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INVITED COMMENTARY

Are kidney transplantation outcomes improved in children weighting 15 kilograms or less in the last decades?

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As perinatal and postnatal care of neonates with impaired kidney function is constantly improving, the number of infants needing renal replacement therapy is increasing. Consequently, the general attitude of clinicians to offer renal replacement therapy (RRT) during the first year of life is changing gradually [1–4]. The ideal renal replacement modality for children and adolescents is renal transplantation (RTX), as both the short-term and long-term medical complications of hemo- and peritoneal dialysis confer inferior survival rates compared to RTX to this patent group [5–7].

Small children (with bodyweight below 10–15 kg) represent a special pediatric subgroup of RTX candidates. Their risk on dialysis is increased (vascular access problems during hemodialysis, increased susceptibility of tunnel infections and peritonitis while on peritoneal dialysis, failure to thrive and to grow, impaired neurocognitive development, etc.), compared to the older cohorts [1]. On the other hand, the poor results of the first transplantation attempt in this age group have for long-time hampered the general acceptance of RTX as a real RRT alternative [2–4]. Technical progress and medical progress (including new immunosuppressive

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therapies and fluid replacement strategies) have revolutionized the segment of RTX of infants [8,9]. Both single-center data and that from registries are reporting at least similar results to adult RTX [10–13]. However, due to the relative small number of patients involved in a single-center analysis and the methodological issues, concerning data from registries remained several uncertainties.

The study involving two large Belgian pediatric centers published in this issue of the *Journal* [14] accurately reflects the evolution of pediatric transplantation in the past forty years. The study presents how the change in patient management has substantially improved the short- and long-term prognosis and may serve as guidance reviewing the main issues of RTX in small children.

The first of such an issue is the source of the donor. Size mismatch between adult-sized kidneys (ASK) and very young recipients is for long-time considered as one of the main obstacles to RTX, as it was the source of major technical problems due – among others – to the enormous perfusion requirements of the new organ compared to the donor's resources. New principles of recipient management have led to dramatic improvement of graft survival [9]. An ASK may even confer protection against acute rejection as a consequence to the larger antigen mass of the kidney compared to the recipient's immune system [10]. On the other hand, an ASK accommodates to the decreased blood supply with reduction in its original glomerular filtration rate (GFR). This involuntary adaptation is thought to be the effect of chronic hypoxia resulting from hypoperfusion [9,15]. As the recipient grows, the grafts originating from adults are not adapting to the increasing demands of the recipient. That means a relative loss of GFR while the absolute GFR will remain stable. On the other hand, the GFR of grafts coming from children may go along with the increasing needs conferred by growth, with comparably acceptable low rates of acute rejections in that cohort [11,16,17].

Renal transplantation results from the very low end of the donor spectrum, namely the kidney from very young children (usually below the age of 5 years), are still afflicted by surgical complications mainly of vascular origin [9,10]. Although there are multiple reports about the feasibility of 'en block' transplantation of infant kidneys, this technique is still not a standard procedure in pediatric transplantation [17,18]. In the Belgian cohort [14], vascular stenosis, thrombosis or hemorrhages occurred in a quarter of RTX of the early period, whereas they occurred in only about one of the ten RTX since 2000. Nevertheless, in the case of kidneys from donors younger than 5 years, delayed graft function (DGF) and graft loss in the first post-RTX year were more than double when compared to the transplantations performed with graft from older donors.

As data on the evolution of GFR are not presented in the recent cohort [14], the adaptation of the graft to the donor's requirements [11,17,19] could not be traced. The decrease in incidence of DGF may be secondary to improved graft management. DGF is associated with a higher risk of acute rejection and is detriment for graft survival both short-term and long-term [20].

Change in immunosuppression over the past decade has led to improvement in graft survival. Introduction of calcineurin inhibitors (CNI) and mycophenolate, and the implementation of triple therapy (steroid, CNI, and mycophenolate) are at the origin of the significant improvement of graft survival. The addition of induction therapy in the low- and medium-risk patients has recently been questioned based on results of large adult controlled studies, although it is part of the standard protocol in many centers [21]. Actual center policy of using induction therapy is different among continents and centers, some using preferentially polyclonal antibodies, others anti-IL-2R antibodies, while there are studies reporting RTX without routine use of induction therapy [10,12,22]. Steroid avoidance or withdrawal is also a popular trend stressing the negative metabolic effects of steroids while perhaps overseeing the pitfalls of need of increased nonsteroidal immunosuppression [23]. In the Belgian cohort [14], steroid treatment has been used in all patients. The main change compared to the first period is the introduction of anti-IL-2R antibody induction, the use of CNI and mycophenolate. Paralleling these changes, the rate of acute rejection decreased impressively, and in particular, early acute rejection has become an exceptional event. For the RTX realized in the most recent period, the rejection-free graft survival achieved the impressive rates of 97% and 87% at 1 and 10 years, respectively. Young recipients are generally naïve concerning immune-modulating viruses such as EBV and CMV and therefore are at particular risk of developing infections and/or cancers under the current strong immunosuppression [13,24]. It is important to note that in this study [14], despite the highly effective immunosuppression in the second period, the incidence of post-transplant lymphoproliferative disorders (PTLD) did not change between the two cycles. These data confirm that the standard immunosuppressive drugs can be used in small recipients. Long-term patient's survival and long-term graft's survival were comparable, if not better, than in adult recipients.

The conclusion from the Belgic experience is that infantile terminal renal failure is no more a hopeless

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state without any perspective. Technical and medical progress rendered RTX a standard procedure for this patient group assuming appropriate conditions are warranted. The occurrence of acute rejection has dramatically decreased resulting in increased patient's and graft's survival. The issue of choice of optimal donor – apart from extremes (very young and senior donors) – seems to be rather academic; the actual standards generally ensure proper function. Standard triple immunosuppression together with antibodies against IL2R may confer sufficient protection to the graft without an unacceptable increase in infection or malignancies, at least in the first decade of patient care.

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Conflicts of interest

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REFERENCES

1. Zurowska AM, Fischbach M, Watson AR, *et al.* Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). *Pediatr Nephrol* 2013; **28**: 1739.
2. Teh JC, Frieling ML, Sienna JL, Geary DF. Attitudes of caregivers to management of end-stage renal disease in infants. *Perit Dial Int* 2011; **31**: 459.
3. Wightman AG, Freeman MA. Update on ethical issues in pediatric dialysis: has pediatric dialysis become morally obligatory? *Clin J Am Soc Nephrol* 2016; **11**: 1456.
4. Wedekin M, Ehrich JHH, Offner G, Pape L. Renal replacement therapy in infants with chronic renal failure in the first year of life. *Clin J Am Soc Nephrol* 2010; **5**: 18.
5. Wolfe RA, Ashby VB, Milford EL, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.
6. U.S. Renal Data System, USRDS. Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.
7. Harambat J, van Stralen KJ, Schaefer F, *et al.* Disparities in policies, practices and rates of pediatric kidney transplantation in Europe. *J Am J Transplant* 2013; **13**: 2066.
8. Gulati A, Sarwal MM. Pediatric renal transplantation: an overview and update. *Curr Opin Pediatr* 2010; **22**: 189.
9. Salvatierra O, Singh T, Shifrin R, *et al.* Successful transplantation of adult sized kidneys into infants requires maintenance of high aortic blood flow. *Transplantation* 1998; **66**: 819.
10. Sarwal MM, Cecka M, Millan MT, Salvatierra O Jr. Adult-size kidneys without acute tubular necrosis provide exceedingly superior long-term graft outcomes for infants and small children a single center and UNOS analysis. *Transplantation* 2000; **70**: 1728.
11. Dubourg L, Cochat P, Hadj-aissa A, *et al.* Better long-term functional adaptation to the child's size with pediatric compared to adult kidney donors. *Kidney Int* 2002; **62**: 1454.
12. Neipp M, Offner G, Rainer L, *et al.* Kidney transplantation in children weighing less than 15 kg: donor selection and technical considerations. *Transplantation* 2002; **73**: 409.
13. Chavers BM, Rheault MN, Matas AJ, *et al.* Improved outcomes of kidney transplantation in infants (age <2 years): a single center experience. *Transplantation* 2017. https://doi.org/10.1097/tp.0000000000001929. [Epub ahead of print]
14. Chiodini B, Herman J, Lolin K, *et al.* Outcomes of kidney transplantations in children weighing 15 kilograms or less: a retrospective cohort study. *Transpl Int* 2018; **31**: 720.
15. Salvatierra O, Sarwal M. Renal perfusion in infant recipients of adult-sized kidneys is a critical risk factor. *Transplantation* 2000; **70**: 412.
16. de Santis Feltran L, Koch Nogueira PC, Ajzen SA, *et al.* Does graft mass impact on pediatric kidney transplant outcomes? *Pediatr Nephrol* 2014; **29**: 297.
17. Laube GF, Kellenberger CJ, Kemper MJ, *et al.* Transplantation of infant en bloc kidneys into paediatric recipients. *Pediatr Nephrol* 2006; **21**: 408.
18. Wang HY, Li J, Liu LS, *et al.* En bloc kidney transplantation from infant donors younger than 10 months into pediatric recipients. *Pediatr Transplant* 2017; **21**: e12845.
19. Herthelius M, Celsi M, Edström S, *et al.* Renal transplantation in infants and small children. *Pediatr Nephrol* 2012; **27**: 145.
20. Chaumont M, Racapé J, Broeders N, *et al.* Delayed graft function in kidney transplants: time evolution, role of acute rejection, risk factors, and impact on patient and graft outcome. *J Transplant* 2015; **2015**: 163757, 9 pages.
21. Hellemans R, Bosmans JL, Abramowicz D. Induction therapy for kidney transplant recipients: do we still need anti-IL2 Receptor monoclonal antibodies? *Am J Transplant* 2017; **17**: 22.
22. Mehrabi A, Kashfi A, Tönshoff B, *et al.* Long-term results of pediatric kidney transplantation at the University of Heidelberg: a 35 year single-centre experience. *Nephrol Dial Transplant* 2004; **19**(Suppl. 4): iv69.
23. Zhang H, Zheng Y, Liu L, *et al.* Steroid avoidance or withdrawal regimens in paediatric kidney transplantation: a meta-analysis of randomised controlled trials. *PLoS One* 2016; **11**: e0146523.
24. Comoli P, Ginevri F. Monitoring and managing viral infections in pediatric renal transplant recipients. *Pediatr Nephrol* 2012; **27**: 705.

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