

## Management of Acute Liver Failure in Infants and Children: Consensus Statement of the Pediatric Gastroenterology Chapter, Indian Academy of Pediatrics

**WRITING COMMITTEE:**

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**Process:** Selected members were requested to prepare guidelines on specific issues, which were reviewed by two other members. These guidelines were then incorporated into a draft statement, which was circulated to all members. On 17<sup>th</sup> December 2011, Kunwar Viren Oswal round table conference was organized by the Apollo Center for Advanced Pediatrics, Indraprastha Apollo Hospital, New Delhi and the Sub-specialty Chapter of Pediatric Gastroenterology, Indian Academy of Pediatrics. Presentations, ensuing discussions, and opinions expressed by the participants were incorporated into the final draft.

**Objectives:** To formulate comprehensive evidence based guidelines for management of acute liver failure in India,

**Recommendations:** Viral hepatitis is the leading cause of acute liver failure (ALF) in India. Search for metabolic etiology, particularly in infants and neonates, and in apparently idiopathic cases needs to be done. Planning for early transfer is important

as the risks involved with patient transport may increase or even preclude transfer at later stages. Management should be in an intensive care setting in select situations. There is currently insufficient evidence to routinely prescribe branched-chain amino acids, non-absorbable antibiotics or lactulose. Group recommends use of N-acetyl cysteine routinely in patients with ALF. Administration of antibiotics is recommended where infection is present or the likelihood of impending sepsis is high. Enteral nutrition is preferred to parenteral nutrition. Protein restriction is not recommended. An international normalized ratio >4 or Factor V concentration of <25% are the best available criteria for listing for liver transplantation. Overall 40-50% of ALF patients survive without transplantation. Survival in patients fulfilling criteria for liver transplantation and not transplanted is 10-20%. Liver transplantation is a definite treatment for ALF with high one- and five-year survival rates.

**Keywords:** *Acute liver failure, Management guidelines, Liver transplantation.*

**A**cute liver failure (ALF) results from rapid death or injury to a large proportion of hepatocytes, leaving insufficient hepatic parenchymal mass to sustain liver function [1]. In order to widen the scope of recognition, and to have a uniformly accepted management strategy of ALF in India, the following consensus statement was formulated based on available publications and experience of experts from India.

**DEFINITION AND DIAGNOSIS**

A number of definitions for ALF have been proposed over the past four decades [2-6]. These definitions have mostly dealt with adults and have failed to capture the complexities associated with ALF in infants and children.

The group recommended Pediatric ALF definition as (a) evidence of liver dysfunction within 8 weeks of onset of symptoms (neonates may have only deranged liver

functions without overt symptoms) (b) uncorrectable (6-8 hours after administration of one dose of parenteral vitamin K) coagulopathy with International Normalized Ratio (INR) >1.5 in patients with hepatic encephalopathy, or INR > 2.0 in patients without encephalopathy and (c) no evidence of chronic liver disease either at presentation or in the past.

Staging of encephalopathy in infants and children is difficult as compared to adults. The group recommends the following grades: Grades I and II are indistinguishable with clinical features of inconsolable crying, inattention to task: with normal or exaggerated deep tendon reflexes: Grade III encephalopathy manifests as somnolence, stupor, combativeness and hyperreflexia. In grade IV, child is comatose [arousable with painful stimuli (IVa) or no response (IVb)] with absent reflexes and decerebration or decortication.

### ***Etiology of ALF in India***

Five studies published between 1996 and 2007 studies from India (Chandigarh, Vellore, Delhi, Kolkata and Pune). enrolling 215 children [8-14] showed acute viral hepatitis to be the commonest cause, either alone or in combination (overall 61-95%: hepatitis A 10-54%; hepatitis E 3-27%; hepatitis B 8-17%; and multiple viruses 11-30%- commonest being hepatitis A+E). Drugs were responsible for ALF in 6-8% cases and other causes in 9-10.5%. Etiology remained unestablished in 6-22% patients. There are no published data from India on ALF in neonates and infants.

### ***Diagnostic Work-up***

The causes of ALF in infants [15-17] and children are given in **Table I**. **Table II** shows the diagnostic work-up recommended to establish the etiology of ALF.

The causes and natural history of ALF in neonates and infants differ from those in older children. In neonates, the commonest etiology reported in Western literature is neonatal hemochromatosis, Herpes simplex virus and less common causes are hemophagocytic lymphohistiocytosis and metabolic disorders (galactosemia, tyrosinemia, mitochondrial cytopathy). In infants, metabolic causes are common (type I tyrosinemia, mitochondrial cytopathy, galactosemia, and hereditary fructose intolerance). Clinical manifestations and diagnosis of common causes of ALF in neonates and infants are shown in **Table III** [18,19].

## **MANAGEMENT**

### ***Transport***

The aim of transporting a child with ALF is to ensure safe and timely transfer to a higher center, preferably with liver transplant facilities. Early action is important as the risks involved with patient transport may increase or even preclude transfer once deeper stages of encephalopathy develop. There should be decisive, frequent and clear communication amongst the teams involved. Any child who has grade III or IV encephalopathy should preferably be intubated and airway secured before transport. A continuous monitoring of heart rate, rhythm, pulse oximetry, and blood pressure should be available. Facilities for infusion of vasoactive drugs, with spare supplies should be available during transport. Well secured vascular access must be assured prior to the transfer.

### ***Management in the Intensive Care Unit***

It is recommended that the child be nursed in a quiet environment preferably in an intensive care setting. A

**TABLE I** CAUSES OF ACUTE LIVER FAILURE IN CHILDREN AND NEONATES

*Infective Viral:* Viral hepatitis (A, E, B or multiple viruses), adenovirus, Epstein-Barr virus, parvovirus, cytomegalovirus, echovirus, varicella, dengue, coxsackie, herpes simplex viruses I, II and VI\*  
*Bacterial:* Septicemia

*Drugs: Dose-dependent:* Acetaminophen, halothane  
*Idiosyncratic reaction:* Isoniazid, non-steroidal anti-inflammatory drugs, phenytoin, sodium valproate, carbamazepine, antibiotics (penicillin, erythromycin, tetracycline, sulfonamides, and quinolones), allopurinol, propylthiouracil, amiodarone, ketoconazole, antiretrovirals  
*Drug combinations:* Isoniazid-rifampicin, trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid

*Metabolic:* Wilson's disease, galactosemia\*, tyrosinemia\*, hereditary fructose intolerance\*, neonatal hemochromatosis\*, Niemann-Pick disease type C\*, mitochondrial cytopathies\*, congenital disorder of glycosylation.

\* Common in neonates and infants.

**TABLE II** DIAGNOSTIC WORK-UP FOR ACUTE LIVER FAILURE

### ***General work-up***

Alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, total and conjugated bilirubin, prothrombin time (INR), PTTK, hemogram, serum electrolytes, blood urea, creatinine, blood and urine cultures, blood group, chest X-ray, serum alpha-fetoprotein, lactate, lactate dehydrogenase, blood ammonia, arterial blood gas, and urine for reducing substances.

### ***Specific work-up***

#### ***Infectious***

IgM anti-hepatitis A virus, IgM anti-hepatitis E virus, hepatitis B virus surface antigen, IgM anti-hepatitis B core antibody, cytomegalovirus PCR, IgM varicella zoster virus, IgM Epstein-barr virus, HIV 1 and 2

#### ***Wilson disease***

Serum ceruloplasmin, 24 hour urinary copper estimation, KF ring. Clue to etiology: alkaline phosphatase / bilirubin ratio <4.0, AST/ALT ratio >2.2 ± evidence of Coombs negative hemolysis

#### ***Autoimmune***

Coombs test, antinuclear antibody (> 1:40), liver kidney microsomal antibody, smooth muscle antibody (>1:20), Immunoglobulin G levels

#### ***Hemophagocytosis***

Serum triglyceride, cholesterol, ferritin and bone marrow biopsy

#### ***Drug overdose***

Acetaminophen, valproate drug levels

central venous line should be placed in order to measure central venous pressure, administer fluids, medications, and blood products, and collect blood samples. Volume resuscitation should be carried out if necessary. The

**TABLE III** CLINICAL MANIFESTATIONS AND DIAGNOSIS OF COMMON CAUSES OF ACUTE LIVER FAILURE IN INFANTS**Neonatal hemochromatosis**

*Maternal:* Still births, previous sib deaths; Antenatal period: IUGR, oligohydramnios, placental edema. Presents usually few hours to sometimes weeks after birth as hypoglycemia, coagulopathy, jaundice, anemia, ascites, anasarca, and splenomegaly with shrunken liver.

*Diagnosis:* Low to normal transaminases, hypoalbuminemia, hypofibrinogenemia, thrombocytopenia, high serum ferritin, low serum transferrin, high transferrin saturation (95 % to 100 %). Lip or salivary gland biopsy shows iron deposition; MRI pancreas shows low signal intensity on T2 imaging.

*Treatment:* Anti-oxidants (acetyl-cysteine and Vitamin E), high dose IVIG in combination with exchange transfusion; liver transplantation if no response.

**Herpes simplex infection**

No positive history in 60 % to 80 % of mothers. Suspect in a sick neonate presenting in first week of life especially if bacterial cultures are not growing anything. Search for vesicles, particularly on scalp.

*Diagnosis:* Viral cultures from vesicles, oropharynx, conjunctiva, blood or CSF; PCR diagnosis from blood or CSF.

*Treatment:* High dose (60 mg/kg/d) acyclovir for 21 days or till PCR is negative. Necessary to document negative CSF-PCR at end of therapy.

**Mitochondrial cytopathy**

Onset in the first week of life or later, transient hypoglycemia, neurological involvement in form of severe hypotonia, myoclonus or psychomotor retardation. *Diagnosis:* Plasma lactate >2.5 mmol/L, molar ratio of plasma lactate/pyruvate > 20:1, paradoxical increase in plasma ketone bodies or lactate after meals Urinary analysis by mass spectroscopy; Genetic mutational analysis for respiratory chain disorders and tandem mass spectrometry for fatty acid oxidation defects.

**Type 1 tyrosinemia**

Coagulopathy with or without cholestatic jaundice, hypoglycemia, hepatomegaly, ascites

*Diagnosis:* High alpha-fetoprotein (mean level: 160,000 µg/mL vs. 84,000 µg/mL in normal term neonate), Increased urinary succinylacetone

*Treatment:* Nitisinone 1 mg/kg/d orally in two divided doses: dietary restriction of phanglamine and tyrosine; Liver transplantation if no response.

**Galactosemia**

Feeding intolerance, vomiting, diarrhea, jaundice, hepatomegaly, lethargy and hypotonia after milk feeding is started; hypoglycaemia, sepsis (particularly *E.coli*), cataract and developmental delay.

*Diagnosis:* Urine positive for non-glucose reducing substances while on lactose feeds; confirmation by blood Galactose-1 phosphatase uridyl transferase enzyme assay.

*Treatment:* Lactose free formula.

fluids should be glucose-based with a glucose infusion rate of at least 4-6 mg/kg/min and titrated as per requirement. Vasoactive drugs should be used if hypotension is unresponsive to saline. Medications that affect level of consciousness should be avoided (unless there is a back-up plan for ventilation) to prevent worsening or assessment of encephalopathy. If sedation is mandatory, 1-2 mg/kg of propofol can be given. The group also recommends monitoring of the following clinical and biochemical parameters until the patient becomes stable: (a) vital signs, including blood pressure every 4 hours, more frequently in an unstable child (b) continuous oxygen saturation monitoring (c) neurological observations/coma grading, electrolyte, arterial blood gases, blood sugar every 12 hourly (more frequently in an unstable child); prothrombin time should be monitored 12 hourly till patient stabilizes or decision

to perform a transplant is taken (d) daily measurements of liver span and prescription review (e) liver function tests, blood urea, serum creatinine, calcium and phosphate at least twice weekly. Surveillance of blood and urine cultures should be done during the course of illness.

*Electrolyte disturbances*

Metabolic, electrolyte, and acid-base disturbances frequently occur in ALF. Hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia and hypomagnesemia are commonly observed. Persistent hyponatremia and hypoglycemia are poor prognostic parameters. Patients with ALF are at an increased risk for hypoglycemia secondary to failure of hepatic gluconeogenesis, hyperinsulinemia and secondary bacterial infections. Intravenous fluids should be tailored in accordance to electrolyte, sugar and renal status of the patient.

*Supportive management*

There is increasing evidence for use of N-acetyl cysteine (NAC) infusion in non-acetaminophen causes of ALF [20]. The group recommends routine use of NAC in the dose of 100 mg/kg/d in all cases of ALF irrespective of the etiology. Though ammonia is an accepted triggering factor in cerebral edema, L-ornithine L-aspartate, lactulose and other non-absorbable antibiotics have not been found to be beneficial. However, if lactulose is administered (preferred in grades I-II HE) care should be taken to avoid over distension of the abdomen. There is evidence to suggest that prophylactic proton pump inhibitors are helpful in prevention of gastrointestinal hemorrhages [21]. The group recommends prophylactic administration of proton pump inhibitors in all cases of ALF.

*Raised intracranial pressure (ICP)*

ICP >20 mm Hg or intracerebral hypertension (ICH) occurring as a consequence of cerebral edema is one of the most dreaded complications of ALF. The most accurate method of diagnosing ICH is by direct ICP monitoring using catheters, since the clinical features manifest only in the late stages. However, since ICP monitoring is associated with a 4-20% risk of local complications and has no survival benefit, it is not routinely recommended. Repetitive transcranial Doppler may be used for non-invasive monitoring of ICH [22]. CT scan or MRI may be required to exclude other causes of raised ICP such as intracerebral hemorrhage.

The induction of hypernatremia has the potential to decrease water influx into the brain and thereby reduce cerebral edema. Prophylactic infusion of 3% saline to maintain sodium at 145-155 mmol/L in patients with severe encephalopathy is associated with fewer episodes of ICH and is preferred over mannitol. Once obvious neurological signs develop or ICP is above 25 mm Hg for over 10 minutes, a bolus over 15 minutes of IV mannitol (0.25-1 g/kg, 20% mannitol) is recommended. This can be repeated if serum osmolality is less than 320 mosmol/L. Urine output should be monitored and ultrafiltration may be necessary in the setting of renal impairment.

Hyperventilation with reduction of pCO<sub>2</sub> to <35 mmHg decreases cerebral blood flow and may be appropriate in the subgroup of ICH patients with cerebral hyperemia. It is not recommended routinely and may be used temporarily in patients with impending herniation where mannitol therapy fails [23]. At present there is no evidence to support use of hypothermia, prophylactic phenytoin or corticosteroids in the management of raised ICP in ALF.

**Coagulopathy**

Patients with ALF develop platelet dysfunction,

hypofibrinogenemia and vitamin K deficiency [24]. Routine correction of coagulopathy and thrombocytopenia is not recommended. Prophylactic fresh frozen plasma (FFP) is also not recommended, as it does not reduce the risk of significant bleeding and obscures the trend of INR as a prognostic marker. However, replacement with FFP is recommended in patients with clinically significant bleeding, while performing invasive procedure or in situations of extreme coagulopathy with INR >7. FFP can be given 15-20 mL/kg every 6 hours or as a continuous infusion at 3-5 mL/kg/hr [25]. Single dose of vitamin K<sub>1</sub> (5-10 mg, slowly with the rate not more than 1 mg/min) is recommended empirically in all patients with ALF. Cryoprecipitate in patients with significant hypofibrinogenemia (<100 mg/dL) is helpful. Recombinant factor VIIa is beneficial in patients with prolonged INR despite FFP, who are volume overloaded [26]. However, the cost of therapy is exorbitant.

Platelet transfusion is not recommended unless a threshold platelet count of 10,000-20,000/mm<sup>3</sup> is reached or there is significant bleeding and platelet count <50,000/mm<sup>3</sup> [5,27]. A platelet count of 50-70,000/mm<sup>3</sup> is usually considered adequate when an invasive procedure is to be performed [5].

*Sepsis*

Infection remains one of the major causes of death in patients with ALF. The most commonly isolated organisms are gram-positive cocci (Staphylococci, Streptococci) and enteric gram-negative bacilli. Fungal infections, particularly *Candida albicans*, may be present in one third of patients with ALF. Prophylactic parenteral and enteral antimicrobial regimens have not been shown to improve outcome or survival in patients with ALF [24, 28]. Therefore, there is insufficient data to recommend routine use of antibiotic prophylaxis in all patients with ALF.

Empirical administration of antibiotics is recommended where infection or the likelihood of impending sepsis is high e.g. surveillance cultures reveal significant isolates, progression of, or advanced stage (III/IV) HE, refractory hypotension, renal failure, presence of systemic inflammatory response syndrome components (temperature >38°C or <36°C, white blood count >12,000 or <4,000/mm<sup>3</sup>, tachycardia).

Empirical antibiotics are also recommended for patients listed for liver transplantation (LT), since infection often results in delisting and immunosuppression post-LT is imminent.

Broad-spectrum coverage with a third-generation cephalosporin, vancomycin/teicoplanin, and fluconazole are recommended wherever indicated.

*Acute kidney injury*

Acute kidney injury (AKI) in patients with hepatic failure might be pre-renal (hypovolemia) or secondary to acute tubular necrosis. Blood urea is unreliable, particularly since its synthesis is impaired in hepatic dysfunction. Determination of the fractional excretion of sodium helps to differentiate pre-renal causes (hypovolemia, hepatorenal syndrome) from acute tubular necrosis. Patients with pre-renal AKI respond to expansion of intravascular compartment with intravenous fluids. Standard charts should be used to modify the dose and dosing interval of drugs in accordance with the degree of renal impairment. The indications for initiating renal replacement therapy include severe or persistent hyperkalemia ( $>7$  mEq/L), uremic encephalopathy, fluid overload (pulmonary edema, severe hypertension), severe metabolic acidosis, hyponatremia (120 mEq/L or symptomatic) or hypernatremia. Peritoneal dialysis is preferred in sick and unstable patients, particularly infants. Use of single-cuff soft or double-cuff catheters and/or an automated device decrease the risk of peritonitis. Hemodialysis is avoided in patients with hemodynamic instability and bleeding tendency, and in the very young.

*Nutrition*

The group felt that there is no evidence that enteral feeding enriched with branched-chain amino acids (BCAA) is beneficial in children with ALF and encephalopathy. There is no role of protein restriction in children with HE. Energy intakes should be increased appropriately to counter the energy catabolism and also factor-in the requirement for maintenance, growth and physical activity. For reliable assessment of current nutritional status, body mass index for age has been shown to be the most accurate [5, 29-31]. If there is a suspicion of a metabolic condition, then all nutrition should be stopped for 24 hours and then restarted keeping the specific condition in mind.

**Liver Transplantation**

LT is the only definite treatment, and has transformed the management of ALF. Several prognostic scoring systems have been devised to predict mortality and to identify those requiring early LT. These include King's College Hospital (KCH) criteria [32], pediatric end-stage liver disease (PELD) score, APACHE II, and Clichy criteria [3]. The KCH criteria have been shown to have a better performance than the Clichy criteria and is widely used. The KCH criteria appear to have a higher specificity than sensitivity for acetaminophen-induced ALF, while its negative predictive value for non-acetaminophen induced ALF is low. The group recommends using an INR  $>4$  or factor V concentration of  $<25\%$  as the best available criteria for listing for LT. Although INR and factor V

concentration as prognostic markers are derived from small population studies, to date, they provide the best available indicators predicting mortality without LT [33]. Acute fulminant Wilsons disease has a high mortality necessitating LT [33]. Special prognostic score is available for children and a score of 11 or more indicates high mortality, with 93% sensitivity and 98% specificity [34]. Contraindications for pediatric LT are active uncontrollable and untreatable sepsis, severe cardiopulmonary disease, multi-organ failure, extra-hepatic malignancy, mitochondrial disease, active substance abuse, and HE grade IV encephalopathy with severe neurological impairment.

**Outcome**

In more than 50% of children with ALF there is poor survival unless LT is offered at the appropriate time [7]. Prognostic factors predicting outcome in ALF include elevated serum bilirubin and prothrombin time, young age of the child, high arterial ammonia and high WBC count, low alanine aminotransferase, and presence of encephalopathy [35-37]. The outcome of ALF also varies with etiology. The prognosis is better with hepatitis A, acetaminophen overdose and ischemia (approximately 60% spontaneous survival), and poor with drug-induced ALF (non-acetaminophen), hepatitis B, and indeterminate cases (25% spontaneous survival).

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