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REVIEW ARTICLE

Liver transplantation

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Abstract

Objective: to review the clinical aspects and the theoretical basis of liver transplantation in children, focusing mainly pre and post surgical periods.

Methods: references were obtained from computerized search in the National Library of Medicine (Medline), recent review articles, and personal files.

Results: great development has occurred in surgical techniques, in organ preservation, in postoperative care, and in immunosuppression methods after the first liver transplantation surgery took place in a child with biliary atresia in 1963. Liver transplantation has become an efficient therapy, widely accepted and used in all age groups. It is a very complex procedure, with many professionals involved and with several legal, ethical and economical implications. We review in this article the clinical aspects before transplantation, including indications, contraindications, clinical and laboratory evaluations, as well as postsurgical aspects, both in the immediate period, after the 1st week, and the long-term outcome, discussing the complications and the treatment of each.

Conclusions: liver transplantation has dramatically improved the survival of pediatric patients with chronic hepatic diseases. Patients of liver transplantation in the pediatric age group present today survival rates of 90% in the different transplantation centers.

J Pediatr (Rio J) 2000; 76 (Supl.2): S198-S208: liver transplantation, pediatric liver transplantation, chronic liver disease.

Introduction

Liver transplantation in human beings is recent: it started about 30 years ago, with the pioneer T. E. Starzl. After he had improved the techniques of the orthotopic liver transplantation in dogs, Starzl carried out the first liver transplantation in man, in 1963.[1] The patient was a child 3 years old with biliary atresia, and he died of hemorrhage in the immediate postoperative period. Up to the 70s, the number of liver transplantation was below 200, and the survival was only 20% in 2 years.[2] The introduction of cyclosporin in clinical practice by R. Calne[3] changed the perspective of transplantation and allowed a significantly higher survival rate. From then on, the liver transplantation gradually became a regular procedure, almost routine, in great medical centers.

There are two basic principles concerning transplantation. The first is of social nature: without donor, there is no transplantation. The second is strictly medical: the transplantation does not start neither end on surgery. To transplant is obviously not only to operate.[4] It is a complex set of measures that associates theoretical knowledge, new surgical techniques, and advanced technology, which allow that organs and/or tissues are removed from a person and transferred to another successfully. Undoubtedly, it is one of the most challenging therapeutic procedures. Due to its extreme complexity, it requires the effort and dedication of a great number of professionals. At the center of the process, the members of some special units will be involved: the surgical center, the intensive care unit, and the laboratory. However, in a hospital that performs transplantation, actually there is no department that can stay indifferent to this activity. The successful performance of the procedure involves several medical and paramedical specialties. Besides, the questions and debates will not be limited to medical aspects, even if they are extremely challenging.

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There are several legal, ethical, and economic implications. It is of paramount importance that the team members work with the clear notion that usually, if on one hand, transplantation saves lives, on the other hand, there is sadness and pain. In the great majority of cases, a life was lost so that another could be maintained. It is known that there is a sequence of events that are necessary for a donation to be carried out. If one link breaks, all the process will be inevitably compromised. Generosity and confidence are the real conductors of this process.[4]

About 5 years ago, we started preparations for pediatric liver transplantation at the Hospital de Clínicas de Porto Alegre.[5] At that occasion, we had done some previsions: a) the demand of patients would be high; b) the community would respond positively to the solicitation of organ donation; c) pediatric liver transplantation would provoke more qualification of the different sectors of Hospital de Clínicas de Porto Alegre because of the multiplying effect that it brings. These previsions did not constitute mere exercise of futurology, and were widely carried out. After the first transplantation in March 1995, pediatric liver transplantation was performed in 41 patients. Currently, April 2000, pediatric liver transplantation is already part of routine at Hospital de Clínicas de Porto Alegre, and a growing number of patients has been referred continuously to evaluation. The amplification of the program, though, depends on the number of donors, and the liver transplantation is, from a certain point of view, a victim of its own success. The good rates of survival stimulate a higher number of potential receptors. In order to face this challenge, the contribution of several segments of the society is indispensable. The collaboration of the National Transplantation Service, from the Brazilian Ministry of Health, and of the Secretarias de Saúde e de Educação of municipalities and states is very important to increase the number of donors and change the current system of allocation of organs, in order to allow a higher number of patients to benefit from transplantation programs in Brazil.[4]

Four different phases may be identified in transplantation. They are: a) pretransplantation phase; b) the procedure itself, and the perioperative period; c) return to functional life; d) long-term evolution.[4] Each phase has its peculiarities. In this article, we will focus only on the clinical aspects of liver transplantation in the pediatric age group.

Pre-transplantation phase

In this period, indications and contraindications are analyzed, and the patient and the family are prepared to the surgery. The need for the evaluation to be performed by multidisciplinary teams should be emphasized. The correction of abnormalities observed in this phase will contribute to decrease the complications of both the operative and the immediate postoperative periods. A minute evaluation of immunizations and of the nutritional status is fundamental. Many times, aggressive measures of orientation/nutritional recuperation are necessary, such as feeding probes, gastrostomy, etc. The moment of inclusion of the patient in the list of active people, which constitutes the timing of the transplantation, is extremely important.

Indications for transplantation

The main indications for this procedure may be grouped in four categories (Table 1): 1) primary hepatic diseases with progressive evolution; 2) nonprogressive hepatic disease of acknowledged morbimortality; 3) metabolic liver disease; 4) fulminant hepatic failure (of known or unknown etiology).[6] There is a bimodal distribution concerning the patients' age.[5] In the first 2 years, patients presenting biliary atresia are usually candidates; after this age, most cases of transplantation happen in children with fulminant hepatitis or with cirrhosis due to other causes than biliary atresia.

Table 1 - Indications for pediatric orthotopic liver transplantation*

Obstructive diseases of the biliary tract
Extrahepatic biliary atresia
Sclerosing cholangitis
Metabolic disease
Alpha-1-antitrypsin deficiency
Tyrosinemia
Glycogenosis type IV
Wilson's disease
Neonatal hemochromatosis
Defects of the urea cycle
Others
Intrahepatic cholestasis
Byler's disease
Alagille's syndrome
Nonsyndromic ductopenia
Idiopathic neonatal hepatitis
Fulminant hepatic failure
Acute viral hepatitis
Induced by drug or toxin
Cirrhosis/Chronic hepatitis
Postviral
Autoimmune
Idiopathic
Tumors
Hepatoblastoma
Hepatocarcinoma
Others
Other causes
Cryptogenic cirrhosis
Congenital hepatic fibrosis
Cystic fibrosis
Cirrhosis secondary to prolonged parenteral nutrition

* Adapted from Balistreri (1998)[6]

Atresia of the extrahepatic bile ducts is the most important indication for liver transplantation in the pediatric age group; it is responsible for 76% of the indications in children younger than 2 years, and for approximately 50% of the general indications.[2,7] Only about 20% of the children operated due to biliary atresia will not be candidates to transplantation.[6] The second group in terms of frequency is the one of metabolic diseases (20 to 25%), and, less frequently, fulminant hepatic failure and other forms of intrahepatic cholestasis.[2.6.7] Primary malign hepatic disease is a rare cause of indication for transplantation in this age group; patients with hepatopathies secondary to systemic diseases, such as cystic fibrosis, are also rare candidates to transplantation.

When should the patient be included in the active list?

The decision of including the patient in the active list, which corresponds to the possibility of performing transplantation at any time, is sometimes very difficult. Some aspects should be considered: risk-benefit ratio of the treatment, local availability of organs, and the probability of evolution by the patient after transplantation. The indication should be done when there is progressive deterioration of the patients' health conditions, but before the appearance of complications that determine excessive risk for the procedure.[2] In this context, the following items are indicators of the need for transplantation[6]:

– cholestasis, itching, and/or ascites that are not clinically treatable;
– portal hypertension with variceal bleeding, with no response to treatment;
– multiple episodes of cholangitis;
– progressively deficient hepatic synthesis (coagulopathy, hypoalbuminemia);
– repercussion in the stato-ponderal growth;
– hepatic encephalopathy (levels I, II, and III).

Contra-indications of transplantation

The list of contraindications is inversely proportional to the experience acquired with the procedure. In Tables 2 and 3, the main absolute and relative contraindications of pediatric liver transplantation are presented.[6,8,9] The social evaluation, mainly in our setting, is extraordinarily worthy.[10,11] In some series, the rate of patients that do not follow the orientations given by transplantation teams reaches up to 50%. The negative repercussions on the patients' evolution that result from this are obvious, with graft loss, rejection, and adverse reactions to drugs in high percentages. The following aspects can be considered as risk factors for nonadhesion to orientations:

– low socioeconomic and comprehensive level;
– particularly complex therapeutic scheme, with a great number of drugs;
– the patient lives far from the transplantation center;
– unstructured family, with insufficient social assistance support.

Table 2 - Absolute contraindications to pediatric liver transplantation*

Positive anti-HIV
Irresectable primary extrahepatic malignancy
Metastatic disease of the liver
Progressive terminal nonhepatic disease
Noncontrolled sepsis
Irreversible neurological damage

* Source: McDiarmid SV et al., 1998[8]; Balistreri W, 1999[9]

Evaluation of candidates to liver transplantation

The pretransplantation evaluation has as main objectives:

– diagnostic confirmation, as well as the confirmation of the need for transplantation;
– establishment of the severity of the disease;
– recognition of potential contraindications to the transplantation;
– treatment and prophylaxis of situations that are unfavorable to the good evolution of the transplantation (vaccination, treatment of infections, nutritional support, psychosocial support);
– patient's and his/her family's education concerning pre and posttransplantation care;
– integration between the patient, his/her relatives, and the transplantation team.[4,5]

It is important to remember that for infants with biliary atresia, one of the most important factors predictive of complications in the posttransplantation period is the protein-energy malnutrition. In reality, malnourished children, at any age, present an increased number of complications when compared to well-nourished ones.[12,13] Mortality rates are twice higher in the former. A recent study with multivariate analysis identified a low level of factor V (<34%) as an independent predictor for the survival of patients with cirrhosis, pointing that 93% of these cirrhotic patients died in 10 months.[14]

Table 3 - Contraindications related to pediatric liver transplantation*

Advanced or partially treated systemic infection
Encephalopathy level IV
Psychosocial and ethical aspects
Portal venous thrombosis extended to mesenteric vessels

* Source: McDiarmid SV et al., 1998[8]; Balistreri W, 1999[9]

The evaluation usually used in children with hepatopathy (with cholestasis) is Malatack's score,[15] which analyzes clinical and laboratory data and identifies three different categories of patients: with low risk, medium risk, and high risk for death within 6 months (Table 4).

Table 4 - Malatack's score15 for cholestatic children*

Cholesterol	< 100 mg/dl	=	15 points
Ascites (history)			15 points
Indirect bilirubin 3 to 6 mg/dl = 11 points	> 6 mg/dl	=	13 points
Activated partial thromboplastin time	> 20 seconds	=	10 points
Points	**High risk:**		**> 40**
	Medium risk:		**28 to 39**
	Low risk:		**0 to 27**

* Source: Malatack JJ, Schaid DJ, Urbach AH, 1987[15]

Laboratory investigation of the candidate to transplantation

Laboratory investigation includes a wide set of different laboratory examinations: biochemical, hematological, immunologic, radiological, etc. Besides collecting material for the exams mentioned, it is indispensable to store material (at least a blood sample) in a freezer for the serum storage of the service.

Specialized evaluations

According to each case, specialized medical evaluations are going to be required: cardiologic, nephrologic, pneumologic, anesthetic, psychiatric, odontological, nutritional, otorhinolaryngological, genetic, and any other that becomes necessary. The social assistant will perform the socioeconomic evaluation.[11] The nephrologic, pneumologic, and cardiologic evaluations are fundamental when there is compromising of the renal function and hepatopulmonary syndrome.

Nutritional evaluation and orientation

Most children and adolescents with chronic hepatopathy present malnutrition and deficiency of vitamins and minerals.[12,13] It is known that good conditions presented by the patients when they undergo transplantation eases the postoperative recovery. On the other hand, when there is compromising of the nutritional status, there is an evident repercussion on the number and intensity of postoperative complications.[12,13] In our patients, about 65% of children with biliary atresia presented lipid depletion, and a more significant number presented dietary inadequacy, which was evidenced through a questionnaire about the patient's dietary habits.[4,5] When children with chronic cholestasis that were candidates to transplantation were evaluated through bone densitometry, the proportion of alteration was very high: 100%.[16] For the nutritional evaluation (Figures 1 and 2), we used the following items:

- anthropometry;
- growth speed;
- bone age (bone densitometry);
- pubertal development;
- manifestations of hypovitaminosis;
- dietary questionnaire.

Considering the importance of diet to the transplantation evolution, we commend intensive supplementation, even if it is necessary to implement quite aggressive methods. In patients with intense anorexia, we used nasogastric and nasoenteral probes, or even gastrostomies (with the buttoned device). In order to calculate caloric reposition, we used the 50th percentile for weight and stature, and we added glucose polymers and medium-chain triglycerides. Figure 1 shows the basis of our calculations.

Immunizations

It is recommended that pediatric patients undergo all the vaccines before transplantation. The live virus vaccines can not be performed after the transplantation, so it becomes very important that they are carried out before surgery. It is important to assure that the routine vaccinal calendar is updated, and all the other vaccines are recommended to be done before surgery. In children older than 6 months, the indicated vaccines are against mumps, varicella, hemophilic, and pneumococcal.[7] Vaccines against hepatitis A and B should also be carried out before the procedure.[7] When the patient is submitted to the live virus vaccine, transplantation should take place only after approximately 1 month, due to the immunosuppression that she/he will receive already in the transoperative period.

Post-transplantation phase

Early postoperative

On the first days after transplantation, the patient stays at the intensive care unit, and is monitored by the intensive care team and followed up by the hepatologist. Although there are some patients that already present extubation conditions at the surgical center, the stabilization and maintenance of the child at the intensive care unit during the first 24-48 hours is recommended; then, the hepatic function can prove satisfactory, as well as the blood flows in the hepatic artery and in the portal vein, through laboratory examinations and Doppler ultrasonography.[7] The surgical procedure is very extensive, and the abdominal incisions

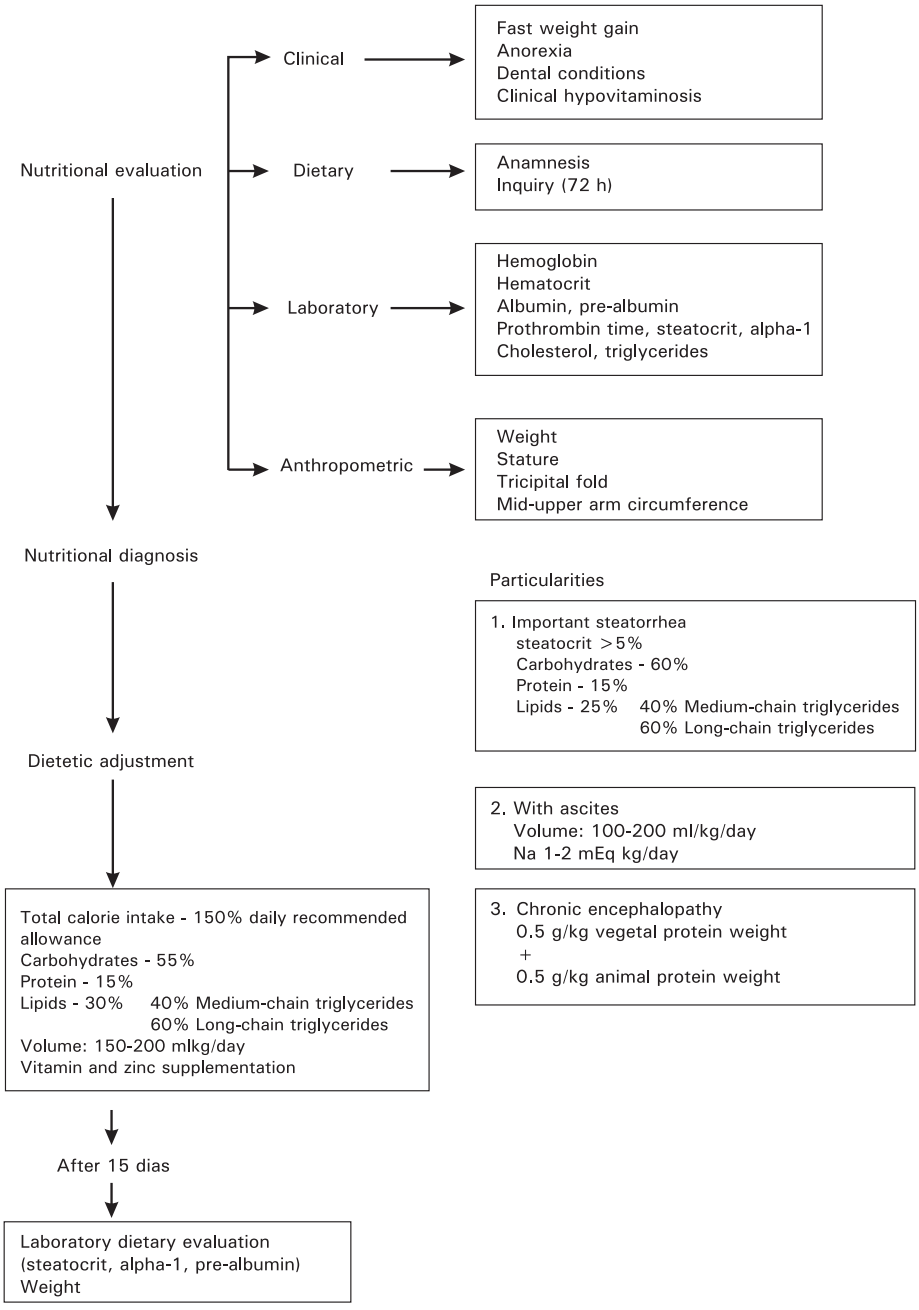

Figure 1 - Nutritional evaluation of pediatric transplantation candidates

are large and painful, which causes the patient to require analgesics and sedatives at high doses; these aspects make the monitoring quite delicate. The hemodynamic and renal handling are especially important and complex in the first postoperative hours of liver transplantation.[17]

The complications that occur in the early postoperative period depend on:

– previous condition of the receptor (nutritional status, infections, ascites, renal insufficiency, encephalopathy);
– graft quality (ischemia time, preservation);
– surgical complications (bleeding, hemodynamic instability during the transoperative period);
– side effects of drugs (renal insufficiency, infections).

The main causes of graft loss during the 1st week are:

– primary liver nonworking;
– thrombosis of the hepatic artery or portal vein;
– septicemia.

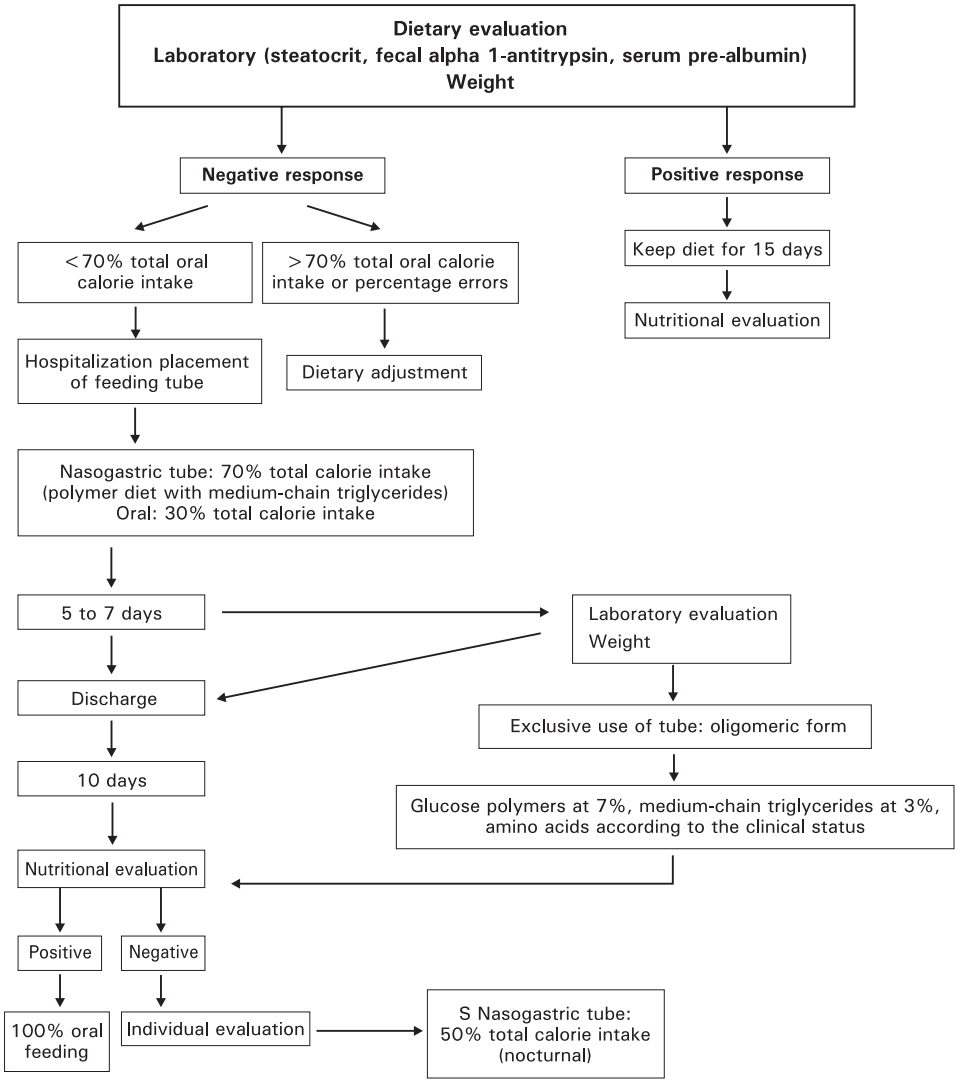

Figure 2 - Nutritional evaluation and orientation of candidates to liver transplantation

The primary liver nonworking is a very serious complication, which occurs in pediatric liver transplantation according to the different centers and requires immediate retransplanttion.[18-20] The suspicion of such condition rises when there is persistent coagulopathy, acidosis, hypercalcemia, and progressively elevated transaminases (above 10,000 ui/l).[7]

The thrombosis of hepatic artery may occur in up to 10% of the cases, but its incidence has been decreasing with the microsurgery technique used in artery reconstruction, as well as in reduced grafts, with large-caliber vessels. Thrombosis of the portal vein is less common.[19]

Septicemia is treated with systemic antibiotics, as well as with antifungal agents, mainly in cases of fulminant hepatitis. Routinely, the use of large-spectrum antibiotics is prophylactically started during the transoperative period, and continued or not in the first 48-72 hours, according to each patient. In our program, we used aztreonam and vancomycin.

Immunosuppression

The most used schemes for immunosuppression after liver transplantation are the following:

- cyclosporin (microemulsion -neoral), prednisone, and azathioprine;
- tacrolimus (prograf) and prednisone.

One of the two basal immunosuppressants (cyclosporin or tacrolimus) is started on the 1st or 2nd postoperative day (usually through nasogastric or enteral probe), according to the renal function, that is, when the urinary debit is at least at 1 ml/kg/hour, and it should be maintained for the patient's

Table 5 - Nutritional recuperation scheme in patients that are candidates to pediatric liver transplantation

Deficiency	Reposition scheme
Calories	130-200 % of RDA
Proteins	2-4 g/kg/day
Fats	30% of calories in the form of fats TCM up to 50% / TCL at 50%
Vitamin A	5.000-20.000 UI/day
Vitamin D	Vitamin D2: 1,200-4,000 UI/day 25-OH-D: 2-4 µ g/kg/day
Vitamin E	10-200 UI/kg/day (acetate) 25 UI/kg/day of TPGS 3,5-7,0 UI/kg/week IM
Vitamin K	2,5-10,0 mg/month/parenteral
Calcium	25-50 mg/kg/day up to 1 g
Magnesium	1-2 mEq/kg/day (acetate)
Iron	4-6 mg/kg/day
Selenium	1-2 µ g/kg/day orally
Zinc	1 mg/kg/day orally (acetate)
Hydrosoluble vitamins	Give the double of the RDA dose

whole life. The doses are variable, according to the monitoring of serum levels, and they follow well established protocols (Tables 6-8).

Steroids are progressively reduced, and, in general, interrupted at 3 months, or at the end of the 1st year, or still they are maintained at very low doses, according to different protocols. The decrease and withdrawal of corticosteroids is faster with the use of tacrolimus, which is particularly important in the pediatric age group, due to its effects on growth.

When azathioprine is used, it is discontinued after 3 months or 1 year. Currently, mycophenolate mofetil (another immunosuppressive drug) is also used, but its use in children is still limited.[21]

Table 6 - Serum levels wanted to cyclosporin according to the posttransplantation period*

Posttransplantation weeks	Serum cyclosporin level wanted
1 to 2 weeks	350 to 400 ng/ml
3 to 4 weeks	250 to 300 ng/ml
5 to 6 weeks	200 to 250 ng/ml
6 to 12 weeks	150 to 200 ng/ml
>12 weeks	100 to 150 ng/ml

* The collection was performed immediately before the following dose intake (vale). The serum level collected 2 hours after the dose intake (peak) should not go over 1,200 to 1,300 ng/ml.

Table 7 - Corticosteroid doses recommended in the cyclosporin protocol according to the postoperative period and to the patient's weight

Postoperative period	Recommended dose	
Transoperative	Methylprednisolone: 20 mg/kg in hepatic reperfusion	
	Weight < 30kg	Weight > 30kg
1st postoperative week	100 mg IV*	200 mg IV
2nd postoperative week	80 mg IV	160 mg IV
3rd postoperative week	60 mg IV	120 mg IV
4th postoperative week	40 mg IV	80 mg IV
5th postoperative week	20 mg IV	40 mg IV
6th postoperative week, up to the first 3 months†	10-15 mg/day O‡	20 mg/day O
4th postoperative month	7.5-12.5 mg/day O	17.5 mg/day O
5th postoperative month	5.0-10 mg/day O	15 mg/day O
6th postoperative month	5.0-7.5 mg/day O	12.5 mg/day O
Maintenance§	5.0 mg/day O	10 mg/day O

* IV = intravenously

† From the 6th postoperative month on, methylprednisolone is replaced with prednisone at about 0.5 to 1.0 mg/kg/day for 3 months in daily morning doses

‡ O = orally

§ From the 1st postoperative year on, prednisone may be kept at 0.1 mg/kg/day or withdrawn according to the individual evaluation of each patient. The use of this drug in alternate days is indicated whenever possible.

Table 8 - Immunosuppression protocol with tacrolimus: recommended doses, serum levels wanted, and dangerous serum levels according to the posttransplantation period considered*

Posttransplantation period	Maximum recommended doses	Serum levels wanted	Dangerous serum levels
0 to 15 days		12-15	>15
15 to 27 days		10-12	>12
30 to 90 days	0,2 mg/kg/day	6-8	>8
3 to 6 m	0,15 mg/kg/day	4-7	>8
>6 m	0,1 mg/kg/day	1-7	>7

* The initial daily dose recommended is 0.3 mg/kg/day (0.15 mg/kg/dose).

Complications after the 1st week

After the 1st posttransplantation week, the most frequent complications are:

- septicemia/infection;
- rejection;
- stenoses or biliary fistulae.

Infection is the most common complication after liver transplantation, occurring in 60 to 70% of the cases.[7,19] In our study, the proved bacterial infection occurred in the first 30 days after surgery in 70% of the patients transplanted.[22] The germs most frequently identified were *Staphylococus aureus* and epidermidis, and *Xantomonas maltophilia*.[22] Most infections are bacterial, mainly those resulting from venous, pulmonary, and urinary accesses. Fungal infections occur in 10% of the children, and they are particularly important when there is acute hepatic necrosis in the pretransplantation period.[7,19] In our patients, fungal infection occurred in 10%, and candida was the most common organism.[22]

Rejection

Acute rejection is less common in infants (20%), but it increases significantly in older children (50-60%).[7] Clinical signs of rejection can be very variable, including fever, abdominal pain, and irritability. Laboratorially, there is increased proofs of hepatic function (transaminases, bilirubins, gammaglutamyltransferase, and alkaline phosphatase). The diagnosis is histological, which makes the liver biopsy become indispensable.[23] Acute rejection is characterized by the triad: mixed inflammatory infiltrate in portal spaces, subendothelial lymphoid infiltration (endothelitis), and presence of inflammatory cells in bile ducts.[23] The treatment of rejection consists of pulsetherapy with corticoids or addition of other immunosuppressive drugs. If there is no laboratory and histopathological remission after the methylprednisolone pulse, the course may be repeated for 3 more days, but the conversion for a more powerful immunosuppressant, such as tacrolimus, may be necessary.

Chronic rejection is much rarer, and it occurs in approximately 10% of the transplanted children at any moment after surgery.[7,19,23] The diagnosis is also histological, and it is suggested by a status of biliary obstruction, with the appearance of jaundice, itching, and hypocholia. Laboratorially, there is an higher increase in bilirubins, gammaglutamyltransferase, and alkaline phosphatase than in transaminases. Biopsy shows the progressive disappearance of the bile ducts, followed by obliteration in the arteries, and fibrosis. Some children respond to increased immunosuppression or delivery of tacrolimus. However, most children require retransplantation.[7,18,19]

Late complications

The complications considered late, or that occur after the first 3 weeks after transplantation, may happen at any moment, and include:

- immunosuppression side effects;
- viral infections (cytomegalovirus and Epstein-Barr virus);
- lymphoproliferative disease;
- biliary stenoses and late thromboses.

There are several effects that are secondary to the immunosuppressive medication, and they should always be remembered and adequately handled. In Table 10, we show the most common ones. Hirsutism and gingival hyperplasia, which are purely cosmetic effects that may, though, bother the patient's life considerably, mainly in case of adolescents, are not side effects of tacrolimus, but only of cyclosporin.[7] Other more serious secondary effects (nephrotoxicity, neurotoxicity) are very similar when we use cyclosporin or tacrolimus. We should always remember that drug side

Table 9 - Doses of corticosteroids recommended in tacrolimus protocol according to the postoperative period

Postoperative period	Recommended dose
Transoperative	Methylprednisolone: 10 mg/kg, intravenously in the hepatic reperfusion
1st to 6th P.P.*	Methylprednisolone: 2 mg/kg intravenously
7th to 13th P.P.*	Prednisone: 1 mg/kg/day orally (1 dose)
14th to 20th P.P.*	Prednisone: 0.75 mg/kg/day orally (1 dose)
21th to 28th P.P.*	Prednisone: 0.50 mg/kg/day orally (1 dose)
2nd month to 3rd month	Prednisone: 0.25 mg/kg/day orally (1 dose)
After this, start alternate-day doses, and then, suspend it.	

* P.P.: postoperative period

effects may be potentiated by other drugs that interfere with the serum levels. In Table 11, some medications that are able to interfere with serum levels of cyclosporin are listed.

Viral infections caused by cytomegalovirus and Epstein-Barr virus are much more frequent in pediatric receptors, which reflects a lower number of patients with positive antibodies before transplantation.[7] Infections caused by cytomegalovirus occur from the 4th week on, even when prophylaxis with acyclovir or ganciclovir is performed during the postoperative period. The risk for diseases caused by cytomegalovirus is higher when the child is negative and receives a positive organ. When the treatment is started early, it is usually effective, and it is performed with intravenous ganciclovir during 2 to 4 weeks, with doses at 5 mg/kg/dose every 12 hours.[6,8,9,19,24-26]

The development of primary infection caused by Epstein-Barr virus is a significant long-term problem, since there is a narrow relationship between primary infection caused by Epstein-Barr virus and posttransplantation lymphoproliferative disease.[25,26] Approximately 65% of the children that undergo transplantation are negative for Epstein-Barr virus, and 75% of them will present primary infection caused by Epstein-Barr virus during the first 6 postoperative months.[7] Disorder associated with Epstein-Barr virus occurs in 13 to 57% of the liver transplantation pediatric receptors, and causes significant problems of morbimortality.[26] It is important to diagnose primary infection caused by Epstein-Barr virus and to decrease immunosuppression whenever possible, in order to try to prevent the progression of this patient towards posttransplantation lymphoproliferative disease.[26] The proliferation spectrum of B cells is very wide, and may range from a benign hyperplasia up to a malign lymphoma. Any organ or tissue may present this lymphocyte proliferation, which is caused by primary infection by Epstein-Barr virus. This situation usually makes the diagnosis difficult. The organs most commonly affected are liver, intestine, and lymphoid tissues of the head and neck.[7,16,19,26] Clinical findings may be extremely variable, depending on the stage and on the organ affected, and it may range from a clinical infectious mononucleosis syndrome or isolated lymphoid involvement, up to a lymphoma. The diagnosis is based on the characteristic histology of the affected organ, which may show polymorphic proliferation of B cells or lymphomatous findings of atypical nucleus and necrosis. The immunofluorescence of immunoglobulin light or heavy chain may differentiate infiltrates in mono or polyclonal. Posttransplantation lymphoproliferative disease seems to be caused by inadequate use of immunosuppressants; so, contrarily to what we thought previously, the incidence is not higher with the use of tacrolimus.[7,26] The treatment consists of reduction or withdrawal of immunosuppression and antiviral drugs (acyclovir or ganciclovir). If there is the appearance of lymphoma, chemotherapy may be necessary. The greatest difficulty is the balance between decreased immunosuppression and the appearance of rejection, which needs to be treated with more immunosuppression.

Late biliary stenoses are usually due to problems in the hepatic artery, and they should be treated radiologically whenever possible. If they are not properly treated, they evolve to cholangitis and biliary cirrhosis. Late hepatic thrombosis usually does not require treatment, since a collateral flow is established. Stenosis of the portal vein due to stenosis of the anastomosis should be treated radiologically or through surgical reconstruction, since it evolves to portal hypertension.[7]

Long-term evolution

Long-term survival after liver transplantation is variable in several centers, but it may reach 90% in the 1st posttransplantation year, and rates of 60 to 80% in the following 5 to 8 years.[7,19]

Table 10 - Effects secondary to immunosuppressive drug

Drug	Complications
Cyclosporin	Myopathies, hirsutism, gingival hyperplasia
Tacrolimus	Hyperglycemia, cardiomyopathy
Cyclosporin/ Tacrolimus	Renal toxicity, neurological toxicity, arterial hypertension, severe infections (lymphoproliferative disease: cytomegalovirus, Epstein-Barr virus)
Steroids	Cushing, hypertension, delayed growth
Azathioprine/ Mycophenolate mofetil	Medullar depression

Table 11 - Some drugs that may interact with cyclosporin, altering cyclosporinemia

Drug	Therapeutic class	Effect on cyclosporinemia
Rifampicin	Tuberculostatic	Decrease
Carbamazepine, phenobarbital, phenytoin, valproic acid	Anticonvulsivant	Decrease
Trimethoprim (isolated or associated)	Chemotherapic	Decrease
Omeprazole	Proton-pump inhibitor	Decrease
Octreotide	Somatostatinergic	Decrease
Ketoconazole, itraconazole, fluconazole	Antifungal	Increase
Erythromycin, doxycylin, roxithromycin, norfloxacin, ticarcillin, imipenen + cilastin	Antibiotic	Increase
Thiazide, furosemide, acetazolamide	Diuretic	Increase
Nicardipine, diltiazen, verapamil	Calcium channel inhibitor	Increase
Oral contraceptives, norethisterone, danazol, levonorgestrel	Steroid	Increase
Prednisone, methylprednisolone	Corticosteroid	Increase
Coumarin, warfarin	Anticoagulant	Increase
Metoclopramide	Antiemetic	Increase
Ethanol	Alcohol	Increase
Pentazocine	Central analgesic	Increase
Tamoxifen	Anti-estrogenic	Increase
Cimetidine, ranitidine	H2 blocker	Increase
Sodium docusate	Laxative	Increase

The main factors that affect survival after transplantation are:

– age (children younger than 1 year present lower survival);
– nutritional status;
– severity of the disease in the postoperative period.

Children that go over the first 3 months after transplantation without serious complications are those that rapidly return to their normal life, with the performance of routine activities for each age group, although they will receive immunosuppressive medication for their whole life, and although they will be submitted to periodical monitoring. There are some studies that indicate that up to 59% of transplanted children do not retake growth.[27] More recent studies, however, have shown that most patients (80%) are going to grow and develop normally.[28,29] Delayed growth seems to be directly related to the use of steroids, which has been decreasing with the use of tacrolimus. Children may initially present an excessive weight gain, which results from the high doses of steroids, increased appetite, and retention of salt and water. In general, patients will retake linear growth after 1 year.

Clinical monitoring

After patients are dismissed, they are frequently seen in weekly intervals at the beginning, then every 15 days, every month, every 3 months, and every 6 months. Every time they have an appointment, laboratory controls and serum levels of immunosuppressants are collected, and the drugs are adjusted.[30]

It is essential to encourage the child and his/her family to retake normal activities and life. From 6 months after the transplantation on, the patient should return to school, sports, and relationships with other children; the family should, little by little, stop treating the child as a sick person. Many families have difficulties in surpassing this period, and need psychological support and follow-up.

The first orthotopic liver transplantation was performed in a child. Since then, continued advances have happened regarding surgical techniques, organ preservation, postoperative care, and immunosuppression methods: transplantation became an effective therapy, widely accepted and used in children with terminal hepatic diseases.

Liver transplantation improved dramatically the survival of pediatric patients with chronic hepatopathies. Patients of the pediatric age group who are submitted to liver transplantation may currently present survival rates that reach 90% in different centers. As posttransplantation survival rates improved progressively, the final medical objective is the complete rehabilitation of these transplanted children. Factors that help in reaching this aim include the improvement of the nutritional status, with adequate growth and development, as well as the improvement of the patients' motor and cognitive capacities, which allows their social reintegration.

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