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# Acute liver failure in children

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## ABSTRACT

Acute liver failure is a complex multi system disorder that results from an acute severe insult to the liver in a previously well child. It has an unpredictable course and high mortality in children. Encephalopathy and uncorrectable coagulopathy are essential pre requisites in diagnosis. Metabolic diseases are the commonest cause in infants. Viral hepatitis predominates in older children. A large percentage of children have no identifiable cause. Management of a child with ALF includes basic intensive care to ensure regulation of fluid status, glucose and electrolyte homeostasis and specific measures to reduce serum ammonia concentration, as well as the prevention and prompt treatment of complications. Important complications that require urgent recognition and management include coagulopathy, cerebral edema, sepsis and renal dysfunction. Cerebral edema is the most important reason for death in acute liver failure. Increasing jaundice, uncorrected prothrombin time and rapidly falling ALT values in a clinically deteriorating patient indicates poor prognosis. Management is aimed at life support and prevention of complications, while facilitating regeneration of the liver. Liver transplantation is the only definitive treatment that improves outcome.

**Key words**: encephalopathy, coagulopathy, cerebral edema, liver transplantation.

## INTRODUCTION

Acute liver failure (ALF) is a complex multi-system disorder that follows an acute, severe insult to the liver causing extensive hepatocyte dysfunction. It is one of the most devastating pediatric emergencies that develop in a previously healthy child and the only medical intervention that has proved to definitely improve survival is liver transplantation.

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## TERMINOLOGY

### Acute Liver Failure

Is a multi system disorder with severe impairment of liver cell function, with or without encephalopathy, occurring in association with hepatocellular necrosis in a patient with no recognizable underlying chronic liver disease.

### Fulminant Hepatic Failure

Is a potentially reversible condition, the consequence of severe liver injury, in which

the onset of hepatic encephalopathy occurs within 8 weeks of the first symptom of illness, in the absence of pre-existing liver disease [1] .This definition will not hold good in newborn/young infants. In addition, chronic liver diseases like Wilson's disease may also have fulminant hepatic failure as the initial presentation.

The major problem is often the lack of clarity on the onset of the first symptom of illness. Therefore the International Association for the study of Liver (IASL) in 1999 classified liver failure based only on the time interval between jaundice and onset of encephalopathy, with the absence of pre-existing liver disease not being a pre-condition [2].

Three forms of liver cell failure were recognized.

**Hyper acute hepatic failure**

Encephalopathy occurring within 10 days of the onset of jaundice.

**Acute hepatic failure**

Encephalopathy developing from 11 to 28 days of onset of jaundice.

**Sub acute Hepatic failure**

Encephalopathy and/or progressive ascites between 4 weeks and 24 weeks of onset of jaundice.

Pediatric Acute Liver Failure (PALF) Study Group in 2006 applied the following revised working definition for the clinical condition of ALF in children [3].

1. Evidence of acute liver injury with no known evidence of chronic liver disease, and

2. Biochemical and/or clinical evidence of severe liver dysfunction as follows:

a. Uncorrectable coagulopathy of hepatic origin, defined as an international normalized ratio (INR) e"1.5, despite the use of vitamin K , plus encephalopathy,

or

b. INR e" 2.0, despite the use of vitamin K, even without encephalopathy.

## ETIOLOGY

Acute liver failure is the end result of a variety of insults to the liver. In a large proportion of children however, no cause is made out. In those in whom it is possible, the etiology varies with the age of the child. Inborn errors of metabolism with acute presentations like galactosemia, tyrosinemia, neonatal hemochromatosis, hereditary fructose intolerance etc and hemophagocytosis are the commonest cause in infants. Viral hepatitis and other chronic metabolic liver diseases are more common in older children.

In India, acute viral hepatitis is the commonest cause and Hepatitis A predominates.[4]

Hepatitis E is being increasingly implicated and Hepatitis B may be responsible in areas of high prevalence. Drugs (including, native drugs and heavy metals also) are an important cause, but are often overlooked. They lead to hepatic failure either directly due to hepatotoxicity or as a result of idiosyncratic reaction [5]. Valproate, Paracetamol, phenytoin and INH are known to cause fulminant Hepatitis. Sodium valproate induced acute hepatic necrosis is most often seen during the initial 4 to 6 months of treatment. Wilson's disease is important in children above 8 years of age. Leptospirosis, Malaria and Dengue fever have also been reported to cause acute liver failure. Common causes of acute liver failure are given in Table 1.

## CLINICAL MANIFESTATIONS

The typical clinical presentation is that of healthy school going child with no significant medical illness in the past presenting with jaundice that initially resembles an ordinary hepatitis, but progressively deepens with appearance of neurological symptoms like altered consciousness, increasing lethargy and disturbed sleep rhythm [6].

Coma, skin/mucosal bleeding, fetor hepaticus, rapidly progressive edema and/or ascites are signs of established severe liver

**Table 1: Common etiology of Acute liver failure**

| Etiology | Neonates & infants | Children |
|---|---|---|
| Metabolic | Galactosemia, tyrosinemia, neonatal hemochromatosis, bile acid synthesis defect, | Wilson's disease, Reye syndrome, GSD Type IV |
| Infections | Hepatitis B, Cytomegalovirus, Ebstein barr virus , | Hepatitis A ,Hepatitis E, Hepatitis B, Leptospirosis, Malaria, Dengue |
| Ischemic / vascular | Severe asphyxia, post cardiac surgery, shock | Budd-chiari syndrome, shock |
| Drugs & toxins | Acetaminophen, valproate | Acetaminophen, valproate, INH, Rifampin, Heavy metals, Native drugs |
| Autoimmunity | None | Autoimmune hepatitis |
| Malignancy | Hemophagocytic lymphohistiocytosis | Leukemia, lymphoma, hemophagocytic lymphohistiocytosis |

failure. The course of this dramatic deterioration from being healthy to a near death situation is usually less than 7 days.

Alteration of sensorium is essential for diagnosis of acute liver failure. The onset is acute and usually progresses over a few days through stages of drowsiness, hypersomnia and unresponsiveness to coma [7]. Early signs of encephalopathy are difficult to appreciate in infants and young children. Unexplained irritability or excessive sleepiness in a child with jaundice should always arouse suspicion. EEG changes (slowing of alpha rhythm down to the delta range) may precede psychological changes early in the course of the disease. Brain MR Spectroscopy has been reported useful in early diagnosis of minimal hepatic encephalopathy.

## PATHOLOGY

Liver biopsy specimens obtained from children from fulminant hepatic failure show patchy or confluent massive hepatocyte necrosis [8]. Bridging necrosis and collapse of the reticulin framework may also be noticed. There will be scanty or absent hepatocyte regeneration (hyporegenerative hepatic necrosis) due to excess of circulating inhibitors of hepatocyte regeneration. In Reye syndrome and fatty acid oxidation defect, microvesicular fatty infiltrates are seen rather than cell necrosis. In acetaminophen toxicity and circulatory collapse leading to acute liver failure centrilobular necrosis is noticed rather than massive necrosis. Recovery from fulminant hepatic failure is characterized by hepatocellular regeneration.

## BIOCHEMICAL EVALUATION

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are significantly elevated, with values of 1,000 to 10,000 IU/L. Very high values are usually

**Table 2: Grading of encephalopathy**

| Stage | Clinical manifestation | EEG changes |
|---|---|---|
| I (prodrome) | Slowness of mentation, behavioral changes, disturbed sleep-wake cycle, incoordination | Minimal |
| II (impending coma) | Drowsiness, confusion, inappropriate behavior, disorientation, mood swings, asterixis | Generalised slowing |
| III (stupor) | Very sleepy but arousable, unresponsive to verbal commands, marked confusion, delirium, hyperreflexia, positive Babinski sign | Grossly abnormal slowing, triphasic waves |
| IV (coma) | Unconscious, decerebrate or decorticate posturing, response to pain present (IV A) or absent (IVB) | Appearance of delta waves, decreased amplitudes |

found in ischemic injury. Aminotransferase levels at admission are not useful in predicting the outcome. A rapidly falling aminotransferase value in the presence of increasing bilirubin level and clinical deterioration in a child signifies 'exhaustion' of the hepatocyte mass and terminal hepatic failure. The serum bilirubin levels usually increase rapidly. Early in the illness the bilirubin is predominantly conjugated due to excretory dysfunction, while later it is mainly unconjugated, reflecting massive destruction of hepatocytes. Acute liver failure with very high transaminases but no hyperbilirubinemia should suggest Reye syndrome.

Prothrombin time is prolonged and uncorrected by vitamin K administration. It represents loss of synthetic function of the hepatocytes. There is decrease in factor V activity (<50%) and elevated amounts of fibrin degradation products in the blood. Additional blood abnormalities found are hypoglycemia, hyperammonemia, lactic acidosis, electrolyte disturbance and hypoalbuminemia [9]. Nonspecific markers of sepsis and multiple cultures are important in management. Tests to determine the specific etiology are indicated after the condition has stabilized.

## COMPLICATIONS OF ACUTE LIVER FAILURE

### Cerebral edema

Cerebral edema is uncommon in stages 1 and 2 but seen in all patients with stage IV encephalopathy and is recognized as a major risk factor for death [10]. It may be cytotoxic or vasogenic edema. Hypotension, hypoxia, hypoglycemia, sepsis, hyperkalemia and GI bleeding worsen intracranial hypertension. Indicators of raised intracranial tension are pupillary abnormalities, muscular rigidity, decerebrate posturing, focal seizures and loss of brain stem reflexes [11].

CT or MRI brain scan will show flattening of the gyri and reduction in ventricular size. Loss of the definition of grey / white matter is a poor prognostic sign. Fixed, dilated pupils indicate irreversible brain damage.

## COAGULOPATHY AND BLEEDING

Failure of hepatic synthesis of clotting factors and fibrinolytic factors, platelet dysfunction and intravascular coagulation are responsible for the coagulopathy. About 50% of patients will have platelet counts below 80,000/cumm. Profound thrombocytopenia is unusual and indicates DIC, hypersplenism or aplastic anemia. Gastrointestinal tract is the common

site of bleeding. While FDP levels are mildly elevated in acute liver failure, very high levels may indicate sepsis.

## ENCEPHALOPATHY

Encephalopathy is an essential pre requisite in the diagnosis of acute liver failure. At present, the main substances implicated are ammonia and other intestinal neurotoxins, false neurotransmitters, and the abnormal ligands acting on the benzodiazepine- GABA receptors [12]. Neurotransmission changes induced by these compounds play a major role in the development of the neurologic disturbances presented by the patients. Medical interventions of proven benefit are based on the ammonia hypothesis, while other mechanisms are being studied for their therapeutic potential [13].

Unlike chronic liver failure, hyperammonemia is always noted in acute liver failure. Elevated ammonia levels result from impaired handling of ammonia by the diseased liver. However, serum ammonia levels do not correlate with the level of encephalopathy, since ammonia transfer across the blood brain barrier is independent of blood levels [14]. The presence of cerebral edema and intracranial hypertension also contribute to the altered sensorium.

### Metabolic disturbances

Hypoglycemia is common and the blood glucose levels may be less than 40 mg/dl. It occurs not only from impaired gluconeogenesis but also from high plasma insulin levels due to ineffective insulin degradation by liver. Frequent monitoring of blood glucose is important, since classic signs and symptoms of hypoglycemia are often masked. Profound refractory hypoglycemia carries a grave prognosis.

Hyponatremia is common despite sodium retention by the kidney. This is either due to S.I.A.D.H or excess administration of hypotonic saline. Hypokalemia may be secondary to hyperaldosteronism, vigorous diuretic use or continuous nasogastric suction. Hyperkalemia may be observed in patients with massive hepatic necrosis and /or hemolysis.

Respiratory alkalosis due to central hyperventilation may be seen early. Metabolic acidosis/ alkalosis and respiratory acidosis can be encountered during the course of the illness.

### Renal Dysfunction

Renal failure may be due to hypovolemia, hepatorenal syndrome or acute tubular necrosis. Hepatorenal syndrome (functional renal failure) is most common and is characterized by low urinary sodium (<20mEq/L), normal urinary sediment and elevated urine to serum creatinine ratio. Blood urea levels may not always reflect the exact renal function, since the diseased liver cannot synthesize urea from ammonia. In addition, G I hemorrhage may produce a disproportionate increase in blood urea. Serum creatinine is therefore a more reliable marker of renal dysfunction in acute liver failure. Dehydration, low mean arterial blood pressure, gastrointestinal bleeding and septicemia can precipitate renal failure.

### Cardiopulmonary complications

Children with ALF may have hyperdynamic circulation with decreased systemic peripheral vascular resistance and increased cardiac output. Pulmonary manifestations are quite common, albeit underestimated. Ventilation perfusion mismatch as a result of pulmonary vasodilatation secondary to circulating vasodilators can lead to severe refractory hypoxemia. Pulmonary edema due to neurogenic cause, loss of vascular integrity and fluid overload is quite common. Aspiration pneumonia and pleural effusion may also complicate the clinical course. Pulmonary hemorrhage is often terminal.

### Infections and systemic inflammatory response syndrome

The risk of acquiring severe bacterial infections is increased in patients with acute liver failure. There is reduced immune response to pathogens and sick children with

poor respiratory effort and weak cough reflex are at high risk for serious infection while in the intensive care unit. Infections worsen the overall prognosis. Systemic inflammatory response syndrome is noted commonly, and its severity correlates with the presence of other complications. Fever and Polymorphonuclear leukocyte response may not always be present. Staph aureus, Coliforms and Candida are commonly responsible for sepsis.

## MANAGEMENT

Acute liver failure is a medical emergency since it may be rapidly fatal. Sick children must be transferred to specialized centers at the earliest for better outcome. Intensive care monitoring and early recognition of complications can help avoid transplantation or death. Management is aimed at life support as well as prevention and treatment of complications, to facilitate regeneration and recovery of the liver. Following initial cardiopulmonary assessment and emergency measures to stabilize the child, a detailed history including that of drugs should be obtained. Clinical examination should focus on signs of chronic liver disease, and involvement of other systems.

### Immediate intensive care

The child must be managed in an intensive care setting with facilities for continuous monitoring [15]. A quiet environment with minimal stimulation reduces acute changes in the intracranial pressure. Patients with encephalopathy are aggressive and may require restraint and sedation. A child with tachycardia, poor peripheral circulation, pallor or dehydration needs fluid resuscitation. Adequate intravenous access with two peripheral lines is imperative. A CVP line is ideal in those with shock, bleeding, cerebral edema and higher grades of encephalopathy. It is ideal to start with about 70% of maintenance IV fluid requirement. Hydration is best monitored with central venous pressure, the target being 6-8 cm of water. All patients should be carefully monitored for the following - Oxygen Saturation, Urine Output, Central venous pressure and blood pressure. Blood gas analysis, Electrolytes, blood sugar, prothrombin time, Blood counts as well as Blood and urine cultures should be done as required. Coma scale and neurologic evaluation should be done immediately and repeated twice daily. A feeding tube and urinary catheter should be inserted. Securing of airway will facilitate elective intubation particularly in patients with stage III & IV coma. This will help prevent aspiration and assist ventilation to bring down the intracranial hypertension. For sedation and paralysis during ventilation, fentanyl and atracurium are recommended.

### Specific therapy

N.Acetyl cysteine (140 mg/kg initially followed by 70 mg/kg 4 hourly) is the specific antidote for paracetamol poisoning. It replenishes the depleted glutathione stores in the liver. It should be given within 12- 15 hours after the ingestion of the drug and continued until the liver failure resolves [16]. There is little evidence of its efficacy in other causes of acute liver failure, but is used as a routine in many centers.

Intravenous acyclovir 150mg/$m^2$/day should be given in those with herpetic hepatitis. Penicillin G and silymarin are accepted antidotes for mushroom poisoning but they offer only modest benefit. Pulse steroid therapy and immunosuppresants are useful in autoimmune hepatitis. NTBC (2-nitro - 4,3 trifluoro-methyl benzolyl -1,3-cyclohexanedione) may benefit children with hereditary Tyrosinemia type 1.

### Diet and Nutrition

A constant intravenous infusion of 10% dextrose in 0.25N saline is recommended [17] to maintain blood sugar above normal levels. Rapid elevation of blood glucose level with bolus doses of dextrose is counterproductive, since it will further stimulate insulin production and rebound hypoglycemia. Total fluid intake should be restricted to two thirds of normal maintenance to decrease cerebral

edema. Protein restriction is not necessary in Grade I and Grade II encephalopathy. In advanced stages, introduce proteins at 0.5 g/kg/day with a gradual increase to 1.5 g/kg/day over the next few weeks as the liver recovers. Vegetable proteins are usually preferred. Micronutrients, Vitamin C, Vitamin E and Zinc must be given. Parenteral nutrition reduces ammonia production. Enteral feeds should be started as early as possible.

**Encephalopathy**

A nasogastric tube must be inserted and continuous drainage of gastric contents must be done. Hypertonic enema should be given soon after admission to evacuate the colonic contents. Subsequently the large bowel should be washed out twice daily. Lactulose should be given orally or with the help of a naso-gastric tube in doses of 0.5 ml/kg/dose (max 30 ml / dose) four times a day to produce 2 – 4 loose stools / day. It decreases urea producing gut organisms and also traps ammonia in the gut. Oral ampicillin, metronidazole, neomycin and oral vancomycin are used to sterilize the gut and prevent ammonia production. Some authors discourage the use of neomycin as it may precipitate renal failure and does not offer advantage when combined with use of lactulose [18]. A recent review suggests that Rifamixin (an analogue of Rifamycin) has the best benefir/risk ratio, but is presently not available in India [19]. Branched chain amino acids, flumazenil and extracorporeal circuits can improve encephalopathy, but results have not consistent to recommend their routine use. Infusion of L ornithine and L aspartate aims to reduce ammonia by augmenting its tissue metabolism into urea and glutamine. There are no standard dosing guidelines for children, but some controlled trials report benefit in mild encephalopathy. Flumazenil a benzodiazepine antagonist, probably has some role in early encephalopathy, when given as a continuous infusion at the rate of 0.01 mg/kg/min. Trials are insufficient to recommend their routine use. Sodium benzoate and phenyl acetate are routinely used to treat hyperammonemia in urea cycle defects. More trials are needed before they can be recommended in encephalopathy from acute liver failure. The role of probiotics in management of encephalopathy needs more convincing proof. Midazolam is considered a safe sedative and anticonvulsant. Phenytoin or phenobarbitone may be required if there are seizures. Newer anticonvulsants like levetiracetam have not been adequately studied.

**Cerebral edema**

Management of raised intracranial tension should be early and vigorous [20]. The head end of bed should be raised to 20 - 30 degrees and the head should be in the neutral position. Mannitol is used when there are signs of intracranial hypertension in doses of 0.5 gm / kg every 4 to 6 hours. Serum osmolality should not exceed 320mOsm/L during treatment. It should be used with caution in patients with renal failure. Hypoxia and hypercapnea should be corrected to reduce vasodilatation. Intracranial pressure (ICP) monitoring should be done if possible. The goal is to keep the ICP below 20 mmHg. Controlled hyperventilation to a PaCO2 of 30 -35 mmHg may be useful to reduce ICP in severe cases. High dose barbiturates or controlled hypothermia (32$^{o}$F to 35$^{o}$F) can be tried if other measures fail. Steroids are not recommended.

**Electrolyte imbalance**

Daily requirement of sodium is 1 mEq/kg/day. Most often fluid restriction is enough for correction of the dilutional hyponatremia which occurs due to inappropriate secretion of anti diuretic hormone. Potassium, phosphate and magnesium need to be supplemented. Hypokalemia is a known risk factor for precipitating encephalopathy and should be corrected. Potassium requirement may be higher (3 to 6 mEq/kg/day) in a child with acute liver failure and therefore maintenance IV fluid should contain not less than 20mEq/L of potassium. Metabolic acidosis may require intravenous sodium bicarbonate, elective ventilation or bicarbonate dialysis.

### Coagulopathy

Vitamin K is routinely administered intravenously. Fresh frozen plasma or blood can be administered for rapid correction of coagulation abnormalities but the risk of fluid overload, protein overload and hypernatremia should be weighed against the benefit. Severe thrombocytopenia requires platelet transfusions. For temporary correction of coagulopathy before an invasive procedure, activated recombinant factor VII can be used in combination with fresh frozen plasma. The recommended dosage is 15-30 mcg/kg every 4 to 6 hrs until hemostasis is achieved.

Gastrointestinal hemorrhage can be life threatening. Cold saline washes every 4 hours along with parenteral PPI's or H2 receptor antagonists can help control gastric bleeding.

### Renal Insufficiency

Renal perfusion should be maintained and nephrotoxic drugs avoided. Pre renal failure may be managed initially with a fluid challenge followed by adequate fluid administration to maintain the CVP. Frusemide can be used in mild renal failure. Dopamine helps maintain renal perfusion. Dialysis should not be delayed if there is renal failure. Since they are hemodynamically unstable, continuous arteriovenous hemofiltration technique is preferred over conventional hemodialysis in hepatorenal syndrome [21].

### Infections

Bacterial and fungal infections are always seen in sick children with acute liver failure. Signs of sepsis may be very subtle. Broad spectrum antibiotics are usually recommended. Amino glycosides are best avoided, since they may contribute to renal failure. All infected indwelling catheters must be removed promptly. There is no clear choice of antipyretic, since they are all potentially hepatotoxic. Tepid sponging is harmless, though not very effective. Paracetamol is most commonly used when an antipyretic is indicated.

### Hypoxia and Respiratory complications

Endotracheal intubation is mandatory in a deeply comatose child. Elective mechanical ventilation should be initiated at the first sign of respiratory failure. Pulmonary edema can be managed with diuretics and correction of plasma oncotic pressure with albumin infusion.

### Temporary Hepatic Support

This helps to support the patient and prevent neurological impairment while awaiting hepatic regeneration or liver transplantation. Plasmapheresis, exchange transfusions, extra corporal blood cleansing, liver assisted devices containing cultured hepatocytes and Cross circulation with animals have been tried. Molecular adsorbant – recirculating system (M.A.R.S) has shown promising results in adults but is expensive and experience in children is limited [22].

## LIVER TRANSPLANTATION

Liver transplantation remains the only definitive treatment that has improved the outcome in acute liver failure. Indications for transplantation vary from one centre to another. It should be considered in all children with stage III or stage IV hepatic coma, prothrombin index less than 20% (PT index = Standard PT / Observed PT x 100), serum bilirubin level > 23 mg/dL [23]. Kings College London criteria include Prothrombin time >100 s (independent of the grade of encephalopathy) OR any three of the following variables (independent of the grade of encephalopathy) - Age <10 years, Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions, Duration of jaundice before onset of encephalopathy >7 days, Prothrombin time >50 sec, Serum bilirubin >18 mg/dl [24]. In general, the indication for transplantation is lack of improvement in encephalopathy and coagulopathy with intensive medical management alone. It should however be early enough so that the neurological dysfunction is still reversible [25].

Acute liver failure of unknown etiology and fulminant presentation of Wilson's disease [26] will most often require liver transplantation as they are less likely to benefit from intensive medical care alone. Paracetamol induced acute liver failure usually responds to intensive medical measures. Contraindications for transplantation include irreversible brain damage, uncontrolled sepsis and severe respiratory distress syndrome. Success rates in liver transplantation for acute liver failure are lower than that done for other indications.

Auxiliary liver transplantation, where the recipient's liver is left in situ to regenerate, while grafting the new liver, can be tried if there are chances of recovery of the diseased liver. The donor liver atrophies once the native liver recovers.

## PROGNOSIS

The cause of liver failure is an important factor that determines the outcome. Hepatitis A infection and Paracetamol poisoning have the best prognosis [27]. Absence of an obvious etiology (indeterminate cause) and higher grades of encephalopathy indicates a poor prognosis. Fulminant Wilson's disease also has a poor prognosis without transplantation.

The severity of the encephalopathy determines survival. Only 18% of children with grade IV hepatic coma survive. Children less than three year, requirement for dialysis and grade IV encephalopathy are poor prognostic factors [28]. Presence of cerebral edema, INR > 2.5 and multiorgan failure are other bad prognostic indicators. Ventilator dependency prior to transplantation is the strongest predictor of ultimate survival as reported by one study [29]. Serum ammonia, aminotransferase levels, hypoglycemia and acidosis do not have prognostic significance. In children who survive fulminant hepatic failure, recovery is usually complete. Overall mortality reported in Indian studies varies from 60 % to 75% [30].

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