lung ischaemia time and permits clamping and antibiotic irrigation of the tracheobronchial airway. Further, as double-lumen endobronchial tubes will not fit into younger children and many paediatric recipients are too unwell to tolerate one-lung ventilation, cardiopulmonary bypass is often necessitated\textsuperscript{145}. The disadvantages of CPB include the negative consequences of the systemic inflammatory response that it initiates and the requirement for anticoagulation\textsuperscript{146}.

The recipient’s lungs are removed and the right and left donor lungs are implanted using end-to-end bronchial, pulmonary arterial and pulmonary venous anastomoses. Peribronchial tissue is sutured loosely around the bronchial anastomoses to provide blood flow by new vessel ingrowth. The pulmonary artery and vein connections are performed. A donor atrial cuff is attached to the recipient’s left atrium, taking care to avoid suture lines near the pulmonary veins thereby reducing the risk of pulmonary vein stenosis\textsuperscript{147}.

When the new lungs have been implanted and perfusion has been re-established, chest tubes are placed (bilateral tubes if double lung transplantation). Before chest closure, flexible bronchoscopy can be performed to check the anastomoses and transoesophageal echocardiogram is obtained to confirm good venous and arterial flows. The patient remains intubated and on mechanical ventilator support while they are transported to the intensive care unit\textsuperscript{148}.

When cadaveric cut down lobar transplants are used the donor right lower lobe is resected and the right upper and middle lobes are implanted, with the anastomosis being performed at the right main bronchus. On the left side the inferior pulmonary vein, interlobar artery distal to its lingual branch and bronchus are resected, and the lower lobe removed\textsuperscript{149}.

With respect to heart-lung transplantation, the following usually occurs\textsuperscript{150}:

- the procedure is performed using cardiopulmonary bypass;
- the heart and lungs are removed with careful preservation of the phrenic nerves and bronchial artery circulation in order to prevent postoperative bleeding complications;
- the donor heart and lungs are inserted, with the tracheal anastomosis performed first;

\textsuperscript{148} Woo M. Overview of lung transplantation. Clinical Reviews of Allergy and Immunology 2008;35:154-63.
\textsuperscript{149} Keating T et al. Paediatric lobar lung transplantation: addressing the paucity of donor organs. MJA 2008;189:173-175
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- the right atrial anastomosis is performed next, followed by the aortic anastomosis; and
- care is taken to keep the donor trachea as short as possible because of the limited vascularity of the area.

**Post-operative management**

The post-operative course consists of approximately a two week hospitalisation period. Ideally, patients remain intubated and ventilated for a maximum of 24 to 48 hours after surgery. Prolonged mechanical ventilation is associated with increased morbidity and mortality. As a result, early extubation is a goal of postoperative management in most treatment centres. Avoidance of complications of hypotension, volume overload, infection and renal dysfunction facilitates early extubation.

Most patients experience post-operative pulmonary oedema due to increased pulmonary vascular permeability that results from ischaemia and reperfusion injury, and due to the interruption of the pulmonary lymphatics. As a result, the early post-operative care of the patient involves maintaining adequate blood pressure and perfusion and gas exchange whilst maintaining renal function and achieving the shortest intubation time possible. This requires close monitoring of fluid balance and careful ventilator management.

Recipients are kept intravascularly hypovolaemic during the first few days after surgery in order to minimise pulmonary oedema. This requires the use of maximally concentrated intravenous medications and the routine use of diuretics.

The immediate postoperative period is also a time when the patient receives large amounts of immunosuppression medication. There is currently no evidence that treatment using isolation is more effective than simple meticulous attention to hand-washing. However, due to the increased risk of infection, surveillance cultures and aggressive treatment of any suspected infections is usually undertaken.

When the patient is extubated and pressor medications are discontinued, transfer from intensive care can occur. Intravenous antibiotics may be continued whilst in an inpatient. Physical therapy is initiated in the intensive care unit and is increased in intensity as the patient becomes ambulatory.

In order to minimise nosocomial infection, facilitate rehabilitation and minimise use of resources many centres discharge patients from hospital to post-transplantation housing that is near the hospital. Here patients continue to attend regular sessions of physical therapy. After surgery patients also undergo surveillance bronchoscopy with transbronchial biopsy. The timing of surveillance procedures varies from centre to centre and is discussed below.

**Induction immunosuppressant therapy**

Acute rejection is a well-established risk factor for the development of bronchiolitis obliterans (BO). Induction immunosuppression may be used in an attempt to minimise the risk of this

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occurring. It has not been definitively established in clinical trials whether induction immunosuppression is effective in achieving this outcome. Further, there are risks associated with the use of induction immunosuppression because agents used for induction are potent immunosuppressants that may potentially increase the risk for infection postoperatively. As a result, the use of induction immunosuppression is not universal and varies according to treatment centre.

The 2009 ISHLT Registry report indicates that in 2008 almost 45% of the paediatric lung transplant recipients received some form of induction immunosuppression. Usage appears to have declined compared with previous years. The reasons for this are not clear.

In general, induction agents can be divided into lympholytic agents and interleukin (IL)-2 receptor antagonists. Lympholytic agents contain antibodies to human lymphocytes and are derived from animal serum. They include rabbit antithymocyte globulin (RATG [Thymoglobulin]), muromonab-CD3 (OKT3 [Orthoclone]), and equine antithymocyte globulin (lymphocyte immune globulin [ATGAM]).

These agents are typically administered for three to five days immediately after transplantation. They may also be used to treat steroid-resistant rejection, where they are typically administered for 10 to 14 days.

Patients receiving OKT-3 may experience a higher incidence of postoperative infection. RATG may be better tolerated than other agents and has been demonstrated to decrease the incidence of acute rejection in a single randomised controlled trial. No study has documented that any of these agents have a beneficial impact on the incidence of BO.

Potential adverse effects include cytokine release syndrome (i.e. chills, fever, vomiting, diarrhoea, headache), increased incidence of infection, increased risk of post-transplantation lymphoproliferative disease (PTLD), and leukopaenia. IL-2 receptor antagonists are monoclonal antibodies that specifically bind to the IL-2 receptor on activated T cells. They include basiliximab (Simulect) and daclizumab (Zenapax). Agents differ in their half-lives and in the number of doses required for immunosuppression. Trials have demonstrated IL-2 receptor antagonists reduce the frequency of acute rejection in adult lung transplant recipients.

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160 Ibid
However, a retrospective study in paediatric lung transplant recipients found no difference in acute rejection or BO compared with controls\textsuperscript{163}.

**Maintenance immunosuppression**

Maintenance immunosuppression is required in all transplant recipients. Agents used include calcineurin inhibitors, cell toxins, corticosteroids, and Rapamycin and its derivatives. Corticosteroids are the most commonly used agents in paediatric lung transplant recipients, followed by calcineurin inhibitors and cell toxins (Figure 3).

**Figure 3: Maintenance immunosuppression at time of follow-up for paediatric lung transplant recipients (2001 to 2008)**

![Graph showing maintenance immunosuppression at time of follow-up for paediatric lung transplant recipients (2001 to 2008)](image)

Reproduced from Aurora et al. 2009

**Calcineurin inhibitors**\textsuperscript{164, 165, 166}

- Cyclosporine and tacrolimus are the drugs used in this category. These agents are the mainstay of immunosuppression and are responsible for the success of transplantation. However, because of an array of potential adverse effects and drug interactions, they have limitations.

- Drug levels are monitored on a regular basis. Doses for lung transplant recipients are usually maintained at higher levels than those for other organ recipients. The serum levels require maintenance at levels high enough to prevent rejection without causing debilitating toxic effects.

- Both drugs can increase the patient's risk of infection, nephrotoxicity, neurotoxicity, GI disturbances, electrolyte derangements, malignancy, and hypertension.

- Multiple trials have compared these two agents; they are equal in prevention of BO and improvement of survival. However, the adverse effect profiles are different. Cyclosporine may cause gingival hyperplasia and hirsutism, whereas tacrolimus may cause more hyperglycemia.


Most paediatric lung transplant centres preferentially use tacrolimus-based regimens as their primary immunosuppression because it has a more manageable adverse effect profile in children and because the gingival hyperplasia and hirsutism that occur with cyclosporine negatively influence compliance, particularly in teenage patients.

Studies suggest that aerosolised cyclosporine may provide a substantial survival advantage to lung transplant recipients receiving the drug, however further studies are necessary.

**Cell toxins**

This category of immunosuppressant agents includes azathioprine (Imuran) and mycophenolate mofetil (MMF, [Cellcept]). Studies comparing azathioprine with MMF in lung transplant recipients have not shown a clear clinical benefit of one agent over the other.

Dosing is often determined by white blood cell count. In addition, MMF serum levels can be measured and dosage adjusted to maintain adequate serum levels.

Potential adverse effects for both of these agents include myelosuppression, infection, and nausea. In addition, azathioprine may cause hepatotoxicity and rash. MMF may cause diarrhea and an increased risk of lymphoproliferative disorders.

**Corticosteroids**

Corticosteroids are the most commonly used group of immunosuppressant agents.

Corticosteroids possess many potential adverse effects, including increased risk of infection, hyperglycaemia, hypertension, cataract formation, bone loss, gastrointestinal disorders, mood alteration, acne, growth suppression, and amenorrhea. At high doses, corticosteroids may cause alterations in serum levels of the calcineurin inhibitors.

**Rapamycin and its derivatives**

This family of drugs consists of sirolimus (rapamycin, [Rapamune]) and everolimus (40-0-[2-hydroxyethyl]-rapamycin [RAD]). The use of rapamycin is rarely reported during the first year post transplant, but is more common at five year follow-up with an estimated 15% of patients on this agent by five years post-transplant.

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• Because sirolimus and RAD work by different mechanisms, they can be used with cyclosporine or tacrolimus.

• One study in lung transplant recipients examined the use of sirolimus as rescue therapy; renal dysfunction was the most common indication. In these 23 adult lung transplant recipients, only two episodes of acute rejection were documented over a median follow-up period of 107 days.

• Sirolimus may have a beneficial effect in patients with chronic rejection because it inhibits proliferation of endothelial and smooth muscle cells in vitro and appears to inhibit vascular injury in vivo. RAD also inhibits smooth muscle proliferation.

• Initially, rapamycin was available only as a suspension, but a tablet form is now available. It is routinely dosed once daily, but evidence indicates that in children more desirable drug levels are maintained with a twice-daily dosing regimen.

• Potential adverse effects of sirolimus include hyperlipidemia and myelosuppression. Lipid profiles must be regularly monitored. Sirolimus has no role in the early post-operative period because it may interfere with wound healing and cause anastomotic dehiscence. Sirolimus is also associated with the development of interstitial pneumonitis.

Clinical follow-up

In some centres the first routine surveillance bronchoscopy is performed within the first week after transplantation. This may be within the first 24 hours, while the patient is still intubated. In other centres, the first bronchoscopy may be deferred, and performed within the first month after transplantation.\(^{175}\)

Protocols for surveillance transbronchial biopsy vary between treatment centres.\(^{177}\) At one large international treatment centre, transbronchial biopsy is performed at one week and one, two, three, six, nine, 12 and 18 months after transplantation. SVHS has published a transbronchial biopsy surveillance schedule of three, six and nine to 12 weeks post transplantation with additional procedures for new-onset symptoms or as a follow-up for acute rejection or CMV pneumonia.\(^{178}\) The optimal monitoring system has yet to be clearly elucidated and is an area where further study is required.\(^{179}\)

Therapeutic drug monitoring is part of the routine post-transplant monitoring has become a standard for transplant care. Many of the immunosuppressive medications have a narrow therapeutic index, and patients have variable pharmacokinetics. This appears to be particularly


relevant in preventing side effects from the agents. Patients are required to monitor their lung function, blood pressure, temperature, and weight daily and advise of any changes\(^\text{180}\).

Rejection or infection frequently results in loss of lung function. For children old enough to perform spirometry, FEV\(_1\) may be monitored on a daily basis in order to detect early changes in lung function. For younger children, home oximetry may be used on a daily basis\(^\text{181}\).

**Outcomes of treatment**

**Survival** \(^\text{182} \ 183 \ 184\)

For patients with end-stage lung and pulmonary vascular disease, transplantation can prolong life substantially. However, the survival statistics for lung and heart-lung transplantation are poor compared with other solid organ transplants including heart, kidney and liver transplants. The 50% mortality associated with heart, kidney and liver transplants occurs at approximately 10 years, compared with a lung and heart-lung 50% mortality which occurs at approximately five years (Figure 4).

Survival after paediatric lung transplantation remains similar to that reported in adults. Internationally, median survival between 1990 and 2007 for paediatric patients was 4.5 years.

**Figure 4: Paediatric versus adult survival for lung transplantation (1990 to 2007)**

Internationally, survival has improved since the commencement of paediatric lung transplantation. When analysed by time period, recipients transplanted between 2002 and 2007 experienced one- and five year survival of 83% and 50% respectively, compared with

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67% and 43% for patients transplanted in the first surgical era (between 1988 and 1994) (Figure 5). Published Australian actuarial survival rates are comparable to ISHLT rates.

**Figure 5: Paediatric lung transplantation survival by time period (1990 to 2007)**

Survival varies by age group. Children aged between one and 11 years experience better survival than those aged between 12 and 17 years, although this difference is not statistically significant.

Survival after paediatric heart-lung transplantation is predominantly influenced by the longevity of the lung allograft rather than the donor heart. As a result, survival after heart-lung transplantation is similar to that of paediatric lung transplantation\(^{185}\). The five year survival post paediatric heart-lung transplantation is currently approximately 45%. Survival has improved since the inception of heart-lung transplant surgery in the 1980s (Figure 6). Between 1982 and 1988, median survival was 1.9 years, compared with 3.8 years in the most recent surgical era (1999 to 2007). As heart-lung transplantation is now performed very infrequently, comparing survival with double lung transplantation is difficult as there needs to be some correction for reported survival between surgical eras. There are no significant differences in survival between age groups following paediatric heart-lung transplantation.

**Figure 6: Paediatric heart-lung transplantation survival by time period (1984 to 2007)**

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\(^{185}\) Dishop M. Pediatric lung transplantation. Pediatric and Developmental Pathology 2008; 11:85-105.
As described above, causes of death vary according to time since transplantation. In the first 30 days after transplant graft failure is the most common cause of death. Between 30 days and one year, infection is the leading cause of death. Between one and five years, BO is the leading cause of death (Table 6).

**Table 6: Leading causes of death after paediatric lung transplantation (1992 to 2008)**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>0 – 30 days</th>
<th>31 days – 1 year</th>
<th>&lt;1 year to 3 years</th>
<th>&lt;3 years to 5 years</th>
<th>&lt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BO</td>
<td>-</td>
<td>9%</td>
<td>39%</td>
<td>41%</td>
<td>43%</td>
</tr>
<tr>
<td>Infection</td>
<td>15%</td>
<td>35%</td>
<td>18%</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td>Graft failure</td>
<td>30%</td>
<td>19%</td>
<td>26%</td>
<td>16%</td>
<td>24%</td>
</tr>
<tr>
<td>Technical</td>
<td>15%</td>
<td>3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Lung re-transplantation is uncommon. There were 57 paediatric re-transplant procedures worldwide reported to the ISHLT between 1994 and 2008, compared with about 65 paediatric lung transplants each year. Survival after re-transplantation is poorer than for primary transplantation. The five year survival was 41% for this time period.

Studies comparing survival benefit from lung transplantation according to clinical diagnosis have demonstrated that paediatric lung transplantation confers survival benefit for all conditions for which transplant is indicated\(^{186}\). There are some data suggesting that patients who have CF or pulmonary vascular disease may experience less survival benefit than those receiving transplant for other conditions. However, this has not been definitively established, and the net effect of transplantation is to also achieve a survival benefit in these patients\(^{190}\).

Adult studies have more conclusively demonstrated survival benefit associated with lung transplantation. Adult patients with all diagnoses except Eisenmenger’s syndrome show a survival benefit from transplantation\(^{191}\)\(^{192}\).

**Quality of life**

The published literature provides a strong body of evidence that patients with lung disease severe enough to undergo listing for lung transplantation have significantly diminished quality of life. It is only recently that significant numbers of survivors of paediatric lung and heart-lung transplant have been available for systematic study of the psychological sequelae of these procedures and impacts of transplantation on quality of life are in their infancy. As a result, although a reasonable number of published studies exist regarding the relationship between lung and heart-lung transplantation and quality of life, missing data and small sample sizes limit


\(^{188}\) Aurora P. Selection of cystic fibrosis patients for lung transplantation. Current Opinions in Pulmonary Medicine 2008; 14:589-94.


the generalisability of findings\textsuperscript{193}. Further, the inability to account for deaths in the scoring of most non-utility-based quality of life questionnaires significantly limits their interpretation, and many studies have not assessed results according to the primary diagnosis leading to the requirement for transplantation, limiting the ability to draw comparisons regarding transplantation and improved quality of life between clinical diagnostic groups\textsuperscript{194,195}.

In spite of these limitations, the published literature overall demonstrates improved quality of life associated with paediatric lung and heart-lung transplantation. In addition, the functional status of long-term paediatric survivors is generally good with approximately 95\% of patients surviving more than one, three and five years experiencing no limitations of activity\textsuperscript{196,197}.

Measures of developmental, cognitive and academic function appear to be stable over time and are generally in the normal range. However, approximately one third of recipients experience behaviour problems. Further, the prevalence of depression is higher than the general paediatric population, but decreases over time\textsuperscript{198,199,200}.

After lung and heart-lung transplantation, patients frequently develop BO which is the leading cause of death long-term. Studies have shown that patients with BO have a significantly reduced quality of life compared with patients without BO\textsuperscript{201,202,203}.

**Complications of treatment**

Lung and heart-lung transplant complications can occur immediately after surgery or be delayed for several years. A high degree of clinical suspicion and close follow-up of transplant patients, including frequent monitoring, are strategies commonly employed to reduce morbidity and mortality in patients who survive the transplant surgery.

The significant complications associated with heart-lung transplantation and lung transplantation are similar, and predominantly relate to the lung allograft\textsuperscript{204}. Complications after


\textsuperscript{194} Noll R. Health-related quality of life after pediatric heart or heart-lung transplantation. Pediatric Transplantation 2005; 9:134-7.


\textsuperscript{204} Date H. Lung and heart-lung transplantation. Cardiology in the Young 2009; 19:45-8.
lung and heart-lung transplantation can be described according to three general phases as outlined in Table 7.

**Table 7: Complications following lung and heart-lung transplantation**

<table>
<thead>
<tr>
<th>Immediate (first week)</th>
<th>Early (first 3 months)</th>
<th>Late (after 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute rejection</td>
<td>Acute rejection</td>
<td>BO</td>
</tr>
<tr>
<td>Infection</td>
<td>Infection</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Surgical complications</td>
<td>Surgical complications</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Early graft dysfunction</td>
<td>Medication side-effects</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperlipidaemia</td>
</tr>
</tbody>
</table>

The risk of organ rejection begins at the time of transplant surgery and remains for the life of the graft and recipient. Lung transplant patients have a higher incidence of rejection than isolated heart, liver or kidney transplant recipients. In heart-lung transplant recipients, the rate of rejection of the lungs is higher than rejection of the heart in the same recipient\(^{205}\).

**Rejection**

Rejection is classified as hyperacute, acute or chronic. The histological grading of rejection is based upon the 2007 revision of the 1996 Lung Rejection guidelines\(^{206}\).

Hyperacute rejection is the result of recipient antibodies binding to donor tissue antigens and causing graft injury. This complication is uncommon due to preformed antibody / panel reactive antibody (PRA) and tissue specific crossmatch testing of recipients to identify patients at risk\(^ {207}\). A positive specific crossmatch suggests anti-donor circulating antibodies that could lead to hyperacute rejection of the allograft and therefore usually results in cancellation of the transplant for that proposed recipient\(^ {208}\). Avoiding transplant in patients with elevated PRAs and positive specific crossmatch and confirming appropriate ABO matching of donor and recipient have reduced the incidence of hyperacute rejection\(^ {209}\). In some cases hyperacute rejection can result in graft loss and death\(^ {210}\).

Acute rejection occurs later than hyperacute rejection and is a serious complication in the postoperative period. It is characterised by poor gas exchange across the respiratory membrane. Patients may present with nonspecific symptoms consistent with infection, including fever, dyspnoea and hypoxia, or may be asymptomatic. Deterioration in pulmonary function tests may be indicative of acute rejection and indicate the need for further investigations with bronchoscopy and lung biopsy\(^ {211}\).

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\(^{205}\) Woo M. Overview of lung transplantation. Clinical Reviews of Allergy and Immunology 2008;35:154-63.


\(^{208}\) Woo M. Overview of lung transplantation. Clinical Reviews of Allergy and Immunology 2008;35:154-63.

\(^{209}\) Ibid


On average, 1.3 episodes of acute rejection develop per patient in the first six months after transplantation\(^{212}\). However, different centres will have different rates, and overall the number of episodes is reducing with time as immunosuppression regimens become more effective. Routine bronchoscopy and transbronchial biopsy are performed three to six monthly in many treatment centres to facilitate early detection of rejection and infectious diseases pathogens. Results of surveillance bronchoscopy case series demonstrate rejection in 12% of symptomatic patients and 4% of asymptomatic patients in the first year after transplant. Rates of infections are approximately 29% in asymptomatic patients and 69% in patients with symptoms. The complication rate for the bronchoscopies themselves is approximately 3%\(^{213}\).

Treatment of acute rejection is normally with systemic corticosteroids, although occasionally other immunosuppressive agents such as Methotrexate or anti-thymocyte globulin may be employed. In the great majority of cases, acute rejection can be treated successfully although repeated episodes of rejection have long-term consequences for graft health\(^{214} \)\(^{215}\).

BO is a form of chronic rejection. It occurs in up to 70% of deceased-donor heart-lung and lung transplant recipients and accounts for over 40% of deaths that occur beyond one year after transplant\(^{216}\).

Acute rejection is the most important risk factor for developing BO. The incidence of BO in living donor lobar lung transplant recipients is lower, presumed due to shorter ischaemic times compared with deceased donor lung transplant patients and better HLA matching\(^{217}\).

The condition is treated primarily by the augmentation of immunosuppression but results are generally unsatisfactory and affected patients usually succumb to the disease. An alternative treatment is re-transplantation which is the only option for advanced BO with respiratory failure\(^{218}\).

**Surgical complications**

Bronchial dehiscence or air leak can occur soon after transplant surgery. Airway anastomotic dehiscence is usually suspected whenever there are large air leaks from the chest tubes and the patient has poor blood gases. The complication is usually present on admission to the intensive care unit, or can occur several days after surgery\(^{219}\). Facilitation of the early revascularisation of airway anastomoses by wrapping the area in a pedicle of viable tissue has greatly reduced the risk of airway dehiscence. Due to concerns regarding the association between the immunosuppressant Sirolimus and airway dehiscence, this agent is usually


avoided in the early post transplant period and also in patients who are at high risk of this complication\(^{220}\). Treatment is prompt surgical evaluation and surgical repair\(^{221}\).

Airway stenosis is more common, occurring in approximately 16% of cases. Most cases are secondary to progressive fibrosis and narrowing at the anastomotic site, but other causes are haematomas, surgical complications and infection, particularly with *Aspergillus* infection\(^{222}\). Treatment is by dilation of the stenosis. Recurrent stenosis usually requires stenting\(^{223}\).

Vascular anastomotic complications are uncommon. They present soon after surgery and usually result from surgical technical problems. Arterial stenosis, venous thrombosis or stenosis and thrombus formation at the left atrial anastomosis suture line or in the pulmonary veins are vascular anastomotic complications that occur in the lung transplant recipient in particular\(^{224}\). Embolisation of thrombi to the systemic circulation resulting in fatal cerebral ischaemia occurs in both lung and heart-lung transplant recipients postoperatively. Transoesophageal echocardiography, high resolution CT scanning and ventilation-perfusion scanning are the diagnostic modalities usually employed to evaluate vascular complications\(^{225}\). Treatment of stenosis can be performed by balloon dilation and stent placement\(^{226}\).

**Primary graft failure and graft injury**

Primary graft dysfunction is the accepted term associated with early hypoxia after lung implantation, unrelated to technical error and excluding hyperacute rejection. It typically occurs within the first few days after transplantation and is of variable severity. It is graded based on a simple clinical scale related to the degree of hypoxia. The nomenclature and criteria have been recently reviewed by a consensus group of the ISHLT\(^{227}\).

The ischaemic and reperfusion injury inherent in the process of harvesting and implanting donor lungs can lead to significant graft dysfunction. Factors linked to primary graft dysfunction include poor allograft preservation or preparation, long ischaemic times and the use of cardiopulmonary bypass. The use of high inspired oxygen concentrations and increased end-expiratory ventilator pressures is avoided due to the potential for worsening injury\(^{228}\)\(^{229}\). However, the majority of patients who develop primary graft failure do not have any risk factors for its development.

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An incidence of this complication between 13% and 35% has been reported depending on the surgical centre\(^{230}\). Clinically, early graft dysfunction presents as non-cardiogenic pulmonary oedema with decreased lung compliance, hypoxia and occasionally pulmonary hypertension in lung graft failure, and with pulmonary hypertension and cardiogenic shock despite maximal inotropic support in cardiac graft failure\(^{231}\). Treatment is usually with mechanical ventilation and careful fluid management, the use of extra-corporeal membrane oxygenation (ECMO) and/or nitric oxide\(^{232}\). If the patient fails to respond to these measures, urgent re-transplantation may be considered\(^{233}\). Mortality can be as high as 40%\(^{234}\).

**Infection**

Infection is a common complication in any immunosuppressed individual. In lung transplant patients, the transplanted organ is at special risk of infection. As a result, infection is the leading cause of mortality in the first year after transplantation and remains a significant cause of morbidity and mortality over the long term after lung transplantation\(^{235}\).

Non-immunologic factors that make the lung more susceptible to infection include the denervation of the lungs with marked blunting of the cough reflex, interference with mucociliary function with impaired airway clearance and mucus stasis, and ischaemia at anastomoses. Immunological factors include the higher dose of immunosuppression used in lung transplantation than in other solid organs\(^{236, 237}\). The underlying disease processes and complications of end stage organ disease represent additional risks for infectious complications. Candidates for lung transplantation with CF in particular are often colonised with fungi and highly resistant gram-negative bacteria. Likewise prolonged hospitalisation times before transplantation increase the risk of nosocomial infection with resistant organisms\(^{238}\).

Bacterial infections are the most commonly occurring infections associated with paediatric lung transplantation, responsible for approximately 63% of all infections. Although viral and fungal infections are less common, they are associated with the highest mortality\(^{239}\).

Viral infections can be relatively mild to life threatening. Human herpes viruses, EBV and adenovirus all cause significant morbidity and mortality. However cytomegalovirus (CMV)
remains the most commonly encountered serious viral infection in lung transplant recipients\(^\text{240}\). Paediatric patients are more likely to be CMV-negative and are at higher risk of CMV infections, especially if the donor was CMV positive. CMV is associated with a wide range of clinical manifestations, including a non-specific CMV syndrome and organ specific tissue invasive disease, particularly of the allograft. Treatment with IV ganciclovir can be administered prophylactically or pre-emptively, before the clinical manifestation of CMV infection\(^\text{241}\). Before widespread use of prophylaxis, CMV was reported to occur in 26% of thoracic organ recipients\(^\text{242}\). Other approaches for the prevention of CMV include the use of CMV seronegative or leukocyte-reduced blood products, and immunoglobulin therapy. Data from multicentre randomised controlled trials evaluating different prevention strategies are not available\(^\text{243}\).

EBV has also been associated with a wide spectrum of clinical disease in paediatric transplant patients, including asymptomatic seroconversion, nonspecific viral illness, mononucleosis, post-transplant lymphoproliferative disease (PTLD) and lymphoma\(^\text{244}\). EBV associated PTLD is a heterogeneous group of clinical syndromes associated with EBV driven lymphoproliferation ranging from benign self-limiting disease to true malignancies. PTLD is the most common post transplant malignancy in paediatric solid organ transplant patients\(^\text{245}\). The most clearly defined risk factor for PTLD is primary EBV infection, often associated with an EBV seropositive donor and seronegative recipient. Reduction of immunosuppression is the most common initial strategy for management of EBV disease, but increases the likelihood of BO\(^\text{246}\). Antiviral agents, intravenous immunoglobulin, monoclonal antibodies, interferon and chemotherapy have also been used however the appropriate indications for their use are debated, and there are no comparative studies of outcomes with various treatments\(^\text{247}\).

Prophylactic antimicrobials against bacteria, viruses and fungi are widely used in most transplant programs, but regimens vary widely between centres. The protocols for various institutions are usually based on the preoperative infectious diseases profile of the recipient, the results of perioperative donor cultures, and cover for common hospital pathogens. Preventive measures are also employed, including immunisation for vaccine-preventable diseases and rigorous infection control practices. Prophylaxis for opportunistic infections, including


**Pneumocystis carinii** and candidiasis, usually commences within the first two weeks of transplantation\(^{248}\).

Fungal or mould infections are less frequent than bacterial and viral infections. However, they carry the highest mortality risk of all infections. The most common fungal infections are *Aspergillus* and *Candida* species. *Coccidiomycosis, Histoplasmosis, Scedosporium* also occur\(^{249}\). Airway colonisation and isolated tracheobronchitis respond to antifungal therapy and surgical debridement in most cases. Survival is decreased in those with disseminated disease\(^{250}\).

**Malignancy**

The overall incidence of malignancy is 6.5% at one year and 8% at five years\(^{251}\). Most malignancies are PTLD which has a range of morphology, classified by the World Health Organisation classification system. Involvement may be intra-thoracic and/or extrathoracic. PTLD is more common in paediatric transplant recipients than it is in adult recipients\(^{252}\).

**Other complications**

In addition to these major complications, a number of other complications occur with lung and heart-lung transplantation, including:

- gastro-oesophageal dysmotility: which is likely to be related to vagus nerve injury. Aspiration of gastric acid has been implicated in deterioration of allograft function and the development of BO. Recipients with CF are also at risk for developing distal intestinal obstruction syndrome\(^{253}\);

- arrhythmias: atrial fibrillation and/or flutter occurs more commonly in lung transplant recipients, the cause of which are likely to be the left atrial suture lines acting as a nidus for post-transplant arrhythmias\(^{254}\);

- renal failure: resulting from haemodynamic compromise, and due to side-effects of commonly used post-transplant medications\(^{255}\);

- impaired growth: paediatric lung and heart-lung transplant recipients do not achieve normal somatic growth. Rate of growth is approximately 64% of predicted values\(^{256}\).

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248 Ibid


neurological complications: are reported to be as high as 47%. Nerve injury of both the phrenic and vagus nerves is commonly associated with surgery. Seizures are common and are associated with immunosuppression medications. Calcineurin phosphatase inhibitors in particular are a cause of cerebral vasoconstriction, with resulting neurological complications; and

diabetes: noted in 20% of patients at one year and 28% of patients at five years, diabetes is associated with the use of immunosuppression medications, including steroids and tacrolimus.


9 Volume-quality associations

Large volume surgical units are desirable for improving surgical outcomes for complex surgical procedures\textsuperscript{259}. Lung and heart-lung transplantation are complex procedures with a high risk of mortality, requiring experienced providers and specialised ancillary staff.

However, large volume lung transplantation centres are uncommon, largely due to the limited availability of donor organs. Internationally, of the 153 centres reporting adult lung transplantation to the ISHLT, 46\% averaged fewer than 10 lung transplants a year. A total of 49\% of adult procedures were performed at 27 centres with an average activity of more than 30 transplants each year, and 21\% of procedures worldwide were performed at the seven centres, with an average activity of 50 or more transplants each year\textsuperscript{260}. In 2009 SVHS performed 40 transplants and AHM performed 56 lung and heart-lung transplants.

Data demonstrate that for adult lung transplantation, mortality at 30 days, one year and five years post-transplant are significantly associated with centre volume (Figure 7). High-volume adult lung transplant centres (performing 20 or more lung transplants per year) have the lowest 30-day mortality (4\% compared with 10\% for centres performing two or less lung transplants a year)\textsuperscript{261}. Mortality at one year post transplant also decreases as surgical centre volume increases.

*Figure 7: Association between transplant centre volume and relative risk of death within one year of adult transplantation (1995 to 2007)*


Low transplant centre volume is also associated with increased five-year mortality in adults who survive one year, indicating the importance of transplant centre experience on factors that affect mortality beyond the surgical procedure itself\(^{262}\).

In the US, adult lung transplant centre funding is linked to surgical volume. Medicaid funding is available to centres performing greater than 10 procedures a year\(^{263}\).

Paediatric lung transplant surgical centre volumes are smaller. Of the 36 centres reporting transplants in 2007, only one reported greater than 10 transplants per year, three reported five to nine a year and the remaining 32 reported fewer than five per year. There is a significant relationship between centre volume of fewer than five paediatric lung transplants per year and increased mortality at one year after transplant. At five years after transplant the effect of centre volume on mortality is not statistically significant\(^{264}\). The analysis is complicated by the fact that the three largest paediatric programs internationally (St Louis Children's Hospital in St Louis, Missouri; Texas Children's Hospital in Houston, Texas and the Great Ormond Street Hospital for Children in London) are all stand-alone paediatric facilities, whilst the majority of smaller programs are closely linked to adult transplant programs. It is understood that the St Louis and Houston centres have close informal links with adult transplant services but minimal links to cardiac services. The Great Ormond Street Hospital model is unusual in that the linkage is with paediatric cardiac transplantation.

Current patient survival post lung transplant for Australian and New Zealand surgical centres as a whole is comparable to the total ISHLT 1-year mortality in paediatric age groups (Table 8).

Table 8: Current patient survival one year post-lung transplant

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Australia &amp; New Zealand</th>
<th>Entire ISHLT registry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number alive</td>
<td>1 year survival rate (%)</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>1-5 years</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>6-10 years</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>11-17 years</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td>18-34 years</td>
<td>71</td>
<td>94.3</td>
</tr>
<tr>
<td>35-49 years</td>
<td>69</td>
<td>89.1</td>
</tr>
<tr>
<td>50-64 years</td>
<td>174</td>
<td>80.4</td>
</tr>
<tr>
<td>65+ years</td>
<td>17</td>
<td>67.3</td>
</tr>
</tbody>
</table>

Source: ISHLT 2010, Quarterly Reports, accessed 20 January 2010

Similar to paediatric surgical centres, the number of heart-lung transplant procedures performed in adults is small. Over 50% of surgical centres that report adult heart-lung transplants to the ISHLT registry perform one procedure per year. Only one international centre performs more than 10 heart-lung transplants a year. Analyses of the impact of centre volume on mortality

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\(^{263}\) Ibid

have not been undertaken for heart-lung transplantation in either adults or children as numbers of procedures are too small for statistically meaningful comparisons\textsuperscript{265}. 

10 Compliance with criteria for inclusion in the NFC Program

Paediatric lung and heart-lung transplantation fulfil the requirements for inclusion in the NFC Program because:

- The surgical management of end-stage paediatric lung disease by lung and heart-lung transplantation is an established clinical practice which is available world-wide. It requires a national population base and service concentration given small numbers of donor organs available to patients requiring transplantation and the influence of institutional surgical caseload on surgical outcomes.

- The current annual caseload in Australia is less than five procedures. This caseload may increase over time with national efforts to improve organ donation rates and the use of DCD, marginal donors and LDLLT.

- Paediatric lung and heart-lung transplantation are high cost procedures, with an estimated total cost of $190,907 for each type of transplantation.

The consultants consider that designating paediatric lung and heart-lung transplantation is appropriate and consistent with the NFC Program objectives because it will enable improved equity of access, through:

- implementation of nationally-agreed guidelines and protocols for referral to and acceptance by the service;

- appropriate resource provision for services; and

- a national framework for monitoring and evaluating the service as it continues to develop.

Recommendation 1

That paediatric lung and heart-lung transplantation meet the relevant criteria for inclusion in the NFC Program.
11 Paediatric lung and heart-lung transplantation in Australia

Key service system relationships

It is proposed that paediatric lung and heart-lung transplants performed should be included in the NFC Program to provide care to Australian children aged six to 15 years with end stage lung and pulmonary vascular disease. In general, lung transplantation should be considered in selected children with end-stage or progressive lung disease or life-threatening pulmonary vascular disease for which there is no other medical therapy.

As identified in Tables 4 and 5, in Australia and New Zealand in the period 2003 to 2009 there were 11 lung and four heart-lung transplants in Australia and New Zealand in patients aged less than 16 years. Table 9 lists the location of the transplant centre and the residence of the transplant recipient.

Table 9: Jurisdiction of residence of lung transplant recipients (<16 years) by transplant facility 2003-2009

<table>
<thead>
<tr>
<th>Jurisdiction of residence of recipient</th>
<th>NSW</th>
<th>Vic</th>
<th>QLD</th>
<th>WA</th>
<th>SA</th>
<th>Tas</th>
<th>NT</th>
<th>ACT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHM</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>SVHS</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>

Source: ANZCOTR 2009, AHM 2010

Indicative of the figures in Table 9, clinicians surveyed from all States and Territories other than NSW reported that they currently refer paediatric patients who require lung or heart-lung transplantation to AHM. NSW respondents reported that they generally refer patients to SVHS, however one resident of NSW was transplanted at AHM in 2009.

Queensland and Western Australia are jurisdictions with local capability to undertake lung and heart-lung transplantation in patients aged 16 years and above. Queensland and Western Australia respondents reported that low bodyweight paediatric patients from both jurisdictions are currently referred to Victoria for transplantation. In Queensland, only patients with a body weight in excess of 40 kg receive transplantation locally. All others are referred to Victoria for transplantation. Similarly, in Western Australia younger paediatric patients are currently referred to AHM and older patients to the Royal Perth Hospital. No respondent reported referring a patient to an international centre for transplantation.
The overall mortality outcomes for 11 patients operated on between 2003 and 2008 are presented in Table 10.

**Table 10: Clinical outcomes for lung transplant recipients (<16 years) 2003-2008**

<table>
<thead>
<tr>
<th>Number of deceased patients</th>
<th>1 out of 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative days to death</td>
<td>483 days</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Bronchiolitis obliterans</td>
</tr>
</tbody>
</table>

Source: ANZCOTR 2009

Given the likely caseload in Australia, key considerations with respect to paediatric lung transplantation, if the technology fulfils the criteria for an NFC program, are:

- should there be one centre or more than one centre?
- should paediatric lung transplants be performed at a paediatric hospital?

These issues were canvassed in the consultation with clinicians nominated by the jurisdictions and with patients, families and support groups.

**Number of sites**

The current annual caseload for paediatric lung and heart-lung transplantation in Australia is less than five procedures annually, but this caseload may increase over time, with national efforts to improve organ donation rates and the use of DCD, marginal donors and LDLLT.

The majority of clinician respondents expressed the view that a single dedicated paediatric lung transplant unit that is staffed by clinicians (including paediatric specialists) with experience and expertise in lung and heart-lung transplantation is appropriate for Australia. It was asserted that a single centre would ensure sufficient service concentration for acquisition of sufficient skills and expertise given relatively small caseloads. Respondents from jurisdictions who have local transplant capability also expressed support for a single paediatric treatment centre for transplantation in paediatric patients aged six to 15 years.

Some jurisdictions, including those with local transplant capability, suggested that staff from a single dedicated unit could provide outreach services for paediatric transplantation assessment in the referring jurisdiction.

A number of respondents stated that current access to paediatric lung and heart-lung transplantation in Australia is inequitable, with paediatric patients from jurisdictions that do not have a local transplant service being perceived to be at a disadvantage compared with those from states with transplantation services. An NFC would be required to ensure that families from outside its jurisdiction receive the support necessary to enable access to treatment. The objective would be to improve overall equity of access by offering a significantly higher level of support to families who need to travel to access services and to the clinicians who are required to care for those families in their home states.

There was support from families for concentration of services to enhance expertise. Families from locations other than Melbourne and Sydney expressed the view that, as relocation was required in order to access treatment, it did not matter to which city they relocated. However, if possible families would prefer care to be provided by local clinicians whilst the patient was waiting and post-transplant.
If two centres are selected for paediatric lung and heart-lung transplantation in Australia, it is likely that neither would have enough caseload to function effectively. There is a small possibility of a single national transplant service being suspended altogether in the case of an infectious outbreak or a staffing crisis resulting in bed closures in the chosen institution. These risks will need to be managed.

**Recommendation 2**

That the current and expected caseload indicates there should be one NFC site for paediatric lung and heart-lung transplantation, with a target population of children and adolescents aged 6-15 years and weighing 20-40 kilograms but with the opportunity to manage older adolescents who are smaller or of low weight or who have complex paediatric issues.

**Paediatric hospital or adult centre**

Two options for locating a paediatric lung and heart-lung transplant service could be considered:

- in a stand-alone paediatric centre, integrated with a paediatric cardiac transplant service (i.e. the Great Ormond Street Children's Hospital model); or
- in an adult centre, integrated with an adult lung transplant service.

As a general principle, children's acute hospital services should be located in a children's hospital, which should be physically as close as possible to an acute general hospital. In the case of existing free-standing children's hospitals, particular attention must be given to ensuring that, through good management and organisation of care, children have access when needed to (a) facilities which may not routinely be found in a children's hospital and (b) specialists, the appointment of whom in a children's hospital could not be justified given the infrequent call on their services.

The majority of clinician respondents felt it is generally preferable for transplantation services to be provided to paediatric patients in a paediatric facility rather than an adult facility. However, it was also acknowledged that the primary consideration for decisions regarding where services are located (paediatric versus adult facilities) should be the safety of the transplantation services and the competence and experience of the unit in management prior to, during and after transplantation. It was therefore acknowledged by respondents that this may mean an adult facility is a more appropriate choice for location of paediatric lung and heart-lung transplantation services. The example of the RCHM's unsuccessful attempts to establish a paediatric lung and heart-lung transplantation service because of low patient numbers and problems maintaining skills was cited by a number of respondents as evidence that paediatric case volumes in Australia are insufficient to sustain a paediatric program within a paediatric facility.

However, a range of limitations were also identified in the provision of paediatric transplantation in an adult facility. Concerns that were raised included:

- limited input of paediatricians in current service arrangements;
- a lack of specialised paediatric medical care provided to patients;

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a lack of specialist paediatric nursing expertise;

inexperience of current treatment centres in the psychological and social management of adolescent patients with life-threatening chronic illnesses;

a lack of child / family-focussed holistic care; and

doctor the potential for an inappropriate single organ focus of care rather than provision of holistic care to the patient, noting that in this case, however, adult lung transplant units have a significant CF patient caseload and experience.

Insufficient access to age-appropriate counselling and support was viewed as a significant problem due to the potential for resulting poor compliance with medical care, and ultimately rejection of the donor organs. It was suggested that most patients who receive lung and heart-lung transplantation are long-term frequent users of the health care system who have established multidisciplinary care arrangements. Counselling and support from existing providers was viewed as the most appropriate strategy for the majority of patients. Systems to ensure access to this counselling and support need to be established and will require better integration of transplant services with local pre-existing paediatric care.

In some cases, clinicians reported their patients were not considered for transplantation unless they were transferred to the care of adult specialists while on the waiting list and also managed post-transplant by adult specialists, which was viewed as inappropriate for paediatric patients.

Families and support organisations were divided in their preferences for receiving treatment in adult versus paediatric facilities.

A number of respondents preferred the adult facility to a paediatric facility. The main reasons cited were:

- staff (nursing staff in particular) treated the patient with more respect and not 'like a child';
- the treating team were experienced and engendered confidence in patients and families;
- the presence of adults who had also received lung transplants gave the patient someone to talk to who was experiencing the same treatment; and
- it was quieter and less disruptive than a paediatric facility which aided recovery.

Disadvantages associated with provision of care in an adult facility included:

- equipment was not always appropriate for paediatric patients e.g. during physiotherapy, exercise bikes were ‘too big’ for patients to use (two families reported that the physiotherapist had purchased a ‘Wii’ game system to assist in delivering physiotherapy that was age- and size-appropriate) and at times invasive equipment had to be sought from a paediatric facility which created time delays in accessing some procedures (including interventional radiology during follow-up);
- access to schooling was insufficient. Families reported access to a tutor in some cases, but late in the patient’s hospital stay, and not of the same standard of education that they were used to through their paediatric hospital;
- most patients reported difficulty accessing counsellors or support people who were comfortable talking to paediatric patients (although the occupational therapist at AHM was viewed favourably by a number of families for her ability to engage with patients in an age-appropriate way);
in some cases the child was placed on an age-inappropriate diet. For some patients (particularly teenage boys) there was not enough food provided, while for others the types of foods were ‘adult’ and there was not the same degree of choice that they were used to in a paediatric hospital;

- patients didn’t have any age-appropriate entertainment (frequent references were made to their paediatric hospital home where access to ‘entertainment stations’, books, games, television, videos and other age-appropriate entertainment was provided); and

- some families reported that doctors in particular did not know how to talk to their child – some spoke ‘down’ to their child whilst others treated their child like an adult, which some families did not feel was appropriate.

Families and patients reported that visiting teams, or teams on staff, who were paediatrically trained would reduce some of the disadvantages of care provided in an adult facility. Visits from play therapists, music therapists, and provision of age-appropriate entertainment were also proposed as ways to improve the hospital experience for paediatric patients.

The advantages of a service located in a children's hospital and integrated with a cardiac transplant service would be that much of the specialist surgical, medical, intensive care and nursing requirements are common to both specialties, effectively allowing the unit the advantages of a higher caseload. The main risk of such integration is that there are minor but important differences in the medical management of cardiac and lung transplant recipients in the early postoperative period, and major differences in late management. Staffing structure, training and local management protocols would need to be adjusted for this.

A further advantage of a children's hospital location is the potential, in the future, for transplantation services to be offered to children below six years of age. Transplantation is indicated in a small number of children in this age group and centres that are experienced in transplanting very young children report results that are at least the equal of those obtained in older children. The main barriers to performing transplantation in infants and pre-school aged children are:

- the availability of very young donors;

- specialised surgical skills (i.e. paediatric cardiothoracic surgeons);

- equipment and skills for monitoring very young recipients (e.g. lung function and bronchoscopy).

Including children aged less than six years in any proposed service would have major implications and would almost certainly mandate that the service is located on a paediatric site. It needs to be borne in mind, however, that as the service consolidates, there will inevitably be inquiries from paediatricians and parents regarding possible transplantation of very young children, particularly if the centre is successful in transplanting children aged six years and above. This factor needs to be considered when the centre is established.
Recommendation 3
That the paediatric lung and heart-lung transplantation service could be:

- integrated with an adult lung transplantation service in an adult centre, with attention to the special infrastructure and service needs of paediatric patients; or
- integrated with a paediatric cardiac transplantation service in a paediatric centre;

noting, however, that:

- the most common configuration nationally and internationally is integration with an adult lung transplantation service:
- previous Australian experience with a service based in a children's hospital was not successful; and
- international experience of integrating paediatric lung and heart-lung transplantation services with paediatric cardiac transplantation services is limited.
12 Model of care

History of programs

With the voluntary cessation in 2001 of paediatric lung transplantation by the RCHM there was no program in the Asia-Pacific region offering specialist paediatric lung or heart-lung transplantation services. The resulting gap in services was filled by two adult programs: AHM, which offered a service on a case by case basis, and SVHS, which offered lung and heart-lung transplantation to adolescents. Both services had high level lung transplant expertise, but neither of these institutions had in-house paediatric services and this temporary arrangement did not lead to comprehensive servicing of the needs of children with severe lung and pulmonary vascular disease.

In 2005, the (then) Victorian Department of Human Services announced the establishment of a Paediatric Lung Transplant Program, which was to operate within the framework of the established adult lung transplant program at AHM, but involving close collaboration with RCHM. This model was adopted to best address the issue of ensuring access to both the requisite transplant experience and competence and high level paediatric competencies.

SVHS and CHW are currently developing a joint model for paediatric lung and heart-lung transplantation. This model is configured to enable patients to receive specialist paediatric support services (including social work, psychology, physiotherapy and dietetics) from the CHW.

Outline of model of care

Major elements of the model of care

Provision of transplantation services requires a number of discrete stages of referral, assessment, maintenance, management and ongoing follow-up. The stages in the model of care are outlined in Figure 8 and described below.

**Figure 8: Model of care**

<table>
<thead>
<tr>
<th>Initial referral to Paediatric Lung Transplant Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
</tr>
<tr>
<td>Referral and initial consultation for lung or heart-lung transplantation</td>
</tr>
<tr>
<td>(may be performed as outpatient or inpatient depending on severity of illness)</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>Formal transplant assessment</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>On-going care whilst on waiting list</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>Lung transplant and post-transplant care</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>Initial patient follow-up post transplant</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>Long term follow-up (treating unit or another adult lung transplant unit in state of residence)</td>
</tr>
</tbody>
</table>
Referral and initial consultation

A comprehensive patient assessment is required at initial consultation to establish the suitability of the patient for transplantation. The primary objectives of initial consultation are:

- to determine whether a transplant is indicated for the patient;
- to determine whether the severity of the patient’s illness is likely to confer survival benefit to the patient;
- to recommend scheduling for the extensive baseline clinical assessment that is required in preparation for transplantation if indicated; and
- to provide counselling to patients and their families regarding transplantation.

The TSANZ Standing Committees have submitted a Consensus Statement on Organ Transplantation from Deceased Donors – Eligibility Criteria and Allocation Protocols, to the Australian Organ and Tissue Authority for consideration and consultation, which is still being undertaken. The protocol stipulates that within Australia and New Zealand assessment, listing and transplantation can only occur after careful evaluation by a recognised multidisciplinary Australian or New Zealand Lung Transplant Unit. These criteria form the basis for assessment processes in both the AHM / RCHM and SVHS / CHW models of care (Attachment 1).

In order to ensure the specialist needs of paediatric patients are considered, paediatric input into transplantation assessment processes is required. However, as few paediatric transplants are performed each year, technical expertise in transplantation rests with adult specialists, who must also be involved in patient assessment. In both the AHM / RCHM and SVHS / CHW models, adult and paediatric specialists perform joint assessment of the suitability of children with end-stage lung and pulmonary vascular disease for lung or heart-lung transplantation.

In the AHM / RCHM model, all transplants are undertaken at the AHM. In the SVHS / CHW model, decisions regarding whether the patient will receive their operation at SVHS or CHW will be made on a case-by-case basis, depending on the maturity and age of the child, on family and child preferences, and according to where the most suitable clinical services are available to meet the individual needs of the patient. For smaller children, this is likely to be CHW and for larger children it may be CHW or SVHS.

Both AHM and SVHS report receiving referrals from other jurisdictions for assessment of patients. Time series data presented above regarding transplants performed at both centres demonstrate transplantation of residents of Victoria, Queensland, Western Australia, South Australia and New South Wales between 2003 and 2009 at AHM and transplantation of residents of New South Wales at SVHS in the same time period.

Internationally, children of all ages and body weights are able to receive lung and heart-lung transplantation. However, the majority of recipients are in adolescent age groups. This corresponds to a body weight of above 25 kg in most cases. Transplantation in very young children is rare as there are few indications for transplantation in younger children and suitable donors are scarce.

The AHM model of care for paediatric lung and heart-lung transplantation provides transplantation to patients who weigh between 20 and 40 kgs. This typically represents an age of between six and 15 years, depending on the clinical diagnosis of the patient. Patients who weigh less than 20 kgs or are less than six years old and who are suitable for transplant would currently need to be referred overseas for treatment, although as previously noted this has occurred just once in 1997 for an Australian resident.
Health technology assessment of proposal to establish paediatric lung and paediatric heart-lung transplantation procedures as a Nationally Funded Centre

The SVHS transplant service has historically provided lung and heart-lung transplantations to patients whose body weight is in excess of 25 kg. The new model of care proposed by SVHS / CHW proposes no minimum body weight for candidates for transplantation. Rather, clinicians will make decisions regarding suitability for transplantation on a case-by-case basis, and influenced by the availability of donor organs. However, it is the intention of clinicians to refer neonates and younger children where local transplantation may be inappropriate overseas for treatment should transplantation be required.

Older adolescent patients are usually suitable for listing with an adult transplant program. These are currently available in Sydney, Melbourne, Brisbane, Perth and Auckland.

The clinical activity at AHM since the establishment of the new collaborative program between AHM and RCHM is summarised in Table 11. Clinical activity data for the SVHS / CHW program are unavailable as the program is currently under development.

Table 11: AHM paediatric lung transplant activity patients aged 8-15 years, weight 22-50 kgs.

<table>
<thead>
<tr>
<th>Year</th>
<th>Referrals</th>
<th>Assessment</th>
<th>Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2007</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2008</td>
<td>11</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>2009 (to November)</td>
<td>9</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31</strong></td>
<td><strong>17</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

Source: ANZCOTR 2009; AHM 2010

Transplant assessment

In order to list the patient for transplant, a thorough preoperative assessment is required. This usually involves admission to hospital for a number of days, and assessment involving the team providing care, including the transplant coordinators, surgeons, physicians, nursing staff, social workers, psychologists, anaesthetists and intensive care staff. Transplant assessment allows the transplant team to gain a complete picture of a child’s medical needs and allows the team to address the following issues:

- Are there any other treatment options apart from transplantation?
- If not, is a lung transplant possible?
- If so, what type of transplant is needed?
- What are the patient’s care requirements whilst on the transplant waiting list?

Assessment incorporates the following investigations in both the AHM / RCHM and SVHS / CHW models of care:

Laboratory studies

- full blood count and differential;
- PT and/or aPTT;
- blood typing and screening;
- renal and liver function and blood borne virus screening;
- preformed reactive antibody panel;
- lipid profile;
Health technology assessment of proposal to establish paediatric lung and paediatric heart-lung transplantation procedures as a Nationally Funded Centre

- serologic tests for rubella, herpes viruses and Epstein-Barr virus (EBV), varicella, toxoplasmosis, and cytomegalovirus (CMV);
- sputum microscopy, culture and sensitivities;
- autoantibodies;
- arterial blood gases; and
- thyroid function.

**Imaging studies**
- chest radiography, CT, and/or MRI;
- ventilation-perfusion scanning;
- echocardiography;
- sinus CT scanning may be indicated, particularly in patients with CF; and
- bone densitometry may be performed in patients with long-term steroid use.

**Other tests**
- pulmonary function testing;
- six-minute walk test;
- tuberculin skin test may be indicated;
- electrocardiography; and
- cardiac catheterisation if indicated.

**Diagnostic procedures**
- bronchoscopy with bronchoalveolar lavage may be indicated.

In both models of care, patients and families are provided with an opportunity to meet with transplant team members and receive information and advice, including:
- risks and benefits of transplantation;
- the operation itself;
- medication regimen post-transplant;
- long term outlook and survival; and
- psychological and social issues and the commitment required of the patient and family.

The AHM / RCHM model of care for transplant assessment incorporates a ‘second opinion’ review by a paediatric respiratory physician to confirm the requirement for transplantation.

Two acceptance criteria that are considered near-obligatory in the leading international paediatric centres are:
- the child is already on full medical therapy; and
- despite the full medical therapy, the predicted life expectancy of the child is poor (usually quoted as two years or less).

In this situation it is very likely that listing the child form transplantation will result on average in extension of life, rather than a reduction in lifespan.
There is some scope for listing children earlier in the course of their disease than this, provided that their quality of life is extremely poor and a quality of life benefit from transplantation is therefore considered to justify the risk of the procedure. Although these specific indications for transplantation are not listed in current consensus documents, we have been advised that European paediatric centres apply these listing criteria at present.

The AHM / RCHM model of care also incorporates review and evaluation of patients recently listed for transplant at a weekly transplant meeting. The meeting includes the lung transplant team and surgeons, intensive care unit staff, anaesthetists and members of the allied health transplant staff. The referring doctor or one of the paediatricians from the paediatric hospital are also invited to attend this meeting. Results of the patient assessment are discussed and a group decision about transplantation is made. The patient, family and the referring doctor are then informed of the decision after the meeting.

**Care on waiting list**

Waiting time for transplantation varies between centres nationally and internationally, and between individual patients placed on the waiting list. This is due to a range of factors, but is predominantly influenced by the amount of time before suitable donor organs become available. Indicative waiting times for paediatric lung transplantation of approximately 120 days have been cited\(^{267}\).

Donor organs may be offered from any hospital in Australia and New Zealand, and typically decisions regarding suitable transplant recipients have to be made within hours of a donor offer. Due to time constraints, patients awaiting transplantation need to be within four hours travelling time from the proposed NFC site. Therefore, patients and their families may need to relocate to the transplantation treatment centre whilst on the waiting list. These patients generate additional pre-transplant costs compared with patients who reside in the city where transplant services are located.

If the child and family do not need to relocate the patient’s usual paediatric team may provide routine care whilst on the waiting list. Alternatively, if the recipient lives in a city with an adult transplant unit, this unit may provide care whilst on the waiting list, with transfer of the patient to the centre performing the surgery occurring when donor organs become available.

Children on the waiting list also usually require regular review (approximately every 6-12 weeks) by the paediatric lung transplant team who will be performing their surgery. These visits also provide an opportunity for education and counselling to be provided to the patient and their family, and for the patient and family to become acquainted with the relevant Transplant Recipient Coordinator. These visits are incorporated into the models of care at both AHM / RCHM and SVHS / CHW. An alternative model is for the child to remain under the care of their local medical team with the transplant centre providing telephone and written guidance as appropriate.

Once the child is listed for transplantation, efforts to optimise the patient’s nutrition and growth are undertaken. The goal of therapy for patients on the transplant waiting list is to optimise their medical care in preparation for the upcoming surgery and to correct deficiencies discovered during the evaluation. This is specific to the clinical conditions for which transplantation is indicated but also includes improving the patient's nutritional status, providing pulmonary rehabilitation, and trying to decrease the number of preoperative pulmonary exacerbations for

\(^{267}\) AHM NFC submission document and SVHSs consultation (November 2009).
which intravenous antibiotics are needed. This may involve enteral feeding and/or the use of appetite stimulants. Where the child is at risk of osteoporosis due to steroid intake and poor nutritional status, bisphosphonate therapy may be commenced. A regular physical rehabilitation program is usually also commenced to improve postoperative functional return.

Both the AHM / RCHM and SVHS / CHW models of care incorporate therapeutic goals for these aspects of rehabilitation and health maintenance.

**Lung transplant operation and post-transplant care**

Specific donor criteria for paediatric patients have not been established internationally. However, the ideal lung donor is a non-smoker of the appropriate body size and blood type with no significant lung disease. The ischaemic time of the donor organs should be minimal, gas exchange should be normal and there should be no pulmonary trauma or infections. Contraindications to lung donation include active malignancy, positive HIV status, hepatitis B or C antibodies, sepsis and significant tobacco use.

Further factors leading to the unsuitability of lungs for transplantation include:

- pulmonary contusion – transplant centres defer transplanting lungs if significant contusions are present;
- fat embolism;
- pulmonary emboli;
- trauma to the lung and airways – early flexible bronchoscopy of the donor may be required to assist in detection and decisions regarding whether repair is a viable option;
- severe infectious pneumonia;
- significant pulmonary aspiration;
- extensive atelectasis;
- significant pulmonary oedema; and
- significant systemic inflammatory response.

The donor is usually screened with a chest radiograph and PaO\(_2\) whilst receiving mechanical ventilation to ensure the chest radiograph is free of infiltrates, atelectasis and pulmonary oedema, and that PaO\(_2\) should meet specific criteria that are determined by ventilator settings. Further evaluation of the donor by flexible bronchoscopy and gross examination of the lungs with the chest open are usually performed. Gross examination may reveal abnormalities not detectable on chest radiograph.

Marginal donors have been used with varying success in selected cases. Marginal may be defined as a donor with an infiltrate / atelectasis, lower PaO\(_2\), older age or smoking history (particularly when greater than 20 pack years). Because of the limited data available on the

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use of marginal donors in children no specific recommendations have been developed regarding their use in paediatric populations.\textsuperscript{270, 271}

\textit{Medical management}

Antibiotic therapy is usually initiated empirically at the time of transplant according to the child's history of airway organisms. The patient may also receive the first doses of immunosuppressive medications and/or induction therapy before the surgical procedure.

\textit{Transplant procedure}

Most transplant procedures performed worldwide for treatment of children and adolescents with end stage lung or pulmonary vascular disease are bilateral lung deceased donor transplants. Other transplant options are single lung deceased donor transplants, heart-lung transplantation or LDLLT. Marginal donors may also be used in some transplant programs. However, their use in paediatric patients is generally not supported in Australian transplant programs. A bilateral lung transplantation is usually preferred in paediatric patients as single lung transplantation involves a potentially difficult post-operative course and high mortality for many conditions affecting children and adolescents.\textsuperscript{272} Further, as the number of potential recipients of paediatric organs is usually fewer than recipients of adult organs (after blood group and size matching have been performed), there is usually only one potential recipient waiting for any potential paediatric donor, negating the ability to treat more than one person with the donor organs.\textsuperscript{273}

Paediatric heart-lung transplantation was the procedure of choice in the 1980s for end stage lung disease, particularly for CF. Since the 1980s most transplant units have moved towards lung transplantation instead of heart-lung transplantation for isolated lung disease in paediatric patients as heart-lung transplantation requires allocation of two organs from the scarce donor organ supply, adds risk of cardiac graft coronary vasculopathy and is less tolerant of ischaemic time compared with heart transplantation alone.\textsuperscript{274} Although both AHM and SVHS/CHW include provision of heart-lung transplantation where indicated, this is not the preferred transplant procedure at either centre where lung transplantation can be performed instead.

The surgical approach in paediatric patients depends on the type of transplant to be performed, the patient’s primary diagnosis, and the surgeon’s experience/preference; but is generally via a bilateral anterolateral clamshell thoracotomy in paediatric patients. The surgical approach at AHM and SVHS is equivalent:

- Bilateral sequential lung transplantation involves transplanting one lung while the patient is supported on their remaining lung. The patient is then supported by their new transplanted lung, allowing the transplantation of the second lung. The transplantation is performed with or without cardiopulmonary bypass (CPB), depending on the treating centre.

\textsuperscript{272} Date H. Lung and heart-lung transplantation. Cardiology in the Young 2009;19:45-8.
\textsuperscript{273} Aurora P. Personal communication, May 2010.
\textsuperscript{274} Date H. Heart and heart-lung transplantation. Cardiology in the Young 2009;19:45-8.
• The recipient’s lungs are removed and the right and left donor lungs are implanted using end-to-end bronchial, pulmonary arterial and pulmonary venous anastomoses. Peribronchial tissue is sutured loosely around the bronchial anastomoses to provide blood flow by new vessel in-growth. The pulmonary artery and vein connections are performed. A donor atrial cuff is attached to the recipient’s left atrium, taking care to avoid suture lines near the pulmonary veins thereby reducing the risk of pulmonary vein stenosis. A central venous catheter for long-term intravenous therapy may be placed at surgery.

• When the new lungs have been implanted and perfusion has been re-established, chest tubes are placed (bilateral tubes if double lung transplantation). Before chest closure, flexible bronchoscopy can be performed to check the anastomoses, and transoesophageal echocardiogram is obtained to confirm good venous and arterial flows. The patient remains intubated and on mechanical ventilator support while they are transported to the intensive care unit.

Many of the procedural aspects of heart-lung transplantation are equivalent, although heart-lung transplantation is reported to be a simpler operation compared with bilateral lung transplantation. In summary:

• the procedure is performed using cardiopulmonary bypass;
• the heart and lungs are removed while carefully preserving the phrenic nerves and addressing bronchial artery circulation in order to prevent postoperative bleeding complications;
• the donor heart and lungs are inserted; the tracheal anastomosis is performed first;
• the right atrial anastomosis is performed next, followed by the aortic anastomosis; and
• care is taken to keep the donor trachea as short as possible because of the limited vascularity of the area.

At both the AHM and SVHS lung transplantation is either performed by or supervised by (in the case of involvement of surgical trainees) cardiothoracic surgeons. Depending on the underlying lung disease, donor organ availability and the size of the donor lungs double lung transplant or heart-lung transplant are usually performed. The AHM has also performed a cut-down bilateral lobar lung transplant from deceased adult donors.

Data regarding paediatric lung and heart-lung transplant operations are available for the AHM / RCHM model of care. Protocols for the transplant operation and post-transplant care of paediatric patients to be provided in the SVHS / CHW combined model are still under development.

Of the 10 paediatric lung and heart-lung transplants (age<16 years) performed by AHM since 2003, three were bilateral segmental transplants, four were lobar cut down procedures and three were heart-lung donor procedures.

After the operation patients at AHM are transferred to the Cardiothoracic Intensive Care Unit (CICU). After leaving intensive care, patients are transferred to the respiratory ward.

To date, median ICU length of stay for children undergoing lung transplantation in the AHM paediatric lung transplant program is 94 hours (range 21 – 1062) and median hospital length of stay is 21 days (range 9 – 96).
Health technology assessment of proposal to establish paediatric lung and paediatric heart-lung transplantation procedures as a Nationally Funded Centre

Specialist paediatric advice is available from RCHM through an established memorandum of understanding that provides cross-credentialing of specialists between the adult and paediatric hospitals.

CHW intend to commence clinical operation of paediatric lung and heart-lung surgical services in the next 12 to 24 months. It is anticipated that on commencement, four transplants a year will be performed. This will increase over time as demand increases and suitable donors become available. It is the view of SVHS staff that supply of suitable organs is about to increase significantly as a result of government organ donor initiatives. Further, the increasing use of ‘marginal donors’ and DCD donors is expected to extend the donor pool by an additional 20% or so.

**Early post-transplant and post-discharge care**

The postoperative course consists of approximately a two week hospitalisation period. Ideally, patients remain intubated and ventilated for 24 to 48 hours after surgery. Avoidance of complications of hypotension, volume overload, infection and renal dysfunction facilitates early extubation.

When the patient is extubated and pressor medications are discontinued, transfer from ICU can occur. Intravenous antibiotics may be continued whilst an inpatient. Physiotherapy is initiated in the intensive care unit and is increased in intensity as the patient becomes ambulatory.

All transplant patients are required to take immunosuppressive medications to prevent rejection. International or national consensus has not been reached on which agents should be prescribed, whether induction therapy should be used, and on protocols for administration, dosing and adjustment. As a result, protocols outlining post-transplantation medication management are not used, nor are they indicated, to specify a set treatment protocol in models of care at AHM or SVHS / CHW.

In general, induction agents can be divided into lympholytic agents and interleukin (IL)-2 receptor antagonists. These agents are typically administered for three to five days immediately after transplantation. They may also be used to treat steroid-resistant rejection, where they are typically administered for 10 to 14 days.

Maintenance immunosuppression is required in all transplant recipients. Agents used include calcineurin inhibitors, cell toxins, corticosteroids, and Rapamycin and its derivatives. Corticosteroids are the most commonly used agents in paediatric lung transplant recipients, followed by calcineurin inhibitors and cell toxins. Drug levels are monitored on a regular basis. For some agents, doses for lung transplant recipients are usually maintained at higher levels than those for other organ recipients due to the increased risk of rejection in lung transplant recipients. The serum levels require maintenance at levels high enough to prevent rejection without causing debilitating toxic effects.

In order to minimise nosocomial infection, discharge of patients from hospital to post-transplantation housing that is near the hospital may be advocated. Here patients continue to attend regular sessions of physical therapy.

Families that do not live near the transplant centre usually remain in accommodation within the city where the transplant facility is located for a period of three months following transplant. Although this is advocated in the models of care adopted at both AHM and the SVHS / CHW, patients whose city of residence has an adult transplant facility may receive ongoing care from transplant specialists in their home jurisdiction before three months has elapsed. This is generally negotiated between clinicians on a case-by-case basis.
After discharge from hospital, patients require outpatient appointments at the transplant clinic. Initially review twice per week is required. The frequency of review decreases as their condition stabilises.

Patients require regular pathology, radiology and diagnostic investigations (including spirometry, oximetry and bronchoscopy), wound care and medication management, including therapeutic drug monitoring. Reviews by transplant physicians, nurses and allied health are incorporated into post-transplant management on discharge.

Transbronchial biopsy surveillance at three, six and nine to 12 weeks post transplantation with additional procedures for new-onset symptoms or as a follow-up for acute rejection or CMV pneumonia are advocated in SVHS / CHW bronchoscopy protocols.

For the first three months after the transplant patients attend a paediatric rehabilitation program. In the AHM / RCHM model of care this includes three sessions a week with the physiotherapist, one session with the occupational therapist and one session with the paediatric lung transplant coordinator. There is also a weekly education session for patients and family members provided by the paediatric lung transplant coordinator in conjunction with other members of the team. The paediatric lung transplant coordinator also meets with parents weekly to assist with any issues that they have following their child’s transplant.

Issues regarding adjustment and transition to new health status and the burden of learning significant amounts of new information following lung transplantation are addressed by staff including the paediatric lung transplant coordinator, occupational therapists, child/adolescent mental health services and social workers, depending on the clinical requirement.

Generally patients do not return to school during the three months after transplantation.

On-going care

Outpatient care post-transplant varies internationally between treatment centres. To prevent complications, or to identify complications early, treatment centres use protocols outlining the frequency of review and the parameters that should be monitored on a routine basis.

In the models of care adopted by AHM and SVHS / CHW, the frequency of outpatient clinic visits decreases over time after the initial intensive three month period. Patients require review every two to three months as determined by the treating physician. In addition to these regular clinic visits, detailed three, six, nine and 12 month evaluations are required that incorporate detailed pathology, endurance testing, radiology and bronchoscopies. Follow-up is life-long.

- For children old enough to perform spirometry, FEV$_1$ may be monitored on a daily basis in order to detect early changes in lung function. For younger children, home oximetry may be used on a daily basis.

- Protocols for surveillance transbronchial biopsy vary between treatment centres internationally. The optimal monitoring frequency for surveillance bronchoscopy and transbronchial biopsy has yet to be clearly elucidated and is an area where further study is required$^{275}$.

Patients who live outside the paediatric lung transplant centre will be referred to a local chest specialist for ongoing care. In most instances, this will be a physician attached to the local adult lung transplant team in their home state or a physician with knowledge and skills in the management of patients after lung or heart-lung transplantation. State-based clinics are

established in New South Wales, Queensland, Victoria, Tasmania, South Australia and Western Australia. New Zealand patients are transferred to Green Lane Hospital for ongoing care. Patients from the Northern Territory and Australian Capital Territory may require specifically tailored follow up that more closely involves specialists in another jurisdiction. Members of the transplant hospital’s paediatric lung transplant team provide advice and conduct review of patients as required by referring clinicians, patients and their families.

Transition of transplant recipients from paediatric to adult services is recognised as a high-risk element of care, and specifically a time when adherence to medication becomes more difficult and the incidence of medical complications rises. The majority of paediatric centres have written transition protocols - this should be a requirement of the NFC.  

Workforce, clinical infrastructure, equipment

In Australasia, paediatric lung and heart-lung transplantation requires a multidisciplinary team with both paediatric and adult transplantation expertise in order to deliver care.

At AHM / RCHM, the multidisciplinary team is comprised of the following members:

- Head of Paediatric Lung Transplantation (1.0 equivalent full time (EFT))
- Paediatric Lung Transplant Coordinator (1.0 EFT)
- Physiotherapist (0.3 EFT)
- Occupational Therapist (0.2 EFT)
- Social Worker (0.2 EFT)
- Dietician (0.1 EFT)
- Paediatric Transplant Coordinator (RCH) (0.1 EFT)

Transplant physician support is provided across available consultant expertise.

Additionally, each patient and family is referred to and reviewed by a psychiatrist from Child and Adolescent Mental Health Service (CAMHS).

A Consultant Paediatrician (0.2 EFT) based at RCH is also proposed for the AHM / RCHM workforce model in order to manage the increasing caseload that is expected to occur as paediatric lung and heart-lung transplantation are performed more frequently in Australia.

In order to accommodate the specialised needs of paediatric lung and heart-lung transplantation patients, paediatric equipment was purchased by the AHM when the local state-funded paediatric lung transplant service was established to enable paediatric resuscitation to be performed that might arise either on the ward, in theatre or within the emergency department.

The SVHS / CHW workforce model is currently being developed. The model includes two specialist paediatric cardiothoracic surgeons who will perform both paediatric and adult lung and heart-lung transplantations at CHW and SVHS in order to maintain surgical skills (given the low numbers of paediatric lung and heart-lung transplants performed annually). The paediatric cardiothoracic surgeons will be supported by two SVHS adult transplant surgeons.

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Transplantation medicine capability is currently being developed by coordinated education and training within the respiratory medicine team at CHW.

Both AHM and SVHS have established cardiothoracic surgical / transplantation training programs. This is important to the successful implementation of the model of care in both States as a network of appropriately trained medical and surgical transplant specialists throughout Australia, with whom transplant centres can refer patients between to ensure after-care (and pre-care to an extent) will enable more care to be delivered locally over time, without the need for patients to travel to Melbourne or Sydney for all aspects of their care.

**Summary**

As noted above, there is some variability in the models of care utilised by services providing paediatric lung and heart-lung transplantation in Australia at present. There is also variability in acceptance criteria for transplantation and a lack of a systematic approach for referral of some patients between the two largest providers. This has the potential to also impact on the quality of service delivery within Australia.

A decision to establish one Australian centre within the NFC Program will need careful monitoring and review to ensure access is improved in line with the NFC objectives.

**Recommendation 4**

That in order to foster innovation and improve quality of service delivery, the small numbers of patients treated annually necessitates maintenance and development of:

- clinical protocols and acceptance criteria, drawing on best practice in the linked adult program and the best international paediatric programs;
- training and succession planning of specialist clinicians including medical practitioners, nurses and allied health clinicians in disciplines including but not limited to respiratory medicine, cardiothoracic surgery, intensive care and anaesthetics;
- outcome evaluation including mortality and morbidity, against international benchmarks;
- research programs;
- program monitoring and development; and
- transition protocols for ongoing paediatric care and then adult care in the home state.

**Recommendation 5**

That a set of key clinical performance indicators specific to mortality, morbidity and quality of life outcomes are developed for paediatric lung and heart lung transplantation which:

- draw from international key clinical performance indicators;
- enable close monitoring and access by jurisdiction of residence; and
- enable monitoring of long-term outcomes following discharge from the transplant unit.

As the NFC Guidance Document emphasises, a clear definition of the start and end point of the episode of care is required. The episode of care covers the inputs and costs associated with pre-care, post treatment and follow-up. Only those elements of pre-care and post treatment that are highly specialised and need to be undertaken by the NFC team should be included in the episode of care. This proposal encompasses care from initial assessment until three months post-transplantation.
Although a number of jurisdictions (New South Wales, Victoria, Queensland and Western Australia) have transplantation expertise that would enable patients to receive follow-up care before three months have elapsed post-transplant, an underlying aim of centralisation of services is to improve quality of paediatric transplant care. In order for this to occur, concentration of paediatric medical expertise post-operatively is also desirable. Therefore, provision of post-operative care to three months post-transplant by the NFC should be encouraged.

**Recommendation 6**

That should paediatric lung and heart-lung transplant be included in the NFC Program, the funding of the episode of care should, as defined within the NFC Guidance Document (January 2010), encompass the time from acceptance on the waiting list until three months after discharge.
13 Costs and financial modelling

Paediatric lung transplantation is an inherently expensive process that is associated with a considerable emotional, physical and financial toll on recipients and their families and carers. Solid organ transplantation raises the issue of cost as it relates to benefit, both to the individual and to society as a whole\textsuperscript{277}. Costs associated with lung and heart-lung transplantation vary between treatment centres. According to US data from the University Health Systems Consortium:

- the median case cost associated with uncomplicated lung transplantation for 33 centres up until to 2007 (involving treatment of 766 cases) was approximately $140,000 (USD); and
- mean length of stay for uncomplicated lung transplantation was 18 days.

Follow-up costs are high. The lifetime cost of care for the lung transplant recipient is estimated at approximately $US425,000 in the US and $US180,000 in the UK\textsuperscript{278,279}. Costs are substantial due to the ongoing pharmacological management, ongoing diagnostic pathology and radiology requirements and need for frequent sub-specialist follow-up\textsuperscript{280}.

Investigators have attempted to determine the cost per year adjusted for the quality of life. Results generally demonstrate that treatment is cost-effective, in view of the gain in quality of life obtained compared with quality of life without transplantation\textsuperscript{281,282}.

The NFC pro forma guidance requires all costs to be directly attributable to each case, with funding provided on a case-by-case basis at an agreed rate.

In Victoria the inpatient casemix payment for an adult lung or heart-lung transplant is in the order of $72,000. Additional reimbursements for pre-care and post-transplant outpatient care would also be generated. Some pharmaceutical costs would also be met through high cost drug programs. Costings are unavailable for operations of the SVHS / CHW service as the model of care is under development. However, information provided regarding the model to date suggests cost will be similar.

The following analysis re-works the unit costs provided by AHM to make an estimate of the likely costs (Table 12). Based on previous years experience (see Table 11) and expected increase in future demand it is assumed that in a given year that:

- there are 16 referrals, of whom four are from the Melbourne metropolitan area;
- of the 16 initial assessments, 10 are formally assessed, with three from Melbourne;
- 10 are placed and maintained on the waiting list for an average of four months;

\textsuperscript{280} University Health Systems Consortium. Available from: http://www.uhc.org
- 6 patients, two of whom are from Melbourne, are transplanted and followed-up for three months after transplant by AHM.

In addition, it is accepted that the ICU/HDU admission is on average nine days and the ward admission 15 days. The costs of readmissions (ICU for one day, ward for eight days and hospital in the home for 14 days) are also included.

The analysis also notably diverges from the AHM submission in that:

- the NFC program funds an episode of care from acceptance onto the waiting list until three months after discharge;
- RCHM admissions whilst on the waiting list would not normally constitute admissions for NFC purposes. Instead these would be covered by usual WIES or cross-border arrangements; and
- the NFC program does not cover the cost of organ retrievals.

New estimates are made for fixed staffing and administrative overhead costs. AHM also proposed NFC funding for an agreed clinical establishment, however NFC Guidance does not currently support this approach.

Table 12: Estimated unit cost at AHM

<table>
<thead>
<tr>
<th>Care pathway</th>
<th>Description</th>
<th>Notes</th>
<th>Rate</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Initial screening assessment – not NFC funded</td>
<td>Interstate travel for initial assessment</td>
<td>Flights and accommodation for 4 days</td>
<td>n/a</td>
<td>$2000</td>
</tr>
<tr>
<td></td>
<td>Patient and family member travel for initial assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td></td>
<td>$2000</td>
</tr>
<tr>
<td>2. Formal transplant assessment – not NFC funded</td>
<td>Travel to Melbourne</td>
<td>Flights &amp; accommodation for 7 days</td>
<td>n/a</td>
<td>$3600</td>
</tr>
<tr>
<td></td>
<td>Patient, 2 family members</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCHM admission</td>
<td>Bed cost</td>
<td>7 days; use NFC Norwood costs</td>
<td>$850</td>
<td>$5950</td>
</tr>
<tr>
<td></td>
<td>Consultation</td>
<td>Multidisciplinary team (MDT)</td>
<td>$1200</td>
<td>$1200</td>
</tr>
<tr>
<td></td>
<td>Investigations</td>
<td>Calculated at MBS rates</td>
<td>$2384</td>
<td>$2384</td>
</tr>
<tr>
<td></td>
<td>Allied health consults</td>
<td>16 allied health hours</td>
<td>$50/hour</td>
<td>$800</td>
</tr>
<tr>
<td></td>
<td>Consumables</td>
<td>High cost drugs</td>
<td>$2500</td>
<td>$2500</td>
</tr>
<tr>
<td></td>
<td>Indirect costs</td>
<td>Use BiPAP</td>
<td>$2500</td>
<td>$2500</td>
</tr>
<tr>
<td></td>
<td>Team meeting</td>
<td>MDT decision re: acceptance</td>
<td>$800</td>
<td>$800</td>
</tr>
<tr>
<td></td>
<td>Staff overhead costs</td>
<td>Allied health; MDT</td>
<td>25%</td>
<td>$700</td>
</tr>
<tr>
<td><strong>Subtotal assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td>$20,434</td>
</tr>
</tbody>
</table>
In accordance with the NFC Guidance Document (January 2010) the costs detailed above for initial screening assessment and the formal transplant assessment are to be borne by the jurisdiction as they are excluded from NFC funding.

### 3. Maintenance on waiting list – NFC funded

<table>
<thead>
<tr>
<th>Review every 6 weeks</th>
<th>Routine review</th>
<th>1 hour physician</th>
<th>$145/hr</th>
<th>$145</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 hours allied health time</td>
<td>$50/hr</td>
<td>$100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Investigations</td>
<td></td>
<td>$500</td>
<td></td>
</tr>
<tr>
<td>Staff overhead costs</td>
<td>Allied health; physician</td>
<td>25%</td>
<td>$60</td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal waiting list Mx** $805

### 4. Theatre – NFC funded

<table>
<thead>
<tr>
<th>Implant operation</th>
<th>Pre-op Pathology</th>
<th>Investigations</th>
<th>At MBS rates</th>
<th>$1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 hour operation</td>
<td>Surgeon</td>
<td>$215/hr</td>
<td>$2150</td>
</tr>
<tr>
<td></td>
<td>10 hour operation</td>
<td>Surgical assistant</td>
<td>$110/hr</td>
<td>$1110</td>
</tr>
<tr>
<td></td>
<td>10 hour operation</td>
<td>Anaesthetist</td>
<td>$145/hr</td>
<td>$1450</td>
</tr>
<tr>
<td>Theatre costs</td>
<td>Clinical costing system</td>
<td>n/a</td>
<td>$14,840</td>
<td></td>
</tr>
<tr>
<td>Staff overhead</td>
<td></td>
<td>25%</td>
<td>$1177</td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal theatre** $21,727

### 5. Intensive care/high dependency unit – NFC funded

<table>
<thead>
<tr>
<th>Post Op ICU/HDU 9 day admission</th>
<th>Overhead costs</th>
<th>9 days</th>
<th>$800/day</th>
<th>$7200</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physician</td>
<td>2 hrs/day</td>
<td>$145/hr</td>
<td>$2610</td>
</tr>
<tr>
<td></td>
<td>Surgeon</td>
<td>30 mins/day</td>
<td>$215/hr</td>
<td>$968</td>
</tr>
<tr>
<td></td>
<td>Nursing</td>
<td>26 hrs/day</td>
<td>$1260/day</td>
<td>$11,340</td>
</tr>
<tr>
<td></td>
<td>Physio</td>
<td>3 hrs/day</td>
<td>$50/hr</td>
<td>$1350</td>
</tr>
<tr>
<td></td>
<td>Intensivist</td>
<td>3 hrs/day</td>
<td>$145/hr</td>
<td>$3915</td>
</tr>
<tr>
<td></td>
<td>Radiology</td>
<td></td>
<td>$2500</td>
<td>$2500</td>
</tr>
<tr>
<td></td>
<td>Pathology</td>
<td></td>
<td>$2500</td>
<td>$2500</td>
</tr>
<tr>
<td></td>
<td>Pharmaceuticals</td>
<td></td>
<td>$6134</td>
<td>$6134</td>
</tr>
<tr>
<td></td>
<td>Consumables</td>
<td></td>
<td>$4770</td>
<td>$4770</td>
</tr>
<tr>
<td></td>
<td>Staff overhead</td>
<td>25%</td>
<td>$5044</td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal ICU/HDU** $48,331
### 6. General Ward Admission – NFC funded

<table>
<thead>
<tr>
<th>Service</th>
<th>Duration</th>
<th>Rate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission for 15 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>1 hr/day</td>
<td>$145/day</td>
<td>$2175</td>
</tr>
<tr>
<td>Nursing</td>
<td>6 hrs/day</td>
<td>$290/day</td>
<td>$4350</td>
</tr>
<tr>
<td>Social work</td>
<td>1 hr/day</td>
<td>$50/hr</td>
<td>$750</td>
</tr>
<tr>
<td>Physio</td>
<td>1 hr/day</td>
<td>$50/hr</td>
<td>$750</td>
</tr>
<tr>
<td>Dietician</td>
<td>1 hr/day</td>
<td>$50/hr</td>
<td>$750</td>
</tr>
<tr>
<td>Speech Therapy</td>
<td>4*1 hour visits</td>
<td>$50/hr</td>
<td>$200</td>
</tr>
<tr>
<td>OT</td>
<td>1 hr/day</td>
<td>$50/hr</td>
<td>$750</td>
</tr>
<tr>
<td>Psychologist</td>
<td>8* 1 hour visits</td>
<td>$50/hr</td>
<td>$400</td>
</tr>
<tr>
<td>Consumables</td>
<td></td>
<td>$2226</td>
<td>$2226</td>
</tr>
<tr>
<td>Diet</td>
<td>Supplements</td>
<td>$300</td>
<td>$300</td>
</tr>
<tr>
<td>Radiology</td>
<td>Daily CXR; 2*CT</td>
<td></td>
<td>$2500</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td>$200/day</td>
<td>$3000</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td></td>
<td></td>
<td>$14,312</td>
</tr>
<tr>
<td>Staff overhead</td>
<td></td>
<td>25%</td>
<td>$2390</td>
</tr>
</tbody>
</table>

**Subtotal ward**  $34,853

### 7. Outpatient care – NFC funded

<table>
<thead>
<tr>
<th>Service</th>
<th>Duration</th>
<th>Rate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient care until discharge from NFC program after 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical reviews</td>
<td>27 reviews</td>
<td>$80/visit</td>
<td>$2160</td>
</tr>
<tr>
<td>Allied health</td>
<td>1 hour/review</td>
<td>$50/hr</td>
<td>$1350</td>
</tr>
<tr>
<td>bronchoscopy</td>
<td>4 times</td>
<td>$2500/time</td>
<td>$10,000</td>
</tr>
<tr>
<td>lung function</td>
<td>9 investigations</td>
<td>$100/time</td>
<td>$900</td>
</tr>
<tr>
<td>CXR</td>
<td>9 times</td>
<td>$60/time</td>
<td>$540</td>
</tr>
<tr>
<td>pathology</td>
<td>9 times</td>
<td>$200/time</td>
<td>$1800</td>
</tr>
<tr>
<td>Drug costs/dietary supplements</td>
<td></td>
<td></td>
<td>$4950</td>
</tr>
<tr>
<td>Staff overhead</td>
<td></td>
<td>25%</td>
<td>$628</td>
</tr>
</tbody>
</table>

**Subtotal**  $22,328
8. Readmission – management of complications – NFC funded

<table>
<thead>
<tr>
<th></th>
<th>ICU Rate calculated on above rates</th>
<th>Ward Rate calculated on above rates</th>
<th>Hospital in the Home Rate calculated on above rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 day</td>
<td>8 days</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td>$5369</td>
<td>$2352</td>
<td>$150</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$26,285</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total Direct care costs $176,763

9. Family accommodation – NFC funded

<table>
<thead>
<tr>
<th>Provision for inpatient stay and 3 months after discharge</th>
<th>9 ICU days; 15 ward days; monitored 90 post-transplant days</th>
<th>114 days</th>
<th>$160/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$18,240</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>$18,240</td>
</tr>
</tbody>
</table>

10. Staff fixed costs – program management and development – NFC funded

<table>
<thead>
<tr>
<th>Program head (physician) 0.2 EFT</th>
<th>$300,000 incl 25 % oncosts</th>
<th>$60,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse program Coordinator 0.5 EFT</td>
<td>$94,000 incl 25 % oncosts</td>
<td>$47,000</td>
</tr>
<tr>
<td>Administration overhead</td>
<td></td>
<td>$10,000</td>
</tr>
</tbody>
</table>

Subtotal $117,000

Total non-direct care costs $135,240
The above NFC costs are summarised in Table 13.

**Table 13: Summary of costs**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Unit Cost</th>
<th>Number per patient</th>
<th>Expected annual caseload</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waiting list review</td>
<td>$805</td>
<td>2</td>
<td>20</td>
<td>$16,100</td>
</tr>
<tr>
<td>Theatre</td>
<td>$21727</td>
<td>1</td>
<td>6</td>
<td>$130,362</td>
</tr>
<tr>
<td>ICU/HDU</td>
<td>$48,331</td>
<td>1</td>
<td>6</td>
<td>$289,986</td>
</tr>
<tr>
<td>Ward</td>
<td>$34,853</td>
<td>1</td>
<td>6</td>
<td>$209,118</td>
</tr>
<tr>
<td>Outpatient review 3 months</td>
<td>$22,328</td>
<td>1</td>
<td>6</td>
<td>$133,968</td>
</tr>
<tr>
<td>Readmission</td>
<td>$26,285</td>
<td>1</td>
<td>6</td>
<td>$157,710</td>
</tr>
<tr>
<td>Family accommodation</td>
<td>$18,240</td>
<td>1</td>
<td>4 (2 Melbourne)</td>
<td>$72,960</td>
</tr>
<tr>
<td>Staff and admin overhead</td>
<td>$135,240</td>
<td>-</td>
<td>-</td>
<td>$135,240</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>$1,145,444</strong></td>
</tr>
<tr>
<td><strong>Cost per transplant</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>$190,907</strong></td>
</tr>
</tbody>
</table>

The cost of $104,921 for the inpatient episode is reasonably comparable to the usual Victorian adult WIES inpatient expense of $72,000.

Based on the analyses presented above, the following recommendations are made.

**Recommendation 7**
That the financial modelling based on the unit costs of the AHM proposal is noted and that it provides guidance for future comprehensive evaluation of the costs of models of care.

**Recommendation 8**
That applicants for selection as an NFC for paediatric lung and heart-lung transplant should be asked to include in their proposal:

- historical and projected ICU and ward length of stays;
- the component costs of ICU and ward overheads; and
- a breakdown of specialist staffing (medical, nursing, allied health) costs so that direct comparisons between submissions can be made.
14 Site selection criteria

Given the clinical infrastructure and staff requirements to provide high-quality and safe services, a number of criteria should be taken into account when applicant sites are evaluated for suitability as the NFC.

Recommendation 9

That should paediatric lung and heart-lung transplant be included in the NFC Program, the following criteria should be used to guide centre selection:

- the integration and/or collaboration of the transplant service with a paediatric cardiothoracic service and the capacity, throughput and specific expertise of that service;
- the ability of the centre to provide paediatric intensive care;
- the integration and/or collaboration of the transplant service with paediatric respiratory, paediatric cardiology, general paediatric, paediatric allied health and paediatric counselling services;
- the ability of the centre to provide a service 24 hours a day, 365 days a year, taking into account staff leave requirements and the need to maintain clinical and practical skills with a relatively low caseload;
- the ability of the centre to support staff delivering services in a high-stress speciality;
- the level of maturity of the model of care and the clinical pathways;
- the level of experience of the institution, cardiothoracic surgeons and other specialists with regard to number of paediatric lung and heart-lung transplants; the clinical outcomes achieved; and the number of suitably experienced specialists across relevant disciplines;
- the ability of the centre to provide adequate support services, including accommodation and psychosocial support services for families who need to relocate for extended periods;
- whether services are provided in a paediatric or adult facility; and if in an adult facility, the mechanisms that will ensure the needs of paediatric patients are met;
- an established research and development program including established systems for monitoring and ongoing data collection; and
- the capacity of the institution to ensure equitable access to transplant care for patients from all States and Territories.

A need was identified through consultation with clinicians across jurisdictions for more transparent and widely communicated information regarding the outcomes achieved from transplantation. Clinicians require up-to-date information regarding treatment options and patient outcomes in order to appropriately advise patients regarding treatment options and to inform referral decisions.
Recommendation 10

That should paediatric lung and heart-lung transplant be included in the NFC Program, the NFC should be supported by each jurisdiction to develop its communication efforts with specialist clinicians involved in the counselling of families whose children may benefit from lung and heart-lung transplantation.
15 Attachments

Attachment 1 - The TSANZ Lung Protocol

Lung referral criteria
1. Acceptable General Organ Donor Criteria
2. Age 5-65 years
3. No significant untreatable lung disease (and no known significant pleural disease for DCD lung donation)
4. Arterial blood gases on 100% FiO\textsubscript{2} and 5cm PEEP >250mmHg (or equivalent PaO\textsubscript{2}/FiO\textsubscript{2} ratio)

Required donor information for allocation

<table>
<thead>
<tr>
<th>Accurate lung disease and treatment history</th>
<th>especially smoking (cigarettes and marijuana), asthma and aspiration may determine single versus bilateral lung transplant considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate height and race</td>
<td>used to estimate total lung capacity</td>
</tr>
<tr>
<td>Weight</td>
<td>only used in consideration of combined heart/lung transplant</td>
</tr>
</tbody>
</table>

Investigations

- ABO Blood group
- Arterial blood gases on 100% FiO\textsubscript{2} and 5cm PEEP
- Chest Xray and lung field measurements within 24hrs
- Fibreoptic bronchoscopy (if possible)
- Donor/recipient lymphocytotoxic cross-match
- Donor/recipient CMV serology
- Donor/recipient EBV serology (if available)
Organ allocation and distribution

The recognised Lung Transplant Unit in the state of the donor’s hospital is offered the donation as detailed below. They have 20 minutes to respond to the offer.

<table>
<thead>
<tr>
<th>State of donor hospital</th>
<th>Lung transplant unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queensland</td>
<td>Queensland</td>
</tr>
<tr>
<td>New South Wales, Australian Capital Territory</td>
<td>New South Wales</td>
</tr>
<tr>
<td>Victoria, Tasmania</td>
<td>Victoria</td>
</tr>
<tr>
<td>Western Australia</td>
<td>Western Australia</td>
</tr>
<tr>
<td>South Australia, Northern Territory</td>
<td>On rotation through above States</td>
</tr>
</tbody>
</table>

If the home state declines the offer, then the lung donation offer is made on to the non-home state recognised Lung Transplant Units, with a 20 minute response time. The non-home state offer is based upon a rotation kept by each state donor co-ordination team, such that the first non-home state offer is rotated through each transplanting state in strict turn. If the first non-home state declines the offer, the next is asked until all units have been asked. If all recognised lung transplant units refuse the offer it is then rotated through any units that have non-nationals awaiting transplantation. The acceptance of lungs by a unit depends on a large variety of technical and logistic factors, including the availability of a suitable potential recipient (see below).

Individual patient allocation

The allocation of donor lungs is complicated by the considerable issues of logistics and the permutations/combinations of the different options of potential lung (and or heart) transplant that a cardiothoracic transplant unit need to consider when donor organs are offered. Donor lungs will be allocated considering the following criteria:

1. ABO compatibility
2. Size compatibility
3. The absence of a positive T cell crossmatch

Where more than one potential recipient meets the above criteria the first choice will be determined by the following process:

1. Clinical urgency* (graded by level of support required and evidence of rapidity of deterioration of underlying indication for transplant)
2. Logistics**
3. Long-term outcome benefit***
4. Recipient waiting time, all other factors being equal
Level of support includes but not limited to the following:

- ECMO
- invasive mechanical ventilation
- non-invasive ventilation
- high-flow $O_2$ requirement
- low-flow $O_2$ requirement
- prolonged or recurrent hospitalization
- other support devices such as continuous IV therapies

Rapidity of deterioration includes, but not limited to:

- change in NYHA functional Class or MRC grade
- significant fall in lung function parameters
- significant fall in $PaO_2$
- significant rise in $PaCO_2$
- significant fall in 6 Minute Walk Test distance
- need for escalation in level of support as above
- time course of progression of radiological changes
- development of symptomatic pulmonary hypertension
- development of refractory right heart failure

** Logistics includes

- time of retrieval and operation room availability
- location of recipients and/or donor: (local, interstate, international)
- type (i.e. road or air) and availability of transport to bring recipient to the transplant centre, and to take retrieval team to donor hospital
- availability of required team members for the retrieval, lung transplant(s) and related cardiac transplants (paired donor heart or domino heart transplant)
- experience of team members
- availability of ICU beds
- operation type (lobar, single, bilateral, heart/lung)
- availability of crossmatching
- concerns regarding donor instability
- donor family wishes regarding timing

*** Long-term outcome benefit includes

- comorbidities such as osteoporosis, gastroesophageal reflux, known coronary or peripheral vascular disease, carriage of pan-resistant organisms, poor rehabilitation potential, history of malignancy, advanced age, lack of compliance, morbid obesity or
malnutrition and other relative contraindications for lung transplantation which have been shown to be associated with an inferior outcome benefit.

**Eligibility of potential recipients for lung transplantation**

Lung transplantation is a highly effective treatment for advanced lung disease; however its use is limited by the scarcity of suitable donor organs. For this reason, lung transplantation is offered only to patients who have end-stage lung disease (life expectancy less than two years without transplantation), and who have exhausted all alternative treatment options. Infant lung transplants (currently not available in Australia and New Zealand) and living related lung transplants have their own specific issues and are not included in these Guidelines.

Assessment, listing and transplantation can only occur after careful evaluation by a recognised multidisciplinary Australian or New Zealand Lung Transplant Unit. Lung transplantation is a complex therapy with significant risks, and a careful evaluation of all organ systems (with appropriate specialist advice as needed) is mandatory to evaluate a potential patient’s risk of short and long-term morbidity and mortality. As there may be significant co-morbidities and contraindications, it follows that not all possible recipients will prove acceptable for transplantation.

There are recent international guidelines that were formulated with Australian input, and Australian and New Zealand units broadly follow these recommendations with local interpretation

Inclusion criteria include:

- respiratory failure despite optimal medical, interventional and surgical treatment.
- poor quality-of-life, potentially with intractable symptoms and repeated hospital admissions (e.g. NYHA Class III-IV)

Exclusion criteria include (but not limited to):

- active malignancy - in general a five year disease free interval is prudent
- irreversible significant dysfunction of other organs or body systems – combined organ transplant (e.g. heart/lung) may be a consideration, but patients must fit Guideline eligibility requirements for both organs and have a plausible strategy for allocation
- non-curable chronic infection
- documented non-adherence, or inability to comply with complex medical therapy or office follow-up (e.g. untreatable psychological or psychiatric condition)
- substance addiction (e.g. alcohol, tobacco or illicit drug use) that is either active or within the last six months

While age is not by itself an absolute exclusion criterion, it is likely that the presence of multiple co-morbidities in patients more than 65 years of age would exclude the majority of such patients from consideration.

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Attachment 2 – Published papers AHM

Burton JH, Marshall JM, Munro P, Moule W, Westall GP; Rehabilitation and Transition after Lung Transplantation in Children; Transplantation Proceedings; 2009; 41: 746-749


Westall GW, Burton JH, Marasco SF, Robertson CF, Snell GI; Lobar Lung Transplantation: a Novel Approach to Reduce Waiting list Mortality in Children Requiring Lung Transplantation; Respirology; March 2008; V13; S2


Westall GP, Merry C, Burton J, Robertson C, Snell GI; The Child with Advanced Lung Disease: Addressing an Unmet Need; Respirology 2007; 12: S1

Merry CJ, Negri JC, Rowland MA, Marasco SF, Esmore D, Snell G; Paediatric Lung Transplantation: Establishment and Early Experience in a Non-Paediatric Hospital. Heart, Lung and Circulation 2007; 16:S49

Attachment 3 - Stakeholder perspectives on the proposal to establish a NFC

Methods of obtaining feedback

An important aspect of this review was seeking advice from referring units about their experiences in dealing with the transplantation centres currently providing paediatric lung and heart-lung transplantation, as well as their views on the service system configuration.

To obtain the views of referring clinicians, a survey with follow-up telephone calls was administered to clinicians in all States and Territories. Clinicians were nominated by the jurisdictions. A copy of the survey is at Attachment 4.

Eleven survey responses were received from clinicians from the following jurisdictions:

- ACT (1);
- NSW (4);
- Queensland (1);
- South Australia (1);
- Tasmania (2);
- Northern Territory (1);
- Western Australia (1).

Face-to-face interviews were also conducted with referring clinicians from Victoria and NSW.

In addition, telephone interviews were conducted with paediatric patients and their families who had undergone paediatric lung or heart-lung transplantation (7 families) or were waiting for transplantation (1 family). Fifteen interviews (6 patients and 9 family members) were conducted with patients and families from the following jurisdictions:

- NSW (6);
- Queensland (2);
- Tasmania (1);
- Victoria (4);
- South Australia (1);
- Western Australia (1).

A survey was also conducted across all jurisdictions of staff and support workers from Cystic Fibrosis Australia, HeartKids Australia, and both organisations’ State-based organisations.

Below, we detail referring clinicians' perspectives as conveyed via the survey responses and interviews, patient perspectives as conveyed via the telephone interviews, and support organisation perspectives provided by survey responses.

Referring clinician feedback

Referral patterns

Respondents from all States and Territories other than NSW reported that they currently refer paediatric patients who require lung or heart-lung transplantation to Victoria. NSW respondents reported that they refer patients to St Vincent’s Sydney.
Queensland and Western Australia are jurisdictions with local capability to undertake paediatric lung and heart-lung transplantation. Queensland and Western Australia respondents reported that low bodyweight paediatric patients from both jurisdictions are referred to Victoria for transplantation. In Queensland, only patients with a body weight in excess of 40 kg receive transplantation locally. All others are referred to Victoria for transplantation. Similarly, in Western Australia younger paediatric patients are referred to the Alfred Hospital and older patients to the Royal Perth Hospital.

No respondent reported referring a patient to an international centre for transplantation.

Processes of referral

Referring centres reported that they have established processes for referral to interstate treatment centres, both for assessment for suitability for transplant and for care once the patient is accepted on the waiting list. Most referring centres reported that they have well-established relationships with their interstate treating centre, and that communication with the transplant team at referral and after assessment of the patient is facilitated by these existing relationships. Though others expressed frustration that liaison with the transplant team may occur through an adult respiratory physician in the referring jurisdiction. This was perceived to create significant disadvantages as consultation between the transplant team and the treating paediatric team is filtered via an adult physician who does not necessarily have a finely attuned appreciation of paediatric issues.

Jurisdictional provision of care

All jurisdictions felt that maximising the amount of support that can be delivered locally is important. There was a perception that the transplant team is seen as a replacement for the current care a patient receives. This was viewed as undesirable and resulted in fragmentation of care. Instead, the ongoing involvement and close communication with the paediatric team that has cared for the patient over team was viewed as vital to ensuring holistic care was delivered, and good long-term outcomes achieved. Further, in the case of jurisdictions with local transplantation capability, the possibility of caring for patients until the time of transplantation, then retrieving the patient and the donor organs simultaneously to the surgical centre performing the transplantation, was raised as a preferred treatment strategy for some patients in order to maintain continuity of paediatric care and minimise family and social impacts associated with the transplantation process.

Better engagement with the referring hospital after transplant for ongoing management was identified by some respondents as an issue that requires resolution. Joint management of patients early post-transplant was seen as desirable to ensure the patient’s paediatric care needs were met and that single-organ or single-issue approaches to care were avoided.

Paediatric versus adult facilities

The majority of respondents felt it preferable for transplantation services to be provided to paediatric patients in a paediatric facility rather than an adult facility. However, it was also acknowledged that the primary consideration for decisions regarding where services are located (paediatric versus adult facilities) should be the competence and experience of the unit prior to, during and after transplantation in children and adolescents, and that this may mean an adult facility is a more appropriate choice for the location of services. Concerns that were raised regarding provision of care to paediatric patients in adult facilities included:

- limited input of paediatricians in current service arrangements;
- a lack of specialised paediatric medical care provided to patients;
• a lack of specialist paediatric nursing expertise;
• inexperience of current treatment centres in the psychological and social management of adolescent patients with life-threatening chronic illnesses;
• a lack of child / family-focussed holistic care; and
• an inappropriate single organ focus of care rather than provision of care as a whole (e.g. in the case of CF, a lack of understanding of the multi-system implications of the disease).

Insufficient age-appropriate access to counselling and support was viewed as a significant problem with current care arrangements. Poor counselling and support was a concern for respondents due to the potential for this to result in poor compliance with medical care, and ultimately rejection of the donor organs. It was suggested that most patients who receive lung and heart-lung transplantation are long-term frequent users of the health care system who have established multidisciplinary care arrangements. Counselling and support from existing providers was viewed as the most appropriate strategy for the majority of patients. Systems to ensure access to this counselling and support need to be established and will require better integration of transplant services with local pre-existing paediatric care.

In some cases, respondents reported their patients were not considered for transplantation unless they were transferred to the care of adult specialists while on the waiting list and also managed post-transplant by adult specialists. This was viewed as inappropriate for paediatric patients.

**Service concentration**

The majority of respondents expressed the view that a single dedicated paediatric lung transplant unit that is staffed by clinicians (including paediatric specialists) with experience and expertise in lung and heart-lung transplantation is appropriate for Australia. It was proposed that a single centre would ensure sufficient service concentration for acquisition of sufficient skills and expertise, given the numbers of children who require transplant services nationally are relatively small. Respondents from most jurisdictions who have local transplant capability also expressed support for a single treatment centre.

Some respondents reported that staff from a single dedicated unit could provide outreach services for transplantation assessment in referring jurisdictions.

**Support for families**

Clinicians reported that current financial and social supports available to families are insufficient to meet family needs as there is insufficient financial assistance provided to families to counter the loss of wages relocation for long periods whilst on a waiting list entails, transport and accommodation expenses leave many families out-of-pocket, and the ongoing care requirements for patients (medical, educational, social) incur significant expense.

**Other issues**

A number of respondents felt that current access to paediatric lung and heart-lung transplantation in Australia was inequitable. Paediatric patients from jurisdictions that did not have a local transplant service were perceived to be at a disadvantage compared with those from jurisdictions with transplantation services. A nationally funded, dedicated paediatric lung transplantation unit that is staffed by professionals with experience and expertise in lung transplant was viewed as a mechanism to improve equity of access, and may result in an increase in referrals for transplantation assessment.
Feedback from families and support organisations

The consultation with families and support organisations addressed the following issues:

- their level of awareness of lung and heart-lung transplantation as treatment options for a small number of patients;
- issues associated with provision of services in adult rather than paediatric facilities;
- issues associated with reducing the number of sites where transplantation is available;
- issues associated with relocation to a surgical centre for the duration of treatment, including waiting list time; and
- their views on support services that families require whilst their child is in hospital for prolonged periods.

Overall experience

Families were generally positive about their experience of lung and heart-lung transplantation and the outcomes of successful surgery were valued highly. In all cases, the only alternative to transplantation was imminent death, and both families and patients expressed the view that the dramatic improvements in quality of life afforded by transplantation, and extension of life expectancy, outweighed the negative aspects to treatment, including the surgery, frequent outpatient attendances, and extensive medication management and invasive follow-up that was required.

Knowledge and awareness

All respondents reported that they became aware of transplantation as a treatment option through their usual treating paediatric health care providers, most commonly their paediatric respiratory physician:

- referrals resulted in assessment at the treating centre where the transplant was to be performed, at which time respondents reported they became very well informed regarding transplantation and its advantages and disadvantages;
- the main advantages of transplantation were reported as improved quality of life and longer duration of life; and
- the main disadvantages were a lack of donors, the risk of rejection, taking immunosuppressant medications, and the possibility of a long waiting time.

Paediatric versus adult facilities

Respondents were divided in their preferences for receiving treatment in adult versus paediatric facilities.

A number of respondents preferred the adult facility to a paediatric facility. The main reasons cited were:

- staff (nursing staff in particular) treated the patient with more respect and not ‘like a child’;
- the treating team were experienced and engendered confidence in patients and families;
- the presence of adults who had also received lung transplants gave the patient some to talk to who was experiencing the same treatment; and
it was quieter and less disruptive than a paediatric facility which aided recovery.

Disadvantages associated with provision of care in an adult facility included:

- equipment was not always appropriate for paediatric patients e.g. during physiotherapy, exercise bikes were ‘too big’ for patients to use (two families reported that the physiotherapist had purchased a ‘Wii’ game system to assist in delivering physiotherapy that was age- and size-appropriate), invasive equipment at times had to be sought from a paediatric facility which created time delays in accessing some procedures (including interventional radiology during follow-up);
- access to schooling for the patient was insufficient. Families reported access to a tutor in some cases, but late in the patient’s hospital stay, and not of the same standard of education that they were used to through their paediatric hospital;
- most patients reported difficulty accessing counsellors or support people who were comfortable talking to paediatric patients (however, the occupational therapist at The AHM was viewed favourably by a number of families for her ability to engage with patients in an age-appropriate way);
- in some cases the diet their child was placed on was age-inappropriate. For some patients (particularly teenage boys) there was not enough food provided, for others the types of foods were ‘adult’ and there was not the same degree of choice that they were used to in a paediatric hospital;
- patients didn’t have any age-appropriate entertainment (frequent references were made to their paediatric hospital home, where access to ‘entertainment stations’, books, games, television, videos and other age-appropriate entertainment was provided); and
- some families reported that doctors in particular did not know how to talk to their child – some spoke ‘down’ to their child whilst others treated their child like an adult, which some families did not feel was appropriate.

Families and patients reported that visiting teams, or teams on staff, who were paediatrically trained would reduce some of the disadvantages of care provided in an adult facility. Visits from play therapists, music therapists, and provision of age-appropriate entertainment were also proposed as ways to improve the hospital experience for paediatric patients.

Access to services

Whilst the need to relocate whilst on the waiting list was acknowledged by families and support organisations, numerous difficulties associated with relocation were identified. These included:

- a lack of social support (being away from family, friends and community);
- being away from the usual treating doctor and treating team made it difficult to maintain good care;
- extended time off work for working parents;
- often long commutes between home and the hospital for family members; and
- finding schooling and child care for other children in the family.

Respondents felt that the level of assistance provided for families was insufficient. Some NSW respondents reported that the “100 kilometre” rule (that families living within 100 kms of a treating centre were not eligible for accommodation and transport) created significant hardship
as they commuted almost 100 km each way during treatment, then weekly for follow-up appointments with their child in the immediate postoperative period. Additional assistance sought included:

- assistance with child care;
- schooling for other children;
- additional transport and meal assistance;
- some flexibility with current access provisions for state-based transport and accommodation assistance schemes;
- advocating with workplaces to ensure extra leave; and
- better emotional and social support for families that are separated (one parent with the child and the other at home with other children).

Having a designated social worker and/or case worker was viewed as a possible mechanism to ensure families received all help available to them – in some cases families reported that they needed more help but were unsure whether this help was already available, just poorly communicated to them.

**Service concentration**

There was support from families for concentration of services to enhance expertise. Families from locations other than Melbourne and Sydney expressed the view that, as relocation was required in order to access treatment, it did not matter to which city they relocated. However, where care could be provided locally whilst on the waiting list, and after the transplantation had occurred, it was the preference of these families to remain in their home jurisdiction with their usual paediatric team and paediatric facility.
Attachment 4 – Referring clinician survey

Dear Doctor

Health technology assessment for Paediatric Lung Transplant

Purpose of letter

The purpose of this letter is to invite you to contribute to a health technology assessment which is considering whether a Nationally Funded Centre (NFC) should be established for paediatric lung and paediatric heart-lung transplantation (patients aged <18 years of age, but at least 25kg).

DLA Phillips Fox (Consultants: Dr Heather Wellington, Dr Kelly Shaw, Dr Paul Woodhouse) have been contracted by NSW Health on behalf of all States and Territories to undertake a health technology assessment, the purpose of which is to determine whether paediatric lung and paediatric heart-lung transplantation meet the criteria for NFC technology.

The NFC Program

NFCs are established to provide Australians with equitable access to certain high cost, low demand, new and emerging medical technologies. NFCs are approved by the Australian Health Ministers’ Advisory Council (AHMAC) and funded from a pool with contributions from all States and Territories according to a weighted population-based formula based.

The objectives of the NFC Program are to ensure that:

- there is maximal access to certain high cost, low demand, new and emerging technologies regardless of geographical location, in the context of workforce and resource availability;
- these technologies are provided efficiently and effectively;
- requirements for high quality and safe introduction and ongoing provision of these technologies have been defined and implemented; and
- health and cost outcomes of these technologies are monitored and evaluated.

For a technology to be considered for provision in a NFC, it must be an established clinical practice requiring a national population base for efficient and effective service provision. The scope of technology eligible for consideration as a NFC includes devices, prostheses, techniques, skills or expertise (or personnel with particular skills or expertise) and/or procedures, or combinations of these. Service delivery of technologies approved as NFC Programs may occur in one or more sites and is restricted to these sites.

As NFC sites are funded by all the States and Territories. Health department officials in each of the jurisdictions are keen to ensure key clinicians have the opportunity to provide their views on relevant issues.

More information about the NFC Program is available at the NFC website:

http://www.nfc.sa.gov.au

Opportunity to contribute to the assessment

The assessment team is particularly interested in your views about the matters identified in the attachment to this letter, but would be pleased to receive any comments you think are pertinent to the assessment.
The views of individuals and/or organisations will remain confidential to the assessment team. The report and recommendations of this assessment will be thematic and will not identify individuals or organisations without their consent.

We would appreciate it if you could respond to this letter by close of business, Wednesday 9 December 2009. Please email your responses to kelly.shaw@pfhealth.com.au.

Further information

Please feel free to contact the following members of the project team if you wish to discuss this assessment:

Dr Heather Wellington (0418 577601, heather.wellington@daphillipsfox.com)
Dr Kelly Shaw (0448 552617, kelly.shaw@pfhealth.com.au)
Dr Paul Woodhouse (0430 338208, paul.woodhouse@pfhealth.com.au).

Yours sincerely

Dr Heather Wellington
MBBS, BMedSci, BHA, FRACMA, LLB
Consultant
Direct +61 3 9274 5022
heather.wellington@daphillipsfox.com
Questions for consideration about paediatric lung and heart-lung transplants

Q1. Does your institution currently undertake lung or heart-lung transplants on patients aged less than 18 years? Yes/No

If yes, please detail the scope of services.

Q2. Have you or your unit referred any patients to an overseas paediatric lung transplant unit in the last 5 years? Yes/No

If yes, please provide details.

Q3. Have you or your unit referred any paediatric patients (<18 years) to an Australian lung transplant unit in the last 5 years for assessment? Yes/No

If yes, please provide details.

<table>
<thead>
<tr>
<th>Year</th>
<th>Hospital name(s)</th>
<th>Age of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
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<tr>
<td>2007</td>
<td></td>
<td></td>
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<tr>
<td>2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Q4. Have any of your paediatric patients had a lung transplant or heart-lung transplant at an Australian unit in the last 5 years? Yes/No

If yes, please provide details.

<table>
<thead>
<tr>
<th>Year</th>
<th>Hospital name(s)</th>
<th>Age of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
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<tr>
<td>2005</td>
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</table>

Q5. From your experience, what issues are important in the referral, assessment, treatment and follow-up of paediatric patients who are referred for and who may undergo a lung transplant? Consider, for example:

- support for referring clinicians to discuss transplant or palliation options with patients and parents;
- information about transplantation services available to you and patients and parents prior to referral;
- consultation and communication with the transplant team at referral and after assessment of the patient;
- specialist consultation services provided by the transplant unit for patients admitted to your health service;
- care of the patient whilst on the waiting list;
- communication with you about the patient whilst on the waiting list;
- support for the family pre and post-transplant;
- follow-up of the patient and communication with you by the transplant unit after discharge.

Please provide comment as appropriate.
Q6. Could the current system for management of children requiring a lung transplant be improved?  Yes/No

If yes, please provide details.

Thank you for taking the time to participate in this assessment. If you require further information, please contact:

Dr Heather Wellington (0418 577601, heather.wellington@dlaphillipsfox.com)
Dr Kelly Shaw (0448 552617, kelly.shaw@pfhealth.com.au)
Dr Paul Woodhouse (0430 338208, paul.woodhouse@pfhealth.com.au).
Attachment 5 - Literature review
Literature review of paediatric lung and heart-lung transplantation

NSW Health on behalf of the Nationally Funded Centres
Reference Group
June 2010
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Terms and abbreviations used in this report

ABS          Australian Bureau of Statistics
ACE          Angiotensin-converting enzyme
AIHW         Australian Institute of Health and Welfare
ANZCOTR      Australia and New Zealand Cardiothoracic Organ Transplant Registry
ANZOD        Australia and New Zealand Organ Donation Registry
APA-FT       Australian Public Affairs – Full Text database
ATGAM        Equine antithymocyte globulin
BAL          Bronchoalveolar lavage
BiPAP        Bilevel positive airway pressure ventilation
BMI          Body mass index
BO           Bronchiolitis obliterans
BOS          Bronchiolitis obliterans syndrome
CF           Cystic fibrosis
CINAHL       Cumulative Index of Nursing and Allied Health Literature
CMV          Cytomegalovirus
CPB          Cardiopulmonary bypass
CPR          Cardiopulmonary resuscitation
DHCA         Deep hypothermic circulatory arrest
DoH          Department of Health (UK)
EBV          Epstein-Barr virus
ECMO         Extracorporeal membrane oxygenation
FEV1         Forced expiratory volume in 1 second
FiO2         Fractional inspired oxygen
GM-CSF       Granulocyte-macrophage colony stimulating factor
IL2          Interleukin 2
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD</td>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>IPAH</td>
<td>Idiopathic pulmonary arterial hypertension</td>
</tr>
<tr>
<td>ISHLT</td>
<td>International Society for Heart and Lung Transplantation</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>LAS</td>
<td>Lung allocation scoring system</td>
</tr>
<tr>
<td>LDLT</td>
<td>Living-donor lobar lung transplantation</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>OKT3</td>
<td>Muromonab-CD3</td>
</tr>
<tr>
<td>PRA</td>
<td>Panel reactive antibody</td>
</tr>
<tr>
<td>PTLD</td>
<td>Post-transplant lymphoproliferative disease</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>RATG</td>
<td>Rabbit antithymocyte globulin</td>
</tr>
<tr>
<td>RCHM</td>
<td>Royal Children's Hospital Melbourne</td>
</tr>
<tr>
<td>SLCH</td>
<td>St Louis Children's Hospital</td>
</tr>
<tr>
<td>SVC</td>
<td>Superior vena cava</td>
</tr>
<tr>
<td>UNOS</td>
<td>United Network for Organ Sharing</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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Introduction

DLA Phillips Fox have been engaged to undertake an assessment of the suitability, or not, of the development of a Nationally Funded Centre for paediatric lung and heart-lung transplantation for Australian children with medical conditions for which these treatments are clinically indicated. As part of the assessment process, the review team have undertaken a targeted search of the health care and management literature regarding paediatric lung transplantation and heart-lung transplantation for chronic medical conditions.

Literature review methods

In the health care literature, the MeSH terms ‘lung transplantation’ and ‘heart-lung transplantation’ were used to search the literature, together with truncated keywords to cover the various subheadings relevant to paediatric care.

These search strategies were used with the international databases Medline, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), Social Sciences Citation Index, Biological Sciences, the Cochrane Library, MD Consult Journals, Web of Science and ProQuest. The ‘grey literature’ was also searched using the same keywords and acronyms. ‘Google’ and ‘Google Scholar’ were interrogated to identify materials of broad relevance. A summary of findings is presented below.

Structure of the current literature review

Drawing on the relevant materials identified, this review outlines the aetiology, clinical presentation and epidemiology of clinical conditions for which paediatric lung and heart-lung transplantation may be indicated, describes the current management of these conditions (with a focus on paediatric transplantation options), discussed the clinical course patients follow, complication rates from different management options, volume-quality relationships across surgical centres, and specialised resource requirements for provision of care. Current evidence regarding the role of paediatric lung transplantation and heart-lung transplantation in clinical medicine, international and national experience in performing transplantation, comparisons with medical treatments in conditions for which transplantation is commonly indicated, and issues and challenges that require resolution are discussed. The impact of paediatric lung transplantation and its management on parents and families, and ethical issues associated with treatment are also described.

Paediatric lung and heart-lung transplantation

Paediatric lung and heart-lung transplantation are treatment options for selected patients with advanced lung disease and cardio-respiratory conditions that have failed to respond to standard medical and surgical therapy\(^1\). Although significant gains have been made in improving lung function and survival for chronic respiratory conditions affecting children, ultimately respiratory failure is the leading cause of mortality in many children affected by severe chronic respiratory and cardio-respiratory disease\(^2\). In some of these children, lung or heart-lung transplantation may prolong survival and improve quality of life.


Outcomes after transplantation were poor until the early 1980s, when the development of immunosuppressive agents such as cyclosporine resulted in reduced complications and longer-term survival. As a result, although lung and heart-lung transplantation had been performed experimentally since the 1960s, the first long-term successful lung and heart-lung transplants were not performed until the 1980s. The first successful isolated lung transplantation was performed in 1983 in an adult with pulmonary fibrosis. This was followed by the first successful paediatric lung transplantation in 1987, performed in a 16 year old female patient with pulmonary fibrosis. Successful paediatric heart-lung transplants were not reported until towards the end of the 1980s.

Lung and heart-lung transplantation have not been compared with medical therapy in published randomised controlled trials. Investigators have most commonly reported the outcomes associated with transplantation from retrospective cohort studies and analyses of registry data and administrative datasets. As a result, comparative quantitative estimates of the improvements in life expectancy and quality of life obtained between transplantation and medical management in paediatric patients are unavailable. Numerous studies have demonstrated that lung transplantation increases life expectancy in the majority of recipients.

**Clinical indications for transplantation**

According to the registry of the International Society for Heart and Lung Transplantation (ISHLT), there were 1207 lung transplantations performed in persons < 18 years of age worldwide between January 1990 and June 2008. Approximately 65% were performed in children aged 12 to 17 years. It should be noted that not all countries with a transplant programme report data to the ISHLT. Therefore, registry data are likely to underestimate true numbers of lung transplants being performed worldwide.

Clinical diagnoses leading to paediatric lung transplantation vary according to age group and are shown in Table 1. In children aged less than one year, congenital heart disease and primary pulmonary hypertension are the leading indications and account for approximately half of all lung transplant procedures. In children aged between one and five years, primary pulmonary hypertension is the leading condition. In children aged six years and above, cystic fibrosis (CF) is the most common diagnosis.
Literature review of paediatric lung and heart-lung transplantation

Table 1 – Age specific indications for lung transplantation (worldwide – 1990 to 2008)

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Age &lt; 1 year</th>
<th>Age 1 – 5 years</th>
<th>Age 6 – 11 years</th>
<th>Age 12 – 17 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>2</td>
<td>5</td>
<td>124</td>
<td>547</td>
<td>678</td>
</tr>
<tr>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>11</td>
<td>22</td>
<td>25</td>
<td>60</td>
<td>118</td>
</tr>
<tr>
<td>Re-transplantation or graft failure</td>
<td>3</td>
<td>8</td>
<td>15</td>
<td>43</td>
<td>69</td>
</tr>
<tr>
<td>Interstitial lung diseases</td>
<td>5</td>
<td>9</td>
<td>17</td>
<td>37</td>
<td>68</td>
</tr>
<tr>
<td>Bronchiolitis obliterans (not re-transplant)</td>
<td>0</td>
<td>9</td>
<td>10</td>
<td>29</td>
<td>48</td>
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<tr>
<td>Congenital heart disease</td>
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<td>8</td>
<td>4</td>
<td>10</td>
<td>43</td>
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<tr>
<td>Interstitial pneumonitis</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Pulmonary vascular disease</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Eisenmenger’s syndrome</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>17</td>
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<tr>
<td>Other</td>
<td>25</td>
<td>17</td>
<td>26</td>
<td>54</td>
<td>122</td>
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<tr>
<td>Total</td>
<td>82</td>
<td>99</td>
<td>234</td>
<td>792</td>
<td>1207</td>
</tr>
</tbody>
</table>

Paediatric heart-lung transplantations are performed far less frequently than paediatric lung transplantations and numbers of transplants performed each year are declining. Between eight and 17 paediatric heart-lung transplantations a year have been performed worldwide since 2002. Approximately 60% of these are performed in adolescents.

The clinical indications for paediatric heart-lung transplantation are similar to those for lung transplantation. The principal diagnoses leading to heart-lung transplant in persons aged less than 18 years are idiopathic pulmonary arterial hypertension (26%), CF (22%) and congenital heart disease (22%).

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Cystic fibrosis

CF is the most common terminal hereditary disease in the Caucasian population, affecting one in every 2 500 births\textsuperscript{13}. In 2001 there were approximately 2 300 people in Australia living with CF; two-thirds of these were children and adolescents\textsuperscript{14}.

CF is a recessive genetic disorder affecting the CF transmembrane regulator protein which is present on all cell surfaces. The condition affects many organs in the body, but primarily the lungs, pancreas, liver and reproductive systems. The most serious effects are on the lungs and pancreas\textsuperscript{15}.

Major advances in the diagnosis and treatment of cystic fibrosis have prolonged life expectancy into adulthood. Although the overall median survival rate for CF is approximately 32 years, life expectancy has improved dramatically in recent years. The median estimated survival for children with CF born in the year 2000 is now approximately 50 years\textsuperscript{16}. The reasons for improved survival are thought to include earlier diagnosis of CF due to neonatal screening, improved nutrition and management of respiratory infections, and management in tertiary CF centres, where it is recommended children visit at least quarterly for multidisciplinary assessment and care\textsuperscript{17}. This improved life expectancy requires strict adherence to intensive and time-consuming treatment regimes\textsuperscript{18}\textsuperscript{19}.

There is currently no cure for cystic fibrosis and treatment aims to slow the progression of the condition through early screening and better management. Management of cystic fibrosis can be a significant burden on the patient and family. Daily treatment regimes are time-consuming and include physiotherapy, high-calorie meals and routine medications. Additionally, chronic lung infections result in repeated hospitalisations, which can adversely affect study and employment\textsuperscript{20}. These factors have a substantial impact on the quality of life of those with cystic fibrosis and their families\textsuperscript{21}.

Each year in Australia there are approximately 10 deaths due to CF recorded in Australian Bureau of Statistics (ABS) mortality data in children and adolescents aged less than 18 years\textsuperscript{22}. Factors that have been associated with a greater risk of death include a forced expiratory volume in 1 second (FEV1) of less than 30% of predicted, elevated pCO\textsubscript{2} and decreased pO\textsubscript{2} on arterial blood gases, female gender, younger age and poor nutritional status. Other factors predictive of increased mortality include increased frequency of hospitalisations, increased need for intravenous antibiotics, height / weight centile, reduced oxygen uptake during exercise, resting heart rate, haemoptysis, and greater than 30% disparity in perfusion difference between lungs\textsuperscript{23}.

**Pulmonary vascular disease**

Pulmonary vascular disease occurs in a number of forms, including primary or idiopathic pulmonary hypertension, congenital heart disease in association with pulmonary hypertension, obstructive pulmonary venous disease, thromboembolic disorders leading to pulmonary hypertension, arteriovenous fistulae of pulmonary vessels, aneurysms of the pulmonary artery, kyphoscoliotic heart disease and pulmonary hypertension associated with parenchymal lung disease\textsuperscript{24}.

The frequency of pulmonary vascular disorders in children, in particular pulmonary arterial hypertension, remains unknown. Each year in Australia there are approximately nine deaths due to pulmonary vascular diseases recorded in ABS mortality data in children and adolescents aged less than 18 years\textsuperscript{25}.

Treatment for pulmonary vascular disease has improved significantly in the past 15 years, largely due to the development of more effective pharmacological agents, and the use of surgical techniques such as atrial septostomy to relieve pulmonary hypertension. Patients receiving maximal medical therapy, but increasing central venous pressure with declining cardiac index on serial cardiac catheterisations have a poor prognosis and may require transplantation to improve life expectancy and quality of life\textsuperscript{26}.

\textsuperscript{20} Burker E. Psychological and educational factors. . Pediatric Pulmonology 2004; 38:413–8.
\textsuperscript{22} ABS Mortality Database. Lung mortality due to cystic fibrosis in persons aged 0-18 years (1999-2006).
\textsuperscript{25} ABS Mortality Database. Lung mortality due to cystic fibrosis in persons aged 0-18 years (1999-2006).
\textsuperscript{26} Haworth S. The management of pulmonary hypertension in children. Archives of Disease in Childhood 2008; 93:620-5.
Pulmonary arterial hypertension

Pulmonary arterial hypertension is a serious progressive condition with poor prognosis if not identified and treated\textsuperscript{27}. Prognosis is worse in children than for adults. Pulmonary arterial hypertension is subdivided into idiopathic pulmonary arterial hypertension and associated pulmonary arterial hypertension\textsuperscript{28}.

The annual incidence of pulmonary arterial hypertension is estimated to range from one to two new cases per million people in the general population\textsuperscript{29}. Although rare, increasingly frequent reports of confirmed cases suggest that more patients have pulmonary arterial hypertension than was previously recognised. The sex incidence in children is approximately 1.8:1 females to males, with no significant difference in younger children compared with older children\textsuperscript{30}.

Until recently, the diagnosis of idiopathic pulmonary arterial hypertension was associated with a mean survival of 10 months in children\textsuperscript{31}. However, as advances in technology have permitted earlier diagnosis and more definitive assessment of disease severity, and treatments have improved, prognosis has improved and survival increased\textsuperscript{32}. Survival of between 85 and 94\% at one year, and between 57 and 72\% at five years have been achieved in overseas specialised treatment centres, with between 10 and 21\% of children progressing to transplantation\textsuperscript{33,34}.

Before the introduction of epoprostenol in 1999 the only medications available were calcium channel antagonists, which are effective only in a minority of patients\textsuperscript{35}. Subsequent introduction of bosentan, a dual endothelin receptor antagonist; and sildenafil, a phosphodiesterase V inhibitor, were found to further improve prognosis\textsuperscript{36,37}.

Sustained pulmonary arterial hypertension is associated with the development of intractable pulmonary vascular disease, which when advanced leads to right heart failure and death, as discussed above\textsuperscript{38}.

Interstitial lung diseases

In children, interstitial lung diseases (ILD) comprise a heterogeneous group of rare, mostly idiopathic disorders characterised by diffuse lung infiltrates, restrictive functional respiratory defects, and disordered respiratory gas exchange\textsuperscript{39}. Each year in Australia there are

\textsuperscript{27} Rosenweig E. Pulmonary arterial hypertension in children. Pediatric Pulmonology 2004;38:2-22.
\textsuperscript{28} Ibid
\textsuperscript{33} Ibid
\textsuperscript{36} Maiya S. Response to bosentan in children with pulmonary artery hypertension. Heart 2006;92:664-70.
\textsuperscript{38} Haworth S. Treatment and survival in children with pulmonary arterial hypertension. Heart 2009;95:312-7.
\textsuperscript{39} Thomeer M. Multidisciplinary interobserver agreement in the diagnosis of idiopathic pulmonary fibrosis. European Respiratory Journal 2008;31:585-91.
approximately four deaths due to ILD recorded in ABS mortality data in children aged less than 18 years\textsuperscript{40}.

ILD is most frequently diagnosed in the first year of life, with a predominance of paediatric entities such as pulmonary interstitial glycogenesis, neuroendocrine cell hyperplasia of infancy and genetic disorders of surfactant metabolism. In older children the pathogenesis is similar to adults\textsuperscript{41}.

The relative frequencies of these disorders are quite different in children compared with adults, and the overall prevalence is lower in children than adults. The precise annual incidence is not known but has been estimated at between 13 and 20 cases per 100,000 population, and increases with age\textsuperscript{42}.

There are few empiric data available to guide the evidence-based management of ILD in children. Most current treatment regimens for children are based on experience gained in small numbers of patients within individual centres, and extrapolated from information provided by adult studies\textsuperscript{43,44}.

The mainstay of treatment is supportive care, including the use of oxygen for chronic hypoxia, maintaining adequate nutrition, annual immunisation for influenza, aggressive treatment of intercurrent infections, strict avoidance of tobacco smoke and air pollutants, and the selective use of bronchodilators\textsuperscript{45}.

Pharmacological management includes the use of immunosuppressive, anti-inflammatory (including corticosteroid) and antifibrotic drugs. Patients with underlying systemic disorders require primary treatment for that disorder. For example, chemotherapy for malignancy, gamma globulin for hypogammaglobulinaemia, anti-infective treatments for chronic infections, and granulocyte-macrophage colony-stimulating factor (GM-CSF) and / or interferon-alpha for alveolar proteinoses where indicated\textsuperscript{46,47}.

Children with ILD may require lung or heart-lung transplantation as forced vital capacity on pulmonary function tests drops below 40\% of predicted values, and other signs of clinical deterioration are present\textsuperscript{48}. Lung and heart-lung transplantation outcomes are similar to those achieved with other clinical conditions. However, transplantation for ILD has been associated with the recurrence of the ILD in the transplanted lungs and has been demonstrated in patients

\textsuperscript{40} ABS Mortality Database. Lung mortality due to cystic fibrosis in persons aged 0-18 years (1999-2006).
with sarcoidosis, Langerhans cell histiocytosis, idiopathic pulmonary haemosiderosis and desquamative interstitial pneumonitis\(^ {49}\).

**Bronchiolitis obliterans**

Bronchiolitis obliterans (BO) is a pathologic process leading to the obstruction and / or obliteration of smaller airways. The histology seen in BO suggests that BO is a ‘final common pathway’ of response to airway epithelial injury from a number of agents and / or mechanisms. The aetiology remains elusive in spite of a growing body of basic science and clinical research\(^ {50}\).

The diagnosis is relatively rare in the general paediatric population. Although the exact incidence is unknown it is estimated to occur in less than 1 in 100 000 children in the general population\(^ {51}\).

There are multiple pathological forms of BO, each with varying clinical associations. BO can be considered according to two separate patient groups; BO occurring in the general population, and BO in patients who have received lung or stem cell transplants. In the general paediatric population BO is usually preceded by respiratory tract infection caused by adenovirus, influenza or measles, or by recurrent aspiration\(^ {52}\). In some patients, collagen vascular diseases (e.g. rheumatoid arthritis), toxic inhalation of gases such as oxides of nitrogen or metal fumes, or ingestion of substances such as alkaloids may precede BO development\(^ {53}\).

In contrast to the general population, the diagnosis of BO in recipients of bone marrow or lung transplants is common. It is estimated that 10% of all bone marrow transplant recipients and 35% to 60% of lung transplant recipients will develop BO. Further, BO is the most common cause of death after lung transplantation, accounting for over 40% of deaths that occur beyond one year after lung transplant\(^ {54}\).

BO is diagnosed histologically but biopsy is an insensitive tool for detection as the pathology occurs focally throughout the lungs. Instead, clinical surrogates are used to indicate the presence of BO, including a decline in FEV1 and FVC. The clinical surrogates are referred to as Bronchiolitis Obliterans Syndrome (BOS) and are applied to the detection of BO in patients post-transplant rather than to cases of BO that occur in the general population\(^ {55}\).

There is no consistently effective treatment strategy for BO. The approaches used include immunosuppression, photopheresis and total lymphoid irradiation. All have showed benefit in some patients but none are uniformly beneficial\(^ {56}\). Other potential options include the use of antimicrobials or statins (a cholesterol-lowering medication that also influences systemic fibrotic

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\(^{50}\) Woo M. Bronchiolitis obliterans is not the primary cause of death in pediatric living donor lobar lung transplant recipients. Journal of Heart and Lung Transplantation 2001;20:496.


\(^{52}\) Ibid


\(^{54}\) Ibid


activity). Re-transplantation is an option in select individuals. However, re-transplantation is a risk factor for death within the first year post-transplant.

**Congenital heart diseases**

Congenital heart diseases are a heterogeneous group of conditions that may lead to requirement for heart-lung or lung transplantation when other surgical treatment options and/or when maximal medical therapy fails. Approximately 36% of heart-lung and 6% of lung transplants are performed for children and adolescents with congenital heart abnormalities, including Eisenmenger Syndrome.

The prevalence of congenital cardiac disease where heart-lung or lung transplantation are indicated is low, and estimated as less than one in one million population.

Current indications for heart-lung or lung transplantation in this patient group include those with severe pulmonary hypertension with right ventricular failure, pulmonary atresia with diminutive pulmonary arteries, and congenital cardiac conditions that have led to irreversible bilateral pulmonary vascular disease.

If not corrected, congenital cardiac defects such as ventricular septal defects, atrial septal defects and patent ductus arteriosus may lead to chronic increased flow from the left to right side of the circulation. Over time, this increases pulmonary vascular resistance, leading to a reversal of the shunt from right to left, resulting in development of cyanosis and progressive functional disability. This is referred to as Eisenmenger syndrome.

Once irreversible changes of pulmonary hypertension are established, there is no longer a role for isolated cardiac surgical repair. Heart-lung transplantation is indicated as the treatments of choice if pulmonary hypertension with an irreparable cardiac defect is present. In patients with pulmonary hypertension and a repairable cardiac defect, the choice of surgical therapy is more complex and may include heart-lung transplantation (the majority of patients), bilateral lung transplantation or single lung transplantation with cardiac repair. Clinical trials comparing the outcomes of these options have not been performed.

**Selection of transplantation type**

Most transplant procedures performed worldwide for treatment of children and adolescents with end stage lung or pulmonary vascular disease are bilateral lung deceased donor transplants. Other transplant options are single lung deceased donor transplants, heart-lung transplantation or living-donor lung transplantation (LDLT).
Single lung deceased donor transplantation has advantages of shorter bypass time, thoracotomy instead of sternotomy, less bleeding and use of the donor organ supply to treat more than one recipient. However single lung transplantation involves a potentially difficult post-operative course and high mortality for many conditions affecting children and adolescents. Further, as the number of potential recipients of paediatric organs is usually fewer than recipients of adult organs (after blood group and size matching have been performed), there is usually only one potential recipient waiting for any potential paediatric donor, negating the ability to treat more than one person with the donor organs. As a result bilateral lung transplantation is usually preferred in paediatric patients.

Paediatric heart-lung transplantation was the procedure of choice in the 1980s for end stage lung disease, particularly for CF. The heart of the recipient in these cases would be used as a donor heart for a patient on the heart transplant list where possible – the so-called domino procedure. However, since the 1980s most transplant units have moved towards lung transplantation for isolated lung disease in paediatric patients.

Paediatric heart-lung transplantation is a simpler operation to perform compared with bilateral lung transplantation, but requires allocation of two organs from the scarce donor organ supply, adds risk of cardiac graft coronary vasculopathy and is less tolerant of ischaemic time compared with heart transplantation alone.

LDLT is an alternative to the transplantation of lungs into a recipient from a deceased donor. The procedure was first performed in a child in 1990. In the most common form of this operation, the recipient undergoes bilateral pneumonectomy, and then receives implantation of lower lobes from each of the two healthy adult donors who are operated on simultaneously.

The use of live donors usually occurs in cases in which the potential recipient mortality is very high while awaiting lung allografts from a deceased donor. Donor selection involves identifying donors with excellent health, adequate pulmonary reserve and a willingness to accept the risks of donation without coercion. Donors must also have no history of tobacco smoking, active lung disease, identifiable risk factors for familial lung diseases, be of normal body weight, correct ABO blood type and have a lung lobe size compatible with the recipient’s hemithorax. In addition, they must not be pregnant, have active malignancy or have active significant infections. A preference is given for family members or spouse or donor with ‘significant

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65 Aurora P. Personal communication, May 2010.
attachment' to the potential recipient\textsuperscript{73}. Given the size of even the shortest adults, LDLT is not a realistic option for children under six years old\textsuperscript{74}.

Approximately 550 live lung donors constitute 98% of the total global experience to date. The mean age of donors to date is 38 +/- 10 years (range 18 to 60 years). Sixty percent of the live lung donors have been male, 76% have been related to the recipient, and 24% have been unrelated. There has been no reported per-operative mortality among donors to date\textsuperscript{75}.

Since the introduction of LDLT, results from a number of transplant centres have been published. Outcomes have varied according to treatment centre. Although some centres have achieved results comparable to deceased donor organ transplant, long-term outcomes after LDLT are generally worse compared with deceased donor recipients\textsuperscript{76} \textsuperscript{77} \textsuperscript{78} \textsuperscript{79}.

**Selection criteria for listing for transplantation**

Paediatric lung or heart-lung transplantation are considered in selected children with end stage or progressive lung disease or life-threatening pulmonary vascular disease for which there is no other medical or surgical therapy. Usually, this means candidates have less than 50% chance of surviving two years without transplant intervention\textsuperscript{80}.

Each transplant centre has slightly different selection criteria, based on their experience and preferences. Irrespective of underlying diagnosis, all candidates should possess\textsuperscript{81} \textsuperscript{82} \textsuperscript{83}:

- a clear diagnosis or adequately delineated trajectory of illness despite optimal medical therapy that puts the individual child at risk of dying without a lung transplant;
- an adequate array of family support;
- adequate access to transplant services and medications after transplantation; and
- adequate evidence of willingness and ability on the part of patient and parent to adhere to the rigorous therapy, daily monitoring and re-evaluation schedule after transplant.

\textsuperscript{73} Barr M. A report of the Vancouver forum on the care of the live organ donors. Transplantation 2006;81:1373-5.
\textsuperscript{75} Sweet S. Pediatric living donor lobar lung transplantation. Pediatric Transplantation 2006;10:861-68.
\textsuperscript{76} Ibid
\textsuperscript{78} 2007 Annual Report of the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Rockville, MD.
• General selection guidelines have been published for some conditions only. For other clinical conditions there are no strict selection criteria\textsuperscript{84} 85.

\textit{Cystic fibrosis}

• baseline FEV1<30% predicted
• hypoxia at rest (PaO\textsubscript{2}<55mmHg)
• hypercapnia (PaCO\textsubscript{2}>50mmHg)
• female or paediatric patient with rapid clinical decline
• greater than two pulmonary exacerbations per year requiring hospital admission or home IV antibiotic therapy

\textit{Idiopathic pulmonary arterial hypertension}

• New York Heart Association functional class III or IV
• unresponsive to medical management
• mean right atrial pressure >10mmHg
• mean pulmonary arterial pressure >50mmHg
• cardiac index <2 l/min/m\textsuperscript{2}

\textbf{Contraindications to transplantation}

Contraindications to lung and heart-lung transplantation include anatomical, surgical, medical and psychological factors.

There is a high degree of variability between treatment centres regarding relative and absolute contraindications for transplantation. Those most commonly agreed upon include\textsuperscript{86} 87 88 89 90.

\textbf{Absolute}

• marked chest wall abnormalities (including severe scoliosis and severe tracheal abnormalities);
• active malignancy;
• sepsis;
• active tuberculosis;
• severe neuromuscular disease;

\textsuperscript{84} Woo M. Overview of lung transplantation. Clinical Reviews in Allergy and Immunology 2008;35:154-63.
\textsuperscript{86} Woo M. Overview of lung transplantation. Clinical Reviews in Allergy and Immunology 2008;35:154-63.
\textsuperscript{87} Wells A. Special considerations in pediatric lung transplantation. Seminars in Respiratory and Critical Care Medicine 2006;27:552-60.
documented, refractory non-adherence with clinical management;
multiple organ dysfunction; and
hepatitis C with histological liver disease.

Relative

• pleurodesis;
• renal insufficiency;
• markedly abnormal body mass index (BMI);
• mechanical ventilation;
• scoliosis;
• poorly controlled diabetes mellitus;
• osteoporosis;
• chronic airway infection with multiply resistant organisms;
• fungal infection / colonisation; and
• hepatitis B surface antigen positive.

Talc pleurodesis is a contraindication in some surgical centres but not others. Formerly, history of pneumonectomy was also considered a strong contraindication due to altered thoracic anatomy. However recent success has been demonstrated in performing transplantation in carefully selected cases where anatomy permits lung transplant.\textsuperscript{91}

Renal insufficiency (creatinine clearance less than 50 mL / 1.73 m\(^2\))
hepatic insufficiency and
left ventricular dysfunction are contraindications for isolated lung transplantation.\textsuperscript{92} However, transplantation is considered if combined with transplantation of the second failing organ. Heart-lung and lung-liver transplantation are established surgical clinical treatments for combined organ failure whereas simultaneous lung-kidney transplantation is rarely performed worldwide.\textsuperscript{93}

Adult patients with high BMI are at increased risk for early death following lung transplantation. Those with low BMI are not particularly at risk, unless the patient has cachexia which is associated with increased risk of waiting list death.\textsuperscript{94} The association between BMI and mortality following lung transplantation is less defined.

Children with cancer generally have to be in remission for one to five years, depending on the cancer type, prior to being listed for lung or heart-lung transplantation.\textsuperscript{95}

Virulent antibiotic resistant bacteria such as \textit{Mycobacterium abscessus} and \textit{Burkholderia cenocepacia} in patients with CF is considered an absolute contraindication in the majority of


\textsuperscript{93} Dishop M. Pediatric lung transplantation. Pediatric and Developmental Pathology 2008;11:85-105.


transplant centres. The presence of *Burkholderia cenocepacia* in particular is associated with early death and poor survival rates after lung transplantation. The presence of multi-resistant *Pseudomonas aeruginosa* is also an absolute contraindication in some transplant centres.

Psychosocial and financial factors are generally assessed in overseas centres prior to listing for lung transplantation. Limitations in insurance coverage and/or payment by insurers in the US may preclude transplantation for some candidates.

Child psychologists and paediatric social workers assess children and their families as a routine component of pre-transplantation evaluation in order to determine whether families and children are likely to be able to comply with the rigorous requirements of management post-surgery. Uncontrolled psychiatric or behavioural disorders are a contraindication to lung transplantation in most treatment centres.

A history of poor compliance with medical care is a relative contraindication in most centres, and is an important consideration for some families. In one study of heart and heart-lung recipients, 9% of children and adolescents were not compliant with their medication regimen and one third demonstrated non-adherence to the overall treatment regimen. This results in increased risk of graft failure. Lung and heart-lung transplantation usually require relocation of the child and parent to the treatment centre from the time of listing. For some families this financial and emotional commitment is not possible.

### International and national clinical activity

**International clinical activity and centre volumes**

The number of centres internationally reporting paediatric lung transplant procedures to the ISHLT has risen over time. According to the most recent ISHLT data, there were 32 centres reporting paediatric transplants to the ISHLT registry in 2006 and 36 in 2007. In 2007, centre volumes were as follows:

- 89% of centres reported performing fewer than five paediatric lung transplants per year;
- 8% (3 centres) performed between five and nine transplants; and
- 3% (1 centre) performed between 10 and 19 transplants.

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Between January 2000 and June 2008 there were 443 paediatric lung transplants performed in North America, 181 performed in Europe, and 35 performed in other countries\textsuperscript{104}. Clinical indications and numbers of recipients in each age range are outlined in Table 1.

Over this time period the majority of paediatric lung transplants internationally were performed in adolescents (66%), with CF the most common clinical indication for transplantation (60%)\textsuperscript{105}. In North America, proportionally fewer lung transplant procedures are performed in adolescents, and fewer performed for CF compared with other countries\textsuperscript{106}:

- in North America, 64% of paediatric lung transplants are performed in adolescents, compared with 80% in Europe and 85% in other countries.
- in North America, 56% of transplants are performed for CF, compared with 65% in Europe and 68% in other countries.
- between January 2000 and June 2008 there were approximately 70 lung transplants reported in recipients aged five years or less in North America and 12 procedures reported elsewhere in the world in this period. This may be in part because outside North America there are few reported donors aged six years or less.

LDLT has become a rare operation internationally. Worldwide, numbers have fallen from a peak of 14 in both 1998 and 1999 to three between January 2005 and December 2007\textsuperscript{107}. With the exception of Japan, most countries in the world do not currently perform LDLT\textsuperscript{108,109}.

\textsuperscript{104} Aurora P. Registry of the International Society for Heart and Lung Transplantation. Journal of Heart and Lung Transplantation 2009;1023-30.
\textsuperscript{105} Mallory G. Paediatric lung transplantation. European Respiratory Journal 2004;24:839-45.
\textsuperscript{107} Ibid
The number of centres reporting heart-lung transplantation in children and adolescents has decreased since the 1990s. Between 2002 and 2008 the number of centres worldwide reporting heart-lung transplants each year has varied between seven and 11, and all of these reported fewer than five transplants a year.

Figure 3: Number of centres reporting paediatric heart-lung transplants by centre volume (1984 to 2008)

In Australia and New Zealand, paediatric lung transplantation services are provided by adult institutions. All adult units (Sydney, Melbourne, Brisbane, Perth and Auckland) accept referral of adolescent patients. If patients are considered too small or too young for the expertise within Australia, clinicians have the option to refer the patient to an overseas unit if clinically indicated. Funding could be provided by an act of grace payment. The youngest patient to receive a lung transplant in Australia to date was nine years of age at the time of transplantation.\(^{114}\)

The Australian and New Zealand Cardiothoracic Organ Transplant Registry (ANZCOTR) contains information on all heart, heart-lung and lung transplants performed across the six Australian and New Zealand Cardiothoracic Transplant centres. An annual report is produced by June each year providing statistical information on numbers of transplants performed, waiting list activity and survival outcomes. The Registry also contributes its Australian de-identified information to the ISHLT on an annual basis.

In all centres, bilateral lung transplantation is the most commonly performed transplant procedure.

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\(^{114}\) ANZCOTR Thirteenth Annual Report. 2009.

**Table 2: Clinical activity by surgical centre, all age groups (2001 to 2008)**

<table>
<thead>
<tr>
<th></th>
<th>Heart-lung transplant</th>
<th>Single lung transplant</th>
<th>Bilateral lung transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>St Vincent’s Sydney</td>
<td>12</td>
<td>22</td>
<td>240</td>
</tr>
<tr>
<td>The Alfred</td>
<td>13</td>
<td>82</td>
<td>231</td>
</tr>
<tr>
<td>Royal Perth</td>
<td>3</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Auckland</td>
<td>0</td>
<td>11</td>
<td>70</td>
</tr>
<tr>
<td>Prince Charles Brisbane</td>
<td>16</td>
<td>11</td>
<td>82</td>
</tr>
<tr>
<td>Royal Children’s Hospital Melbourne (RCHM)*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44</strong></td>
<td><strong>138</strong></td>
<td><strong>624</strong></td>
</tr>
</tbody>
</table>

*RCHM has recorded no pulmonary transplant activity since 1999

Heart-lung and lung transplantation clinical data for paediatric patients were not provided in the most recent ANZCOTR report for individual treatment centres. However, the registry report demonstrates that, across treatment centres, both heart-lung and lung transplants are being performed in paediatric patients.

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**ANZCOTR Thirteenth Annual Report. 2009.**
Table 3: Age of recipients across treatment centres (2001 to 2008)\textsuperscript{117}

<table>
<thead>
<tr>
<th>Year</th>
<th>Heart-lung transplant</th>
<th>Bilateral lung transplant*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of transplants performed</td>
<td>Mean age</td>
</tr>
<tr>
<td>2001</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>2002</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>2003</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>2004</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>2005</td>
<td>5</td>
<td>37</td>
</tr>
<tr>
<td>2006</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>2007</td>
<td>6</td>
<td>38</td>
</tr>
<tr>
<td>2008</td>
<td>5</td>
<td>36</td>
</tr>
</tbody>
</table>

*No single lung transplants were performed in patients aged less than 18 years between 2001 and 2008.

The Australian Institute of Health and Welfare provides Australian lung and heart-lung transplantation clinical activity data by age category. According to the AIHW hospitalisations data there were 40 lung and three heart-lung transplantations performed in persons aged between five and 19 years between 2000-01 and 2007-08.

Table 4: Paediatric lung transplantation clinical activity, Australia (2000-01 to 2007-08)\textsuperscript{118}

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>00-01</th>
<th>01-02</th>
<th>02-03</th>
<th>03-04</th>
<th>04-05</th>
<th>05-06</th>
<th>06-07</th>
<th>07-08</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>1-4</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10-14</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>15-19</td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>All age groups (0-85+)</td>
<td>85</td>
<td>82</td>
<td>86</td>
<td>83</td>
<td>80</td>
<td>83</td>
<td>100</td>
<td>91</td>
<td>690</td>
</tr>
</tbody>
</table>

\textsuperscript{117} ANZCOTR Thirteenth Annual Report. 2009.  
\textsuperscript{118} AIHW National Hospital Morbidity Database 2009
Table 5: Paediatric heart-lung transplantation clinical activity, Australia (2000-01 to 2007-08)\textsuperscript{119}

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>00-01</th>
<th>01-02</th>
<th>02-03</th>
<th>03-04</th>
<th>04-05</th>
<th>05-06</th>
<th>06-07</th>
<th>07-08</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>15-19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>All age groups (0-85+)</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>29</td>
</tr>
</tbody>
</table>

Peer-reviewed published data are available regarding outcomes of paediatric lung transplantation at St Vincent's Hospital, Sydney. The adult lung transplant program commenced at this facility in 1986 and the paediatric program in 1991. Between 1991 and 2006, there were 37 adolescent recipients of heart-lung (6 patients) or lung (31 patients) transplants. The major indications were CF and congenital heart disease. In this cohort:

- mean waiting time was 273 days (range of five to 964 days);
- median inpatient stay was 11 days (range seven to 94 days);
- the five year survival was 55%; and
- BOS developed in 51% of patients.

The demand for paediatric lung and heart-lung transplantation exceeds the availability of donor organs, both within Australia and worldwide. This is of concern for children awaiting appropriate size-matched donor organs. Review of the Australian and New Zealand Organ Donation Registry between 1998 and 2007 demonstrates that in Australia, of 605 lung retrievals and 47 heart-lung retrievals there were 28 lung donors and seven heart-lung donors younger than 14 years of age\textsuperscript{120}. In New Zealand between 1993 and 2007, of 116 lung retrievals and one heart-lung retrieval there were three lung donors and no heart-lung donors younger than 14 years of age\textsuperscript{121}. Despite some use of ‘extended’ donor organs (e.g. from older donors), only 30% to 50% of available lungs are actually suitable for transplantation. National waiting list mortality rate data are limited, but estimates of 20% have been reported\textsuperscript{122}.

However, the majority of paediatric lung transplant recipients are in the adolescent age group. Most of these adolescents are able to take donor organs from small adults, and therefore it is not mandatory that they wait for paediatric donors. Further, as there is little paediatric lung transplant activity in Australia and New Zealand, it is possible that paediatric intensive care

\textsuperscript{119} Ibid
\textsuperscript{120} Australia and New Zealand Organ Donation Registry Report. 2008. ANZOD. Appendix 1.
\textsuperscript{121} Australia and New Zealand Organ Donation Registry Report. 2008. ANZOD. Appendix 2.
providers do not always approach potential cardiothoracic donors. As there are no data to support or refute this hypothesis, this is an area that requires ongoing research and evaluation.

The Alfred Hospital in Melbourne has developed protocols for lung retrieval from donors after cardiac death, to increase the donor pool by adding to the traditional ‘donation after brain death’ pool. There is no Australian program for LDLT at this time.

**Description of the treatment**

Determining which children may benefit from lung transplantation is often not straightforward; the correct timing of the referral to a transplant centre is also difficult to determine. The decision to perform transplantation is based on many factors, including past experience (both centre-specific and that in published reports), the scarcity of donor organs, and the specific wishes of patients and their parents or guardians.

**Timing of referral**

Indications for lung transplantation in children have expanded, and referral to a transplant centre should be considered in virtually any child with limited life expectancy because of lung disease. However, exactly when lung transplantation should be considered during the specific disease process requires detailed attention to not only the trajectory of the underlying illness but also to psychosocial factors, such as the readiness of the patient emotionally to the demands of daily therapy and frequent procedures.

Lung transplantation is a procedure of last resort and, when performed, should ideally provide the patient an improved likelihood of survival and an improved quality of life. There are no strict guidelines regarding the appropriate time to refer patients for assessment of suitability for lung or heart-lung transplant. Early referral is preferred by most treatment centres as it allows the patient, family and treatment team to establish a therapeutic relationship, which facilitates adherence to therapeutic interventions in the long-term.

The Transplantation Society of Australia and New Zealand has developed a draft national protocol for organ transplantation: eligibility and allocation criteria. This draft is currently out for public consultation. According to the protocol, within Australia and New Zealand assessment, listing and transplantation can only occur after careful evaluation by a recognised multidisciplinary Australian or New Zealand Lung Transplant Unit. Recent international guidelines that were formulated with Australian input, and which Australian and New Zealand units broadly follow, form the basis for the evaluation process.

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123 Aurora P. Personal communication, May 2010.
The best time for referral of paediatric patients for heart-lung transplantation is difficult to estimate with certainty because of the heterogeneity of patients in this group and the sometimes very long waiting times before donor organs become available. Regarding the Eisenmenger syndrome, some surgical centres follow guidelines for IPAH proposed by the International Society for Heart and Lung Transplantation, whereas other centres would only refer patients with advanced symptoms consistent with the New York Heart Association (NYHA) functional class IV. For other congenital cardiac conditions, some centres recommend referral of patients with any cardiac anomaly where there is persistent NYHA class III or IV symptoms despite maximal medical therapy, low or declining 6-minute walk distance, cardiac index of less than 2 litres/minute/m$^2$, or right arterial pressure exceeding 15mmHg$^{130}$. 

**Timing of transplantation**

The goals of lung and heart-lung transplantation are to prolong life and to improve quality of life. Careful patient selection and timing of transplantation are critical to achieving these goals. Liou et al. published data in 2007 suggesting children with CF do not experience survival benefit from lung transplantation$^{131}$. Subsequent analysis of the researchers’ data demonstrated significant flaws in the methods used in the study, but also highlighted the importance of timing for surgery as a factor that significantly influences the survival benefit achieved through transplantation$^{132}$. A thorough understanding of the disease course of the prospective recipient is necessary in order to time transplantation as late as possible to achieve the maximal survival benefit, whilst timing transplantation early enough to minimise the risk of dying on the waiting list$^{133}$.$^{134}$. Further, in order to achieve the best survival benefit, systems for allocation of donor organs and selection of appropriate patients for transplantation need to be supported by policies and protocols that enable good decision-making regarding timing of the surgery$^{135}$.$^{136}$. 

Criteria regarding donor organ allocation vary between countries. In some countries, time accrued on the waiting list is used as the criterion for allocation. In the case of lung transplantation, the practice of early listing is a problem with this approach, as is the risk that transplantation will be performed too early in the disease course for a survival benefit to be gained, whilst others with a more urgent need for transplantation, and in whom survival benefit could be obtained, die on the waiting list$^{137}$. In comparison, listing for heart-lung transplantation needs to be relatively early as there may be a longer wait compared with lung transplantation (up to several years)$^{138}$.  

Other countries use urgency of need as the principal criterion for transplantation. The child should already be on full medical therapy, and in spite of full medical therapy, the predicted life expectancy for the child should be poor (usually quoted as two years or less)\textsuperscript{139}. Centres in Australia and the UK prioritise sicker patients for transplantation\textsuperscript{140}. Difficulties with this system arise due to the fluctuating clinical course many patients may follow, and difficulties empirically determining who the most urgent cases are\textsuperscript{141,142}.

In the US, the United Network for Organ Sharing (UNOS) revised lung allocation scoring (LAS) system (2006) is used to determine waiting list priority for transplantation by attempting to balance urgency and outcome. This system preferentially allocates lungs from paediatric donors to paediatric patients. A LAS is calculated for each patient 12 years of age and older on the waiting list. Factors involved in lung allocation score calculation include the following\textsuperscript{143,144}:

- forced vital capacity;
- pulmonary arterial diastolic pressure;
- oxygen requirement at rest;
- age;
- BMI;
- diabetes mellitus, insulin-dependent;
- functional status;
- 6 minute walk distance;
- mechanical ventilation; and
- diagnostic group (A=emphysema; B=pulmonary hypertension, idiopathic and congenital heart disease; C=septic lung disease including CF; D=ILD).

Donor lungs for children aged less than 12 years of age continue to be allocated by time accrued on the waiting list. ABO blood type and distance between the donor and transplant centres are also considered in allocating donor organs\textsuperscript{145}.

Potential recipients of a heart-lung transplant appear on both the heart and lung match lists. When either organ is offered to them, based on status and waiting time for hearts, LAS (if aged 12 years or older) or waiting time (if aged less than 12 years) for lungs, the other organ automatically defaults to the heart-lung recipient. Due to problems encountered with this

\textsuperscript{139} Doherty G, Aurora P. Update on paediatric lung transplantation. Paediatric Respiratory Review 2010; 11:54-61.
\textsuperscript{141} Ibid
approach, the Thoracic Organ Transplantation Committee in the US is continuing to study the best approach for allocation of organs to heart-lung recipients\textsuperscript{146}.

**Preoperative assessment**\textsuperscript{147 148 149}

In order to list the patient for transplant, a thorough preoperative assessment is required. This usually involves hospital admission for a number of days, and assessment involving a team of transplant coordinators, surgeons, physicians, nursing staff, social workers, psychologists, anaesthetists and intensive care staff. The diagnosis of and alternatives to transplantation are taken into consideration, along with social and psychological factors important to the wellbeing of the child and likelihood of long-term successful outcomes post-transplant\textsuperscript{150}.

**Laboratory Studies**

- full blood count and differential: to establish baseline values and screen for underlying immunodeficiency;
- Prothrombin time (PT) and/or activated partial thromboplastin time (aPTT): to detect abnormalities of blood coagulation that may complicate surgery;
- blood typing and screening: to match the donor and recipient;
- renal function: for baseline monitoring before immunosuppression and antimicrobials are commenced;
- liver function and blood borne virus screening: to assess for contraindications to transplantation;
- preformed reactive antibody panel: to assess the risk of development of hyperacute rejection;
- lipid profile: for baseline monitoring before immunosuppression is commenced;
- serologic tests for rubella, herpes viruses and Epstein-Barr virus (EBV), varicella, toxoplasmosis, and cytomegalovirus (CMV): to screen for previous exposure and the need for vaccination;
- sputum microscopy, culture and sensitivities: to direct the choice of antimicrobial agents after transplantation;
- autoantibodies: ongoing monitoring of patients with autoimmune disease;
- arterial blood gases: to provide a measure of lung function; and
- thyroid function: prior to commencement of immunosuppression medications.

**Imaging Studies**

- chest radiography and CT scanning: to evaluate the extent of disease and to determine the size of the thorax and vessels;

\textsuperscript{146} Ibid
\textsuperscript{148} Wells A. Special considerations in pediatric lung transplantation. Seminars in Respiratory and Critical Care Medicine 2006;27:552-60.
\textsuperscript{150} Crossland D. Heart and heart-lung transplant. Paediatrics and Child Health 2007;17:6-10.
• ventilation-perfusion scanning: to assist in determining the function of both lungs and, in a bilateral sequential procedure, to determine which lung should be replaced first;
• echocardiography: to evaluate cardiac function and assess for pulmonary hypertension;
• sinus CT scanning: performed in some centres to determine the need for surgical intervention in patients with CF before transplantation (because the sinuses contain organisms that may reinfect the lower respiratory tract after transplantation); and
• bone densitometry: performed in some centres to assess risk for fractures in patients with end-stage lung disease as patients often have a history of steroid use.

Other Tests
• pulmonary function testing: to help determine the degree of impairment, timing of lung transplantation and provide baseline data for postoperative comparison;
• six-minute walk test: to help determine the timing of lung transplantation;
• tuberculin skin test: performed in patients from endemic areas of TB infection in order to rule out active tuberculosis (an absolute contraindication to lung transplantation);
• electrocardiography: to assess for right ventricular hypertrophy or other cardiac dysfunction; and
• cardiac catheterization: if indicated, to measure degree of pulmonary hypertension or to assess benefits of vasodilator therapy.

Diagnostic Procedures
• bronchoscopy with bronchoalveolar lavage may be indicated to isolate pathogens from the lower airways or to document clearance of atypical mycobacteria.

Preoperative management

Once the child is listed for lung transplantation, efforts to optimise the patient's nutrition and growth are undertaken. This may involve enteral feeding and/or the use of appetite stimulants. Where the child is at risk of osteoporosis due to steroid intake and poor nutritional status, bisphosphonate therapy may be commenced. A regular physical rehabilitation program is usually also commenced to improve postoperative functional return. The preoperative period is also used for ongoing education and counselling to allow the family the opportunity to prepare emotionally and financially for the transplantation process\textsuperscript{151}.

Medical Therapy

Treatment varies depending on the primary diagnosis. The goal of therapy for patients on the transplant waiting list is to optimize their medical care in preparation for the upcoming surgery and to correct deficiencies discovered during the evaluation. This is specific to the clinical conditions for which transplantation is indicated but also includes improving the patient's nutritional status, providing pulmonary rehabilitation, and trying to decrease the number of preoperative pulmonary exacerbations for which intravenous antibiotics are needed\textsuperscript{152}.

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If the patient has psychosocial contraindications to transplantation, attempts may be made to correct those conditions by providing patients and their families with the assistance they need to successfully care for their child. If that assistance is ineffective and if transplantation is otherwise deemed appropriate, some centres pursue placement of the child with alternative caregivers. In other centres, the need for placement is considered a contraindication to transplantation\textsuperscript{153}.

**Surgical Therapy**

Surgical intervention prior to transplant may vary depending on the primary diagnosis. For example, patients with CF and end-stage lung disease may develop pneumothoraces and require surgical intervention. Generally, any thoracic procedure before transplantation may increase the risk of bleeding and intraoperative or immediate postoperative mortality and is therefore avoided if possible. Other surgical interventions that may be performed prior to transplant include the placement of a gastrostomy tube for enteral feeding and sinus surgery in patients with chronic infection in order to enable effective treatment of the sinus as a potential nidus for postoperative infection\textsuperscript{154,155}.

**Peri-operative management**

**Donor lungs**

Lung allografts can be obtained from deceased (i.e. brain dead) donors, non-heart beating (i.e. deceased cardiac) donors or from lobes obtained from live donors who are ABO compatible and who are an appropriate match for lung lobe size (LDLT)\textsuperscript{156}.

The criteria for acceptability for lung donors have been derived from experience rather than from clinical trials. The ideal lung donor should be a non-smoker of the appropriate body size and blood type with no significant lung disease. The ischaemic time should be minimal, gas exchange should be normal, and there should be no pulmonary trauma or infections. A comprehensive review of factors that influence allograft survival for lung transplantation in general was completed by the Pulmonary Council of the ISHLT\textsuperscript{157}. However, specific criteria for paediatric patients have not been established. Contraindications to lung donation include active malignancy, positive HIV status, hepatitis B or C antibodies, sepsis and significant tobacco use. Further factors leading to the unsuitability of lungs for transplantation include:

- pulmonary contusion – chest wall trauma is common among lung donors due to the high prevalence of trauma as an underlying cause of death. Except when a specific recipient is in critical condition, most transplant centres would defer transplanting lungs if significant contusions were present\textsuperscript{158};

\textsuperscript{155} Dobbin C. The impact of pan-resistant bacterial pathogens on survival after lung transplantation in cystic fibrosis: results from a single large referral centre. Journal of Hospital Infection 2004; 56:277-82.
• fat embolism – fat embolism as a result of long bone fractures is common with 9% of donors demonstrating evidence of fat embolism in one clinical trial. Fat embolism may not be apparent prior to transplantation of the lungs into the recipient. Upon reperfusion, this may result in a cascade of inflammation in the recipient which can lead to major graft dysfunction;

• pulmonary emboli – pulmonary emboli are common in donors who have experienced significant trauma prior to death. In one case series, 28% of donor lungs demonstrated evidence of pulmonary embolism. Many transplant recovery surgeons perform a retrograde flush of the donor organs with preservation solution in order to dislodge emboli prior to implantation;

• trauma to the lung and airways – it is rare to sustain trauma to the central airways but this can result from blunt chest injury. Early flexible bronchoscopy of the donor may assist in detection and decisions regarding whether repair is a viable option;

• pneumonia – this is a cause of graft unsuitability if the infection is severe. Approximately 20% of donors have ventilator-assisted pneumonia. If it is unlikely antimicrobial therapy given to the recipient peri- and post-operatively is unlikely to successfully treat the infection, the donor may be unsuitable;

• pulmonary aspiration – aspiration pneumonia may preclude successful use of donor lungs if, after initial bronchoscopy there is evidence of persistent radiographic infiltrate, with resulting irretrievable lung injury;

• atelectasis – atelectasis occurs commonly in the lungs of donors who are brain dead due to the inability of the donor to cough, change postural position or breathe deeply. There are a range of strategies that address collapsed alveoli. However, if atelectasis is extensive, donation may be inappropriate;

• pulmonary oedema – as primary graft dysfunction due to ischaemia-reperfusion injury is a common and serious complication immediate post lung transplantation, some centres are cautious in accepting donor lungs that have been resuscitated after significant oedema of any aetiology, and

• systemic inflammatory response – recent clinical research has demonstrated that an intense systemic inflammatory response occurs during the process of brain death. The use of high doses of corticosteroids has become common practice in the


management of the potential brain donor due to the evidence that its use improves the probability that the lungs will be suitable for transplantation\textsuperscript{166}. The donor is usually screened with a chest radiograph and PaO\textsubscript{2} whilst receiving mechanical ventilation to ensure the chest radiograph is free of infiltrates, atelectasis and pulmonary oedema, and that PaO\textsubscript{2} should meet specific criteria that are determined by ventilator settings\textsuperscript{167}. Further evaluation of the donor by flexible bronchoscopy and gross examination of the lungs with the chest open are usually performed. Bronchoscopy is used to detect erythematous Airways suggestive or gastric aspiration, and purulent secretions that do not clear with suctioning. Gross examination may reveal abnormalities not detectable on chest radiograph\textsuperscript{168}. Whilst individual practice varies between treatment centres, the lung procurement generally involves the following elements\textsuperscript{169,170}:

- a circumferential dissection of the trachea is performed between the ascending aorta and superior vena cava, opening both pleural spaces, examining the lungs, and cannulating the distal main pulmonary artery;
- the donor is anticoagulated with heparin;
- prostaglandin E\textsubscript{1} is injected into the main pulmonary artery;
- the aorta is then clamped and the left atrial appendage is amputated to vent the pulmonary venous return;
- preservation solution is injected into the main pulmonary artery;
- iced slush is applied topically to the lungs while the lungs are ventilated with a low FiO\textsubscript{2} (<0.4) and low tidal volumes, in order to maintain a minimum required peak airway pressure (<20cm H\textsubscript{2}O);
- after the infusion of the pulmonary and cardiac preservation solution is complete the cardiac procurement is completed;
- if a bilateral lung transplant is to be performed, the left atrial cuff is shared between the cardiac and pulmonary procuring teams;
- once the heart is removed, the lungs are removed \textit{en bloc} with the descending thoracic aorta, thoracic oesophagus stapled at either end and the mediastinal pleura;
- the trachea is occluded with the lungs inflated to low airway pressure (15-20cm H\textsubscript{2}O); and
- the lungs are then placed in cold preservation solution in a transport container packed in ice.

Minimising damage from ischaemic-reperfusion injury is important. Antegrade and retrograde flush using ice-cold saline or crystalloid flush solutions, inflation using 100\% oxygen, and

maintenance of hypothermia are all employed to reduce the allograft metabolic demands and decrease cellular injury\textsuperscript{171}.

Marginal donors have been used with varying success in selected cases. Marginal may be defined as a donor with an infiltrate / atelectasis, lower PaO\textsubscript{2}, older age, or smoking history (particularly when greater than 20 pack years). Because of the limited data available on the use of marginal donors in children no specific recommendations have been developed regarding their use in paediatric populations\textsuperscript{172,173}.

Medical management

Antibiotic therapy is usually initiated empirically at the time of transplant according to the child's history of airway organisms\textsuperscript{174}.

Whether the patient also receives the first doses of immunosuppressive medications and / or induction therapy before the surgical procedure is program specific. The use of an induction agent to either eliminate T lymphocytes or inhibit T cell function is somewhat controversial primarily due to concerns regarding the increased risk of infection associated with the use of these agents\textsuperscript{175}. Approximately 45\% of paediatric lung transplant recipients receive induction therapy with either interleukin-2 receptor antagonists or cytolytics\textsuperscript{176}. These agents are discussed below.

Transplant procedure

Very few paediatric single-lung transplants are performed. Most children undergo bilateral sequential lung transplantation for a number of reasons: two lungs are typically available from paediatric donors, two lungs of similar size promotes symmetrical thoracic growth, and patients with CF require bilateral lungs to prevent risk of infection from a diseased native lung to a single transplanted lung\textsuperscript{177}.

The surgical approach in paediatric patients depends on the type of transplant to be performed, the patient’s primary diagnosis, and the surgeon’s experience / preference; but is generally via a bilateral anterolateral clamshell thoracotomy in paediatric patients\textsuperscript{178}.

Bilateral sequential lung transplantation involves transplanting one lung while the patient is supported on their remaining lung. The patient is then supported by their new transplanted lung, allowing the transplantation of the second lung. The transplantation is performed with or without cardiopulmonary bypass (CPB), depending on the treating centre\textsuperscript{179}. CPB may be used as it allows the native lungs to be deflated, thereby facilitating their surgical removal, may reduce the

\textsuperscript{171} Woo M. Overview of lung transplantation. Clinical Reviews of Allergy and Immunology 2008;35:154-63.
\textsuperscript{177} Dishop M. Pediatric lung transplantation. Pediatric and Developmental Pathology 2008;11:85-105.
donor lung ischaemia time, and permits clamping and antibiotic irrigation of the tracheobronchial airway. Further, as double-lumen endobronchial tubes will not fit into younger children, and many paediatric recipients are too unwell to tolerate one-lung ventilation, cardiopulmonary bypass is often necessitated. The disadvantages of CPB include the negative consequences of the systemic inflammatory response that it initiates and the requirement for anticoagulation.

The recipient’s lungs are removed and the right and left donor lungs are implanted using end-to-end bronchial, pulmonary arterial and pulmonary venous anastomoses. Peribrochial tissue is sutured loosely around the bronchial anastomoses to provide blood flow by new vessel ingrowth. The pulmonary artery and vein connections are performed. A donor atrial cuff is attached to the recipient’s left atrium, taking care to avoid suture lines near the pulmonary veins thereby reducing the risk of pulmonary vein stenosis.

When the new lungs have been implanted and perfusion has been re-established, then chest tubes are placed (bilateral tubes if double lung transplantation). Before chest closure, flexible bronchoscopy can be performed to check the anastomoses, and transesophageal echocardiogram is obtained to confirm good venous and arterial flows. The patient remains intubated and on mechanical ventilator support while they are transported to the intensive care unit.

Many of the procedural aspects of heart-lung transplantation are equivalent, although heart-lung transplantation is reported to be a simpler operation compared with bilateral lung transplantation. In summary:

• the procedure is performed using cardiopulmonary bypass;
• the heart and lungs are removed while carefully preserving the phrenic nerves and addressing bronchial artery circulation in order to prevent postoperative bleeding complications;
• the donor heart and lungs are inserted; the tracheal anastomosis is performed first;
• the right atrial anastomosis is performed next, followed by the aortic anastomosis; and
• care is taken to keep the donor trachea as short as possible because of the limited vascularity of the area.


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Postoperative management

The postoperative course consists of approximately a two week hospitalisation period. Ideally, patients remain intubated and ventilated for a maximum of 24 to 48 hours after surgery. Prolonged mechanical ventilation is associated with increased morbidity and mortality. As a result, early extubation is a goal of postoperative management in most treatment centres. Avoidance of complications of hypotension, volume overload, infection and renal dysfunction facilitate early extubation.

Most patients experience postoperative pulmonary oedema due to increased pulmonary vascular permeability that results from ischaemia and reperfusion injury, and due to the interruption of the pulmonary lymphatics. As a result, the early postoperative care of the patient involves maintaining adequate blood pressure/ perfusion and gas exchange whilst maintaining renal function and achieving the shortest intubation time possible. This requires close monitoring of fluid balance and careful ventilator management.

Recipients are kept intravascularly hypovolaemic during the first few days after surgery in order to minimise pulmonary oedema. This requires the use of maximally concentrated intravenous medications and the routine use of diuretics.

The immediate postoperative period is also a time when the patient receives large amounts of immunosuppression medication. There is currently no evidence that treatment using isolation is more effective than simple meticulous attention to hand-washing. However, due to the increased risk of infection surveillance cultures and aggressive treatment of any suspected infections are usually performed.

When the patient is extubated and pressor medications are discontinued, transfer from intensive care can occur. Intravenous antibiotics may be continued whilst an inpatient. Physical therapy is initiated in the intensive care unit and is increased in intensity as the patient becomes ambulatory.

In order to minimise nosocomial infection, facilitate rehabilitation and minimise use of resources many centres discharge patients from hospital to post-transplantation housing that is near the hospital. Here patients continue to attend regular sessions of physical therapy. After surgery patients undergo surveillance bronchoscopy with transbronchial biopsy. The timing of surveillance procedures varies from centre to centre and is discussed below.

Induction immunosuppressant therapy

A well-established risk factor for the development of BO is a history of acute rejection. Induction immunosuppression may be used by treatment centres in an attempt to minimise the risk of this occurring. It has not been definitively established in clinical trials whether induction immunosuppression is effective in achieving this outcome. Further, there are risks associated with the use of induction immunosuppression because agents used for induction are potent immunosuppressants that may potentially increase the risk for infection or malignancy.

References:

postoperatively\(^{188}\). As a result, the use of induction immunosuppression is not universal and varies according to treatment centre (Figure 4).

Consensus has not been reached on whether induction therapy should be used, and centres which use induction therapy have not reached a consensus as to the best agent to use. The 2009 ISHLT Registry report indicates that in 2008, almost 45% of the paediatric lung transplant recipients received some form of induction immunosuppression. Usage appears to have declined compared with previous years. The reasons for this are not clear\(^{189}\).

**Figure 4: Induction immunosuppression for paediatric lung transplantation (2001 to 2008)**

In general, induction agents can be divided into lympholytic agents and interleukin (IL)-2 receptor antagonists\(^ {190}\). Lympholytic agents contain antibodies to human lymphocytes and are derived from animal serum. They include rabbit antithymocyte globulin (RATG [Thymoglobulin]), muromonab-CD3 (OKT3 [Orthoclone]), and equine antithymocyte globulin (lymphocyte immune globulin [ATGAM])\(^ {191} \, 192\).

- These agents are typically administered for three to five days immediately after transplantation. They may also be used to treat steroid-resistant rejection, where they are typically administered for 10 to 14 days\(^ {193}\).
- Patients receiving OKT-3 may experience a higher incidence of postoperative infection. RATG may be better tolerated than other agents and has been demonstrated to decrease the incidence of acute rejection in a single randomised controlled trial. No study has documented that any of these agents have a beneficial impact on the incidence of BO\(^ {194}\).

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\(^{191}\) Rebellato L. A comprehensive definition of the major antibody specificities in polyclonal rabbit antithymocyte globulin. Transplantation 1994; 57:685-94.


\(^{194}\) Ibid
Potential adverse effects include cytokine release syndrome (i.e. chills, fever, vomiting, diarrhoea, headache), increased incidence of infection, increased risk of post-transplantation lymphoproliferative disorder (PTLD), and leukopaenia\textsuperscript{195}. IL-2 receptor antagonists are monoclonal antibodies that specifically bind to the IL-2 receptor on activated T cells. They include basiliximab (Simulect) and daclizumab (Zenapax). Agents differ in their half-lives and in the number of doses required for immunosuppression\textsuperscript{196}. Trials have demonstrated IL-2 receptor antagonists reduce the frequency of acute rejection in adult lung transplant recipients. However, a retrospective study in paediatric lung transplant recipients found no difference in acute rejection or BO compared with controls\textsuperscript{197}.

**Maintenance immunosuppression**

Maintenance immunosuppression is required in all transplant recipients. Agents used include calcineurin inhibitors, cell toxins, corticosteroids, and Rapamycin and its derivatives. Corticosteroids are the most commonly used agents in paediatric lung transplant recipients, followed by calcineurin inhibitors and cell toxins.

*Figure 5: Maintenance immunosuppression at time of follow-up for paediatric lung transplant recipients (2001 to 2008)*

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**Calcineurin inhibitors\textsuperscript{198,199,200}**

- Cyclosporine and tacrolimus are the drugs used in this category. These agents are the mainstay of immunosuppression and are responsible for the success of


\textsuperscript{196} Garrity E. Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. Transplantation 2001; 71:773-7.


transplantation. However, because of an array of potential adverse effects and drug interactions, they have limitations.

- Drug levels are monitored on a regular basis. Doses for lung transplant recipients are usually maintained at higher levels than those for other organ recipients. The serum levels require maintenance at levels high enough to prevent rejection without causing debilitating toxic effects.
- Both drugs can increase the patient’s risk of infection, nephrotoxicity, neurotoxicity, GI disturbances, electrolyte derangements, malignancy, and hypertension.
- Multiple trials have compared these two agents; they are equal in prevention of BO and improvement of survival. However, the adverse effect profiles are different. Cyclosporine may cause gingival hyperplasia and hirsutism, whereas tacrolimus may cause more hyperglycemia.
- Most paediatric lung transplant centres preferentially use tacrolimus-based regimens as their primary immunosuppression because it has a more manageable adverse effect profile in children and because the gingival hyperplasia and hirsutism that occur with cyclosporine negatively influence compliance, particularly in teenage patients.
- Studies suggest that aerosolized cyclosporine may provide a substantial survival advantage to lung transplant recipients receiving the drug, however further studies are necessary.

**Cell toxins**

- This category of immunosuppressant agents includes azathioprine (Imuran) and mycophenolate mofetil (MMF, [Cellcept]). Studies comparing azathioprine with MMF in lung transplant recipients have not shown a clear clinical benefit of one agent over the other.
- Dosing is often determined by white blood cell count. In addition, MMF serum levels can be measured and dosage adjusted to maintain adequate serum levels.
- Potential adverse effects for both of these agents include myelosuppression, infection, and nausea. In addition, azathioprine may cause hepatotoxicity and rash. MMF may cause diarrhoea and an increased risk of lymphoproliferative disorders.

**Corticosteroids**

- Corticosteroids are the most commonly used group of immunosuppressant agents.

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Corticosteroids possess many potential adverse effects, including increased risk of infection, hyperglycaemia, hypertension, cataract formation, bone loss, gastrointestinal disorders, mood alteration, acne, growth suppression, and amenorrhea. At high doses, corticosteroids may cause alterations in serum levels of the calcineurin inhibitors.

Rapamycin and its derivatives

This family of drugs consists of sirolimus (rapamycin, [Rapamune]) and everolimus (40-0-[2-hydroxyethyl]-rapamycin [RAD]). The use of rapamycin is rarely reported during the first year post transplant, but is more common at five year follow-up with an estimated 15% of patients on this agent by five years post-transplant.

Because sirolimus and RAD work by different mechanisms, they can be used with cyclosporine or tacrolimus.

One study in lung transplant recipients examined the use of sirolimus as rescue therapy; renal dysfunction was the most common indication. In these 23 adult lung transplant recipients, only two episodes of acute rejection were documented over a median follow-up period of 107 days.

Sirolimus may have a beneficial effect in patients with chronic rejection because it inhibits proliferation of endothelial and smooth muscle cells in vitro and appears to inhibit vascular injury in vivo. RAD also inhibits smooth muscle proliferation.

Initially, rapamycin was available only as a suspension, but a tablet form is now available. It is routinely dosed once daily, but evidence indicates that in children more desirable drug levels are maintained with a twice-daily dosing regimen.

Potential adverse effects of sirolimus include hyperlipidemia and myelosuppression. Lipid profiles must be regularly monitored. Sirolimus has no role in the early postoperative period because it may interfere with wound healing and cause anastomotic dehiscence. Sirolimus is also associated with the development of interstitial pneumonitis.

Follow-up

Outpatient care post-transplant varies between treatment centres. Patients require frequent outpatient clinic sessions and pulmonary rehabilitation. To prevent complications, or to identify complications early, treatment centres use protocols outlining the parameters that should be monitored on a routine basis.

Therapeutic drug monitoring is part of the routine post-transplant monitoring has become a standard for transplant care. Many of the immunosuppressive medications have a narrow

therapeutic index, and patients have variable pharmacokinetics. This appears to be particularly relevant in preventing side effects from the agents. Patients are required to monitor their lung function, blood pressure, temperature, and weight daily and advise of any changes\textsuperscript{210}.

Rejection or infection frequently results in loss of lung function. For children old enough to perform spirometry, FEV1 may be monitored on a daily basis in order to detect early changes in lung function. For younger children, home oximetry may be used on a daily basis\textsuperscript{211}.

**Bronchoscopy**

In some centres the first routine surveillance bronchoscopy is performed within the first week after transplantation. This may be within the first 24 hours, while the patient is still intubated. In other centres, the first bronchoscopy may be deferred, and performed within the first month after transplantation\textsuperscript{212,213}.

Protocols for surveillance transbronchial biopsy vary between treatment centres\textsuperscript{214}. At one large international treatment centre, transbronchial biopsy is performed at one week and one, two, three, six, nine, 12 and 18 months after transplantation. St Vincent’s Hospital, Sydney, has published a transbronchial biopsy surveillance schedule of three, six and nine to 12 weeks post transplantation with additional procedures for new-onset symptoms or as a follow-up for acute rejection or CMV pneumonia\textsuperscript{215}. The optimal monitoring system has yet to be clearly elucidated and is an area where further study is required\textsuperscript{216}.

**Outcomes of treatment**

Lung and heart-lung transplant complications can occur immediately after surgery or be delayed for several years. A high degree of clinical suspicion and close follow-up of transplant patients, including frequent monitoring, are strategies commonly employed to reduce morbidity and mortality in patients who survive the transplant surgery.

**Complications**

The significant complications associated with heart-lung transplantation and lung transplantation are similar, and predominantly relate to the lung allograft\textsuperscript{217}. Complications after lung and heart-lung transplantation can be described according to three general phases, outlined in Table 6.

\textsuperscript{215} Morton J. Successful lung transplantation for adolescents at a hospital for adults. Medical Journal of Australia 2007; 278-82.
\textsuperscript{217} Date H. Lung and heart-lung transplantation. Cardiology in the Young 2009; 19:45-8.
Table 6 – Complications following transplantation

<table>
<thead>
<tr>
<th>Immediate (first week)</th>
<th>Early (first 3 months)</th>
<th>Late (after 3 months)</th>
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<tbody>
<tr>
<td>Hyperacute rejection</td>
<td>Acute rejection</td>
<td>Bronchiolitis obliterans</td>
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<tr>
<td>Infection</td>
<td>Infection</td>
<td>Malignancy</td>
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<td>Surgical complications</td>
<td>Surgical complications</td>
<td>Hypertension</td>
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<tr>
<td>Early graft dysfunction</td>
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<td></td>
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<td>Diabetes</td>
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<td>Hyperlipidaemia</td>
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Rejection

The risk of organ rejection begins at the time of transplant surgery and remains for the life of the graft and recipient. Lung transplant patients have a higher incidence of rejection than isolated heart, liver or kidney transplant recipients. In heart-lung transplant recipients, the rate of rejection of the lungs is higher than rejection of the heart in the same recipient.\(^{218}\)

Rejection is classified as hyperacute, acute or chronic. The histological grading of rejection is based upon the 1996 Lung Rejection Study Group guidelines and is based on the intensity of cellular infiltration and presence or absence of eosinophilic hyaline fibrosis.\(^{219}\)

Hyperacute rejection is the result of recipient antibodies binding to donor tissue antigens and causing graft injury. This complication is uncommon due to testing of recipients to identify patients at risk.\(^{220}\) While there is insufficient time for tissue matching prior to transplant, all recipients and donors are screened for preformed antibodies or panel reactive antibody (PRA). A PRA level greater than 25 in the recipient should trigger a prospective specific crossmatch between the donor and recipient. A positive specific crossmatch suggests anti-donor circulating antibodies that could lead to hyperacute rejection of the allograft and therefore usually results in cancellation of the transplant for that proposed recipient.\(^{221}\) Avoiding transplant in patients with elevated PRAs and positive specific crossmatch, and confirming appropriate ABO matching of donor and recipient have reduced the incidence of hyperacute rejection.\(^{222}\) Treatment involves the use of plasmapheresis and cyclophosphamide therapy. However, in some cases hyperacute rejection can result in graft loss and death.\(^ {223}\)

Acute rejection occurs later than hyperacute rejection and is a serious complication in the postoperative period. It is characterised by poor gas exchange across the respiratory membrane. Patients may present with nonspecific symptoms consistent with infection, including fever, dyspnoea and hypoxia, or may be asymptomatic. Deterioration in pulmonary function

\(^{218}\) Woo M. Overview of lung transplantation. Clinical Reviews of Allergy and Immunology 2008;35:154-63.


\(^{221}\) Woo M. Overview of lung transplantation. Clinical Reviews of Allergy and Immunology 2008;35:154-63.

\(^{222}\) Ibid

tests may be indicative of acute rejection and indicate the need for further investigations with bronchoscopy and lung biopsy\textsuperscript{224}.

According to published data from one treatment centre, an average of 1.3 episodes of acute rejection develops per patient in the first six months after transplantation\textsuperscript{225}. However, different centres will have different rates, and overall the number of episodes is reducing with time as immunosuppression regimens become more effective. Routine bronchoscopy and transbronchial biopsy are performed in many treatment centres three to six monthly to facilitate early detection of rejection and infectious diseases pathogens. Results of surveillance bronchoscopy case series demonstrate rejection in 12% of symptomatic patients and 4% of asymptomatic patients in the first year after transplant. Rates of infections are approximately 29% in asymptomatic patients and 69% in patients with symptoms. The complication rate for bronchoscopies is approximately 3%\textsuperscript{226}.

Treatment of acute rejection is normally with systemic corticosteroids, although occasionally other immunosuppressive agents such as Methotrexate or anti-thymocyte globulin may be employed. In the great majority of cases, acute rejection can be treated successfully although repeated episodes of rejection have long term consequences for graft health\textsuperscript{227, 228}.

**Bronchiolitis obliterans (BO)**

BO is a form of chronic rejection. It occurs in up to 70% of deceased-donor heart-lung and lung transplant recipients and accounts for over 40% of deaths that occur beyond one year after transplant\textsuperscript{229}. Histological and surrogate clinical criteria for the diagnosis are discussed above. Acute rejection is the most important risk factor for developing BO. The incidence of BO in living donor lobar lung transplant recipients is lower, presumed due to shorter ischaemic times compared with deceased donor lung transplant patients and better HLA matching\textsuperscript{230}.

The condition is treated primarily by the augmentation of immunosuppression, but results are generally unsatisfactory and affected patients usually succumb to the disease. Alternative treatment options are described above. They include re-transplantation which is the only treatment option for advanced BO with respiratory failure\textsuperscript{231}.

**Surgical complications**

Bronchial dehiscence or air leak can occur soon after transplant surgery. Airway anastomotic dehiscence is usually suspected whenever there are large air leaks from the chest tubes and poor blood gases in the recipient. The complication is usually present on admission to the


\textsuperscript{228} Scott J. Paediatric incidence of acute rejection and obliterative bronchiolitis. Transplant International 2008;7:404-6.


\textsuperscript{230} Woo M. Bronchiolitis obliterans is not the primary cause of death in pediatric living donor lobar lung transplant recipients. Journal of Heart and Lung Transplantation 2001;20:491-6.

intensive care unit, or can occur several days after surgery\textsuperscript{232}. Facilitation of the early revascularisation of airway anastomoses by wrapping the area in a pedicle of viable tissue has greatly reduced the risk of airway dehiscence. Due to concerns regarding the association between the immunosuppressant Sirolimus and airway dehiscence, this agent is usually avoided in the early post transplant period and also in patients who are at high risk of this complication\textsuperscript{233}. Treatment is prompt surgical evaluation and surgical repair\textsuperscript{234}.

Airway stenosis is more common, occurring in approximately 16% of cases. Most are secondary to progressive fibrosis and narrowing at the anastomotic site, but other causes are haematomas, surgical complications and infection, particularly with \textit{Aspergillus} infection\textsuperscript{235}. Treatment is by dilation of the stenosis. Recurrent stenosis usually requires stenting\textsuperscript{236}.

Vascular anastomotic complications usually present soon after surgery and are uncommon. They usually result from surgical technical problems. Arterial stenosis, venous thrombosis or stenosis and thrombus formation at the left atrial anastomosis suture line or in the pulmonary veins are all vascular anastomotic complications that occur in the lung transplant recipient in particular\textsuperscript{237}. Embolisation of thrombi to the systemic circulation, resulting in fatal cerebral ischaemia occur in both lung and heart-lung transplant recipients postoperatively. Transoesophageal echocardiography, high resolution CT scanning and ventilation-perfusion scanning are the diagnostic modalities usually employed to evaluate vascular complications\textsuperscript{238}. Treatment of stenosis can be performed by balloon dilation and stent placement\textsuperscript{239}.

\textbf{Primary graft failure and graft injury}

Primary graft dysfunction is the accepted term associated with early hypoxia after lung implantation, unrelated to technical error and excluding hyperacute rejection. It typically occurs within the first few days after transplantation and has variable severity. It is graded based on a simple clinical scale related to the degree of hypoxia. The nomenclature and criteria have been recently reviewed by a consensus group of the International Society for Heart and Lung Transplantation\textsuperscript{240}.

The ischaemic and reperfusion injury inherent in the process of harvesting and implanting donor lungs can lead to significant graft dysfunction. Factors linked to primary graft dysfunction include poor allograft preservation or preparation, long ischaemic times and the use of cardiopulmonary bypass. The use of high inspired oxygen concentrations and increased end-
expiratory ventilator pressures is avoided due to the potential for worsening injury.241 242 However, the majority of patients who develop primary graft failure do not have any risk factors for its development.

The incidence of this complication has been reported between 13% and 35% depending on the surgical centre.243 Clinically, early graft dysfunction presents as non-cardiogenic pulmonary oedema, with decreased lung compliance, hypoxia and occasionally pulmonary hypertension in lung graft failure, and with pulmonary hypertension and cardiogenic shock despite maximal inotropic support in cardiac graft failure.244 Treatment is usually with mechanical ventilation and careful fluid management, the use of ECMO and/or nitric oxide.245 If the patient fails to respond to these measures, urgent re-transplantation may be considered.246 Mortality can be as high as 40%.247

**Infection**

Infection is a common complication in any immunosuppressed individual. In lung transplant patients, the transplanted organ is at special risk of infection. As a result, infection is the leading cause of mortality in the first year after transplantation and remains a significant cause of morbidity and mortality over the long term after lung transplantation.248

Non-immunologic factors that make the lung more susceptible to infection include the denervation of the lungs with marked blunting of the cough reflex, interference with mucociliary function with impaired airway clearance and mucus stasis, and ischaemia at anastomoses. Immunological factors include the higher dose of immunosuppression used in lung transplantation than in other solid organs.249 250 The underlying disease processes and complications of end stage organ disease represent additional risks for infectious complications. Candidates for lung transplantation with CF in particular are often colonised with fungi and highly resistant gram-negative bacteria. Likewise prolonged hospitalisation times before transplantation increase the risk of nosocomial infection with resistant organisms.251

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Bacterial infections are most commonly occurring infections associated with pediatric lung transplantation, responsible for approximately 63% of all infections. Although viral and fungal infections are less common, they are associated with the highest mortality\textsuperscript{252}.

Viral infections can be relatively mild to life threatening. Human herpes viruses, Epstein-Barr virus (EBV) and adenovirus all cause significant morbidity and mortality. However cytomegalovirus (CMV) remains the most commonly encountered serious viral infection in lung transplant recipients\textsuperscript{253}.

Paediatric patients are more likely to be CMV-negative and are at higher risk of CMV infections, especially if the donor was CMV positive. CMV is associated with a wide range of clinical manifestations, including a non-specific CMV syndrome, and organ specific tissue invasive disease, particularly of the allograft. Treatment with IV ganciclovir can be administered prophylactically or pre-emptively, before the clinical manifestation of CMV infection\textsuperscript{254}. Before widespread use of prophylaxis, CMV was reported to occur in 26% of thoracic organ recipients\textsuperscript{255}. Other approaches for the prevention of CMV include the use of CMV seronegative or leukocyte-reduced blood products, and immunoglobulin therapy. Data from multicentre randomised controlled trials evaluating different prevention strategies are unavailable\textsuperscript{256}.

EBV has also been associated with a wide spectrum of clinical disease in paediatric transplant patients, including asymptomatic seroconversion, nonspecific viral illness, mononucleosis, post-transplant lymphoproliferative disorder (PTLD) and lymphoma\textsuperscript{257}. EBV associated PTLD is a heterogeneous group of clinical syndromes associated with EBV driven lymphoproliferation ranging from benign self-limiting disease to true malignancies. PTLD is the most common post transplant malignancy in paediatric solid organ transplant patients\textsuperscript{258}. The most clearly defined risk factor for PTLD is primary EBV infection, often associated with an EBV seropositive donor and seronegative recipient. Reduction of immunosuppression is the most common initial strategy for management of EBV disease, but increases the likelihood of BO\textsuperscript{259}. Antiviral agents, intravenous immunoglobulin, monoclonal antibodies, interferon and chemotherapy have also been used however the appropriate indications for their use are debated, and there are no comparative studies of outcomes with various treatments\textsuperscript{260}.

Prophylactic antimicrobials against bacteria, viruses and fungi are widely used in most transplant programs, but regimens vary widely between centres. The protocols for various

\textsuperscript{252} Woo M. Overview of lung transplantation. Clinical Reviews in Allergy and Immunology 2008;35:154-63.
\textsuperscript{256} Campbell A. Strategies for the prevention of CMV infection and disease in paediatric liver transplantation recipients. Pediatric Transplantation 2004;8:619-27.
institutions are usually based on the preoperative infectious diseases profile of the recipient, the results of perioperative donor cultures, and cover for common hospital pathogens. Preventive measures are also employed, including immunisation for vaccine-preventable diseases and rigorous infection control practices. Prophylaxis for opportunistic infections, including *Pneumocystis carinii* and candidiasis, usually commences within the first two weeks of transplantation\textsuperscript{261}.

Fungal or mould infections are less frequent than bacterial and viral infections. However, they carry the highest mortality risk of all infections. The most common fungal infections are *Aspergillus* and *Candida* species. *Coccidiomycosis*, *Histoplasmosis*, *Scedosporium* also occur\textsuperscript{262}. Airway colonisation and isolated tracheobronchitis respond to antifungal therapy and surgical debridement in most cases. Survival is decreased in those with disseminated disease\textsuperscript{263}.

**Malignancy**

The overall incidence of malignancy is 6.5% at one year and 8% at five years\textsuperscript{264}. Most malignancies are post-transplant lymphoproliferative disease (PTLD) which have a range of morphology, classified by the World Health Organisation classification system, where involvement may be intra-thoracic and / or extrathoracic. PTLD is more common in paediatric transplant recipients than it is in adult recipients\textsuperscript{265}.

**Other complications**

In addition to these major complications, a number of other complications occur with lung and heart-lung transplantation, including:

- gastro-oesophageal dysmotility: which is likely related to vagus nerve injury. Aspiration of gastric acid has been implicated in deterioration of allograft function and the development of BO. Recipients with CF are also at risk for developing distal intestinal obstruction syndrome\textsuperscript{266};

- arrhythmias: atrial fibrillation and / or flutter occurs more commonly in lung transplant recipients, likely due to the left atrial suture lines acting as a nidus for post-transplant arrhythmias\textsuperscript{267};

- renal failure: resulting from haemodynamic compromise, and due to side-effects of commonly used post-transplant medications\textsuperscript{268};

\textsuperscript{261} Ibid

\textsuperscript{262} Singh N. Fungal infections in the recipients of solid organ transplantation. Infectious Diseases Clinics of North America 2003;17:13-34.


\textsuperscript{265} Dishop M. Pediatric lung transplantation. Pediatric and Developmental Pathology 2008;11:85-105.


• impaired growth: paediatric lung and heart-lung transplant recipients do not achieve normal somatic growth. Rate of growth is approximately 64% of predicted values\textsuperscript{269},

• neurological complications: are reported to be as high as 47%. Nerve injury of both the phrenic and vagus nerves is commonly associated with surgery. Seizures are common and are associated with immunosuppression medications. Calcineurin phosphatase inhibitors in particular are a cause of cerebral vasoconstriction, with resulting neurological complications\textsuperscript{270}; and

• diabetes: noted in 20% of patients at one year and 28% of patients at five years, diabetes is associated with the use of immunosuppression medications, including steroids and Tacrolimus\textsuperscript{271}.

\textbf{Mortality}\textsuperscript{272} 273 274

For patients with end-stage lung and pulmonary vascular disease, transplantation can prolong life substantially. However, the survival statistics for lung and heart-lung transplantation are poor compared with other solid organ transplants, including heart, kidney and liver transplants. The half-life of heart, kidney and liver transplants is approximately 10 years, compared with a lung and heart-lung half-life of approximately five years.

Survival after paediatric lung transplantation remains similar to that reported in adults. Internationally, median survival between 1990 and 2007 for paediatric patients was 4.5 years.\textit{Figure 6: Paediatric versus adult survival for lung transplantation (1990 to 2007)}

Internationally, survival has improved since the commencement of paediatric lung transplantation. When analysed by time period, recipients transplanted between 2002 and 2007

\textsuperscript{269} Sweet S. Pediatric lung transplantation at St Louis Children’s Hospital. American Journal of Respiratory and Critical Care Medicine 1997;155:1027-35.


experienced one and five year survival of 83% and 50% respectively, compared with 67% and 43% for patients transplanted in the first surgical era (between 1988 and 1994). Published Australian actuarial survival rates are high. At St Vincent’s Hospital, Sydney, an overall five year survival of 55% was reported between 1991 and 2006 in paediatric patients. Since 2000, adolescent five year survival has been high, with 74% of patients still alive at five years²⁷⁵.

**Figure 7: Paediatric lung transplantation survival by time period (1990 to 2007)**

Survival varies by age group. Children aged between one and 11 years experience better survival than those aged between 12 and 17 years, although this difference is not statistically significant.

As described above, causes of death vary according to time since transplantation. In the first 30 days after transplant graft failure is the most common cause of death. Between 30 days and one year, infection is the leading cause of death. Between one and five years, BO is the leading cause of death.

**Table 7: Leading causes of death after paediatric lung transplantation (1992 to 2008)**²⁷⁶

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>0 – 30 days</th>
<th>31 days – 1 year</th>
<th>&lt;1 year to 3 years</th>
<th>&lt;3 years to 5 years</th>
<th>&lt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BO</td>
<td>-</td>
<td>9%</td>
<td>39%</td>
<td>41%</td>
<td>43%</td>
</tr>
<tr>
<td>Infection</td>
<td>15%</td>
<td>35%</td>
<td>18%</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td>Graft failure</td>
<td>30%</td>
<td>19%</td>
<td>26%</td>
<td>16%</td>
<td>24%</td>
</tr>
<tr>
<td>Technical</td>
<td>15%</td>
<td>3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


Lung re-transplantation is uncommon. There were 57 paediatric re-transplant procedures reported to the ISHLT between 1994 and 2008. Survival after re-transplantation is poorer than for primary transplantation. The five year survival was 41% for this time period.

Survival after paediatric heart-lung transplantation is predominantly influenced by the longevity of the lung allograft rather than the donor heart. As a result, survival after heart-lung transplantation is similar to that of paediatric lung transplantation\textsuperscript{277}. The five year survival post paediatric heart-lung transplantation is currently approximately 45%. Survival has improved since the inception of heart-lung transplant surgery in the 1980s. Between 1982 and 1988, median survival was 1.9 years, compared with 3.8 years in the most recent surgical era (1999 to 2007). As heart-lung transplantation is now performed very infrequently, comparing survival with double lung transplantation is difficult as there needs to be some correction for reported survival between surgical eras.

\textit{Figure 8: Paediatric heart-lung transplantation survival by time period (1984 to 2007)}

There are no significant differences in survival between age groups following paediatric heart-lung transplantation.

Studies comparing survival benefit from lung transplantation according to clinical diagnosis have demonstrated that paediatric lung transplantation confers survival benefit for all conditions for which transplant is indicated\textsuperscript{278,279,280}. There is some data suggesting that patients who have CF or pulmonary vascular disease may experience less survival benefit than those receiving transplant for other conditions. However, this has not been definitively established, and the net effect of transplantation is survival benefit in these patients also\textsuperscript{281}.

Adult studies have more conclusively demonstrated survival benefit associated with lung transplantation. Patients with all diagnoses except Eisenmenger’s syndrome showed a survival benefit from transplantation\textsuperscript{282,283}.

\textsuperscript{277} Dishop M. Pediatric lung transplantation. Pediatric and Developmental Pathology 2008; 11:85-105.
\textsuperscript{279} Aurora P. Selection of cystic fibrosis patients for lung transplantation. Current Opinions in Pulmonary Medicine 2008; 14:589-94.
Quality of life

The published literature provides a strong body of evidence that patients with lung disease severe enough to undergo listing for lung transplantation have significantly diminished quality of life. It is only recently that significant numbers of survivors of paediatric lung and heart-lung transplant have been available for study, and systematic study of the psychological sequelae of these procedures and impacts of transplantation on quality of life are in their infancy. As a result, although a reasonable number of published studies exist regarding the relationship between lung and heart-lung transplantation and quality of life, missing data and small sample sizes limit the generalisability of findings. Further, the inability to account for deaths in the scoring of most nonutility-based quality of life questionnaires significantly limits their interpretation, and many studies have not assessed results according to the primary diagnosis leading to the requirement for transplantation, limiting the ability to draw comparisons regarding transplantation and improved quality of life between clinical diagnostic groups.

In spite of these limitations, the published literature overall demonstrates improved quality of life associated with paediatric lung and heart-lung transplantation. In addition, the functional status of long-term paediatric survivors is generally good with approximately 95% of patients surviving more than one, three and five years experiencing no limitations of activity. Measures of developmental, cognitive and academic function appear to be stable over time and are generally in the normal range. However, approximately 1/3 of recipients experience behaviour problems. Further, the prevalence of depression is higher than the general paediatric population, but decreases over time.

The positive impact of transplantation on improved quality of life is offset by the complications associated with treatment, particularly the development of BO. After lung and heart-lung transplantation, patients frequently develop BO, which is the leading cause of death long-term. Studies have shown that patients with BO have a significantly reduced quality of life compared with patients without BO.

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Quality issues

Volume-quality associations

Large volume surgical units are desirable for improving surgical outcomes for complex surgical procedures. Lung and heart-lung transplantation are complex procedures with a high risk of mortality, requiring experienced providers and specialised ancillary staff.

However, large volume lung transplantation centres are uncommon, largely due to the limited availability of donor organs. Internationally, of the 153 centres reporting adult lung transplantation to the ISHLT 46% averaged fewer than 10 lung transplants a year. A total of 49% of adult procedures were performed at 27 centres with an average activity of more than 30 transplants per year, and 21% of procedures worldwide were performed at the seven centres, with an average activity of 50 or more transplants per year.

Data demonstrate that for adult lung transplantation, mortality at 30 days, one year and five years post-transplant are significantly associated with centre volume. High-volume adult lung transplant centres (performing 20 or more lung transplants per year) have the lowest 30-day mortality (4% compared with 10% for centres performing two or less lung transplants a year).

Mortality at one year post transplant also decreases as surgical centre volume increases.

Figure 9: Association between transplant centre volume and relative risk of death within one year of adult transplantation (1995 to 2007)

Reproduced from Christie et al. 2009

References

Literature review of paediatric lung and heart-lung transplantation

Transplant centre volume is also associated with five year mortality among adults surviving one year, indicating the importance of transplant centre experience to factors that affect mortality beyond the surgical procedure itself. In the US, adult lung transplant centre funding is linked to surgical volume. Medicaid funding is available to centres performing greater than 10 procedures a year.

Paediatric lung transplant surgical centre volumes are smaller. Of the 36 centres reporting transplants in 2007, only one reported greater than 10 transplants per year, three reported five to nine a year and the remaining 32 reported fewer than five per year. There is a significant relationship between centre volume of fewer than five paediatric lung transplants per year and increased mortality at one year after transplant. At five years after transplant the effect of centre volume on mortality is not statistically significant.

Similar to paediatric surgical centres, the number of heart-lung transplant procedures performed in adults is small. Over 50% of surgical centres that report adult heart-lung transplants to the ISHLT registry perform one procedure per year. Only one international centre performs more than 10 heart-lung transplants a year. Analyses of the impact of centre volume on mortality have not been undertaken for heart-lung transplantation in either adults or children as numbers of procedures are too small for statistically meaningful comparisons.

**Adult versus paediatric transplant centre service delivery**

Paediatric-specific lung and heart-lung transplant centres exist in the US and Europe. Worldwide, approximately half of procedures are performed in the three largest paediatric centres – St Louis and Houston in the US, and Great Ormond Street in the UK. In Europe, most paediatric centres focus on adolescents. In the US, younger paediatric lung recipients (<12 years of age) are rarely transplanted at adult centres whereas adolescent recipients (12-17 years of age) may be transplanted at either a paediatric or adult transplant centres.

Published data comparing outcomes of transplantation in adult versus paediatric centres are limited. US comparisons have been made, but may not be directly applicable to the Australian context due to differences in allocation of donor organs and severity of illness in recipients of transplants. Further, US paediatric centres are defined as per the Medicare designation, which specifies that any centre conducting ≥ 50% of their transplants in paediatric (0-17 years of age) recipients is a paediatric centre.

According to this classification, lung transplantation of a paediatric patient at a US centre identified as “Adult” is associated with a statistically significant increased risk of mortality compared with paediatric centres. While results may vary by transplant recipient and by transplant center, on average, adolescent lung transplant recipients have better post-transplant outcomes when transplanted at paediatric centres compared with adult centres. Further

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298 Ibid


303 Ibid
investigation to determine the factors responsible for this difference is required. Comparisons of patient satisfaction, acceptability of services and other indices of quality of care between adult and paediatric lung transplantation centres have not been published.

**Ethical issues associated with treatment**

Paediatric lung and heart-lung transplantation are complex and demanding forms of treatment that require intensive and invasive ongoing surveillance and management for the life of the patient. The emotional impacts associated with paediatric lung and heart-lung transplantation are significant and commence before transplanted organs are received. Recipient candidates negotiate the medical system whilst significantly physically disabled, experience an unknown period of waiting for donor organs, the possibility they may die on the waiting list before donor organs are received, and the specific emotional impacts associated with receipt of deceased donor organs. Transplantation places significant demands on the patient, family and caregivers of the recipient. It is therefore essential to ensure the patient and family are completely and realistically informed of the transplantation process prior to their decision, including patient selection and indications, donor criteria, surgical technique, long-term follow-up, outcomes, and living-related lobe donations if applicable.

Before paediatric lung and heart-lung transplantation were available, palliative care was the focus of therapeutic care for patients whose anticipated survival was less than two years. Concerns have been raised that placement on a waiting list for transplantation may complicate palliative care, as an expectation that life-extending therapy may become available is created but not necessarily achieved. Deaths on the waiting list are common and there is a chance that successful transplantation will not occur. It may be difficult for patients, families and carers to undergo a process of transition towards acceptance of death in these circumstances. The Australian Health Ethics Committee of the National Health and Medical Research Council has published guidance documents regarding broad ethical and social issues associated with organ transplantation. These include consent issues, organ procurement, resource allocation and living donor-associated issues. Guidance is not specific to paediatric lung or heart-lung transplantation.

A range of ethical issues associated more broadly with transplantation have been debated in the literature. Few definitive positions have been reached on these issues. Issues include:

- **distributive justice –** what is fair with respect to the allocation of donor organs when demand exceeds supply?
- **re-transplantation –** is it fair to provide a patient with a second organ when there are patients on waiting lists that have not received their first?
- **live organ donation –** is it fair to risk one person's life to possibly save another?

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304 Ibid
In addition, both the source and method of obtaining the organ to transplant are major ethical issues in the international context. “Transplantation tourism” is a documented practice that has the potential to violate human rights or exploit the poor, to have unintended health consequences, and to provide unequal access to services, all of which ultimately may cause harm. Some consider the practice a violation of basic human rights according to Articles three and four of the Universal Declaration of Human Rights.

**Ethics and cost**

Paediatric lung transplantation is an inherently expensive process that is associated with a considerable emotional, physical and financial toll on recipients and their families and carers. Solid organ transplantation raises the issue of cost as it relates to benefit, both to the individual and to society as a whole. Costs associated with lung and heart-lung transplantation vary between treatment centres. According to US data from the University Health Systems Consortium:

- the median case cost associated with uncomplicated lung transplantation for 33 centres to 2007 (involving treatment of 766 cases) was approximately $140,000 (USD); and
- mean length of stay for uncomplicated lung transplantation to 2007 was 18 days.

Follow-up costs are high. The lifetime cost of care for the lung transplant recipient is estimated at approximately $425,000 (USD) in the US and $180,000 (USD) in the UK. Costs are substantial due to the costs associated with ongoing pharmacological management, ongoing diagnostic pathology and radiology requirements, and need for frequent sub-specialist follow-up.

Investigators have attempted to determine the cost per year adjusted for the quality of life. Results generally demonstrate that treatment is cost-effective, in view of the gain in quality of life obtained compared with quality of life without transplantation.

**Summary**

Paediatric lung and heart-lung transplantation are established treatment options for patients with a wide variety of end-stage lung and pulmonary vascular diseases. The clinical indications for both transplant types are similar. Bilateral sequential lung transplantation is more commonly performed than heart-lung transplantation. The majority of patients receiving both lung and heart-lung transplants are adolescents. The principal diagnoses leading to the requirement for lung and heart-lung transplantation are CF and IPAH respectively.

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Demand for donor organs exceeds supply. Most donor lungs are acquired from donors after brain death. Donation after cardiac death and the use of ‘marginal’ donors are alternative sources of lung allografts. LDLT is also an accepted source of donor lungs. However, LDLT clinical activity appears to be decreasing worldwide.

Selection criteria for lung and heart-lung transplantation have been established and contraindications to transplantation proposed. There continues to be evolution as to what is regarded a contraindication to transplantation. Timing of transplantation is critical to ensure maximal survival benefit is achieved. Timing needs to balance the need to not transplant too early (before the natural history of the underlying clinical condition warrants intervention) or too late (which increases the risk of the patient dying whilst on the waiting list).

Preoperative assessment is comprehensive and patients require ongoing maximal preoperative medical therapy to treat their underlying condition, supplemented by medical and / or surgical management to optimise the patient’s health prior to transplantation being performed.

Surgical management is complex. Research is largely insufficient to provide definitive recommendations regarding the evidence-based intra-operative patient care or guide specific protocol development. As a result, specific protocols regarding intra-operative management vary between treatment centres.

Post-operative monitoring and management also varies between treatment centres. The mainstay of post-operative care is the regular, frequent monitoring of the patient for the emergence of complications, including regular bronchoscopy and trans-bronchial biopsy, intensive rehabilitation and education, and the ongoing pharmacological management, including the use of combination immunosuppressive therapy.

Complications can occur immediately after surgery or be delayed for several years. The significant complications associated with heart-lung transplantation and lung transplantation are similar, and predominantly relate to the lung allograft.

In appropriately selected patients paediatric lung and heart-lung transplantation prolong life. The five year survival after paediatric lung transplantation is comparable to that of heart-lung transplantation, and survival in paediatric patients is comparable to that achieved in adult patients. The five year mortality is approximately 50%. Survival is poor compared with other solid organ transplants, including heart, kidney and liver transplants, where 50% mortality occurs at approximately 10 years. The five year survival following LDLT is poorer than deceased donor lung transplant.

Internationally, the number of paediatric lung transplants is modest at approximately 65 per year, and has decreased from its peak in the mid 1990s. The number of paediatric heart-lung transplants performed internationally is smaller than lung transplant numbers, with between eight and 17 procedures performed worldwide each year since 2002. Numbers have also decreased from the peak in the 1990s. Numbers of paediatric LDLT have declined to an average of one per year worldwide between 2005 and 2007, a decrease from the peak of 14 procedures per year in the late 1990s.

An association between transplant centre annual caseload and mortality has been demonstrated for both adult and paediatric lung transplantation. Centres performing fewer than five paediatric procedures per year experience a higher mortality than those performing greater than five procedures. Worldwide, numbers of procedures are insufficient for associations between higher centre volumes and mortality, or heart-lung transplant centre volume and mortality to be assessed. However, studies in adult transplant patients demonstrate lower mortality in centres performing greater than 20 lung transplant procedures a year.
Outcomes between adult and paediatric transplant centres have not been extensively studied. Available data suggest the outcomes of adolescent lung transplantation performed in paediatric centres may be superior to those of adult centres.

There are numerous ethical issues that influence service configuration and the extent of service delivery. Many of these have not been resolved and account for some of the variability in service delivery and models of care between different countries worldwide, and between surgical centres within the same country.