Liver Transplantation in Critically Ill Children

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In children as in adults, liver transplantation (LT) is the standard of care for end-stage liver disease. Over the last 20 years, the advancement of surgical techniques, liver disease prioritization, and better immunosuppression regimens led to very successful outcomes for most children and adolescents undergoing the procedure. The improvement of pre- and posttransplant intensive care played a crucial role in increasing the overall survival and reducing morbidity, especially for patients suffering from acute or acute-on-chronic liver failure. In this chapter we address the main aspects to consider when caring for infants, children, and adolescents before and after LT.

Main Aspects of Liver Transplantation in Children

Surgical Approaches

Surgical approaches to pediatric LT have significantly evolved since Thomas Starzl's first case in 1963 [1]. Transplantation of size-matched whole livers, which was limited by the scarcity of appropriate-sized organs, was gradually replaced by reduced-size grafts, which allows even small children to receive LT from adult donors. Whole liver transplantation (WLT) went from being almost 100% of pediatric LT in the 1980s to representing <60% of procedures in North America and <30% of LT in Europe in the last 10 years [2–4]. Transplantation of left lateral

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segmental grafts (LLS, Couinaud's segments 2 and 3) is now the most common type of LT for small children, WLT being mostly reserved for older children and adolescents. LLS are traditionally obtained by reducing adult donors' organs. Nevertheless, this approach results in using only part of the organ, wasting the entirety of the right lobe. Since small children represent the biggest proportion of pediatric LT receivers, such a strategy negatively impacts adult patients on the waiting list. Significant progress to tackle the problem of organ shortage was achieved with the diffusion of split LT (SLT), consisting in the division of the deceased donor liver into two transplantable grafts, and living donor LT (LDLT). The latter results from the transplant of children with LLS resected from healthy adult donors. Combination of SLT and LDLT now represents almost 70% of pediatric LT in Europe, 40% in North America, and >95% in Japan [2, 4, 5]. LDLT was developed to answer cadaveric organ shortage. First accomplished in 1988, LDLT provides significant advantages on WLT (reduction of ischemia) and on SLT (most notably shorter wait time and preoperative control of graft steatosis through diet and exercise) [6, 7]. The experience of LDLT led to the extension of the in situ division of the liver parenchyma technique to SLT and LLS procurement. This approach shortens the ischemia time (essential when organs are shared across very large territories) and improves the control of bleeding, at the expense of an increased surgical complexity and operation time [8]. Anyhow, the surgical approach depends also on recipient- and donor-related anatomic issues. Special conditions such as portal vein thrombosis or tumor extension in the recipient, or vascular anomalies in the donor, impact the surgical strategy. In some selected centers, partial orthotopic liver transplantation, which consists in replacing a portion of the native liver by a size-matched partial graft, leaving the rest of the recipient's liver in place, has provided interesting results for children with acute liver failure (ALF), and is a still controverted option for some inborn errors of liver metabolism [9]. By temporarily restoring liver functions, partial LT represents a bridge to native liver regeneration for selected patients with ALF, ready to be explanted as soon as the patient's own liver recovers, avoiding lifelong immunosuppression.

The choice of the surgical approach to LT depends on the recipient's underlying diagnosis and clinical condition, the donor characteristics, local surgical expertise, and organ allocation policies

Donor Selection

When selecting donors for pediatric LT, several factors need to be considered. First of all the size of the graft needs to provide sufficient parenchymal mass to restore the function while avoiding the complications related to the transplantation of an organ too big to accommodate a child's abdominal cavity. The minimal hepatic mass needed has not been clearly established and depends on the standard liver

volume of the recipient and the size of the donor's organ and of its LLS. Since preservation injury is more important in deceased donors, the calculated mass necessary for reduced-size or split liver grafts is usually greater than the mass needed for LDLT. A small-for-size graft syndrome develops when the graft volume is insufficient for the recipient's metabolic demands. To avoid this, a graft-to-recipient weight ratio ≥0.8% (ideally 1–4%) or a donor-to-recipient standard liver volume ratio ≥40% are recommended [10, 11]. Whereas calculation of the former requires the actual weight of the graft, which complicates organ allocation, estimation of the latter is only based on body surface area (standard liver volume = 706.2 x body surface area + 2.4) [11]. In daily practice, many centers rely on donor-to-recipient weight ratio (DRWR) to quickly assess the suitability of potential donors. Although no clear guidelines exist, donors are considered suitable for pediatric WLT if the resulting DRWR is between 0.5 and 2. Since LLS accounts for 25–30% of the total liver volume, the accepted DRWR for SLT and LDLT is usually between 2 and 12 [2]. Interestingly, a recent analysis of the liver transplant wait-list in the U.S. revealed that 50% of the organs that were declined for size resulted to be in the ideal range for size match by body surface area [12]. Hyper-reduced grafts and monosegmental grafts open the possibility to transplant very small infants using cadaveric or living adult donors without the complications of large-for-size grafts. Nevertheless, such approaches require advanced surgical skills that are not developed in all transplant centers.

Liver donor–recipient matching is based on ABO compatibility. Nevertheless, although associated with a greater rate of complications, the use of ABO-incompatible donors is sometimes considered for young children (<1.5–2 years) in critical conditions, with identical outcome in terms of graft survival [13]. Pretreatment with rituximab and plasmapheresis exchange and a more aggressive immunosuppressive regimen led to significant improvements in graft survival after LDLT even for older children [7].

Donor organ quality has a significant impact on the success of LT. Donors should be young (older than 3–6 months of age and ideally <40 years if LDLT or SLT are considered) and not obese, with near-normal liver function tests (≤2–3 times the upper limit of the normal), have no history of liver disease, an intensive care unit stay <5 days and be hemodynamically stable [14]. Whereas the use of livers from older donors does not seem to be associated with worse short-term outcome in adult recipients, a higher incidence of intrahepatic biliary strictures has been described for pediatric recipients [15, 16]. Although livers with >20% macrovesicular steatosis are associated with an increased risk of allograft loss, the use of organs from overweight and obese donors (BMI 25–35 kg/m^2), but not from severely obese donors (BMI >35), does not result in decreased graft or patient survival [17, 18]. The impact of donor's liver steatosis on postoperative outcome is greater in case of graft reduction (for which >10% macrovesicular steatosis at biopsy is usually considered a relative contraindication) or long cold ischemia time. Whereas the use of livers from donors with hypernatremia has been associated with an increased risk of graft dysfunction and poor outcome in adults, pediatric data showed no increase in mortality or complications and suggest that it might be acceptable [19, 20].

In the case of LDLT, donor well-being is the primary focus, and it is assured by delegating donor selection and evaluation to an independent team. A fully informed consent, absence of any coercion, and the possibility to opt out at any time are mainstays of the process. The criteria listed above are also applicable to living-related donor selection, with the added advantage of disposing of more time to test for genetic conditions in the case of LT for metabolic disorders. Nevertheless, accelerated living donor evaluation in <48 h can be safely achieved for children with ALF in those centers with a carefully organized process in place.

Overall, although decision support models have been and are being designed, no clear rule exists and each cadaveric donor must be assessed by balancing the quality of the organ with the health status of the potential recipient [21–23]. The consequences of accepting high-risk organs on posttransplant morbidity and mortality should be properly weighted, always taking into consideration the long life expectancy of children undergoing LT. Nevertheless, it is important to remember that 55% of the children that died on the liver transplant wait-list in the U.S. had been offered an organ that was refused and eventually transplanted into another pediatric recipient [12].

Outcomes and Surgical Complications

More than 50 years after the first operation was performed in a child, pediatric LT has become a very successful procedure that has transformed the prognosis of children with end-stage liver disease. Current 1-year survival rate after LT is >95% for chronic conditions and >85% for ALF in most reference centers worldwide (Fig. 1).

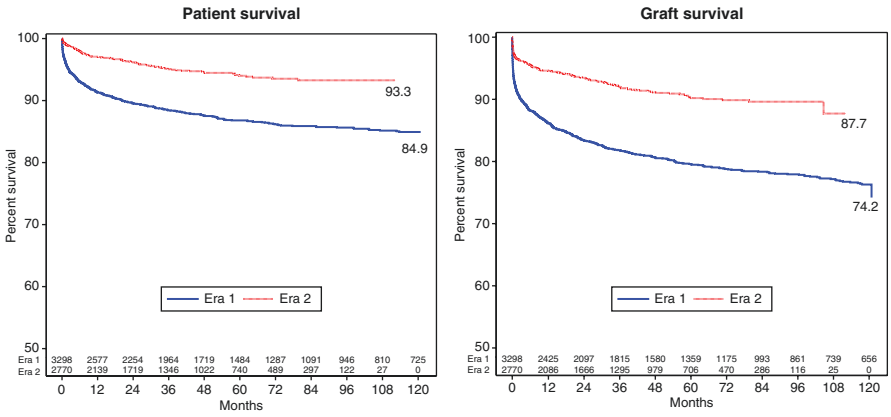

Fig. 1 Kaplan-Meier plot of patient (left) and graft (right) survival after pediatric liver transplantation by era (data from the Society of Pediatric Liver Transplantation). Era 1 includes all the patients who received their first transplant between Jan 1995 and Dec 2009, and Era 2 is defined as any transplant after Jan 2011. The number of participants at risk of event over time is reported above the x axis (data lock 21 September 2020) [3]

Long-term patient and graft survival progressively improved with the introduction of more effective immunosuppressive regimens and refinement of surgical techniques and donor selection criteria. Recently published large series describes 20-year patient and graft survival rates of 69–79% and 53–64%, respectively, with better results observed for nonurgent indications and up to 80% graft survival in children undergoing LDLT for biliary atresia [24–26]. Reported outcomes are overall similar between WLT and reduced-liver variants, with LDLT being comparable to WLT for both short and long-term graft and patient survival [4, 27, 28]. Nevertheless, incidence of vascular thrombosis and retransplantation were reported to be lower in small recipient receiving technical variant allografts (especially LDLT) compared to WLT, with better 1-, 5-, and 10-year graft survival [29]. Graft survival 5 years after pediatric LT is now >80% (about 80% for ALF and >87% for biliary atresia, and closer to 90% after LDLT in most experienced centers), and >65% after retransplantation [28, 30].

Upon reperfusion of the graft, liver function progressively recovers, leading to a rapid improvement of the patient's conditions. In rare occasions (up to 7% of pediatric LT), the graft fails soon after reperfusion, without an identifiable cause. What is defined as primary nonfunction rapidly leads to death if no urgent retransplantation is performed. Long warm ischemia time, patient's hemodynamic instability, and low cardiac output have been identified as risk factors. Theoretical spontaneous recovery of the graft is possible, as in ALF, if the patient survives long enough to allow for the organ's regeneration. When graft dysfunction is milder and progressively resolves without the need for retransplantation, it is defined as early graft dysfunction.

Surgical complications after LT are common, require prompt multidisciplinary management and can occasionally lead to graft loss and even patient death. Biliary complications, such as biliary leaks, anastomotic, and non-anastomotic strictures or excluded bile ducts, represent the most frequent surgical problem after pediatric LT, overall affecting 10–30% of the recipients (Table 1) [31]. Incidence of such complications is traditionally reported to be higher for reduced-size grafts, although differences are minimized by surgical experience [31–33]. Since bile ducts are perfused only by the hepatic arterial flow, ischemia is the main risk factor for biliary complications. Liver parenchymal reduction put the vascularization of the left hepatic duct at risk. Moreover, bile ducts are more susceptible to ischemia damage because of the presence of bile salts in its lumen that attack the biliary epithelium. This is amplified by any arterial complication, such as thrombosis or stenosis. While biliary leaks usually manifest in the first week after LT with clear signs, stenoses present later, with absent or mild symptoms and sometimes very subtle signs (with >50% of the patients not showing bile duct dilation) [34]. Treatment of biliary complications needs to be aggressive in order to avoid secondary biliary cirrhosis and graft loss. Whereas surgical approach is usually preferred for biliary leaks, a less-invasive radiological interventional approach with long-term, temporary stenting can provide excellent results for biliary stenoses in experienced centers [32, 34].

Biliary leaks and strictures represent a frequent complication, increasing post-transplant morbidity

Table 1 Summary of vascular and biliary complications at 30 and 90 days

	Donor organ type				
	Live *N* = 972	Whole *N* = 3263	Reduced *N* = 785	Split *N* = 873	Total *N* = 5893
Total early follow-up assessment					
Total at 30 days	953	3167	761	847	5728
Total at 90 days	493	1556	273	462	2784
Portal vein thrombosis 30 days					
Yes	46 (4.8%)	92 (2.9%)	48 (6.3%)	46 (5.4%)	232 (4.1%)
No	717 (75.2%)	2350 (74.2%)	548 (72.0%)	670 (79.1%)	4285 (74.8%)
Missing	190 (19.9%)	725 (22.9%)	165 (21.7%)	131 (15.5%)	1211 (21.1%)
Portal vein thrombosis 30–90 days					
Yes	3 (0.6%)	1 (0.1%)	0	1 (0.2%)	5 (0.2%)
No	332 (67.3%)	998 (64.1%)	134 (49.1%)	300 (64.9%)	1764 (63.4%)
Missing	44 (8.9%)	171 (11.0%)	57 (20.9%)	35 (7.6%)	307 (11.0%)
Data not collected	114 (23.1%)	386 (24.8%)	82 (30.0%)	126 (27.3%)	708 (25.4%)
Hepatic artery thrombosis 30 days					
Yes	49 (5.1%)	259 (8.2%)	48 (6.3%)	40 (4.7%)	396 (6.9%)
No	711 (74.6%)	2185 (69.0%)	548 (72.0%)	676 (79.8%)	4120 (71.9%)
Missing	193 (20.3%)	723 (22.8%)	165 (21.7%)	131 (15.5%)	1212 (21.2%)
Hepatic artery thrombosis 30–90 days					
Yes	2 (0.4%)	6 (0.4%)	0	1 (0.2%)	9 (0.3%)
No	333 (67.5%)	993 (63.8%)	134 (49.1%)	300 (64.9%)	1760 (63.2%)
Missing	44 (8.9%)	171 (11.0%)	57 (20.9%)	35 (7.6%)	307 (11.0%)
Data not collected	114 (23.1%)	386 (24.8%)	82 (30.0%)	126 (27.3%)	708 (25.4%)
Biliary complications 30 days					
Yes	140 (14.7%)	269 (8.5%)	119 (15.6%)	147 (17.4%)	675 (11.8%)
No	496 (52.0%)	1756 (55.4%)	397 (52.2%)	436 (51.5%)	3085 (53.9%)
Missing	188 (19.7%)	709 (22.4%)	165 (21.7%)	129 (15.2%)	1191 (20.8%)
Data not collected	129 (13.5%)	433 (13.7%)	80 (10.5%)	135 (15.9%)	777 (13.6%)
Biliary complications 30–90 days					
Yes	29 (5.9%)	45 (2.9%)	24 (8.8%)	35 (7.6%)	133 (4.8%)
No	422 (85.6%)	1335 (85.8%)	189 (69.2%)	392 (84.8%)	2338 (84.0%)
Missing	42 (8.5%)	176 (11.3%)	60 (22.0%)	35 (7.6%)	313 (11.2%)

Data from the Society of Pediatric Liver Transplantation
Data where donor organ type is missing is excluded from these analyses *(data lock 21 September 2020)* [3]

Vascular complications are not rare and a source of significant morbidity (Table 1). Hepatic artery thrombosis (HAT) develops in 5–8% of patients and is the main cause of graft loss after pediatric LT [31, 35]. Similar incidence was observed for WLT, SLT, or LDLT [31, 36]. Although prolonged ischemia, cytomegalovirus infection, or hypercoagulable state are known risk factors for early HAT, technical issues (kinking, narrow anastomosis, small arteries, or mismatched vessel size), as

well as a graft-to-recipient weight ratio >4%, are the most commonly identified cause [37]. Early HAT presents in the first 10 days after LT, usually with bile duct necrosis and subsequent necrosis of the liver and sepsis. Urgent retransplantation is required to save the patient's life. Nevertheless, especially in children, HAT can present in a more subtle way, with delayed biliary leak or intermittent septic episodes related to bile duct injury.

Preventing screening for HAT by Doppler ultrasonography during the first week post-LT allows for an early detection of HAT and aggressive treatment. Considering the high mortality, retransplantation is the treatment of choice, but revascularization, either surgical or endovascular, is usually attempted to gain time [38]. Portal vein complications, of which portal vein thrombosis (PVT) is the most severe, affect 3–8% of patients after pediatric LT [31, 39]. Reduced-size grafts, a graft-to-recipient weight ratio >4%, as well size discrepancies between donor and recipient and the use of cryopreserved interposition vascular grafts are associated with an increased incidence of PVT [31, 40, 41]. A small portal vein in the recipient, usually found in patients with biliary atresia, and abundance of portosystemic shunts (which reduce blood flow through the portal vein) are significant risk factors for PVT [42, 43]. Early PVT presents as graft dysfunction, which can be mild or severe enough to result in acute graft failure and require urgent retransplantation. Late-onset PVT is usually silent, with progressive portal hypertension developing with all its complications. Anticoagulation is usually tried but it is rarely effective, and surgical thrombectomy and reconstruction of the portal anastomosis is the treatment of choice. Interventional radiological approach is usually preferred for late-onset PVT, but it is increasingly being considered for early PVT as well. Unlike HAT and PVT, complete hepatic vein outflow obstruction (presenting as an acute Budd-Chiari syndrome) is a very rare complication. Nevertheless, incomplete obstruction resulting in prolonged ascites (which is an otherwise common and spontaneously resolving phenomenon after pediatric LT) is more often diagnosed at Doppler ultrasonography (especially with reduced-size grafts) and treated by endovascular dilation [39, 44].

Waiting for a Transplant

End-stage liver disease resulting from different acute or chronic conditions is the main indication for LT. Once the need for LT is identified, the patient is evaluated to assess his/her eligibility, identify causes for potential complications, put in place preventive measures to optimize the outcome and minimize wait-list mortality. Although most of the patients can afford to wait for LT at home, pretransplant decompensations requiring intensive care are not rare, while some children with most severe or acute conditions require close monitoring in the pediatric intensive care unit (PICU).

Indications

Chronic cholestatic diseases constitute the most frequent indication for pediatric liver transplantation, with biliary atresia alone justifying 33–40% of transplants in North America [3, 30]. Progression towards liver failure following chronic viral or autoimmune hepatitis accounts for only 3% of transplants, while inborn errors of liver metabolism and liver tumors are responsible for 14% and 8% of them, respectively. About 6–13% of liver transplants are performed for ALF, whereas acute decompensation of chronic conditions due to infectious complications or gastrointestinal bleeding (acute-on-chronic liver failure, ACLF) are less frequent in children, although also less well identified in available registries.

Pretransplant Evaluation and Listing

Pretransplant evaluation is a standardized process that allows the multidisciplinary transplant team to thoroughly assess the patient's physical and psychological condition, and sometimes reassess the underlying diagnosis [45]. Conducted with the participation of several pediatric subspecialists, the process examines every system to pinpoint potential contraindications, identify problems requiring immediate treatment and flag conditions that might increase the pre-, peri-, and postoperative risk of developing specific complications. The evaluation allows surgeons, hepatologists, and intensive care specialists to better know the patient and his/her family, and define the best strategy for LT. It also allows infectious disease specialists, cardiologists, hematologists, pulmonologists, nephrologists, endocrinologists, nutritionists, and dentists to put in place and carry out preventive measures and procedures (e.g.. vaccination) to avoid or limit complications. Other specialists, such as oncologists, neurologists, geneticists, or experts in metabolic diseases are involved for specific indications. Psychosocial assessment of patient and family is also crucial part of the process. The evaluation also allows the family and the patient to familiarize with the team, ask questions and fully understand (and prepare for) potential complications, and the risk of death. Visiting the facilities, and especially the PICU, is part of the process. The transplant coordinator plays a pivotal role in this process, assuring that all exams and consultations are successfully performed in a short period of time while limiting the stress on the family. The coordinator establishes him/herself as the main contact for the patient and family, designs with them the logistics of the pretransplant follow-up and actions upon an organ offer and, in case of LDLT, coordinate with the medical team evaluating the donor. The results of the evaluation are then gathered and presented to the review board in order to decide on the patient's listing for LT. Once the process is well established, in case of ALF or ACLF, the evaluation can be accelerated and conducted over a few hours to allow for an expedited listing.

Organ allocation is based on strictly regulated criteria that vary from country to country. For adults, it is most often based on the model for end-stage liver disease (MELD) score or its derivatives (e.g. MELD-Na), which objectively consider several clinical criteria (total bilirubin, international normalized ratio [INR], and creatinine) to establish the patient's risk of death at 3 months [46]. Pediatric liver disease prioritization is often based on MELD score (≥12 years of age) and on the pediatric end-stage liver disease (PELD) score for younger children. The latter adds growth failure, age <1 year, and albumin plasma levels to the equation, without creatinine [47, 48]. Some countries and provinces do not use MELD/PELD for pediatric patients and give priority to children on most adult recipients. Children with ACLF or very severe chronic conditions have priority on the list, although maximum priority is given to pediatric patients with ALF. Most countries have organ allocation policies allocating livers from pediatric donors to children first [49]. Exceptions scores are assigned for liver tumors, HAT, hepatopulmonary syndrome, and portopulmonary hypertension, and several genetic and metabolic diseases prioritize children that would otherwise suffer from severe morbidity. Other exceptions can be accepted after review from an independent board.

Pretransplant Management and Complications on the Waiting List

During the days or months separating the listing of a patient for transplant to the actual operation, the focus of caregivers is centered on preventing and managing complications. Portal hypertension, with ascites, hepatic encephalopathy (HE) and esophageal varices, poses the biggest risk and requires careful therapeutic follow-up with diuretics, laxatives, and nonabsorbable antibiotics, periodical albumin perfusion, and prophylactic endoscopic variceal banding to avoid potentially severe decompensations or bleeding. Occasional septic complications, often related to spontaneous bacterial peritonitis or cholangitis, are not unusual and might temporarily preclude LT, requiring temporary inactivation on the list. Pruritus, osteopenia, and impaired bone metabolism related to severe cholestasis need prompt treatment and supplementation to prevent pathologic fractures and improve the quality of life. Early diagnosis of HE and hepatorenal or, more rarely, hepatopulmonary syndrome or portopulmonary hypertension, is crucial to start adequate medical management and adapt prioritization on the waiting list. Although close pretransplant follow-up allows for outpatient management of many of these complications, patients often experience recurrent hospitalizations, and intensive care is often required during decompensations to treat septic shock or provide renal replacement therapy for hepatorenal syndrome or HE. The patient nutritional status needs special focus before LT. Growth failure and sarcopenia have an important impact on posttransplant outcome, especially for younger children, and are often underestimated by MELD/PELD score calculation [50, 51]. Thorough assessment, aggressive nutritional

treatment, often requiring nasogastric tube feeding or parenteral nutrition, and, when possible, exercise are needed to optimize caloric intake and accelerate posttransplant recovery. Since sarcopenia increases the risk of developing HE and protein restriction has been demonstrated not to be necessary in patients with HE, protein intake should be optimized to the nutritional needs of the patient [51–53].

Nutritional status before the transplant is determinant in diminishing post-transplant morbidity and improving chances of survival

Post-transplant Management

Early management after pediatric LT requires close monitoring in the PICU. Whereas restoration of liver functions usually occurs over few hours after organ reperfusion, the complexity of extrahepatic organs involvement and the need for preventing and early identifying not-so-rare and potentially life-threatening complications make posttransplant monitoring resource-intensive.

Liver Function

Recovery of liver function starts soon after reperfusion of the organ and progresses rapidly. Serum aminotransferases remain high, or even increase, for a few days after LT (especially for segmental grafts), and, alone, should not be considered as sign of complications or underlying problems with graft recovery. Similarly, γ-glutamyltransferase (GGT) levels typically transiently increase after LT, and subsequently slowly decrease to normal levels over several days or weeks. Because of the slow clearance of delta-bilirubin, serum bilirubin levels take several weeks to decrease independently from graft functional recovery. Coagulation abnormalities are also common during the first 48 h from LT, although progressive improvement of the INR is expected, and no correction is usually required. Serum lactate and ammonia levels are considered reliable markers of graft function and should be monitored closely over the first 24–48 h. Neurological recovery is another important sign of improving graft function and, even when prolonged sedation is required for the management of extrahepatic complications, proper and recurrent assessment of sedation needs after LT is important.

Monitoring Potential Complications

Close monitoring in the PICU of all LT recipients for 24–48 h is required for an early detection of the potential complications listed above, which, when considered together, affect >50% of the patients [31]. Early postoperative hemorrhage is not

uncommon after LT, with patients with portal hypertension and adhesions from previous abdominal surgeries being at higher risk. Abdominal drainage should be frequently measured, and the risk for surgical reassessment should be balanced against the evidence showing a negative impact of perioperative transfusions on survival [54]. Absence of clinical and biochemical improvement over the first hours from transplant should raise the suspicion of serious complications such as primary non-function, HAT or PVT (see above), which should be promptly excluded. Slow improvement over the first week after LT might hide vascular complications or an early graft dysfunction. Aggressive screening for vascular problems by Doppler ultrasonography (every 12 h, if possible, for the first 5 days and then daily for 5–7 days) is warranted to quickly identify complications. Vasopressors should be withdrawn as soon as possible to reduce the risk of thrombosis and, if no active bleeding detected, prophylaxis with heparin should be started within 24 h from LT, to be subsequently switched for acetylsalicylic acid once the risk of bleeding reduced.

Although ascites after pediatric LT is frequently observed after uncomplicated procedures, it might also be a sign of vascular and biliary complications. Periodical confirmation of its sterility and characterization of its composition by measuring bilirubin and triglyceride levels allow for early detection and subsequent treatment of bowel perforations, biliary leaks, and chylous ascites [44].

Careful screening and prophylaxis for potential infections is also a crucial part of the posttransplant management. Surgery, induction of immunosuppression, ascites, and the presence of invasive equipment make the patient especially vulnerable during the first days and weeks after LT. More than one-third of pediatric transplant recipients develop bacterial or fungal infections in the first month [55]. Careful assessment of the donor's serology and sterility analyses conducted on the graft are important. Strict hygiene measures that need to be respected by all personnel are required during the first weeks to prevent infections. Clinical and biochemical signs should be monitored closely, and adequate peri-operative antibiotic prophylaxis assured. Central venous accesses, biliary leaks and bowel perforations are the main cause for bacteremia [55]. Aggressive treatment guided by microbial identification, with appropriate antifungal prophylaxis, is key to obtain an early control of the infection. In case of mismatch between donor's and recipient's serologies for cytomegalovirus, adequate prophylaxis with specific immunoglobulins (CytoGam) should be promptly initiated within 72 h from LT to prevent the development of the disease. Long-term antifungal prophylaxis is usually required for all patients, especially when steroids are used to induce immunosuppression, and it is usually started over the first few days/weeks after transplant.

Immunosuppression and Rejection

Immunosuppression (IS) is required after LT to prevent graft rejection. Progressive discovery and implementation of new immunosuppressive regimens played a pivotal role in the improvement of graft and patient survival after LT [56]. Unfortunately,

no evidence-based guidelines or consensus exist on posttransplant IS in children, and significantly different practices are observed across reference centers worldwide. All protocols are based on the principle of providing minimal levels of IS to prevent rejection while reducing toxicity. Posttransplant regimens are composed of an induction phase focused at minimizing acute rejection during the first days and weeks after LT, and a maintenance phase, which aims at inducing tolerance and reducing toxicity on the long term, while preventing acute and chronic rejection. Since T cells play a major role in acute allograft rejection, most immunosuppressive approaches are focused on them. Calcineurin inhibitors are the mainstay of treatment. Tacrolimus showed better patient and graft survival than cyclosporine, with less acute rejection, and it is now used for both induction and maintenance treatment in 95% of pediatric transplant recipients [57, 58]. A higher dose of tacrolimus is required during the first 3 months from LT. In the absence of rejection, plasma though level target is then progressively reduced, to reach maintenance levels 1 year after transplant. Nephrotoxicity is the most frequently observed side effect of tacrolimus treatment and requires close monitoring [59]. New-onset diabetes, hypertension, hyperlipidemia, and hypomagnesemia are also commonly observed. PTLD is a more rare but potentially fatal complication that requires prompt diagnosis and treatment [60]. Tacrolimus has also been associated with the development of food allergies and eosinophilic gastroenteritis in younger transplant recipients [61].

For induction, tacrolimus is most often combined with steroids (50% of pediatric LT in the U.S.) or with steroids and an antimetabolite (more frequently mycophenolate mofetil, in 25% of patients) [30]. Addition of an antimetabolite allows for reducing the dose of tacrolimus for nephroprotection. Steroid-sparing regimens with tacrolimus combined with interleukin-2 receptor antagonists (anti-CD25 antibodies, e.g. basiliximab) are increasingly used and showed improved rejection-free survival, decreased steroid-free rejection, and fewer complications [62–65]. Lymphocyte-depleting antibodies (e.g. thymoglobulin), which result in T-cell depletion and can cause significant systemic reactions, can be used instead of interleukin-2 receptor antagonists to reduce the use of steroids.

After 3 months, most patients are on a maintenance regimen, which most often is based on tacrolimus monotherapy or tacrolimus associated with an antimetabolite. Most children (75%) receive no steroids on the long term [66]. Since nonadherence is a significant cause of graft loss and late mortality in adolescence, significant effort must be dedicated to ensure proper compliance with the treatment. Extended-release tacrolimus, which allows for once-a-day dosing and proved to be comparable to standard dosing in terms of safety and efficacy, is often used in adolescents to facilitate adherence to treatment [67, 68].

Acute cellular rejection is common during the first year after LT, with reported incidence of 20–60% [30, 66]. A single episode of acute rejection was shown to have no effect on long term graft or patient survival. Rejection is more common during the first 3 months and is almost always asymptomatic, being discovered by increasing aminotransferases and GGT levels and confirmed at liver biopsy.

Intravenous administration of high-dose methylprednisolone for 1–5 days represents the first line of treatment. Subsequent tapering regimens vary widely according to the severity of the rejection, the response of the patient and institutional practice. Steroid treatment is effective in 80–90% of patients [66]. Children showing no improvement are defined as having steroid-resistant rejection and require lymphocyte-depleting antibodies, addition of mycophenolate, and maintenance of higher tacrolimus target levels for at least 3 months. Addition of mTOR inhibitors such as sirolimus can be considered in case of nonresponse.

The incidence of chronic rejection has been decreasing over the years thanks to the improvement in immunosuppressive regimens. Although biopsy-proven chronic rejection affects <10% of pediatric transplant recipients, its treatment (which consists in addressing nonadherence, increasing tacrolimus target levels, and adding mTOR inhibitors) is cumbersome and often leads to retransplantation [24, 25, 66]. Antibody-mediated rejection is an even rarer finding after liver transplantation. A well known complication after ABO-incompatible LT, it typically presents within the first 2 weeks as acute graft dysfunction often associated with fever and thrombocytopenia. Signs of acute injury with positive complement 4d staining at liver biopsy and donor-specific antibodies (DSA) are required to confirm the diagnosis [69]. Recently, antibody-mediated rejection is being increasingly detected after ABO-compatible LT, and criteria for its diagnosis are evolving [70]. Individualized treatment with corticosteroids, immunoglobulins, anti-CD20 antibodies (rituximab), plasmapheresis, or eculizumab allows for resolution of graft dysfunction in many patients.

The liver is an immunological organ, and its microenvironment has unique tolerogenic properties. Spontaneous liver allograft tolerance in animals is well described. IS withdrawal have been shown to be possible in children as in adults [71, 72]. In the largest pediatric series published by Kyoto University Hospital, 35% of LDLT patients met the criteria to withdraw IS (>2 years posttransplant, normal graft function, and no rejection over the preceding year). Of those, 44% resulted to be tolerant 1 year after withdrawal, although progressive fibrosis was often identified at biopsy and improved over reestablishment of minimal IS [73]. Data from a still unpublished prospective, multicenter, pediatric clinical trial (iWITH, NCT01638559) recently showed that 37% of the 88 patients undergoing IS withdrawal were operationally tolerant after 1 year. Interestingly, from the analysis of liver biopsies required to enter this study, the authors discovered that subclinical chronic allograft injury was indeed common even among this selected population, with almost 40% of long-term pediatric patients with normal liver tests showing liver fibrosis (Ishak stage ≥2) [74]. Although these data are encouraging and suggest that a significant proportion of patients might indeed develop tolerance over time and not need IS anymore, it is not possible yet to predict who will be tolerant upon IS withdrawal and who will end up with rejection and graft fibrosis instead. Therefore, IS withdrawal after LT is still not currently recommended.

Conclusion

Pediatric liver transplantation is now standard of care in many centers around the world. Waiting for the development of alternative cell therapy and regenerative medicine-based approaches, LT has solidly demonstrated its efficacy and overall safety across all age groups. Advancement of surgical techniques, IS regimens, and intensive care protocols led to a very significant improvement in short- and long-term graft and patient survival. Optimization of organ allocation policies to prioritize young children and reserving pediatric donors for pediatric recipients will further reduce mortality. Meanwhile, implementation and development of LDLT programs is needed to reduce the waiting time for transplant. This, together with growing surgical expertise with graft reduction, has the potential to expand the number of available organs, with the potential to virtually eliminate mortality on the wait list. Optimization of pretransplant nutritional status has emerged as a key factor to decrease posttransplant morbidity. Specialized posttransplant PICU expertise is then pivotal to allow for quick identification of posttransplant complications and improvement of pretransplant care. Studies to assess how different IS regimens can reduce long-term graft fibrosis and potential loss are warranted, while better understanding of the role of antibody-mediated rejection after LT is needed. Ongoing and future trials might lead to the identification of criteria and, ideally, biomarkers, to identify patients developing operational graft tolerance in order to program targeted IS withdrawal.

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