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Management of hepatic encephalopathy in children

Ravindra Arya,1 Sheffali Gulati,1 Satish Deopujari2

ABSTRACT

Hepatic encephalopathy is a common metabolic condition in children, having a significantly different aetio-pathogenesis from that in adults. The present paper reviews the medical interventions of proven efficacy and also discusses recent advances from various fields as applicable to management of children with this disorder, focusing on measures other than liver transplant. The most important component of managing a child with hepatic encephalopathy is basic intensive care with regulation of fluid status, glucose and electrolyte homeostasis. Specific management includes measures to reduce serum ammonia concentrations, and the prevention and prompt treatment of complications. Methods to reduce ammonia target various steps in its metabolism. This includes reducing its production in and absorption from the intestine and promoting its metabolism in the liver. Significant secondary complications occurring in fulminant hepatic failure which require urgent recognition and management include coagulopathy, cerebral oedema and renal dysfunction. Children with hepatic encephalopathy also have several other paediatric care issues such as fever, requirement for sedation, etc, where the choice of drug is not straightforward and is often different from other settings. This is reviewed here along with an attempt to provide rational choices based on available evidence. Certain controversial and experimental approaches to treatment of fulminant hepatic failure are also discussed, but clearly delineated from the established management protocol. Finally, the role of artificial liver support devices is discussed, with the realisation that they can provide an effective bridge during the time when a patient is waiting for a suitable donor for liver transplant.

Hepatic encephalopathy (HE) is an important and common metabolic disturbance in children. Conventionally, encephalopathy has been the defining criteria for fulminant hepatic failure (FHF), but less commonly it may complicate chronic hepatocellular disease as well. FHF is described as a clinical entity resulting from massive necrosis or from severe functional impairment of hepatocytes in the absence of pre-existing liver disease, and evolving over 8 weeks or less.1 It has been realised that FHF is entirely reversible provided the liver is not subjected to additional stress and is allowed to regenerate. Hence, traditionally, management has consisted of preventing and treating complications and letting nature take its course. The key issue is to stop ongoing hepatocyte damage, but at present no treatment is known to reverse hepatocyte injury or to promote hepatic regeneration.1 Around three decades ago the first steps were taken to develop systems which can overtake the function of the liver while it recovers. The advent of liver transplantation has a major impact on management and prognosis. In this review we discuss the established protocols as modified by recent evidence and current trends in the management of HE.

It should be emphasised that the pathophysiology of HE in children is very different from that in adults where it is usually imposed on the background of chronic liver disease and cirrhosis. In children it is usually a true ‘acute’ liver failure. Causes of HE in children are varied and range from viral hepatitis to inborn errors of metabolism, as opposed to predominant alcoholic liver disease in adults. Secondly, in children, cerebral oedema is an important complication which may remain unrecognised in the early stages.

Currently there are four main theories for the genesis of neurological impairment in FHF. These include accumulation of ammonia and false neurotransmitters in the brain, abnormal ligand(s) acting on γ-amino butyric acid–benzodiazepine (GABA-BDZ) receptors, and deposition of manganese in basal ganglia.2 Most of the medical interventions of proven value are based on the ‘ammonia hypothesis’ whereas the other three mechanisms are being increasingly explored for their therapeutic potential. The exact pathogenesis is not known completely. Recently there has been an interest in the role of nitric oxide inhibition in the pathogenesis of HE. Administration of a non-selective nitric oxide-synthase inhibitor in a rat model was noted to have detrimental effects on the severity of hepatic damage and motor activities.3 This suggests that constitutive nitric oxide-synthase activities play a major protective role in rats with FHF.

There is a paucity of literature on various interventions in children with HE. Many of the studies quoted in this paper are primarily or exclusively based on the adult population. While preparing this review we have been cognisant of the fact that even the basic biochemical mechanisms are only partially representative of those in children. Our focus has been on strategies for management of FHF other than liver transplant.

SUPPORTIVE CARE

A child with HE should ideally be managed in an intensive care environment with an active pediatric liver transplant programme, but this is seldom practical in a resource limited setting like ours. The first step in management involves taking care of the airway, breathing and circulation (the ABCs), as in all emergencies. Airway control may be achieved using emergency or preferably elective intubation, sedation and/or neuromuscular paralysis. The goals are to protect the airway, prevent aspiration or assist ventilation in a comatose child, or for management of raised intracranial pressure.
Fluid management

After resuscitation the first issue to be addressed is fluid balance. It is important to aim for a normovolaemic state as both under- and over-hydration are detrimental. Various degrees of fluid restriction have conventionally been recommended. It is pragmatic to start at roughly 70% of maintenance requirements and adjust frequently as needed. Hydration status is best monitored by central venous pressure, the target being 6–8 cm H2O. An accurate weight chart updated at least twice a day is also an acceptable surrogate. Urine output monitoring is essential as a monitor of hydration and an indicator of renal function. The intravenously (IV) administered fluid acts as a vehicle for electrolytes and glucose which are significantly disturbed in this condition.

Potassium

Hypokalaemia is often induced by diuretics, vomiting or diarrhoea in addition to strong kaliuretic drive of secondary hyperaldosteronism. Hypokalaemia and the accompanying alkalosis impair ammonia detoxification, increase renal ammonia production, and lead to increased diffusion of ammonia across the blood–brain barrier. Potassium requirements have been estimated to be 3–6 mEq/kg/day. The parenteral fluid can provide 40 mEq/l of potassium when given under electrocardiographic monitoring; still there may be a need for oral supplementation at times.

Sodium

Total sodium intake of 1 mEq/kg/day is usually adequate to prevent development of ascites. Despite hyponatraemia, these patients usually have total body sodium overload. Commonly, inappropriate secretion of antidiuretic hormone results in diutional hyponatraemia which is best managed by fluid restriction as discussed above. If free water clearance needs to be increased, diuretics should preferably be combined with salt-poor albumin. Use of hypertonic saline may be considered in case of serum sodium <120 mEq/l and/or falling rapidly. In desperate situations one can push the upper limit of daily sodium administration up to 4 mEq/kg/day, but this is rarely warranted.

Supplementation of calcium, phosphorus or magnesium may be required, depending on their serum concentrations.

Glucose

Prevention and treatment of hypoglycaemia is important in these sick babies. Initial IV fluid should have at least 100 mg/ml of glucose (10%) and infusion should be titrated to maintain blood glucose between 120–240 mg/dl. Higher concentrations of dextrose solutions may be needed and may necessitate placement of a central line, if not placed already for central venous pressure monitoring.

Hence the starting fluid of 10% dextrose in 0.25 N saline has been recommended which should have a minimum of 20 mEq/l of potassium. The commercially available balanced solution Isolyte-P fulfills these requirements, provided the glucose concentration is enhanced to 10%. Various other electrolytes may be added to this as required and obviate the need for empirical and complicated ‘hepatic drip’ formulas, which inherently assume that the electrolyte status of all patients is similar. It is almost never the case.

AMMONIA METABOLISM

Reducing nitrogen load

Traditionally, the most important contributor to pathogenesis of HE is the accumulation of ammonia. This occurs due to impaired metabolism resulting from liver dysfunction and development of porto-systemic shunting (less common in children). As discussed above, most medical measures of proven efficacy attempt either to block the production of ammonia from protein metabolism in the intestinal tract or to prevent its absorption.

Cleaning the gut

A nasogastric tube should be put in place as soon as possible to detect and remove any blood, and to institute continuous gravity drainage. This avoids precipitating haemorrhage due to gastric mucosal injury which may occur with suction. Traditionally, a bowel wash or enema with 50% solution of magnesium sulphate is used; other retention enemas (20% lactose or 1% pH modulated neomycin) are limited by availability and lack of evidence. It is important to realise that the acidification of colonic lumen is responsible for efficacy of enemas and not just passive cleansing effect alone (discussed further in section on lactulose). Uribe et al. conducted a randomised controlled trial comparing acidifying enemas (lactitol and lactose) versus tap water in acute porto-systemic encephalopathy and found water enemas to be ineffective.

Antibiotics

Various antimicrobial agents have been used in patients with HE for ‘cleansing’ the intestines. These include ampicillin, metronidazole, vancomycin or rifamixin (a synthetic analogue of rifampicin). Of these, rifaximin displays a wide spectrum of antibacterial activity against Gram-negative and Gram-positive bacteria, both aerobic and anaerobic, and a very low rate of systemic absorption. A recent systematic review concluded that it has the highest benefit/risk ratio in the overall treatment of HE and should be the agent of first choice, but availability is a limiting factor.

These guidelines must consider available evidence for intestinal colonisation by the urease forming Helicobacter pylori. This ammoniagenic bacterium has been found to precipitate HE in cirrhotic individuals, especially in the presence of gastric hypochlorhydria. Although it has been pointed out in a recent publication that the importance of H pylori in the pathogenesis of HE is not rigorously defined, and the efficacy of eradication regimens has not been proven in controlled studies, the authors themselves recommended the practice of eradicating this organism. Hence, the antibiotic regimen must aim for H pylori eradication.

Proteins

Previously protein restriction or even total elimination was advocated until the sensorium improved. The recent trend is for an early introduction of proteins starting 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 tolerated better and are safer compared to animal proteins because they are less ammoniagenic due to relatively poor methionine and aromatic amino acid content. The fibres present in vegetable matter also exert some laxative effect and help in incorporation and elimination of nitrogen. Bianchi et al. conducted a randomised crossover comparison of these two protein types and concluded that supplementation with vegetable protein may result in a substantial improvement in nitrogen balance without precipitating or worsening the encephalopathy. The physiologic shedding of gut epithelial cells also adds to the amount of luminal protein to be converted into ammonia by bacteria.

Lactulose

Lactulose is a disaccharide (β-galactosidofructose) which reaches the caecum unaltered, where it is split by the intestinal flora into
component sugars—galactose and fructose. These sugars are further metabolised to the organic acids including lactic, formic and acetic acids, decreasing the lumen pH to ~5.5. It results in the preferential formation of the less absorbable ammonium ion over ammonia. Lactulose also promotes the growth of lactose forming bacteria in the intestine and suppresses ammoniagenic organisms such as bacterioides, because the low pH environment is hostile to the survival of these urease producing intestinal bacteria. It has been found that colonic bacteria preferentially metabolise lactulose over blood when both are present. This is of value in HE precipitated by gastrointestinal haemorrhage. Further, the bacterial metabolism of haemoglobin and some other animal proteins can generate short chain fatty acids which are detoxified by lactulose. The dose given should be sufficient to produce at least three soft, acidic (pH <6) stools per day.14 Diarrhoea secondary to lactic acid, which acts as an osmotic cathartic, must be avoided as it may lead to hypernatraemia and/ or dehydration.

Lactitol (β-galactoside sorbitol) is a related compound which is almost equally effective. It is cheaper and less sweet so may be more acceptable. Incidence of some side effects like flatulence is also less as compared to lactulose.16 17 The (adult) dose is 30–40 g/day.18 In patients with lactase deficiency, lactose also becomes a non-absorbable sugar and has been found to be an effective alternative.19 Concurrent use of lactulose with antibiotics is an apparent controversy, because its mechanism of action depends on it being split by intestinal bacteria which can be potentially eliminated by antibiotics. However, this should not really be an issue if the antimicrobial drugs are selectively targeted against ammoniagenic microorganisms. The antibiotic regimen should be so designed that the bacteria remaining in the intestine must be able to metabolise lactulose. The available evidence suggests an additive effect of antimicrobials in reducing the intestinal production of ammonia, accompanied by an improved clinical response, in the majority of patients who have an inadequate response to lactulose alone.20 21

Probiotics
Theoretically, populating the intestine with ‘friendly’ non-urease producing bacteria may decrease enteral ammonia load. Macbeth et al22 first suggested in an uncontrolled study that high oral doses of Lactobacillus acidophilus might have a beneficial effect in patients with cirrhosis who have HE. Subsequently, one small controlled study showed that the addition of L acidophilus supplements for 1–4 weeks produced clinical improvement in 71% of patients with HE refractory to neomycin alone. However, the results in a crossover analysis in three patients suggested that treatment with L acidophilus alone was ineffective.23 Oral administration of Enterococcus faecium was found to reduce systemic ammonia levels and was at least as effective as lactulose in patients already on a moderately protein restricted (1 g/kg) diet. The bacterium was given for three periods each of 4 weeks with a 2 week treatment-free interval. In contrast to lactulose, the therapeutic effect of E faecium was sustained during treatment-free intervals. No adverse effects were reported.24 Recently, Czech workers have investigated the effects of Enterococcus coli Nissle (Mutaflor) on intestinal colonisation, endotoxin values, neurological status and liver function in adult patients with liver cirrhosis and mild HE.25 The treated group displayed significant improvement of intestinal colonisation and a trend towards significant reduction of endotoxin concentrations and improvement of liver function assessed with the Child-Pugh classification during a follow-up of about 3 months. We believe that probiotic use should be practised in children with early HE as supported by the above limited evidence and lack of reported adverse effects.

Increasing ammonia metabolism
Ornithine-aspartate
All the measures discussed above aim to decrease the ammonia production and absorption from the intestine. Infusion of l-ornithine and l-aspartate attempts to reduce serum ammonia by increasing its tissue metabolism to urea and glutamine, respectively. In the portal hepatic ornithine acts as a substrate for ureagenesis and activates urea cycle enzymes ornithine transcarbamylase and carbamoyl phosphate synthase. This ‘forward kinetics’ of urea cycle probably consumes ammonia and decreases its concentration in the blood. In the hepatic perivenous scavenger cells, which lack enzymes of urea cycle, aspartate (and other decarboxylates) stimulate glutamine synthetase and provide alternate pathway for ammonia detoxification. Unfortunately, there are no standard paediatric dosing guidelines. However, the package insert of one formulation recommends up to 20 g/day diluted in maintenance fluids, at an infusion rate not exceeding 5 g/h, with serum creatinine monitoring.26 Controlled trials suggest useful therapeutic effects in patients with mild encephalopathy.26–29 Recently the Czech Hepatology Society working group on portal hypertension has supported its use in their recommendations.30

Benzoate and phenyl acetate
In the hyperammonaemia associated with inborn errors of metabolism, use of benzoate and phenylacetate is a standard practice. They react with glycine to form hippurate and with glutamine to form phenacetylglutamine, respectively. Studies, including one from India, have supported the use of these compounds in patients with HE, and sodium benzoate was found to be as effective as lactulose.31 32 Unfortunately sodium phenylacetate is not commonly available in India, but benzoate is cheap and widely available.

MANAGEMENT OF COMPLICATIONS
Gastrointestinal bleed
The most devastating component of the coagulopathy of hepatic decomposition is the gut bleed. Blood in the gut lumen is troublesome because of its high protein content (15–18 g/100 ml). Also the high isoeucine content of haemoglobin makes it more ammoniagenic then other proteins of animal origin. Initial measures consist of IV vitamin K1, and histamine-2 receptor antagonists which should be given prophylactically. Subsequent management of uncontrolled coagulopathy involves use of fresh frozen plasma 10–15 ml/kg which can be repeated until the bleeding is controlled. Empiric use of transfusion in the absence of acute uncontrolled haemorrhage or the need for an invasive procedure, should be avoided because the volume overload can foster the development of disastrous renal compromise. Administration of blood products may also alter the value of prothrombin time, an important prognostic marker.13 Plasma- pheresis may correct the bleeding diathesis without causing volume overload, but availability is an important limiting factor. In cases with co-existing thrombocytopenia, platelet transfusion should be used, aiming for a count >50 000/μl.

Cerebral oedema
Cerebral astrocytes are rich in glutamine synthase (GS) and metabolism ammonia by producing glutamine which is osmotoxic and causes cytotoxic oedema. It also acts as a precursor for the neurotransmitter amino acid glutamate which causes
Increased intracranial pressure (ICP) compromises cerebral blood flow and may cause herniation. It is desirable to monitor ICP, if available. Initial measures to manage raised ICP include elevation of the head, avoidance of neck flexion, and controlled hyperventilation to an arterial carbon dioxide pressure (Paco2) of 30–35 mm Hg.2 An ICP of >30 mm Hg or progressively rising has been used as criteria for using mannitol, but it can be given prophylactically, if adequate renal function and volume status can be assured. Mannitol is a hypertonic solution and may compromise perfusion to other tissues including brain and kidney. Hence, it is contraindicated once the dreaded hepato-renal syndrome (HRS) sets in. Steroids are not useful and probably dangerous as they increase infectious and electrolyte complications. They do not improve hepatocyte regeneration and do not affect the overall course of FHF.34 35 Autoimmune hepatitis is an entity where they are potentially useful, but there is no evidence for their utility in the acute fulminant stage.

The second mechanism for increased ICP in HE is cerebral vasodilatation resulting from loss of autoregulation.36 Modification of cerebral blood flow and oxygen metabolism are newer avenues for investigation in treatment of raised ICP. Continuous acetylcysteine infusion in patients with grade 4 HE has been reported to improve cerebral blood flow and the cerebral metabolic rate for oxygen. Epoprostenol (prostaglandin I2) has also been shown to improve the cerebral metabolic rate for oxygen.37

**Investigational neuroprotective strategies**

Recently creatine has been found to have a putative role against ammonia toxicity in cell cultures. Leite et al38 studied certain markers of injury in rat cortical astrocytes suffering acute ammonia toxicity. S100B protein, particularly extracellular S100B, is used as an indictor of glial activation or commitment in cerebral oedema,39 but its role in HE is not clear. Induced hypothermia, hypertonic saline, propofol sedation, and indomethacin are some of the newer therapies that have been shown to improve survival in patients with severe intracranial hypertension,36 and their role in children with FHF is worth investigating.

**Infections**

Infections are probably the next common cause of mortality after cerebral oedema in children with FHF. Almost half of these patients show evidence of serious infections including peritonitis, pneumonia, urinary tract infections, and septicaemia. *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most common isolates, but Gram-negative bacteria, anaerobes and *Candida* can also be found.41 Rational antimicrobial coverage guided by appropriate cultures should be provided.

**Renal complications**

About half of the patients with HE have evidence of renal impairment in the form of different syndromes which are not mutually exclusive. These include pre-renal azotaemia, intrinsic renal defect in the form of acute tubular necrosis and the overlapping HRS, which is most dangerous. HRS is defined as a functional renal failure that occurs in the absence of any underlying structural pathology. It has been classified into two types:

- Type 1 HRS is the rapidly progressing variety occurring in patients with FHF associated with hyponatraemia, hyperkalaemia and pronounced rise in serum creatinine and blood urea nitrogen.
- Type 2 HRS is more stable and occurs in cases with relatively preserved liver function.

The exact pathogenesis is unknown, but probably involves decreased renal perfusion. It is better to prevent it because the management options for established HRS are limited. Prevention is attempted by avoiding such risk factors as poor nutritional status, hyponatraemia, hyperkalaemia and decreased plasma osmolarity. Liver transplant is the only treatment of proven value but some patients continue to require dialysis even after transplant.4 Treatment of HRS type 1 with vasopressin analogues (terlipressin) is recommended before liver transplantation in order to improve renal function.49 The role of large volume paracentesis, peritoneal dialysis, haemodialysis, haemofiltration and renal vasodilators is controversial.

**CONTROVERSIES IN DRUG TREATMENT**

**Antipyretic**

There is no clear guide to choice of a non-steroidal anti-inflammatory agent in children with FHF, perhaps because none is entirely safe. Tepid sponging is harmless and moderately effective, hence should always be instituted first. Preparations of paracetamol containing a supposed hepato-protective agent are not supported by appropriate trials.

**Sedatives and anticonvulsants**

Theoretically, oxazepam has been recommended as the drug of choice in a dose of 10–30 mg/day.40 Lack of a parenteral formulation precludes its use in very sick children who are maintained nil orally. Midazolam is a good choice in such babies. For sedation and paralysis during assisted ventilation, fentanyl and atracurium are recommended.

**Flumazenil**

This is an imidazo benzodiazepine (BDZ) antagonist with high affinity for BDZ receptor (GABA-BDZ receptor–chloride ion channel complex).41 There are uncontrolled reports of clinical and electrophysiological amelioration of HE with its use.42 Due to rapid hepatic clearance, it has a short half life (0.7–1.3 h). Thus it is used as continuous IV infusion at the rate of 0.01 mg/kg/min. Common adverse effects include agitation, confusion, dizziness and nausea. There has been concern over dangerous adverse effects such as seizures and cardiac arrhythmias, but they were reported in patients with overdoses of BDZs and/or tricyclic antidepressants.43 Flumazenil has probably some role in early HE and in defining neurologic reversibility in selecting candidates for liver transplantation.

** Branched chain amino acids (BCAAs)**

Use of BCAAs is supported by the ‘false neurotransmitter’ hypothesis of pathogenesis of HE. It is believed that relatively reduced concentrations of branched chain amino acids (leucine, isoleucine, and valine) as opposed to those of aromatic amino acids (phenylalanine, tyrosine, and tryptophan) may promote neurological deterioration by production of aberrant...
neurotransmitter-like molecules. Earlier, there was controversy about their use. In 1996, Charlton did a systematic review of randomised controlled trials using the parenteral formulas enriched with BCAAs and found improvement in encephalopathy but not mortality. He concluded that differences in the control treatments, duration of therapy, selection of patients, precipitating events, and exclusion criteria make the interpretation of these conflicting results difficult. It was believed that they may have nutritional advantage but do not consistently improve sensorium, and perhaps have some efficacy in adults with advanced cirrhosis and chronic encephalopathy who cannot accept conventional proteins orally. It has been shown that most patients with cirrhosis who require parenteral feeding tolerate standard synthetic amino acid preparations.

In 2006, Charlton again reviewed the data from two large randomised controlled trials concerning the impact of BCAA supplementation in prophylaxis of long term morbidity and mortality in patients with cirrhosis. In the first study (n=174), the combined adverse event rates were seen to be significantly reduced in the BCAA supplementation arm, although this was not true for individual complications. In a still larger (n=646) study, long term BCAA supplementation was found to be associated with decreased frequency of hepatic failure and overall complication frequency. Both studies found improved nutritional status associated with BCAA supplementation. Hence, we believe that early use of BCAAs may decrease the rate of complications in HE, and their use in the maintenance protocol may offer nutritional benefit.

Carnitine
In animals and in cultured neurons, l-carnitine and acetyl-l-carnitine (ALCAR) have been shown to counteract some of the toxic effects of ammonia. A significant reduction in P100 latencies of visual evoked potentials was identified 30 min after ALCAR infusion in HE patients as opposed to control subjects, and the results retained significance in before-and-after comparison also. This suggests that a single intravenous dose of ALCAR may transiently improve neuronal function in cirrhotic patients with persistent encephalopathy and hyper-ammonaemia. Another study of 150 patients with HE from Italy, in which about 80% cases were caused by viral hepatitis B and C, found significant reduction in fasting serum ammonia and improvement in psychometric scores on l-carnitine use. Carnitine has a role in mitochondrial shuttle with importance in energy transduction at the cellular level, but its mechanism and role in children with FHF are not exactly defined presently.

Zinc
Reding et al studied the utility of zinc supplementation in HE, based on the fact that two of the key enzymes of the urea cycle are zinc containing metalloproteins and increased renal zinc wasting, which have been demonstrated in patients with cirrhosis. Significant improvement in psychometric test scores and reduction in ammonia concentrations have been demonstrated with the normalisation of plasma zinc values. Controlled studies have demonstrated beneficial effect of zinc supplementation as well as refuted its effectiveness. We believe that, realising the role of zinc in enzyme function, its supplementation should be done routinely in children with HE.

Manganese chelation
In the last decade various workers observed hyperintense globus pallidus in T1 weighted magnetic resonance scans of individuals with cirrhosis and/or liver failure. It was proposed that this manganese deposition may contribute to the pathogenesis of some aspects of HE, such as the extrapyramidal disorder. This suggestion is based on two facts: clinical similarity between chronic HE and manganese intoxication; and reversal of clinical features along with magnetic resonance findings after liver transplantation. Manganese deposition in basal ganglia was also correlated with severity of HE. The potential of appropriate chelating agents to improve neurological status in patients with liver disease is being actively investigated. As already pointed out, the pathogenesis of HE in children is not superimposed on a background of chronic liver dysfunction, so the relevance of these observations to paediatric practice requires further evaluation.

N-acetylcysteine
This agent is a specific antidote in cases of FHF due to an overdose of paracetamol (acetaminophen). It probably works by replenishing glutathione stores and preventing free radical damage. It is useful if started within 10–16 h along with other supportive measures. The regimen consists of giving 140 mg/kg orally followed by 70 mg/kg every 4 h for 17 doses spread over 72 h or until the serum paracetamol concentration falls to zero. At this dose, it is remarkably free of toxicity.

Other drugs
Many different drugs have been tried at times for the management of FHF and have been either proven ineffective, harmful, or their place remains undefined. Reduced neurotransmission in the dopaminergic system has been demonstrated in HE. L-dopa was found to improve clinical and electroencephalographic arousal response and increased renal perfusion, but the effect was neither sustained nor significant. Similarly, bromocriptine was used but did not cause any reduction in mortality. Limited evidence exists to show that silimarin prevents the entry of Amanita mycotoxin into the hepatocytes. These agents probably have limited therapeutic use in selected aetiologies, but there is no evidence to recommend them for routine use. It is prudent to avoid them due to lack of demonstrated benefit, and potential or actual toxicity against the liver and kidney.

LIVER TRANSPLANT
The advent of liver transplantation has had a large impact on prognosis. Reported 2 year survival rates have more than doubled to roughly 75% after transplant from the earlier rates of ~55%. In adults, King’s college criteria (table 1) have been used as early indicators of poor prognosis in acute liver failure. Since transplantation became an accessible option for these patients, the criteria have been used for deciding the need for transplantation in a particular patient. Broadly, the indication

Table 1 | King’s college criteria

<table>
<thead>
<tr>
<th>Patients with paracetamol induced liver failure:</th>
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<tr>
<td>Arterial pH &lt;7.3</td>
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<tr>
<td>International normalised ratio (INR) &gt;6.5</td>
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<tr>
<td>Serum creatinine &gt;300 µmol/l</td>
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<td>Encephalopathy (grade III/IV)</td>
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<th>Patients with non-acetaminophen acute liver failure:</th>
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<tr>
<td>INR &gt;6.5 or</td>
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<tr>
<td>&gt;Three of the following five criteria:</td>
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<tr>
<td>Patient age &lt;11 years or &gt;40 years</td>
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<tr>
<td>Serum bilirubin &gt;300 µmol/l</td>
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<tr>
<td>Time from onset of jaundice to the development of coma &gt;7 days</td>
</tr>
<tr>
<td>INR &gt;3.5 or</td>
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<tr>
<td>Drug toxicity, regardless of whether it was the cause of the acute liver failure.</td>
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Adapted from O’Grady et al.
for transplantation is failure of encephalopathy and coagulopathy to improve with medical management alone. It should be early enough when the neurological dysfunction is still reversible to prevent permanent secondary organ damage. Nazar et al. have recommended considering urgent transplant when the international normalised ratio (INR) reaches 4, particularly in very young children; however, there is a lack of well defined uniform patient selection criteria for the paediatric population. Cost and organ availability are also significant impediments, fostering innovative approaches to overcome them. 30

TEMPORARY HEPATIC SUPPORT

Artificial hepatic support devices aim to remove putative toxins from the circulation and provide deficient hepatic factors. Their development was based on well recognised reversibility of FHF and they temporarily take over hepatic function while the liver regenerates and recovers, somewhat analogous to the use of dialysis in renal compromise. After the advent of liver transplant and the increasing availability of therapeutic choices for pre- and post-transplant management, research interest in these systems decreased somewhat. Methods of temporary hepatic support tried so far (table 2) compare unfavourably against liver transplant. Recent advances in other fields such as stem cell research, material science and nanotechnology have created some new areas for investigation, like extracorporeal cellular systems simulating liver or packaging crucial enzymes into artificial carriers. It is now realised that they can play a significant role in the period when a patient awaits for transplant and, as witnessed by the recent increase in the number of publications on this subject, 39 71–73 it has become once again a focus of scientific attention.

Finally, we have categorised the measures discussed in this paper into three headings based on the above evidence and some personal bias (table 3). In table 3, please check the abbreviations have been spelt out correctly in the footnote. Those included under ‘yes’ have proven value or at least a high balance of probability in their favour, those under ‘no’ are harmful or probably useless, and those under ‘may be’ represent a heterogeneous group comprising interventions without any proven value or with insufficient evidence. It is obvious that most of the established measures include intensive care and reduction of tissue ammonia, while management of complications and pharmacotherapy is still controversial. Liver transplant is the only intervention of curative value, while liver assist devices are increasingly being investigated for providing a bridge until the time of transplant. It is highly probable that future research will reshuffle these categories. Please identify five key references from the current list, which will then be put in a box at the end of the article.

Table 2 Methods of temporary hepatic support

<table>
<thead>
<tr>
<th>Method(s)</th>
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<td>Non-biological</td>
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<tr>
<td>1. Haemodialysis</td>
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<tr>
<td>- Conventional</td>
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<tr>
<td>- Polyacrylonitrile membrane</td>
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<tr>
<td>2. Molecular Adsorbent Recirculating System (MARS or Albumin Dialysis)</td>
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<td>- Liver support system most frequently used worldwide in adults 35</td>
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<td>- Appears to offer distinct advantages over hepatocyte based systems 39</td>
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<tr>
<td>- Allows detoxification of albumin related and hydroxylatable substances, thus maintaining the patient’s homeostasis 12</td>
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<td>- In a study of 10 patients with HBV associated FHF, there were significant improvements in HE grading, mean arterial pressure, plasma renin activity, bilirubin, ammonia and creatinine values (all p &lt; 0.001). There were also significant improvements in various disease severity scoring systems evaluated including MELD, APACHE II, APACHE III, sequential organ failure assessment score. Meanwhile, platelet count was significantly decreased (p &lt; 0.001). One patient was successfully bridged to liver transplantation. Three patients were alive at 3 months of follow-up 58</td>
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<td>3. Hemoperfusion</td>
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<tr>
<td>- Over microencapsulated charcoal</td>
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<td>- Over albumin coated resin (Amberlite XAD-7)</td>
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<tr>
<td>4. Exchange transfusion</td>
<td></td>
</tr>
<tr>
<td>5. Plasmapheresis Biological</td>
<td></td>
</tr>
<tr>
<td>1. Cross circulation</td>
<td></td>
</tr>
<tr>
<td>- Human donor—neurologically normal/irreversibly comatose</td>
<td></td>
</tr>
<tr>
<td>- Baboon donor</td>
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<tr>
<td>2. Hemoperfusion through a isolated liver</td>
<td></td>
</tr>
<tr>
<td>- Human cadaveric</td>
<td></td>
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<tr>
<td>- Animal</td>
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</tr>
<tr>
<td>3. Extra corporeal liver assist device</td>
<td></td>
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<tr>
<td>- Mass of liver cells in a hollow fibre bioreactor</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Current status of various interventions for treatment of FHF

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>May be</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive care</td>
<td>Steroids</td>
<td>Platelet transfusion</td>
</tr>
<tr>
<td>- Intensive care</td>
<td>- Plasmapheresis</td>
<td>- Acetylcysteine, epoprostenol, creatine, induced hypocapnia, hypertonic saline, propofol sedation, indomethacin</td>
</tr>
<tr>
<td>- Glucose and electrolyte homeostasis</td>
<td>- Probiotics</td>
<td>- Paracentesis, peritoneal dialysis, haemodialysis, haemofiltration</td>
</tr>
<tr>
<td>Ammonia metabolism</td>
<td>- Prevention of gut bleed, FP</td>
<td>- Mannitol</td>
</tr>
<tr>
<td>- Intestinal cleansing</td>
<td>- Vasopressin</td>
<td>- Flumazenil</td>
</tr>
<tr>
<td>- Non-absorbable sugars</td>
<td>- Manganese chelators</td>
<td>- Camitine</td>
</tr>
<tr>
<td>- Antibiotics (rifaxin, metronidazole)</td>
<td>- N-acetylcysteine</td>
<td>- Silimarlin</td>
</tr>
<tr>
<td>- H pylori eradication</td>
<td>- l-dopa</td>
<td>- Bromocriptine</td>
</tr>
<tr>
<td>- Probiotics</td>
<td>- Bromocriptine</td>
<td>- Liver transplant</td>
</tr>
<tr>
<td>- Omithine-aspartate</td>
<td>- Calcium</td>
<td>- Hemoprotective systems</td>
</tr>
<tr>
<td>- Sodium benzoate</td>
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</tr>
</tbody>
</table>

Controversies

- BCAAs, branched chain amino acids; FFP, fresh frozen plasma; FHF, fulminant hepatic failure; PCM, paracetamol.

Adapted from Arya and Chansoria. 6

FHF, fulminant hepatic failure; HBV, hepatitis B virus; HE, hepatic encephalopathy; MELD, model for end stage liver disease.
Key learning points

- Fulminant hepatic failure is reversible, if adequately managed.
- Hepatic encephalopathy in children is different from adults aetiopathogenetically.
- Maintenance of fluid, glucose and electrolyte homeostasis is the most important aspect of management of hepatic encephalopathy.
- Conventional measures for specific treatment of hepatic encephalopathy target reduction of blood ammonia concentration, by interrupting its metabolism at various sites.
- Common complications, which should be anticipated and recognised and managed promptly, include coagulopathy, cerebral oedema, infections and renal dysfunction.
- Rational drug choice should be made in these often critically ill children for paediatric care issues like sedation, analgesia, fever treatment, nutritional support and supplementation, etc.
- Liver transplant has revolutionised the management of hepatic encephalopathy, but several constraints exist especially in resource limited settings.
- Methods of temporary hepatic support merit further attention and development in order to be applied in routine clinical practice.

Selected current research issues

- Defining the role of probiotics in the management.
- Efficacy of neuroprotective agents, especially creatine and induced hypothermia.
- Place and role of manganese chelation.
- Translational research into biological and mechanical hepatic support systems with a view for wider clinical application.

Key references


MULTIPLE CHOICE QUESTIONS (ANSWERS AFTER THE REFERENCES)

1. Fulminant hepatic failure evolves over a period of less than:
   A. 4 weeks
   B. 6 weeks
   C. 8 weeks
   D. 10 weeks

2. The most common cause of mortality in fulminant hepatic failure is:
   A. Cerebral oedema
   B. Infections
   C. Hepato-renal syndrome
   D. Gastro-intestinal bleed

3. Which of the following is/are targeted to decreasing serum ammonia levels in patients with hepatic encephalopathy?
   A. Protein restriction
   B. Lactulose
   C. Sodium benzoate
   D. All of the above

COMPETING INTERESTS

None.

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES


ANSWERS
1. C, 2, A, 3, D