Early and late factors impacting patient and graft outcome in pediatric liver transplantation: summary of an ESPGHAN Monothematic Conference

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Abstract

As pediatric liver transplantation comes of age, experts gathered to discuss current paradigms and define gaps in knowledge warranting research to further improve patient and graft outcomes. Identified areas ripe for collaborative research include understanding the molecular and cellular mechanisms of tolerance and the role of donor-specific antibodies, considering ways to expand donor pool, minimizing long term side effects of immunosuppression, and fine-tuning surgical techniques to minimize biliary and vascular complications.

Key words: liver transplantation, research goals, tolerance, pediatric, complications
**Introduction**

Liver transplantation (LT) in children has transformed the prognosis of acute and chronic liver disease. Yet, for multiple reasons, much is still unknown about the long-term outcomes of pediatric liver transplant (LT) recipients. One of the main reasons is the relative lack of multi-center collaboration, something mandatory if the hurdles of comparatively low patient volume are to be overcome. The purpose of the First ESPGHAN Monothematic Conference on Pediatric LT held in Hannover, Germany, in late 2013 was to bring together international experts to review and discuss gaps in current knowledge, and develop strategies to fill these gaps collaboratively at a global level.

Recommendations for research in pediatric LT have already been put forward eloquently (1). As might have been anticipated, the ESPGHAN group conclusions overlap several of the suggestions made by The Studies in Pediatric Liver Transplantation (SPLIT) group (Figure 1). Pediatric liver transplantation is now more than four decades old. Survival following LT has much improved since its inception, with most centers reporting 1-year survival rates in excess of 90% (2-4). It follows that both the ESPGHAN and the SPLIT groups focused much more on improving and fine-tuning long-term outcomes than early post-operative care. The purpose of this summary is to build on the previous SPLIT recommendations by emphasizing which points are supported by the international community and highlighting the novel clinical and research priorities which emerged from the ESPGHAN meeting. Most areas of overlap will not be covered. These include long term kidney and cardiovascular issues, as well as expanding...
indications. This manuscript aims to highlight the conclusions of the meeting discussions to provide a point of reference for future clinical and research projects to improve graft and patient outcomes.

Early postoperative outcomes have improved immensely in the last 40 or more years owing to the substantial progress in organ harvesting, conservation and transport, and the establishment of successful and reliable surgical techniques. Thus, the focus the community caring for pediatric LT recipients has naturally shifted toward long-term outcomes. However, a few areas impacting early patient and graft outcomes are still laden with uncertainties and lack of consensus.

Different donor availabilities and allocation practices worldwide lead to contrasting needs in clinical research: while the SPLIT group focuses on donor-specific issues with the aim to develop a donor-risk-index (DRI), the ESPGHAN group focused on expanding donor pool with the aim to reduce death and morbidity on the waiting list (WT), a challenge which still plagues most pediatric LT programs worldwide.

**Early factors to improve patient outcomes**

- Considering ABO incompatible grafts to expand the donor pool
Avoiding pre-transplant mortality is a worldwide concern. Each procurement area struggles with its own obstacles to transplanting patients in a timely fashion. One way to increase donor pool is to consider ABO-incompatible (ABOi) grafts.

It has now been shown that children under the age of 2 at transplant may be optimal candidates for ABOi grafts given that their outcomes are comparable to those of ABO compatible grafts in the modern era (5). The rationale is that isohaemagglutins develop with age, and that ABO matching is not required in children <1 year. For older children, the risk of early complications after ABOi LT seems to be higher than in ABO compatible (ABOc) recipients. However, the use of rituximab has improved patient and graft survival (6). Current national matching systems tend to favor ABOc deceased donors for infants, children and adults, limiting access to ABOi donors. Blood group constraints are fewer in living donor LT (LDLT), and some centers shared that they used ABOi in living-related transplants (7). It is accepted that ABOi LT in children >1y requires a modified, intense IS protocol which has not been standardized. Based on discussion among participants, the most commonly used approach includes adaptation to age of the recipient and isohaemagglutinin levels. There is no consensus on the need for plasmapheresis before or after LT, but most centers in attendance favor one dose of rituximab 2-3 weeks prior to LDLT, high dose steroids during LT then tapered, high dose tacrolimus (trough levels of 10-15 ng/ml) early following LT, and MMF for 3 months. The first 3 months post LT are accepted to be critical for graft survival after which standard IS seems effective, although there is no hard, long-term evidence. Therefore, it follows that the urgent goals for research in this area are
➢ To define which patient population most benefits from ABOi LT.
➢ To draft a standardized protocol for treatment and monitoring of the ABOi recipient.
➢ To assess prospectively the safety and efficacy of such a protocol on a multicenter basis in order to ultimately impact allocation policies.
➢ To follow prospectively ABOi recipients to gain insight into liver-specific alloimmunity.

Long-term factors to improve patient outcome

Long-term goals for pediatric liver transplant recipients should extend beyond survival of a healthy graft. In this section we examine the importance of focusing on long-term well-being as expressed by quality-of-life and neurocognitive outcome, and we examine how to improve surgical and medical issues to attain this goal.

General

- **Long-term quality of life, cognitive and neuro-developmental outcome**

An increasing number of reports demonstrate that psychosocial adjustment, schooling, and health-related quality of life (HRQOL) are negatively impacted by pediatric LT. Only 32% of children alive 10 years after pediatric LT in the US and Canada have achieved an “ideal outcome” defined as stability of the original graft on mono-immunosuppression (IS) therapy, normal growth, and absence of the most common post-transplantation complications. Therefore, expansion of metrics beyond survival rates are needed to wholly capture short- and long-term
implications of LT, for delivering improved patient care, encouraging compliance and informing organ allocation policies.

The Pediatric Liver Transplant Quality of Life (PeLTQL), a novel disease-specific 26-item HRQOL instrument created for pediatric LT recipients is now available to further understanding of quality of life years restored by LT (8). Specific research needs to focus on how

- To extend HRQOL assessment using uniform tools (PeLTQL) into clinical practice to assess both longevity and quality of life with a view to offer appropriate school and psychosocial support.

*Surgical*

- **Management of vascular complications**

As early recipients come of age, a number of late vascular and biliary complications are emerging. Although often surgical in nature, the possible contribution of immune-mediated processes remains to be elucidated.

Causes of late portal hypertension (PH) after LT in children include portal vein thrombosis (PVT), chronic rejection, or biliary cirrhosis. Management depends on graft function and degree of fibrosis. Etiology is probably multifactorial including surgical and possibly as immune factors (9). With severe fibrosis or cirrhosis, initial management is supportive, while trans-jugular intra-hepatic porto-systemic shunts (TIPS) offer a bridge to re-transplantation. Patients with healthy
grafts and portal or hepatic vein stricture are often amenable to angioplasty, while those with established PVT are best served by an early meso-Rex bypass (10). That these late complications impact both graft longevity and HRQOL is self-evident. Therefore, to minimize the risk of post-transplant PH surgeons and physicians should work together

- To prevent venous complications by optimizing surgical techniques, improving early diagnosis, implementing early interventions and understanding the role of immunity in venous complications.
- To prevent intrahepatic causes of post LT PH by developing strategies to avoid long-term graft injury.
- To prevent long-term portal vein complications by improving our understanding of post LT liver growth especially in technical variants.
- To understand the role of hemostatic factors in the risk of PVT

- Management of biliary complications

Biliary complications may be responsible for as much as 15% of late graft losses (3, 11). The incidence of anastomotic biliary strictures reported after pediatric LT varies from 5-20% (12). Surgical technique and preservation solution may contribute to stricture formation (13), and 40% of strictures appear late (V. Corno, unpublished). Non-surgical factors impacting intra-hepatic biliary health late after transplant are less well characterized, and may include immune-mediated and toxic processes (14). As up to 67% of anastomotic strictures remain asymptomatic or
undetectable for a long time, a pre-emptive approach may allow early detection and management thereby minimizing morbidity and mortality.

There is no standard protocol for surgical or percutaneous treatment of biliary strictures (BiSt) after LT. The success rate of balloon dilatations associated with prolonged internal-external drainage (from 1-6 months or more) varies from 33-100% (15). As PTC is less invasive than surgery and minimizes the risk of additional vascular complications, the participants agreed that it is the method of choice in most cases, especially for intrahepatic strictures. The delegates agreed that identifying when and how to treat biliary strictures using PTC is a priority. Thus, proposed areas ripe for clinical research are

- To agree on a common definition and classification of BiSt.
- To develop screening methods for early identification of BiSt.
- To determine whether pre-emptive management of BiSt is beneficial.
- To determine the optimal type and duration of drainage.
- To develop management methods for refractory stenoses.
- To prevent BiSt by focusing on modifiable surgical, donor and recipient factors.
- To improve our understanding of immune-mediated biliary injury in the long-term graft.

*Medical*

- **Late infectious complications after LT in children**

Among the late complications highlighted by the ESPGHAN group were late viral infections affecting pediatric solid organ (SOT) recipients. Four viruses warrant attention: influenza
viruses, respiratory syncytial virus, cytomegalovirus (CMV), and Epstein Barr virus (EBV). The role of immunity in approaching late viral infections is two-fold: i) to understand how and in whom to minimize IS to avoid infections while protecting the graft ii) to develop adoptive immunotherapy techniques to combat active viral infections.

For the respiratory viruses, areas to address in future research include but are not limited

- To assess the burden and cost of these infections in SOT recipients.
- To develop prevention and surveillance strategies in order to maximize outcomes.

CMV and EBV arguably represent the greatest threat for host and graft. Although careful monitoring has decreased the rate of CMV infection in children following LT, and prophylaxis is common practice (16-17), collaborative efforts are still needed

- To define infection and disease burden with greater accuracy.
- To determine the optimal duration and type of prevention, including the use of prophylaxis or pre-emptive treatment approaches.
- To address the cost-effectiveness of monitoring, pre-emptive therapy, and prophylaxis.

- **Epstein-Barr virus and post-transplant lymphoproliferative disorder (PTLD)**

EBV-mediated malignancy remains a cause of early and later mortality for which consensus towards diagnostic and therapeutic approach is lacking.
EBV monitoring is now the recommended norm. Yet, the optimal way to perform and interpret quantitative EBV viral load for surveillance, diagnosis and disease monitoring remains highly variable. Prospective studies are needed to determine the significance of chronic, sustained elevations of EBV loads after transplantation.

Although pediatric LT recipients with sustained elevations of viral loads have a lower risk of PTLD than their heart transplant counterparts, PTLD remains a serious complication following SOT with a cumulative incidence of 2-3% (18). In the absence of reliable biomarkers, the diagnosis of PTLD rests on clinical judgment, EBV-DNA load monitoring, imaging and biopsy; the latter is required to confirm the diagnosis. Reducing IS has been documented to be the best pre-emptive intervention in high-risk populations. When that fails, restoring T-cell function, reducing the infected B-cell mass, and targeting EBV (19) are possible approaches. Treating some forms of PTLD with rituximab as monotherapy or in combination with chemotherapy is considered standard of care (20). Risk-adapted approaches are currently being evaluated, in which patients are initially treated with rituximab and only receive chemotherapy if they do not respond. While adoptive transfer of EBV-specific T cells has shown promise in early clinical studies (21-22), larger studies are needed. Rapid EBV-specific T-cell production methods should render this approach feasible in the future (23), although challenges such as toxicity of IS still need to be circumvented. The pediatric SOT community should work collectively to continue to fine-tune PTLD surveillance and treatment. Attainable goals include
To define, apply and evaluate an international standard for measuring EBV viral load.

- To determine the role of host or viral factors in defining the risk of PTLD including type and level of IS.
- To identify adjunctive tests to predict the risk of PTLD.
- To identify viral load cut-offs for IS withdrawal.
- To determine the timing of rituximab, chemotherapy and cell-based therapies.

Given that viral infections and PTLD are accepted to be the hallmark of over-immunosuppression, it follows that the ESPGHAN experts emphasized the need to optimize IS utilization and improve our comprehension of immunity in the pediatric LT recipient while aiming to understand and promote the molecular and cellular mechanisms leading to tolerance. At present, tailoring IS comprises several facets including calcineurin-inhibitor sparing, steroid free IS, mTOR inhibitor based IS, and IS withdrawal. Two areas of warrant discussion for their respective roles in monitoring the patient during IS optimization: protocol (or surveillance) liver biopsies and the role of donor-specific antibodies (DSA).

- **Role of protocol liver biopsy**

The liver graft in the stable pediatric recipient with normal serum aminotransferase levels is prone to develop chronic changes only diagnosed by liver biopsy. Through natural history studies, it is accepted that histological findings include de novo auto-(allo-) immune hepatitis, “idiopathic” chronic hepatitis and fibrosis (24). Studies of serial biopsies in pediatric recipients
have suggested that the prevalence of graft hepatitis and fibrosis increases with time (24), although at the time of print there is new evidence of the contrary (25), and that late pediatric graft fibrosis without inflammation may be related to low-grade AMR (26). The panel debate pro- and contra- protocol biopsies raised the following points:

The arguments for protocol biopsies:

1. Abnormal histology exists in stable LT recipients with normal liver function tests and an unremarkable post – transplant course. Histological findings may inform decisions about IS weaning aiming for operational tolerance.

2. Histological changes in the long-term graft are progressive, which progression might be avoided by early intervention.

The arguments against protocol biopsies:

1. The origin of the injury is unknown.

2. Since the etiology is unknown, decision-making regarding optimal management is challenging and the risk unjustified.

➢ The consensus was that protocol biopsies may improve management provided they are part of a prospective, well-designed and executed interventional study with a standardized scoring system, something which the group is developing collaboratively at the present time.
Role of donor specific antibodies in LT

Exploring tolerance and individualized immunosuppression to minimize side effects without jeopardizing graft and patient health cannot be undertaken without examining in great detail the role of humoral immunity on the liver graft. We need to determine if a future interventional trial will need to target antibody-mediated events as well as the commonly-accepted cellular processes leading to graft injury.

The definition of antibody-mediated rejection (AMR) in LT is currently restricted to uncommon necrotic or cholestatic damage associated with measured serum DSAs and C4d immunostaining. DSA may influence the graft in more subtle ways. De-novo DSA are now accepted to be implicated in adverse outcomes including the chronic histopathological changes appreciated on long-term biopsies (25, 27). In the few pediatric studies to date, DSA/C4d assessment suggests that humoral immunity may be a player in “idiopathic” late graft fibrosis (26), a finding which extends to inflammatory changes as suggested by new reports available at the time of print (25). Further studies are required to understand the meaning of DSA in pediatric LT in order

- To comprehend the significance of anti HLA IgG subclasses.
- To understand the significance of Mean Fluorescence Intensity (MFI).
- To clarify if positive DSA and/or positive C4d indicate the need to modulate immunosuppression.
Taken together, protocol liver biopsies and an improved understanding of the role of humoral immunity in LT should ultimately become useful tools in following the patient in whom one of the following IS optimization strategies is being implemented.

*Immunosuppression*

- **Calcineurin-inhibitor sparing**

Long-term side effects of CNIs threaten long-term outcomes and lifespan of pediatric LT recipients. There are two factors at play in CNI toxicity: the patient and the drug. Only the drug type and trough level are modifiable, and it is accepted that decreasing target CNI trough levels is beneficial in preventing side effects including the risk of PTLD and cardiovascular and renal complications. Conversely, differences in CYP3A5 genotype are not modifiable (28). Genotypic and phenotypic variability may be associated with some of the wide and toxic trough-level fluctuations observed in the early post-transplant period and jeopardizing long-term kidney health, for example. Further, they may underlie individual susceptibility to CNI side effects. Since CNIs are still routinely used, the proposed research priority is

  - To develop rapid and reliable assays to genotype both recipients and donor organs at the time of transplant in order to taylor CNI doses and avoid short- and long-term toxicity.

- **Steroid-free immunosuppression**

Steroids are another source of drug-induced toxicity potentially compromising long-term outcomes. Therefore, they are often considered the low-hanging fruit to be removed from IS
protocols. The main reason for steroid-free IS in pediatric LT is to avoid their debilitating side-effects (29). Several studies point to the advantages of a steroid-free approach (29). First, intra-operative or early intravenous steroid boluses do not protect against ischemia reperfusion injury. Second, steroids do not alter the rate of acute cellular rejection in 250 living donor pediatric LT recipients with or without steroids (R. Reding, unpublished data). Next, steroids do not impact the development of long-term graft fibrosis (30). Finally, in patients without steroids, linear growth in the first year post-transplant is improved and the incidence of infections reduced without increasing tacrolimus exposure compared to a steroid-treated group (31). Although steroids may not be necessary for satisfactory short term outcomes, concerns were raised regarding their potentially beneficial long-term effect (30). The question of steroid exposure and long-term operational tolerance is still under investigation (32). Therefore, salient priorities for research are:

- To identify which patients might most benefit from a steroid-free approach.
- To develop immune monitoring methods which allow tailoring IS individually.

Naturally, in addition to tweaking current IS regimens, exploring less well known members of the IS armamentarium seems to be an important goal.

- **mTOR inhibitor based immunosuppression**

The use of mammalian target of rapamycin inhibitors (mTORi) appears recommended in adult patients transplanted for cancer (33). In addition, mTORi are interesting for their CNI-sparing and
renal sparing effects. In adult recipients, it is currently recommended to start mTORi four weeks after transplantation to prevent delayed wound healing and avoid hepatic artery thrombosis.

The pediatric experience has been limited to off label use in single center series for its renal sparing effect, as rescue IS for resistant graft rejection and following PTLD or transplantation for malignancy (34). Emerging data suggest that everolimus, an mTORi with a short half-life, in children may be efficacious, but which patients will benefit from the drug needs to be defined further. Importantly, safety is still a concern, something which the group agreed should be investigated collaboratively, with respect to renal function, linear growth and fertility. The groups suggested the following aims for clinical improvement and research in this area:

- To assess the toxicity if used a) as monotherapy and b) long-term.
- To test its role in immunosuppression for oncological indications to LT.
- To measure its impact on long-term graft fibrosis.
- To quantify its impact on graft regeneration following transplantation.

Mitigating the side effects of IS may come with its own set of risks and consequences for long-term QOL and somatic health. It is unclear whether minimizing IS puts the graft at risk of long-term, silent injury, and if so, in which subset of patients. Therefore, it is the opinion of this group of experts that improving our understanding of long-term graft health and injury with a special focus on both cellular and humoral immunity is a crucial step in the future management of pediatric LT recipients.
• **Withdrawal of immune suppression after LT**

The current accepted definition of operational tolerance is stable liver function and stable liver histology in the absence of immunosuppression. Normal graft function has been reported in patients withdrawn from IS for life threatening infections or malignancy, as well as by physician-prescribed, protocolized withdrawal or, by non-compliance. It has been suggested that approximately 20% of long-term adult and pediatric LT recipients may be successfully withdrawn from IS (35). IS withdrawal might exacerbate or accelerate the known, progressive architectural changes which occur over time (26). Research priorities include delineating the impact of withdrawal on the emergence of alloantibodies and the evolution of graft histopathology (35-37), and identifying biomarkers to predict successful withdrawal (38), thereby mitigating the risk of withdrawal. Finally, prospective tolerance induction protocols (39), utilizing non-myeloablative approaches with infusion of a donor bone marrow cellular product to achieve donor-recipient chimerism are underway in living donor renal transplantation. The toxicities of these regimens for patients with chronic liver disease limit their use in LT, as benefits may not outweigh the risks in children. Therefore, there is substantial interest in exploiting other tolerance mechanisms through the use of autologous, *ex vivo* expanded regulatory T cells, mesenchymal stem cells, or immature dendritic cells (33). Research goals in this area should include:

- Documenting the benefit of IS withdrawal on extra-hepatic outcomes.
- Identifying tolerance biomarkers that would reduce the risk of attempted IS withdrawal.
➢ Developing tolerance-inducing protocols, possibly through the use of cellular therapies.

In conclusion, pediatric LT is an established and highly successful treatment for many acute and chronic liver diseases, but it is increasingly evident that long-term survival is marred by problems including unforeseen surgical complications, infections, IS-related side-effects and neurocognitive difficulties. Ensuring long-term event-free patient survival and quality of life are now key points towards which the international community agrees that research efforts should be directed (Table 1). In addition to minimizing known consequences of IS toxicity, time has come to focus efforts on our comprehension of cellular and humoral injury. Major challenges such as the implications of improving immunosurveillance should in the future be tackled through pooled experience and international consortia and collaborative efforts, several of which are under way.

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References


Figure 1

- Donor risk
- Adherence
- Transition

SPLIT

- ↓ surgical complications
- Extending indications for LT
- Individualized IS
- Long term allograft injury
- Improving health for long term survivors

ESPGHAN

- ↑ Donor pool
- ↓ Post LT infection
- Novel IS strategies
- Management of long term surgical complications
- QOL & Cognition

EXTENDING INDICATIONS FOR LT & MANAGEMENT OF COMPLICATIONS
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LD: living donor, DD: deceased donor, PeLTQL: Pediatric Liver Transplant Quality of Life, HRQOL: Health Related Quality of Life, LT: liver transplant, BiSt: biliary strictures, IS: immunosuppression