Pediatric Renal Transplantation

FROM THE GUEST EDITOR

Enrique Jaureguizar Monereo, MD, PhD, Profesor, Autonoma University of Madrid
Chief of Paediatric Urology Department
Pedro López Pereira, MD, PhD, Profesor, Autonoma University of Madrid, Consultant
of Paediatric Urology Department, University Hospital La Paz, Madrid

Renal transplant is the treatment of choice for children with end-stage renal disease. The possibility of obtaining a living related donor is more frequent for paediatric patients than adults and unquestionably, laparoscopic live-donor nephrectomy is the gold standard technique. In paediatric receptors, pretransplant evaluation is extremely important to identify and treat those patients with lower urinary tract dysfunction to avoid possible negative effects on the graft.

As Guest Editor, I invited several specialists from different Transplant Paediatric Renal Units over the world to share their experience in those aspects with the most topicality in the field of Paediatric Renal Transplantation with us. Authors have undisputed expertise in their topic and I hope that readers can enjoy reading this issue and learn something from it.

FROM THE EDITOR

Elizabeth B. Yerkes, MD

Pediatric urologists have highly varied degrees of interest and involvement in the evaluation and care of children who require renal replacement in the form of live or deceased donor renal transplantation. As one less frequently involved in post-transplant medical management or harvest/vascularization of the graft, I found this Edition to be a wonderful update. I thank Dr. Jaureguizar Monereo and all of the other contributors for their dedication to a better life for these children!

At our institution, all members of our group care for children with obstructive uropathy and other conditions with potential for advanced chronic kidney disease. This is the case with our colleagues in Kidney Diseases as well. When it comes time to provide clearance for transplantation, the children are evaluated by one or more of a smaller group from both Divisions with the goal of consistency and ease of communication. We are working on same day multispecialty appointments to ensure consistent urologic follow-up and for family convenience. This is obviously a challenging patient subset to work with, so multiple sets of eyes on their progress are beneficial.

There is of course always room for improvement, and a variety of barriers may exist. I would welcome brief comments from any of the readers regarding how care of this group has been best coordinated at other institutions. How have you optimized multidisciplinary care? How is the urologist involved in pre-, intra- and post-care? How do you ensure follow-up of the kidney and bladder? Have you overcome any unique barriers? These comments will be compiled and shared in a special section in a future edition of DPU. Please send to me and to Lorraine O’Grady at eyerkes@luriechildrens.org and logrady@prri.com.
Live Related or Deceased Donor in Pediatric Renal Transplantation: Clinic and Surgical Differences from the Surgeon Point of View

Eduardo Ruiz, Section on Pediatric Urology, Service of Pediatric Surgery
Department of Pediatrics Hospital, Italiano de Buenos Aires, Argentina

Introduction
Live related donors (LRD) for pediatric patients with end stage renal disease (ESRD) are usually young and healthy parents or relatives with a strong desire to help extremely ill children and teenagers; so the possibility to obtain a LRD for pediatric patients is most of the times more frequent than in adults. Shorter cold ischemia, lower acute rejection rates and the possibility to organize a pre-emptive transplantation (Tx) are responsible of the better outcome in children. In a large group of patients like the NAPRCTS 2006 (9000 Tx) LRD shows an statistically better outcome (5%) than DD in a 5 year follow up.1

Unfortunately, there are two clinical scenarios in which children and young patients have a difficult situation: 1) because of blood group incompatibility or parent’s illness (hypertension, diabetes, renal pathology, etc.) they have no live related donor available and 2) when due to the original diagnosis that led to ESRD (like oxalosis, membranoproliferative glomerulonephritis and focal and segmental glomerulosclerosis) have a poor prognosis of graft survival due to the high rate of recurrence of the original illness in the transplanted kidney.2

Though recipient´s preoperative work up is similar in both types of transplant (LRD, DD) there are some differences in immunosuppressive medication, surgical approach and technical details during the procedure.

Immunosuppressive Protocols
Immunosuppressive protocols have been changing in the last 30 years with the purpose to reduce the frequency of rejection episodes and morbidity related to drugs. Corticosteroids like methylprednisone, a more selective antimitabolite like mycophenolate mofetil (replaced azathioprine in 1993) and tacrolimus which has been used since 2001 (a calcineurin inhibitor) is the most frequently used immunosuppressive protocol in LRD and DD.3

Since 1999, patients for LRD Tx have been receiving a five doses course of perioperative daclizumab (Zenapax ®)1mg/kg/day, a humanized anti-CD25 monoclonal antibody, but patients for DD Tx have been receiving a polyclonal anti-T-lymphocyte antibodies (ATG) like thymoglobulin.4 Acute rejection is a very rare complication nowadays in LRD Tx in children.

Preoperative Surgical Considerations
The possibility to perform preoperative clinical and radiological work-up of living related donors permits to select most of the time the most suitable kidney. Marginal LRD with infrequent conditions as asymptomatic ureteropelvic junction obstruction (UPJO), renal ptosis or angiomyolipoma in kidneys with a contralateral normal kidney are not an absolute contraindication of live donor Tx and could be elected as potential donors. These asymptomatic “renal pathologies” could be repaired or treated during donation procedure on the bench or even during the recipient’s surgery (figure 1) with excellent postoperative results and function. This open mind approach is useful to expand the live donor pool.

Surgical Differences
One of the most striking differences between DD and LRD Tx is the immediate large volume of urine produced by the graft as soon as vascular clamps are released from the recipient’s large vein and arterial vessels. This important postoperative urine production permits anaesthesiologists to use large amounts of intravenous liquids during surgery to maintain an adequate arterial and venous pressure in order to maintain good arterial flow and pressure in the renal artery after releasing the vascular clamps. Intraoperative immediate diuresis from the graft after surgery is also very important because permits to use immunosuppressive drugs like tacrolimus in adequate doses since the early beginning and helps to avoid tubular necrosis as a trigger for acute rejection and graft dysfunction.

Laparoscopic assisted donor nephrectomy is only related to live donor Tx and has added more bench time surgery because most of the time the kidney vessels need more preparation and the excess of perinephric fat must be excised. As we always use the recipient’s right side for kidney transplantation and the vessels have to lie posteriorly in the retroperitoneum, we prefer to free the renal pelvis from the lower kidney pole to modify the ureteropelvic angle (up-down kidney) during bench surgery when the graft is from the donor’s right side. Probably the most important technical difference between LRD and DD is related to the possibility to use donor’s vena cava and aorta in DD. This possibility permits in some patients to maintain a cuff in the renal artery and vein, simplifying vascular anastomosis and avoiding the possibility of arterial stenosis especially in young donors (children). We don’t like to maintain arterial cuffs in DD Tx in small recipients because a renal artery can be kinked after closing the abdominal wound; we prefer to maintain renal vessels as short as possible. When the graft is a very small patient and the two kidneys are used for Tx we prefer to use donor’s aorta and cava vein to anastomose with recipient’s aorta or vena cava but two separated vascular anastomosis for each kidney can be performed succesfully, as has been previously reported.5

Pre-emptive transplantations are approximately a quarter of all Tx because many families want to avoid dialysis. By this reason most of pre-emptive Tx are with a LRD, so in order to avoid dialysis any remained kidney function is maintained and nephrectomy done simulta-

Figure 1: Left side (White arrow) UPJO in previously known donor’s kidney. Right side (Black arrow) Pyeloureteroanastomosis discarding donor’s ureter.

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Live Related or Deceased Donor (continued from previous page)

neously with the Tx. If bladder capacity or compliance is poor, the ureter of the excised kidney could be used to augment bladder capacity (ureterocystoplasty) during the same surgical procedure (figure 2). If bladder emptying is a problem and urethral catheterization (CIC) difficult or impossible, distal native ureter could be used to create a continent urinary stoma or even a simultaneous Mitrofanoff procedure can be done without jeopardizing renal Tx. 6

Conclusion

Preoperative complete evaluation of recipient and donor (when possible), team approach, adequate use of native ureters, proper bench surgery and adapted vascular technique for LRD or DD are the main points to obtain the best clinical results in Tx in pediatric patients.

References


Figure 2: Left side (White arrow) Donor’s ureter after Politano reimplantation into the bladder. Right side (Black arrow) Simultaneous ureterocystoplasty with a large folded left ureter.

Laparoscopic Live-Donor Nephrectomy: Outcome of Allograft Function in Paediatric Recipients

María José Martínez Urrutia MD, PhD, Profesor, Autonoma University of Madrid, Pedro López Pereira M.D., Ph.D., Profesor, Autonoma University of Madrid, Consultant, Roberto Lobato Romero, MD, Angel Alonso Melgar, MD, Maria del Carmen Mseguer, MD
Department of Paediatric Urology and Department of Paediatric Nephrology. University Hospital “La Paz”, Madrid, Spain

Renal transplantation is the treatment of choice for children with end-stage renal failure, and live donor kidney transplantation is currently the best option for these patients. The outcomes of Living Donor Renal Transplantation (LDRT) are superior to results obtained with cadaveric renal transplants or any form of dialysis. 1 The recipient receives a kidney from healthy donor with a minimal ischemic time and excellent organ function is guaranteed, offering long-term benefits with respect to social and growth development and even pre-emptive transplantation. 2

Recipient age at the time of transplantation, race, pre-transplantation dialysis and early rejection are factors that determine graft survival in children who received a LDRT. 3

Laparoscopy has emerged as an attractive alternative to open surgery in donor nephrectomy harvesting. Laparoscopic Donor Nephrectomy (LDN) results in a markedly decreased postoperative patient morbidity and a shorter recovery. Since the introduction of laparoscopic nephrectomy for kidney procurement in 1995, 4 many transplant centers have adopted this technique as their standard of care. 5 This has led to a gradual transfer of the technique to paediatric recipients. The number of living donor transplants in paediatric recipients has suffered an increase thanks to laparoscopic nephrectomy. However, in our opinion, the impact of this type of nephrectomy on graft function in the paediatric recipient has not been sufficiently evaluated.

Impact of Laparoscopic Donor Nephrectomy on Graft Function in Paediatric Recipient

Different studies have shown LDN to be safe and that it provides minimal patient morbidity, short convalescence and an equivalent graft survival compared with open donor nephrectomy. 6 However, the pneumoperitoneum that is created during laparoscopy and the longer warm ischemia time that is noted could produce adverse effect on graft survival.

Pneumoperitoneum has a significant effect on renal hemodynamics and intraoperative urine output. Direct renal compression and reduced renal vein blood flow mediated by the pneumoperitoneum, lead (continued on next page)
Live Donor Nephrectomy

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...laparoscopic kidney procurement was associated with an increased rate of delayed graft function, which is an independent risk factor for rejection during the first year post-transplant.¹²

Recipient age at the time of transplantation, race, pre-transplantation dialysis and early rejection are factors that determine graft survival in children who received a LDRT.³

There were no significant differences between the two groups of recipients. The follow-up period is shorter for the laparoscopic donor group than for the open nephrectomy group (Table 2). All kidneys were successfully transplanted. The decrease in SCr during the first 24 hours post-transplant was slower in the laparoscopic group than in the open surgery group (195 vs 20 second) (Table 1).

Table 1 - Donor’s Data

<table>
<thead>
<tr>
<th>DONORS</th>
<th>Lap DN (16)</th>
<th>Open DN (47)</th>
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</thead>
<tbody>
<tr>
<td>Age/Gender</td>
<td>40.8 ±7(25% M)</td>
<td>41.61 ±7(34% M)</td>
</tr>
<tr>
<td>OR Time</td>
<td>146 min.</td>
<td>112 min.</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>3.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Warm ischemia time</td>
<td>195 sec.</td>
<td>20 sec.</td>
</tr>
<tr>
<td>Cold ischemia (h)</td>
<td>1.8 ± 0.3</td>
<td>1.9 ±0.5</td>
</tr>
</tbody>
</table>

Table 2. Recipient’s Characteristics

<table>
<thead>
<tr>
<th>RECIPIENTS</th>
<th>Lap DN</th>
<th>Open DN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>56%</td>
<td>57%</td>
</tr>
<tr>
<td>Age at RT (years)</td>
<td>9.3 ± 5</td>
<td>11.5 ± 5</td>
</tr>
<tr>
<td>Weight/Height at RT (Kg/cm)</td>
<td>30.6 ± 3.8/125.3 ± 6.4</td>
<td>36.3 ± 2.5/133.3 ± 4.1</td>
</tr>
<tr>
<td>Dialysis time (month) HD/PD (%)</td>
<td>10.5 ± 3.9 (19/37)</td>
<td>10.01 ± 2.6 (27/19)</td>
</tr>
<tr>
<td>Mismatches</td>
<td>1.88 ± 0.22</td>
<td>2.3 ± 0.11</td>
</tr>
<tr>
<td>Induction therapy</td>
<td>Basiliximab</td>
<td>Basiliximab,Thymoglobin</td>
</tr>
<tr>
<td>Follow-up</td>
<td>16 ± 3 months</td>
<td>75 ± 6 months</td>
</tr>
</tbody>
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Live Donor Nephrectomy  

The incidence of acute rejection was similar in both groups. At 36 months, patient and graft survival rates were 100% LDN vs 98% ODN and 94% LDN vs 93% ODN, respectively.

The advent of LDN has contributed to an increase of available live donor kidneys for paediatric recipients. This procurement technique is safe and has no adverse impact on paediatric recipient’s outcomes. Although these data support the continued use of laparoscopically procured living donor kidneys in paediatric renal transplantation, future studies are warranted continued to identify the impact of LDN on renal cortical damage and chronic rejection.

References


Table 3. Comparative outcome in recipient of Laparoscopic Open Donor Nephrectomy allograft

<table>
<thead>
<tr>
<th></th>
<th>Lap DN</th>
<th>Open DN</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate diuresis</td>
<td>94%</td>
<td>96%</td>
<td>ns</td>
</tr>
<tr>
<td>↓ (%) S. Cr 1st 24</td>
<td>9.5 ± 2.3</td>
<td>4.72 ± 0.57</td>
<td>0.007</td>
</tr>
<tr>
<td>ICU stay</td>
<td>72.63 ± 67</td>
<td>73 ± 27</td>
<td>ns</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>15 ± 7.07</td>
<td>13 ± 3.99</td>
<td>ns</td>
</tr>
<tr>
<td>Urological</td>
<td>18.75%</td>
<td>15%</td>
<td>ns</td>
</tr>
<tr>
<td>Time nadir SCr (days)</td>
<td>9.5 ± 2.3</td>
<td>4.72 ± 0.57</td>
<td>0.007</td>
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</tbody>
</table>

Table 4. Graft function results in paediatric recipients

<table>
<thead>
<tr>
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<tr>
<th></th>
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<th>Open DN</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time nadir SCr (days)</td>
<td>9.5 ± 2.3</td>
<td>4.72 ± 0.57</td>
<td>0.007</td>
</tr>
<tr>
<td>GFR 1 week (mean ± sd)</td>
<td>140 ± 126</td>
<td>113 ± 32</td>
<td>ns</td>
</tr>
<tr>
<td>GFR 1 month</td>
<td>166 ± 101</td>
<td>115 ± 33</td>
<td>0.007</td>
</tr>
<tr>
<td>GFR 6 months</td>
<td>122 ± 24</td>
<td>87 ± 17</td>
<td>0.000</td>
</tr>
<tr>
<td>GFR 1 year</td>
<td>129 ± 45</td>
<td>88 ± 27</td>
<td>0.001</td>
</tr>
<tr>
<td>GFR 2 years</td>
<td>110 ± 64</td>
<td>82 ± 30</td>
<td>ns</td>
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Kidney Transplantation in Children with Lower Urinary Tract Dysfunction (LUTD)

Kidney transplantation is the best option in children with end stage renal disease (ESRD). Children with lower urinary tract dysfunction (LUTD) have classically been considered as poor candidates for kidney transplantation. This was due to the fear that the LUTD would lead to further deterioration of the grafted kidney. LUTD leading to ESRD mainly includes: posterior urethral valves (PUV), neurogenic bladder (NB) and more rarely bladder exstrophy (BE). In the latter two, the treatment should have the main objective of preventing renal deterioration since these children are often born with normal kidneys. Unfortunately, especially in developing countries, children with these two conditions still go into ESRD.

This paper will review our current view on the management of children in ESRD due to these 3 pathologies.

1) Posterior Urethral Valves

Despite the improvement in the management of children with PUV, a significant proportion of them will still evolve during childhood toward ESRD, due to the association of the lower urinary tract obstruction with renal dysplasia, in which effects are worsened by the urinary tract infections and the valve bladder syndrome. During the last 3 to 4 decades the mortality related to PUV has fallen from 50% to 3-10%, but there is still a hidden mortality due to an increase in the medical termination of affected pregnancy and to stillbirths. We reviewed the PUV cases in Robert Debré hospital since 1989, and the incidence of renal insufficiency was 15% during childhood (13% in children with prenatal diagnosis of PUV and 20% in those without). Heikkilä et al. have reported on the late evolution of 200 patients treated between 1953 and 2003 at a median age at evaluation of 31 years (range 6 to 69). They estimated the life time risk of ESRD to be 28.5%, but no patient in their series had ESRD after 34 years of age. Early presentation, pneumothorax, bilateral vesicoureteral reflux and recurrent urinary tract infections after the abolition of urethral obstruction were associated with an increased risk of end stage renal disease at follow-up. This indicates that the vast majority of patients with PUV needing a kidney transplant are children or young adults.

The initial experience in kidney transplantation for children with a history of PUV was disappointing. Churchill et al. reported unfavorable outcome with approximately 40% 5-year graft survival. Our group in Necker has compared the results of renal transplantation in 66 boys with PUV and 116 boys with uropathy that did not involve the lower urinary tract. We demonstrated that renal transplantation in children is not associated with a high rate of graft failure. This has been confirmed by others. Bartsch et al. reported the results of 26 boys with PUV compared to other causes of renal transplantation: the 5 year patient and graft survival were similar. It is also the case for the 15 boys with PUV reported by Okutesh et al. However, in our experience a significant increase in serum creatinine was noted at 10 years in children with PUV in comparison to controls. This was reported to be due to the long term effect of bladder dysfunction on the graft.

Hence at 10 years after kidney transplantation, mean serum creatinine was 140.3+/−36.0 and 285.7+/−36.2 micromol/l in asymptomatic boys and those with a voiding disorder, respectively (p<0.01).

A careful evaluation of the indications for bladder function is mandatory before kidney transplantation in patients with PUV. Most of these patients have an extensive evaluation of their bladder from the neonatal period with the aim of delaying the worsening of kidney function. In the worst cases, clean intermittent catheterization (CIC) either through the urethra or through a Mitrofanoff appendicovesicostomy, urinary nocturnal drainage and anticholinergic agents are indicated. Transplantation into the native bladder requires that the bladder have a normal compliance and a sufficient capacity. In the past our group had advocated that many of these patients with kidney failure should undergo bladder augmentation because the compliance was felt to be insufficient. Bartsch et al. have shown that although graft survival was similar in PUV patients with or without bladder augmentation, the kidney function was lower in the augmented group. These authors advocate a limited intervention to the bladder prior to the transplantation in these children. Botto et al. have recently reported (ESPU 2012) the improvement of bladder function in 15 PUV children after kidney transplantation, most probably because of the reduction of the polyuria seen in these patients.

In conclusion, it is mandatory to take care of the valve bladder syndrome before these children reach ESRD. The treatment allows delaying the transplantation but should try to limit the indications of bladder augmentation as much as possible.

2) Neurogenic Bladder and Bladder Exstrophycases

As already mentioned, the treatment of these conditions has the main objective of preventing kidney failure since most of these children have normal kidneys at birth. Despite this objective, some children ultimately require renal replacement therapy. Most of them have had a bladder augmentation and are on CIC. Many studies have shown

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that these children are good candidates for kidney transplantation with implantation of the graft ureter in the augmented bladder.\textsuperscript{6,7} The child and graft survival at 5 years do not appear to be different in these children in comparison to children grafted for an ESRD for other causes.

Children with an augmented bladder and CIC present a significant increase in the incidence of urinary tract infection (UTI) after kidney transplantation, particularly if they already had UTIs before the transplant. Traxel et al.\textsuperscript{8} have shown that the use of gastric augmentation, oral antibiotics and/or gentamicin bladder irrigation significantly reduce the incidence of UTIs after kidney transplantation as does the implantation of the graft ureter with an anti-refluxing procedure.

The long term follow-up of children with bladder augmentation at the Mayo Clinic\textsuperscript{9} has clearly identified among others immunosuppression as a major risk factor of bladder cancer. It indicates the need for a close follow-up of the bladder from 10 years following bladder augmentation.

In extreme cases, it might be preferable to implant the kidney in a Bricker ileal conduit. Broniszczak D et al.\textsuperscript{10} have reported favorable results with a short follow-up of 32 months in 26 children with 97% graft survival.

Children with ESRD and LUTD represent a challenging population but they may be offered kidney transplantation with satisfactory results if they benefit from a careful follow-up of both their graft function and their bladder.

References
Renal transplantation is the treatment of choice for children with end stage renal disease and is a common treatment/practice in paediatric hospitals.

Short term graft survival has clearly improved—one year survival was 91.2% with a live donor and 80.7% with a cadaveric donor between 1987-1995, and 95.3% and 93.4%, respectively, in 1996-2007. This improvement has also been seen in long term survival, but if the evolution of graft loss over time is evaluated, it has barely changed/hardly been modified, and long term graft survival is a major challenge of difficult analysis and solution.

Attaining good graft renal function and maintaining that function over the long term in a child is even more important than in adults, given the greater life expectancy. Paediatric series show an excellent seven year patient survival of 92.4±.04%. Given the deleterious effect of chronic renal disease on growth, the phosphocalcium metabolism, anemia, cardiovascular risk factors, etc., maintaining good renal function in paediatric recipients maintains their quality of life.

The first limitation on long term study of the paediatric experience that one encounters is the short follow up on our patients who graduate/pass to adult nephrology units, making it very difficult to analyze their evolution over a long period of time. The large series in children, like the American registry, NAPRTCS, limits its results to 5-7 years and the same occurs with other series.

Publications on the experience in single centers confirm good patient survival, while graft survival is more variable. Renal graft survival is limited by multiple immunological and non immunological factors that contribute to limiting graft function or even its loss.

Non-Immunological Factors

The incidence of nephropathy due to poliovirus was 4.6% in the NAPRTCS series, causing graft loss in 24% of the cases within 24 months. We have advanced in our understanding of this pathology, but there is still much to know on its treatment and prevention. Close vigilance of the infection and a reduction in immunosuppression are currently considered a good therapeutic strategy, although they present the risk of rejection.

The recurrence of the primary renal disease is a negative factor for graft survival and represents 6.8% of lost grafts. Despite the important advances in genetics, which allow us to better identify patients at risk of recurrence, the best treatment strategy for when the disease recurs is still to be defined.

Factors like race influence graft survival, motivating a need for more intense studies on pharmacokinetics, pharmacodynamics and pharmacogenetics that will optimize the individualization of immunosuppression for each patient.

Donor factors are important in graft evolution; results have been optimized by decreasing the use of very small/young donors. There is a consensus that establishes the priority of paediatric recipients and the use of live donors is widely accepted in children. Even with these donors, factors like chronic ischemia associated to the disparity in sizes between donor and receptor may favor chronic damage in the graft.

An important factor that is difficult to evaluate and may be underestimated is therapeutic noncompliance, basically by adolescents, that contributes to graft loss and/or deterioration. Late acute rejection is attributed to poor compliance and its response to treatment is poor, perhaps due to the tardiness of the diagnosis and because the response mechanisms to the rejection, inflammation, and repair that contribute to chronic damage are already well-established. Irregularity in taking the immunosuppressors contributes to the development of acute subclinical and/or clinical rejection and also to the risk of drug toxicity, since it can lead to errors in the changes in/adjustments to the immunosuppression and very probably also contributes to the genesis of late humeral rejection. Detecting patients at risk of noncompliance in order to provide them with sustained psychological support is important to achieve their involvement in their treatment, empower their self care and increase their responsibility. The use of new slow release drugs like Advagraf, which only needs a single daily dose, may be very interesting in improving compliance in these patients.

Factors that contribute to the increased morbidity and mortality in adult transplant recipients are not well studied in children. Arterial hypertension is the most frequent complication, but its etiology is not always well determined, and the use of new tools like MAPA that would allow us to evaluate the true dimension of the problem should be widened.

Hypercholesteremia is less studied in children than adults and its pharmacological treatment is infrequent, while diabetes is less frequent than in adults.

The incidence of cancer in transplant children is 2.43% and it represents 10.6% of the deaths in the NAPRTCS, but we do not know the possibility of developing cancer later or its impact on survival.

Diagnostic Elements to be Considered

The development of the Banff graft classification system to histologically evaluate the graft has given us a reproducible tool with an elevated clinico-pathological and international acceptance that is irreplaceable for the pathological diagnosis of the graft. The incorporation of new techniques and markers like CD4 detection has contributed to the definition of new diagnoses—such as antibody-mediated chronic rejection—and has limited others—like chronic graft nephropathy that is limited to the coexistence of tubular atrophy and interstitial fibrosis.

New diagnostic tools like donor specific anti-HLA antibodies, humoral response activation markers that are part of the diagnostic pillars for humoral rejection in both its chronic and acute forms, have been incorporated to our arsenal. In recent years our knowledge/understanding of humoral rejection has much advanced regarding both the acute form—for both diagnosis and treatment—as well as its prevention with new aggressive treatment protocols in patients with hyperimmunization (although these are less effective against the chronic form).

A great advance in our knowledge of graft evolution has been provided by the protocol biopsies that are not too frequent in children but that have demonstrated the poor limited reliability of the habitual methods to estimate renal graft function. The increase in creatinine levels and decrease in glomerular filtration are late markers of renal damage, and new markers like cystatin C have been added to the evaluation of graft renal function. The frequency of renal biopsy in suspected graft rejection has increased (from 46% of the instances in 1987 to 96% in 2007, according to NAPRTCS), improving the anatomopathological identification of lesions that are susceptible to immunosuppressive modification.

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Long Term Renal Transplant

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Obviously, paediatric transplantation has peculiarities that make it different and a common effort is necessary to allow us to advance day by day achieving progressive improvements in these children’s treatment. The need for clinical assays in children and multidisciplinary support to allow them an integral development is still unattained.

References

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Other Factors to be Considered in Pediatrics

The time when our patients are transferred to adult units should be planned and discussed with the patient. Although the importance of this transfer for graft prognosis is not well established, it seems logical to individualize each case and establish good cooperation with the adult team that will receive our grown-up child.

The coexistence of other pathologies in our patients is frequent and contributes to increasing morbidity and mortality. Also, chronic renal disease is increasing in recipients of other solid organ transplants, helping to swell the waiting list for these patients with pluripathologies.

Importance of the Advances in Immunosuppression

In general, immunosuppression in children is based on multiple agent therapy, i.e., triple therapy, supported by a short induction treatment in which the use of anti-CD25 [anti-IL2R, daclizumab] is generalized. OKT3 [anti-CD3] is falling into disuse and the use of polyclonal antibodies, basically ATG [anti-thymocyte globulin], has increased in some centers or in high risk patients. There is little experience in the use of these monoclonal antibodies in children, so they are still not used much.

In immunosuppression maintenance therapy, tacrolimus is more used than cyclosporine by many paediatric centers. Initially it was much favored due to its esthetic advantages over cyclosporine and the decrease in acute rejection episodes. With time, tacrolimus has been confirmed to allow better renal function and graft survival than cyclosporine.

The risk of anticalcineurinic [CNI] drug toxicity has led to the use of m-TORI in paediatric patients. Although well designed studies are still lacking, its use as primary immunosuppression has not developed/spread much but it is being used in cases where anticalcineurinic toxicity or chronic graft nephropathy are suspected.

Immunosuppression without corticosteroids, or their minimization, in paediatric patients is an old problem that has received special attention in the last years, supported by the use of new and potent immunosuppressors. There is now experience in patients of not using the initial corticosteroids and others in which a shortened initial use has been followed by good evolution. Other studies support new innovative formulas to induce tolerance. Promising tolerance induction studies have begun in adults but we still do not know of their potential for children. The development of new techniques employing biomarkers and advances in metabolomics and proteomics will help us to identify and predict the immune response in the future.