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Drug Treatment of Encephalopathy Associated with Fulminant Liver Failure

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Abstract

Hepatic encephalopathy is a complex neuropsychiatric syndrome that may complicate either chronic or acute liver failure. Hepatic encephalopathy associated with fulminant liver failure is characterised by the development of cerebral oedema and intracranial hypertension, and has a poor outcome in severe cases if liver transplantation is not performed. Medical management of hepatic encephalopathy in fulminant liver failure is essentially directed toward the prevention and treatment of cerebral oedema and intracranial hypertension. Mannitol infusion should remain the main pharmacological treatment of cerebral oedema. Despite a lack of randomised clinical trial data, thiopental (thiopentone) has been widely accepted as an effective means of treating intracranial hypertension when mannitol fails. Acetylcysteine seems to have a beneficial effect by improving the cerebral blood flow and the cerebral metabolic rate for oxygen. The effectiveness of lactulose

is well established in chronic hepatic encephalopathy but not in fulminant liver failure. As the precise pathogenesis of hepatic encephalopathy in patients with fulminant liver failure is unknown, there is no specific treatment of this syndrome. In spite of a large number of published articles on the treatment of hepatic encephalopathy, only a few randomised, controlled studies are available. Indeed, except for the rare cases in which treatment of the underlying cause of disease is possible, the treatment of patients with fulminant liver failure is currently emergency liver transplantation.

Hepatic encephalopathy is a complex neuropsychiatric syndrome that may complicate either chronic or fulminant liver failure. Acute hepatic encephalopathy occurring in patients with fulminant liver failure needs to be differentiated from hepatic encephalopathy that occurs as a complication of chronic or acute-on-chronic liver failure. These syndromes differ with respect to their pathophysiology, clinical presentation and prognosis. The most important characteristic of hepatic encephalopathy associated with fulminant liver failure is its association with cerebral oedema, which is usually absent from the course of chronic liver disease. In fulminant liver failure, the onset of encephalopathy is often abrupt, whereas it is progressive in chronic liver diseases. The prognosis of acute hepatic encephalopathy is poor, with mortality reaching 80% in the absence of liver transplantation. Hepatic encephalopathy arising from chronic liver disease does not have the dismal outcome seen in fulminant liver failure.

Emergency orthotopic liver transplantation is a well established treatment for patients with fulminant liver failure, and 1-year survival rates range from 47 to 92%. Therefore, it should be understood that the goal of medical treatment of hepatic encephalopathy is only to minimise the risk of irreversible neurological damage and to reduce mortality while waiting for a liver graft. Despite a large number of published articles on the treatment of hepatic encephalopathy, only a few well performed randomised controlled studies are available, as stressed by excellent recent reviews.[1-7] Moreover, the treatment of encephalopathy in fulminant liver failure is derived from experience in acute-on-chronic and chronic liver disease. The evidence for the same approach in patients with fulminant liver failure lacks support from randomised controlled clinical trials. A clear understanding of the pathophysiology of hepatic encephalopathy associated with fulminant liver failure, and a critical assessment of its treatment, is therefore required.

1. Pathophysiology

It is important to distinguish between hepatic encephalopathy and cerebral oedema. Hepatic encephalopathy is a reversible neurochemical and neurophysiological state that occurs when hepatic function fails to maintain homeostasis, whereas cerebral oedema is an increase in brain volume accompanying a wide variety of pathological processes.

1.1 Encephalopathy

The pathophysiology of hepatic encephalopathy remains unclear, but it is widely accepted that it is multifactorial.[8] Hepatic encephalopathy is caused, at least in part, by the accumulation of substances that are normally cleared by the liver. The pathophysiology of encephalopathy and cerebral oedema have been well summarised.[9-11] There are several theoretical considerations which may explain why brain function is impaired in liver failure, but no proposed theory is mutually exclusive.

1.1.1 Hyperammonaemia and Glutamate Theory

First observed in 1893 by Hahn, Pavlov and coworkers,[12] hepatic encephalopathy (initially described as a 'meat intoxication') results from the accumulation of neurotoxic substances, such as ammonia, in the brain due to impaired hepatic metabolism and clearance. Hyperammonaemia is though to have a 'direct' effect on neuronal membranes or on postsynaptic inhibition, and an 'indirect' effect on neuro-

nal dysfunction due to disturbance of glutamate neurotransmission.

1.1.2 False Neurotransmitter Theory

Impaired liver function alters the plasma amino acid profile, resulting in alterations to brain metabolism of normal neurotransmitters. In either fulminant or chronic liver failure, plasma aromatic amino acids are increased, probably because of failure of hepatic deamination. Branched-chain amino acids are decreased, secondary to the hypercatabolic and hyperinsulinaemia-like states that are observed in either chronic or fulminant liver failure. In fulminant liver failure, ammonia-induced alterations in brain concentration ratios of aromatic amino acids could account for altered neuronal excitability and contribute to encephalopathy.[13-15]

1.1.3 Neuroinhibition Theory

Encephalopathy may result from increased brain tissue levels of neuroinhibitory substances such as γ-aminobutyric acid (GABA). Elevated CNS levels of ammonia as well as increased GABA-mediated neurotransmission are currently considered major elements in the pathophysiological process.[16-18] It has been shown that a moderately elevated concentration of ammonia enhances GABA-ergic transmission by direct activation of GABA receptors, and can further inhibit the CNS by synergistic interactions with benzodiazepine receptor ligands. Moreover, benzodiazepine-like substances have been implicated in the pathogenesis of the encephalopathy of acute liver failure. Elevated concentrations of 1,4-benzodiazepines have been detected in brain tissues of animals and humans with fulminant liver failure.[19]

1.2 Cerebral Oedema

Cerebral oedema results from a rapid increase in the water content of the brain, caused by loss of cell membrane integrity (cytotoxic oedema) and changes in the permeability of the blood-brain barrier (vasogenic oedema). Vasogenic oedema is characterised by increased permeability of brain capillary endothelial cells to macromolecules, such as plasma proteins, leading to a shift of water from vascular to extravascular compartments. Cytotoxic oedema, secondary to increased intracellular concentrations of osmotically active substances, is characterised by swelling of all the cellular elements of the brain: neurons, glia and endothelial cells. Once grade III to IV encephalopathy develops, the patient is at a high risk of developing cerebral oedema.[11]

1.2.1 Cytotoxic Oedema

Numerous experimental models of fulminant liver failure have described neuropathological alterations in astrocytes.[20,21] Astrocytes are the most numerous cells in the brain and confer impermeable properties to the blood-brain barrier and modulate inflammatory responses. Astrocyte swelling is not specific to fulminant liver failure, but also occurs after injury of metabolic aetiology, ischaemia, trauma and in other forms of encephalopathy associated with liver disease.[22,23] In fulminant liver failure, an increase in 2 intracellular solutes (sodium and glutamine), has been proposed as an explanation of brain swelling. It is suggested that sodium increases as a consequence of the inhibition of Na^+-K^+ ATPase pumps by circulating inhibitors.[24-27] Glutamine is generated within astrocytes as a result of the combination of ammonia with glutamate, a reaction catalysed by glutamine synthetase, an enzyme localised in astrocytes.[28] The brain lacks the urea cycle for ammonia detoxification, and brain concentrations of glutamine are markedly increased in experimental models of fulminant liver failure as well as in human autopsy material.[29,30]

Changes in osmolar environment are regulated by activating short term and long term regulatory mechanisms. In long term adaptation (i.e. chronic liver failure), downregulation of membrane transporters involved in the entry of organic solutes into the brain is initiated.[31] These solutes include amino acids (taurine, alanine), polyalcohols (*myo*-inositol, sorbitol) and methylamines (betaine, glycerylphosphocholine). Measurement of brain organic solutes in fulminant liver failure using nuclear magnetic resonance (NMR) spectroscopy reveals an increase in glutamine without change in *myo*-inositol concentration.[32,33] On the contrary, in patients with chronic hepatic encephalopathy, *myo*-inositol was

shown to be decreased, and glutamine increased, in those with overt encephalopathy.[34] Acute administration of ammonia to isolated astrocytes results in the loss of intracellular taurine, while exposure over several days reduces uptake of *myo*-inositol.[35] NMR spectroscopy demonstrated a decreased brain *myo*-inositol content in patients with chronic hepatic encephalopathy and reversal of this spectral abnormality following treatment.[36,37]

These experiments suggest that, in the acute development of brain oedema associated with fulminant liver failure, there is insufficient time to compensate for this increase in solutes, resulting in brain swelling.[33,35,38] The absence of long term regulation in fulminant liver failure probably explains the lack of classic signs of intracranial hypertension, such as papilliary oedema or projectile vomiting.

Hyperammonaemia seems to be directly linked to the pathogenesis of brain swelling, and the following lines of evidence confirm this assertion. Hyperammonaemic conditions in humans, such as children with urea cycle enzyme deficiencies and adults with postchemotherapy hyperammonaemia, are associated with brain oedema and spectroscopic abnormalities.[39,40] A continuous infusion of ammonia over several hours is associated with brain oedema or intracranial hypertension in animals.[41,42] Inhibition of glutamine synthesis with methionine-sulfoximine results in inhibition of brain swelling *in vivo*.[41,43]

1.2.2 Vasogenic Oedema

The mechanism of this process is not well elucidated and somewhat controversial. Cerebral blood flow (CBF) has been shown to be seriously impaired in animal models and in patients with fulminant liver failure.[44,45] Different pathophysiological hypotheses have been developed. Wendon et al.[44] have recorded low CBF and high cerebral lactate production in adults with fulminant liver failure and grade IV encephalopathy. These data suggest a possible relationship between cerebral hypoxia and the development of cerebral oedema. In this study, hyperventilation resulted in a significant decrease in both CBF and cerebral metabolic rate for oxygen and a significant increase in lactate production.

In patients with fulminant liver failure, autoregulation of CBF has been shown to be impaired.[46,47] Toxic substances released by the diseased liver are certainly responsible for cerebral injury and subsequent defective autoregulation of CBF.[48] Loss of this function may result in cerebral hypoxia during arterial hypotension and cerebral hyperaemia during arterial hypertension. The absence of cerebral reactivity to CO_2 during hypercapnia implies that cerebral arterioles are nearly maximally dilated.[49,50] Spontaneous hyperventilation, observed in patients with fulminant liver failure, may counterbalance this 'vasoparalysis' by increasing cerebrovascular tone.[51]

To underline the importance of impaired autoregulation of CBF in the pathogenesis of vasogenic oedema and intracranial hypertension, a nonblind trial of short term mechanical hyperventilation of patients with fulminant liver failure and grade IV hepatic encephalopathy outlined its efficacy in restoring CBF.[51] In this study, patients with severe associated renal failure failed to respond to hyperventilation. It remains to be evaluated if this refractory vasoparalysis is of pathophysiological importance for the high frequency of cerebral oedema in patients with fulminant liver failure and renal failure.

2. Treatment

It is essential to understand that currently the only curative treatment for patients with fulminant liver failure complicated by severe hepatic encephalopathy is emergency liver transplantation.

Figure 1 provides a general scheme for management of hepatic encephalopathy associated with fulminant liver failure.

2.1 General Measures

Prevention of aggravation of the underlying liver disease is of major importance in the management of fulminant liver failure. Any drug should be strictly evaluated, since it could precipitate an exacerbation of the disease. Therefore, drug treatment of hepatic

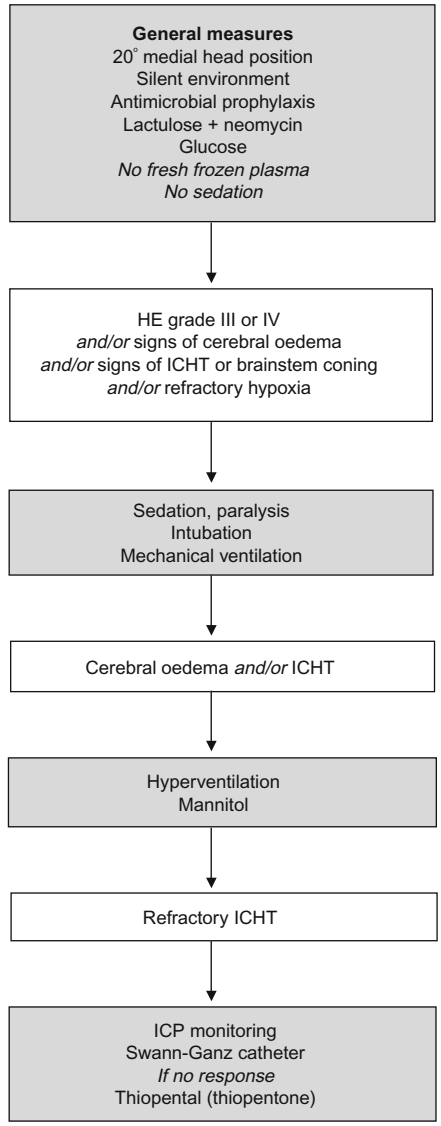

Fig. 1. Simplified algorithm for management of hepatic encephalopathy (HE) in patients with fulminant liver failure. **ICHT** = intracranial hypertension; **ICP** = intracranial pressure.

encephalopathy associated with fulminant liver failure should be limited to: (i) preventing conditions that precipitate the development of cerebral oedema; and (ii) the treatment of intracranial hypertension and conditions that could contraindicate emergency liver transplantation. Patients should, if at all possible, be admitted to an intensive care unit where liver transplantation facilities are available. The establishment of specialised liver failure units has been followed by a progressive improvement in patient survival rates.

Generally accepted measures for the treatment of hepatic encephalopathy include correction and avoidance of any factor that could potentially ag-

gravate encephalopathy, such as hypoglycaemia, hypoxia, haemorrhage, sepsis, drug toxicity and electrolyte and acid-base abnormalities. Sedative and hypnotic agents must be avoided, not only because their use in hepatic failure may enhance hepatotoxicity, but also because they hamper surveillance of the course of hepatic encephalopathy, a major factor in the decision to perform emergency liver transplantation.

The development of sepsis is the greatest threat to successful management of patients with fulminant liver failure. Bacterial infections have been shown to occur in 80%, and fungal infection in 32%, of patients with fulminant liver failure. Infection prophylaxis and strict infectious surveillance has been shown to improve the prognosis of patients with fulminant liver failure.[52-54] Prophylactic intestinal decontamination has also proven beneficial in reducing Gram-negative infections in these patients. These results were confirmed by a randomised controlled trial that showed that selective parenteral (cefuroxime) and enteral (colistin, tobramycin or amphotericin B) antimicrobials given before evidence of sepsis in patients with at least grade II hepatic encephalopathy reduce the risk of developing infectious complications.[55] However, a recent randomised trial showed that enteral decontamination gives no benefit over prophylactic parenteral antibacterials (ceftazidime or flucloxacillin) alone.[56]

2.2 Hepatic Encephalopathy

2.2.1 Prevention of Ammonia Toxicity

Hyperammonaemia should be aggressively treated. Steps should be taken to reduce the production and absorption of ammonia. Intestinal production of ammonia can be reduced by restricting nitrogen intake and inhibiting urease-producing colonic bacteria. Despite their hypercatabolic state, patients with fulminant liver failure should be put on a low-protein diet (1 g/kg/day) sufficient to maintain nitrogen balance, and endogenous ammoniagenic substrates should removed from the intestinal lumen by the osmotic cathartic action of non-absorbable disaccharides such as lactulose (β-galactosidofructose) or lacticol (β-galactosidosorbitol).

The efficacy of oral lactulose in the treatment of acute-on-chronic and chronic hepatic encephalopathy remains somewhat controversial (table I).[57-62] Despite the lack of a controlled trial on lactulose use in fulminant liver failure, ammonia detoxification through oral disaccharides is strongly supported by the extensive evidence on the importance of hyperammonaemia in the pathogenesis of cerebral oedema and intracranial hypertension associated with fulminant liver failure (see the discussion in section 1). Therefore, the relative inefficiency of enteral disaccharides in the hepatic encephalopathy associated with chronic liver failure may be explained by the major role of hyperammonaemia in the pathogenesis of cerebral oedema, a clinical complication not seen with chronic liver disease.

The daily dosage of lactulose should be titrated to result in 2 to 4 daily soft stools. Moreover, lactulose lowers colonic pH as a result of the production of organic acids by bacterial fermentation. This decreased pH environment is hostile to the survival of urease-producing intestinal bacteria and may promote the growth of non-urease–producing lactobacilli, resulting in reduced production of ammonia in the colonic lumen. This acidic lumen will decrease ammonia absorption by non-ionic diffusion, but also extract ammonia from the blood to the lumen.[63]

Oral antibacterials with activity against urease-producing bacteria, such as neomycin, also reduce the production of intestinal ammonia and have proven value.[64] A small fraction of this drug can be

Table I. Controlled trials of lactulose versus placebo in hepatic encephalopathy

Reference	Type of hepatic encephalopathy	Number of patients	Effect
Elkington et al.[57]a	Chronic	7	+
Simmons et al.[58]	Acute-on-chronic	21	+
Germain et al.[59]	Chronic	18	±
Blanc et al.[60]	Acute-on-chronic	80	=

a Lactulose + neomycin versus placebo.

+ indicates better than control; ± indicates equivocal results; **=** indicates equal to control.

absorbed from the gastrointestinal tract and may have ototoxic and nephrotoxic effects. Other oral antibacterials have been shown to have similar efficiency to neomycin, e.g. metronidazole 800 mg/day for 1 week or rifaximin 1200 mg/day.[65,66]

New therapies that focus on the increased systemic metabolism of ammonia are emerging. Sodium benzoate or sodium phenylacetate, which react with glycine to form hippurate and with glutamine to form phenacetylglutamine, respectively, may be as effective as lactulose.[67] Controlled trials suggest that L-ornithine-L-aspartate significantly reduces ammonia levels and has useful therapeutic effects in patients with cirrhosis.[68-70]

2.2.2 Branched-Chain Amino Acids

A reduced ratio of branched-chain amino acids to aromatic amino acids has been related to the development of hepatic encephalopathy. Infusions of solutions containing high concentrations of branched-chain amino acids have been used to treat acute and chronic hepatic encephalopathy. The results have been extremely conflicting. Analysis of controlled trials indicates that there is no evidence that they reduce hepatic encephalopathy in fulminant hepatic failure or affect mortality.[71-74]

2.2.3 Flumazenil

Experimental and clinical studies have suggested that activation of the GABA/benzodiazepine receptor complex may be involved in hepatic encephalopathy.[75] GABA is the principal inhibitory neurotransmitter of the brain. It is also generated in the intestinal tract by the action of bacteria on nitrogenous compounds and is normally degraded in the liver. During liver failure, it has been suggested that GABA escapes hepatic metabolism and induces an increased number of its own receptors.[76] It has been also demonstrated that GABA and benzodiazepine receptors are functionally and physically coupled.[75] Recent observations indicate the presence of an endogenous benzodiazepine agonist in animals or patients with hepatic encephalopathy.[19,75] Thus, endogenous benzodiazepines could increase the inhibitory action of GABA. Some experimental studies have demonstrated that flumazenil, a benzodiazepine receptor antagonist, could induce clinical and electroencephalographic (EEG) improvements in rat and rabbit models of hepatic encephalopathy.[77,78] However, these results were not confirmed by all authors.[79]

Table II. Controlled trials of flumazenil versus placebo in hepatic encephalopathy

Reference	Type of hepatic encephalopathy	Number of patients	Effect
van der Rijt et al.[82]	Chronic	8	=
Cadranel et al.[83]	Chronic	5	+
Meier et al.[84]	Chronic	49	±
Pomier-Layrargues et al.[85]	Chronic	21	±
Cadranel et al.[86]	Chronic	14	+
van der Rijt et al.[87]	Acute + chronic	18	=
Groeneweg et al.[88]	Chronic	32	=
Gyr et al.[89]	Chronic	49	+

+ indicates better than control; ± indicates equivocal results; = indicates equal to control.

Improvement of hepatic encephalopathy after flumazenil treatment has also been reported in patients with chronic liver disease and portosystemic encephalopathy (table II).[80-89] Clinical experience with flumazenil in patients with hepatic encephalopathy arising from fulminant liver failure is limited. To date, uncontrolled reports of intravenous administration of flumazenil in 23 episodes of hepatic encephalopathy in 21 patients with fulminant liver failure have been published, with a short term success rate of 39% (table III).[90-93] Most of these improvements have been documented both clinically and electrophysiologically, as assessed by EEG findings and evoked responses. In these reports, improvement occurred within a few minutes to an hour of administration of flumazenil and lasted for about 2 hours. However, these results were not confirmed by all authors.[92,93] Moreover, as stressed by Devictor et al.,[93] failure to demonstrate a response to flumazenil in fulminant liver failure is closely related to a high grade of hepatic encephalopathy and the presence of clinical signs of cerebral oedema. Therefore, to date, no evidence justifies the use of flumazenil in the management of fulminant liver failure since it affects neither survival

nor the development of neurological complications.

2.3 Cerebral Oedema

The main aim in the management of cerebral oedema is to alleviate the development of intracranial hypertension. Generally accepted measures for the prevention of intracranial pressure are to avoid any stimulation. Tracheal and bronchial aspiration should be done with care and minimised, and seizures must be treated aggressively. Recent studies indicate that elevation of the head by 20 to 30° is beneficial to patients with fulminant liver failure.[94,95] But one of the most important elements in the prevention of intracranial hypertension is maintaining the patient in a silent environment.

N-Acetylcysteine has been advocated to have beneficial effects, not only after paracetamol (acetaminophen)-induced fulminant liver failure but also with fulminant liver failure arising from other causes.[44] Its main action seems to be located at the level of the microcirculation, increasing oxygen delivery and consumption, but it does not seem to have any effect on the defective CBF autoregulation observed with fulminant liver failure.[48] Any effect of N-acetylcysteine on survival has not been yet demonstrated.[96,97]

2.4 Intracranial Hypertension

Assisted ventilation should be undertaken in virtually all patients with advanced hepatic encephalopathy and signs of intracranial hypertension in order to prevent bronchoaspiration and to more accurately manage the clinical condition. It may also be required in patients with lower grades of hepatic encephalopathy grade and hypoxia. In these situations, sedation and paralysis are required for comfort and to avoid periods of agitation.

According to uncontrolled studies,[98] monitoring of intracranial pressure (ICP) seems to be helpful in directing therapy toward treatment of intracranial hypertension and in preoperative management of patients undergoing emergency liver transplantation. Because of the relatively high incidence of complications, including infection and intracranial bleeding, arising from monitoring of ICP, prospective controlled trials are needed to confirm the benefits of ICP monitoring in patients with fulminant liver failure.[98-101]

Medical treatment of intracranial hypertension classically involves 3 main approaches: mild hyperventilation, osmotic agents such as mannitol, and coma induced by barbiturates.

As discussed in section 1.2.2, moderate short term hyperventilation (PCO_2 25 to 30 mmHg) may cause transient improvement of CBF autoregulation and subsequently decrease intracranial pressure. This observation prompted investigators to examine the effect of hyperventilation in randomised trials in patients with fulminant liver failure.[102] However, a controlled study found no influence of prophylactic hyperventilation on survival rate, although the onset of intracranial hypertension was delayed.[102] These results need critical assessment: although hyperventilation has been shown to produce a transient (about 12 hours) decrease of intracranial hypertension[102] and improve cerebral autoregulation,[51] the effect is offset by the kidneys compensating for respiratory alkalosis and probably also by an increase in cerebral lactate and non-oxidative metabolites.[44] Therefore, in intubated and mechanically ventilated patients, mild hyperventilation may certainly be valuable in short term treatment as long as PCO_2 is not decreased below 24 mmHg, where cerebral anoxia and ischaemia may occur.

Mannitol was the first treatment that was shown in a randomised controlled clinical trial to improve

Table III. Nonblind trials of flumazenil in fulminant liver failure

Setting	Reference	Number of patients (episodes)	Number of patients (episodes) with a positive response to treatment
Adult	Scollo-Lavizzari & Steinmann[90]	2	2
	Grimm et al.[91]	9 (11)	4 (6)
	Sutherland & Minuk[92]	1	0
Paediatric	Devictor et al.[93]	9	1

the survival of patients with fulminant liver failure complicated by grade IV encephalopathy.[103] Mannitol 0.5 g/kg bodyweight is given as a rapid intravenous infusion of a 20% solution whenever ICP rises above 30 mmHg for more than 5 minutes or, in the absence of ICP monitoring, when clinical signs suggestive of cerebral oedema are recorded. The dose may be repeated as necessary until the serum osmolarity is approximately 310 mOsm/L. Because of mannitol nephrotoxicity, urine output must be monitored hourly, and if a diuresis does not occur plasma osmolarity needs to be checked before additional doses of mannitol are given.

Barbiturates have been proposed for the treatment of intractable intracranial hypertension because of their ability to decrease cerebral flow through an effect on cerebral metabolism and oxygen consumption.[104] The effectiveness of barbiturate coma in the treatment of intracranial hypertension secondary to head injury has been assessed in a few randomised trials with inconclusive results.[105-107] Despite the lack of controlled trials, thiopental (thiopentone) infusions seem to be effective in patients with fulminant liver failure for controlling episodes of intracranial hypertension which do not respond to other therapies, and appear to improve survival.[108,109] Thiopental is usually given as a bolus (1 mg/kg) followed by a continuous infusion (1 to 2 mg/kg/h). Its use is limited by systemic hypotension that may require vasoconstrictive agents to maintain cerebral perfusion pressure. Since the pharmacokinetic properties of thiopental are extensively modified in liver failure, monitoring of its administration is particularly important in patients with acute liver failure. Moreover cardiovascular complications should be feared and closely monitored.[110] Once barbiturate coma is induced, all brain stem reflexes may be lost, and brain death cannot be diagnosed using clinical or EEG criteria.

2.5 Artificial Hepatic Support

The aim of artificial hepatic support devices is to bridge severely deteriorating patients to emergency liver transplantation or to spontaneous recovery and regeneration of the native liver. Various forms of liver support have been tested, but all fit into 2 general categories: nonbiological (mechanical) and biological.

Nonbiological support, such as haemodialysis, charcoal haemoperfusion and blood/plasma exchange, has been unable to alter the course of the illness.[111-116] Haemodialysis and haemofiltration are certainly valuable in the management of cerebral oedema, when mannitol is used, or in cases with fluid imbalance and electrolyte abnormalities, particularly with associated renal failure.[117] Renal replacement therapy may reinforce the management of circulatory instability, and more particularly of cerebral vasoparalysis.[51] The problem with nonbiological devices is that they are metabolically inert and therefore do not replace the metabolic functions of the liver. Plasmapheresis both removes potentially toxic compounds from the patient's blood and provides potentially beneficial compounds from the donor, but fails to show a survival benefit in fulminant liver failure.[11]

Multiple attempts have been made to develop extracorporeal bioartificial liver supports (BAL).[118-125] Since none of these systems have been able to replace all liver functions for any significant length of time, the present focus of these studies is to use BAL to arrest and reverse cerebral oedema and intracranial hypertension. BAL treatment alone, in the absence of aggressive standard medical therapy, certainly does not reverse a severe clinical course. The first phase I clinical trial using BAL was published recently. Among the 18 patients with fulminant liver failure, 16 were successfully bridged to emergency liver transplantation without neurological sequelae, and 1 patient recovered fully without emergency liver transplantation.[126] Although this remarkable survival ratio requires confirmation by a randomised controlled trial, BAL yields encouraging perspectives in the management of fulminant liver failure, both as a bridging procedure to emergency liver transplantation and as a key to liver replacement therapy.

The history of therapies for acute liver failure is one of repeated cycles of great enthusiasm based on a limited, uncontrolled but always positive pub-

lished experience. It was this history which led to the apt 'advice' of Benhamou et al.[127] to patients with acute liver failure: 'Be published or perish.' Thus, rigorous and critical evaluation of therapies in fulminant liver failure is mandatory.

2.6 Auxiliary Liver Transplantation and Hepatectomy

The main difficulty in managing fulminant liver failure is characterised by the anguished decision whether or not to transplant. The risk of performing an emergency liver transplantation too early in patients who could spontaneously recover, or not transplanting others who will not recover, is a permanent concern in assessing the need for this procedure. Auxiliary liver transplantation is characterised by the preservation or partial removal of native diseased liver and transplantation of an 'auxiliary' liver allograft that will permit regeneration of the native liver, since the liver graft maintains homeostasis or at least supports the failing liver.[128]

This concept of a 'spare wheel' liver is an attractive procedure for patients with fulminant liver failure who may recover spontaneously. However, new and important questions emerge: are the indications for auxiliary liver transplantation identical to those for orthotopic liver transplantation, and how can we evaluate the potential for regeneration of the native liver, since simple needle biopsy may not be representative? Uncontrolled studies of auxiliary liver transplantation in fulminant liver failure show a survival rate of 48 to 69%, identical to that obtained with emergency liver transplantation,[129-133] although morbidity is higher in auxiliary liver transplantation than in orthotopic liver transplantation because of the increased complexity of the procedure. Auxiliary liver transplantation should be considered an important alternative to emergency liver transplantation. It allows regeneration of the native liver and eventual withdrawal of immunosuppression.

On the basis of uncontrolled studies, hepatectomy has been advocated as a method of improving circulatory abnormalities, mean arterial pressure and autoregulation of CBF.[134-137] Hepatectomy is of interest as a bridging procedure to emergency liver transplantation in patients with severe fulminant liver failure and serious haemodynamic instability.

Table IV. Prognostic and severity indicators in fulminant liver failure

Reference	Setting	Predictors of poor prognosis
Bernuau et al.[138]	Adult: viral hepatitis	Hepatic encephalopathy *and* Factor V <20% of normal (age <30 years) or <30% of normal (age >30 years)
O'Grady et al.[139]	Adult: paracetamol (acetaminophen)-induced	Arterial blood pH <7.3 (independent of hepatic encephalopathy) *or* Prothrombin time >100 sec *and* serum creatinine level >300 μmol/L *and* hepatic encephalopathy stage III or IV
	Adult: other causes	Prothrombin time >100 sec (independent of hepatic encephalopathy) *or* Any 3 of the following criteria: age <11 years or >40 years cause is NANB hepatitis, halothane or drugs delay between jaundice and onset of hepatic encephalopathy >7 days prothrombin time >50 sec serum total bilirubin level >300 μmol/L
Takahashi et al.[140]	Adult: viral hepatitis and NANB hepatitis	Risk score based on total and conjugated bilirubin, age, white blood cell count, coexisting disease, liver enzyme level and prothrombin time
Debray et al.[141]	Paediatric: hepatitis A	Serum total bilirubin level >400 μmol/L *and* prothrombin time <21% (irrespective of grade of hepatic encephalopathy)

NANB = non-A non-B.

Life support in the absence of a liver has been maintained for up to 60 hours with a satisfactory outcome. Wider use of total hepatectomy with extracorporeal liver assist devices and/or with intensive plasmapheresis awaits more careful study in animal models before it can reasonably be applied to humans.

2.7 Liver Transplantation

To date, emergency liver transplantation is the only effective treatment for fulminant liver failure. Liver transplantation should be considered for patients reaching grade III and IV coma because of fulminant hepatic failure. It is difficult to assess both the necessity and the correct time for transplantation. If too early, the operation may be unnecessary; if too late, chances of success are reduced.

The decision to transplant is based on many factors predicting severity and outcome (table IV).[138-141] The issue of low sensitivity compared with higher specificity for death is a major limit in the use of these selection criteria.[142] The low predictive value of prognostic criteria has led to the suggestion that all patients with fulminant liver failure should be listed for emergency liver transplantation either on admission to hospital or when they reach hepatic encephalopathy grade III.[143-145] But it remains clear that cautious evaluation of every patient with fulminant liver failure is mandatory: the cause of fulminant liver failure and the evolution of hepatic encephalopathy, coagulopathy and systemic complications are all of prime importance in the decision to transplant or not. Absolute contraindications to emergency liver transplantation are active ongoing infection, refractory hypoxia, uncontrolled haemodynamic failure and brain death or irreversible neurological injury.

Published results show a survival between 50 and 90% (table V).[146-159] Variation in survival is dependent on the severity of the illness at the time of transplantation and the criteria used to decide on the need for the procedure. Despite the lack of a controlled trial on the survival impact of emergency liver transplantation, there is no doubt of the efficiency of this treatment.

Table V. Results of emergency liver transplantation (ELT) for fulminant liver failure

Setting	Reference	Number of ELTs	Survival (%)
Adult	Vickers et al.[146]a	16	56
	Emond et al.[147]	19	58
	Williams & O'Grady[148]	56	58
	Ascher et al.[149]	19	92
	Moreno Gonzalez et al.[150]	35	47
	Dodson et al.[151]	115	60
	Bismuth et al.[152]	116	68
Paediatric	Devictor et al.[153]	19	68
	Tan et al.[154]	12	61
	Dawan et al.[155]	37	62
	Bhaduri & Mieli-Vergani[156]	29	50
	Rivera-Penera et al.[157]	38	79
	Bonatti et al.[158]b	15	53
	Tissières et al.[159]	57	63

a Adult and paediatric series.

b Patients <1 year old.

3. Conclusion

In conclusion, medical treatment of hepatic encephalopathy associated with fulminant liver failure necessitates the understanding of the pathophysiology of this syndrome. Hepatic encephalopathy in patients with acute liver failure is characterised by the association of neuropsychiatric lesions and cerebral oedema, an acute complication with a dismal outcome. Except for the rare cases in which treatment of the underlying cause of the disease is possible, the treatment of patients with fulminant liver failure is currently emergency liver transplantation. Therefore, the goal of medical treatment of hepatic encephalopathy is only to minimise the risk of irreversible neurological damage and to prolong the patient's life while awaiting a graft. This field has opened up exciting new areas of clinical experience for the critical care physician. It is becoming apparent that, for many of these patients, optimum management in the intensive care unit can make

the difference between death and survival with excellent quality of life after liver transplantation.

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