Indications to Liver Transplantation in Children

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Overview

Paediatric liver transplantation (LT) accounts for 10% of all hepatic transplants and is now considered the gold standard treatment for children affected by life-threatening, not otherwise curable, hepatic disorders without age limits. Children affected by end-stage liver disease and acute liver failure share many similarities with their adult counterpart with regard to the pre-transplant assessment. However, many peculiarities exist for the paediatric age concerning indications (mainly primary liver tumours and genetic-metabolic disorders) and contraindications to LT, as well as modalities to assess liver dysfunction. Similarities and differences among the paediatric and the adult population requiring LT will be discussed in the chapter.

29.1 Introduction

Paediatric liver transplantation (LT) accounts for about 10% of all liver transplants [1] and is now considered the gold standard treatment for children affected by life-threatening liver disorders not otherwise curable [2]. Since the first paediatric LT performed by Thomas Starzl in 1963, LT has become one of the most successful paediatric transplant programs in terms of patient survival and quality of life [3]. According to the United Network for Organ Sharing (UNOS) and the European

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Liver Transplant Registry (ELTR), the survival of patients who underwent LT during childhood is 95%, 88% and 75% at 1, 5 and 10 years after LT, respectively. Current achievements are due to improvement of surgical procedures, optimization of immunosuppressive regimens and implementation of liver allocation systems over time.

29.2 Indications to Paediatric Liver Transplantation

In most countries, the paediatric candidate to LT is a subject aged 0–17 years upon first registration on the national transplant waiting list. LT must be considered as a therapeutic option when liver replacement has the potential to: (i) significantly increase life expectancy in comparison to what is predicted according to the evolution of the disease; (ii) determine a substantial improvement in the quality of life of the child.

The indications that may lead to the execution of LT in the paediatric age can be divided into seven main aetiological categories, as reported in Table 29.1. According to the ELTR, these indications are epidemiologically distributed as reported in Fig. 29.1. Overall, biliary atresia is the main indication to LT in childhood. As disorders requiring LT are constantly expanding, the list of diseases reported in Table 29.1 should not be considered as exhaustive but representative of the most frequent diseases leading to LT during the paediatric age.

Table 29.1 Aetiological classification of the main disorders leading to paediatric LT

1. Chronic liver disorders with cirrhotic evolution	**4. Genetic-metabolic disorders**
Cholestatic liver diseases	Alfa 1 anti-trypsin deficiency
Alagille syndrome	Crigler-Najjar syndrome
Biliary atresia	Cystic fibrosis
Parenteral nutrition-associated liver disease	*Fibrocystic liver disorders*
Primary bile acid synthesis defects	Glycogen storage disorders
Progressive familial intrahepatic cholestasis	Maple syrup urine disease
Immune-mediated liver disorders	Mitochondrial liver disease
Autoimmune hepatitis	Primary hyperoxaluria
Gestational alloimmune liver disease	Tyrosinemia
Sclerosing cholangitis	Urea cycle defects
Cryptogenic cirrhosis	Wilson disease
2. Acute liver failure	**5. Complications of portosystemic shunts**
3. Primary liver tumours	Hepatic encephalopathy
Haemangioendothelioma	Hepatopulmonary syndrome
Hepatoblastoma	Portopulmonary syndrome
Hepatocellular carcinoma	
6. Re-transplantation	
7. Other causes (chronic viral hepatitis, non-cirrhotic portal hypertension, Budd-Chiari syndrome, liver trauma)	

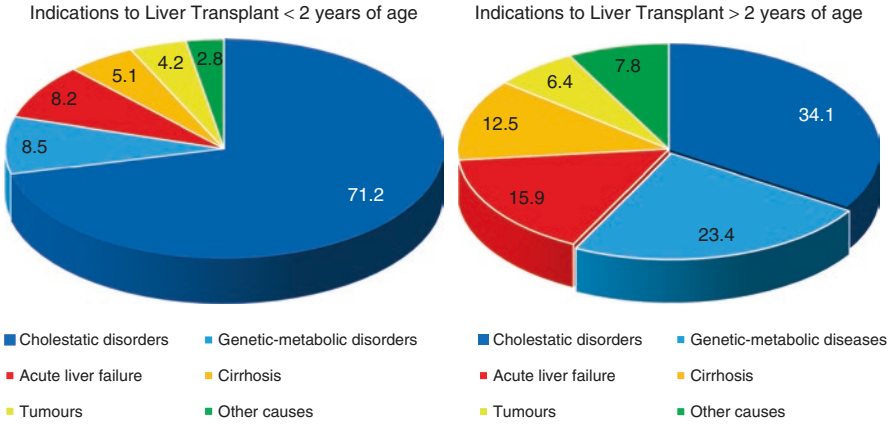

Fig. 29.1 Indications for paediatric LT in children <2 years of age (left) and between 2 and 17 years of age (right) according to the European Liver Transplant Registry (ELTR)

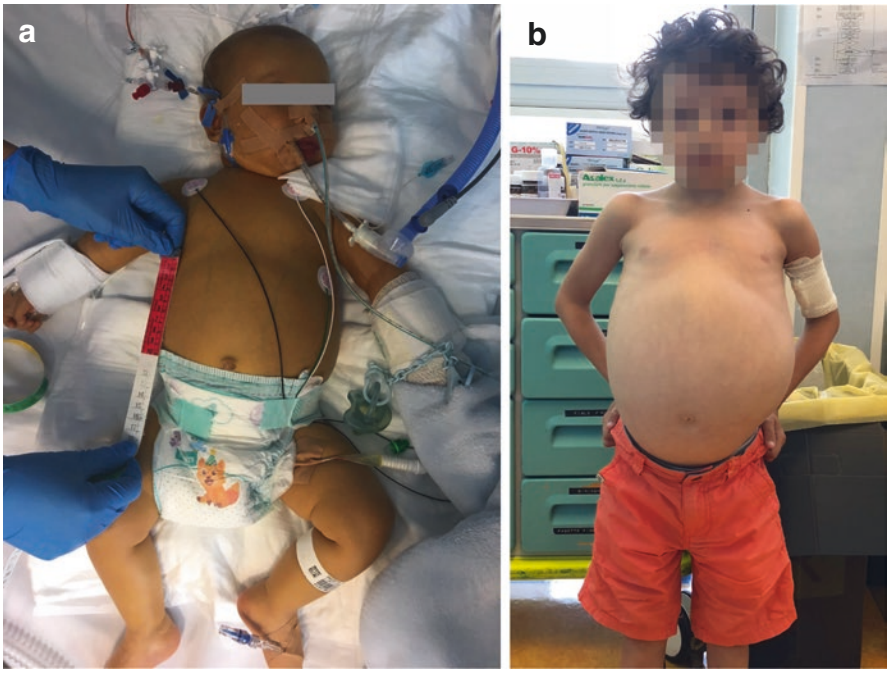

Fig. 29.2 (**a**) Seven-month-old Infant with end-stage liver disease admitted in the paediatric intensive care unit after hypovolemic shock due to massive oesophageal variceal bleeding while on the LT waiting list. (**b**) A 9-year-old boy affected by Caroli syndrome on LT waiting list for severe portal hypertension with massive hepatosplenomegaly and recurrent episodes of variceal bleeding

29.3 Chronic Liver Disorders with Cirrhotic Evolution

Chronic liver disorders are the most frequent indication for LT during childhood. Inclusion on the transplant waiting list may be determined by the presence of organ failure (i.e. end-stage liver disease) and/or by the occurrence of severe complications of cholestasis, cirrhosis or portal hypertension [2] (Fig. 29.2). The timing of LT is crucial. If LT is performed too early, the surgical risk may not be justifiable. On the other hand, if LT is considered or performed too late, the surgical outcome may be hampered by the critical conditions of the patient [2].

The severity of liver dysfunction is assessed with simple, objective and verifiable scoring systems by which patients on the waiting list are prioritized based on their risk of short-term mortality (i.e. within 90 days) without LT [4, 5]. The paediatric end-stage liver disease (PELD) score is used for subjects under 12 years of age, while the model for end-stage liver disease (MELD) is used for those aged over 12 years. PELD is calculated, using a mathematical algorithm, on the basis of the following factors: international normalized ratio (INR), total bilirubinaemia, albuminaemia, age and presence of poor growth (height < −2 SD compared to the average) (Table 29.2). An automatic PELD calculator is available on the Organ Procurement and Transplantation Network (OPTN) website, which provides PELD scores on a continuous scale of values ranging from 0 (100% probability of survival) to 40 (7% probability of survival) and corresponding to the 3-month survival probability without LT. In the presence of PELD values >17 [6] and MELD values >15 [7, 8], LT confers a significant survival benefit and therefore it is recommended to include the patient on the waiting list; when PELD and MELD are >10, it is recommended to refer the patient to a transplant centre to initiate the pre-LT assessment [9]. To date, there is no threshold value of PELD or MELD beyond which the transplantation is futile [6]. Although PELD values >28 [6] and MELD values >35 [10] are associated with greater morbidity and mortality after LT, even in these patients the "transplant benefit" is greater than the risks related to the procedure [7].

Complications of cholestasis (e.g. intractable pruritus, hepatic osteodystrophy and poor growth), cirrhosis and portal hypertension (e.g. ascites, spontaneous bacterial peritonitis, bleeding from oesophageal varices and hepato-renal syndrome) can lead to LT regardless of hepatic function, as they have a significant negative impact on the patient's prognosis: if one of these conditions is present, child survival without LT is reduced by 20–50% in comparison to that of children with compensated

Table 29.2 PELD score

• Paediatric End-Stage Liver Disease (PELD) scoring system incorporates the following criteria:
– Albumin
– Total bilirubin
– INR
– Growth failure
– Age (<1 y)
• PELD score = 0.436 (age [<1 y]) – 0.687 × Log e (albumin g/dL + 0.480 × Log e (total bilirubin mg/dL) + 1.857 × Log e (INR) + 0.667 (growth failure [<−2 SD present])

cirrhosis [9]. Approximately, 50% of paediatric LT recipients are included in the waiting list due to one or more complications of chronic hepatopathy, rather than PELD and MELD scores (i.e. extra-PELD or extra-MELD indications) [11].

29.4 Acute Liver Failure

Paediatric acute liver failure (PALF) is a complex and rapidly progressive clinical syndrome that represents the common final stage of many disorders, some of them known, others yet to be identified [12]. The criteria for the diagnosis of PALF include: (1) onset of hepatic failure ≤8 weeks from the beginning of clinical liver disease in a child with no previous evidence of a chronic liver disease; (2) presence of coagulopathy (i.e. INR ≥2) not corrected by vitamin K regardless of the presence of neurological anomalies or presence of coagulopathy (i.e. INR ≥1.5 and <2) not corrected by vitamin K together with clinical evidence of hepatic encephalopathy [13, 14]. Unlike the adult definition of acute liver failure, hepatic encephalopathy is not a mandatory requisite to diagnose PALF as it may not be clinically apparent until the final stages of the disease, especially in young patients.

The aetiology of PALF is different from that of adults. The cause remains unknown in approx. 50% of cases [14, 15]. In the remaining 50%, the causes are distributed as follows: paracetamol intoxication (12.5%), metabolic diseases (10%), autoimmune hepatitis (7%), drug-induced liver injury (3.3%), infections (6%) and other (15%) [16]. The high proportion of PALF of indeterminate aetiology is often determined by an incomplete diagnostic workup [16]. Therefore, in all patients with PALF, investigations should be promptly initiated to define the aetiology of the liver disease in order to start, when possible, aetiological treatments (e.g. n-acetylcysteine in paracetamol toxicity, steroid therapy in autoimmune hepatitis). Efforts should be particularly oriented towards the identification of treatable disorders (e.g. autoimmune hepatitis, Wilson's disease and galactosemia).

Transplant-free mortality in PALF is variable and ranges from 5% to 37% [15–19]. The main causes of death are multi-organ failure, cerebral oedema and infections [18, 20]. A range of 21–60% of patients with PALF require transplantation [15, 16, 18]. LT has dramatically improved the prognosis of PALF. However, given the extraordinary regenerative capacity of the liver, the indication to perform a LT should be weighed against the probability of spontaneous liver recovery and/or disease response to medical therapies [21]. This assessment can be challenging, since the outcome of PALF may vary depending on several factors (e.g. aetiology, age and severity of hepatic damage). As concerns the aetiology, the risk of death and the likelihood of requiring LT are greater in subjects with PALF of undetermined origin [16, 18]. Age at onset of PALF is an independent prognostic factor for survival. Children <3 years of age, and in particular infants aged <3 months, have a higher risk of death and need for LT [14, 15, 22]. The poorer outcome of these children is mainly related to the aetiology of PALF [i.e. Herpes simplex virus (HSV) hepatitis, neonatal hemochromatosis, hemophagocytic lymphohistiocytosis, metabolic disorders] and to the difficulty in recognizing the neurological complications of liver

failure in this age group [23–25]. Moreover, parameters consistent with severe liver injury are unfavourable prognostic factors for spontaneous liver recovery: INR > 4, bilirubin >235 umol/L, factor V < 25%, leucocytes >9x10^9/L, hepatic encephalopathy grade 3–4 or rapidly progressive neurological impairment [20, 23, 24, 26]. Several prognostic models have been proposed to establish the need for LT. To date, however, only the King's College Criteria for Acetaminophen Toxicity and the Revised King's College Score for Liver Transplantation in Wilson disease have been validated.

Although LT has improved the prognosis of PALF, the post-transplant outcome of children with PALF is worse than that of subjects transplanted for other indications, due to increased risk of multi-organ failure, infections and neurological complications [18, 25, 27]. Survival at 6 months after LT is 74.5% [18, 28]. Age < 1 year, grade 4 hepatic encephalopathy and need for dialysis before LT are associated with an increased risk of post-transplant mortality [18, 22].

In situations when clinical conditions are critical (i.e. worsening of hepatic encephalopathy and/or rapidly deteriorating clinical picture and/or presence of negative prognostic factors), but there's still the possibility of a spontaneous recovery of the liver (e.g. PALF secondary to drugs or toxics), auxiliary LT may be considered [21].

29.5 Primitive Liver Tumours

Primitive hepatic malignancies account for 1–2% of all paediatric tumours [29]. According to the ELTR and UNOS databases, these conditions constitute the indication to LT in 5–10% of paediatric recipients. Hepatoblastoma, hepatocellular carcinoma and haemangioendothelioma are the most frequent liver tumours possibly requiring LT during childhood [29, 30].

LT is indicated in the presence of an unresectable hepatic tumour after exclusion of extrahepatic metastatic disease [2]. Previous neoadjuvant chemotherapy or surgical procedures do not represent a contraindication to transplant. A multidisciplinary evaluation is mandatory to ascertain the indication to transplant and to coordinate surgery with oncologic treatments, so as to determine the correct timing for LT. To this end, children affected by liver tumours should be promptly referred to a paediatric transplantation centre.

Prognosis after LT is favourable, although children transplanted for liver malignancies present a higher risk of early surgical complications and neoplastic recurrence (hepatocellular carcinoma > hepatoblastoma > haemangioendothelioma) [29–32]. The Pediatric Liver Unresectable Tumor Observatory (PLUTO) prospectively analysed 366 children who underwent LT for primitive liver tumours (237 hepatoblastoma, 58 hepatocellular carcinoma, 35 haemangioendothelioma and 36 other tumours) from 1987 to 2007. Overall survival rates were 80.7%, 71.7% and 66%, respectively, at 1, 5 and 10 years after LT; graft survival rates were 73%, 62% and 55%, respectively, at 1, 5 and 10 years; tumour-free survival rates were 92%, 84% and 79% at 1, 5 and 10 years after LT [31]. More recent studies, albeit retrospective and smaller, reported higher survival rates [33].

29.6 Genetic-Metabolic Disorders

LT is now the standard treatment for many inherited metabolic disorders and genetic diseases [2]. These conditions are a heterogeneous group of disorders which, in relation to LT, may be classified according to the presence of liver dysfunction and/or extrahepatic involvement [34]. Liver can either be structurally and functionally intact (e.g. primitive hyperoxaluria) or may show a variable degree of impairment (e.g. Wilson's disease). The genetic-metabolic defect can either be limited to the liver (e.g. urea cycle disorders) or involve multiple organs (e.g. methylmalonic acidaemia).

According to these criteria, genetic-metabolic diseases can be classified in four groups:

1. **Diseases with intrahepatic genetic-metabolic defects and associated liver dysfunction** (e.g. alfa-1-antitrypsin deficiency, Wilson's disease and tyrosinemia). LT leads to complete resolution of the disease. Indication and timing of LT are based on the severity of liver dysfunction.
2. **Diseases with multi-organ genetic-metabolic defects and associated liver dysfunction** (e.g. mitochondrial diseases and cystic fibrosis). LT cures the hepatic dysfunction, but does not have any therapeutic effect on the extrahepatic manifestations of the disease.
3. **Diseases with intrahepatic genetic-metabolic defects and normal liver function** (e.g. urea cycle defects, primary hyperoxaluria, Crigler-Najjar syndrome). LT allows for complete resolution of the disease and prevents the occurrence of further extrahepatic manifestations. Indication and timing of LT are established according to the severity (actual or potential) of the extrahepatic manifestations.
4. **Diseases with multi-organ genetic-metabolic defects and normal liver function** (e.g. maple syrup urine disease, methylmalonic acidaemia). LT allows for palliation of the primitive disorder, reduces the risk of metabolic decompensations, improves extrahepatic manifestations and leads to a better quality of life.

At present, the diseases comprised in groups 1 and 3 are well-established indications for LT. On the opposite, the opportunity to perform LT in disorders included in groups 2 and 4 is still under debate. The risks associated with surgery and immunosuppression should be balanced with the potential benefits of organ replacement (e.g. reduction of the risk of metabolic decompensation, amelioration of prognosis and quality of life) [35, 36].

The wide heterogeneity of genetic-metabolic disorders hampers the possibility of accurately defining the post-transplantation outcome of this group of patients. Arnon et al. evaluated the outcome of 446 children who underwent LT for genetic-metabolic disorders from 1995 to 2008 in the SPLIT registry. Survival rates at 1 and 5 years were higher in this group of patients compared to that of subjects transplanted for other indications (95% and 89% vs. 91% and 87%). Moreover, this population showed a better graft survival and a lower rate of surgical complications [37].

29.7 Complications of Portosystemic Shunts

Portosystemic shunts may be congenital (i.e. due to rare vascular malformations) or acquired (i.e. secondary to portal hypertension). In the presence of portosystemic shunts, the portal blood reaches the systemic circulation bypassing liver metabolism. The prolonged exposure of the pulmonary vessels to toxic vasoactive metabolites normally degraded by the liver can cause hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH). Clinical manifestations, diagnostic criteria and grades of severity of HPS and PPH are the same as those of adults [38].

HPS occurs in 3–20% of paediatric patients. Except for O_2 supplementation, no other pharmacological treatment exist [38]. LT represents the only therapy and grants the resolution of hypoxaemia in 85% of cases within 6–12 months. Severe HPS ($paO_2 < 50$ mmHg) is burdened by higher post-LT mortality [38].

PPH occurs in <1% of paediatric patients. Treatment is based on the use of vasodilator drugs (e.g., Prostacycline, Bosentan and Sildenafil) [39] and on LT. The success of LT depends on PPH severity: in moderate (mean pulmonary arterial pressure [mPAP] 36–35 mmHg) and severe (mPAP >45 mmHg) forms, the risk of death due to right heart failure during or after surgery is higher and proportional to the degree of pulmonary hypertension. The long-term outcome is variable: in some cases, PPH slowly resolves, in others it persists or worsens overtime [40]. In adults, a mPAP of 35 mmHg (spontaneous or with vasodilator treatment) is the upper limit to ensure an acceptable post-LT survival; values >45–50 mmHg despite maximal pharmacological therapy are a contraindication to LT as they are associated with high peri-operative mortality [38, 40]. These thresholds also apply to the paediatric population [41].

29.8 Re-Transplantation, Graft Dysfunction and Graft Complications

Ten to twenty percent of paediatric patients who undergo LT eventually require one or more re-transplantation(s) [42, 43]. The main indications are primary graft non-function, chronic rejection, vascular and biliary complications [44]. Less frequently, the recurrence of the primary hepatic condition [e.g. sclerosing cholangitis, progressive familial intrahepatic cholestasis type 2 (PFIC2)] may lead to re-transplantation [7].

The Studies of Pediatric Liver Transplantation (SPLIT) database evaluated the outcome of 246 children who underwent re-transplantation between 1996 and 2004 in 45 North American centres: survival rates at 3 months and 1 year were lower than those after the first LT (74% vs. 92% and 67% vs. 88%), in agreement with similar studies [42, 43]. Negative prognostic factors included: age <1 year, prolonged INR, hyperbilirubinaemia, creatinine elevation and ongoing life support at the time of re-transplantation [42–44]. In addition, early re-transplantation (<30 days) was associated with a worse survival rate than late re-transplantation (>30 days): 66% vs. 80% and 59% vs. 74% respectively at 3 months and 1 year after transplant [44].

29.9 Contraindications to Liver Transplantation

The success of paediatric LT in terms of patient and graft survival has, over time, led to the broadening of transplant indications, along with a reduction of limitations. However, multisystemic conditions which cannot be reverted by organ replacement or extrahepatic malignancies still constitute a contraindication to LT.

Contraindications to LT can be classified as follows:

- **Systemic infections (bacterial, fungal or viral) uncontrolled by medical therapy and untreatable by liver transplantation.** These conditions are associated with high mortality after surgery [1]. LT should be withheld until microbiological tests have been proven negative for at least 48 hours. Isolated case reports described a positive outcome of LT in children with acute liver failure due to Herpes simplex infection [45, 46].
- **Severe PPH unresponsive to medical treatment.** Severe pulmonary hypertension with mean pulmonary artery pressure (mPAP) >45 mmHg despite maximal medical treatment represents a contraindication to LT, due to the high mortality rates and the non-reversibility of the condition after surgery [38, 40].
- **Mitochondrial disorders with severe multi-organ involvement.** Establishing the feasibility of LT in subjects with mitochondrial disorders can be challenging, due to the wide phenotypic variability of these disorders. In most cases multisystemic and neuromuscular involvement are synchronous to hepatic dysfunction. In some patients, however, neurological impairment may progress gradually and metachronously to liver disease [47] and sparse cases with isolated liver disease have been described [48]. To date, LT is contraindicated only in those patients who show an evident neuromuscular involvement at the time of pre-transplantation assessment, since a progression of neurological impairment is expected [49]. Thus, the feasibility of LT should be established for the single patient. Acute liver failure due to valproate also represents an absolute contraindication to LT since the survival rate is only 20% at 1 year and null at 10 years after transplantation [50].
- **Niemann-Pick disease type C.** Niemann-Pick disease is a genetic condition characterized by neurological and multisystemic visceral involvement. LT is always contraindicated as it does not modify the neurological progression of the disease [1].
- **Metastatic unresectable hepatic malignancies.** The presence of a metastatic extrahepatic unresectable malignancy generally represents a contraindication to LT [2]. Patients affected by hepatoblastoma with isolated pulmonary metastasis could be evaluated for LT if they respond to adjuvant chemotherapy and secondary lesions can be resected [51].
- **Extrahepatic primitive malignancies.** The presence of an extrahepatic malignancy represents a contraindication to LT regardless of tumour staging [52]. In these patients, LT can be considered only after stable remission of the oncological disease. Nonetheless, LT can be considered in association with oncological treatments in highly selected cases after a multidisciplinary discussion

evaluating the prognosis of the neoplastic disease and the risks related to transplantation [53].

Finally, note that age and body weight do not represent a contraindication to LT in children. Studies evaluating the outcome of neonates and infants ≤3 months of age showed a graft survival rate similar to that of the entire paediatric population, even though with higher risk for early complications and longer hospitalization [54, 55].

▶ **Tip** The paediatric candidates to liver transplantation own significant peculiarities in comparison to their adult counterpart and need to be managed by paediatric liver transplant referral centres.

Key Points

- LT is one of the most successful paediatric transplant programs and accounts for about 10% of all LTs.
- PELD (<12 years) and MELD (>12 years) scores predict the risk of short-term mortality without LT in children with chronic liver diseases.
- LT has improved the survival of PALF from <30% in the pre-transplant era to the current >70%.
- LT is indicated in children with primary unresectable liver tumours and no other therapeutic options.
- LT is indicated in children with genetic-metabolic disorders when it guarantees the resolution of liver disease or allows the prevention of extrahepatic manifestations.
- LT is indicated in children with HPS and mild-to-moderate PPH.
- Liver re-transplantation has a poorer outcome compared to the first LT. Regardless, it should be offered to children with severe graft dysfunction as it could provide a survival benefit.
- Uncontrolled systemic infections, severe PPH despite maximal therapy, metastatic unresectable malignancies, mitochondrial disorders with multisystemic/neuromuscular involvement, valproate-induced PALF and Niemann-Pick type C constitute absolute contraindications to LT.

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