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Acute Liver Failure

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ABSTRACT

Acute liver failure in children is a rare but potentially fatal disease. Causes of ALF in neonatal period are different from those in early or late childhood. Despite the improvement in the paediatric intensive care, liver transplantation remains the only effective treatment. Use of newer treatment modalities (liver assist devices and hepatocyte transplantation) is still in experimental phase. Management requires early recognition, prompt diagnosis of treatable condition, supportive therapy and prevention of complications hence these children should ideally be treated in a specialist unit.
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Key words : *Acute liver failure; Children; Liver transplantation*

Acute liver failure is a rare disorder in children but carries 70% mortality without liver transplantation. It is defined as "a rare multisystem disorder in which severe impairment of liver function (INR ≥ 1.5 with encephalopathy or INR ≥ 2 with or without encephalopathy) occurs in association with hepatocellular necrosis in a patient with no recognized underlying chronic liver disease".[1] There is a subtle difference from the acute liver failure in adults where hepatic encephalopathy is the cornerstone of diagnosis but in children especially in infancy not only it is very difficult to identify signs of early encephalopathy but also, encephalopathy can be a very late presentation.

ETIOLOGY

The etiology of acute liver failure (ALF) varies depending on the age of the child with metabolic liver disease and infection being most likely in neonates and infants. Viral hepatitis (Non A-E hepatitis) and drug-induced hepatitis are the most common causes in older children and adolescents. Etiology of ALF not only provides indication of prognosis but also dictates specific management options.

"Causes of Acute Liver Failure And Diagnostic TESTS"

INFECTIVE	Diagnostic test
Viral hepatitis A, B, B + D, E	Viral Serology
Others (Adeno virus, Parvovirus, Herpes Simplex) Non A–E	Viral serology diagnosis of exclusion hepatitis
DRUGS	
Paracetamol	History, Paracetamol levels
Mushroom poisoning	
METABOLIC	
Galactosemia	GAL-1-PUT level
Tyrosinemia	Urinary succinyl acetone
Hereditary fructose intolerance	History, enzyme analysis
Neonatal hemochromatosis	Transferrin saturation, lip biopsy
Niemann-Pick disease type C	Bone marrow
Wilson's disease	Copper parameters, caeruloplasmin, mutational analysis, KF rings
Mitochondrial cytopathies	Muscle biopsy, skin fibroblast and Liver biopsy for resp chain enzyme
Congenital disorders of glycosylation	Transferrin isoeclectrophoresis
AUTOIMMUNE	
Type 1 autoimmune hepatitis	High IgG, Auto antibodies
Type 2 autoimmune hepatitis	Auto antibodies
Giant cell hepatitis with Coombs-positive hemolytic anemia	Liver biopsy, positive Coomb's test

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VASCULAR/ISCHEMIC	
Budd-Chiarri syndrome	Doppler US Scan, CT or MRI
Acute circulatory failure	History
Heat stroke	History
Cardiomyopathies	History, examination, ECG & ECHO
INFILTRATIVE	
Leukemia/Lymphoma	Bone Marrow Aspirate
Hemophagocytic lymphohistiocytosis	Bone Marrow Aspirate

MANAGEMENT

The goals in the evaluation of any child with ALF are:

- To determine the etiology of the liver failure, as this could have an impact on treatment and prognosis.
- To assess the severity of liver failure and the need for transfer to a liver transplant centre.
- To provide hepatic support till child recovers spontaneously or has liver transplantation.
- To anticipate and prevent complications (hepatic encephalopathy and cerebral edema, sepsis, gastrointestinal bleeding, renal failure, and multiorgan failure)

Assessment should include a detailed history about the presentation, duration of illness and its progression, history of recent travel and drug or toxin exposure, either inadvertent or intentional. A family history of parental consanguinity or a history of failure to thrive and neurodevelopmental delay would point towards the possibility of an underlying metabolic disorder.

Physical examination is usually not helpful in establishing etiology of the ALF. A progressively shrinking liver in the face of worsening coagulopathy is a bad prognostic sign. Encephalopathy, especially in the early stages, is difficult to diagnose in the young infant or child, but can present as fretfulness, irritability, poor feeding and lethargy - signs which are not uncommon in any ill, frightened or hospitalised child.

General management includes

- Nursing in a quite environment
- Avoidance of stimulation and pain
- Avoid sedation. If patient needs sedation, he/she should be electively intubated for assisted ventilation
- Fluid restriction to 2/3rd maintenance
- Prevention of hypoglycaemia (maintain glucose levels >4.0 µmol/l)
- Gastroprotective measures with Ranitidine 2 mg/kg bd and sucralfate 2–4 g/day
- Prevention of sepsis using broad spectrum antibiotics and antifungal agents

NEUROLOGICAL COMPLICATIONS

Cerebral edema is the most serious complications of ALF with resultant intracranial hypertension and hepatic encephalopathy (HE). Children with Grade I-II encephalopathy should be managed with skillful nursing in a quiet environment with frequent monitoring of their neurological status. Children with signs of agitation or Grade III or IV encephalopathy should be electively ventilated and nursed with head elevated at 30 degrees.

Intracranial pressure (ICP) monitoring in ALF is still an ongoing debate. At King's College Hospital ICP is monitored using subdural transducers if there are signs of increased ICP. Aim of ICP monitoring is to maintain ICP below 20-25 mm Hg and cerebral perfusion pressure (mean arterial blood pressure – ICP) at > 50 mm Hg but it has not shown to affect the final outcome.

For clinical signs of increased ICP, Mannitol is the drug of choice. It should be used as a rapid bolus of 0.5 g/Kg as a 20% solution of Mannitol over a 15-minute period. The dose can be repeated if the serum osmolarity is less than 320 mOsm/L. In anuric patients, a diuresis is simulated by ultrafiltrating three times the administered volume over the next half hour. Sodium thiopental can be used in controlling mannitol-resistant cerebral edema in a bolus dose of 2 to 4 mg/Kg over 15 minute followed by a slow intravenous infusion of between 1 and 2 mg/Kg/h.[2]

Since sub clinical seizure activity has been suggested as a contributing factor for the development of cerebral edema, phenytoin infusion has demonstrated a significant reduction in the seizure activity and the incidence of cerebral edema.[3]

Recent reports suggest that induction and maintenance of hypernatremia (145-155 meq/l) by administration of 30% hypertonic saline can reduce the incidence and severity of intracranial hypertension in patients presenting with ALF[4] but a larger study will be required to prove its role as a prophylactic measure. Hypothermia (core body temperature of 32°C) has been shown to be effective in the management of severe intracranial hypertension with lowering of ICP and improvement of cerebral perfusion pressure in adults[5] but there are no studies regarding the use of hypothermia or maintenance of hypernatremia in children with ALF.

RENAL FAILURE

Incidence of acute renal failure is between 10-15% in pediatric ALF.[6] It is very important to anticipate and prevent renal failure by maintaining circulating volume with colloid or fresh frozen plasma. Causes could be prerenal or renal (direct toxic effect on kidneys or hepatorenal syndrome or acute tubular necrosis). Extracorporeal renal support in the form of hemofiltration may be necessary (75% of cases with paracetamol induced ALF and 30% of patients with other etiologies of ALF) if there is an established acute renal failure or if there is concern about the fluid management.

METABOLIC DERANGEMENTS

Symptomatic or asymptomatic hypoglycemia can be present in 40 % of ALF, hence it is mandatory to monitor blood glucose regularly. Presence of metabolic acidosis requires maintaining intravascular volume but sometimes requires bicarbonate correction whereas respiratory acidosis (due to central cause or due to respiratory cause) will require early intervention with elective intubation. Rarely respiratory alkalosis due to hyperventilation can be present in grade I encephalopathy.

HEMODYNAMIC CHANGES

Hemodynamic changes are characterized by hyperdynamic circulation with decreased systemic peripheral vascular resistance and increased cardiac output – a state similar to systemic inflammatory response syndrome. Invasive hemodynamic monitoring (PiCCO or LiDCO) provides early evidence of circulatory failure and is helpful in rationalizing fluid management and the choice of vasopressors.

COAGULOPATHY

The prothrombin time expressed as an INR is used as an indicator of the severity of the liver damage, hence correction of coagulopathy is indicated only if the patient is already listed for transplant or prior to an invasive procedure such as insertion of a central line or ICP monitors. The risk of hemorrhage correlates with the severity of thrombocytopenia rather than severity of coagulopathy. Common sites of internal hemorrhage include the gastrointestinal tract, nasopharynx, lungs, and retroperitoneum. Intracranial hemorrhage is uncommon. The presence of significant disseminated intravascular coagulation usually indicates sepsis or secondary hemophagocytic lymphohistiocytosis.

INFECTION

There is an increased incidence of infections in acute liver failure, which is attributed to impaired immune system. Risk factors for infections include coexisting renal failure, cholestasis, treatment with thiopental and liver transplantation. Broad-spectrum prophylactic intravenous antibiotics have been shown to reduce the incidence of culture-positive bacterial infection from 80 to 20%.[7] Commonest bacterial organism is staphylococcus. Deterioration of HE after initial improvement, a markedly raised leukocyte count, pyrexia unresponsive to antibiotics, and established renal failure are strong indicators of fungal infection. An active uncontrolled infection is also a relative contraindication for liver transplantation

LIVER SUPPORT DEVICES

In ALF, loss of functioning hepatocytes and Kupffer cells leads to impairment of synthetic, detoxifying, and biotransformatory activity. Theoretically, a support device that provides all these functions would be ideal either as a bridge to liver transplant or, ideally, to obviate the need for it by supporting liver function while the native liver regenerates. Liver support devices could be either cleansing devices, which perform only the detoxifying function of the liver or a bioartificial liver support system that have a theoretical advantage of providing the synthetic as well as detoxifying properties.

Recently developed cleansing devices such as Biologic-DT and the molecular adsorbent recirculating system (MARS) attempt to remove protein-bound toxins by perfusion over resins or albumin. Use of MARS in ALF in adults has been associated with hemodynamic stabilization, improvement in mental status and HE.[8] Though preliminary results were encouraging, a controlled pilot study of the ELAD did not show any significant benefit.[9] A recent meta-analysis, considering all forms of devices together demonstrated no efficacy for bioartificial liver devices for the treatment of ALF.[10]

LIVER TRANSPLANTATION

Overall survival rate for liver transplantation in children with ALF is 60-70% as compared to 90 % survival after liver transplantation in children with chronic liver disease. Absolute contraindications for liver transplantation are fixed and dilated pupils, severe respiratory failure (ARDS), uncontrolled sepsis whereas relative contraindications are increasing inotropic support, infection under treatment, significant irreversible neurological involvement, and underlying systemic disease not correctable by transplantation.

Optimal use of the donor liver is essential because of the scarcity of the donor organs, which require proper patient selection. In paracetamol overdose the criteria for transplant listing in children are the same as for adult patients *i.e.* pH <7.3 or Prothrombin time >100 s and

Table 1. Parameters to Predict Death or Survival without Liver Transplantation

	Sensitivity	Specificity
INR = 4	86	73
Bilirubin =235 μmol/L	85	65
Age <2 yr	93	52
WBC >9 x 10°/l	89	71

(WBC: white cell count)

serum creatinine >300 μmol/L in patients with grade III or IV encephalopathy.[11] For all other conditions, the task of defining transplantation criteria in children with ALF is difficult because of different etiologies. The authors have developed a prognostic model for ALF in children, using data from 44 children (29 children died and 15 children survived without liver transplantation). Multivariate logistic regression and ROC curves analysis showed that maximum INR, maximum bilirubin, age and white blood cell count were the parameters able to predict death or survival without liver transplantation. Presence or absence of encephalopathy had no predictive value, but degree of encephalopathy in those children who developed it was associated with poor outcome (grade I–II, 44% mortality; grade III–IV, 78% mortality, $p < 0.002$).[1] Table 1 Shows sensitivity, specificity for each parameter.

Recent advances in surgical technique have expanded the donor pool by the use of reduced grafts, splits grafts and living-related donor grafts.

AUXILIARY TRANSPLANTATION

Auxiliary orthotopic liver transplantation (APOLT) is a technique where part of the native liver is removed, and replaced with either the respective left or right lobe of a reduced graft. The advantage of this procedure is that the native liver is retained, and if sufficient hepatic regeneration was to occur, immunosuppression could be withdrawn and the liver graft allowed to atrophy or be surgically removed. Of 16 children who received APOLT in the author's unit, overall survival was 87%, six of whom have shown evidence of liver regeneration. Of these six, immunosuppression has been stopped successfully in four and the other two are on tapering doses.[12] APOLT provides the option to discontinue what would have otherwise been the need for life-long immunosuppression and for this reason would be the transplant procedure of choice for most patients. There are however, several conditions where this procedure would not be appropriate, those in which the native liver is already cirrhotic, or where there is a risk of hepatic malignancy (*e.g.* tyrosinemia). In addition, the technical pre-requisites are that the child with ALF is of an adequate size and that an appropriate sized match organ becomes available.

HEPATOCYTE TRANSPLANTATION

Taking the concept of auxiliary liver transplant, further Hepatocyte transplantation has been tried in experimental animals with improved survival. In a small number of clinical studies, variable improvement in encephalopathy, coagulopathy, and hyperammonemia has been reported. The procedure has shown some encouraging results as a bridge to transplant but remains experimental.

CONCLUSION

ALF is a multisystem disorder with high mortality requiring multidisciplinary team approach for its management. Liver transplantation is the only effective treatment option. Liver assist devices and Hepatocyte transplantation, though promising, are still in experimental phase. Future efforts should concentrate on designing more effective supportive management, identifying the underlying cause and its treatment.

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