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doi:10.1016/j.jhep.2004.11.004

What lessons have we learned in pediatric liver transplantation?

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The first out of the five initial patients to undergo liver transplantation was a child suffering from extrahepatic biliary atresia. This child was treated by Starzl in 1963 [1]. He died as the other four of this first series in Denver, and as subsequent ones in Paris or Cambridge [2]. Since then, remarkable progress have been made and again the special needs of pediatric recipients turned out to work as pacemaker for development of surgical techniques, immunosuppression, imaging and medical care of the recipient, split and living related liver transplantation. These steps were mostly undertaken by teams in Hannover, Paris, Brussels and Chicago [3–7]. After these innovative surgical variants had been applied successfully in children, mortality on the waiting list decreased dramatically in this age group. However, rising numbers of adult patients on the waiting list and decreasing numbers of suitable brain death deceased donors were responsible for another increase of mortality on the waiting list of adult patients. This prompted the transplant centers world wide to extend innovative techniques such as split and living related transplantation even in the adult population [8,9].

With a delay of some years, immunosuppression experienced innovative changes as well. High dose steroids and azathioprine used in the 70th were replaced by ciclosporine A plus steroids in the 80th and tacrolimus plus steroids in the 90th [10–12]. In children the use of interleukin 2 receptor (IL2ra) antibodies contributed to a significant reduction in the prevalence of rejection without increased infection rates [13]. Today more and more new drugs with different ways of action are being evaluated. Protocols without steroids or very low steroids have been started. The trend goes to individualized immunosuppression. In the near future,we may see the application of immuno-tolerance inducing drugs rather than immunosuppression.

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Abbreviations APOLT, auxiliary partial orthotopic liver transplantation; CMV, cytomegalo virus; CyA, cyclosporine A; EBV, Epstein-Barr virus; ELTR, european liver transplantation registry; IL2ra, interleukin-2 receptor antibody; PTLD, posttransplant lymphoproliferative disease; SPLIT, study of pediatric liver transplantation; UNOS, united network for organ sharing.

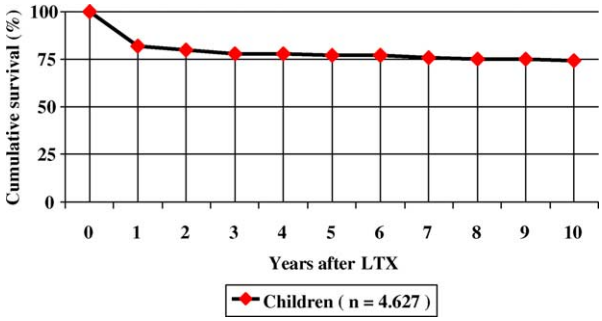

Fig. 1. High standard of 10 year survival in pediatric liver transplantation (ELTR-report 2002, [26]). This report includes pediatric patients from the beginning of transplantation.

The third impact on results in liver transplantation derives from imaging procedures. In split liver and living related liver transplantation intraoperative Doppler ultrasound examination has become essential, since many serious complications of the vascular tree may only be detected early and treated successfully by this technique [14,15].

Of course, there are other factors such as intensive care, anti-infective therapies, enteral and parenteral nutrition which contribute to an improved outcome after liver transplantation in children.

There are however, substantial problems left to be solved even after a high survival rate has been achieved in pediatric liver transplantation (Fig. 1). Immunotolerance has only been observed in individual patients occurring by chance and not induced by an active therapy. Life long immunosuppression increases the risk of drug related secondary diseases such as arterial hypertension, arteriosclerosis, renal insufficiency, diabetes mellitus and the development of skin malignancies or post transplant lymphoproliferative disease [16,17].

1. Lesson 1: Development of technical variants

The first steps in introducing new surgical techniques were performed in parallel in Paris and Hannover, where the first split transplantations have been performed [4,5]. However, these techniques were not applied routinely. The next steps were the adaptation of a full size graft to the specific size needs of a pediatric recipient by reducing a whole liver to a left lobe or to a left lateral segment [6]. The rest of the donor liver was decreased. By this technique, pediatric small sized recipients with a body weight below 10 kg could be accepted for transplantation which otherwise would have died. However, this procedure reduced the number of organs, which were at disposal for adult recipients. The logical consequence thus was the development of living donation and reactivation of split technique. These techniques provided organs outside the normal donor pool in case of living donation and enabled to overcome donor organ shortage by providing organs for two recipients derived from a single deceased donor [18,19]. At the beginning, the recipient of the right liver had a much worse outcome compared to the pediatric recipient of the left lateral segment. The technical solution of this disadvantage was achieved later on by the experience gathered from living related liver transplantation. The first series of living related pediatric liver transplantation was performed in Chicago in the late 80 and in the early 90th by the same surgeon in Hamburg [20,21]. There were many debates on the ethical issue of this operation which exposed a healthy individual to the risks of a major abdominal surgery [21]. The mortality of organ donation from a life donor has been reduced to less than one per 1000 in pediatric liver transplantation. But still, it is not zero [21]. After reports of donor fatalities in 1994, no further reports of donor losses in pediatric living donation have been published. The causes of death in these cases were pulmonary embolism and side effects of analgetic therapy. As a result, strong efforts were made to identify patients at risk for thrombophilic events by sophisticated examinations of the clotting system (Table 1). In a series of 73 donors an abnormality in the coagulation system was the reason to exclude a donor in 20% of the cases [22]. A recommendation of living donation to a parent or relative is not given as soon as one of these risk factors is identified [22]. Thereafter, living donation was used in Japan where it was the only way of transplanting patients because religious beliefs did not allow organ donation from deceased donors (see review by Tanaka and Yamada in this forum). Therefore, it was logical to extend living donation finally to adult-to adult donation [23,24]. Based on the surgical experience of these operations, split techniques were modified. In situ and ex-situ splits were performed with the same technique as in living donation and extended to operations, which used right lobes or extended left lobes for organ donation. The surgical progress derived from the experience in living donation thus contributed to a better performance of split transplantation [25–27].

In experienced centers with more than 40 transplants per year, published results show that there is no difference with regard to transplant survival in living, split organ donation, reduced or full size organ donation in the pediatric population. However, in series such as the SPLIT [28], UNOS [25] and ELTR [26] reports, where also data from

Table 1
Risk factors related to thrombophilic state leading to exclusion from living liver donation as used in the Hamburg protocol [20]

Risk factor	Exclusion criterion
History of thrombosis	Yes
Significant varicosis	Yes
Body mass index	>30: yes
Protein-S deficiency	Homozygote: yes, heterozygote: (+)
Protein C deficiency	Homozygote: yes, heterozygote: (+)
Factor V leiden mutation	Homozygote: yes, heterozygote: (+)