CLINICS

REVIEW

Long-term outcomes of children after solid organ transplantation

Jon Jin Kim, Stephen D. Marks*

NHS Foundation Trust, Great Ormond Street Hospital for Children, Department of Pediatric Nephrology, London/England, United Kingdom.

Solid organ transplantation has transformed the lives of many children and adults by providing treatment for patients with organ failure who would have otherwise succumbed to their disease. The first successful transplant in 1954 was a kidney transplant between identical twins, which circumvented the problem of rejection from MHC incompatibility. Further progress in solid organ transplantation was enabled by the discovery of immunosuppressive agents such as corticosteroids and azathioprine in the 1950s and ciclosporin in 1970. Today, solid organ transplantation is a conventional treatment with improved patient and allograft survival rates. However, the challenge that lies ahead is to extend allograft survival time while simultaneously reducing the side effects of immunosuppression. This is particularly important for children who have irreversible organ failure and may require multiple transplants. Pediatric transplant teams also need to improve patient quality of life at a time of physical, emotional and psychosocial development. This review will elaborate on the long-term outcomes of children after kidney, liver, heart, lung and intestinal transplantation. As mortality rates after transplantation have declined, there has emerged an increased focus on reducing longer-term morbidity with improved outcomes in optimizing cardiovascular risk, renal impairment, growth and quality of life. Data were obtained from a review of the literature and particularly from national registries and databases such as the North American Pediatric Renal Trials and Collaborative Studies for the kidney, SPLIT for liver, International Society for Heart and Lung Transplantation and UNOS for intestinal transplantation.

KEYWORDS: Survival; Morbidity; Cardiovascular; Kidney Function; Quality Of Life.

Kim JJ, Marks SD. Long-term outcomes of children after solid organ transplantation. Clinics. 2014;69(S1):28-38.

E-mail: stephen.marks@gosh.nhs.uk

*corresponding author

Tel.: +44 20 7405 9200 extension 0292

INTRODUCTION

Patient survival after transplantation has improved substantially over the last decades. For example, 5-year survival for deceased donor renal transplantation increased from 91% in the 1987-1995 era to 96% in the 1996-2007 era (1). The published data on patient and allograft survival rates for children after kidney, liver, heart, lung and intestinal transplantation are summarized in Table 1.

Improvements have mainly occurred in the peri-operative period and have been attributed to better surgical and micro-anastomosis techniques, improved donor procurement and matching schemes and advanced HLA testing methods. HLA typing is now more precisely performed by direct DNA sequencing, and HLA antibodies are detected through flow cytometric bead-based technology (2). Flow cytometry has the advantage of being highly sensitive and enables the prediction of alloimmune responses before transplantation, which can be utilized in virtual cross-matching. This technology also enables the detection of alloantibodies synthesized *de novo* after transplantation. However, there are concerns that modern bead-based techniques may be too sensitive and identify non-clinically relevant antibodies because of differences in the conformation of the antigen between the beads *in vitro* and the actual *in vivo* protein structure (2). Regardless, the incidence of hyper-acute rejection resulting from pre-formed antibodies is now very low.

Transplantation in infants requires special consideration because of the mismatch in donor and recipient size and because the indications, such as congenital abnormalities of the kidney and urinary tract for renal transplantation, biliary atresia for liver transplantation and congenital heart disease for cardiac transplantation, are specific to children. Transplantation in infants is also associated with decreased patient and allograft survival rates. In renal transplantation, the overall patient survival rate is 93% at 3 years compared with 96–99% for older children receiving deceased donor transplants, although the difference is not as large for living donor transplants (1). However, if they survive the immediate post-operative period, infants exhibit comparable outcomes to older children.

A recent development that has increased organ availability is transplantation across the ABO blood group

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2014(Sup01)06

Table 1 - Patient and allograft survival of children after kidney, liver, heart, lung and intestinal transplantation. Living Donor, Deceased Donor.

Organ	Patient survival (%)			Allograft survival (%)		
	1 year	5 year	10 year	1 year	5 year	10 year
Kidney, LD (top), DD (bottom) (1)	98.4	96.1	92.4	96.5	84.3-87	54
	97.4	93.3	86.6	95.1	66-78.0	51
Liver (15)	84-89.8	82-84.8	77	84-93	81-88	75
Heart (13)	80	68	58	86-90	68-75	
Lung (12)	83	54	44 (7 yr)	78-88	35-41	
Intestinal (34)	80-95	77	46	88	74	58

barrier. The Paediatric Heart Transplant Study database of 931 ABO-incompatible cardiac transplants performed in recipients less than 15 months old reported reduced rejection and no differences in mortality (3). In a small single-center study of liver transplantation for infants under 5 kg, survival was comparable to ABO-compatible transplants (4). Infancy is considered to be an immune-privileged time for transplantation because infants have a less-developed immune system and higher acceptance of ABO mismatches. In older children, antibody removal using, for example, plasma exchange and rituximab, can be utilized to decrease blood group antibody levels to acceptable levels (aiming for a dilution ratio of 1:8) (5). In a series of 52 consecutive kidney transplants, Shishido et al. reported no differences in glomerular filtration rates (GFRs) or patient and allograft survival rates compared with ABO-compatible transplants (6). The levels of blood group antibody titers remained low after transplantation, which suggests a degree of accommodation towards blood group glycoproteins. In ABO-incompatible liver transplantation, a recent meta-analysis also revealed similar patient and allograft outcomes compared with ABO-compatible patients (7).

It is particularly difficult to perform transplantation in sensitized patients with positive cross-matches who exhibit positive preformed HLA antibodies. This is often expressed as the percentage of panel-reactive antibodies (PRA), which is tested against a set HLA panel, or the calculated reaction frequency (cRF), which uses the value for the specific HLA antibody calculated against the known population frequency (8). A high PRA or cRF value limits the availability of donors because patients with persistently positive HLA are excluded from the donor pool. These patients also exhibit lower allograft and patient survival rates and higher rates of allograft rejection after transplantation (9,10). Antibody-depleting strategies using plasma exchange, double filtration plasmapheresis, intravenous immunoglobulin (IVIg), rituximab and, more recently, the plasma cell-depleting agent bortezomib have produced variable results in children (8,11). However, this sensitized group is growing because of the increase in patients requiring re-transplantation who are sensitized to their failed allografts.

Mortality is highest immediately after transplantation, particularly in to technically difficult patients (12,13). If patients survive beyond this period, late mortality is low and is more often associated with the side effects of immunosuppression. In fact, conditional survival for infant heart transplants who survived the first transplant year approaches 20 years [19.2 years for those transplanted between the ages of 1-10 years and 15.9 years for older children (13)]. The causes of mortality therefore evolve after transplantation, with the major late causes of mortality including sepsis, cardiovascular causes and post-transplant lymphoproliferative disorder (PTLD) (14). Chronic allograft dysfunction leading to loss of the allograft is also an important cause of mortality and will be discussed subsequently. Infections have overtaken rates of rejection as the major cause of hospital admission (13).

The rate of PTLD is highest in the first few years after transplantation, which is related to higher doses of immunosuppression, although the risks still persist longer than a few years. The risk of developing PTLD is <5% after renal, liver and heart transplantation (15,16) and <10% after lung and intestinal transplantation. Pediatric patients are at a higher risk of developing PTLD because more of them are EBV-naïve. Therefore, routine monitoring for EBV viremia in these patients allows immunosuppression to be adjusted but does not predict which patients will develop PTLD (17). SOT recipients are also at risk for other types of cancers, particularly skin cancer, genitourinary cancer, Kaposi sarcoma and papillary thyroid cancer.

Allograft survival

Although allograft survival in the immediate post-operative period has improved substantially, there have been no significant improvements in longer-term allograft survival. Figure 1 presents the renal allograft survival rates after living donor transplantation by era in North America, which are also representative of the rates for other transplant recipients worldwide (1). There is no longer a sharp decline in allograft survival early after transplantation, but the slope of allograft survival has not changed between transplant eras. The change in early survival can partly be explained by better control of early acute allograft rejection. Acute renal allograft rejection in the first year after transplantation has decreased from 54% pre-1990 to 8.6% in 2010 (1). Acute cardiac allograft rejection in the first year after transplantation has decreased from 60% to 40% in the last decade (18).

In the long term, chronic allograft dysfunction is caused by both immune and non-immune causes. Infections play an important role in patient morbidity and also lead to graft decline. Children with congenital abnormalities of the kidney and urinary tract with bladder dysfunction are prone to repeated urinary tract infections, and this is exacerbated by immunosuppression after transplantation. The polyomavirus, BK virus, is renotrophic and can cause tubulo-interstitial nephritis. In lung transplant recipients, early phase respiratory viral infections are linked to worsened allograft outcomes, and CMV has been implicated in bronchiolitis obliterans.

Chronic antibody-mediated rejection (AMR) has been postulated to be one of the main reasons for the slow

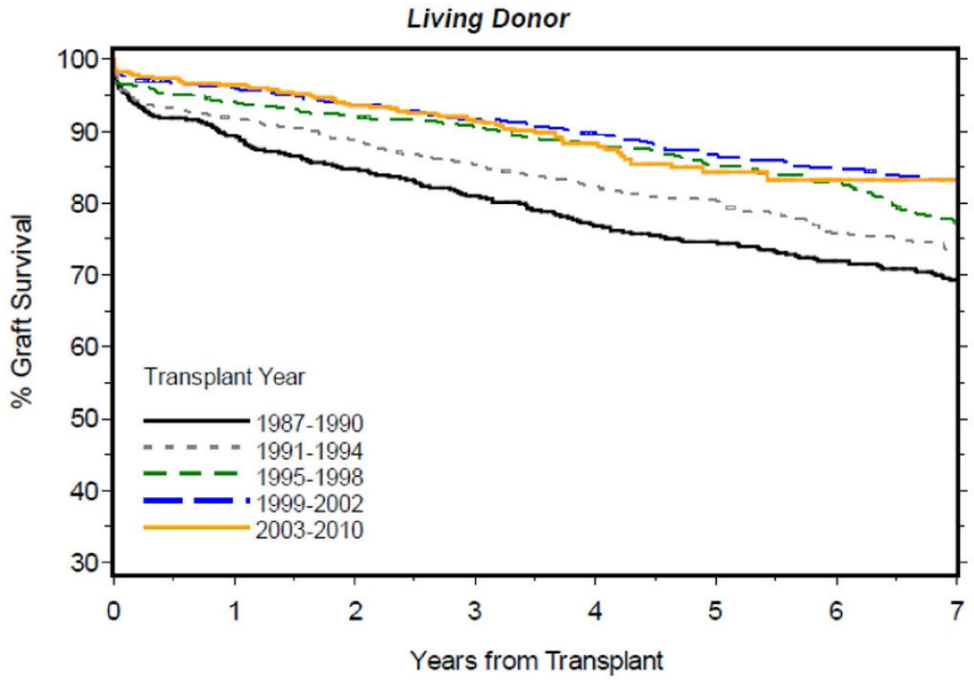

Figure 1 - Renal allograft survival after living donor transplantation by era. Taken from the NAPRTCS 2011 Annual Report (1).

invariable progression to allograft loss (19,20). Chronic AMR has been associated with the *de novo* development of post-transplant donor-specific antibodies (DSA) (21). These antibodies are produced by B-cells that have developed high-affinity receptors targeting HLA mismatches arising from the graft and have undergone class switching from IgM to IgG with subsequent maturation to plasma cells and memory B-cells (22,23). Memory B-cells and memory T-cells are difficult to address using current immunosuppressive therapy. One option is to use rituximab, a B-cell depleting agent, and IVIg, which promotes antibody immunomodulation, to treat active disease and to increase baseline suppression with the addition of mycophenolate mofetil (MMF), which has B-cell anti-proliferative effects (24). The reasons why some patients develop DSA are not known, but one clear factor is non-compliance with immunosuppressive medications. In addition, DSA levels can fluctuate in pediatric patients and do not always lead to chronic allograft dysfunction (25). This is an area under intense investigation, and future techniques may involve immunoglobulin profiling and complement-fixing HLA antibodies (26,27).

AMR is characterized by microvascular injury on allograft biopsy staining and is associated with complement activation detected by C4d staining. In the IHSLT registry, AMR of pathological Grade 2 or higher was present in 18% of protocol endomyocardial biopsies, representing 59% of patients (28). Patients with Grade 3 AMR had more cardiac allograft vasculopathy and increased cardiovascular mortality. The role of AMR in liver transplantation is currently under investigation. C4d staining is present not only in AMR but also in recurrent liver disease and hepatic necrosis (29). However, C4d staining in the presence of DSA often co-exists with cellular rejection and can be steroid-resistant (30).

Current immunosuppression strategies usually consist of a calcineurin inhibitor (CNI) and an anti-proliferative agent in addition to corticosteroids, with variable use of monoclonal antibodies at induction (1,12,13). Current immunosuppression strategies aim to balance the prevention of rejection and the side effect profile. Tacrolimus has generally replaced ciclosporin as the first-line CNI because of its better potency and reduced nephrotoxicity (1,12,13,31). Basiliximab and daclizumab are IL2R-alpha monoclonal antibody inhibitors that are effective T-cell activation blockers, but they have not been demonstrated to improve renal allograft outcomes in pediatric renal transplant recipients when used in addition to the standard triple therapy of prednisolone, azathioprine and tacrolimus (32). However, the use of IL2R-alpha monoclonal antibody inhibitors allows rapid weaning of other immunosuppressive agents, such as corticosteroids (33). The use of induction agents has also increased in heart and lung transplantation but has not been associated with improvements in graft outcomes at 5 years post-transplant (12,13). In intestinal transplantation, the use of IL2-blockers has been effective at reducing acute rejection rates but can be associated with an increased risk of PTLD long after transplantation (34).

Tolerance is defined as stable allograft function in the absence of any immunosuppression. Tolerance can be induced via bone marrow transplantation, as has been described in a case series of multiple myeloma patients who subsequently received renal transplants from the same donor (35). However, caution is warranted, as bone marrow transplantation carries a high risk of mortality currently exceeding that of standard solid organ transplants and therefore remains an experimental procedure. Recently, a modified reduced induction regimen with infusion of a facilitating cell population has been described with positive results. Persistent graft chimerism and stable allograft function appear to be present at one-year follow-up, but longer-term results are pending (36).

Tolerance has also been reported in patients who have been weaned from immunosuppression either through non-compliance or secondary to medical reasons. However, these cases remain rare, particularly in the pediatric literature. Spontaneous tolerance has best been described in liver transplantation, and currently active trials are aiming at active immunosuppression weaning with close follow-up (37,38). Studies of liver transplant tolerance have reported an increase in NK and NKT cells (39). In adult renal transplant tolerant patients, two cross-validated microarray studies have reported an increase in B cell frequency with a concomitant increase in B cell gene transcript signature (40,41). Studies are currently under way to prospectively validate these gene markers for tolerance.

Tolerance can also be viewed as a continuum rather than a separate state. There have been concerns that tolerance may not be meta-stable and that infections could tip the balance towards rejection. Therefore, a compromise may involve accepting minimal immunosuppression (such as utilizing a single immunosuppressive agent) rather than a complete cessation of all immunosuppression. The challenge is to identify biomarkers of tolerance to enable safe weaning of immunosuppression.

Cardiovascular risk factors

Cardiovascular-related deaths are a major component of mortality. Transplant recipients often exhibit increased cardiac dysfunction and usually present unexpectedly in extremis. The main causes of cardiac death include heart failure and arrhythmias (42), in contrast with the general population, in which the major cause is progressive ischemic heart disease. There are also differences in cardiac lesions, as transplant recipients tend to exhibit global arteriosclerotic calcification in the intima and media, in contrast to the atherosclerotic lipid plaques found in elderly patients. However, transplantation itself can improve cardiac outcomes (14). For example, renal transplant recipients exhibit improvements in cardiac hypertrophy and reductions in diastolic dysfunction after transplantation, although not in all cases and often not back to the normal condition (43-45).

Cardiovascular risk factors after transplantation are interlinked and are increased as side effects of immunosuppression. Hypertension is common, as it is described in 50-75% of renal transplant recipients, and is associated with left ventricular hypertrophy (46,47). The prevalence of hypertension in liver transplant patients is reported to be 15-30% (48,49). Transplant recipients require 24-hour ambulatory blood pressure monitoring to unmask nocturnal hypertension (46,49,50). Hypertension is a side effect of corticosteroids and CNI, which also increases the risk of metabolic syndrome [obesity, dyslipidemia and diabetes mellitus (51,52)]. Corticosteroids increase the risk of developing new-onset diabetes after transplantation (NODAT) by increasing peripheral insulin resistance, and CNI has a direct toxic effect on insulin-producing beta-islet cells in the pancreas. Registry studies have reported a prevalence of CNI of 1.8-2%, 3% and 3-7% in cardiac, liver and renal transplant recipients, respectively, and CNI is closely associated with the level and type of immunosuppression (53-55). In particular, although it provides a lower rejection rate, tacrolimus also results in an increased risk of NODAT compared with ciclosporin (31,56). In one study, tacrolimus had an odds ratio of 9.1 for development of NODAT compared with ciclosporin (57). In renal transplantation, two different strategies have been investigated, namely corticosteroid withdrawal and CNI minimization, which are discussed below. Obesity is an increasing healthcare problem that has clear cardiovascular consequences. The prevalence of obesity has also risen in pediatric renal transplant recipients from 8% before 1985 to 12.5% after 1985, with a more recent study estimating the prevalence of diabetes to be as high as 30% (58,59). Obesity is associated with a higher risk of death from cardiopulmonary causes (adjusted relative risks of 3.65 for living donors and 2.94 for deceased donors) and higher rates of allograft loss (19% *vs.* 10%) in transplanted children. In liver transplantation, the risk is 14-16% and remains high long after transplantation (15,60). Obesity following cardiac transplantation occurs less frequently and is estimated at 8%, possibly because of the focus of corticosteroid withdrawal and the use of statins (61). The use of statins in other solid organ transplant recipients requires further investigation (62).

Renal dysfunction

Renal dysfunction is an important cause of morbidity after transplantation. In severe cases, renal dysfunction can lead to end-stage kidney disease requiring dialysis and/or transplantation, but even in mild to moderate cases, renal dysfunction can cause bone mineral disease, vascular calcification and cardiomyopathy. The prevailing risk factors common to solid organ transplant recipients include renal dysfunction at the time of transplantation and the use of CNI. Renal decline is often an insidious process and requires long-term routine monitoring. Follow-up studies of renal function after transplantation are not comparable because of differences in GFR estimations or measurements and different definitions of CKD. One future option for standardization is to use the definitions set by KDIGO.

The prevalence of renal dysfunction in liver recipients was found to be 17.6% (GFR <90 mL/min/1.73 m^2) at a mean of 5.2 years post-transplantation based on SPLIT data (63). However, the prevalence of CKD was higher in two other studies (25% and 32%) examining longer-term data closer to ten years after transplantation despite their use of a lower GFR cut-off (60 and 70 mL/min/1.73 m^2, respectively (63,64). In cardiac transplant patients, the rate of freedom from late renal dysfunction (GFR <60 mL/min/1.73 m^2) was 71% and 57% at five and ten years (65). The prevalence of more severe renal dysfunction, defined as the requirement for dialysis and transplantation or as a plasma creatinine level above 221 μmol/L, was 11% at 10 years post-transplantation (66). In lung transplant recipients, renal dysfunction was estimated to be 10% at 1 year, 23% at 5 years and 35% at 7 years post-transplantation (67); 21% of intestinal transplant patients were found to exhibit stage IV or V chronic kidney disease with GFR <29 mL/min/1.73 m^2 after five years (68).

An important cause of nephrotoxicity is CNI usage with ciclosporin and tacrolimus, which can cause glomerular vascular constriction and shrinkage and in the long term can result in interstitial fibrosis and arterial hyalinosis. However, patients exhibit variability in the nephrotoxic effects of CNI because of genetic polymorphisms in the enzymes involved in CNI metabolism, particularly MDR1

and CYP3A, and may suffer renal damage despite being within the target drug range (69). Of the two CNIs, tacrolimus is associated with less nephrotoxicity. Tacrolimus is associated with better GFRs and lower rejection rates than ciclosporin in pediatric renal transplant recipients (31). In patients with CNI toxicity, one option is CNI minimization or even withdrawal with intensification or substitution of alternative immunosuppressive agents, such as MMF or sirolimus. The timing of CNI withdrawal is important, as nephrotoxicity from CNI is not reversible when performed too late, but the chances of successful withdrawal are improved if undertaken later after transplantation (70,71). Although CNI minimization has been shown to be effective in stabilizing renal function decline, it must be monitored with caution, as there has been evidence of increased rejection rates (72-75). In addition, longer-term follow-up studies are needed to ensure that the improvements are maintained, particularly without an increase in AMR. For patients on MMF, drug monitoring is important to ensure adequately high therapeutic dosages, which may explain the increase in rejection in other studies (76,77). Among patients on the mTOR inhibitors sirolimus and everolimus who exhibit improved renal function, there is a high incidence of side effects, including aphthous ulcers, dyslipidemia, myeloid suppression and proteinuria, necessitating the conversion to alternative medications (78) and counterfoing the benefit of CNI minimization (73,74,79). A new immunosuppressive agent that was recently approved by the FDA is the co-stimulatory inhibitor belatacept. In the phase 3 trial BENEFIT, adult transplant recipients prescribed belatacept with CNI avoidance exhibited better GFRs at 3 years post-transplantation (80). However, patients who are EBV-naïve are contra-indicated for this treatment because of the higher rate of PTLD, which would exclude a large number of pediatric patients from treatment with belatacept.

Growth

Because of their underlying chronic conditions, children with organ failure are usually shorter than their peers prior to transplantation but exhibit improved growth after transplantation. Growth is important, as it is linked to better functional outcomes in employment, education and marital life (81,82).

NAPRTCS data have demonstrated that catch-up growth is best achieved in children transplanted younger, especially those below six years of age (Figure 2) (1). In children who had achieved final adult height, the mean Z-score was found to be -1.40; however, improvement was observed over the years, with the most recent cohort exhibiting Z-scores of -0.94 (1). Pediatric renal transplant recipients treated with daclizumab, mycophenolate mofetil and a quick corticosteroid wean over 4 days in the TWIST study exhibited a mean SDS change of 0.16 compared with 0.03 in the standard regimen group at 6 months with no increase in rejection rates; longer-term data are being currently analyzed (33). In a more recent study with 3-year outcomes, growth was also better in the corticosteroid-free regimen in a subgroup analysis of pediatric renal transplant recipients under 5 years of age (change in SDS score: -0.43 *vs.* -1.07). The corticosteroid-free regimen was safe, with similar allograft survival, and the patients exhibited lower blood pressure and cholesterol levels (83). These results have been reproduced in other studies, which should prompt consideration of early corticosteroid withdrawal if not complete corticosteroid avoidance in uncomplicated transplants (84-87).

The use of recombinant human growth hormone remains controversial, especially as it may confer an increased risk of PTLD. In the most recent Cochrane update, children who were treated with growth hormone (28 IU/m^2/week) exhibited an increased height velocity of 3.88 cm/year (88). In one non-randomized study, final height was significantly higher in patients treated with growth hormone, although the height in the control group was well

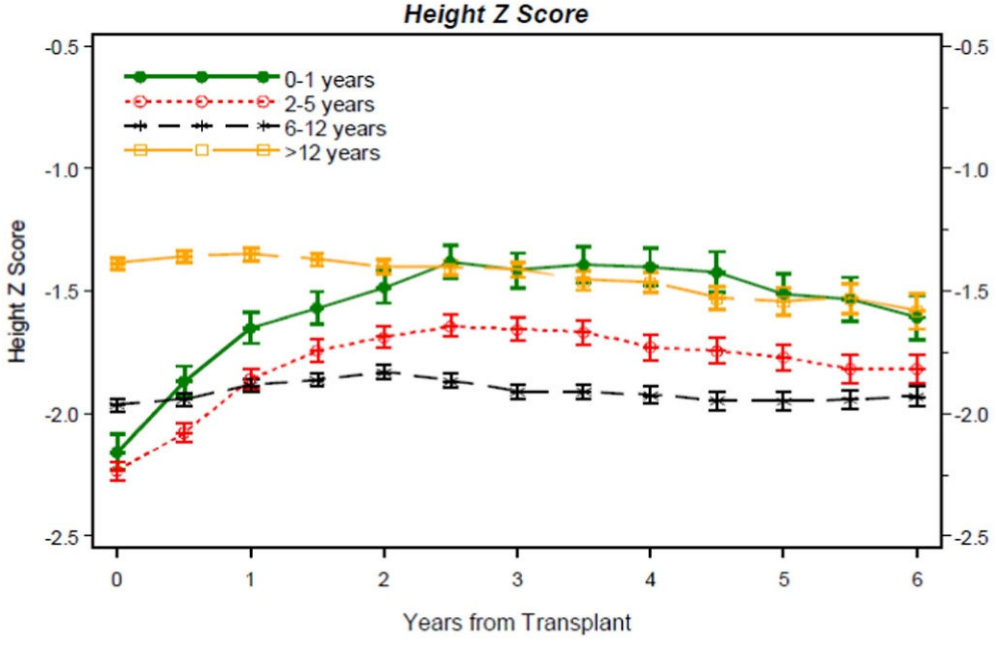

Figure 2 - Catch-up growth according to the age at renal transplantation. Taken from the NAPRTCS 2011 Annual Report (1).

below the average (Z-score -1.88 *vs.* -3.48) (89). However, the cost of this treatment is prohibitory in resource-poor countries and has to be balanced against maximizing nutrition and caloric intake, which can also produce very good height outcomes (90). However, some studies did not report the final adult attained height, and 25(OH) vitamin D deficiency has also been associated with short stature (91). It should be noted that puberty is not delayed in the majority of pediatric transplant recipients, although they invariably exhibit delayed bone age and achieve final height later (92).

Liver transplant recipients also exhibit catch-up growth after transplantation. Similar to kidney transplantation patients, children undergoing liver transplantation in the current era exhibit better height outcomes (82). Improvements in SDS scores are largest immediately after transplantation, partly because of the normalization of digestive enzymes and food digestion. In the SPLIT registry, the mean SDS score at 5 years after transplantation was -0.5 in the most recent cohort (82). Growth plateaus 3-5 years after transplantation and, in a study examining 15-year outcomes, height remained static at -0.47 SDS (93). Improved height gain is associated with less corticosteroid exposure and non-metabolic conditions (82). Corticosteroid-free and corticosteroid withdrawal regimens have also been used successfully (87,94).

Pediatric cardiac transplant recipients maintain their height SDS score with little catch-up growth despite improvements in weight (95). Lung transplant recipients tend to be transplanted in their teens and exhibit growth complications associated with their underlying disease, which is typically cystic fibrosis. Growth after intestinal transplantation is dependent on the re-establishment of feeding and rejection episodes. Lacaille et al. managed to achieve normal growth in two-thirds of their series of 31 children (96).

Quality of life

Although life-saving, solid organ transplantation is not curative, and transplanted children continue to exhibit chronic health problems throughout their life. Therefore, transplantation should focus on extending the length of life and also increasing the quality of life. The WHO defines health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. This requires a holistic approach from the multidisciplinary transplantation team with involvement of primary care physicians, psychologists, social workers and the school, focusing on minimizing attention problems and school absenteeism and maximizing long-lasting relationships with peers and overall school performance.

Quality of life (QoL) can be measured by various indices, which can be general or disease specific. General indices allow comparisons to the general population and across populations but do not address specific issues related to transplantation. Transplant-specific indices are more sensitive to changes in a child's condition and are more useful for measuring longitudinal changes. When possible, QoL questionnaires should be answered by the children themselves. However, there is good agreement between the results reported by children and those reported their parents, although the agreement is higher for observable behaviors than for non-observable emotional and social functions (97).

Qualitative interview studies are also useful in identifying concerns and highlight generic concerns such as physical health limitations, emotions (including fears and worries about future health, sadness arising from knowledge of their parents worrying about them and self-blame for imposing worry on family members) and school/social concerns (such as poor attendance and bullying).

Pediatric renal transplant recipients exhibit good overall outcomes after transplantation (98,99). A questionnaire study of children transplanted before 1999 reported fair or good outcomes in 95% despite a high prevalence of side effects, and 50% of patients were married and reported satisfaction in their married lives (81,100). The rate of unemployment approached 27%, which was comparable that in the general population, and a significant proportion of the patients achieved a university qualification (81,98). However, overall QoL scores were lower than those of healthy peers (101-103). The worst outcomes of transplant patients are related to the side effects of treatment (including body image, obesity, short stature and ulcers) and correlate to non-adherence, which in turn correlates to allograft function (102). Patients also exhibit an increased incidence of somatic complaints and anxiety and depression (98,104). A study utilizing DSM IV criteria reported a 65% risk of lifetime psychiatric disorders in transplant patients compared with 60% in CKD patients and 37.5% in controls (105).

Data from the SPLIT registry, including QoL data, are available for multi-center studies. These data demonstrate lower physical and psychosocial functioning compared with matched peers but equivalent functioning to children with other chronic conditions. PedsQL 4.0 Generic Core Scales were all significantly lower in transplant patients ($p<0.001$), with effect sizes ranging from 0.25 for self-reported emotional functioning to 0.68 for self-reported school functioning (with effect sizes greater than 0.5 considered moderate and 0.8 considered large) (106,107). Patients reported better scores than their parents. Time from transplantation did not impact QoL, but length of stay, number of subsequent days of hospitalization, lower height z-scores, older age and a history of seizures exerted a negative impact on QoL (106,107). In summary, transplant patients exhibit lower QoL compared than the general population but equivalent QoL to other chronic disease patients.

Heart transplantation leads to dramatic improvements in functional status and allows children to return to age-appropriate activities, including physical recreational activities and school (108,109). One qualitative study found that pediatric cardiac transplantation patients described their lives as 'mostly good' or 'fun' and noted that they valued the normal aspects of life (110). Another study reported that the majority (78%) of patients exhibited improved psychological functioning after cardiac transplantation, which was maintained after a decade. Good physical rehabilitation and lifestyle were typically reported in 10% of patients transplanted in the early era who survived more than 20 years (111). However, there is a subset of patients with identifiable psychosocial problems, including anxiety, depression and behavioral problems (108,112-114).

QoL studies for lung transplant recipients are limited (115), although a reduced intensity of psychosocial problems has been suggested (116). In adult QoL studies, general satisfaction with the transplantation decision and

improved QoL scores compared with patients awaiting transplant have been reported, but significant findings of pain have also been reported (117,118). An important study highlighted lower QoL scores in caregivers of lung transplant recipients that were correlated with patient survival rates (119), thus indicating an important avenue of support to improve transplant outcomes.

In intestinal transplantation, one early study reported similar QoL scores to population controls in self-reported questionnaires but lower scores in parent assessments (120). Therefore, despite the effects of disease on their health, these children did not report that their daily functioning was affected, which is an important point when counseling families. This result was reproduced in two recent studies (121,122).

Socioeconomic factors play an important role in the psychosocial support network of children and their families. Single-parent households, low level of caregiver education and family conflicts are negative predictors of QoL (106,107,123). A study evaluating family QoL scores found that transplantation significantly disrupted daily activities but did not affect family functioning as assessed by the Family Assessment Device (107). The parents of transplant children also suffer symptoms of post-traumatic stress disorder, with a prevalence of nearly 40% determined using DSM IV criteria in one study (124,125). Psychological effects on siblings should also be considered in future research. Physicians can minimize family disruption and potentially improve compliance and outcomes by minimizing hospital visits and facilitating follow-up assessments and blood tests at local hospital networks.

The cognitive functioning of pediatric transplant recipients needs to be considered in conjunction with normal brain development. However, cognitive function is determined by the underlying condition, as some diseases present during infancy at the time of rapid neurodevelopment and will therefore exhibit a larger impact on cognitive function. Studies generally demonstrate a lower neurocognitive score in transplant patients compared with the general pediatric population. One study of pediatric renal transplant recipients reported an FSIQ of 87 (normative mean 100, SD 15) (126). Early renal transplantation has been suggested to improve cognitive function in infants (127). In liver transplantation patients, the FOG/SPLIT group highlighted a high prevalence of cognitive delays and learning problems, with 26% of patients exhibiting 'mild to moderate' IQ deficits and 4% exhibiting 'serious delays' (128). However, these studies were performed in previous transplant eras. More recent results may be more encouraging, and longitudinal data are required to determine whether there is any change or improvement in cognitive function (125,129). Children with heart transplants are affected by their period of cyanosis and any prolonged episodes of brain ischemia resulting from circulatory arrest and cardiopulmonary bypass. Heart transplantation therefore improves cognitive function, and developmental and academic assessments have generally been in the normal range (114,130).

Transition

Adolescence is a time when allograft recipients can rebel with non-adherence to immunosuppression and may consequently lose their functioning graft. Therefore, it is important not only to provide additional support to young adult allograft recipients but also to ensure that they have a smooth transition to adult physicians, surgeons and multidisciplinary teams. The ideal transition process should be individualized according to the needs of the patient and not the requirements of the services. The patient transition should involve adolescent-trained physicians, surgeons, nurse specialists, pharmacists and allied health professionals, including the psychosocial team and other multidisciplinary team members, such as youth workers. Most transplant centers provide a dedicated clinic within the adult setting rather than a combined pediatric-adult clinic and have no direct input or continuity from pediatric services. However, the success of these clinics is dependent on good communication between the two services, including meetings between the pediatric and adult clinic staff to plan coordinated care and the involvement of youth workers and transition link staff, such as nurse specialists (who can escort young people to the adult clinics if required). However, a better model can be provided in which both pediatric and adult professionals provide ongoing care in a joint clinic from adolescence through to adulthood, the duration of which can be individualized (131). Transition programs are set up to improve patient-related outcome measures and patient experiences. However, improvement of patient outcomes can only be achieved by careful preparation during the transitioning process, with joint transition clinics identifying issues and overcoming potential difficulties. Initially, young adults should have their fears allayed through the allocation of a key liaison member of the staff assisting in an informal visit to the adult unit during the preparation for transfer. Young adults may be reluctant to leave friends and healthcare personnel, or they may lack maturity or have adherence issues and an ongoing dependence on their parents or guardians. The parents may be reluctant to leave familiar staff and clinic surroundings and may resist attempts by the adult service to enhance the self-advocacy of the child. Financial or time barriers may also impede successful transition from the healthcare system. Excellent communication channels are necessary between pediatric and adult services, with the transfer of documentation (including inpatient and outpatient medical and nursing notes, operation notes and longitudinal laboratory data, including histopathology and radiology results and specialist reports). Pediatric medical and nursing staff may exhibit emotional attachment to patients and lack confidence in the potential care given by health professionals in the adult clinic because of differences in the attitudes and priorities of adult services. Adult medical and nursing staff may lack confidence in managing adolescents because of inadequate training in child and adolescent development or the impact of chronic disease. The staff may be concerned regarding different dynamics of consultation (such as the presence of parents in consultations). They may also lack confidence in the pediatric staff if aware of differences in the attitudes and priorities of pediatric services (such as feeling that the pediatrician has not managed the patient correctly or has transferred the patient either too early or too late).

CONCLUSION

Historically, many children died with organ failure prior to the introduction of transplantation. Solid organ transplantation has revolutionized the lives of these patients, and

there have been improvements in both patient and allograft survival rates through advances in medical therapies and surgical techniques. However, significant ongoing morbidities are still associated with the patients' underlying chronic conditions and transplantation. The challenge for the future is to individualize care, including tailoring immunosuppressive therapies to minimize acute and chronic allograft dysfunction and rejection and the treatment of infectious, metabolic, cardiovascular and other complications of transplantation.

AUTHOR CONTRIBUTIONS

Kim JJ and Marks SD drafted the initial manuscript and approved the final manuscript as submitted.

REFERENCES

1. North American Pediatric Renal Trials and Collaborative Studies. 2011 Annual Transplant Report. [30 October 2013]; Available from: https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf.
2. Picascia A, Infante T, Napoli C. Luminex and antibody detection in kidney transplantation. Clin Exp Nephrol. 2012;16(3):373-81, http://dx.doi.org/10.1007/s10157-012-0635-1.
3. Henderson HT, Canter CE, Mahle WT, Dipchand AI, LaPorte K, Schechtman KB, et al. ABO-incompatible heart transplantation: analysis of the Pediatric Heart Transplant Study (PHTS) database. J Heart Lung Transplant. 2012;31(2):173-9, http://dx.doi.org/10.1016/j.healun.2011.11.013.
4. Gelas T, McKiernan PJ, Kelly DA, Mayer DA, Mirza DF, Sharif K. ABO-incompatible pediatric liver transplantation in very small recipients: Birmingham's experience. Pediatr Transplant. 2011;15(7):706-11, http://dx.doi.org/10.1111/j.1399-3046.2011.01541.x.
5. Barnett AN, Hudson A, Hadjianastassiou VG, Marks SD, Reid CJ, Maggs TP, et al. Distribution of ABO blood group antibody titers in pediatric patients awaiting renal transplantation: implications for organ allocation policy. Transplantation. 2012;94(4):362-8, http://dx.doi.org/10.1097/TP.0b013e31825b7608.
6. Shishido S, Hyodo YY, Aoki Y, Takasu J, Kawamura T, Sakai KK, et al. Outcomes of pediatric ABO-incompatible kidney transplantations are equivalent to ABO-compatible controls. Transplant Proc. 2012;44(1):214-6, http://dx.doi.org/10.1016/j.transproceed.2011.12.017.
7. Wu J, Ye S, Xu X, Xie H, Zhou L, Zheng S. Recipient outcomes after ABO-incompatible liver transplantation: a systematic review and meta-analysis. PloS one. 2011;6(1):e16521, http://dx.doi.org/10.1371/journal.pone.0016521.
8. Asante-Korang A, Jacobs JP, Ringewald J, Carapellucci J, Rosenberg K, McKenna D, et al. Management of children undergoing cardiac transplantation with high Panel Reactive Antibodies. Cardiol Young. 2011;21 Suppl 2:124-32, http://dx.doi.org/10.1017/S1047951111001703.
9. Mahle WT, Tresler MA, Edens RE, Rusconi P, George JF, Naftel DC, et al. Allosensitization and outcomes in pediatric heart transplantation. J Heart Lung Transplant. 2011;30(11):1221-7, http://dx.doi.org/10.1016/j.healun.2011.06.005.
10. Wright EJ, Fiser WP, Edens RE, Frazier EA, Morrow WR, Imamura M, et al. Cardiac transplant outcomes in pediatric patients with pre-formed anti-human leukocyte antigen antibodies and/or positive retrospective crossmatch. J Heart Lung Transplant. 2007;26(11):1163-9, http://dx.doi.org/10.1016/j.healun.2007.07.042.
11. Reinsmoen NL, Lai CH, Vo A, Jordan SC. Evolving paradigms for desensitization in managing broadly HLA sensitized transplant candidates. Discov Med. 2012;13(71):267-73.
12. Aurora P, Edwards LB, Kucheryavaya AY, Christie JD, Dobbels F, Kirk R, et al. The Registry of the International Society for Heart and Lung Transplantation: thirteenth official pediatric lung and heart-lung transplantation report–2010. J Heart Lung Transplant. 2010;29(10):1129-41, http://dx.doi.org/10.1016/j.healun.2010.08.008.
13. Kirk R, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: Fourteenth Pediatric Heart Transplantation Report–2011. J Heart Lung Transplant. 2011;30(10):1095-103, http://dx.doi.org/10.1016/j.healun.2011.08.005.
14. Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA. Change in mortality risk over time in young kidney transplant recipients. Am J Transplant. 2011;11(11):2432-42.
15. Ng VL, Alonso EM, Bucuvalas JC, Cohen G, Limbers CA, Varni JW, et al. Health status of children alive 10 years after pediatric liver transplantation performed in the US and Canada: report of the studies of pediatric liver transplantation experience. J Pediatr. 2012;160(5):820-6 e3, http://dx.doi.org/10.1016/j.jpeds.2011.10.038.
16. Webber SA, Naftel DC, Fricker FJ, Olesnevich P, Blume ED, Addonizio L, et al. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. Lancet. 2006;367(9506):233-9, http://dx.doi.org/10.1016/S0140-6736(06)67933-6.
17. Hocker B, Fickenscher H, Delecluse HJ, Bohm S, Kusters U, Schnitzler P, et al. Epidemiology and morbidity of Epstein-Barr virus infection in pediatric renal transplant recipients: a multicenter, prospective study. Clin Infect Dis. 2013;56(1):84-92, http://dx.doi.org/10.1093/cid/cis823.
18. Gossett JG, Canter CE, Zheng J, Schechtman K, Blume ED, Rodgers S, et al. Decline in rejection in the first year after pediatric cardiac transplantation: a multi-institutional study. The Journal of heart and lung transplantation. J Heart Lung Transplant. 2010;29(6):625-32, http://dx.doi.org/10.1016/j.healun.2009.12.009.
19. Loupy A, Hill GS, Jordan SC. The impact of donor-specific anti-HLA antibodies on late kidney allograft failure. Nat Rev Nephrol. 2012;8(6):348-57, http://dx.doi.org/10.1038/nrneph.2012.81.
20. Kfoury AG, Snow GL, Budge D, Alharethi RA, Stehlik J, Everitt MD, et al. A longitudinal study of the course of asymptomatic antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2012;31(1):46-51, http://dx.doi.org/10.1016/j.healun.2011.10.009.
21. Ho EK, Vlad G, Vasilescu ER, de la Torre L, Colovai AI, Burke E, et al. Pre- and posttransplantation allosensitization in heart allograft recipients: major impact of de novo alloantibody production on allograft survival. Hum Immunol. 2011;72(1):5-10, http://dx.doi.org/10.1016/j.humimm.2010.10.013.
22. Zarkhin V, Kambham N, Li L, Kwok S, Hsieh SC, Salvatierra O, et al. Characterization of intra-graft B cells during renal allograft rejection. Kidney Int. 2008;74(5):664-73, http://dx.doi.org/10.1038/ki.2008.249.
23. Tsai EW, Wallace WD, Gjertson DW, Reed EF, Ettenger RB. Significance of intragraft CD138+ lymphocytes and p-S6RP in pediatric kidney transplant biopsies. Transplantation. 2010;90(8):875-81, http://dx.doi.org/10.1097/TP.0b013e3181f24e3c.
24. Billing H, Rieger S, Ovens J, Susal C, Melk A, Waldherr R, et al. Successful treatment of chronic antibody-mediated rejection with IVIG and rituximab in pediatric renal transplant recipients. Transplantation. 2008;86(9):1214-21, http://dx.doi.org/10.1097/TP.0b013e3181880b35.
25. Miettinen J, Peräsaari J, Lauronen J, Qvist E, Valta H, Pakarinen M, et al. Donor-specific HLA antibodies and graft function in children after renal transplantation. Pediatr Nephrol. 2012;27(6):1011-9, http://dx.doi.org/10.1007/s00467-012-2101-4.
26. Honger G, Hopfer H, Arnold ML, Spriewald BM, Schaub S, Amico P. Pretransplant IgG subclasses of donor-specific human leukocyte antigen antibodies and development of antibody-mediated rejection. Transplantation. 2011;92(1):41-7, http://dx.doi.org/10.1097/TP.0b013e31821cdf0d.
27. Sutherland SM, Chen G, Sequeira FA, Lou CD, Alexander SR, Tyan DB. Complement-fixing donor-specific antibodies identified by a novel C1q assay are associated with allograft loss. Pediatr Transplant. 2012;16(1):12-7, http://dx.doi.org/10.1111/j.1399-3046.2011.01599.x.
28. Everitt MD, Hammond ME, Snow GL, Stehlik J, Revelo MP, Miller DV, et al. Biopsy-diagnosed antibody-mediated rejection based on the proposed International Society for Heart and Lung Transplantation working formulation is associated with adverse cardiovascular outcomes after pediatric heart transplant. J Heart Lung Transplant. 2012;31(7):686-93, http://dx.doi.org/10.1016/j.healun.2012.03.009.
29. Ali S, Ormsby A, Shah V, Segovia MC, Kantz KL, Skorupski S, et al. Significance of complement split product C4d in ABO-compatible liver allograft: diagnosing utility in acute antibody mediated rejection. Transpl Immunol. 2012;26(1):62-9, http://dx.doi.org/10.1016/j.trim.2011.08.005.
30. Musat AI, Agni RM, Wai PY, Pirsch JD, Lorentzen DF, Powell A, et al. The significance of donor-specific HLA antibodies in rejection and ductopenia development in ABO compatible liver transplantation. Am J Transplant. 2011;11(3):500-10.
31. Trompeter R, Filler G, Webb NJ, Watson AR, Milford DV, Tyden G, et al. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. Pediatr. 2002;17(3):141-9.
32. Grenda R, Watson A, Vondrak K, Webb NJ, Beattie J, Fitzpatrick M, et al. A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. Am J Transplant. 2006;6(7):1666-72.
33. Grenda R, Watson A, Trompeter R, Tonshoff B, Jaray J, Fitzpatrick M, et al. A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. Am J Transplant. 2010;10(4):828-36.
34. Mazariegos GV, Steffick DE, Horslen S, Farmer D, Fryer J, Grant D, et al. Intestine transplantation in the United States, 1999-2008. Am J Transplant. 2010;10(4 Pt 2):1020-34.
35. Fudaba Y, Spitzer TR, Shaffer J, Kawai T, Fehr T, Delmonico F, et al. Myeloma responses and tolerance following combined kidney and nonmyeloablative marrow transplantation: in vivo and in vitro analyses. Am J Transplant. 2006;6(9):2121-33.
36. Leventhal J, Abecassis M, Miller J, Gallon L, Ravindra K, Tollerud DJ, et al. Chimerism and tolerance without GVHD or engraftment

syndrome in HLA-mismatched combined kidney and hematopoietic stem cell transplantation. Sci Transl Med. 2012;4(124):124ra28.
37. Feng S, Ekong UD, Lobritto SJ, Demetris AJ, Roberts JP, Rosenthal P, et al. Complete immunosuppression withdrawal and subsequent allograft function among pediatric recipients of parental living donor liver transplants. JAMA. 2012;307(3):283-93, http://dx.doi.org/10.1001/jama.2011.2014.
38. Li L, Wozniak LJ, Rodder S, Heish S, Talisetti A, Wang Q, et al. A common peripheral blood gene set for diagnosis of operational tolerance in pediatric and adult liver transplantation. Am J Transplant. 2012;12(5):1218-28.
39. Martinez-Llordella M, Lozano JJ, Puig-Pey I, Orlando G, Tisone G, Lerut J, et al. Using transcriptional profiling to develop a diagnostic test of operational tolerance in liver transplant recipients. J Clin Invest. 2008;118(8):2845-57.
40. Newell KA, Asare A, Kirk AD, Gisler TD, Bourcier K, Suthanthiran M, et al. Identification of a B cell signature associated with renal transplant tolerance in humans. J Clin Invest. 2010;120(6):1836-47, http://dx.doi.org/10.1172/JCI39933.
41. Sagoo P, Perucha E, Sawitzki B, Tomiuk S, Stephens DA, Miqueu P, et al. Development of a cross-platform biomarker signature to detect renal transplant tolerance in humans. J Clin Invest. 2010;120(6):1848-61, http://dx.doi.org/10.1172/JCI39922.
42. Filler G. Challenges in pediatric transplantation: the impact of chronic kidney disease and cardiovascular risk factors on long-term outcomes and recommended management strategies. Pediatr Transplant. 2011; 15(1):25-31, http://dx.doi.org/10.1111/j.1399-3046.2010.01439.x.
43. Bullington N, Kartel J, Khoury P, Mitsnefes M. Left ventricular hypertrophy in pediatric kidney transplant recipients: long-term follow-up study. Pediatr Transplant. 2006;10(7):811-5, http://dx.doi.org/10.1111/j.1399-3046.2006.00565.x.
44. Kim GB, Kwon BS, Kang HG, Ha JW, Ha IS, Noh CI, et al. Cardiac dysfunction after renal transplantation; incomplete resolution in pediatric population. Transplantation. 2009;87(11):1737-43, http://dx.doi.org/10.1097/TP.0b013e3181a63f2f.
45. Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, et al. Abnormal cardiac function in children after renal transplantation. Am J Kidney Dis. 2004;43(4):721-6.
46. Basiratnia M, Esteghamati M, Ajami GH, Amoozgar H, Cheriki C, Soltani M, et al. Blood pressure profile in renal transplant recipients and its relation to diastolic function: tissue Doppler echocardiographic study. Pediatr Nephrol. 2011;26(3):449-57, http://dx.doi.org/10.1007/s00467-010-1724-6.
47. Mitsnefes MM, Schwartz SM, Daniels SR, Kimball TR, Khoury P, Strife CF. Changes in left ventricular mass index in children and adolescents after renal transplantation. Pediatr Transplant. 2001;5(4):279-84, http://dx.doi.org/10.1034/j.1399-3046.2001.005004279.x.
48. Bayrakci US, Baskin E, Ozcay F, Gulleroglu K, Ozbay F, Sevmis S, et al. Abnormal circadian blood pressure regulation in liver transplanted children. Pediatr Transplant. 2012;16(2):160-4, http://dx.doi.org/10.1111/j.1399-3046.2012.01646.x.
49. McLin VA, Anand R, Daniels SR, Yin W, Alonso EM. Blood pressure elevation in long-term survivors of pediatric liver transplantation. Am J Transplant. 2012;12(1):183-90.
50. McGlothan KR, Wyatt RJ, Ault BH, Hastings MC, Rogers T, DiSessa T, et al. Predominance of nocturnal hypertension in pediatric renal allograft recipients. Pediatr Transplant. 2006;10(5):558-64, http://dx.doi.org/10.1111/j.1399-3046.2006.00521.x.
51. Wilson AC, Greenbaum LA, Barletta GM, Chand D, Lin JJ, Patel HP, et al. High prevalence of the metabolic syndrome and associated left ventricular hypertrophy in pediatric renal transplant recipients. Pediatr Transplant. 2010;14(1):52-60, http://dx.doi.org/10.1111/j.1399-3046.2009.01141.x.
52. Goldsmith D, Pietrangeli CE. The metabolic syndrome following kidney transplantation. Kidney Int Suppl. 2010(118):S8-14, http://dx.doi.org/10.1038/ki.2010.210.
53. Burroughs TE, Swindle JP, Salvalaggio PR, Lentine KL, Takemoto SK, Bunnapradist S, et al. Increasing incidence of new-onset diabetes after transplant among pediatric renal transplant patients. Transplantation. 2009;88(3):367-73, http://dx.doi.org/10.1097/TP.0b013e3181ae67f0.
54. Simmonds J, Dewar C, Dawkins H, Burch M, Fenton M. Tacrolimus in pediatric heart transplantation: ameliorated side effects in the steroid-free, statin era. Clin Transplant. 2009;23(3):415-9, http://dx.doi.org/10.1111/j.1399-0012.2008.00934.x.
55. Hathout E, Alonso E, Anand R, Martz K, Imseis E, Johnston J, et al. Post-transplant diabetes mellitus in pediatric liver transplantation. Pediatr Transplant. 2009;13(5):599-605, http://dx.doi.org/10.1111/j.1399-3046.2007.00603.x.
56. Filler G, Webb NJ, Milford DV, Watson AR, Gellermann J, Tyden G, et al. Four-year data after pediatric renal transplantation: a randomized trial of tacrolimus vs. cyclosporin microemulsion. Pediatr Transplant. 2005;9(4):498-503, http://dx.doi.org/10.1111/j.1399-3046.2005.00334.x.
57. Greenspan LC, Gitelman SE, Leung MA, Glidden DV, Mathias RS. Increased incidence in post-transplant diabetes mellitus in children: a case-control analysis. Pediatric Nephrol. 2002;17(1):1-5, http://dx.doi.org/10.1007/s004670200000.
58. Hanevold CD, Ho PL, Talley L, Mitsnefes MM. Obesity and renal transplant outcome: A report of the North American Pediatric Renal Transplant Cooperative Study. Pediatrics. 2005;115(2):352-6, http://dx.doi.org/10.1542/peds.2004-0289.
59. Denburg MR, Pradhan M, Shults J, Jones A, Palmer JA, Baluarte HJ, et al. Longitudinal relations between obesity and hypertension following pediatric renal transplantation. Pediatric Nephrol. 2010; 25(10):2129-39, http://dx.doi.org/10.1007/s00467-010-1572-4.
60. Perito ER, Glidden D, Roberts JP, Rosenthal P. Overweight and obesity in pediatric liver transplant recipients: prevalence and predictors before and after transplant, United Network for Organ Sharing Data, 1987-2010. Pediatr Transplant. 2012;16(1):41-9, http://dx.doi.org/10.1111/j.1399-3046.2011.01598.x.
61. Kaufman BD, Chuai S, Dobbels F, Shaddy RE. Wasting or obesity at time of transplant does not predict pediatric heart transplant outcomes: analysis of ISHLT pediatric heart transplant registry. J Heart Lung Transplant. 2009;28(12):1273-8, http://dx.doi.org/10.1016/j.healun.2009.07.020.
62. Riella LV, Gabardi S, Chandraker A. Dyslipidemia and its therapeutic challenges in renal transplantation. Am J Transplant. 2012;12(8):1975-82.
63. Campbell K, Ng V, Martin S, Magee J, Goebel J, Anand R, et al. Glomerular filtration rate following pediatric liver transplantation–the SPLIT experience. Am J Transplant. 2010;10(12):2673-82.
64. Harambat J, Ranchin B, Dubourg L, Liutkus A, Hadj-Haissa A, Rivet C, et al. Renal function in pediatric liver transplantation: a long-term follow-up study. Transplantation. 2008;86(8):1028-34, http://dx.doi.org/10.1097/TP.0b013e318187748f.
65. Feingold B, Zheng J, Law YM, Morrow WR, Hoffman TM, Schechtman KB, et al. Risk factors for late renal dysfunction after pediatric heart transplantation: a multi-institutional study. Pediatr Transplant. 2011; 15(7):699-705, http://dx.doi.org/10.1111/j.1399-3046.2011.01564.x.
66. Kirk R, Edwards LB, Aurora P, Taylor DO, Christie JD, Dobbels F, et al. Registry of the International Society for Heart and Lung Transplantation: Twelfth Official Pediatric Heart Transplantation Report-2009. J Heart Lung Transplant. 2009;28(10):993-1006, http://dx.doi.org/10.1016/j.healun.2009.08.008.
67. Aurora P, Edwards LB, Christie JD, Dobbels F, Kirk R, Rahmel AO, et al. Registry of the International Society for Heart and Lung Transplantation: Twelfth Official Pediatric Lung and Heart/Lung Transplantation Report-2009. J Heart Lung Transplant. 2009;28(10):1023-30, http://dx.doi.org/10.1016/j.healun.2009.08.002.
68. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349(10):931-40.
69. Grenda R, Prokurat S, Ciechanowicz A, Piatosa B, Kalicinski P. Evaluation of the genetic background of standard-immunosuppressant-related toxicity in a cohort of 200 paediatric renal allograft recipients–a retrospective study. Ann Transplant. 2009;14(3):18-24.
70. Groetzner J, Kaczmarek I, Schulz U, Stegemann E, Kaiser K, Wittwer T, et al. Mycophenolate and sirolimus as calcineurin inhibitor-free immunosuppression improves renal function better than calcineurin inhibitor-reduction in late cardiac transplant recipients with chronic renal failure. Transplantation. 2009;87(5):726-33, http://dx.doi.org/10.1097/TP.0b013e3181963371.
71. Mourer JS, Hartigh J, van Zwet EW, Mallat MJ, Dubbeld J, de Fijter JW. Randomized trial comparing late concentration-controlled calcineurin inhibitor or mycophenolate mofetil withdrawal. Transplantation. 2012;93(9):887-94, http://dx.doi.org/10.1097/TP.0b013e31824ad60a.
72. Krischock L, Gullett A, Bockenhauer D, Rees L, Trompeter RS, Marks SD. Calcineurin-inhibitor free immunosuppression with mycophenolate mofetil and corticosteroids in paediatric renal transplantation improves renal allograft function without increasing acute rejection. Pediatr Transplant. 2009;13(4):475-81, http://dx.doi.org/10.1111/j.1399-3046.2008.01031.x.
73. Hocker B, Tonshoff B. Calcineurin inhibitor-free immunosuppression in pediatric renal transplantation: a viable option? Paediatr drugs. 2011;13(1):49-69.
74. Flechner SM, Kobashigawa J, Klintmalm G. Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. Clin Transplant. 2008;22(1):1-15.
75. Weintraub L, Li L, Kambham N, Alexander S, Concepcion W, Miller K, et al. Patient selection critical for calcineurin inhibitor withdrawal in pediatric kidney transplantation. Pediatr Transplant. 2008;12(5):541-9, http://dx.doi.org/10.1111/j.1399-3046.2007.00847.x.
76. Hazzan M, Labalette M, Copin MC, Glowacki F, Provot F, Pruv FR, et al. Predictive factors of acute rejection after early cyclosporine withdrawal in renal transplant recipients who receive mycophenolate mofetil: results from a prospective, randomized trial. J Am Soc Nephrol. 2005;16(8):2509-16, http://dx.doi.org/10.1681/ASN.2005030312.
77. Tonshoff B, David-Neto E, Ettenger R, Filler G, van Gelder T, Goebel J, et al. Pediatric aspects of therapeutic drug monitoring of mycophenolic

acid in renal transplantation. Transplantation Rev (Orlando). 2011; 25(2):78-89, http://dx.doi.org/10.1016/j.trre.2011.01.001.
78. Hymes LC, Warshaw BL. Five-year experience using sirolimus-based, calcineurin inhibitor-free immunosuppression in pediatric renal transplantation. Pediatr Transplant. 2011;15(4):437-41, http://dx.doi.org/10.1111/j.1399-3046.2011.01477.x.
79. Dell-Olio D, Kelly DA. Calcineurin inhibitor minimization in pediatric liver allograft recipients. Pediatr Transplant. 2009;13(6):670-81, http://dx.doi.org/10.1111/j.1399-3046.2009.01184.x.
80. Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010;10(3):535-46.
81. Broyer M, Le Bihan C, Charbit M, Guest G, Tete MJ, Gagnadoux MF, et al. Long-term social outcome of children after kidney transplantation. Transplantation. 2004;77(7):1033-7, http://dx.doi.org/10.1097/01.TP.0000120947.75697.8B.
82. Alonso EM, Shepherd R, Martz KL, Yin W, Anand R. Linear growth patterns in prepubertal children following liver transplantation. Am J Transplant. 2009;9(6):1389-97.
83. Sarwal MM, Ettenger RB, Dharnidharka V, Benfield M, Mathias R, Portale A, et al. Complete steroid avoidance is effective and safe in children with renal transplants: a multicenter randomized trial with three-year follow-up. Am J Transplant. 2012;12(10):2719-29.
84. Klare B, Montoya CR, Fischer DC, Stangl MJ, Haffner D. Normal adult height after steroid-withdrawal within 6 months of pediatric kidney transplantation: a 20 years single center experience. Transpl Int. 2012;25(3):276-82, http://dx.doi.org/10.1111/j.1432-2277.2011.01400.x.
85. Delucchi A, Valenzuela M, Lillo AM, Guerrero JL, Cano F, Azocar M, et al. Early steroid withdrawal in pediatric renal transplant: five years of follow-up. Pediatric Nephrol. 2011;26(12):2235-44, http://dx.doi.org/10.1007/s00467-011-1934-6.
86. Hocker B, Weber LT, Feneberg R, Drube J, John U, Fehrenbach H, et al. Improved growth and cardiovascular risk after late steroid withdrawal: 2-year results of a prospective, randomised trial in paediatric renal transplantation. Nephrol Dial Transplant. 2010;25(2):617-24, http://dx.doi.org/10.1093/ndt/gfp506.
87. Diem HV, Sokal EM, Janssen M, Otte JB, Reding R. Steroid withdrawal after pediatric liver transplantation: a long-term follow-up study in 109 recipients. Transplantation. 2003;75(10):1664-70, http://dx.doi.org/10.1097/01.TP.0000063938.49112.C2.
88. Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. Cochrane Database Syst Rev. 2012;2:CD003264.
89. Gil S, Vaiani E, Guercio G, Ciaccio M, Turconi A, Delgado N, et al. Effectiveness of rhGH treatment on final height of renal-transplant recipients in childhood. Pediatric Nephrol. 2012;27(6):1005-9, http://dx.doi.org/10.1007/s00467-011-2090-8.
90. Rees L, Shroff R, Hutchinson C, Fernando ON, Trompeter RS. Long-term outcome of paediatric renal transplantation: follow-up of 300 children from 1973 to 2000. Nephron Clin Pract. 2007;105(2):c68-76, http://dx.doi.org/10.1159/000097601.
91. Shroff R, Knott C, Gullett A, Wells D, Marks SD, Rees L. Vitamin D deficiency is associated with short stature and may influence blood pressure control in paediatric renal transplant recipients. Pediatric Nephrol. 2011;26(12):2227-33, http://dx.doi.org/10.1007/s00467-011-1920-z.
92. Tainio J, Qvist E, Vehmas R, Jahnukainen K, Holtta T, Valta H, et al. Pubertal development is normal in adolescents after renal transplantation in childhood. Transplantation. 2011;92(4):404-9, http://dx.doi.org/10.1097/TP.0b013e3182247bd5.
93. El Moghazy WM, Ogura Y, Harada K, Koizumi A, Uemoto S. Can children catch up in growth after living donor liver transplantation? Liver Transpl. 2010;16(4):453-60.
94. Gras JM, Gerkens S, Beguin C, Janssen M, Smets F, Otte JB, et al. Steroid-free, tacrolimus-basiliximab immunosuppression in pediatric liver transplantation: clinical and pharmacoeconomic study in 50 children. Liver Transpl. 2008;14(4):469-77, http://dx.doi.org/10.1002/lt.21397.
95. Peterson RE, Perens GS, Alejos JC, Wetzel GT, Chang RK. Growth and weight gain of prepubertal children after cardiac transplantation. Pediatr Transplant. 2008;12(4):436-41, http://dx.doi.org/10.1111/j.1399-3046.2007.00826.x.
96. Lacaille F, Vass N, Sauvat F, Canioni D, Colomb V, Talbotec C, et al. Long-term outcome, growth and digestive function in children 2 to 18 years after intestinal transplantation. Gut. 2008;57(4):455-61.
97. Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. Health Technol Assess. 2001;5(4):1-157.
98. Karrfelt HM, Berg UB. Long-term psychosocial outcome after renal transplantation during childhood. Pediatr Transplant. 2008;12(5):557-62, http://dx.doi.org/10.1111/j.1399-3046.2007.00859.x.
99. Sundaram SS, Landgraf JM, Neighbors K, Cohn RA, Alonso EM. Adolescent health-related quality of life following liver and kidney transplantation. Am J Transplant. 2007;7(4):982-9.
100. Bartosh SM, Leverson G, Robillard D, Sollinger HW. Long-term outcomes in pediatric renal transplant recipients who survive into adulthood. Transplantation. 2003;76(8):1195-200, http://dx.doi.org/10.1097/01.TP.0000092524.75807.84.
101. Qvist E, Narhi V, Apajasalo M, Ronnholm K, Jalanko H, Almqvist F, et al. Psychosocial adjustment and quality of life after renal transplantation in early childhood. Pediatr Transplant. 2004;8(2):120-5, http://dx.doi.org/10.1046/j.1399-3046.2003.00121.x.
102. Anthony SJ, Hebert D, Todd L, Korus M, Langlois V, Pool R, et al. Child and parental perspectives of multidimensional quality of life outcomes after kidney transplantation. Pediatr Transplant. 2010;14(2):249-56, http://dx.doi.org/10.1111/j.1399-3046.2009.01214.x.
103. Falger J, Landolt MA, Latal B, Ruth EM, Neuhaus TJ, Laube GF. Outcome after renal transplantation. Part II: quality of life and psychosocial adjustment. Pediatric Nephrology. 2008;23(8):1347-54.
104. Noohi S, Khaghani-Zadeh M, Javadipour M, Assari S, Najafi M, Ebrahiminia M, et al. Anxiety and depression are correlated with higher morbidity after kidney transplantation. Transplant Proc. 2007;39(4):1074-8, http://dx.doi.org/10.1016/j.transproceed.2007.04.002.
105. Berney-Martinet S, Key F, Bell L, Lepine S, Clermont MJ, Fombonne E. Psychological profile of adolescents with a kidney transplant. Pediatr Transplant. 2009;13(6):701-10, http://dx.doi.org/10.1111/j.1399-3046.2008.01053.x.
106. Alonso EM, Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, et al. Cross-sectional analysis of health-related quality of life in pediatric liver transplant recipients. J Pediatr. 2010;156(2):270-6 e1, http://dx.doi.org/10.1016/j.jpeds.2009.08.048.
107. Alonso EM, Neighbors K, Barton FB, McDiarmid SV, Dunn SP, Mazariegos GV, et al. Health-related quality of life and family function following pediatric liver transplantation. Liver Transpl. 2008 Apr;14(4):460-8, http://dx.doi.org/10.1002/lt.21352.
108. Uzark KC, Sauer SN, Lawrence KS, Miller J, Addonizio L, Crowley DC. The psychosocial impact of pediatric heart transplantation. J Heart Lung Transplant. 1992;11(6):1160-7.
109. Sigfusson G, Fricker FJ, Bernstein D, Addonizio LJ, Baum D, Hsu DT, et al. Long-term survivors of pediatric heart transplantation: a multicenter report of sixty-eight children who have survived longer than five years. J Pediatr. 1997;130(6):862-71, http://dx.doi.org/10.1016/S0022-3476(97)70270-1.
110. Green A, McSweeney J, Ainley K, Bryant J. In my shoes: children's quality of life after heart transplantation. Prog Transplant. 2007 Sep;17(3):199-207; quiz 208.
111. Ross M, Kouretas P, Gamberg P, Miller J, Burge M, Reitz B, et al. Ten- and 20-year survivors of pediatric orthotopic heart transplantation. J Heart Lung Transplant.2006;25(3):261-70, http://dx.doi.org/10.1016/j.healun.2005.09.011.
112. DeMaso DR, Twente AW, Spratt EG, O'Brien P. Impact of psychologic functioning, medical severity, and family functioning in pediatric heart transplantation. J Heart Lung Transplant. 1995;14(6 Pt 1):1102-8.
113. Wray J, Radley-Smith R. Longitudinal assessment of psychological functioning in children after heart or heart-lung transplantation. J Heart Lung Transplant. 2006;25(3):345-52, http://dx.doi.org/10.1016/j.healun.2005.09.018.
114. Wray J, Radley-Smith R. Beyond the first year after pediatric heart or heart-lung transplantation: Changes in cognitive function and behaviour. Pediatr Transplant. 2005;9(2):170-7, http://dx.doi.org/10.1111/j.1399-3046.2005.00265.x.
115. Lanuza DM, Lefaiver CA, Farcas GA. Research on the quality of life of lung transplant candidates and recipients: an integrative review. Heart Lung. 2000;29(3):180-95.
116. Lanuza DM, Lefaiver C, Mc Cabe M, Farcas GA, Garrity E, Jr. Prospective study of functional status and quality of life before and after lung transplantation. Chest. 2000;118(1):115-22, http://dx.doi.org/10.1378/chest.118.1.115.
117. Gross CR, Savik K, Bolman RM, 3rd, Hertz MI. Long-term health status and quality of life outcomes of lung transplant recipients. Chest. 1995;108(6):1587-93, http://dx.doi.org/10.1378/chest.108.6.1587.
118. Smeritschnig B, Jaksch P, Kocher A, Seebacher G, Aigner C, Mazhar S, et al. Quality of life after lung transplantation: a cross-sectional study. J Heart Lung Transplant. 2005;24(4):474-80, http://dx.doi.org/10.1016/j.healun.2003.12.013.
119. Myaskovsky L, Posluszny DM, Schulz R, DiMartini AF, Switzer GE, DeVito Dabbs A, et al. Predictors and outcomes of health-related quality of life in caregivers of cardiothoracic transplant recipients. Am J Transplant. 2012;12(12):3387-97.
120. Sudan D, Horslen S, Botha J, Grant W, Torres C, Shaw B, et al. Quality of life after pediatric intestinal transplantation: the perception of pediatric recipients and their parents. Am J Transplant. 2004;4(3):407-13.
121. Ngo KD, Farmer DG, McDiarmid SV, Artavia K, Ament ME, Vargas J, et al. Pediatric health-related quality of life after intestinal transplantation. Pediatr Transplant. 2011;15(8):849-54, http://dx.doi.org/10.1111/j.1399-3046.2011.01590.x.

122. Abu-Elmagd KM, Kosmach-Park B, Costa G, Zenati M, Martin L, Koritsky DA, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg. 2012;256(3):494-508, http://dx.doi.org/10.1097/SLA.0b013e318265f310.
123. Taylor RM, Franck LS, Gibson F, Donaldson N, Dhawan A. Study of the factors affecting health-related quality of life in adolescents after liver transplantation. Am J Transplant. 2009;9(5):1179-88.
124. Young GS, Mintzer LL, Seacord D, Castaneda M, Mesrkhani V, Stuber ML. Symptoms of posttraumatic stress disorder in parents of transplant recipients: incidence, severity, and related factors. Pediatrics. 2003;111(6 Pt 1):e725-31, http://dx.doi.org/10.1542/peds.111.6.e725",-1,"xxx/6.e725.
125. Farley LM, DeMaso DR, D'Angelo E, Kinnamon C, Bastardi H, Hill CE, et al. Parenting stress and parental post-traumatic stress disorder in families after pediatric heart transplantation. J Heart Lung Transplant. 2007;26(2):120-6, http://dx.doi.org/10.1016/j.healun.2006.11.013.
126. Qvist E, Pihko H, Fagerudd P, Valanne L, Lamminranta S, Karikoski J, et al. Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood. Pediatr Transplant. 2002;6(1):53-62, http://dx.doi.org/10.1034/j.1399-3046.2002.1o040.x.
127. Motoyama O, Kawamura T, Aikawa A, Hasegawa A, Iitaka K. Head circumference and development in young children after renal transplantation. Pediatr Int. 2009;51(1):71-4, http://dx.doi.org/10.1111/j.1442-200X.2008.02653.x.
128. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Cognitive and academic outcomes after pediatric liver transplantation: Functional Outcomes Group (FOG) results. Am J Transplant. 2011;11(2):303-11.
129. Kaller T, Schulz KH, Sander K, Boeck A, Rogiers X, Burdelski M. Cognitive abilities in children after liver transplantation. Transplantation. 2005;79(9):1252-6, http://dx.doi.org/10.1097/01.TP.0000161251.20520.42.
130. Chinnock RE, Freier MC, Ashwal S, Pivonka-Jones J, Shankel T, Cutler D, et al. Developmental outcomes after pediatric heart transplantation. J Heart Lung Transplant. 2008;27(10):1079-84, http://dx.doi.org/10.1016/j.healun.2008.07.012.
131. Harden PN, Walsh G, Bandler N, Bradley S, Lonsdale D, Taylor J, et al. Bridging the gap: an integrated paediatric to adult clinical service for young adults with kidney failure. BMJ. 2012;344:e3718, http://dx.doi.org/10.1136/bmj.e3718",-1,"xxx/bmj.e3718.