

Paediatric recipient

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Guidelines

1. In relation to age at the time of transplantation we recommend that:
 - There be no lower age limit set for transplantation (1B)
 - In infants under 1 year of age, transplantation should be performed in highly specialised units with extensive experience in paediatric transplantation (Ungraded)
 - In infants under 1 year of age, adult live donors should be used in preference to cadaveric donors. (1C)
2. In all patients but particularly in adolescents we recommend that:
 - Risk factors for non-adherence are identified prior to transplantation. (1D)
 - Specific strategies are implemented to actively manage factors and behaviours that contribute to non-adherence. (1D)
3. We recommend that children with urological abnormalities be carefully assessed prior to transplantation (Ungraded) and that abnormalities in bladder emptying are corrected before transplantation (1D)
4. We suggest that asymptomatic vesicoureteric reflux does not require correction prior to transplantation. (2C).
5. We suggest that children with Wilms tumour wait at least 2 years following completion of chemotherapy before undergoing transplantation (2D).
6. We suggest that post-transplant anticoagulation be considered for children with thrombophilic disorders (2D).
7. We recommend that mental retardation should not preclude an individual from consideration for transplantation (1C).

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

None provided.

IMPLEMENTATION AND AUDIT

Nil suggested.

BACKGROUND

Renal transplantation is considered the treatment of choice for children with ESKD. Kidney transplants are now performed routinely in many paediatric centres around the world with excellent reported graft (1- and 5-year graft survival up to 95%) and patient survival (5- and 10-year patient survival of 70-100% and 75-95%, respectively) [1, 2]. A number of studies have shown the important benefits of transplant in improving cognitive development [3-5] and growth [6] of children. In recognition of these unique benefits of transplant to children and adolescents, many countries including Australia give priority to paediatric recipients on deceased donor waiting lists in order to expedite transplantation and keep waiting time short [2, 7, 8].

Absolute contraindications to kidney transplantation in children and adolescents are not significantly different to adult transplantation and include immunological incompatibility (ie positive

crossmatch), active infection, malignancy or substance abuse. In some genetic conditions, combined organ transplantation (e.g., liver–kidney transplantation) should be considered as the treatment of choice. Additional factors that may impact on paediatric recipient suitability are discussed in more detail below.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for child or pediatrics (including adolescent and infant) were combined with the MeSH term, kidney transplantation. This was then combined with further searches using the MeSH and text words for prognosis, survival, mortality, graft survival and survival analysis. Animal and adult studies were specifically excluded. The search was carried out in Ovid MEDLINE from 1950 to September 2009 (Week 3).

Date of search: September 2009.

WHAT IS THE EVIDENCE?

Age

(i) Infants and young children

Young age has previously been identified as an important factor affecting patient survival. A North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) review of transplants performed from 1987 - 1997 reported that recipient age less than 2 years was the single most important risk factor for graft failure (RR=1.95) [9]. Young age has also been associated with worse transplant-related mortality, with a Dutch study showing a mortality rate in children aged less than five approximately double that of children aged 6-10 years [10]. However, more recent reports suggest that transplantation can be performed safely and with excellent outcomes in even very small children. A summary of case series from the last decade detailing outcomes for infants and young children are shown in Table 1.

Data in children less than 1 year of age are sparse and limited to a report from a single transplant centre [11, 12] and a NAPRTCS registry analysis [13]. Humar and colleagues [11] reported no significant differences in patient and graft survival in children aged <1 yr at the time of transplant compared to those 1-4 yrs and 5-13 years. In contrast, the NAPRTCS report demonstrated significantly worse patient survival in the 0-1 year age group, but comparable graft survival with older age groups [13]. Taken together, these reports suggest that transplantation in children this age is feasible but is likely to be most successful when performed at highly specialised, high transplant volume paediatric centres. Additionally, both these studies reported that adult live donors are preferred in this recipient population.

A number of centres have reported outcomes for children 1-5 years of age and under 15kg in weight (Table 1). These studies [14-20] suggest that transplantation can be performed safely in this group of patients with outcomes of both patient and graft survival comparable to older children and adults.

(ii) Adolescents

Poor graft survival in adolescents is a global finding [13, 21-23] and appears to be related to a high incidence of late acute rejection episodes, with non-adherence to immunosuppressive regimens considered an important contributory factor [13, 24]. Whilst this has led to suggestions to delay transplantation in adolescents to improve adherence, an ANZDATA analysis has shown that waiting time on dialysis was an independent risk factor for failure of LRD transplants in adolescents [25]. Pre-emptive grafts were associated with a 50% reduction in the risk of graft failure and 5- and

10-year graft survival rates were comparable to other age groups. The authors concluded that delaying transplantation in adolescents may expose them to increased risk of poor outcomes [25]. As such, rather than delaying transplantation in adolescents it is recommended that strategies are put in place for the identification and management of non-adherence (see [24, 26, 27]).

Dew et al [28] conducted a systematic review and meta analysis of the annual event rate and risk factors of non-adherence in paediatric solid organ transplant patients. The review identified a total of 61 studies of which 30 (1,313 patients) included kidney transplant patients, with 18 studies specifically addressing non adherence. Non adherence outcomes included multiple components of medical adherence in addition to immunosuppression medication (e.g. clinic appointments, diet, smoking etc.). The overall non-adherence rate to immunosuppression was 12.5 cases per 100 persons per year (95% CI 7.6 to 18.2) with no significant difference between organ type. The assessment of risk factors for non-adherence was limited by the small number of studies that examined potential risk factors. As a consequence immunosuppression, clinic appointments, test and global non adherence were combined. Whilst a number of significant correlations were found, the effect sizes were generally small to modest with the most robust associations found for lower family cohesion/support and greater child psychological distress. As a consequence Dew et al considered that other factors such as provider-related and healthcare systems-related factors may prove to be stronger risk factors for non-adherence in both adults and children [28].

Comorbid Conditions

(a) Urological

Posterior urethral valves is reported as the cause of ESKD in 7% of children in Australia and New Zealand [29], while other conditions such as reflux nephropathy, hypoplastic/dysplastic kidney disease and neurogenic bladder are frequently associated with urological abnormalities. Overall, 20-40% of children requiring transplant will require urological assessment as part of their pre-transplant assessment [29-31].

Adams et al [30] reported on a series of 349 transplants with 66 (18.6%) in children with lower urinary tract disorders. The 1 and 5 year graft survival rate was reported as worse for the group with lower urinary tract abnormalities, but no statistical details were provided. In contrast, a 2004 review found that while urological complications were higher when kidneys are transplanted into reconstructed bladders or urinary diversions, the graft and patient survival rates in most series were comparable to transplantation into non-reconstructed bladders [32]. A number of other case series have confirmed that renal transplantation in children with bladder dysfunction can achieve similar results to those obtained in the general transplant population [31, 33-37]. Studies in specific patient groups such as those with neurogenic bladder secondary to myelomeningocele [38] or posterior urethral valves [39] have also demonstrated patient and graft outcomes comparable to children without urological abnormalities.

Only limited observational data exist to guide the timing of correction of urological abnormalities. A recent study in children with neurogenic bladders who required augmentation cystoplasty found no difference in graft outcomes in those who underwent pre-transplant correction when compared to those treated after transplantation [40]. Similarly, another small case series reported no significant difference in graft survival between a group that underwent bladder reconstruction prior to transplant compared to a group with post-transplant augmentation [41]. However, in that same study [41] 3 patients in the group augmented after transplant developed significant ureteric pathology, of which one developed graft failure. The authors concluded that augment prior to transplant might better protect the renal graft and specifically the transplant ureter.

(b) Obesity

Conflicting results exist on the relationship between obesity and transplant outcomes in adults and only limited information is available on transplant outcomes for obese children. In one study [42],

children who were obese pre-transplant (defined as BMI \geq 95thile for gender, age and race) had significantly worse glomerular filtration rate at one year post-transplant compared to non-obese recipients who remained non-obese or became obese after transplant. A subsequent larger study utilising data from the NAPRTCS Registry found that graft loss as a result of thrombosis was more common in obese recipients (19% vs 10% in non-obese) [43]. In the same study [43], there was no significant difference in the patient and allograft survival between obese and non-obese children.

(c) Malignancy

Wilms tumour is an embryonal cancer of the kidney that occurs mainly in young children. Five to 7% of children with this condition will have bilateral tumours and some of these children will progress to ESKD. In an early case series of 20 patients, Penn [44] reported that children transplanted <1 year after treatment of the tumour had a 47% incidence of recurrence or metastases compared to a zero incidence in those transplanted later. The largest study to date on data taken from the NAPRTCS Registry compared 43 children with Wilms tumour and 43 children with Denys-Drash syndrome (DDS - pseudohermaphroditism, mesangial sclerosis and Wilms tumour) to 7469 patients with other diagnoses. The Wilms tumour and DDS groups had comparable rates of acute rejection and graft and patient survival at 6 months, 1 and 3 years, to recipients with other diagnoses [45]. One child transplanted after 6 months on dialysis, died <6 months after transplant with recurrence of Wilms tumour. There were no graft failures due to recurrent Wilms tumour. Although data is limited to a small number of case series, current recommendations suggest that children with Wilms tumour should wait until 2 years following completion of chemotherapy before undertaking transplantation [2].

(d) Haemostatic

In adults, inherited and acquired thrombophilic risk factors (e.g. factor V Leiden mutation) have been associated with early graft loss and increased rejection episodes (summarised in [46]). However, a recent study reported that patients with thrombophilia had no difference in the rate of thromboembolic events or acute rejection episodes compared to those without hypercoagulability [47]. Data on children are limited but in one prospective study of 66 paediatric patients, 27% were found to have hypercoagulable disorders (protein C, S, and antithrombin III deficiency, antiphospholipid antibodies, factor V Leiden, prothrombin, and methylenetetrahydrofolate reductase (MTHFR) mutation). These patients were treated with an intensified anticoagulant regimen and no thrombosis occurred in either group. As with the adult study, there was no difference in groups in the incidence of acute rejection and GFR after mean follow-up of 3 yrs [48], suggesting that hypercoagulable states are not a contraindication to transplantation.

(e) Mental Retardation

Whilst mental retardation has historically been considered a relative contraindication to transplantation, more recently it is recognised that individuals with intellectual disability should not be precluded from assessment for potential transplantation on the basis of mental retardation alone. [49]. In a review of published and unpublished data up to 2006, Martens et al [50] reported 100% 1-year and 90% 3-year patient survival in children with mental retardation, comparable to nationally reported data on general recipients. Ohta et al [51] studied outcomes in 25 paediatric renal transplant recipients with mental retardation (5 severe, with immobility). After median follow-up of 20 months, all patients survived, had good graft function and showed improved quality of life. In this series, the incidence of complications associated with transplantation were similar to a control group of recipients without mental retardation [51].

SUMMARY OF THE EVIDENCE

In summary, transplantation is the primary goal for children with end stage kidney disease and results in improvements in growth, physical and intellectual development. Data from a number of case series show that there is no younger age limit to transplantation, although it is recommended that transplantation of infants under 1 year of age be performed in highly specialised units with extensive experience in paediatric transplantation. Whilst poor adherence remains a significant cause of graft failure in the adolescent age group, delaying transplantation may be associated with poorer outcomes and is not recommended. Children with urological abnormalities require careful pre-transplant assessment with consideration given to correction of bladder abnormalities prior to transplantation. Other comorbid conditions such as obesity, mental retardation and haemostatic defects should not be considered a contraindication to transplantation.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation. CMAJ. 2005 November 8; 173(10): S1–S25

- Very young age and small size should not prevent early referral for transplant evaluation (Grade B).
- Cognitive or neurodevelopmental delay is not an absolute contraindication to renal transplantation in children (Grade B).

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Clinical trials on identification and management of non-adherence.

CONFLICT OF INTEREST

Steven McTaggart has no relevant financial affiliations that would cause a conflict of interest according to the Conflict of Interest statement set down by KHA-CARI.

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APPENDIX

Table 1. Effect of Age on Transplant Outcome

Reference	Population			Donor		Outcomes				
	Patients	Age	Weight	DD* (%)	LD* (%)	Patient Survival		Graft Survival		
Infants										
Smith [13]	395	< 1yr	NA†	NA	NA	NA		5 years	81% (LD) 54% (DD)	
Khwaja [12]	46	Mean 9.4 mths (±2.4)	Mean 8.2 kg (±1.5)	6	40	1 year	NA	1 year‡	91%	
						5 years‡	100%	5 years‡	80%	
						10 years‡	85%			
Young Children										
Tyden [14]	21	Median 16 months	Median 9 kg	6 (19)	15 (71)	5 yrs - 87% (LD) 5 yrs - 44% (DD)		5 yrs - 87% (LD) 5 yrs - 44% (DD)		
Millan [15]	45	Mean 24.4 mths (±14.2)	Mean 11.2 kg (±2.6)	16 (36)	29 (64)	2 years	100%	2 years	100%	
						8 years	90%	8 years	85%	
Neipp [16]	64	Not stated	Mean 11.4 kg	44 (65)	24 (35)	1 year	93%	1 year	92%	
						5 years	91%	5 years	85%	
						10 years	91%	10 years	85%	
Ojogho [17]	21	Mean 3 yrs (±1.2)	Mean 13.3 kg (±5.4)	10 (48)	11 (52)	100% (mean follow-up 80 months)		1 year	95%	
								5 years	88%	
								10 years	88%	
Kamel [18]	19	Mean 4.7 yrs Range 1.5-9 yrs	Median 14.4 kg Range 9-20 kg	19 (100)	Nil	1 year	90%	1 year	79%	
						5 years	90%	5 years	73%	
						10 years	82%	10 years	65%	
Becker [19]	40	Median 2.7 yrs Range 0.9-5.9 yrs	Median 9.2 kg Range 7.2-10.9 kg	24 (60)	16 (40)	1 year	93%	1 year	90%	
						5 years	90%	5 years	80%	
						10 years	90%	10 years	66%	
						15 years	87%	15 years	56%	
Mickelson [20]	24	Mean 3.1 yrs Range 1.8-5.7 yrs	Mean 13.4 kg Range 9.0-15.7 kg	17 (71)	7 (29)	NA		2 years	92%	
								5 years	92%	

*DD - deceased donor; LD - Live donor
†NA - not available; ‡ - post-cyclosporine