# Clinical outcome after Renal Transplantation in Small Children ≤ 15 kilos: 38 years of Dutch experience

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**Objectives:** Although kidney transplantation in the smallest recipients (<15 kg) is a delicate task, it is the treatment of choice when end-stage-renal-disease (ESRD) is reached. We recently conducted a systematic review in which we showed that after an improvement of graft survival in the early eras (<2000), a stabilisation is seen over the more recent eras (>2010). Although improved immunosuppressants have resulted in increased graft survival in the past, we hypothesize that their side effects (e.g. nephrotoxicity and infections) prevent further improvement. The aim of the current study is to investigate the clinical outcome of small children after renal transplantation in the Netherlands, focussing on long term outcome (rejection, GFR and graft survival) and on immunosuppression side effects (e.g infection, nephrotoxicity) and to relate these outcomes to the immunosuppression protocol used.

**Method:** All children in the Netherlands weighing 15 kilograms or less at the time of renal transplantation were included in our study. Data regarding graft survival were obtained from the Dutch Organ Transplantation Registry (NOTR). Other variables were extracted from reviewing medical charts.

**Results:** In total, 80 transplantations in children ≤ 15 kg were performed from 1983 till 2020 in the Netherlands. The 1-, 5- and 10-years overall patient survival was 97.4%, 97.4% and 94.8%, respectively. The graft survival was 82.7%, 67.9% and 32.9% at 1-, 5-, 10-year post-transplantation. The Kaplan-Meier indicates a better survival between era 1 (1980 – 1989), era 2 (1990 – 1999), era 3 (2000-2009) and era 4 (2010 – 2020). While graft survival improved over the years (1980-2020) in our cohort, graft survival rates did not improve substantially anymore between the two recent eras (2000-2009 versus 2010-2020).

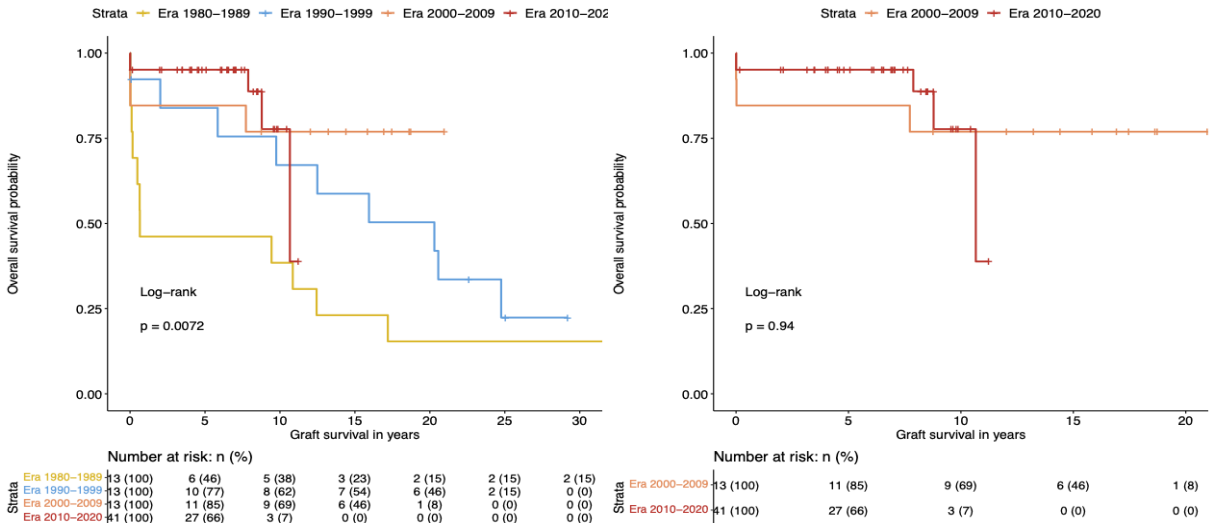


*Figure 1. Kaplan-Meier curve of all included children. Left the analysis of all children and right the analysis of the most recent eras. The risk table describes the number of patients at risk.*

Our hypothesis that infections are responsible for the stabilisation in graft survival was tested. Indeed, the one-year post-transplantation infection rate (data available in 44 patients) was high with 6.23 infections/year (SD: 2.86). The immunosuppression protocols have evolved greatly over time, with most recently the introduction of a prednisone free protocol (TWIST, n=34 patients) with higher tacrolimus and cellcept levels.

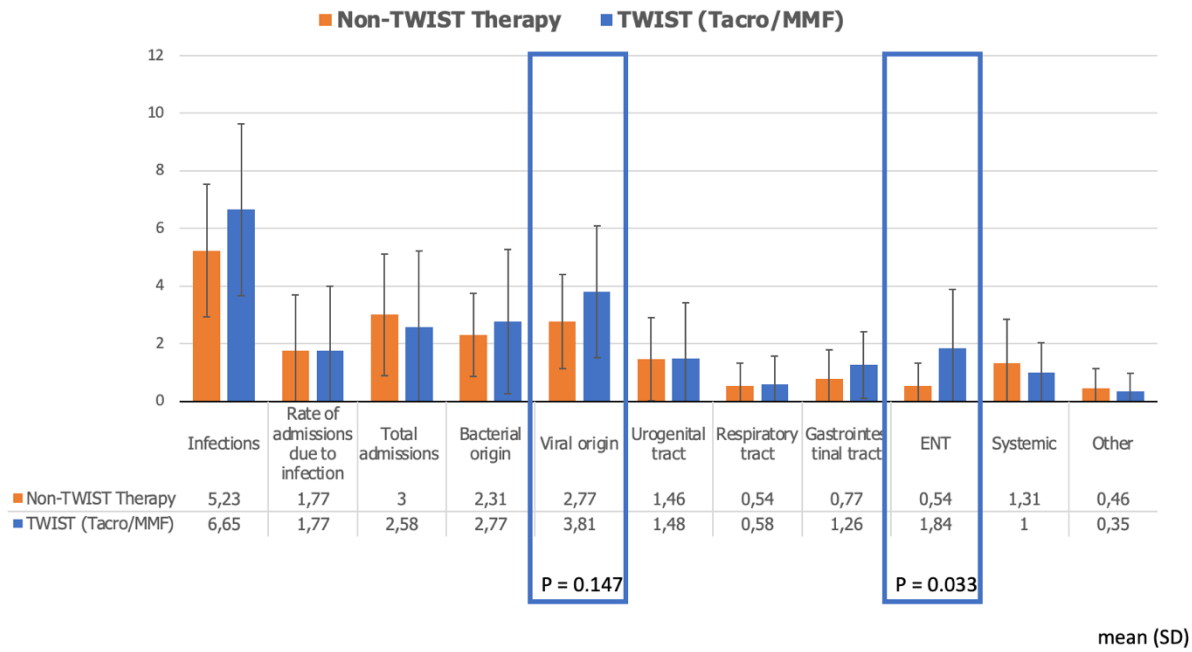


*Figure 2. Summary of infections 1-year post-transplantation in TWIST group vs non-TWIST group. Abbreviations: ENT, ear-nose-throat*

Comparing the infection burden in TWIST versus non-TWIST treated patients showed significantly more ear, nose and throat infections (1.84 vs 0.54, p=0.033) in the TWIST treated group. In the patients with a high rate of infections, two or more immunosuppression changes were made in almost 60% of patients. (p = 0.069). Comparable growth rates were seen between TWIST and non- TWIST treated patients (not tested for significance).

| | **Infection rate 1-3/1y** | **Infection rate 3-5/1y** | **Infection rate =>6/1y** | **P-test** |
|---|---|---|---|---|
| **Number of patients** | 7 | 10 | 27 | |
| **Tracts** | | | | |
| Urogenital* | 0.29 (0.76) | 0.40 (0.97) | 2.19 (1.86) | **0.002** |
| Respiratory* | 0.14 (0.38) | 0.50 (1.08) | 0.70 (0.95) | 0.356 |
| Gastrointestinal* | 0.71 (0.95) | 0.80 (0.79) | 1.33 (1.24) | 0.266 |
| ENT* | 0.57 (0.79) | 0.60 (0.70) | 2.00 (2.15) | **0.046** |
| Systemic* | 0.43 (0.53) | 1.30 (1.49) | 1.19 (1.18) | 0.276 |
| Other* | 0.14 (0.38) | 0.70 (0.67) | 0.33 (0.62) | 0.145 |
| **Immunosuppression** | | | | |
| Switch ≥2/1y (%) | 3 (42.9) | 0 (0.0) | 12 (57.1) | 0.069 |
| Restart steroids (%) | 1 (14.3) | 3 (33.3) | 15 (55.6) | 0.112 |
| Tacrolimus trough levels* | 9.07 (1.70) | 8.21 (2.96) | 8.05 (3.83) | 0.872 |
| Side-effect of immunosuppression leukopenia (%) | 0 (0.0) | 2 (20.0) | 5 (18.5) | 0.452 |

*Table 1. **Summary of infections 1-year post-transplantation in groups of low/medium/high infection rate**. Table describes, the origins (bacterial or viral), location of the infection, the number of changes to immunosuppression, the need to restart steroids in the TWIST group, the tacrolimus trough levels, the side-effect of the immunosuppression leukopenia. Abbreviations: ENT, ear-nose-throat. *, (mean (SD))*

**Conclusion:** Our results show that in the Netherlands, clinical outcome after renal transplantation in small children has improved greatly but shows no further improvement in the most recent era. The high burden of ENT infections in patients treated with the most recently implemented TWIST protocol, demanded the clinician to make more often a change in immunosuppression protocol. In our opinion both (higher infection rate and more immunosuppression changes) might have a negative impact on further graft survival improvement. Is the TWIST protocol the most optimal choice for small children?