

## Lung transplantation: does age make a difference?

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*Significant similarities between the challenges of lung transplantation in patients of all ages should lead to better access to this life-saving surgery for children and adolescents*

Lung transplantation (LTx) is firmly established as a therapy for end-stage lung and pulmonary vascular diseases in patients aged over 18 years and into the seventh decade of life.<sup>1,2</sup> However, for those under the age of 18, be they child or adolescent, the role of LTx is less clear.<sup>3,4</sup> In Australia, this has contributed to a perception that the risk of undertaking LTx in children and adolescents does not warrant the reward. Indeed, presently in this country, there is no major paediatric hospital offering a lung transplant program, likely recognising the complexity of treating such patients coupled with the potential risk of achieving poor results with a low case load — the reality is that the projected case numbers will only be of the order of four to eight per year across Australia and New Zealand.

Thus, by focusing on successful LTx outcomes for an adolescent population, the article by Morton and colleagues in this issue of the Journal (*page 278*)<sup>5</sup> highlights a number of the key issues regarding the efficacy and utility of LTx for younger Australians. Although adolescence refers to a transitional state from childhood to adulthood, patients 15 years and younger are generally excluded from adult hospitals and those 18 years and above excluded from paediatric hospitals. Two-thirds of the patients in the study by Morton et al could have been “routinely” treated in adult hospitals. Notwithstanding this limitation, the report gives important insight into the issues, experience and successful outcomes that can be achieved in younger lung transplant recipients.

From this article, it is apparent that in Australia, a well developed, large adult LTx unit is able to use its highly specialised services to overcome some of the problems and deficiencies that can limit a stand-alone service for such a small population as children and adolescents requiring LTx. However, the age of any potential Australian lung transplant recipient is critically important — at this time, this technology is not being routinely offered to younger children. Indeed, at present, Australia’s youngest ever lung transplant recipient was aged 9 years at the time of LTx.<sup>6</sup> The improved outcomes for LTx now described in adolescents<sup>5</sup> should provide an impetus to provide access for younger potential LTx recipients. In looking to achieve this advance, we need to keep in mind that the transplant recipient’s age can matter in several different ways.

Fortunately, severe lung disease warranting consideration of LTx in children and adolescents is relatively rare, although interestingly, it does have a bimodal distribution. The International Society for Heart and Lung Transplant (ISHLT) Registry 2005 paediatric report notes about 65 procedures performed worldwide each year.<sup>7</sup> In older paediatric patients, typically over 12 years of age, about 70% will have cystic fibrosis as the primary indication for LTx, whereas in infants aged less than 3 years, the indication in about 60% is congenital heart disease or pulmonary hypertension. Despite the perception that transplant recipients fare worse if they are younger, the recent ISHLT Registry reports a half-life of around 5 years after LTx, and no significant survival difference between adults, adolescents and the very young.<sup>7</sup> Rates of early graft

dysfunction and late graft dysfunction (ie, bronchiolitis obliterans syndrome [BOS]) are also similar. However, causes of death are quite different, with adults and adolescents dying from respiratory failure related to BOS, and younger children dying from infection. The functional status of survivors is excellent, with over 80% reporting no activity limitations at 5 years,<sup>7</sup> although morbidity related to the obligatory immunosuppressant drugs is very common across all age groups.

Further, there are some specific issues (medical, psychosocial and legal) associated with LTx in adolescents and children compared with adults. Post-transplant lymphoproliferative disorders, growth retardation, respiratory tract infections and medical non-adherence appear much more commonly in children.<sup>8</sup> As discussed by Morton and colleagues, facilitating compliance with therapies and medication are particularly challenging areas when working with adolescents.<sup>5</sup> As an example, immunosuppressive protocols need to reflect potential concerns about physical appearance. Also, a particular “at risk” period arises when paediatric LTx recipients transition from paediatric to adult care.<sup>9</sup> Performing major surgery with substantial short-term and long-term mortality risks in a patient unable to give consent presents ethical and legal dilemmas.

For paediatric patients with severe lung disease, recent technological advances provide the potential to build on the excellent results of LTx in adolescents presented by Morton et al.<sup>5</sup> Minimal waiting list mortality is a critical component of any assessment of the efficacy and utility of organ transplantation. Thus, the management of severe lung disease by experienced teams, with appropriate use of newer therapies such as bi-level positive airway pressure (BiPAP), dornase alfa and azithromycin in patients with cystic fibrosis, may lead to a successful “bridge to transplant”. Similarly, intravenous epoprostenol, oral bosentan and sildenafil may provide a bridge to transplant for patients of all ages with severe pulmonary hypertension.

The study by Morton et al included several terminally ill individuals transplanted after support with mechanical ventilation or extra-corporeal membrane oxygenation.<sup>5</sup> Morton and colleagues are to be commended for their successful endeavour, but we contend that further detailed discussion about excessive early mortality<sup>10</sup> and resource use is needed before bridging in this fashion is routine in any age group. Such bridging has become increasingly used in the United States (11% of all LTx in 2006<sup>11</sup>) and we believe that many, including ourselves, would argue that Australia does not have the intensive care facilities and staff to routinely bridge in this manner.

There are also other developments that should increase transplant opportunities and access to LTx for children and adolescents, hopefully shortening waiting times, thereby further decreasing waiting list mortality, and potentially allowing at least the possibility of retransplantation in the event of late graft dysfunction. One possibility is that large-volume LTx transplant centres (typically not small-volume paediatric-only centres, as yet) might increase

organ availability by using extended donor lungs (eg, where there are secretions or an abnormal chest x-ray, etc),<sup>12</sup> or cadaveric or living-related lobar transplants (eg, so-called “cut-down lungs”).<sup>13</sup> The use of cut-down lungs typically involves transplanting one lobe from each of two adults to make a bilobar transplant for a child or smaller adolescent. Although this resource-intensive and challenging operation is possible, some question the philosophy of undertaking the only known procedure to have a “potential 300% mortality”.<sup>13</sup> Donation-after-cardiac-death (DCD) retrieval of lungs for transplantation (as distinct from the usual donation-after-brain-death retrieval) is also now a viable prospect being used to acquire adult lungs for LTx,<sup>14</sup> and will soon be extended to paediatric DCD lung donation.<sup>15</sup>

Thus, evidently, expanding the complexity and extent of LTx offered to children and adolescents might consume significant resources, so LTx results must be carefully considered and evaluated to ensure continued successful outcomes. In this regard, we note with great interest the recent institution of a complex mathematical lung allocation score model by the American United Network for Organ Sharing (UNOS).<sup>16</sup> This model uses disease-relevant clinical and physiological variables to predict who will get the most significant improvement in survival with LTx and, therefore, who should be preferentially transplanted. Although historically based, the model will evolve with ongoing clinical experience and should be able to provide new evidence to guide future practice. Interestingly, because of differences in diagnostic categories and post-LTx outcomes in younger lung transplant recipients, the UNOS lung allocation score is only to be applied to those aged over 12 years.<sup>16</sup>

So, although there are important differences to consider when evaluating the efficacy and utility of LTx across the wide age-spectrum of disease and physiology in the very young, adolescents and adults with terminal lung disease, there is also significant overlap. Medical and allied health experts in paediatric and adolescent medicine have much to offer adult LTx programs venturing into adolescent transplantation; their involvement should be routine. Similarly, units experienced in adult LTx bring knowledge and technology to paediatric and adolescent LTx that can only benefit the small number of critically ill young Australians previously without local access to LTx expertise.

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