MINI REVIEW

Acute liver failure in children

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Summary The management of children with acute liver failure mandates a multidisciplinary approach and intense monitoring. In recent years, considerable progress has been made in developing specific and supportive medical measures, but clinical studies have mainly concerned adult patients. There are no specific medical therapies, except for a few metabolic diseases presenting with acute liver failure. Liver transplantation still remains the only definitive therapy in most instances. Recent clinical studies suggest that hepatocyte transplantation may be useful for bridging patients to liver transplantation, for providing metabolic support during liver failure and for replacing liver transplantation in certain metabolic liver diseases.

Introduction

Acute Liver Failure (ALF) is a rare but potentially devastating process that often leads to urgent liver transplantation when it is believed that liver regeneration is unlikely [1–3]. Its true incidence in the pediatric population is unknown but ALF accounts for 10 to 15% of all pediatric liver transplantsations [1–3]. Exhaustive and up-to-date reviews have been published in the pediatric literature [4–10]. In neonates and infants, metabolic diseases are the main cause of ALF for which specific medical therapies may in some instances preclude the need for liver transplantation [1,9]. In older children, viruses (especially virus A), drug-induced hepatotoxicity and autoimmune hepatitis are the most common identified causes of ALF, but the cause for ALF still remains undetermined in a large proportion of children [3,8,11].

Consensual recommendations regarding management of ALF in adults have been published but these remain scarce in pediatrics [6,7,9]. The purpose of this mini-review is to focus on the specificities of ALF in children, i.e. recent advances in the definition, emerging causes, clinical presentation and discuss controversies in its management. Specific medical therapies available for a few metabolic diseases presenting with ALF in infancy will be discussed.

ALF is a multi-systemic disorder

ALF has been originally described as a severe liver injury occurring in a patient without a previous history of liver disease who develops encephalopathy within 8 weeks of the initial symptoms. This definition appears inadequate in children and infants who may present with ALF revealing an
Asymptomatic underlying metabolic disease involving the liver, who may present with encephalopathy unrelated to ALF or may not develop encephalopathy in the course of ALF despite an unfavorable outcome. Therefore, ALF is defined in children as a multi-systemic disorder in which severe impairment of liver function, with or without encephalopathy, occurs in a child with no recognized underlying chronic liver disease. This definition carries several new concepts. First, ALF is not one disease involving the liver but rather one consequence of multiple organ dysfunction. Second, children with ALF, especially newborns and infants, may present without any sign of hepatic encephalopathy. Third, ALF in children may reveal an underlying chronic liver disease.

While the cause of ALF still remains indeterminate in a large number of cases, new causes of ALF have been recognized.

Causes of ALF can be schematically grouped into six categories: metabolic, infective, toxic, autoimmune, vascular, and malignancy-induced ALF [3,9,12–14]. However, the cause of ALF remains indeterminate in 18 to 47% of cases, depending upon the exhaustiveness of the work up screening [12–14]. This large difference could be explained by a center effect, 18% being reported by a single center, and 47% by a consortium of centers (Table 1). The most common causes in neonates and infants are metabolic diseases, whereas viral hepatitis and drug-induced ALF are predominant in children [1,3,9,12–14]. Hepatitis A or E are the main causes of ALF in countries where these viruses are endemic. With extensive metabolic and viral screening, the rate of undetermined causes of ALF has, however, decreased. Herpes hominis type 6 virus induced hepatitis and mitochondrial chain respiratory disorders have been recently recognized as causes of ALF in children [1,9,15–17].

Early identification of the cause of ALF is of paramount importance for different reasons. In some cases, ALF may be reversed with immediate initiation of specific therapies. This is principally the case of metabolic diseases (such as galactosemia, fructosemia, and hereditary tyrosinemia type 1, and Wilson’s disease), and of autoimmune hepatitis or acetaminophen-induced-ALF [1,15]. On the other hand, some diseases not cured with liver transplantation (such as leukemia, Reye syndrome and mitochondrial respiratory chain disorders with neurological involvement) are an absolute contraindication to transplantation. Even more difficult, is the selection of children who may recover spontaneously without transplantation (Fig. 1).

Specificities of ALF in children

Clinical presentation
Clinical symptoms vary according to the cause of ALF and the age of the child [4–10]. In the newborn, symptoms are nonspecific, sometimes only related to an altered general condition, failure to thrive, and vomiting. In infants or older children, there is usually a prodromic phase of malaise, nausea, and anorexia. Most often jaundice develops subsequently. However, jaundice may not develop (especially when the cause of ALF is a metabolic disease or toxic) and clinical diagnosis of ALF becomes much more difficult.

Hemorrhage may occur spontaneously, and involves mainly the digestive tract. Severe hypoglycemia, that may lead to seizures, is frequently noted as a result of impaired glycogen storage, decreased gluconeogenesis, hyperinsulinism and increased glucose use [4–10]. Hepatic encephalopathy may be absent in spite of severe liver dysfunction or develop within a few hours to days or weeks from onset of liver failure. In the newborn, signs of hepatic encephalopathy are not specific and may be limited to behavioral changes, preceding the onset a coma. In older children, signs and symptoms are identical to those in adults but the classical symptoms of asterixis, tremors, and fetor hepaticus are often absent. Hepatic encephalopathy has been classified into four grades [3]. Five types of electroencephalographic pattern have been described and have a prognostic value [3].

Laboratory tests
These are required urgently, and include liver-specific tests to assess the degree of liver injury and function, standard biochemical tests to assess haematological, renal, and electrolyte abnormalities and specific laboratory screening to identify the different causes of ALF in children according to age [4–10].

Medical management in the pediatric intensive care unit: current status and controversies
ALF is a challenging medical condition that requires intensive care management to prevent or treat major complications (as hepatorenal syndrome, encephalopathy, brain oedema, intracranial hypertension, bleeding, infections, and multi-system organ failure) with the hope that the liver function will recover or that liver transplantation can be performed. Management of ALF should be performed in a pediatric ICU within a liver transplantation center, where continuous monitoring and multidisciplinary expertise are available [6–10,18,19].

The child should be admitted to the ICU as soon as he/she shows signs of clinical or electric hepatic encephalopathy, and/or if co-factor V activity decreases below 50% of normal or if the prothrombin time activity decreases to below 50% of normal, and/or other organ dysfunctions occur [6–10,19].

General Supportive Care
The mainstay of medical care is to minimize ALF complications and to limit additional morbidity [19]. One key to managing patients with ALF is avoidance of administering drugs that have no proven beneficial effect.

Metabolic Disorders
Continuous glucose administration is necessary and often requires a central venous line to deliver high-concentration glucose in a smaller volume. Phosphate, magnesium, and potassium supplementation is often required. Enteral nutrition (gastric, duodenal) is recommended (stress ulcer
<table>
<thead>
<tr>
<th>Cause</th>
<th>BICETRE (1986-2006) Monocenter study</th>
<th>PALF&lt;sup&gt;a&lt;/sup&gt; (1999-2008) Multicenter study&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Infants &lt; 1 yr &lt;br&gt; (&lt;em&gt;n&lt;/em&gt; = 107)&lt;br&gt; ≥ 1 yr &lt;br&gt; (&lt;em&gt;n&lt;/em&gt; = 128)&lt;br&gt; Total &lt;br&gt; (&lt;em&gt;n&lt;/em&gt; = 235)</td>
<td>Infants &lt; 7 months &lt;br&gt; (&lt;em&gt;n&lt;/em&gt; = 149)&lt;br&gt; ≥ 1 yr ≥ 7 months &lt;br&gt; (&lt;em&gt;n&lt;/em&gt; = 554)&lt;br&gt; Total &lt;br&gt; (&lt;em&gt;n&lt;/em&gt; = 703)</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactosemia, tyrosinemia,</td>
<td>54 (50%)</td>
<td>27 (18%)</td>
</tr>
<tr>
<td>hemochromatosis, Wilson disease,</td>
<td>27 (21%)</td>
<td>41 (7%)</td>
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<tr>
<td>Reye syndrome, fatty-acid</td>
<td>81 (34%)</td>
<td>68 (10%)</td>
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<td>oxidation disorder, mitochondrial</td>
<td></td>
<td></td>
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<tr>
<td>cytopathy</td>
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<tr>
<td>Infectious</td>
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<tr>
<td>HAV, HBV, herpes simplex, HHV6,</td>
<td>19 (18%)</td>
<td>20 (13%)</td>
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<tr>
<td>EBV, enterovirus, adenovirus,</td>
<td>33 (26%)</td>
<td>25 (4%)</td>
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<tr>
<td>parvovirus B19, Dengue fever.</td>
<td>52 (22%)</td>
<td>45 (6%)</td>
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<td>Undetermined</td>
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<tr>
<td>Acetaminophen, sulfamide, sodium</td>
<td>10 (9%)</td>
<td>61 (49%)</td>
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<tr>
<td>valproate, sulfasalazine,</td>
<td>32 (25%)</td>
<td>268 (48%)</td>
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<tr>
<td>halothane, amanita phalloides,</td>
<td>42 (18%)</td>
<td>329 (47%)</td>
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<tr>
<td>chemotherapy</td>
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<td></td>
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<tr>
<td>Autoimmune</td>
<td></td>
<td></td>
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<tr>
<td>Giant cell hepatitis, LKM</td>
<td>8 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>or LC1 autoimmune hepatitis</td>
<td>7 (5%)</td>
<td>48 (9%)</td>
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<td>Hematologic diseases</td>
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<tr>
<td>familial lymphohistiocytosis,</td>
<td>7 (7%)</td>
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<td>macrophage activation syndrome,</td>
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<tr>
<td>leukemia</td>
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<td></td>
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<tr>
<td>Vascular diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veno-occlusive disease, Budd</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Chiari syndrome, Ischemic liver</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>38 (25%)</td>
<td>64 (12%)</td>
</tr>
</tbody>
</table>

HAV: hepatitis A virus; HBV: hepatitis B virus; HHV: human herpes virus; EBV: Epstein-Barr virus; LKM: liver kidney microsome; LC1: liver cytosol 1.

<sup>a</sup> PALF: Pediatric Acute Liver failure Study Group adapted from [11–12].

<sup>b</sup> The consortium consists of 20 active pediatric liver transplant centers.
Hemorrhage and Digestive Tract Bleeding

In the absence of bleeding, it is not recommended to correct the coagulopathy because doing so will interfere with the evaluation of liver function (Factor V activity, prothrombin time). Exceptions include the need for an invasive procedure and the occurrence of active bleeding. Procedures can be performed under cover of platelet administration in cases of profound thrombopenia and recombinant activated factor VII [19]. Administration of fresh frozen plasma is hampered by the risk of volume and protein overload and should be thoughtfully evaluated. Vitamin K is routinely administered intravenously. Sucralfate is preferred to histamine H2 antagonists to prevent gastric bleeding.

Cardiopulmonary Failure

Hypovolemia may be present at admission, but fluid resuscitation should be monitored carefully because of the high risk of volume overload, especially if renal failure occurs. Pulmonary edema is an underestimated complication of ALF, which may be related to the development of central neurogenic pulmonary edema coupled with fluid overload (syndrome of inappropriate antidiuretic hormone, hyperaldosteronism). In addition, ventilation-perfusion mismatch (loss of vasoconstrictive hypoxia mechanism due to circulating vasoactive substances) occurs and results in severe refractory hypoxemia. The hemodynamic profile of ALF patients is characterized by cardiac hyperkinesia with elevated cardiac indices and low systemic vascular resistances [20].

Vasoplegia with hypotension or haemodynamic instability despite adequate fluid expansion will generally respond to α-adrenergic agents (norepinephrine [noradrenalin]). As adrenal insufficiency can occur in ALF, hydrocortisone may be beneficial once hemodynamic instability occurs. Although myocardial dysfunction is unusual, echocardiographic examination may help to appreciate pulmonary pressure, preload condition, and contractility. Respiratory failure, especially severe hypoxemia, may occur and require mechanical ventilation.

Renal Failure

Every effort should be made to protect the renal function, maintaining adequate renal perfusion and avoiding nephrotoxic drugs. Hepatorenal syndrome is the result of the action of vasoconstrictor systems (i.e., the renin-angiotensin system, the sympathetic nervous system, and arginine vasopressin) on the renal circulation activated as a homeostatic response to improve the extreme underfilling of the arterial circulation [21]. It is characterized by a low urine sodium output and elevated urinary-to-plasma ratios for creatinine and osmolarity. Pharmacological treatment such as Terlipressin, a vasopressin analog, may improve circulatory function by causing vasoconstriction of the dilated splanchic arterial bed, which subsequently suppresses the activity of the endogenous vasoconstrictor systems and results in an increase in renal perfusion [22]. Such therapy may be used in children, although there are no studies that have been conducted in this subgroup of patients. If renal failure occurs, dialysis should not be delayed. Continuous, rather than discontinuous, renal replacement therapy is preferred. Hepatorenal syndrome will reverse in most cases after liver transplantation.

Brain protection and liver support

Cerebral edema and, ultimately, intracranial hypertension should be aggressively prevented and treated. Invasive ICP monitoring is used in some centers but noninvasive monitoring of cerebral arterial flow, using repetitive transcranial-Doppler examination is emerging as a useful tool to identify intracranial hypertension [23]. This noninvasive monitoring will certainly be more widely used in the future.

Present treatment modalities include the use of 20% mannitol (0.5—1 g/kg intravenously) which reduces brain oedema by inducing osmotic diuresis, and removal of fluid by hemofiltration [24]. Recent studies indicate that moderate hypothermia (32—34 °C) is also efficient in preventing oedema and high intracranial pressure, probably by decreasing the transcapillary hydrostatic pressure gradient, reducing ammonia brain extraction and restoring cerebral blood flow autoregulation [25]. Barbiturates which produce cerebral vasoconstriction may be considered when severe intracranial hypertension does not respond to other therapies and was shown to effectively decrease the ICP [26]. In our opinion, it is important to recall that rational fluid
therapy, adequate ventilation, and temperature control are of direct importance to controlling cerebral capillary water flux in children with ALF. These simple interventions should be secured before more advanced experimental technologies are instituted to treat these patients, such as the use of liver support devices.

Extracorporeal liver assist devices

During the past 40 years, extracorporeal liver assist devices (ELS) have been developed for patients with ALF [27—31]. The goal is to remove circulating toxins that are either produced or not metabolized by the failing liver and to stabilize the patient’s condition to allow time for organ procurement or spontaneous regeneration of the native liver. ELS (i.e., hemoadsorption with charcoal column, sequential hemodialysis, exchange blood transfusion or conventional plasmapheresis) have been unsuccessful with regards to survival or neurological improvement. High volume continuous venovenous hemo(dia)filtration procedures have been shown to dramatically improve the neurological status and stabilize hemodynamics in some children with ALF (personal unpublished observations). The latest liver support techniques are bioartificial livers using hepatocytes, or non-biological detoxification systems, such as albumin dialysis (the Molecular Adsorbents Recirculating System (MARS®) or fractionated plasma separation and adsorption (FPSA) with the Prometheus® system [28—31]. At present, their efficacy has not been demonstrated but only suggested from a compilation of anecdotal cases reports. Therefore, albumin dialysis such as Mars, Prometheus and continuous venovenous single pass albumin hemodiafiltration cannot be recommended outside properly conducted randomized controlled trials that should demonstrate evidence that these systems affect survival in ALF [28]. However, such trials are difficult to design for several methodological reasons [28]. First, ALF is a rare condition in children as in adults. The wide heterogeneity of the causes of pediatric ALF is also an important methodological limit. Considering that liver supports could, per se, support all causes of ALF in children is certainly inadequate. Finally, inclusion of patients in a prospective study would be difficult as long as the criteria for emergency liver transplantation and consequently the indications for liver support are not validated in children.

Specific therapeutic approaches to ALF in children

Specific medical therapies that may preclude the need for liver transplantation have been developed mainly for some metabolic diseases presenting with ALF.

Galactosaemia

Galactosaemia (an autosomal recessive disorder caused by a deficiency of galactose-1-phosphate uridyl transferase (GALT) activity) and hereditary fructose intolerance (an autosomal recessive disorder caused by a deficiency of aldolase B activity) are easily managed with a galactose or fructose-free diet respectively, reversing ALF within a week.

Neonatal haemochromatosis

Neonatal haemochromatosis is a rare perinatal disorder associated with intrahepatic and extrahepatic iron accumulation that spares the reticuloendothelial system and causes extensive liver damage with late fetal loss or early neonatal death. With supportive care alone, the outcome of this condition is extremely poor. Neonatal liver transplantation has been performed with poor success. Early antioxidant treatment has been proposed without proven efficacy. Recently, as neonatal hemochromatosis is considered to be an alloimmune disease, treatment with high dose intravenous IgG in combination with exchange transfusion improved the outcome with a 75% survival without liver transplantation [32].

Hereditary tyrosinaemia type 1

Hereditary tyrosinaemia type 1 is a rare autosomal recessive disorder caused by a deficiency of fumarylacetoacetate hydrolase, which is the final enzyme of the tyrosine catabolic pathway, leading to accumulation of fumaryl and maleylacetoacetate and their saturated derivatives, i.e. succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney damage [33,34]. The main clinical presentation of this defect is ALF in infancy with survival rates less than 20% at one year of age despite restriction of phenylalanine and tyrosine from the diet. Until 1992, liver transplantation was the only effective treatment for HT. Since 1993, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (Nitisinone), an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase that prevents the formation and accumulation of fumaryl and maleylacetoacetate and their saturated derivatives became available, and proved curative [33,34]. Less than 10% of infants fail to respond to Nitisinone therapy and require a liver transplant.

Inborn Error in Bile Acid Synthesis

Specific defects have been identified in the enzymes catalyzing reactions responsible for changes to the steroid nucleus and side chain of cholesterol and its intermediates in the pathway leading to the formation of cholic and chenodeoxycholic acids. The Δ⁴⁺-3-oxosteroid 5β-reductase deficiency is the main defect in primary bile acid synthesis that has been recognized as a cause of neonatal liver failure [35]. Early diagnosis is important because infants with this defect may be successfully treated by oral administration of cholic acid therefore precluding the need for liver transplantation [36].

Other causes of ALF

Although rare, herpetic ALF has a poor prognosis. Acyclovir should be started preventively in all newborns with ALF, as delayed initiation is most often lethal. Acetaminophen is a dose-related hepatotoxin. If acetaminophen intoxication is suspected, specific therapy with N-acetylcysteine should be started without delay and may still be useful 48 h after ingestion [37].
If early enough, gastric lavage and activated charcoal administration should be performed in cases of suspected mushroom poisoning. Penicillin G and silybin (silymarin) are the accepted antidotes. However, mushroom poisoning still has a low transplant-free rate of survival.

**Fulminant Wilson disease and fulminant autoimmune hepatitis**

Fulminant Wilson disease and fulminant autoimmune hepatitis with hepatic encephalopathy are considered to be uniformly lethal without transplantation. However, if initiated prior to the onset of hepatic encephalopathy, chelating agents and immunosuppressive therapy respectively may preclude the need for a liver transplantation.

**Emergency Liver Transplantation raises crucial questions**

Emergency liver transplantation remains the mainstay of therapy in children with ALF, associated with a long-term survival ranging from 52% in infants to 79% in older children [2,3,15]. In a multicenter observational study of 141 children transplanted for ALF, pretransplant factors associated with a poor postoperative outcome were a grade IV encephalopathy, age below 1 year, and dialysis pre transplantation [38].

The advent of liver transplantation in this setting raises several crucial questions.

**When should the child be listed for liver transplantation?**

Decisions rely on the cause and severity of ALF, the potentiality of spontaneous liver regeneration, the availability of a specific therapy that may reverse ALF and the comorbidities, especially the risk of permanent neurologic damage. Fulminant Wilson disease and undetermined ALF carry the worst prognosis, whereas children with hepatitis A or acetaminophen induced ALF have a greater chance of spontaneous recovery without transplantation (Fig. 1).

The most common criteria used in adults to assess the need for transplantation, fail to be adequate in children, due mainly to a very weak negative predictive value [39]. As in adult studies that showed that the severity of associated organ dysfunction correlated with hepatic encephalopathy and outcome, the PRISM score was shown to reflect the severity of ALF in children [39].

Although scoring systems may be relevant for epidemiologic purposes, the decision to transplant depends on dynamic clinical and biochemical assessment of the patient’s condition. Emergency liver transplantation should be considered if hepatic encephalopathy greater than grade II is associated with a cofactor V activity below 20% or a prothrombin time below 20% or INR ≥ 2 [3]. These levels should be adjusted for the age of the child (in infants, encephalopathy may be absent or difficult to diagnose) and the cause of ALF. Other criteria that indicate emergency liver transplantation include a rapid decrease in liver size, seizures, ascites, hepatorenal syndrome, a fibrinogen level < 1 g/L, bilirubinemia > 400 µmol/L, worsening lactic acidosis, and hyperammonemia > 150 mmol/L.

**When should the child not be listed for liver transplantation?**

Liver transplantation may be contraindicated in 11–20% of cases [1,3]. Diseases not cured with liver transplantation such as malignant disease (i.e. leukemia, lymphoproliferative syndrome, lymphohistiocytosis), Reye syndrome and mitochondrial respiratory chain disorders with neurologic involvement are contraindications to transplantation. As well, uncontrolled intracranial hypertension or uncontrolled multiorgan failure should contra-indicate transplantation due to the poor outcome. On the other hand, children expected to recover spontaneously or under specific therapies should not be listed prematurely for emergency liver transplantation.

**How find a liver graft in time?**

The issue is to transplant the child before multiple organ dysfunction and irreversible hepatic encephalopathy develop. The use of split liver grafts and living related donors has a favorable impact in decreasing pretransplant mortality in pediatric patients [41,42].

Other techniques such as auxiliary transplantation are still in the field of research, but results from small series are encouraging, especially for noncirrhotic metabolic disorders. In these cases, auxiliary transplantation has similar patient and graft survival compared with orthotopic transplantation [15,40].

In countries where the availability for a liver graft is poor, extracorporeal systems may serve as a bridge to transplantation allowing time to find a liver graft.

**Perspectives**

Recent clinical studies suggest that hepatocyte transplantation may be useful for bridging patients to liver transplantation, for providing metabolic support during liver failure and for replacing liver transplantation in certain metabolic liver diseases [43,44]. To date, hepatocyte transplantation has been performed in only a small number of adult patients with ALF with encouraging results [44].

**Conclusion**

ALF in children is a challenging medicosurgical condition that requires a prompt multidisciplinary approach and intensive care management to identify the etiology and prevent or treat major complications with the hope that the liver function will recover or that liver transplantation can be performed. While improvements in supportive medical care and specific medical therapies over the past decade have had a substantial impact on survival, these conditions continue to carry a high mortality rate, unless emergency liver transplantation can be performed. Consequently, increasing interest has centred on the possibility of providing temporary liver support based on extracorporeal devices (artificial
and bioartificial) or on hepatocyte transplantation, either as a bridge to liver transplantation or ideally to obviate the need for it.

Disclosure of interest

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