Title- Emergencies in Pediatric hepatology

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Abstract:

Etiology of several liver diseases in children are age specific and many of these conditions if not diagnosed early and managed timely have significant repercussions towards their long term outcome. We address this subject in the following five clinical scenarios that cover most of the diagnostic and therapeutic emergencies in children.

The wide spectrum of conditions causing liver disease in infants may present as conjugated jaundice and that could be the only symptom of time-sensitive disorders such as biliary atresia, metabolic disorders, infections, hematological and alloimmune disorders where an algorithmic multistage testing is required to establish the correct diagnosis. Early administration of vitamin K in cholestatic infants, use of specific milk formulae and disease specific medications are essential to avoid mortality and life-long morbidity.

Management of pediatric acute liver failure requires co-ordination with a liver transplant centre, safe transport and detailed age-specific etiological work-up. Central to survival is supportive care with clinical stabilization until transplantation if indicated.

Gastrointestinal bleeding due to varices may present as the initial manifestation or during follow up in patients with portal vein thrombosis or chronic liver disease. We discuss the initial stabilisation and management options including pharmacological therapy followed by endoscopic and radiological interventions.

Liver-based metabolic disorders may present as hyperammonaemia or hypoglycaemia with minimal or no abnormality of liver enzymes. Early recognition and specific therapies can be lifesaving or avoid neurological sequelae.

Liver tumors and liver trauma are both rare occurrences in children and are best managed by a multidisciplinary team in a specialist centre.
Key Points:

1. Emergencies in pediatric hepatology include both seriously unwell children with acute liver failure, variceal bleed, liver trauma or encephalopathy and seemingly well children with neonatal cholestasis or a liver mass that are a diagnostic urgency.

2. In infantile cholestasis, algorithmic multistage tests are necessary for early accurate diagnosis while addressing complications of fat soluble vitamins particularly vitamin K and use of specialist milk formulae.

3. In pediatric acute liver failure establishing diagnosis, expert supportive and disease-specific care along with identification of liver transplant candidates and its timing.

4. Liver based inborn errors of metabolism causing hyperammonaemia, hypoglycaemia, acidosis or aminoacidopathies may present with encephalopathy that need early recognition and metabolic stabilisation for better neurological outcomes.

5. Rapid work-up of liver masses is essential to identify malignancies, vascular tumors/malformations and infective lesions to offer etiology specific treatments.
**Introduction:**

In the practice of pediatric hepatology, conditions considered as emergencies vary from seriously unwell children requiring immediate intensive care to stable, well-thriving infants with liver disease. Timely recognition and appropriate multidisciplinary management of these disorders can result in favourable outcomes. A comprehensive discussion on all emergencies is beyond the scope of this article. We have focused on common emergency scenarios that cover the vast majority of the general pediatric hepatology practice. We opted to focus on five clinical scenarios: infants with liver disease, acute liver failure, management of bleeding varices, liver-based metabolic disorders, liver tumors and trauma. While it is to be acknowledged that the understanding and approach to some of these emergencies are heavily influenced by data from adult literature, many disorders causing liver disease are unique to children or manifest differently in this population. Unlike in adults, many diagnoses in children are age dependent. We discuss the available evidence or the lack of it in this age group and highlight variations in practices between children and adults. The review will be of interest to practising pediatric hepatologists, gastroenterologists, adult hepatologists caring for patients with childhood liver diseases and other health care professionals involved in the management of children with liver disease.

**Infant with liver disease – a diagnostic emergency**

Infants presenting a new diagnosis of liver disease constitute the largest group in pediatric hepatology. An infant presenting with liver disease should be managed as an emergency even if the child does not look acutely unwell. Establishing a correct diagnosis and recognising and treating complications like coagulopathy, hypoglycaemia and other metabolic derangements in a timely fashion could prevent life-limiting or life-changing sequelae. Some of the time-sensitive diagnoses include metabolic disorders such as galactosemia and tyrosinemia type 1, hemophagocytic lymphohistiocytosis, herpes simplex infection, gestational
alloimmune disease (GALD) and Biliary atresia (BA). BA constitutes around 25% of all causes of neonatal-onset cholestasis managed in liver centres.(1) Infants with BA look deceptively well but delayed diagnosis and treatment beyond 2 months of age is generally associated with poor native liver survival. 70% of infants with BA who undergo a Kasai portoenterostomy at an age of <30 days survive with their native liver to an age of 2 years with a bilirubin of <6mg/dl while this number is reduced to 50% and 0% in those operated beyond 90 and 120 days of age.(2)

The diagnostic challenge stems from the fact that about 60% of term and 80% of preterm new born babies develop physiological unconjugated jaundice.(3) The recognition of conjugated jaundice or infantile cholestasis (IC) is often missed amongst these cases. Prolonged jaundice longer than 2 weeks of age in a term infant and 3 weeks in a premature infant should trigger investigations for IC.(4) This includes any child in whom the parent or the health care worker reports pale stools or yellow diaper staining of urine. Around 37% of doctors and nurses and 66% of parents do not identify pale stools correctly in the absence of stool colour card as a guide.(1, 5) Infant stool colour cards can improve recognition of pale stools by parents from 66 to 87%.(6) Stool colour card as a population screening tool for biliary atresia has been shown to be cost-effective in screening for biliary atresia.(7, 8)

**Emergency interventions before definitive diagnosis**

Infants with liver disease may present acutely with complications resulting from bleeding due to vitamin K deficiency or liver failure and metabolic decompensation such as hypoglycaemia. These complications are managed in parallel to the rapid work-up for an etiology. Vitamin K deficiency induced coagulopathy can lead to cutaneous hematomas, gastrointestinal bleeds and intracranial bleeds. Intracranial bleeding due to vitamin K deficiency is more common with delayed diagnosis of biliary atresia with a frequency of up to 11% in Japanese infants and may result in serious neurological sequelae.(9) Hypoglycaemia
may occur as a result of neonatal acute liver failure or endocrine disorders. It tends to be out of proportion to the liver dysfunction in galactosemia where one-fourth of children present with hypoglycaemia.(10) Hypoglycaemia in the setting of preserved liver synthetic function may suggest endocrine disorders such as panhypopituitarism with or without septo-optic dysplasia.(11) In neonates with liver failure prompt administration of acyclovir to treat Herpes Simplex infection and switching feeds to a lactose free formulation to treat galactosemia are early interventions to improve outcomes while awaiting confirmatory test results.(12)

**Diagnosis:**

In view of the broad etiological spectrum in infants with liver disease, diagnostic protocols often employ multistage tests while taking into account the urgency of each diagnosis and their relative frequency. Clinical features and other organ involvements could provide clues to the cause of neonatal cholestasis (Table 1). The cholestasis may be multi factorial as in neonates with a history of prematurity, sepsis, necrotizing enterocolitis, intestinal surgeries and parenteral nutrition. A family history of affected siblings is usually seen in inherited disorders. GALD, though not inherited, also presents with history of affected siblings. A thorough history and examination for dysmorphisms and other organ involvement including endocrine, cardiac, neurological involvement help suggest an etiology.

Elevated Transaminases in isolation are less useful in reaching a diagnosis. However, very high serum transaminase values may suggest a viral etiology (Herpes Simplex in infants) or ischemic hepatitis. Normal transaminases disproportionate to the liver dysfunction may be seen with extensive parenchymal loss in neonatal liver failure as in cases of GALD.(13) A normal or low gamma glutamyl transpeptidase (GGT) raises the possibility of Progressive Familial Intrahepatic Cholestasis type 1 and 2 , Tight Junction Protein -2 disease, NR1H4 or MYO5B gene mutations or bile acid synthetic disorder.(14) Low serum bile acid level with a
low/normal GGT may suggest bile acid synthesis defect. An algorithm for diagnosis and investigations available to make a diagnosis are detailed in figure 1 and table 2.

Children with biliary atresia, neonatal presentation of choledochal cyst, neonatal sclerosing cholangitis, choledocholithiasis and inspissated bile duct syndrome invariably present with pale stools. Demonstration of pigmented stools rules out biliary atresia at that point in time. The role of hepatobiliary scintigraphy is restricted to children in whom the stools are ambiguous where there may be a benefit in avoiding a liver biopsy, such as in preterm infants. Other disorders with severe cholestasis may also present with pale stools.(15, 16) Liver biopsy has had a central role in rapid diagnosis of biliary atresia with accuracy rates of 88-96.8%. (15, 17) It also provides clues towards biliary ductal paucity and transporter defects when immunohistochemistry is used. Ultrasound is most useful for the diagnosis of choledochal cyst where a cyst and/or biliary dilatation is demonstrated. MRCP may be required to investigate further. The role of ultrasound in the diagnosis of biliary atresia is quite variable across centres. A small gallbladder with poor contractility, cyst at the porta hepatis, triangular cord sign, subcapsular plexus and dominant hepatic artery are described as diagnostic features in BA. The finding of triangular cord sign has been made objective by measuring the echogenic anterior wall of right portal vein.(18) A metanalysis of the role of ultrasound in diagnosing biliary atresia showed that combination of the triangular cord sign and an abnormal gallbladder for diagnosis achieved a summary sensitivity of 0.95 (95% CI, 0.70–0.99), summary specificity of 0.89 (95% CI,0.79–0.94),(19) Yet this data from specialised units is not universally replicated. ERCP examination in centres with the expertise may help avoid laparotomy by demonstrating biliary tree patency in cases where diagnosis remains doubtful even after liver biopsy. The reported successful ERCP completion rate is 89.2% with no procedure-related complications, positive predictive value of 92.2% and negative predictive value of 97.1%.(20)
The advent of next-generation sequencing has improved recognition of genetic disorders such as Alagille syndrome, bile acid transporter defects, bile acid synthetic disorders, storage and other metabolic disorders. The availability of targeted gene panels and the invasive nature of liver biopsy has decreased the need for biopsy in making the diagnosis of many of these disorders.(21)

**Acute liver Failure**

Acute liver failure (ALF), though uncommon in the population, is an important cause of mortality. About 12.5% of all liver transplants in children are performed for ALF (22-24). Pediatric acute liver failure (PALF) differs from adult in its,

I) Definition

II) Etiology and

III) Selection criteria for liver transplantation (LT)

The challenges in management of PALF include-

i. Timely transfer to a specialist liver centre

ii. Establishing etiology

iii. Predicting need for LT

iv. Supportive management while awaiting liver transplant surgery or native liver recovery to minimise mortality and long-term complications like neurological injury.

**Recognition, referral and transfer**

PALF is defined as a hepatic-based coagulopathy with biochemical evidence of acute liver injury leading to an International Normalised Ratio (INR) $\geq 1.5$ not correctable by Vitamin K in the presence of clinical hepatic encephalopathy (HE) or an INR $\geq 2.0$ irrespective of the presence of encephalopathy, in patients with no known evidence of chronic liver disease.(25) Behavioural changes of children in the hospital environment may be difficult to differentiate.
from early HE. Many children may not be noted to be encephalopathic until much later in the course of their liver failure. Thus PALF differs from the definition of ALF in adults where HE is a mandatory criterion. (26) Some of the disorders presenting as PALF, like Wilson disease (WD), autoimmune liver disease, GALD and tyrosinemia type 1, may have a degree of fibrosis and chronicity on histopathology. Thus they may not fit the classic definition of acute liver failure in the strict sense. Yet their current classification as PALF is driven by the presentation and natural history that mimics acute liver failure.

Patients with worsening coagulopathy should be discussed with or transferred to the nearest liver centre with liver transplant facilities. The criteria for transfer varies based on the local health care setup and etiology (eg: higher INR threshold for paracetamol toxicity). Suggested transfer criteria to a specialist centre are, (i) Paracetamol toxicity with INR>3 and increasing or any degree of extrahepatic dysfunction (ii) Non-paracetamol ALF with INR persistently >2.

**Etiology and diagnosis of PALF**

The etiology of PALF is largely different from that in adults. It also varies between the various age-groups in pediatrics while retaining a geographical variation. Supplementary table-1 lists the various etiologies reported in children across various age groups and geographical areas. (25, 27-30) Hepatitis A still continues to be an important cause of PALF in countries from South America and South-east Asia. (28, 30)

A thorough etiological work-up allows for disease-specific treatment and also help in prognostication. (31) Data suggests wide variability in work-up of PALF, especially with screening for autoimmune liver disease and metabolic liver diseases. (32) The limitations include the limited time available for investigations, turnaround times and easy availability of investigations. There is a room for quality improvement in the form of standardised age-appropriate etiological work-up. (Table 3).
In the diagnosis of WD presenting as PALF, serum caeruloplasmin and 24 hour urine copper are unreliable for diagnosis. An alkaline phosphatase to total bilirubin ratio of <4 and AST:ALT ratio >2.2 yielded an AUROC of 0.98. Coombs negative hemolytic anaemia when present supports the diagnosis. (42)

Autoimmune liver disease presenting as PALF (AI-PALF) constitutes 2-6% of all PALF. (25, 27, 43, 44) Type 2 AILD with anti-LKM-1 antibody positivity is more likely to present as PALF. (45) Among children with AILD, those with anti-LKM-1 positivity are typically younger [median 7.4 (0.8-14.2) year] than those expressing anti-SMA antibody [10.5 (2.3-14.9) year]. (45) The diagnosis is compounded by the fact that autoantibodies may be present in 20% of indeterminate PALF and 22% of PALF due to other etiology, especially WD. Anti LKM-1 positivity is more specific to an autoimmune etiology than ANA or anti-SMA antibody positivity. (46) IgG level may be normal in 14-20% of patients with AI-PALF. (44, 47) Diagnostic testing should use an extended panel, including anti-Liver cytosol and anti-soluble liver antigen antibodies. In up to 36% of cases with type 2 AILD, anti-Liver cytosol antibody could be the only positive antibody. (48) All patients labelled as AI-PALF were positive for autoantibodies in two studies on AI-PALF even though children with AILD are known to have negative autoantibodies at the time of diagnosis. (44, 45, 47) Coagulopathy precludes a liver biopsy even though transjugular biopsy is an option. Massive hepatic necrosis, presence of lymphoid follicles, a plasma cell-enriched inflammatory infiltrate, and central perivenulitis are considered distinctive feature of fulminant presentations of AILD. (49) Massive hepatic necrosis type 4 and 5, considered more specific for autoimmune etiology in adults, varies in frequency from 0-66% in pediatric series. (44, 47, 49) The validity of such histological patterns is doubtful in children.

Indeterminate-PALF (ID-PALF) constitutes 43-49% of PALF. (25, 47) This is probably a heterogenous group that includes unknown or undetected viral infections, drug induced liver
injury, undiagnosed metabolic/genetic disorders and disorders of immune dysregulation. ID-PALF is associated with low rates of native liver survival. Occult paracetamol toxicity is probably an important cause. Paracetamol adducts are seen 11% with an ID-PALF. Adduct-positive ID-PALF had a spontaneous survival of 76% compared to 44% in adduct-negative patients (p=0.03).(50) Metagenomic next-generation sequencing and whole exome sequencing in ID-PALF are expected to find subgroups of infective and metabolic/genetic disorders respectively, possibly leading to more individualised care. Role of liver biopsy is controversial in the diagnosis of PALF. Although transjugular biopsy may be safe, the need for general anesthesia is usually a deterrent in children who are not already on assisted ventilation suggesting their severity of illness and need for liver transplantation. Liver biopsy could assist treatment decisions in conditions like AILD and WD where clinical or biomarkers have not been helpful.(51) Di Giorgio et al advise against liver biopsy in differentiating AI-PALF and ID-PALF.(47)

**Management of PALF**

Management of PALF should always be a multi-disciplinary approach that includes liaising with the nearest specialist liver centre. Transfer to specialist liver centres with facilities for liver transplant is determined by limitations in local expertise, particularly availability of intensive care.

Disorders where etiology-specific treatment is available are listed in table 4. Supportive non-transplant care attempts to alleviate the extrahepatic dysfunction resulting from the liver failure so as to sustain life until the liver regenerates while at the same time maintaining the appropriate metabolic milieu and perfusion to allow for hepatic regeneration. This involves monitoring the liver dysfunction including INR and extrahepatic dysfunction while appropriately timing interventions. (Table 5)
Only one in thirteen patients with fulminant WD survive without LT despite albumin dialysis and chelation.(69) Single pass albumin dialysis and plasmapheresis to remove circulating copper are at best bridges to LT.(70) Plasmapheresis has been used in PALF due to WD presenting with hemolysis and renal dysfunction (Grade 1C evidence).(71-77) The new Wilson Index suggests that a score of ≥11 has a positive predictive value of 88% for LT.(78).

Collating the results from literature,12 of the 29 (41.4%) cases of AI-PALF treated in literature have shown response to steroids.(44, 45, 47, 79, 80). The comparative response in adults is 10-41%.(81, 82) While interpreting such data, it is to be remembered that nearly 10-50% of children do not get treated with steroids in view of their advanced state of liver failure.(44, 47) Early grades of HE (< grade 3) and lower MELD score (<27) were associated with response to steroids suggesting that AI-PALF probably offers a narrow window for responsiveness to treatment prior to loss of a critical hepatocyte mass.(82) In adults, response to a 2 week course of steroids is considered a more definitive proof but there is no equivalent pediatric data.(83) The role of plasma exchange as a specific treatment for AI-PALF is not well established .(84)

The pattern of activated CD8 infiltration reflecting a process akin to HLH has been demonstrated in ID-PALF.(85) Immunosuppression protocols based on a demonstration of CD8+ cytotoxic T-cell predominant liver injury in liver biopsy of children with indeterminate hepatitis and PALF have shown spontaneous survival in 5 patients of which only one was ever listed for LT.(86) The role of corticosteroids in ID-PALF and hepatitis associated aplastic anaemia is doubtful considering that the outcomes are no different from that in historical controls.(87)

Among other therapies, the use of N-acetyl cysteine (NAC) in non-acetaminophen liver failure is controversial. Data from a prospective adult study showed a benefit in transplant-free survival with NAC in patients with coma grade I–II.(88) A retrospective pediatric study
showed improved transplant-free survival, lower length of stay and improved post liver transplant survival.\((89)\) However in the prospective study of the use of NAC in PALF did not lead to improvements in 1-year survival \((NAC \text{-} 73\% \text{ vs placebo } 82\% \text{ p}=0.19)\).\((90)\)

The role of plasmapheresis in ALF in adults had been studied by Larsen et al in an open, randomised, controlled study and showed that high volume plasmapheresis with fresh-frozen plasma increases transplant-free survival after 3 months in patients who did not undergo emergency LT, especially in those who fulfilled the criteria for poor prognosis but were not listed for LT due to contraindications.\((60)\) Studies in children involve fewer patients without a control group and hence have not demonstrated a survival advantage. In a study in children by Chevret et al, a group of 15 children with PALF requiring emergency LT with HE grade>2 and/or hemodynamic instability requiring vasopressors underwent high-volume hemofiltration therapy \((\text{ultrafiltrate flow} > 80 \text{ mL/kg/hr})\) without a control group and showed an improvement in mean arterial pressure, serum creatinine and HE grade. Survival outcomes in this specific group is not available as the study also involved children with acute on chronic liver failure and primary non-function of transplanted graft.\((59)\) Ide et al showed a similar decrease in catecholamine index with a combination of continuous veno-venous hemodiafiltration and plasma exchange.\((58)\) Similarly marginal benefit from the use of plasma exchange in the setting of life threatening bleeds or increased requirement for coagulation factor support was reported in a small pediatric study\((65)\) Data from other pediatric series do not confirm its efficacy suggesting the need for further studies.\((91, 92)\)

The use of extracorporeal liver support systems in children is a subject of a few case series, making it difficult to recommend any guidance of its routine use in PALF.\((93)\)

**Prognostication and listing for LT**

Advances in medical management and LT has decreased the mortality from 72\% in the pre-liver transplant era to 14\% currently.\((23, 24)\) Every patient admitted with PALF is assessed
for the risk of mortality without transplant. Available prognostication systems associate single point or multi-point assessments to outcome events which is either death or transplant.(94)

The available prognostic markers include those indicating degree of liver dysfunction, extrahepatic dysfunction, systemic inflammatory response syndrome, age and etiology affect outcomes.(23, 25, 27, 28, 30, 95-98). The various parameters known to affect outcomes and the scoring systems combining these parameters that are validated in PALF are detailed in supplementary tables 2 and 3.(23-25, 27, 28, 30, 95, 97-102)

Median waiting times for LT vary among centres. While patients await LT, focus is on keeping them stable with the measures listed in table-5. Children listed for LT will need ongoing monitoring for features of clinical improvement or worsening that will necessitate delisting. Untreated or progressive infection despite 48 hours of appropriate antimicrobial treatment, invasive fungal infections, rapidly escalating inotrope requirements, objective evidence of brain death and acute respiratory distress syndrome indicate possible futility of LT.(103) Pre-existing advanced or progressive neurological impairment, mitochondrial disorders, active extrahepatic malignancy and multisystem disease may preclude children from LT.

The UK National Health Service Blood and Transplant listing criteria for super-urgent listing for PALF is based on the King’s college hospital score.(104) (supplementary table 4) The Clichy-Villejuif criteria that incorporates factor V levels is more often used in Europe and was predominantly validated in adults with viral hepatitis.(30, 105)

**Management of acute variceal bleeding**

*Causes of variceal bleeding in children*

Variceal bleeding in children could results from cirrhotic or non-cirrhotic causes of portal hypertension. Among children who present with variceal bleeding, the respective
proportions of causes in pediatric portal hypertension (PHTN) in the developed and developing countries are reported respectively as portal venous obstruction in 33% and 84.5%, intrahepatic non-cirrhotic portal hypertension in 12% and 5.5% and cirrhosis in 55% and 10%. Among intrahepatic causes of non-cirrhotic portal hypertension, congenital hepatic fibrosis is the single most common cause accounting for 44-92% of cases. In developing countries, non-cirrhotic portal fibrosis and Budd Chiari syndrome also contribute significantly as etiology. (106, 107)

Among patients with cirrhosis evaluated for LT at least one-fourth have been known to have had an episode of variceal bleeding. (108) Biliary atresia is a common cause of chronic liver disease in children and the onset of portal hypertension is often rapid and disproportionate to the liver synthetic dysfunction. Hence BA is the etiology in at least one-third of all such bleeding children with cirrhosis in the developed world. (107) Nearly 20% of BA present with variceal bleed in follow-up compared to 3% in Alagille syndrome. (109, 110) Three-fourths of children with BA who bleed do so before 21/2 years of age. The risk of bleeding is related to the presence of ascites, total serum bilirubin concentration, prothrombin time, and portal vein diameter. (110)

**Management of variceal bleed**

Children presenting with large volume gastrointestinal bleeding should be assessed for airway, breathing, circulation and blood glucose. Airway intubation may be required in view of encephalopathy, shock or the use of a balloon tamponade (BT) device. At least two intravenous access are to be secured. Intravenous bolus of a crystalloid is required in those who are hypotensive. Rapid pushes of bolus in a normotensive child can precipitate or increase bleeding. A restrictive transfusion strategy with a target hemoglobin between 7-8 g/dl is recommended based on the experience in adults. (111)

Early control of variceal bleed can be achieved by pharmacotherapy with octreotide. Octreotide infusion at 1-5 microgram/kg/hour after a single bolus of 1 microgram/kg helps in
decreasing portal pressure by causing splanchnic vasoconstriction. The reports of use of Octreotide in pediatric portal hypertension is restricted to case series. Octreotide controls bleed in around 70% of patients, with hyperglycaemia and abdominal pain being the only adverse events.(112-114) Terlipressin has the advantage of subcutaneous intermittent administration but experience in children is limited. Abdominal cramps, diarrhoea and hypertension are potential complications with Terlipressin with similar or lower rates of bleed control when compared to octreotide.(115) Children with chronic liver disease with coagulopathy may need transfusion of coagulation factors in addition to vitamin K. The use of coagulation factors should be restricted to those with VB unresponsive to pharmacological and endoscopic therapy. Platelet transfusion is also restricted to such patients with a platelet count of <50,000 platelets per microlitre. The use of proton pump inhibitors in recommended for gastric mucosal bleeding prophylaxis.

Endoscopic therapy is recommended in patients once hemodynamic stability is achieved. A patient who is refractory to pharmacological therapy and unstable hemodynamically may require BT and the choice of the device is usually dictated by the local expertise. 75% children respond to octreotide infusion the rest can usually be controlled on endoscopic therapy with recourse to BT being a rare event.(112) The high complication rates associated with BT is a major deterrent to its overenthusiastic use. Endoscopy should preferably be performed electively within 24 hours if the bleed is controlled pharmacologically but may be required as an emergency if not controlled by octreotide alone.(116, 117) In practice, only 28% endoscopies are performed within 24 hours and this has not been associated with adverse outcomes.(118) Endoscopic variceal ligation (EVL) is the preferred modality of therapy when the esophageal varices are big and banding device can be passed into the esophagus (usually in children >10-12 kg).(119) 100% bleeding control has been reported .(120) In small children where banding is not possible sclerotherapy can be used effectively.
Sclerotherapy of esophageal varices has been shown to control bleed in 97% cases. Octreotide infusion may be tapered gradually over a day or two following endotherapy. The median period of octreotide infusion was 4 days in a pediatric series of 70 VB episodes.

Gastric variceal bleeding requires a different approach to management. Gastroesophageal varices on the lesser curvature may be managed with EVL but gastroesophageal varices on the greater curvature and isolated gastric varices in the fundus should not be banded or sclerosed. Cyanoacrylate glue injection is the standard of care. The use of lipiodol along with glue may result in delayed polymerisation and higher chances of embolization. In a series including 28 children who underwent sessions for bleeding gastric varices achieved hemostasis in all patients. Early rebleeding is known to occur from ulceration and incomplete obliteration. Late bleeding may also occur due to glue cast extrusion. A repeat endoscopy within a week may be required to ensure complete obliteration. All patients who have received glue injection are kept on proton pump inhibitors until follow-up endoscopies confirm the absence of a gastric ulceration.

Endoscopic ultrasound guided transluminal glue injection maybe required in those in whom the bleeding prohibits adequate visualisation by convention endoscopy. This may be combined with coil injection of the varix to act as a scaffolding that facilitates polymerisation of the glue and limits the amount of glue required for obliteration and also the chances of systemic embolization. This may be more relevant in large gastric varices >20 mm. Yet the size of EUS scopes and the limited availability of expertise has limited widespread adoption of this technique. Also, there is no evidence to show that it may be superior conventional endoscopic technique of glue injection.

In patients in whom pharmacotherapy and endotherapy have failed, Transjugular intrahepatic portosystemic shunt (TIPSS) should be considered to control variceal bleed, especially in Budd-Chiari syndrome and congenital hepatic fibrosis. In cirrhotic
patients, TIPSS usage could lead to encephalopathy. Hence it should be offered to children with minimal synthetic dysfunction of the liver or as a bridge to liver transplant. In very young children, TIPSS is limited by the availability of appropriate size stents and technical expertise.

It is desirable to use prophylactic antibiotics in all children with cirrhosis with variceal bleed to cover for gram-negative infections. In the absence of guidelines in children, only 54% receive prophylactic antibiotics after VB.

New onset ascites or increase in ascites often follows variceal bleeding in patients with cirrhosis. This is often a reflection of the degree of synthetic dysfunction in these patients. Children with portal vein obstruction who have massive bleeding leading to low albumin may also develop transient ascites. Restricting sodium administration, early switch to oral feeds and diuretics once the bleed has been controlled help in ascites management. Mortality due to uncontrolled bleeding and in the first 6 weeks following bleeding from varices can be up to 8% in BA and other cirrhotic patients. Mortality is uncommon in portal vein obstruction (1.7%). Almost 57% developed morbidity associated with prolonged hospital stay result from either ascites (34%), infection (30%), respiratory complications (24%), ICU admission (20%), re-bleed (11%), encephalopathy (7%), acute kidney injury (6%) and failure to control bleed (4%). Serum total bilirubin value predicts morbidity in patients with variceal bleed.

While clarity and innovation in primary prophylaxis of young children are awaited, there is a need to effectively manage variceal bleeding in children to decrease mortality and morbidity.

**Liver mass**

The finding of liver mass/masses in infants and children necessitate urgent investigations to determine the nature of the lesion. Diagnoses include liver abscess, malignancies and vascular tumours. Tumor markers like alpha-feto protein and axial imaging
computerised tomography and or magnetic resonance imaging usually establish the diagnosis with an occasional need for liver biopsy.

This review would focus on the emergency presentations of tumors including symptomatic hepatic hemangioma in infants and bleeding in a liver mass.

Infants with hepatic hemangioma may present with large or multifocal lesions that are symptomatic with high output cardiac failure. Abdominal distention may lead to the respiratory compromise and abdominal compartment syndrome. This may be accompanied by consumptive thrombocytopenia and hypothyroidism. Initial stabilization may include judicious use of diuretics in those with early symptoms or inotropes and ventilation in those with significant hemodynamic and respiratory compromise. Use of propranolol at 1-3 mg/kg/day is beneficial in children not in heart failure. Pre-operative cross sectional imaging could delineate the blood supply to the tumour. The most established treatment is selective transcatheter embolization of the arterial supply of the hemangioma. Depending on the centre’s expertise and preference, hepatic artery ligation also could be helpful. Liver transplantation may be required rarely.

Bleeding from liver tumours may result from intraperitoneal rupture of tumour, intratumoral bleeding or very rarely hemobilia in adults as with hepatocellular carcinoma (HCC) and cholangiocarcinoma. Intra-tumoral bleeding without rupture presents as an incidental imaging finding or as sudden onset abdominal pain and distension. In very young infants, this could result in significant hemodynamic compromise. In contrast, intraperitoneal rupture is often catastrophic. Unlike adults where HCC and telangiectatic adenomas are common causes of intraperitoneal rupture, in the pediatric age group this is often seen with hepatoblastoma (HB) and infantile hemangioma. The reported incidence of HB rupture is variable (5-16%) in view of the unclear definitions of rupture in the earlier co-operative study groups. The 2017 PRETEXT staging system for the PHITT trial proposed a clearer
definition for rupture. (140) Clinically manifest intraperitoneal rupture presents with pallor, abdominal pain, sudden abdominal distention and hemodynamic compromise. 82% of intraperitoneal rupture in HB is spontaneous which may precede or follow chemotherapy. The rest may be due to liver biopsy (18%) or without a definite documentation of trauma. (136) Rupture after biopsy is often seen in those with a subcapsular hematoma prior to biopsy.

**Stages of management**

*Stabilization:* Children presenting with hypovolemia and anaemia are resuscitated with adequate volume replacement, transfusions and inotropes when necessary. Shock and abdominal distention leading to respiratory compromise may necessitate respiratory support. Coagulopathy and thrombocytopenia are often seen in adults with rupture of HCC occurring in the background of a chronic liver disease with hepatic insufficiency. It could be seen in children with ruptured HB as a result of massive transfusions, shocked liver with decreased hepatic reserve or thrombocytopenia induced by chemotherapy necessitating blood product support.

*Early diagnostic investigations:* An ultrasound would detect the liver mass, hematomas within the mass and the subcapsular area and intraperitoneal fluid with suggestion of hemorrhage. Triple phase abdominal CT angiography should be done as soon as the child is hemodynamically stable. This confirms the hemoperitoneum, any liver hematoma including any subcapsular component, contrast extravasation indicates active bleeding and identifies the vessel supplying the bleeding tumour which could be targeted for intervention. When spontaneous rupture is the initial presentation of HB, it also poses a diagnostic challenge. Characterising the tumour could be more difficult at this stage because of the hematoma and could be better done with a subsequent contrast MRI. (135)

*Definitive management:* Transarterial embolization (including transumblical route in neonates) is now the intervention of choice in ruptured hepatic tumours with ongoing bleed. (141-144) Embolization is possible in 90% of adults but success rates in children is not
known as reported cases are few. Small calibre tortuous vessels and anatomical variation could increase procedural complexity.(135, 137, 145) In patients who cannot be stabilized hemodynamically or with failed radiological embolization, emergency laparotomy is indicated, sometimes just with sonographic evidence of hemoperitoneum. Emergency liver resection is rarely done as it may have higher mortality and morbidity. Hemostasis is achieved with perihepatic packing and temporary clamping of hepatic pedicle.(135, 146) Once stabilized, staged procedures are planned.(146) and could include attempts at intraoperative or post-operative radiological embolization.(143)

Liver trauma
Liver trauma in children results from blunt or penetrating injuries and can affect other organs as well. Increasingly liver trauma is managed conservatively. In a single centre study, 90% of liver injuries were successfully managed with non-operative management.(147) However easy access to intervention radiology and ERCP is essential.(148) An algorithm for management of blunt and penetrating liver injuries is outlined in figure-2.(147-149) After the initial stabilization and control of bleed, children will need follow-up for biliary and vascular complications.

Metabolic encephalopathy due to liver based inborn errors of metabolism (IEM)

Manifestations and diagnosis:
Metabolic encephalopathies resulting from IEM present early in life in infants and children even though disorders such as ornithine transcarbamylase deficiency could present for the first time in adulthood with encephalopathy. Having ruled out other causes of encephalopathy (infections, toxins and primary neurological conditions), a family history of metabolic disorders, unexplained infant deaths, consanguinity, neonatal onset encephalopathy,
recurrent episodes and associated neurodevelopmental impairment could suggest IEM as a possible etiology. These episodes may have an abrupt onset in a previously healthy child or may present initially as only behavioural changes, ataxia and vomiting. The encephalopathy may progress with a fulminant course to coma or may have a fluctuating course that is mistaken for improvement.

Common IEM that can present as emergency are urea cycle disorders, organic acidemias, aminoacidopathies, fatty acid oxidation disorders, mitochondriopathies and glycogen storage disorders. Even though many of these disorders may manifest across the entire spectrum of the pediatric age group, aminoacidopathies, organic acidemias and urea cycle disorders have an onset early in the neonatal period. Disorders such as fatty acid oxidation disorders more often have an onset in childhood when longer periods of starvation than in early infancy and superimposed illness precipitate an encephalopathy.

Children with suspected metabolic encephalopathy should have plasma glucose, serum electrolytes, plasma ammonia, liver function tests with prothrombin time and blood gas analysis for acid-base imbalances measured immediately. Markedly elevated plasma ammonia levels in the absence of severe liver dysfunction suggest an IEM as etiology. Ornithine transcarbamoylase deficiency may present with abnormal transaminase levels unlike in other urea cycle disorders but the degree of liver dysfunction may not explain the very high plasma ammonia levels. Further interpretation might require quantitative plasma amino acid levels, plasma and urine acyl-carnitine profile, serum lactate and urine organic acids analysis.

Hypoglycaemia in a new-born could be the result of severe systemic illness or sepsis. Early onset hypoglycaemia could be part of decreased reserves in a small for gestational age baby or an infant of a diabetic mother. Endocrine disorders can present with hypoglycaemia in a newborn. In the absence of the above, inborn errors of metabolism should be suspected. The evaluation usually includes liver function tests, serum insulin, growth hormone and cortisol
levels, C-peptide, serum beta-hydroxybutyrate, urine ketones and reducing substances, plasma amino acids, urine organic acids, plasma free fatty acid levels, acyl carnitine profile, plasma lactate and pyruvate levels. (Figure 3) (150-152)

Early management and stabilization:

The emergency management of these disorders is aimed at rapid normalisation of metabolic derangement to improve survival and decrease neurological morbidity. Immediate correction of hypoglycaemia, ensuring adequate hydration and treatment of suspected infections is highly recommended. Hyperammonaemia is treated with Sodium phenylbutyrate, Sodium benzoate, arginine, carnitine and avoidance of alkalosis. High anion-gap acidosis is treated with intravenous glucose and insulin, corrections of acidosis, intravenous carnitine, vitamin B12 and biotin. Hemofiltration is necessary with a plasma ammonia of >300μmol/L, severe acidosis with pH<7.2 or plasma leucine level >1500-2000micromol/l. At least 100kcal/kg/day is provided to avoid endogenous protein breakdown and protein is introduced at 1gm/kg body weight and gradually increased. Parenteral nutrition is necessary to ensure an anabolic state where enteral feeding is not possible.

Conclusions:

The conditions discussed above constitute most of the common diagnostic and therapeutic challenges in pediatric hepatology presenting as emergencies. In infants with cholestasis, early diagnosis of biliary atresia and other time-sensitive disorders improve outcomes. Simple interventions such as vitamin K administration can prevent neurological morbidity. PALF patients need stabilisation and investigations in consultation with a liver transplant centre. The use of octreotide in variceal bleeding achieves effective bleeding control and stabilisation before endoscopy or transfer to a liver centre. Liver trauma and liver tumors are better managed by a multidisciplinary approach in specialist centres. Several IEM can
present with liver dysfunction, their early identification and treatment in collaboration with metabolic experts is essential to improve their outcomes.

**Legend:**

Table 1: Clinical clues to diagnosis in an infant with cholestasis

Table 2: Disease specific investigations for diagnosis in infantile cholestasis

Supplementary table 1: Etiology of PALF across different geographical areas and age groups

Table 3: Evaluation for etiology in Pediatric acute liver failure

Table 4: Disorders causing PALF that have etiology-specific treatment options

Table 5: Supportive care in Pediatric Acute Liver Failure

Figure 1: Etiology in infantile cholestasis and the algorithmic approach

Figure 2: Management of liver trauma in children

Figure 3: Approach to diagnosis in an infant with metabolic encephalopathy

Supplementary table 2: Parameters known to predict outcomes in Pediatric acute liver failure

Supplementary table 3: Composite scoring systems in the prognostication of Pediatric acute liver failure

Supplementary table 4: Listing criteria in the United Kingdom for Acute liver failure

**References:**


Table 1: Clinical clues to diagnosis in an infant with liver disease

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial dysmorphism</td>
<td>Down syndrome, Zellweger syndrome, Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome, Smith Lemli Opitz syndrome, Alagille syndrome (difficult to appreciate in neonates)</td>
</tr>
</tbody>
</table>
| Abnormalities in eye examination       | *Cataract* - Congenital rubella, galactosemia, Zellweger syndrome, Wolman disease  
*Posterior embryotoxon and Drusen* – Alagille syndrome  
*Cherry-red spot* – Gaucher's and Niemann-Pick disease  
*Septo-optic dysplasia* - Hypopituitarism |
| Skin changes                           | *Icthyosis, hypotrichosis* – Neonatal sclerosing cholangitis  
*Cutaneous laxity* – ARC syndrome, Transaldolase deficiency  
Lymphoedema – Aagenaes syndrome |
| Congenital cardiovascular defects      | *Pulmonary and peripheral pulmonary stenosis, tetrology of Fallot* - Alagille syndrome  
*Atrial and ventricular Septal Defects, preduodenal portal vein, absent Inferior vena cava* – Biliary atresia |
| Skeletal abnormalities | Vertebral anomalies – Alagille syndrome  
*Patellar stippling on X-ray – Zellweger syndrome* |
|------------------------|-------------------------------------------------|
| Neuromuscular involvement | *Hypotonia – Down syndrome, Zellweger syndrome, Wolman syndrome, Congenital disorders of glycosylation, mitochondrial disorders, Gaucher and Niemann-Pick disease*  
*Seizures – Congenital intrauterine infections, Disseminated herpes infection, Hypoglycaemia due to any cause of liver failure, galactosemia, fructosemia*  
*Arthrogrypopsis – ARC syndrome* |
| Massive splenomegaly | Gaucher’s and Niemann-Pick's disease |
| Ascites | Ascites without liver failure – Spontaneous rupture of bile duct  
Ascites with liver dysfunction – Any cause of neonatal liver failure |
| Genital abnormalities | *Micropenis - Septo-optic dysplasia*  
*Ambiguous genitalia - Smith-Lemli-Opitz syndrome* |
| Renal anomalies | *Cysts – ciliopathies*  
*Dysplasia – ARC syndrome* |
Table 2: Disease specific investigations for infants with liver disease
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis, Urinary tract infection</td>
<td>Blood culture, urine culture.</td>
</tr>
<tr>
<td>Congenital intrauterine infections</td>
<td>Review of maternal serology, history of infection during pregnancy, In the neonate – urine CMV PCR, Guthrie card blood spot DNA, VDRL serology test, toxoplasma serology, Rubella serology</td>
</tr>
<tr>
<td>Neonatal herpes simplex infection</td>
<td>Serum HSV PCR</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>Full blood count, serum triglycerides, ferritin, fibrinogen, soluble CD25, bone marrow aspiration and trephine biopsy, perforin expression, Natural killer cell degranulation and cytotoxicity, perforin mutations, SAP and XIAP expression</td>
</tr>
<tr>
<td>Gestational alloimmune disease</td>
<td>Buccal mucosal biopsy for salivary gland iron staining, MRI abdomen, serum ferritin, Total iron binding capacity</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>RBC Galactose-1-phosphate uridyl transferase levels before any RBC transfusion</td>
</tr>
<tr>
<td>Tyrosinemia type 1</td>
<td>Urine succinyl acetone, mutational analysis</td>
</tr>
<tr>
<td>Hereditary fructose intolerance, Arthrogryposis renal</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>dysfunction cholestasis syndrome, Dubin-Johnson syndrome, GRACILE syndrome, McCune Albright syndrome, Citrin deficiency, Down syndrome, Transaldolase deficiency, Ciliopathies</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial hepatopathy</td>
<td>Serum lactate, pyruvate, genetic testing</td>
</tr>
<tr>
<td>Ornithine transcarboxymylase deficiency</td>
<td>Serum ammonia, plasma and urine amino acids, genetic testing</td>
</tr>
<tr>
<td>Spontaneous rupture of bile duct</td>
<td>Hepatobiliary radioisotope scan</td>
</tr>
<tr>
<td>Lipid storage disorders - Gaucher's, Niemann-Pick type A, B, C</td>
<td>White cell enzymes, skin biopsy for fibroblast culture and filipin staining, genetics, eye examination, Bone marrow aspiration and biopsy</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Panhypopituitarism, Hypothyroidism</td>
<td>Random serum cortisol, If low Short Synacthen test, Thyroid function test, MRI brain, genetic mutations</td>
</tr>
<tr>
<td>Congenital leukaemia</td>
<td>Full blood count, Bone marrow aspiration, biopsy, flow cytometry</td>
</tr>
</tbody>
</table>
| Biliary atresia                                              | Ultrasound – Cyst at the porta, triangular cord sign, small irregular gallbladder, polysplenia/asplenia, situs inversus  
Liver biopsy – Expanded portal tract with fibrosis and inflammation, bile ductular reaction, bile plugs  
Operative cholangiogram to confirm the diagnosis |
| Choledochal cyst, Choledocholithiasis                        | Ultrasound, MRCP |
| Neonatal sclerosing cholangitis, Neonatal ichthyosis sclerosing cholangitis hypotrichosis (NISCH) syndrome | Liver biopsy, Genetic studies |
| Bile acid transporter defects                                | GGT, Genetics, liver immunohistochemistry |
| Syndromic paucity of bile ducts (Alagille syndrome)          | Echocardiography, eye examination, vertebral radiography, liver biopsy and Genetics |
| Bile acid synthetic disorders                                | GGT, Serum bile acid, Urine bile acid profile, Genetics |
| Alpha-1-antitrypsin deficiency                               | Alpha-1-antitrypsin level and phenotype |
| Cystic fibrosis                                              | Immunoreactive trypsinogen, Genetics |
| Cholesteryl ester storage disease                            | Serum cholesterol, triglycerides, Lysosomal acid lipase levels, Genetics |
| Zellweger syndrome                                           | Very long chain fatty acid, Genetics |
| Congenital disorder of glycosylation                         | Transferrin electrophoresis, Genetics |
CMV – cytomegalovirus, PCR – Polymerase chain reaction, VDRL – Venereal Research Disease Laboratory, HSV – Herpes Simplex virus, RBC – Red Blood Cell, MRI – Magnetic resonance Imaging, MRCP – Magnetic resonance cholangiopancreatography, GGT – Gamma glutamyl transpeptidase
### Table 3: Evaluation for etiology in Paediatric acute liver failure

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs/toxins*</td>
<td>Serum Paracetamol level, Urine screen for toxins/drugs</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>Serum total IgG, anti-Smooth muscle antibody, anti-Liver kidney microsomal Antibody, Anti-nuclear antibody, anti-Liver cytosol antibody, antibody to soluble liver antigen, liver biopsy³</td>
</tr>
<tr>
<td>Viral infections</td>
<td>Serum PCR for herpes simplex virus, Serology for acute Epstein-Barr virus infection, EBV PCR, adenovirus PCR, parvovirus PCR, enterovirus PCR, cytomegalovirus PCR, HBV DNA PCR, HBsAg, IgM anti HBcAb, IgM anti HAV, anti HEV antibody</td>
</tr>
<tr>
<td>Haematological disorders – Hemophagocytic lymphohistiocytosis, Congenital leukaemia, lymphomatous infiltration</td>
<td>Full blood count, Blood film, Lactate dehydrogenase, serum triglycerides, serum ferritin, serum fibrinogen, soluble CD25, Granzyme B, bone marrow aspiration and trephine biopsy, NK cell activity, perforin mutations</td>
</tr>
<tr>
<td>Metabolic and genetic work-up</td>
<td>Red blood cell Galactose-1-phosphate uridyl transferase, Urine succinyl-acetone, Urine organic acids, plasma amino acids, serum</td>
</tr>
</tbody>
</table>
lactate, serum pyruvate, Genetic analysis for mitochondrial genetics and Wilson’s disease, serum caeruloplasmin, 24-hour urine copper, serum carnitine and acyl carnitine profile, urine ketones, ** genetics for mutations suggesting NBAS deficiency, E3 deficiency, Wolcott-Rallison syndrome, CALFAN syndrome (SCYL1 mutations), TRMU mutations, MARS, LARS, RINT1, PCK1 mutations, Fatty acid oxidation disorders(47-55)

Whole exome sequencing for indeterminate etiology group

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Ultrasound with Doppler of hepatic veins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational alloimmune disease</td>
<td>Buccal mucosal biopsy, serum ferritin, transferrin saturation, MRI abdomen for iron deposition in the viscera.</td>
</tr>
</tbody>
</table>

HAV – Hepatitis A virus, HEV – Hepatitis E virus, HBsAg – Hepatitis B surface antigen, anti HBc Ab – Antibody to hepatitis B core antigen, PCR – Polymerase chain reaction, * serum paracetamol adducts is not widely available, $ - Role of liver biopsy is controversial, **- Disorders causing recurrent acute liver failure
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosinemia type 1</td>
<td>Nitisinone</td>
</tr>
<tr>
<td>Paracetamol toxicity</td>
<td>N-acetyl cysteine</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>Immunosuppression protocols</td>
</tr>
<tr>
<td>HSV infection</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Drug induced liver injury</td>
<td>Withdrawal of offending drug</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Galactose free formula</td>
</tr>
<tr>
<td>Fatty acid oxidation disorders</td>
<td>Dextrose infusion</td>
</tr>
<tr>
<td>NBAS deficiency</td>
<td>Dextrose/lipid infusion</td>
</tr>
<tr>
<td>Gestational Alloimmune Liver Disease</td>
<td>Double volume exchange transfusion and intravenous immunoglobulin administraion</td>
</tr>
<tr>
<td>Acute HBV</td>
<td>Anti HBV antivirals</td>
</tr>
<tr>
<td>Acute Budd-chiari syndrome</td>
<td>Hepatic venoplasty and stenting</td>
</tr>
</tbody>
</table>
Table 5: Supportive care in Paediatric Acute Liver Failure

<table>
<thead>
<tr>
<th>Systems needing support</th>
<th>Monitoring/investigations</th>
<th>Intervention and remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway and Respiratory support</td>
<td>SpO₂, pO₂, pCO₂ and pH.</td>
<td>- Assisted ventilation in Grade III/IV encephalopathy or agitation with lower encephalopathy grades</td>
</tr>
<tr>
<td>Fluid, electrolyte and metabolic management</td>
<td>- Serum sodium, serum potassium, serum phosphate, serum magnesium, serum calcium, CVP, urine output, Serum urea and serum creatinine, Plasma glucose, plasma lactate, pH</td>
<td></td>
</tr>
<tr>
<td>Renal support</td>
<td>- Hypophosphataemia/hyperphosphatemia more common with paracetamol toxicity(57)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hypomagnesemia more common with plasmapheresis(58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Target euvolemma to ensure cerebral perfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Start with 80% maintenance fluid for age and weight.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Rapid fluid boluses can worsen cerebral edema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Dextrose infusion to prevent hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Early CRRT with combination of factors - oliguria/anuria, fluid overload, Hyponatremia &lt;130 meq/L, Hyperkalaemia, high</td>
<td></td>
</tr>
</tbody>
</table>
| Cardiovascular support | Heart rate, blood pressure, invasive arterial blood pressure, urine output, capillary refill time, Temperature gradient, Mixed venous oxygen saturation in patients on inotropes, trend in CVP, stroke volume variations, pulse pressure variations and response to fluid administration in hypotension | - Noradrenaline after a trial of fluid is often the inotrope of choice to treat hypotension in PALF.  
- Relative adrenal insufficiency is known to occur. Corticosteroids may alleviate refractory hypotension(61)  
- Plasmapheresis in those with high inotrope requirement(62-64)  
- With escalating inotrope requirement (features of ‘toxic-liver’) heptectomy while awaiting emergency liver transplantation | - Hypocalcaemia and acidosis possible if regional citrate anticoagulation is used for CRRT(59)  
- lactate/metabolic acidosis unresponsive to fluid therapy, Persistent hyperammonaemia >150 umol/L after adequate hydration  
- Epoprostenol may be used for CRRT to prevent clotting(60)  
- No evidence for use of lactulose for lowering ammonia in case of constipation. May result in gaseous gut distention that may affect transplantation surgery  
- No evidence to support use of LOLA/Rifaximin |
Neurological monitoring and support (65, 66)

- GCS/AVPU, HE staging, features of raised ICT – bradycardia, dystonia and hypertension, pupillary abnormalities, any focal neurological deficits, seizures
- Rule out hypoglycaemia with altered sensorium.
- Limited data on invasive ICP monitoring. 7% bleeding complications (65)
- ONSD not reliable to monitor ICP
- Reverse jugular venous oxygen saturation measurement is intermittent, prone to jugular venous thrombosis and is an indirect measure of ICP, the interpretation of which is influenced by confounding factors
- Transcranial doppler - quantitative assessment of waveforms, particularly the Windkessel effect or quantitative estimates using the pulsatility index, mean blood flow velocity and arterial pressure. This lacks correlation across

- Prevention of raised ICT/neurological injury - Fever control, head end elevation to 30 degrees, sedation, minimise stimulation, avoid fluid overload while ensuring good CPP, Maintain serum sodium between 145-150 mEq/L. Nurse with minimal stimulation in a quiet environment
- Sedation in agitated or ventilated patient. Avoid benzodiazepines. Morphine/Fentanyl preferred. Adequate sedation during airway suction
- Early CRRT with renal impairment or presence of HE > grade 2 with ammonia >150 umol/L or an absolute serum ammonia value of >200 umol/L after fluid resuscitation (67)
- Ammonia scavengers such as sodium benzoate and sodium phenyl butyrate are beneficial in ALF secondary to urea cycle disorders.
- 3% saline, 20% mannitol (contraindicated in AKI) and transient hyperventilation may be used for spurt in ICP. Monitor serum sodium, osmolarity or pCO2
| Coagulation and haematological support | the various phases of raised ICP and intermittent nature of measurement is a drawback.  
- Any sudden worsening of sensorium/focal signs - cross sectional imaging for intracranial bleed | - No sufficient evidence for use of anticonvulsants to prevent subclinical seizures in higher grades of HE(68).  
- Hepatectomy in a very select patient where necrotic liver is believed to be causing raised intracranial hypertension. |
|-------|--------|-----------------|
| Bleeding manifestations, Prothrombin time (INR), plasma fibrinogen level, platelet counts | - Correction of INR by coagulation factors affects monitoring and decision-making for listing for liver transplantation  
- Coagulation factor support only for bleeding and invasive procedures  
- No evidence for threshold of INR for transfusion of factors.  
- Platelet count above 50,000 platelets/ml could minimise bleeding risk  
- Plasma exchange for life threatening bleeds or increased requirement for coagulation factor support (> 30mL/kg of FFP in 24hr) (69)  
- Stress ulcer prevention – Proton pump inhibitor | |
<p>| INR does not predict bleeding risk | | |
| Secondary Infection | - Fever, features of SIRS | - Prophylactic broad spectrum antibiotics and antifungals decrease frequency of infections. Effect on mortality not known(70-72) |</p>
<table>
<thead>
<tr>
<th>Nutrition</th>
<th>Enteral feed when possible, with 1g/kg/day of protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology non-specific supportive care</td>
<td>- N-acetyl cysteine infusion – when there is a suspicion of paracetamol toxicity.</td>
</tr>
</tbody>
</table>

SIRS non-specific and could be a result of liver failure/necrosis. CRP unreliable as a marker of sepsis
- Daily surveillance cultures(41)
- Suspect infection in case of sudden worsening/ hypotension/ unexplained AKI/ encephalopathy/ SIRS

Selective gut decontamination not recommended

1. Sepsis
2. Urinary tract infection
3. Congenital intrauterine infections
4. Neonatal herpes simplex infection
5. Haemophagocytic lymphohistiocytosis
6. Gestational alloimmune disease
7. Galactosemia
8. Tyrosinemia type 1
9. Hereditary fructose intolerance
10. Mitochondrial hepatopathy
11. Cholestasis of multifactorial etiology in a sick newborn
   (TPN, sepsis, prematurity, necrotising enterocolitis)
12. Urea cycle disorders
13. Spontaneous perforation of bile duct
14. Lipid storage disorders - Gaucher's, Niemann-Pick type C
15. Panhypopituitarism
16. Congenital leukemia
17. Other rare metabolic disorders