

End-stage Liver Disease and Liver Transplant: Current Situation and Key Issues

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Pediatric liver transplantation is no longer considered an experimental treatment. Programs now care for patients who received a liver transplant more than 20 years ago. Hence, patients transplanted in childhood have now become adults and even parents themselves. Five-year survival approaches 85% to 90% and many of the early concerns of orthotopic liver transplant (OLT) are now largely resolved (1,2).

The aim of this article is to identify the current challenges in pediatric OLT. It is directed to all physicians who care for pediatric patients from the early prospect of liver transplant to posttransplant life.

Besides assessing current information on transplant results, the coauthors of this article have identified a number of issues that they consider as the most important that need to be addressed in 2008. Some are only an update of old questions, and others are newly identified problems. The recommendations from the group are summarized at the end of each specific issue and in the consensus guidelines.

SPECIFIC ISSUES

Indications for Liver Transplant

What Are the Definition and Features of End-stage Liver Disease?

Definition. End-stage liver disease (ESLD) is the consequence of many chronic liver diseases, leading to

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irreversible impairment of liver function, architecture (cirrhosis), and blood supply. The main liver functions that need to be considered are bile excretion, synthesis of clotting factors (quantified by international normalized ratio and/or factor V levels) and other proteins such as albumin, glycemic control, and ammonia metabolism. Impairment of a single important liver function, with otherwise intact liver functions, is characteristic of a number of inherited metabolic disorders.

Architectural changes in the liver mainly include fibrosis and cirrhosis. These conditions can be diagnosed clinically, with the help of ultrasound imaging including the elastography (FibroTest) technique (3), although the latter is not universally available. Biopsies are not usually necessary to confirm cirrhosis because the decision to proceed with liver transplantation is rarely based upon liver histology in patients with ESLD and clinical findings of portal hypertension.

Portal hypertension is the primary blood supply change. It leads to esophageal varices, other collaterals, and porto-systemic shunts, adding to the functional insufficiency. The portal vein blood flow can be slow or absent, leading inexperienced ultrasonographers to incorrectly diagnose thrombosis. The portal flow also can be reversed and the portal vein may be unusually small (see below).

Varices and Variceal Bleeding. Esophageal varices are a major concern with ESLD patients. Indeed, they can rupture and be a source of life-threatening bleeding. Esophageal varices banding is more efficient, safer, and less toxic than sclerotherapy, with fewer complications, and should be the preferred technique whenever possible. However, banding devices are not designed for infants, and these devices can not be used in

small children (<5–7 kg). Beta-blockers also are commonly used, but have not been validated as effective primary or secondary variceal bleeding prophylaxis in children. Prophylactic sclerotherapy is not recommended, while prophylactic banding may be considered on a case-by-case basis.

Splenic Artery Aneurysm. Children with longstanding portal hypertension—such as biliary atresia with biliary drainage and compensated cirrhosis—may rarely develop aneurysms of the splenic artery; sudden rupture leads to rapid collapse and deaths. Detection can be done by ultrasound Doppler after filling the stomach with liquids, or by nuclear magnetic resonance angiography or with a spiral computed tomography scan. Aneurysm detection should be part of the ultrasound Doppler examination, and may be considered as a risk if detected (4).

Hepatopulmonary Syndrome. Portal hypertension may be complicated by hepatopulmonary syndrome, a condition in which deoxygenated blood moves through prealveolar shunts or dilated capillaries to the left heart. This condition is often underdiagnosed at its initial clinical stage. Systematic pulse oximetry screening for hypoxia in the upright position in cirrhotic patients is recommended on a yearly basis. Hepatopulmonary syndrome is suspected if arterial oxygen saturation is lower than 90% in patients breathing room air in the upright position, chest radiograph is normal, and a “bubble” echocardiogram shows intrapulmonary shunting. Additional investigation to quantify the shunt may include microaggregated albumin scan or the multiple inert gas extraction technique. Hepatopulmonary syndrome is an indication for semiurgent OLT (5).

Liver Ischemia and Necrosis. In late stages of cirrhosis, in addition to the loss of portal flow to the liver, the arterial blood supply is impaired during diastole. In such cases, the perfusion of the liver depends exclusively on blood flow during systole. Thus, if blood pressure decreases (dehydration caused by gastroenteritis, bleeding varices, etc) the child may be at risk for sudden liver ischemia and

necrosis. This can be evaluated by measurement of the arterial resistance index. The prognostic signification of a resistivity index >1 requires further validation (6).

Interpretation of Liver Enzymes. In patients with biliary atresia, AST and ALT activities are often elevated to approximately 200 to 300 IU/L. Sudden increase of ALT/AST levels to greater than 1000 IU/L may occur as a result of ischemia. Liver failure may result, and the patient may require urgent liver transplant. In addition, γ -glutamyltransferase activity, which is high in the early course of biliary atresia, tends to normalize in ESLD patients.

Which Diagnosed Diseases Lead to OLT and When Can We Propose OLT?

Many diseases are good indications for pediatric OLT. Several cities (Denver and Cincinnati in the United States, Brussels in Belgium, Taipei in Taiwan, Porto Alegre in Brazil, Buenos Aires in Argentina, Birmingham in the United Kingdom, Brisbane in Australia, and locations in India) have been surveyed to determine the distribution of those indications. A summary of this worldwide survey is shown in Table 1.

Biliary atresia remains the number-one indication for pediatric liver transplantation and accounts for approximately half of all liver transplants being performed worldwide. In Belgium and Taiwan biliary atresia is the indication for the vast majority of liver transplants, given that each country reported that 67% of all transplants performed were for this disease. Other cholestatic diseases (including progressive familial intrahepatic cholestasis, Alagille syndrome, total parenteral nutrition–related cholestasis, and idiopathic neonatal hepatitis) were the indication for transplant in approximately 8% of all procedures.

The next most frequent indication for pediatric liver transplantation was fulminant (acute) liver failure. In the majority of the countries, the etiology of fulminant failure was unknown or presumed secondary to non-A-E viral hepatitis. In contrast, Argentina reported the highest rate of fulminant liver failure as an indication for

TABLE 1. Reasons for orthotopic liver transplant (OLT)

Diagnosis	Frequency, mean % of all transplants	Range, % (data origin)
Biliary atresia	49.1	36.3 (Argentina)—67 (Belgium, Taiwan)
Fulminant liver failure	14.3	2.7 (Taiwan)—32 (Argentina)
Autoimmune hepatitis and primary sclerosing cholangitis	7.8	1.3 (Taiwan)—13 (Brazil)
Other cholestatic diseases	7.6	2 (India)—13 (Taiwan)
Other metabolic disorders	7.1	2 (India)—11.3 (UK)
Cryptogenic cirrhosis of a previous graft	6.1	1.3 (Taiwan)—10 (India)
α -1 Antitrypsin deficiency	3.3	0 (Taiwan)—7 (US)
Tumors (mainly unresectable hepatoblastoma)	2.5	0 (Brazil)—5 (US)
Cystic fibrosis	2.1	(only US, UK, and Belgium reported)

transplant (32% of all transplants), with the majority of these cases (58%) due to hepatitis A infection (7,8), an unusual indication in North America, Europe, and Asia.

Autoimmune diseases of the liver (autoimmune hepatitis and primary sclerosing cholangitis) were the indication in nearly 8% of all transplants. Metabolic diseases—including but not limited to tyrosinemia, urea cycle defects, hyperoxaluria, Wilson disease, and glycogen storage diseases—accounted for 7% of all transplants. α -1 Antitrypsin deficiency alone was the indication in approximately 3% of all transplants (9). Posttransplant cryptogenic cirrhosis, a condition presumably caused by poor compliance to immunosuppression regimens, accounts for up to 6.1% of all transplants. In regard to liver tumors, hepatoblastoma represented >70% of tumors in pediatric hepatic transplantation, whereas tumors in general accounted for approximately 3% of all transplants (10). ESLD from cystic fibrosis was the indication for transplant in 2% of transplants; however, this indication was only reported by the United States, the United Kingdom, and Belgium.

Listing of Patients for Transplantation With Failed Kasai. To list a child with biliary atresia after hepatoporoenterostomy or Kasai operation, the natural history of the patient post-Kasai must be taken into consideration. OLT is indicated when Kasai hepatoporoenterostomy fails to restore sufficient bile flow or when life-threatening complications of biliary cirrhosis occur. In most patients, biliary atresia is an ongoing process with progressive portal hypertension and deterioration of the liver function, which sooner or later requires an OLT. In Western countries, short-term clearance of jaundice can be achieved in 50% to 60% of the patients after Kasai and most of them have a good chance of surviving with their native liver for more than 10 years (11,12).

The optimal timing for OLT is crucial because in the cases in which OLT is needed, lack of access to a liver graft at the appropriate time may significantly reduce the chances of survival of patients with biliary atresia. The preoperative condition of the child predicts postoperative outcome because poor nutritional status and advanced liver failure reduce the chances of a successful procedure. Technical innovations, such as split-donor or living related-donor drafts, can help avoid a long waiting period. Thus, OLT in children younger than 1 year old already has become routine in highly specialized centers and the mortality rate of children while waiting for a liver graft has decreased in recent years (2,13).

The outcome of biliary atresia after Kasai hepatoporoenterostomy is predicted by postoperative serum bilirubin level. In a US multicenter study (12), a total serum bilirubin level less than 2 mg/dL at 3 months post-Kasai was found to strongly correlate with good outcome at

2 years, whereas serum bilirubin >6 mg/dL at 3 months post-Kasai predicted a poor outcome. Intermediate serum bilirubin values (2–6 mg/dL) at 3 months post-Kasai were associated with an intermediate risk.

Early planning and preparation of the child for OLT as soon as failure of the Kasai operation is established is therefore necessary, with special attention to the prevention and correction of malnutrition. OLT may be necessary as early as at 6 months of life because of rapid worsening of the liver disease. In addition, even after successful Kasai, progressive inflammation and fibrosis of the intrahepatic bile ducts develops to varying degrees, leading to biliary cirrhosis and the need for OLT in 70% to 80% of patients. As yet, no parameters have been established that reliably monitor the ongoing intrahepatic process of the disease.

After successful Kasai, the patient can be stable and survival with the native liver has been reported up to adulthood. In these cases, the most common complications that may lead to the need for OLT are recurrent bacterial cholangitis, progressive portal hypertension with intractable bleeding, poor liver blood supply, malnutrition, intractable ascites, progressive hepatic synthetic failure, hepatopulmonary syndrome, and portopulmonary hypertension.

Criteria for Transplantation in Nonjaundiced Patients. A number of diseases, such as cystic fibrosis or α -1-antitrypsin deficiency, cause compensated cirrhosis. In such cases, cholestasis is minimal and synthetic function remains satisfactory. The patient has, however, a typical “cirrhotic status,” including low muscle mass, delayed growth and puberty, splenomegaly, and hypersplenism, also sometimes including abdominal pain, poor appetite, or malabsorption. Other diseases affect quality of life without being life threatening, such as extensive xanthomas or intractable pruritus in some Alagille or progressive familial intrahepatic cholestasis patients. Thus, neither the physicians nor the parents can be certain of the ideal timing for liver transplant. Waiting until the child is able to understand and take part in the decision seems reasonable, but may delay the decision for optimal timing of transplant.

Experience shows that after the transplant is performed, parents and children frequently believe that the decision for transplantation should have been made earlier. Indeed, not only does OLT save lives, but it also dramatically improves the patient’s condition as the body returns to a normal state, allowing for a normal life.

Therefore, OLT should be considered when the child cannot function in normal childhood social activities or achieve normal educational goals, or has limitation in his physical activities. There is probably little benefit to postponing liver transplant.

Preemptive Transplantation for Metabolic Disorders. Several inborn errors of liver metabolism are successfully managed medically, although patients remain at risk for sudden metabolic decompensation leading to irreversible consequences. This is best illustrated in urea cycle disorders, familial hypercholesterolemia, and Crigler-Najjar syndrome. The quality of life under medical and dietary treatment often is poor. Indeed, patients often are subjected to a restricted diet with poor palatability. They also experience poor appetite, have only partial control of the disease-related symptoms, and can suffer sudden, irreversible complications, etc. It is of paramount importance to strengthen the links between metabolic units and liver transplant units and to increase mutual knowledge of the benefits and limits of medical–dietary treatment versus liver transplant (9).

For metabolic diseases, liver cell transplant is a promising emerging procedure (see below), and successes have been reported in patients with urea cycle disorders, Crigler-Najjar syndrome, clotting factor deficiencies, and other defects. The current problem remains the partial metabolic control obtained and the limited durability of the response. However, liver cell transplant may be an intermediate step to stabilize metabolic patients while waiting for liver transplant, or when liver transplant is not indicated. Indeed, the procedure has the advantage of being fully reversible (see below) (14,15).

When to Refer and/or Register a Child for Liver Transplantation

This question remains a subject of high concern. Indeed, many patients with liver disease are taken care of in medical units not linked to a transplant center. Thus, transplant as a solution for liver disease is not always considered in due course; patients are referred late in the course of the disease, leading to life-threatening and hospital-binding complications. Physicians are not always aware of the waiting time to obtain a new liver. Because they eventually refer the patients when the first complications occur, they themselves do not experience the difficult management of complicated ESLD patients. Such patients often remain hospitalized for prolonged periods before receiving a liver graft. This could, in some cases, be avoided by earlier referral. In addition, this places additional pressure on the family to perform a living donation.

Any chronic liver disease patient should have early access to a transplant center to balance the pros and cons of liver transplant. This should help ensure better time management of the full process. In addition, it is important to have a joined evaluation of the indication of OLT by a pediatric hepatologist involved with transplant patients. Unfortunately, such multidisciplinary teamwork is not always available. Thus, a second opinion from a second transplant center may be useful.

How to Evaluate the Allocation of a Liver for Transplantation

In 1999 a report published by the US Institute of Medicine stated that despite the best efforts of the liver transplant community, demand exceeded the supply of available organs and that the allocation system was confusing and difficult to understand. Both the Institute of Medicine and the Department of Health and Human Services agreed that donor organs should be allocated on the basis of medical need and acknowledged the need for a measure of medical urgency for liver transplant candidates. From this series of events, the Medical End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scoring systems were born. Based on data retrieved from the Studies of Pediatric Liver Transplantation registry, the PELD scoring system was developed and implemented in 2002. PELD score was calculated using an algorithm based on total serum bilirubin, international normalized ratio, serum albumin, evidence of growth failure, and age of younger than 1 year. The MELD scoring algorithm, used for patients older than 12 years, was based on serum bilirubin, international normalized ratio, and serum creatinine.

It was recognized that the calculated PELD or MELD scores would not reflect risk for pretransplant mortality for a proportion of children who required liver transplant (tumors, metabolic liver disease, or hepatopulmonary syndrome). Consequently, centers could request addition of exception points from their regional review board if the providers judged that the calculated score does not reflect the severity of the patient's disease. It is generally agreed that patients listed should not have life-threatening irreversible extrahepatic disease, evidence of extrahepatic cancer, or a history of substance abuse, and that they must have a support system for care outside the hospital.

The main criterion is projected 1-year survival for the recipient of a transplant compared with survival without a transplant. For older children with sclerosing cholangitis or autoimmune hepatitis, data exist to make this calculation. Patients with a MELD score >15 have an increased 1-year survival following liver transplant compared with patients without liver transplant. For children younger than 12 years, the threshold is not as well defined, owing in part to decreased power associated with the analysis of this smaller population. For diseases in which the risk of the primary illness (eg, biliary atresia and failed Kasai, or unresectable hepatoblastoma) far outweighs that of transplantation, the decision is clear. The data are sparse for patients with complications of portal hypertension without renal insufficiency (bleeding, hepatopulmonary syndrome, recurrent cholangitis, and bacterial peritonitis). For such patients, it is indicated to reach a consensus among the transplant team after discussion based on the latest literature available (16,17).

We must recognize that this approach does not reflect the complexity of the situation. Pediatric liver transplant candidates are a distinct population with respect not only to age but also to primary diagnosis, pretransplant comorbidities, type of graft, posttransplant complications, and potential for a longer period of posttransplant survival. Ultimately, the decision to list a patient as a candidate for liver transplantation will need to take into account not only the survival but also the number of high-quality life-years restored, a measure that incorporates both survival rate and the quality of the time survived. However, until pretransplant mortality reflects the primary disease and not the limited donor organ supply, the decision to list a patient for liver transplant must be based on the relative risk of transplantation compared with the natural course of the primary illness. The survival benefit of liver transplantation, defined as the difference between posttransplant and waiting list mortality, has been used in adults awaiting liver transplantation to make such a determination (18). Moreover, it is a dynamic process. As survival rate after transplantation increases, the relative risk may shift toward liver transplant. The average waiting time on the list is around 180 to 300 days for nonliving donor candidates, and the mortality on the waiting list varies from 3% to 6%.

Follow-up of the Transplanted Child

Ideal Immunosuppressive Protocol for OLT

There is no consensus on the ideal immunosuppression regimen (19). Indeed, in the early days of liver transplant, fear of rejection led physicians to perform multiple control biopsies, and any histological sign of rejection resulted in intensified immunosuppression. Even so, rejection was not prevented and many patients died from complications of overimmunosuppression, mainly posttransplant lymphoproliferative diseases. Thereafter, the trend has progressively been to minimize immunosuppression, and the concept of graft tolerance has emerged. The hypothesis being that immunotolerance required an initial immune conflict, it was necessary to facilitate immunosuppression, not only in the immediate posttransplant period but also in the long term. However, it is not known whether this attitude is excessive. Likewise, it is not known whether minimizing immunosuppression leads to mild progressive changes (eg, sinusoidal or portal fibrosis), which actually seem to increase in the years following OLT, even without clearcut signs of rejection or posttransplant immune hepatitis.

Possible immunosuppressive protocols are as follows:

- Initial therapy with tacrolimus and prednisolone with discontinuation of prednisolone/prednisone after 3 months

- Induction therapy using antithymocyte globulins or specific anti-interleukin-2 receptor antibodies
- If renal function is impaired (glomerular filtration rate <50 mL/min per 1.73 m²): induction with thymoglobulin and prednisolone, introduction of tacrolimus by day 7, then switch to sirolimus after 8 to 12 weeks. Prednisone/prednisolone is discontinued after 3 months.

Main Concerns About Early and Long-term Complications

Complications and Immunosuppression. Outcome measures depend on the population examined and the time since transplantation. Advances in immunosuppressive regimens, antiviral therapy, and surgical techniques have dramatically improved survival rates. Nevertheless, early technical complications related to use of technical variants and extended criteria for graft selection remain a challenge during the early posttransplant period. The issues to be addressed include donor selection, donor organ preservation, and early peritransplant support to optimize function of marginal organs. Even with these challenges, the population of long-term survivors of liver transplantation has grown and is now 10-fold greater than the number of transplantations done each year. For longer term outcome, patients face complications due to excess immunosuppression (cancer and opportunistic infections), inadequate immunosuppression (acute allograft rejection, chronic rejection, and late graft dysfunction), and nonimmune complications (bone, cardiovascular risk factors, and renal disease). For both children and adults, the risk is substantial. A proportion of children who undergo liver transplantation are at increased risk for renal disease and bone disease. Although the development of these complications is clearly multifactorial, currently used standard immunosuppressive therapy is likely to be a major risk factor. In pediatric liver transplant recipients, the relative contribution of immunosuppressive regimens to posttransplant complications may be greater, as children generally lack many of the comorbidities common in adult transplant recipients. The potential impact of renal dysfunction on a child is also distinct from that for an adult, in part because children may live long enough to develop significant end-organ damage. To preserve end-organ function in bone, kidneys, and so forth, it is critical to identify patients at increased risk so that we can move rapidly to mechanistic studies and clinical trials of renal-sparing immunosuppressive agents. Even better, a biological measure of donor-specific immune responsiveness would permit us to tailor immunosuppression and perhaps prevent complications, both immune and nonimmune, associated with long-term immunosuppression. By doing so, we also may identify those at low risk who do not require a change from present immunosuppressive therapy.

Retransplantation for Recurrent Disease or Nonadherence to Treatment. Retransplantation accounts for 7% to 10% of procedures. Retransplantation is indicated for problems in the immediate posttransplant period (hepatic artery thrombosis, primary nonfunction, acute rejection) and for chronic problems. Soltys et al (20) queried the Studies of Pediatric Liver Transplantation registry to identify risk factors for allograft loss more than 1 year after transplantation. Transplantation for tumors, steroid-resistant rejection, reoperation in the first 30 days, and >5 admissions during the first posttransplant year were independently associated with late graft loss. Adherence was not determined. The relationship of adherence to retransplantation remains uncertain because measurement of adherence is a difficult process and no measure (physician assessment, pill counts, electronic monitoring) has been shown to be reliable. Variation in tacrolimus levels correlates with risk of late rejection (21,22). Variation in drug blood levels may be due to nonadherence, but there has been no independent assessment of adherence to test the hypothesis. In the end, poor adherence is not specific to OLT patients but to all chronic diseases, and it is likely that a subset of patients develop late allograft loss as a result of nonadherence to medical regimen (20–22). Long after transplantation, many patients and parents are not aware of the persistent risk of rejection. Omitting or stopping medication may not lead to acute symptoms, and visits to the outpatient clinic and for blood tests become less frequent. This may result in the classic picture of chronic rejection manifested by the vanishing bile duct syndrome, which requires intense immunosuppression, more frequent blood sampling and biopsies, and in some cases retransplantation. It is imperative to emphasize to patients and families the importance of adherence to posttransplant therapies and monitoring.

Besides clearcut vanishing bile duct syndrome, a proportion of patients requiring retransplantation have so-called cryptogenic cirrhosis, which can be a mixture of poor adherence, posttransplant immune hepatitis, insufficient immunosuppression, or simply natural history of the graft. Although many transplant physicians hope that the initial liver transplant will last for a patient's entire life, no child has so far lived much more than 30 years with a single transplanted liver. Chronic hepatitis of the graft is reported in up to 64% of the patients 10 years post-OLT, and these patients have a significant risk of developing progressive fibrosis and cirrhosis of the graft (23).

De Novo Posttransplant Immune Hepatitis. De novo immune hepatitis of the graft, with hypergammaglobulinemia and autoimmune markers (smooth muscle, anti-nuclear, and liver and kidney microsomal antibodies) resembling classical autoimmune hepatitis, may occur as a more specific cause of progressive

liver graft damage, and systematic autoimmune marker screening should be included in posttransplant biological follow-up. These patients respond poorly to calcineurin inhibitor increase and better to steroids, azathioprine, or mycophenolate (23,24).

Posttransplant Lymphoproliferative Disease. Posttransplant lymphoproliferative disease (PTLD) is another persisting concern following pediatric liver transplantation. The proportion of Epstein-Barr virus (EBV)-naïve patients is higher in young children. For this reason, these patients are more prone to develop PTLD. Usually, EBV is acquired during the transplant procedure because most donors test positive for EBV. Primary infection is detected usually around 3 months after OLT and is often asymptomatic. Regular EBV PCR monitoring allows detecting this event, and should lead to minimizing of immunosuppression if tolerated. Clinical symptoms of PTLD include acute necrotic tonsillitis, adenopathies, gastrointestinal symptoms, and unexplained fever. Many other clinical presentations may occur, with PTLD masses developing in any part of the body, including the liver graft itself. The risk of PTLD is linked not only to the viral load itself but also to the lack of anti-EBV-specific T lymphocytes (25).

To avoid PTLD, the first step is to reduce or discontinue calcineurin inhibitors. This action can lead to recovery, and EBV viral load can decrease with the simultaneous appearance of anti-EBV T lymphocytes in the peripheral blood. If, at that point, the patient develops allograft rejection, then immunosuppression must be restarted, except in rare cases in which patients become tolerant.

When there are important lymphoid masses, and when stopping immunosuppression gives no response, anti-CD20 antibodies (rituximab) should be given because a significant proportion of the lymphoid tissue expresses the CD20 antigen. Anti-CD20 also can be given when immunosuppression cannot be decreased or stopped because of the risk of concurrent rejection. In a case of failure to respond to the above treatments, low-dose cyclophosphamide and prednisone achieves full response in 75% of patients (26).

Whether in the course of PTLD, long after recovery, or even without prior PTLD, around 1% of patients will develop true lymphoma (Hodgkin or Burkitt type). These patients must then be treated by chemotherapy, following the same scheme used for any other oncological patient. New hope may come from anti-EBV vaccination before transplantation (27).

CONSENSUS GUIDELINES

Features of ESLD should be assessed with the following:

- Endoscopies indicated in case of variceal bleeding. Elastic banding is the preferred technique to treat

bleeding varices. Prophylactic banding may on a case-by-case basis be considered. Prophylactic sclerotherapy is not recommended.

- Liver ultrasound and Doppler of the hepatic artery and portal vein on an annual basis. This is proposed as an option to screen for liver tumors, rare cases of splenic artery aneurysms, reversed portal blood flow, and increasing resistivity index of the hepatic artery.
- Systematic pulse oximetry screening for hypoxia in cirrhotic patients to detect hepatopulmonary syndrome.

The need for OLT requires individualized management, including:

- Early planning and preparation of the child for OLT as soon as it has been established that Kasai hepatoportoenterostomy has failed
- Proposition of OLT for nonjaundiced children, such as when the child's quality of life is significantly impaired, when he has significant social limitations, when he cannot achieve adequate educational goals, or when he has limitations in physical activity
- Strengthen the links between metabolic units and liver transplant units, to increase mutual knowledge of the benefits and limits of medical–dietary treatment versus liver transplant in case of metabolic disorders
- Early access, in due time, to a transplant center for any chronic liver disease patient to balance the pros and cons of liver transplant. A second opinion from a second transplant center may be useful.

Possible immunosuppressive protocols are as follows:

- Initial therapy with tacrolimus and prednisolone/prednisone with attempted discontinuation of prednisolone/prednisone after 3 months
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Follow-up of liver transplant patients is necessary to assess possible early and long-term complications. This requires

- Identification of patients at increased risk for renal and bone disease, and biological measurement of donor-specific immune responsiveness to tailor immunosuppression

- Emphasis to patients and families about the importance of long-term posttransplant treatment to prevent late rejection or graft loss
- Reduction or discontinuation of calcineurin inhibitors to avoid posttransplant lymphoproliferative disease; anti-CD20 antibodies (rituximab) should be given if PTLD does not respond to stopping immunosuppression; cyclophosphamide and prednisone should be considered as alternatives or if there is no response to previous measures; however, immunosuppression (eg, sirolimus) must be restarted if patients reject the liver
- Treatment of patients with standard chemotherapy regimens for the development of true lymphoma (Hodgkin or Burkitt type)

RESEARCH AGENDA: NEW PERSPECTIVES

Liver Cell Transplantation

Liver cell transplantation is an emerging procedure under investigation. Indeed, the first results have been encouraging. The most attractive indication is inborn errors of liver metabolism. The reason to develop this technique is to avoid removal of a healthy parenchyma that could be repaired instead of being replaced. The aim also is to avoid the short- and long-term complications of OLT (see above) and theoretically preserve the native liver for future therapies such as stem cells or gene therapy. The infused liver cells ideally will colonize the recipient liver parenchyma and produce the missing enzyme or protein product. Biochemical efficacy has been reported in Crigler-Najjar syndrome, Refsum disease, type I glycogen storage disease, factor VII deficiency, and urea cycle disorders (14,15). In urea cycle disorders, engraftment of the cells and in vivo enzyme activity were detected. However, only partial control of the metabolic disturbances has been achieved to date in about 50% of cases, and the durability of the response is limited. Continuous tests to improve the technique include efforts in cryopreservation and selection of transplanted cells.

Stem Cell Transplantation

Stem cell transplantation is another promising procedure. These cells can be of hematopoietic or mesenchymal origin. The latter can be obtained from various tissues, including bone marrow, skin, cord blood, or the liver itself (28). These mesenchymal cells have the potential to be differentiated into partially functional hepatocytes in vitro. When transplanted in animal models, these cells engraft, proliferate in the recipient liver, and differentiate into human functioning hepatocytes (29). Human

clinical testing will proceed, after preclinical safety studies with candidate cells.

A combination of stem cell technology and liver cell transplantation has the potential to improve the durability of response to liver cell transplantation and bring full metabolic control in patients with inborn errors of liver metabolism.

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