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## Challenges in pediatric renal transplantation

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### Abstract

Transplantation in children is the best option to treat renal failure. Over the last 25 years the improvements in therapy have dramatically reduced the risk of early acute rejection and graft loss, however the long term results in terms of graft survival and morbidity still require search for new immunosuppressive regimens. Tolerance of the graft and minimization of side effects are the challenges for improving the outcome of children with a grafted kidney. Notwithstanding the difficulties in settling in children large multicenter trials to derive statistically useful data, many important contributions in the last years brought important modifications in the immunosuppressive therapy, including minimization protocols of steroids and calcineurin inhibitors and new induction drugs. New methods for diagnosis of anti HLA antibodies and some new protocols to improve both chance and outcome of transplantation in immunized subjects represent area of ongoing research of extreme interest for children.

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**Key words:** Kidney transplantation; Children; Immunosuppressive therapy; Acute humoral rejection; Desensitization

**Core tip:** Several novelties in the immunosuppressive treatment regimens in kidney transplantation in children are becoming available, with the aim of reducing the long terms side effects, particularly growth retardation, infections and malignancies, as well as improving the long term survival of the graft through a better treatment of chronic rejection. Moreover new induction drugs and specific protocols addressed to sensitized subjects may widen the possibility to receive a graft even for highly immunized children. These innovative aspects of therapy in kidney transplantation in children are reviewed.

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### INTRODUCTION

In children and adolescents affected by chronic renal failure the treatment of choice is kidney transplant. Transplantation indeed, is advocated even before dialysis as the best option to treat the metabolic, psychological and familiar derangement induced by renal failure.

Over the last 25 years remarkable improvements have been reached not only in terms of graft and patient survival<sup>[1,2]</sup> but also for comorbidities and full rehabilitation<sup>[3]</sup>. However the optimal immunosuppressive and supportive treatments assuring long term and high quality survival have not been standardized yet.

The immunosuppressive regimens adopted in the last 25 years have dramatically reduced the risk of acute rejection and graft loss within the first months after transplant but concerning the long term results the rate of graft loss is still high, particularly in patients receiving a transplant as small children and facing adolescence with an aged graft. They are bearing the cumulative risks of prolonged therapies,

malignancies, infections and cardio vascular diseases. Cardiovascular risk is one of the most important aspects clarified in recent years as conditioning patient survival and requiring a proactive and systemic preventive approach since the early phases of renal failure<sup>[4]</sup>.

While primary non function and delayed graft function reduction have allowed progressive improvements of short term allograft survival, data on the long run are still not fully satisfactory. Optimal management of chronic allograft nephropathy remains one of the critical challenges to improve long-term kidney transplant outcomes in children. Both immunologic and non immunologic factors are involved in the pathogenesis of chronic allograft nephropathy, often in a subclinical way, and great efforts are frequently required for prompt diagnosis and appropriate treatment. The search for non invasive markers of immunological damage has not produced so far predictive and satisfactory tools to avoid the graft biopsy and protocol biopsies often are advocated also in children for better follow up<sup>[2]</sup>.

The utopic search for an ideal immunosuppressive regimen able to allow tolerance of the graft and the minimization of the side effects due to over-or under-immunosuppression in children match with the difficulties in settling multicenter trials with sufficiently large number of enrolled patients to derive statistically useful data.

However, several pivotal studies have consistently improved the perspective outcome of children with a grafted kidney, assessing new challenging frontiers in this delicate area.

## STEROID MINIMIZATION, EARLY INTERRUPTION AND AVOIDANCE IN PAEDIATRIC KIDNEY TRANSPLANTATION

For more than 40 years steroid therapy has been a cornerstone of immunosuppressive therapy in renal transplantation. Despite their effectiveness, steroids are associated with severe well known side effects including glucose intolerance, diabetes, hypertension, hyperlipidemia, cataract formation, osteoporosis, fractures, mood and cosmetic changes. In children, steroid therapy has the additional very important drawback of marked growth retardation. Because of these side effects, many efforts have been made on trying to withdraw, minimize or avoid steroid therapy in paediatric renal transplantation.

The early attempts of steroid withdrawal after kidney transplantation in children were performed in the late eighties (1987-1990). However the high rate of acute rejections observed suggested the need of steroids for maintenance therapy in paediatric patients.

The introduction of new powerful immunosuppressive agents and new effective induction therapy led to the development in the last years of new trials aimed at steroid early withdrawal or avoidance in children.

One of the first report was the randomized controlled trial (RCT) from Benfield *et al*<sup>[5]</sup>, who used anti CD25

monoclonal Ab (basiliximab), sirolimus, calcineurin inhibitors (CNIs) and steroids for 6 mo. Before randomization a renal biopsy was performed in each case. Fifty nine of the 132 enrolled children were randomized to maintain 0.15 mg/kg per day of prednisone while the remaining 73 children to steroid withdrawal. There was a trend ( $P < 0.06$ ) of increased frequency of acute rejection in the steroid-free group, and moreover, after three years follow-up, frequency of graft loss or death in the steroid-free group became statistically significant ( $P < 0.002$ ). The study started in 2001 but was discontinued in 2004 because of an unanticipated high risk of post-transplant lymphoproliferative disorders (PTLD). In the steroid-free group, 106/107 children treated for  $> 6$  mo had at least one adverse event during the first 6 mo and most worrying, 10 children developed PTLD. From this study it was concluded that in children it is possible to withdraw or avoid steroids if other immunosuppressive agents are given in large doses; however high immunosuppression carries an increased risk of PTLD, which was considered unacceptable.

More satisfying data came from the TWIST RCT led by Grenda *et al*<sup>[6]</sup> in Europe aimed at investigating the effect of steroid withdrawal on children's growth. All 220 children were treated with daclizumab 1 mg/kg at transplantation and at day 14, tacrolimus (TAC) 0.3 mg/kg per day (target through levels 10-20 ng/mL on days 0-21; 5-15 ng/mL on days 22-186) in combination with mycophenolate mofetil (MMF) 1200 mg/m<sup>2</sup> per day for 2 wk, followed by 600 mg/m<sup>2</sup> per day. In addition to these drugs, children were randomized to (1) arm with steroid withdrawal, assuming methylprednisolone (MP) 300-600 mg/m<sup>2</sup>, with daily reduction (60, 40, 30, 20 mg/m<sup>2</sup>) and discontinuation at day 5; and (2) arm with steroids: MP 300-600 mg/m<sup>2</sup> and 40 mg/m<sup>2</sup> days 2-7, reduced from day 43 to 183 at discretion of investigators.

The primary end point was fully achieved in pre-pubertal children, who showed a significant benefit from steroid early discontinuation in modification of height standard deviation score. In the latter group, the absolute change in mean height at 6 mo was significantly better. The estimated rate of children free from biopsy proven acute rejection at protocol biopsy performed after 6 mo was 89% *vs* 92%, thus not proving any statistical difference between children with or without steroid discontinuation. Outcome of rejection, as well as graft and patients' survival were similar in the two groups. However, the follow-up was very short, being six months only.

There was a need for longer follow-up, provided by the Stanford University group, which has been the leader in trying the steroid minimization strategy. Sarwal *et al*<sup>[7]</sup> addressed to complete steroid avoidance in a multicenter RCT with three years of follow-up. The protocol was based on a common treatment with TAC 0.15 mg/kg per day (12-14 ng/mL day 0-7; 10-12 ng/mL from 2<sup>nd</sup> wk; 4-6 ng/mL at 1 year and 3-5 ng/mL after 1<sup>th</sup> year) in association with MMF: 1200 mg/m<sup>2</sup> per day for 2 d, than 600-900 mg/m<sup>2</sup> per day. Children were randomized

in two arms, including: (1) Steroid free arm, daclizumab 2 mg/kg pre transplant, at weeks 2, 4, 6, 8, 11 and months 4, 5, 6; (2) Steroid based arm, daclizumab 1 mg/kg pre transplantation, at weeks 2, 4, 6, 8. Moreover, prednisone was given, MP 10 mg/kg perioperatively, followed by 2 mg/kg and 0.5, 0.3, 0.2, 0.1, 0.15, 0.1 mg/kg per day at the end of weeks 1, 2, 4, 6, 16. The dose of 0.1 mg/kg was achieved no later than six months post transplantation.

After three years of follow-up no significant difference in estimated glomerular filtration rate was found between the two groups as well as in protocol biopsies at 6, 12 and 24 mo, despite some borderline changes were slightly more frequent in the steroid-free group. This observation induced further subanalysis on subclinical inflammation and chronic renal graft injury in children who underwent this NIH organized RCT<sup>[6]</sup>. No difference between steroid and steroid free regimens was found as far as T mediated rejection or T mediated borderline changes were concerned. There was a significant increase in blood pressure in children on steroids in comparison to those without it as well as an increase in cholesterol. Changes in height-Z score from baseline tended to be different in the two groups over the first months after transplantation (as observed in TWIST RCT) but this effect was lost after one year of transplantation. From this RCT it was concluded that three year follow up of steroid free regimen in unsensitized recipients at first transplantation with double dose of daclizumab in comparison to children on steroids was safe and did not increase the frequency of PTLD. However, no significant difference was observed in linear growth at three years even though at 6 mo there was a better growth in the steroid free group. In this study 13% of children had a failure to maintain steroid-free regimen and had a worse prognosis compared to those who maintained the steroid-free protocol, mostly due to difficulty to control acute rejection or to recurrence of original glomerulonephritis.

A recent systematic review by Pascual *et al*<sup>[9]</sup> including children and adults, concluded that the issue of steroid withdrawal is still controversial. After analysis of 9 RCT and 1934 subjects investigated, death and graft loss were similar in steroid avoidance and control patients, with no differences between CsA and TAC studies. After steroid avoidance, acute rejection was more frequent than conventional steroid use in CsA trials but not when TAC was used. Steroid avoidance was associated with less frequent new-onset diabetes mellitus, but this decrease was only evident with CsA, whereas this difference was not significant analyzing TAC studies. Despite this trend, the corresponding interaction tests were not statistically significant for acute rejection and new-onset diabetes mellitus, respectively.

The conclusions from this meta-analysis were that steroid avoidance or early withdrawal within the first two weeks is safe in kidney transplant recipients receiving induction with anti-interleukin-2 receptor antibodies or thymoglobulin and a drug regimen based on calcineurin inhibitor and MMF. However, the real benefits remain unclear.

## CALCINEURIN INHIBITORS–FREE PROTOCOLS IN PAEDIATRIC RENAL TRANSPLANTATION

CNI carry relevant side effects, including hirsutism, hypertension, diabetes, seizures and renal toxicity which contributes to long term graft loss. Hence the search for CNI free protocols is one of the frontiers for renal transplantation in children. The Renal transplantation Center in Atlanta reported a five-year experience using sirolimus (SRL)-based, CNI-free immunosuppression in pediatric renal transplantation<sup>[10]</sup>. A cohort of low-risk renal pediatric transplant recipients was switched from TAC to SRL. All children received basiliximab induction and TAC, MMF, and prednisone. Conversion was pursued in cases at first transplant without history of nephrotic syndrome and without histologic evidence for acute rejection at three months after transplantation. Fifty-one children were converted from TAC to SRL. SRL was discontinued in 11 cases over the first year because of adverse events, particularly in 20% of the cases for aphthous ulcers. The remaining 40 children had 91% graft survival at five years. Acute rejection was detected in 13% of patients during the first year after conversion. BK viremia was detected in 20% and proteinuria in 7%. This study concluded that SRL-based immunosuppression associated with a CNI-free regimen can be successful in selected lower-risk patients, though the side effects are relevant.

A very relevant issue in children transplantation is growth since height is compromised by previous long term-uremia, dialysis treatment, and children undergoing renal transplantation have to face the need of steroids after transplant, which further limits the possibility of attaining a satisfactory final height. A report from Heidelberg Group has recently investigated the growth in pediatric kidney transplant recipients on an everolimus *vs* an MMF-based steroid-free immunosuppressive regimen<sup>[11]</sup>. Indeed some concerns were raised about the possible interference of mammalian target of rapamycin inhibitors (mTORi) in pediatric transplant recipients with bone growth by inhibition of growth factor signaling and growth plate chondrocyte proliferation. The study focused on longitudinal growth over 2 years in steroid-free pediatric kidney transplant recipients. Fourteen children on a steroid-free maintenance immunosuppressive regimen with low-dose everolimus (EVR) associated with low-dose CsA were compared to 14 children on steroid-free protocol and standard MMF regimen in conjunction with a standard CNI dose. No difference in change in height standard deviation score was detected between EVR and MMF groups. Similarly, the percentage of prepubertal patients experiencing catch-up growth, was similar in children in the two protocols. The Authors concluded that low-dose EVR does not have a negative impact on growth in pediatric renal transplant recipients.

A recently proposed drug for CNI free protocol is belatacept (which differs from abatacept only for two amino

acids), a fusion protein constituted by the Fc fragment of human IgG1 linked to the extracellular domain of CTLA-4, which is crucial for T-cell costimulation. In pediatric kidney transplantation belatacept is a promising agent for allowing steroid-free and CNI free immunosuppression. In a recent report<sup>[12]</sup> in living donor kidney transplant belatacept was used monthly in association with daily sirolimus. Belatacept and sirolimus effectively prevented kidney allograft rejection without CNIs or steroids when used following alemtuzumab induction. The effect of a similar protocol in children is under investigation.

## NEW INDUCTION PROTOCOLS FOR RENAL TRANSPLANTATION IN CHILDREN

Alemtuzumab (Campath-1H) a humanized monoclonal antibody directed against CD52, is a new interesting option for induction with good results also in children<sup>[13,14]</sup>. Alemtuzumab recognizes CD52, a glycoprotein expressed on T and B lymphocytes, monocytes and natural killer cells<sup>[15,16]</sup>. This drug is the most efficient presently available lymphocyte-depleting agents, inducing, after a single administration, a prompt and prolonged depletion of circulating lymphocytes. Alemtuzumab was used since 1998<sup>[17]</sup> with the interesting result of allowing a low-dose CsA monotherapy. Recent RCT in adults have shown lower frequency of acute rejection in comparison to basiliximab in patients non at high immunological risk<sup>[18,19]</sup>. In children the first relevant experience was from Kidney Transplantation Center in Moskow, as Kaabak *et al.*<sup>[20]</sup> reported, in living related pediatric renal transplants. The rationale was to eradicate peripheral lymphomonocytes and induce donor-specific tolerance, by infusing two doses of 30 mg alemtuzumab, one 12-29 d prior to transplantation and the other at surgery. They reported a large experience on 101 living-donor kidney transplantations in pediatric recipients. The maintenance immunosuppression included low doses CNI and MMF. The mean follow-up was 3 years. Graft survival was 96% at one year and 89% at three years. Acute rejection was detected at protocol biopsies in 26% of children at one year and in 35% at two years, while no rejection was detected thereafter. The conclusion from this study were that alemtuzumab pretreatment before living related kidney transplantation is a good option allowing a reduction in usual doses of CNI and obtaining satisfactory middle-term results.

A subsequent study performed by the Portland Group of pediatric kidney transplantation<sup>[21]</sup> investigated the effects of alemtuzumab, 0.5 mg/kg for a maximum of 30 mg, in 25 children undergoing cadaveric kidney transplantation, in whom the drug was given after anesthesia, before kidney transplantation. MP was given 10 mg/kg peri-operatively and before revascularization. Children received steroid therapy for other four days. TAC as monotherapy was initiated at day 1 (target through levels of 8-10 ng/mL over 6 mo, then 6-8 ng/mL). MMF

was added only in cases of high immunological risk or prolonged delayed graft function. Over a mean follow-up of two years, TAC monotherapy was maintained in 48% of children, and steroids were avoided in 80%. The actuarial survival rate at 3 years was 100%. Acute rejection rate was 12% within the first year and 16% in the following two years. The frequency of BK or CMV infection was 16%. The Authors concluded that alemtuzumab induction with TAC monotherapy is a good option for children with low immunological risk ensuring excellent short and medium-term follow-up outcome.

A recent report provided interesting results of 7 years follow-up in children treated with alemtuzumab and corticosteroid minimization after cadaveric renal transplantation<sup>[22]</sup>. The maintenance therapy was a steroid-free regimen with TAC and MMF immunosuppression. All children had immediate graft function and graft survival was excellent (95%). No patient had cytomegalovirus infection, PTLN or polyoma BK nephropathy. The conclusion of this study was that steroid avoidance provided a good outcome with adequate immunosuppression after single-dose alemtuzumab with maintenance therapy with TAC and low-dose MMF.

## DESENSITIZATION PROTOCOLS IN CHILDREN

Over the last years a growing interest has been focused on donor-specific antibodies (DSA Ab) for a previously unsuspected role in graft function and survival<sup>[23]</sup>. Acute antibody-mediated graft rejection is a problem involving children as well as adults, but even more relevant is becoming the role of DSA Ab as one of the mayor causes of graft loss<sup>[24]</sup>. Children candidates to a kidney transplant, particularly after a first failed graft, more often than in the past present with antibodies against HLA antigens, often at high titres, raising the problem of the risk of hyperacute or acute humoral rejections and reducing the chances of being transplanted<sup>[25,26]</sup>. The new flow cytometry based techniques used to investigate the presence of anti HLA antibodies have a much higher sensitivity than complement dependent cytotoxicity assays and are able to reveal panels of antibodies whose capacity to bind complement and induce antibody mediated lysis of target cells is not ascertained. For some years the true role of these low titres antibodies has not been clearly defined: hyperacute rejection is not common but either acute rejection and a chronic damage induced by these antibodies has been demonstrated<sup>[23,24]</sup>.

Sensitization may occur after blood transfusion with red blood cells not appropriately washed or filtered, however the main origin of sensitization is a previous transplant. Proteins as well as stem cells of donor origin have been demonstrated to be persistently present even after removal of the graft, being able to maintain the persistence of immunological stimulus<sup>[25]</sup>. De novo antibodies, mostly directed against HLA, have been detected in a United States multicenter report in up to 24% of children with renal transplant. Six percent of these antibodies were DSA

Ab and 6% anti MHC class 1 related chain A (MICA), and were equally found either on steroid-free or steroid-based regimens<sup>[25]</sup>. The presence of anti HLA and anti MICA Ab was significantly associated with acute and chronic rejection with faster graft loss. Similar results were reported by a single center Italian study<sup>[26]</sup> in 82 children who underwent kidney transplantation, without prior DSA Ab: 23% of this cohort developed after 4 years of follow-up de novo DSA Ab, mostly directed against HLA-DQ antigens. A significant correlation was found between DSA Ab and chronic antibody-mediated rejection. The conclusion of both studies<sup>[25,26]</sup> were that children developing DSA Ab are at risk of graft dysfunction and that there is the need of developing new strategies to prevent antibody mediated graft damage and progression to graft failure.

In candidates to a kidney transplant persistent large panel of antibodies against HLA and PRA > 50% require a desensitization approach for increasing the chance of receiving a graft. Several protocols have been proposed also in children aiming at reducing the antibody titres. The desensitizing protocols include removal of DSA by high-dose *i.v.* immunoglobulins administration (IVIg), plasmapheresis, immunoadsorption, or a combination of the two approaches. In the attempt of reducing recurrence of DSA Ab, rituximab has been introduced in the last years. In some cases immunosuppression with alkylating agents is also considered<sup>[23]</sup>. The major drawbacks of these protocols are the risk of infections and the rebound of antibodies allowing a short window interval time for receiving a transplant, requiring repeated desensitization if a suitable donor is not found. In pediatric age, due to low numbers of desensitized patients there is a lack of large studies.

Most protocols are based on intravenous immunoglobulins which in children have been reported to be effective even when used alone in significantly reducing PRA. Al-Uzri *et al.*<sup>[27]</sup> showed that weekly infusion for three consecutive weeks every 12 wk of high-dose (500 mg/kg) Immunoglobulins reduced PRA to zero, and the effect lasted for over three years. Tyan reported a case where IVIG were successfully used to reduce PRA from 95% to 15% and allow retransplant in a 13 years old boy<sup>[28]</sup>.

In adults Immunoglobulin infusion alone have not produced satisfactory results, hence different protocols of combination treatment with other drugs or procedures have been tried and adopted also in children. The combination of rituximab with plasmapheresis was able to maintain over longer time the immunoglobulin depleting effect of plasmapheresis maintaining the lowering effect so as to allow the use of this protocol also in deceased-donor transplant. Rituximab cannot by itself reduce anti HLA antibody level, but can prevent clonal B cells expansion and consequently DSA production. The advantage of rituximab (1 g/1.73 m<sup>2</sup>) for children is the wide experience in pediatric nephrotic syndrome which reported low incidence of infections and of major complications and effects lasting sometimes even one year, avoiding the need for vascular access and repeated procedures, like in the case of plasmapheresis. Rituximab was

given in some protocols after plasmapheresis<sup>[29]</sup>.

Billing *et al.*<sup>[30]</sup> treated children with active chronic DSA Ab rejection with 4 weekly doses of 1 g/kg IVIg followed by one single dose of rituximab (375 mg/m<sup>2</sup>). They reported a significantly lower loss of GFR over 6 mo of treatment in 4/6 cases. These results were confirmed in a larger trial enrolling 20 children followed over 2 years, with a response rate (evaluated as reduction of GFR loss) in 70% of the patients. Meanwhile, there was a reduction of 60% of antibodies against both HLA class I and Class II<sup>[31]</sup>.

Another drug used to successfully prevent or reduce DSA Ab is MMF (390 to 500 mg/m<sup>2</sup> per day), which gave satisfactory results in a 4-year-old child<sup>[32]</sup>.

New treatments, like Eculizumab which is a complement inhibitor directed against terminal complement protein C5, and the proteasome inhibitor Bortezomib, are theoretically useful to block the final effects of preformed anti HLA antibodies and their noxious effect, but still not yet experienced in sensitized children. A recent retrospective study reported 4 cases of children with grafted kidneys who were treated with bortezomib for high levels of DSA and acute antibody mediated rejection<sup>[33]</sup>. Children received four doses of bortezomib 1.3 mg/m<sup>2</sup> at day 1, 4, 8 and 11. All of them were treated with various drug combinations, including rituximab, methylprednisolone, plasmapheresis or IVIg. The conclusion from this limited series were that bortezomib therapy is an effective and safe methods for a rapid reduction in DSA levels, although its effectiveness from the clinical point of view was not clearly defined in this preliminary experience in children.

## CONCLUSION

In agreement with a recent systematic review performed by the Cochrane group<sup>[34]</sup> to highlight the current trends in immunosuppression in pediatric renal transplantation, when we focus on challenging new frontiers for these children, we still face an uncertain horizon. Newly proposed drugs, including belatacept and alemtuzumab, carry serious side-effects, and interleukin-2 receptor antagonists remain the safest and effective agents for pediatric kidney transplantation. The new steroid-free regimens can improve growth and not hamper graft survival over a short follow-up, however, long-term outcome remains to be determined. mTOR inhibitors, sirolimus and everolimus, are a promising option for primary immunosuppression as CNI sparing agents, however beneficial results on long term graft survival are still to be proven. Desensitization protocols are being performed, but benefits and harms are still to be analyzed and long-term graft survival analysis studies are needed.

In spite of these apparently non optimistic considerations, the improvement of the short and long term results of kidney transplantation in children have been so impressive over the last decades, that we optimistically think that the new frontiers presently representing a challenge will be achieved in a few years as consistent point for further improving the

outcome of kidney transplanted children.

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