IV.11 Paediatrics (specific problems)

Section IV.11 was prepared by Professor Pierre Cochat (Département de Pédiatrie, Hôpital Edouard-Herriot and Université Claude Bernard, Lyon, France) and Professor Gisela Offner (Medical School Hannover, Department of Pediatric Nephrology, Hannover, Germany) on behalf of the European Society for Paediatric Nephrology (ESPN). In the following section, only guidelines that differ from those for adults will be given.

Guidelines

A. Kidney transplantation should be the treatment of choice for end-stage renal disease (ESRD) in children (up to 16 years of age). Because the incidence rate of ESRD is very low, ~1–2 children per million general population or 4–6 children per million childhood population, kidney transplantation in children should be performed in specialized paediatric centres with multidisciplinary experts, i.e. transplant surgeons, anaesthetists and paediatric nephrologists, and optimally should be supported by psychologists, paediatric nurses and social workers. (Evidence level C)

B. Due to the urgent need for transplantation, children should have priority in the allocation systems. In addition, pre-emptive transplantation from either live or cadaveric donors should be offered to all paediatric transplant candidates whenever possible. These protocols will reduce the time on dialysis, thus limiting the retardation of growth and development. (Evidence level C)

C. Absolute contra-indications to renal transplantation in children are extremely rare but should be respected: uncontrollable malignancy, ABO incompatibility, the presence of a current positive cross-match or multi-organ failure. There are few relative or transient contra-indications: history of cancer (Wilms tumour), viral infection (HIV, HBV, EBV), very young age (<6 months), severe mental retardation and/or additional disabilities. (Evidence level C)
D. In contrast to adult patients, primary renal diseases responsible for ESRD in children are mostly congenital and hereditary disorders (60%). Children with massive vesico-ureteric reflux or permanent urinary infection should undergo nephroureterectomy to avoid the development of sepsis. In children with ESRD not due to any urinary tract malformation, pre-transplant bilateral nephrectomy of the native kidney should be considered in the case of severe arterial hypertension, heavy proteinuria or risk of renal cancer.

(Evidence level C)

E. Psychosocial evaluation of future transplant recipients and their parents is necessary in assessing compliance with management of dialysis and after transplantation. Poor compliance worsens the outcome of paediatric renal transplantation.

(Evidence level C)

F. Routine childhood vaccination should be completed whenever possible prior to transplantation, in addition to vaccination against hepatitis B and varicella.

(Evidence level C)

G. The pharmacokinetics of immunosuppressive drugs often differ between adult and paediatric recipients. Therefore, drug monitoring is mandatory in order to find the correct drug dosage.

(Evidence level C)

H. Today the actuarial probability of graft survival at 1 year should exceed 90% in unselected renal transplant children, and the acute rejection rate should be lower than 30%.

(Evidence level C)

I. Special attention should be paid to specific risk factors in paediatric transplantation, such as thrombotic complications, EBV and CMV infections, post-transplant lymphoproliferative disease (PTLD) and recurrence of original renal disease, mainly in patients with focal segmental glomerulosclerosis (FSGS) or atypical haemolytic–uraemic syndrome (HUS).

(Evidence level C)

Commentary on Guidelines IV.11: Paediatrics (specific problems)

Paediatric hallmarks

Patients’ age. Paediatrics designates the medicine of patients from birth up to 16 or 18 years of age according to individual countries. Growth, maturational and development are the main pathophysiological characteristics of childhood. Special education and training are therefore required for professionals who take care of such patients.

Special care. Special attention should be paid to children according to body size, level of understanding, familial and social conditions, and children rights. For example, investigations and treatments should be explained with adequate language, pain should be evaluated adequately, and vein punctures and blood sampling should be limited. In addition, intensive care, haemodynamic monitoring, and nutritional and fluid requirements should be adapted.

Emotional aspects. The emotional participation should be respected at the social, familial and individual level, without any profit.

Clinical trials. A special licence is mandatory for any medication in children. Thus, paediatric clinical trials are recommended in children with special conditions, including ethical and legal approaches, adequate endpoints, metabolic and pharmacokinetic particularities, age-dependent adverse events, etc.

Donors. Due to emotional reasons, parents are often willing to donate a kidney, and the percentage of living related donors is therefore much higher than for adult recipients.

Primary disease. Special causes of end-stage renal failure are found in children, such as urinary tract malformations, renal hypoplasia and dysplasia, inherited renal diseases and recurrent diseases.

Results. Technical problems and recurrence of primary disease cause more graft failures in children than in adults. The influence of a specialized paediatric transplant and nephrological environment has a direct effect on the results (e.g. intensive care, nurse training, nutrition, pharmacology and psychology).

Guideline A. In the 1991 report of the ERA, the average incidence of new patients under 15 years of age accepted for renal replacement therapy (RRT) was 4–6 children per million childhood population. The proportion of different age groups was 13% under 2 years of age, 20% between 2 and 5 years, 25% between 6 and 9 years of age, and 42% between 10 and 15 years of age [1]. A significant increase in the youngest age group was observed during the last decade.

Pre-transplant evaluation is performed by a multidisciplinary team, focusing on nutritional status, statural growth and development [2]. Information about living or cadaveric donation should be given at an early stage of renal failure. Indications for urological reconstruction and or bilateral nephrectomy of the native kidneys should be considered.

Guideline B. There are several arguments against long-term dialysis in children, including decreased growth velocity, difficulties in nutritional care, poor school attendance, inadequate familial and social activity, need for vascular or peritoneal access, increased risk of renal osteodystrophy and metabolic disturbances [2–4]. There is a consensus to give priority to children on the waiting list: e.g. in Eurotransplant, the age is part of a scoring system (mean waiting time of 1 year in children vs 5 years in
adults); in France, recipients under 16 years of age have a special allocation list (mean waiting time of 10.4 months in children vs 27.3 months in adults) [5].

The level of pre-emptive transplantation has reached 30–40% in some centres, thereby allowing better graft survival and quality of life [2,3,6–8].

Guideline C. Each child has to be transplanted, but transplantation in children with severe mental retardation and/or additional disabilities has to be discussed with the parents and sometimes assisted by the decision of an ethical committee.

In patients with ESRD due to Wilms tumour, a waiting time of 2 years between the last chemotherapy and transplantation is required.

Transplantation in very small children is hazardous and should be limited to a few specialized centres with trained surgeons, paediatric intensivists and nephrologists. It seems reasonable to propose renal transplantation in children over 6–12 months of age or 5–10 kg body weight [9,10].

Guideline D. Primary renal diseases in children starting RRT differ greatly from those in adults (Table IV.10) [11].

Pre-transplant cystography is mandatory in all patients with urinary tract malformation or a history of repeated urinary tract infection, or when a pelvic dilation has been shown by ultrasound examination [12]. Urodynamic studies are indicated in any child with urinary tract malformation in order to plan bladder augmentation and/or pelvic floor training prior to transplantation.

Bilateral nephrectomy of the native kidneys is recommended in cases of massive vesico-ureteric reflux independent of infection, severe uncontrolled hypertension, risk of malignancy (Denys-Drash syndrome, isolated diffuse mesangial sclerosis) or the presence of severe proteinuria [2]. Children with focal segmental glomerulosclerosis (FSGS) and residual renal function may require bilateral nephrectomy in order to allow an early diagnosis of post-transplant recurrence and to avoid graft thrombosis due to hypercoagulability associated with ongoing hypoalbuminaemia [13]. Children with Finnish-type nephrotic syndrome require bilateral nephrectomy in order to improve their nutritional status, decrease the risk of vascular thrombosis and improve their general condition before transplantation.

Guideline E. In the long term, a significant number of graft losses are due to non-compliance. Prophylactic interventions can improve this condition: continuous education, individual medical information and psychological assistance. The transfer of children from paediatric units to adult units is associated with a theoretical high risk of graft loss due to non-compliance. Simple interventions, such as early preparation for the transfer and alternating out-patient visits between the paediatric and adult nephrology units, are recommended.

Guideline F. It is recommended to have patients on the waiting list after having completed routine vaccination, if possible. Hepatitis B and varicella vaccinations should be added. Anti-hepatitis A and anti-pneumococcal vaccination are recommended.

Guideline G. There are several arguments in favour of an individual pharmacokinetic profile in children. This is due to an increased distribution volume in small children, together with maturation of drug metabolism in the gut, liver and renal graft [14,15].

New immunosuppressive protocols using tacrolimus or MMF may allow steroid withdrawal, a critical issue in paediatrics [16,17].

Guideline H. The current actuarial graft survival in unselected renal transplant children is 85–90% at 1 year, and is expected to exceed 90% with new immunosuppressive strategies [5,18,19]. In addition, recent results demonstrate an acute rejection rate of 22% during the first year post-transplantation [20].

Special attention should be paid to the presentation of acute rejection in small children with oversized kidney grafts, because the increase in serum creatinine is delayed due to relatively high nephron mass. Such patients require an early Doppler sonography and further biopsy.

Guideline I. The risk of graft thrombosis is increased in recipients with nephrotic syndrome, with small arteries from small donors, and with inherited abnormal procoagulant activity. Such complications can be ameliorated by the use of heparin or low-molecular-weight heparin in the early post-operative period, i.e. during the first 10–15 days [21].

Due to the frequent lack of immunization in young recipients, there is a high risk of primary CMV and EBV infection because most donors are CMV and/or EBV positive. The risk of EBV-induced PTLD can be estimated from specific DNA-PCR; in the case of

<table>
<thead>
<tr>
<th>Primary disease</th>
<th>Children (%)</th>
<th>Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>38.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Aplasia/hypoplasia/dysplasia</td>
<td>19.4</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Obstructive uropathys</td>
<td>16.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Congenital nephrotic syndrome</td>
<td>2.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>24.3</td>
<td>15</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>11.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>4.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>5.3</td>
<td>10–15</td>
</tr>
<tr>
<td>Metabolic kidney disease</td>
<td>3.3</td>
<td>0.5</td>
</tr>
<tr>
<td>(e.g. cystinosis, oxalosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemolytic–uraemic syndrome/thrombotic thrombocytopenic purpura</td>
<td>2.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.1</td>
<td>20–25</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.0</td>
<td>10–15</td>
</tr>
<tr>
<td>Other</td>
<td>25.7</td>
<td>15</td>
</tr>
</tbody>
</table>
a high number of copies, immunosuppression should be reduced, if possible.

Recurrence of the primary disease accounts for 10\% of graft loss. The main cause is the recurrence of FSGS, a condition without evidence of a proven protocol [13,22] able to reduce or limit this recurrence.

**Conclusions.** The approach to very long-term prognosis is a major issue in paediatric nephrology. The number of renal diseases leading to ESRD diagnosed in utero is increasing, and reliable information is based only on a perfect knowledge of the long-term outcome of the transplanted patient with a whole-life treatment. It is therefore mandatory to provide longitudinal documentation from paediatric and adult nephrology using registries and healthcare networks.

**References**


**SECTION IV: Long-term management of the transplant recipient**