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Auxiliary liver transplant for acute liver failure in children – a systematic review of case reports and case series

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Auxiliary liver transplant for acute liver failure in children – a systematic review of case reports and case series

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Abstract

Pediatric acute liver failure is a rare pathology, but it is associated with high morbidity and mortality. Its therapeutic approach is based on supporting the child's vital functions, while managing the many complications that come with it. Orthotopic transplant is the only treatment that improves survival, but it does so with the consequence of immunosuppression for life. Considering this, auxiliary liver transplant emerged as an improved approach. This technique aims to provide a graft that supports the function of the damaged native liver until its regeneration.

This review intends to provide insight about complications and outcomes of the auxiliary liver transplants that have already been performed. To reach this goal, we did a literature research using Medline, Embase, Scopus and Web of Science databases, and found 502 articles. After an initial selection based on titles and abstracts, we applied the following exclusion criteria: "follow-up time < 6 months", "not referring complications", and "not referring the immunosuppression scheme (double vs triple)". 14 articles were analyzed, which comprise 45 cases of pediatric acute liver failure treated with auxiliary liver transplant.

Among the 45 cases, there were 26.7% females and 73.3% males. Mean age was 8.7 years and mean follow-up time was 5.5 years. 75.6% had a double immunosuppression scheme and 24.4% a triple one. The main complications registered were infections, pancytopenia, vascular problems, biliary problems, and rejection. Mortality rate was 22.2%. The main cause of death was sepsis (70.0%). Immunosuppression withdrawal was possible in 68.6% of the survivors.

Auxiliary liver transplant is a safe option, with an acceptable rate of complications and mortality, whilst having the great advantage of allowing the discontinuation of immunosuppressors in the majority of the survivors.

Keywords: acute liver failure; pediatric; liver transplant; auxiliary liver transplant

Introduction

Acute liver failure (ALF) is defined as an acute liver dysfunction associated with hepatic encephalopathy, which develops within 8 weeks after the onset of symptoms.[1,2] However, in children, encephalopathy may not be present or may not be found until an advanced stage of the disease.[1–4] Because of this, several definitions have emerged for acute liver failure in pediatrics. The most recent is from the Pediatric Acute Liver Failure Study Group,[1] which used the following criteria for definition: (1) children with no known evidence of chronic liver disease; (2) biochemical evidence of acute liver injury; (3) hepatic-based coagulopathy, defined as a prothrombin time (PT) ≥ 15 seconds or international normalized ratio (INR) ≥ 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or a PT ≥ 20 seconds or INR ≥ 2.0 regardless of the presence or absence of clinical hepatic encephalopathy.

ALF is a rare disease with high morbidity and mortality.[3,5,6] Mortality at the pre-transplant era was around 70-95%.[7,8] After the introduction of transplantation as a treatment modality, the reported survival rate varies between 55.0 and 90.0%,[9] with a clear improvement over the years.

Most cases of ALF in children remain with unknown cause,[1,4,5] despite the most extensive investigations, using multiple diagnostic exams. Of the identified etiologies, the most common are viral infections (hepatitis A-E, herpes simplex virus (HSV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and varicella-zoster virus (VZV)), drugs and toxins intoxication, especially paracetamol. Other frequent etiologies are Wilson's disease, hemochromatosis, metabolic diseases (tyrosinemia, galactosemia, fructose intolerance, among others that are very rare), mitochondrial diseases, Reye's syndrome and autoimmune hepatitis.[1,5,10] The research for the cause of ALF should be directed according to the age of the child, since the etiologies are different depending on the age group.[1,11] In infants, metabolic diseases and infections (especially HSV) are the most common etiologies, and in older children and adolescents, autoimmune hepatitis, Wilsons's disease, paracetamol intoxication and infections are the main causes.[1,11]

The approach of patients with ALF is based on keeping them in an intensive care environment, where they can be monitored and closely followed.[2] They will need support of multiple organ functions, since liver failure will lead to failure of other organs and systems, such as increased intracranial pressure and cerebral edema, increased risk of infections, acute renal failure, cardiovascular abnormalities, and severe coagulopathy.[2] Transferring the patient to a hospital where liver transplant can be performed is a priority.[2,6]

Orthotopic liver transplantation (OLT) is the only treatment that has been proven to improve survival.[5,12] The decision to perform a transplant is not fully enlightened in the literature. There are several predictor criteria of prognosis and mortality validated for adults, and the most recognized are the King's College criteria.[12,13] But although they are often applied in pediatrics, there is no scientific evidence of the validity of their use.[12,13]

Before OLT, ALF had two possible outcomes, either the liver regenerated on its own or the patient would die.[14] With OLT, a third outcome is added.[14] However, children submitted to an OLT are bound to immunosuppression for life, with all the consequences that this entails, especially infections and

neoplasms. It is in this perspective that auxiliary liver transplantation (ALT) arises. ALT involves transplanting part or a whole liver, keeping the native liver in situ (in part or whole), with the aim of ensuring liver function (supported by the graft) until the native liver regenerates and can meet the patient's needs again.[15,16] Despite being an attractive alternative, it is not the standard of care.

The goal of this review is to understand whether the results of the ALT performed so far justify its choice as the preferred approach for patients who require liver transplantation due to ALF. We intend to verify the complications that arise in these patients, as well as mortality. Finally, we will evaluate how many patients stopped immunosuppression.

Methods

We performed a literature review using Medline, Embase, Scopus, and Web of Science databases, between October 2019 and October 2020. The search terms used were "acute liver failure", "auxiliary liver transplant" and the MESH term "Liver Failure, Acute". 502 articles were found (Figure 1).

The articles were selected by two independent investigators, without conflicts between them. After removing the duplicates, 253 articles remained. We made an initial selection based on titles and abstracts, using inclusion criteria, specifically being written in English or Portuguese, including cases of auxiliary liver transplantation due to acute liver failure, and patients' age being comprised between 0 and 18 years. 24 articles resulted from this selection.

Exclusion criteria defined priorly to the beginning of the research were applied to the 24 articles, and were the following: not mentioning complications, follow-up time less than 6 months and not mentioning the immunosuppression scheme used (double or triple). The analysis was performed in a total of 14 articles, which included 45 cases of acute liver failure treated with auxiliary liver transplantation.

From each article, demographic (age and gender), clinical (cause of acute liver failure, symptoms, laboratory values), surgical technique (hepatic lobe transplanted), complications, immunosuppression scheme, follow-up time and outcome (mortality, immunosuppression status) data were collected.

Methodological quality assessment of the articles was carried out using the proposed tool made by Murad et al.[17] We excluded question 4, 5 and 6, for being more related to drug adverse effects. All the articles had 4 or 5 points in the remaining 5 questions. Therefore, we recognize adequate methodological quality for all the reports and case series found.

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 26.0. All the studied variables were categorical (cause of acute liver failure, immunosuppression scheme, immunosuppression status, episodes of rejection, need for new transplant, and mortality). The association between categorical variables was assessed using chi-square or fisher's exact test. Statistical significance was set to $p < 0.05$.

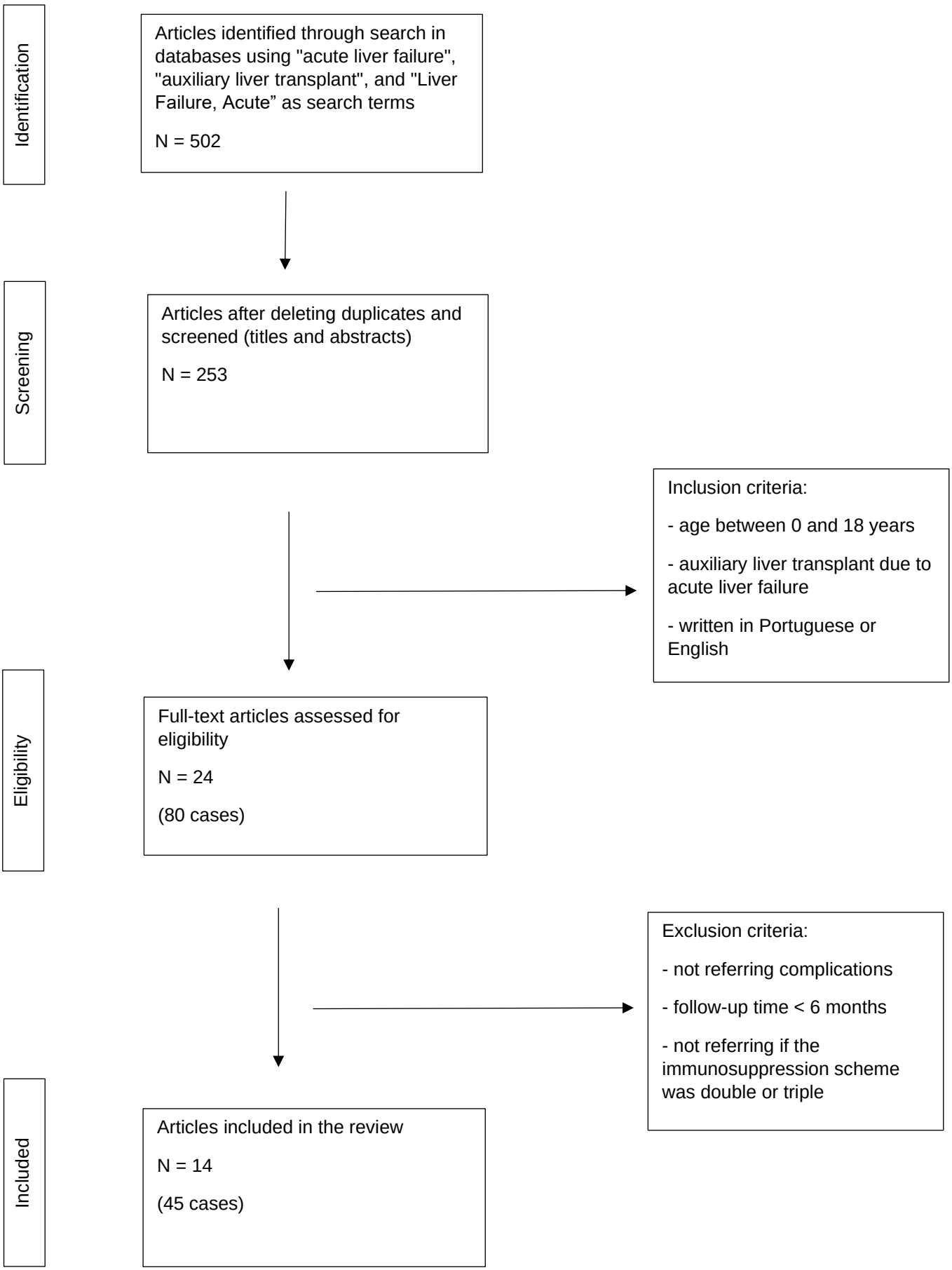

Figure 1. PRISMA flow diagram – representation of the literature research and article selection

Results

Our review included 14 articles[15,16,18-29], which involved 45 pediatric patients who underwent an auxiliary liver transplant, as treatment for acute liver failure.

Patient demographics and clinic

Of the 45 cases analyzed, 12 (26.7%) were female and 33 (73.3%) were male. The ages varied between 6 months and 17 years old, with a mean age of 8.7 years (Table 1).

In 1 case it was not referred if the patient was encephalopathic. In the remaining 44 cases, 40 (90.9%) patients had hepatic encephalopathy, of which 34 referred the encephalopathy grade (4 (11.8%) had grade II encephalopathy, 13 (38.2%) had grade III, and 17 (50.0%) had grade IV). It was not possible to obtain the coagulation parameters of the 4 (9.1%) patients who were not encephalopathic at the time of transplant.

Coagulation parameters were mentioned in 41 cases, by INR or PT values (in seconds or percentage of activity). 25 cases referred the INR, with a median value of 4.51 (range between 1.74 and 15). 7 cases referred the PT in seconds, with a mean value of 29.3 seconds (range between 16 and 56 seconds). 9 cases referred the prothrombin activity, with a mean value of 15% (range between 10 and 20%).

In most cases (n=28; 62.2%) the cause of acute liver failure remained unknown. The identified etiologies were hepatitis A (n=6; 13.3%), paracetamol intoxication (n=4; 8.9%), hepatotoxic mushrooms (n=2; 4.4%; 1 case by consumption of Amanita phalloides and another case with a non-reported species), Reye's syndrome (n=2; 4.4%), autoimmune hepatitis (n=1; 2.2%), hepatic toxicity secondary to isoniazid (n=1; 2.2%), and varicella-zoster virus infection (n=1; 2.2%).

The average follow-up time was 5.5 years, with a minimum time of 6 months and a maximum of 14 years. 10 (22.2%) patients died during follow-up.

Table 1. Patient demographics and clinical data of 45 cases of ALT for ALF

Case no.	Article	Sex	Age (yr)	Cause of ALF	Encephalopathy	Coagulopathy	Graft	IS scheme
1	Cortes et al.[18]	F	16	Paracetamol intoxication	Grade IV	INR 15	LLS + caudate	Double
2	Teomete et al.[19]	M	4	Idiopathic	Present	NR	LLS	Double
3	Shanmugam et al.[20]	F	2.5	Hepatitis A	Present	INR 6	LLS	Double
4	Çag et al.[21]	M	0.6	Reye's syndrome	Present	17% prothrombin activity	RL	Double
5	Faraj et al.[15]	14M 6F	14	Idiopathic	4 patients without HE 3 grade II 6 grade III 7 grade IV	INR 3.3	LL	Triple
6			2.25	Idiopathic		INR 2.4	LLS	Triple
7			4	Autoimmune hepatitis		INR 4.4	LLS	Triple
8			15	Idiopathic		INR 2.9	RL	Double
9			4	Mushrooms		INR 13	RL	Double
10			13	Idiopathic		INR 3.2	RL	Double
11			8	Idiopathic		INR 2.05	LLS	Double
12			15	Paracetamol intoxication		INR 1.8	RL	Double
13			2.5	Paracetamol intoxication		INR 3.4	RL	Double
14			8	Idiopathic		INR 4.7	LLS	Double
15			12	Idiopathic		INR 2.9	LLS	Double
16			15	Idiopathic		INR 7.5	WL	Double
17			13	Idiopathic		INR 5.5	RL	Double
18			11	Idiopathic		INR 2.2	RL	Double
19			14	Idiopathic		INR 1.83	LLS	Double
20			12	Idiopathic		INR 2.5	RL	Double
21			16	Idiopathic		INR 9.31	LL	Double
22			1	Idiopathic		INR 3.29	LLS	Double
23			2.5	Idiopathic		INR 2.3	LLS	Double
24			12	Idiopathic		INR 5.3	LL	Double
25	Cillo et al.[22]	M	10	Isoniazid	Grade III	INR 1.74	LLS	Double
26	Kasahara et al.[23]	M	1.8	Idiopathic	Present	NR	LLS	Double
27		M	1.5	Idiopathic	Present	NR	LLS	Double

28	Boudjema et al.[24]	M	4	Hepatitis A	Grade IV	10% prothrombin activity	LLS	Triple
29		M	12	Hepatitis A	Grade IV	17% prothrombin activity	LL	Triple
30		M	15	Hepatitis A	Grade IV	12% prothrombin activity	LL	Triple
31		M	15	Idiopathic	Grade IV	20% prothrombin activity	RL	Triple
32		M	0.6	Reye's syndrome	Grade IV	17% prothrombin activity	RL	Triple
33		F	14	Paracetamol intoxication	Grade IV	18% prothrombin activity	RL	Triple
34	Rodeck et al.[16]	M	5	Idiopathic	Grade II	14% prothrombin activity	LLS	Double
35		M	6	Idiopathic	Grade III	14% prothrombin activity	LLS	Double
36	Rosenthal et al.[25]	F	13	Mushrooms (Amanita phalloides)	Present	PT 56 seconds	LL	Triple
37	McCarthy et al.[26]	M	14	Idiopathic	Grade III	INR 3.2	LL	Triple
38	Rela et al.[27]	F	3	Hepatitis A	NR	NR	LLS	Double
39	Sudan et al.[28]	F	6	VZV	Grade IV	PT 23 seconds	LLS	Double
40		M	6	Idiopathic	Grade IV	PT 33 seconds	LLS	Double
41		M	8	Idiopathic	Grade III	PT 16 seconds	LLS	Double
42		M	10	Idiopathic	Grade IV	PT 42 seconds	LL	Double
43		M	9	Hepatitis A	Grade III	PT 16 seconds	WL	Double
44		M	17	Idiopathic	Grade III	PT 19 seconds	WL	Double
45	Chartier et al.[29]	M	5	Idiopathic	Grade III	INR 3.15	LLS	Double

ALT – auxiliary liver transplant; ALF – acute liver failure; VZV – varicella-zoster virus; IS – immunosuppression; LL – left lobe; LLS – left lateral segment; RL – right lobe; WL – whole liver; HE – hepatic encephalopathy; PT – prothrombin time; yr – years

Surgical technique

More than half (n=30; 66.7%) of the patients received left lobes, of which 21 were left lateral segments, 8 were left lobes and 1 was a left lateral segment and caudate lobe; 12 (26.7%) received right lobes; and 3 (6.7%) received whole livers. All grafts (n=45; 100%) were placed in orthotopic position.

Only 8 articles refer the origin of the graft, of which 4 were from living donors and 4 were from cadavers. 7 cases refer that the donor and the recipient had compatible blood groups.

The anastomosis of the hepatic veins was made with a piggyback technique for right lobe grafts, with anastomosis of the inferior vena cava of the donor and the recipient. In left lobe grafts, the direct anastomosis between the left hepatic vein of the donor and the recipient was the chosen option.

The anastomosis of the portal vein was done through direct anastomosis in all cases, varying only the use of the main, left, or right branches. In 2 patients portal flow modulation techniques were used, recurring to absorbable ligatures.[15,26]

Of the 45 cases, 40 reported the technique used for arterial reconstruction. In most cases (n=34; 85.0%) a graft from the donor's iliac artery was placed between the infrarenal aorta of the recipient and the hepatic artery of the donor (common, left or right, depending on the cases). In the remaining 6 (15.0%) patients arterial anastomoses were direct, without grafts.

The technique used for biliary reconstruction is referred in 38 cases. In most cases (n=35; 92.1%) it was done through hepaticojejunostomy in Roux-en-Y. In 2 (5.3%) patients, a choledocho-cholecystostomy was initially performed, however, due to complications (clot obstruction and hemorrhage), it was converted into hepaticojejunostomy.[16] In 1 (2.6%) patient a duct-to-duct biliary anastomosis was performed.[28]

Primary closure of the abdomen was not possible in 2 patients.[16]

The cold ischemia time is referred in 13 of the 45 cases. Mean cold ischemia time was 9 hours and 54 minutes (range between 7 hours and 18 hours and 58 minutes).

Complications

The most frequent complications were infections, and they were also the main cause of mortality. 7 patients died due to sepsis, 1 died due to herpetic bronchiolitis and 1 died following peritonitis. The only non-infection-related death was of neurological origin, due to cerebral edema.

In addition to infections, there were also hematologic, pulmonary, hemorrhagic, renal, neurologic, vascular, and biliary complications, among others (Table 2). The number of re-operations was not possible to obtain from the analyzed cases. None of the cases mentioned intra-operative complications.

Pancytopenia was registered in 9 (20.0%) patients. In the majority it was already present prior to transplantation. Of the 10 patients who died, 4 (40.0%) had pancytopenia, and died due to infections.

There were 21 episodes of rejection, in 13 (28.9%) patients. 20 were acute rejections and 1 chronic. Acute rejection episodes were managed with corticosteroid therapy in 18 cases, and with anti-thymoglobulin in 2, which were successful in 19 of the 20 cases (95.0%). In 1 case of acute rejection

medical therapy was not enough, and an OLT was required. In the episode of chronic rejection, an OLT was also necessary.

A re-transplant was necessary in 6 (13.3%) patients. In addition to the 2 patients who had new transplants due to acute (does not refer time of re-transplant) and chronic (15 months post-transplant) rejection episodes, the other causes for new transplant were graft ischemia due to sepsis (day 40 post-transplant), hepatic artery thrombosis (day 22 post-transplant), hepatic vein thrombosis (day 15 post-transplant), and recurrent hepatitis (day 34 post-transplant). Of the new transplants, only the one due to hepatic vein thrombosis was an ALT.

Table 2. Complications of 45 cases of ALT

Complications		No.
Infection	Sepsis	8
	CMV	6
	EBV	3
	Rotavirus	1
	Herpetic bronchiolitis	1
	Peritonitis	1
	Abscesses	2
Hematologic	Pancytopenia	9
	PTLD	1
Vascular	Hepatic artery thrombosis	1
	Hepatic vein thrombosis	1
	Portal vein thrombosis	1
	Reverse portal flow	1
	Portal flow steal	1
Biliary	Strictures	3
	Obstruction	1
	Leak/Perforation	3
	Bilioma	1
Pulmonary	Pleural effusion	6
	Pneumothorax	1
	Empyema	2
Hemorrhagic	Intra-abdominal hemorrhage	11
Neurologic	Convulsions	1
	Cerebral edema	1
	Psychomotor developmental delay	1
Renal	Renal failure	4
Graft dysfunction		1
Recurrent hepatitis		1
Rejection	Acute	20
	Chronic	1
Acute pancreatitis		1
Acanthosis nigricans		1
Bowel perforation		3
Skin rash		1

ALT – auxiliary liver transplant; CMV – cytomegalovirus; EBV – Epstein-Barr virus; PTLD – post-transplant lymphoproliferative disease

Note: some patients had more than one complication.

Immunosuppression scheme

The majority (n=34; 75.6%) of the patients had a double immunosuppression scheme, and the remaining (n=11; 24.4%) had a triple scheme (Table 3).

Of the 10 patients who died, 9 (90.0.%) did a double scheme and only 1 (10.0%) did a triple. There is no statistically significant association between the use of a double or a triple scheme and mortality (p=0.409).

Of the 8 patients who had rejection episodes, 6 (75.0%) were doing double and 2 (25.0%) were doing triple immunosuppression schemes. There is no statistically significant association between the type of scheme and the occurrence of rejection (p=1.000).

A total of 6 new transplants were performed, of which 4 (66.7%) were done in patients doing a double scheme and 2 (33.3%) in patients with a triple scheme. There is no statistically significant association between the scheme used and the need for new transplantation (p=0.624).

Table 3. Immunosuppression scheme of 45 cases of ALT

Immunosuppression scheme	Drugs	No. of cases
Double	tacrolimus + corticosteroid	24 (61.5%)
Double	cyclosporine + corticosteroid	9 (23.1%)
Triple	cyclosporine + corticosteroid + azathioprine	4 (10.3%)
Double	tacrolimus + azathioprine	1 (2.6%)
Triple	cyclosporine + corticosteroid + mycophenolate	1 (2.6%)

ALT – auxiliary liver transplant

Note: Only 39 of the 45 cases referred the specific drugs used. In the remaining 6 cases they only refer that they used a triple scheme, with either tacrolimus or cyclosporine, plus corticosteroid and azathioprine.

Post-transplant follow-up

Not all articles addressed the follow-up imaging protocol. Faraj et al.[15] reported native liver biopsy in the first week, and then CT scan and hepatobiliary scintigraphy every 3 months up to 1 year, and yearly afterwards. McCarthy et al.[26] refers doppler ultrasound performed 2 times per week during the first 2 weeks, and CT scan and hepatobiliary scintigraphy at 2 weeks, and at 3 months post-transplant. Boudjema et al.[24] reported daily doppler ultrasound in the first week, and then weekly until the first month, hepatobiliary scintigraphy at 2 weeks post-transplant and then monthly, and native liver and graft biopsies every week until the first month, and then monthly. Sudan et al.[28] referred daily doppler ultrasound during the first week and then monthly. Biopsies of the graft were performed when a rejection episode was suspected.

Complete liver regeneration was documented by biopsy in 25 (55.6%) of the 45 patients, and partial regeneration in 8 (17.8%). 2 (4.4%) patients had CT scans demonstrating increased volume of the native

liver, however there was no biopsy to document regeneration. The remaining 10 (20.0%) patients had no regeneration, of which 6 died, and 4 were alive and maintaining immunosuppression (2 due to OLT). Of the 10 patients who died, 6 had no regeneration, 3 had partial and 1 had complete native liver regeneration.

Immunosuppression withdrawal

Complete cessation of immunosuppression was possible in 24 patients, corresponding to 53.3% of all patients and 68.6% of the survivors. 4 (8.9%) patients were in the process of immunosuppression withdrawal at the time of the publication of the case reports, and 7 (15.6%) maintained immunosuppression at the time of the publications. (Table 4)

Of the 24 patients that have completely stopped immunosuppression, 3 do not report when they did so. Of the remaining 21, at 6 months, 3 (14.3%) had already stopped. After 1 year, 6 (28.6%) patients stopped immunosuppression, and after 2 years, a total of 15 (71.4%) patients are completely free of immunosuppression.

There is no statistically significant association between any cause of acute liver failure and stopping immunosuppression (all p values > 0.05).

Of the 24 patients who stopped immunosuppression, in 6 (25.0%) the graft was surgically removed, in 16 (66.7%) the graft was left in situ and showed signs of atrophy in follow-up CT scans, and in 2 (8.3%) the graft completely disappeared after stopping immunosuppression.

Table 4. Follow-up and immunosuppression status of 45 cases of ALT

Case No.	Article	IS status	IS status details	Time of IS stop (years)	Total FU (years)
36	Rosenthal et al.[25]	Stopped	--	0.02	0.75
34	Rodeck et al.[16]	Stopped	--	0.04	4
24	Faraj et al.[15]	Stopped	--	0.33	2
12	Faraj et al.[15]	Stopped	--	0.58	10
45	Chartier et al.[29]	Stopped	--	0.58	2.5
4	Çag et al.[21]	Stopped	--	0.83	14
37	McCarthy et al.[26]	Stopped	--	1.17	2
43	Sudan et al.[28]	Stopped	--	1.17	1.17
20	Faraj et al.[15]	Stopped	--	1.25	4

39	Sudan et al.[28]	Stopped	--	1.25	1.25
6	Faraj et al.[15]	Stopped	--	1.42	11
11	Faraj et al.[15]	Stopped	--	1.42	10
5	Faraj et al.[15]	Stopped	--	1.83	14
19	Faraj et al.[15]	Stopped	--	1.92	5
2	Teomete et al.[19]	Stopped	--	2.00	6
3	Shanmugam et al.[20]	Stopped	--	2.50	2.5
40	Sudan et al.[28]	Stopped	--	3.00	3
22	Faraj et al.[15]	Stopped	--	3.33	3
13	Faraj et al.[15]	Stopped	--	3.42	9
9	Faraj et al.[15]	Stopped	--	8.25	11
7	Faraj et al.[15]	Stopped	--	8.83	11.75
1	Cortes et al.[18]	Maintains IS	6 months FU	NA	0.5
8	Faraj et al.[15]	Death	Death at day 8 post-transplant	NA	NA
10	Faraj et al.[15]	Maintains IS	IS weaning at 132 months post-transplant	NA	11
14	Faraj et al.[15]	Maintains IS	Maintains IS due to OLT	NA	NR
15	Faraj et al.[15]	Death	Death at day 9 post-transplant	NA	NA
16	Faraj et al.[15]	Maintains IS	Without evidence of native liver regeneration	NA	NR
17	Faraj et al.[15]	Maintains IS	IS weaning at 81 months post-transplant	NA	6.75
18	Faraj et al.[15]	Maintains IS	Without evidence of native liver regeneration	NA	NR
21	Faraj et al.[15]	Death	Death at day 52 post-transplant	NA	NA
23	Faraj et al.[15]	Maintains IS	IS weaning at 34 months post-transplant	NA	2.8
25	Cillo et al.[22]	Maintains IS	Maintains IS due to OLT	NA	2
26	Kasahara et al.[23]	Death	Death at day 55 post-transplant	NA	NA

27	Kasahara et al.[23]	Death	Death at day 144 post-transplant	NA	NA
30	Boudjema et al.[24]	Death	Death at 1,5 months post-transplant	NA	NA
31	Boudjema et al.[24]	Maintains IS	Maintains IS due to OLT	NA	5
33	Boudjema et al.[24]	Maintains IS	IS weaning at 2 years post-transplant	NA	2
35	Rodeck et al.[16]	Death	Death at 2 months post-transplant	NA	NA
38	Rela et al.[27]	Maintains IS	6 months FU	NA	0.5
41	Sudan et al.[28]	Death	Death at day 103 post-transplant	NA	NA
42	Sudan et al.[28]	Death	Death at day 43 post-transplant	NA	NA
44	Sudan et al.[28]	Death	Death at day 150 post-transplant	NA	NA
28	Boudjema et al.[24]	Stopped	--	NR	8
29	Boudjema et al.[24]	Stopped	--	NR	7
32	Boudjema et al.[24]	Stopped	--	NR	5

ALT – auxiliary liver transplant; IS – immunosuppression; NA – non applicable; NR – not referred; FU – follow-up; OLT – orthotopic liver transplant

Discussion

Pediatric ALF is a rare disease, but it leads to substantial morbidity and mortality.[3,5,6] Definitive treatment in most cases involves liver transplantation. The introduction of OLT as a therapeutic option for ALF has clearly improved the survival of these patients.[5,12] Despite the undeniable advantages that OLT has, it does not do so innocuously, leading to the need for long-term immunosuppression. Taylor et al. concluded, in a review about the quality of life of children undergoing OLT, that it negatively affects them in physical, psychological, social, family functioning and general well-being parameters.[30] Parmar et al. postulated that adherence to therapy is one of the predictors of poorer quality of life after transplantation.[31] It is in this scenario that ALT stands out as an alternative to OLT.

The first reported case of a successful ALT for the treatment of ALF was in 1991, by Gubernatis et al.[32] Since then, several cases have been published, including in children. The main purpose of ALT is to stop immunosuppression after regeneration of the native liver.[15,16] Lodge et al. compared quality of life among adults submitted to ALT and OLT, concluding that in the ALT group patients obtained higher scores in the SF36 quality of life questionnaire, while maintaining a normal liver function.[33] There is a lack of such studies in children, but they would be important, since quality of life is the major improvement from OLT to ALT.

ALT's technical difficulties are one of the reasons why many centers continue to use OLT as their preferred approach. Regarding children, a key factor is choosing the volume of liver to transplant. We found that the left lobe is preferably used, since, due to its smaller dimensions, it is easier to fit in orthotopic location. In addition, maintaining the native right lobe allows for a larger native liver, which, after regeneration, will more easily support the metabolic functions of the child, after atrophy or excision of the graft. The use of CT scans of the donor and the recipient, prior to transplant, seems to be a good approach in order to calculate both hepatic volumes and thus decide on the ideal volume of liver to transplant. This avoids liver failure due to insufficient hepatic volume after ALT. Additionally, it prevents from having excessive hepatic volume and thus not being able to close the abdomen.

None of the cases evaluated in our review were in heterotopic position. The orthotopic position is chosen in most cases reported in the literature, both in adults and in children. This is because there were many complications with the heterotopic position.[32,34] When a whole liver or a right lobe is used, the graft is implanted with the inferior vena cava under the native liver, and here the caval pressure is very high, consequently compromising venous outflow.[32,34] The left lobe is implanted onto the inferior vena cava under the left lateral segment, in a position that leads to hepatic vein stretch, also affecting venous outflow.[34] Portal flow is shared between the graft and the native liver, and since the graft suffers venous congestion due to reduced venous outflow, preferential portal flow is to the native liver, causing graft disfunction.[24,32,34] Also, keeping the native liver intact will create a lack of space in the abdomen, with closure and wound healing problems, particularly in small children.[34]

Another technical aspect addressed in 2 cases was the modulation of the portal flow.[15,26] Portal flow steal corresponds to the phenomenon of preferential flow to the liver with the lowest resistance.[35] In a case of orthotopic ALT, portal flow is shared between the native liver and the graft. Usually, the graft has the lowest resistance in an early phase, since the native liver is injured, and thus has extensive necrosis and edema.[35] This is the ideal scenario. But in some cases, the graft suffers from ischemic-reperfusion injury, inadequate outflow, or is small-for-size. Consequently, its resistance increases, with the risk of exceeding the native liver's, resulting in portal flow steal to the native liver, with graft failure. There are techniques to avoid this, such as portal vein ligation or banding.[35] Rela et al. suggested that portal banding is the safest option, and states that it is almost always required in cases of ALT for metabolic liver diseases, and only rarely in ALF.[35]

The disproportional caliber between the vessels of the donor and the recipient is another difficulty that can arise in a scenario of transplantation in children, and ALT is no exception. Rela et al. suggested an approach to this situation, which avoids the use of a graft.[27] Through the anastomosis of the left hepatic artery of the donor with the common hepatic artery of the recipient, it was possible to obtain compatible calibers, and thus avoid the use of a graft, facilitating the surgical technique.[27]

The immunosuppression scheme does not differ from that used in an OLT. Calcineurin inhibitors, including cyclosporine and tacrolimus, and corticosteroids are the basis of treatment. Other immunosuppressors such as mycophenolate mofetil or azathioprine are sometimes associated. We found that double schemes were used in most cases, and preferably with tacrolimus rather than cyclosporine.

Post-transplant imaging evaluation is an important part in the follow-up of these patients. In our review, two-thirds of the patients who stopped immunosuppression did so up to 2 years after the transplant. Therefore, it is necessary a tighter follow-up in this period. The follow-up protocol is variable from center to center, however it is common to use doppler ultrasonography regularly in the first month, as well as CT scan and hepatobiliary scintigraphy afterwards. Regular first month doppler ultrasonography allows early detection of the most feared complications, namely vascular, such as hepatic artery and vein thrombosis, or portal flow steal, giving the chance to deal with them before their consequences are irreversible. CT scan and hepatobiliary scintigraphy will provide information about evolution of both native liver and graft, regarding volume and function, thus allowing to choose the best moment to start immunosuppression withdrawal.

Regarding the native liver, biopsies should be done according to the results of CT scan and hepatobiliary scintigraphy. More specifically, when these exams suggest that it has increased in volume and recovered function, the biopsy should confirm this before making the decision to suspend immunosuppression. Graft biopsies are recommended when rejection is suspected.

In our review, we found that it was possible to suspend immunosuppression in 68.6% of survivors. Patients in which the ALT goal was not met, and therefore maintained long-term immunosuppression, were not harmed in comparison to patients who undergo OLT, they simply are equal. So, not being able to stop immunosuppressors in all patients is not a valid critique of this alternative approach.

Whether or not to remove the graft after native liver regeneration is also a question that arises with ALT. In our review, there were 2 cases of complete disappearance of the graft, and 16 cases of graft atrophy, all without related complications. In 6 patients it was decided to remove the graft. This is relevant since, after stopping immunosuppressors, the graft may suffer necrosis, and thus affect native liver survival.[24] On the other hand, its removal represents the need for another surgery, with the risk of native liver lesion.[24] The decision must be made in a case-by-case basis, considering that by slowly tapering the immunosuppressors it is possible to maintain the graft and let it atrophy on its own, without a substantial risk of complications.[20]

The mortality rate in our review was 22.2%, which is comparable to what is observed in groups submitted to OLT. Baliga et al. registered 26.0% mortality rate after performing OLT in 141 patients with ALF, and the main cause of death was multiorgan failure (19.4%).[2] Farmer et al. referred a 10-year mortality of 27.0% after OLT for ALF, and the main cause of death was multisystem organ failure/sepsis (69.0%).[9] In both reports, the causes of death matched what we found in our review.

In the cases analyzed in the present review, we can observe a high rate of complications, with emphasis on vascular complications, which may jeopardize the survival of the graft and even the patient. 2.2% of the patients had hepatic artery thrombosis (HAT), with the need for new transplant. After OLT, Farmer et al. and Weiner et al. reported an incidence of 5.7%[9] and 7.7%[36] of HAT, respectively. We found an 46.7% incidence of rejection episodes in our review. It was one of the most frequent complications, comparably to what was registered by Farmer et al. and Weiner et al. in OLT groups, with 39.0% acute rejection episodes and 8.2% chronic rejections[9] and 30.8% acute rejection episodes[36], respectively.

Pancytopenia is common after ALF. Its severity ranges from a mild bone marrow suppression to aplastic anemia (pancytopenia associated with medullary hypoplasia). It is a complex problem since it is associated with subsequent mortality due to infections. In our review, 20.0% of the patients had pancytopenia. Farmer et al. reported an incidence of aplastic anemia of 11.5%[9] and Weiner et al. reported 15.4%[36]. Pancytopenia is present before the transplant in most cases, so it is not a problem related to the transplant, but something that may compromise the post-transplant survival. The general management involves anti-thymocyte and anti-lymphocyte globulins, cyclosporine, and corticosteroids, yet in some cases bone marrow transplant is necessary.[37,38]

Weiner et al. reported a large cohort of patients submitted to ALT (not included in our review for not stating the immunosuppression scheme used).[36] They also compared the results of ALT to OLT, and concluded that although ALT had better survival rates, it was not a statistically significant difference.[36]

Since ALT is not the established therapeutic for acute liver failure, there is a lack of published studies about it. In this review, we only found case reports and case series. That represents a low level of scientific evidence. However, in a rare pathology, and when investigating a new treatment, this type of publications may represent an important tool, allowing for a systematic review and synthesis, and thus providing an evidence-based insight.[17]

The follow-up of some patients was not very prolonged at the time the case reports were published, so some information remains indefinite, since we do not know if those who maintained immunosuppression will be able to stop it, and if in the subsequent follow-up any complications would have emerged, especially deaths.

We also consider the possibility of publication bias, with a preponderant tendency to publish cases with favorable results. Therefore, we suggest conducting studies in centers that already have some experience in performing ALT, and comparing it to OLT. We also suggest the need for further studies comparing the quality of life of patients who have been submitted to ALT or OLT, since a better health-related and even general quality of life is the biggest difference between both approaches.

Conclusion

Children are a particularly attractive group for performing ALT, since their survival is predictably long and, consequently they especially benefit from the possibility of stopping immunosuppression, and thus avoiding its long-term complications.

We verified that there are serious complications associated with ALT, with emphasis to infections, vascular problems, rejection episodes, and pancytopenia, but they also occur with OLT. Mortality rate after ALT is not insignificant, however it is similar to what happens after OLT.

In conclusion, ALT is a safe option, with an acceptable rate of complications and mortality. It has the great advantage of cessation of immunosuppression in the majority (68.6%) of the survivors.

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