MANAGEMENT OF LIVER FAILURE

I. CORALL AND R. WILLIAMS

Clinical presentation

In considering a patient in liver failure it is important to distinguish between fulminant hepatic failure (FHF) and episodes of acute hepatic decompensation in patients suffering from chronic liver disease (CLD), as the basis for treatment differs. Fulminant hepatic failure has been defined by Trey and Davidson (1970) as encephalopathy developing within 8 weeks of the onset of symptoms in a patient whose liver function before the onset of the illness was presumed to be normal. In these patients the liver damage is potentially reversible. Treatment is supportive, and is aimed at the associated multi-organ failure. Artificial liver support systems are used to buy time, and to give more chance for the surviving hepatocytes to regenerate, for it is on regeneration that survival depends.

The commonest causes for FHF in the United Kingdom are viral hepatitis and paracetamol overdose (table I). Rarer causes include fatty liver of pregnancy, mushroom poisoning and idiosyncratic drug reactions.

Presentation is with a rapidly deteriorating neurological state combined with a gross prolongation of prothrombin time and increased serum aminotransferase concentrations. Jaundice may not be found initially, because of the rapidity of onset of the syndrome. Initial diagnosis can be made difficult by the fact that acute viral hepatitis may present as a predominantly cholestatic picture, with severe upper right quadrant pain, simulating an acute intra-abdominal surgical emergency. If a laparotomy is undertaken in these circumstances (and every effort should be directed to prevent this) mortality is high—as high as in patients with CLD who are operated on when in liver failure (Powell-Jackson, Greenway and Williams, 1982). During the early stages of FHF, hypoglycaemia can develop; serum glucose concentrations should be measured at least every 1 h and hypoglycaemia treated by i.v. infusion of 10% dextrose solution.

At this initial stage of diagnosis and treatment, it is important to consider the likelihood of a paracetamol overdose. Antidote therapy is available (Prescott, 1978; Prescott et al., 1979), but is effective only if given within 14 h of ingestion of the overdose. If it is given in time, the patient is unlikely to develop severe liver damage. Unfortunately, most patients do not present within this period, as at this time they are usually well clinically and biochemically, signs of liver failure not developing until 48–72 h after ingestion of the paracetamol. Prolongation of prothrombin time is usually the first laboratory abnormality to be detectable.

As the syndrome progresses, the neurological state worsens (table II) and a large number of associated problems begin to develop, necessitating the intensive care management of these patients, preferably in a unit specifically designed for their treatment (Ward et al., 1977). The multisystem nature of the syndrome is indicated by the acid–base, pulmonary, vasomotor, cardiovascular and haematological problems, in addition to progressive encephalopathy and associated cerebral oedema. Clinically, the deteriorating neurological state may be followed by the progress of dilating pupils which will become increasingly sluggish in the reaction to light, as the signs of decorticate and

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Median age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>30</td>
</tr>
<tr>
<td>Viral Hep. A</td>
<td>27</td>
</tr>
<tr>
<td>B</td>
<td>29</td>
</tr>
<tr>
<td>NANB</td>
<td>30</td>
</tr>
<tr>
<td>Halothane</td>
<td>45</td>
</tr>
<tr>
<td>Others</td>
<td>33</td>
</tr>
</tbody>
</table>

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TABLE II. Clinical grading of hepatic encephalopathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mental state</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Euphoria, occasionally depression, Fluctuant, mild confusion, Slowness of mentation and affect, Untidy, slurred speech, Disorder in sleep rhythm</td>
</tr>
<tr>
<td>II</td>
<td>Drowsy but responds to simple commands, Inappropriate behaviour</td>
</tr>
<tr>
<td>III</td>
<td>Sleeps most of the time, but rousable, Marked confusion, Incoherent speech</td>
</tr>
<tr>
<td>IV</td>
<td>Unrousable, may or may not respond to noxious stimuli</td>
</tr>
</tbody>
</table>

decerebrate rigidity develop. Papilloedema in this situation is unusual. Unless the cerebral oedema can be controlled, up to 80% of these patients will die as a direct result of brain stem herniation (Silk et al., 1977).

The Intensive Care management of these patients is designed specifically to define and correct the biochemical, cardiovascular, pulmonary and renal complications of the syndrome. Artificial liver support, by removing circulating toxins, may aid in controlling both the cerebral oedema and the vasomotor instability. The use of prostacyclin (PGI₂) infusions during extracorporeal haemoperfusion has minimized the platelet damage and associated severe arterial hypotension that was seen during earlier haemoperfusions. Early extracorporeal charcoal haemoperfusion—in Grade 3 encephalopathy—can reduce the incidence of cerebral oedema in these patients from 78% to about 44%, with a consequent increase in survival (Gimson et al., 1982). By contrast, rates of survival of only 13–17% have been found in patients given standard conventional ITU therapy alone (Silk and Williams, 1978; Ring-Larsen and Palazzo, 1981). In centres specializing in liver failure, facilities should be available for aggressive mannitol treatment of cerebral oedema (including intracranial pressure measurement) and ultrafiltration, which is often required because of fluid overload.

Transfer to such a centre should be undertaken before encephalopathy deepens (preferably in Grade 1–2 coma) as, once a certain stage of encephalopathy has been reached, the g-forces involved in road, rail and air travel can induce brain stem herniation. If the patient has deteriorated beyond Grade 2 encephalopathy before transfer then, depending on the blood-gas status, the patient may well have to be transferred with the trachea intubated and, possibly, intermittent positive pressure ventilation instituted. In these circumstances, medical and nursing attendants, trained to deal with the intubated and ventilated patient, should accompany the patient during transfer, whether it be by road or, preferably, by helicopter. An hourly blood glucose measurement should not be forgotten at this time as sudden hypoglycaemia, if not detected, can result in permanent neurological damage. During transfer it would be preferable if the patient could be nursed with the chest at a 33° angle to the lower half of the body, as this minimizes the effects of venous back pressure on the developing cerebral oedema. There will be occasions, however, when the cardiovascular instability often present in Grade 3 or Grade 4 coma will not permit this position to be adopted. If this situation should occur, attention to small details, such as the avoidance of tight bandages around the patient’s neck securing the endotracheal tube (which may occlude jugular flow) and avoiding extreme flexion, rotation or extension of a patient’s head (impeding intracranial venous drainage), helps to minimize potential increases in ICP during transportation. It is a feature of the encephalopathy associated with FHF that, in the absence of hypoxic neurological damage, when hepatic function begins to return to normal, neurological signs improve rapidly over 2–3 weeks, resulting in a complete return to normal neurological function.

ITU care

A suitable ITU environment for treatment of these patients was described by Ward and colleagues (1977) and, with minor modifications, their recommendations are pertinent in 1986. It is worth considering if staff regularly involved with the treatment of these patients should receive vaccination with a currently available vaccine against hepatitis B since, although patients suffering from a paracetamol overdose pose no infective problems, those suffering from HBs Ag infection may do so.

Thought also needs to be given to the handling of potentially infected material such as blood samples, ventilator circuits, suction catheters and bed linen. Disposables such as perfusion circuits, drip sets, i.v. and urinary catheters need to be identified and suitably disposed of. Over the years in the unit at King’s College Hospital, the staff
have become used to these routines, and no insuperable problems have been caused by the sometimes highly infected patients treated. It is foreseeable, however, if these patients were not transferred to centres used to treating them, that ordinary ITU routines may prove inadequate in preventing cross-infection either to other patients or to the staff involved in their treatment.

FULMINANT HEPATIC FAILURE
CEREBRAL OEDEMA

Incidence and aetiology

Since Lucke (1944) initially described postmortem findings of cerebral oedema in patients dying from FHF, it has become recognized as perhaps the most common cause of death, not because the disease process itself has changed, but because of an increased awareness of its occurrence and the ability to quantify its progress accurately by the use of intracranial pressure transducers (Pirola, Ham and Elmslie, 1969; Ware, D'Agostino and Combes, 1971; Silk et al., 1977; Gimson et al., 1982; Editorial, 1984). However, there does seem to be a variation in the development of this condition related to the cause of FHF. In one series (Gimson et al., 1983) cerebral oedema occurred in 39% of patients suffering from hepatitis A, in 72% of patients with hepatitis B and in some 65% of patients suffering from FHF as a result of non-A non-B hepatitis. Interestingly, Conomy and Swash (1968) have documented increases in ICP with cerebral oedema in patients with chronic liver disease with episodes of acute hepatitis. Other centres have recorded this also, and we have seen occasional examples, but it is much less common than in FHF.

Sustained increases in ICP beyond 30 mm Hg produce clinical signs of increased intracranial pressure. However, such increases may be produced by factors other than cerebral oedema, such as vascular distension as a result of increased PaCO₂, or vasomotor paralysis (Langfitt, 1968) resulting from abolition of cerebral autoregulation. Clinically increased ICP as a result of these three causes are indistinguishable, and it is probable that, in patients with FHF, all three causes may well co-exist during the course of the disease.

Cerebral oedema manifests itself only during Grade IV encephalopathy and has been classified into two types: cytotoxic and vasogenic. In the cytotoxic form, the blood–brain barrier (BBB) is intact and the oedema, a low molecular weight ultrafiltrate, is intracellular. In the vasogenic form, BBB permeability is increased and both circulatory toxins and plasma proteins will egress from the capillaries to the extracellular space.

The occurrence of cerebral oedema in Grade IV encephalopathy has led investigators to the conclusion that it may be related to the high concentration of toxins found in the circulation at this time, possibly causing impairment of the membrane Na⁺-K⁺-ATPase system (Klatzo, 1967). BBB permeability is increased by substances such as ammonia, methyl octanoate, mercaptans, and phenols which are all found in the circulation of patients with FHF. Of the two types of cerebral oedema, recent studies would tend to favour the vasogenic form as predominating in patients with FHF (Ede et al., 1986; Seda et al., 1984).

Diagnosis

Clinically, increases in muscle tone with hyperpronation and decerebrate posturing are early signs. Sluggishly reacting pupils occur early. Other clinical signs such as vomiting, headache, bradycardia and papilloedema are rare. Hyperventilation and opisthotonos occur early in severe cases, and brain stem coning soon occurs if active treatment is not started. Signs of increasing ICP can be masked if the patient's lungs are being ventilated in the presence of neuromuscular blocking drugs. Early use of an intracranial pressure transducer is required in these patients.

At King's College Hospital, an extradural sensor (Ladd Industries, Vermont, U.S.A.) is inserted via a 13-mm fronto–parietal burr hole—preceded by an infusion of 2 units of FFP to correct partially the coagulation defect that is present at this stage of the disease. Use of such a device enables accurate measurement of ICP (that is, assessment of the effect of treatment) and calculation of the cerebral perfusion pressure (MAP–ICP). The latter must be kept greater than 40 mm Hg.

Treatment

As has already been mentioned, hypoxia, jugular vein compression and hypercapnia all affect ICP, so these influences should be minimized before active treatment is started. This should commence when ICP has reached 30 mm Hg (Editorial, 1984).
**Steroid therapy**

Dexamethasone 32 mg per day failed to reduce either the mortality or the occurrence of cerebral oedema in patients with FHF in a carefully controlled study (Canalese et al., 1982). As steroid therapy may have an inhibitory effect on hepatic regeneration, its use is therefore not recommended.

**Oncotic therapy**

The hypoalbuminaemia seen in these patients encourages formation of oedema, and infusion of albumin with a loop diuretic, to maintain normovolaemia, has been found experimentally to decrease ICP (Albright, Latchan and Robinson, 1984). Caution should be observed to avoid circulatory overload as this increases ICP (Cuypers, Matakis and Potolicchio, 1976). Thus, central venous and pulmonary artery wedge pressure measurements are essential. Albumin and fresh frozen plasma are the agents of choice. Gelatin derivatives should be avoided as they influence the activity of fibronectin.

**Hyperventilation**

This leads to reduction in $P_{aCO_2}$, with consequent cerebral vasoconstriction. As a short term treatment it has proved useful in neurosurgery, but care must be taken to ensure that the $P_{aCO_2}$ does not decrease to less than 3 kPa, as this increases brain lactate, with consequent deleterious effects on the cerebral oedema.

Long term hyperventilation has been assessed in these patients to see if the incidence of cerebral oedema could be reduced. In a controlled trial, Ede and colleagues (1984) hyperventilated one group of patients to $P_{aCO_2} < 5$ kPa but $> 3$ kPa, and found no decrease in the incidence of cerebral oedema compared with their control group. Thus, although increased ICP may be decreased actively by hyperventilation, this benefit does not persist. Long term hyperventilation as a treatment for increased ICP in these patients cannot be advised although, in the short term, in combination with hyperosmolar diuretics, it is the treatment of choice.

**Osmotic diuretics**

**Glycerol.** Initial interest was stimulated by reports from Matthew and colleagues (1972) of the beneficial effects infusions of glycerol had in both neurosurgical patients and those with cerebral infarction. Record and colleagues (1975) were unable to demonstrate any beneficial effects of glycerol in patients with FHF and its use as an osmotic diuretic in these patients is not recommended.

**Mannitol.** By contrast with glycerol, mannitol has been shown both to reduce ICP and to alter the classical signs of cerebral oedema in patients with FHF (Canalese et al., 1982). The maximum decrease in ICP usually occurs some 20 min after commencement of the infusion and may be of the order of 22 mm Hg as found in the study by Canalese and colleagues, in which 20% mannitol 1 g kg$^{-1}$ was infused via a central venous catheter and repeated as ICP increased. Clearly, adequate renal function has to be established before such a regimen is started. However, if the patient is oliguric or anuric, then a bolus dose of 50 ml of 20% mannitol is worth trying. It should be noted that, to achieve maximal reductions in ICP, mannitol has to be infused rapidly—full haemodynamic monitoring with both left and right atrial pressure measurements is highly desirable.

Before repeating a mannitol infusion, plasma osmolality must be checked and should not exceed 320 mosmol kg$^{-1}$. If haemodialysis is in progress, full doses of mannitol can be given regularly. Infusions should be made through a standard blood filter to minimize the risk of mannitol crystals entering the circulation.

The loop diuretic, frusemide, may well have synergistic actions with mannitol in the reduction of increased ICP (Pollay et al., 1983) and has in itself proved useful in the reduction of both cytotoxic and vasogenic cerebral oedema (Clasen, Pandolfi and Casey, 1974; James, Bruce and Welsh, 1978).

**CARDIOVASCULAR PROBLEMS**

**Causes**

The causes of the circulatory impairment seen in FHF are not fully understood, but are probably multifactorial and result in a circulation with a low systemic vascular resistance and a compensatory high cardiac output (Rueff and Benhamou, 1973). In the later stages of Grade IV encephalopathy, the illness is characterized by a severe hypotension.

Various hypotheses have been put forward to explain this phenomenon, and have included "false" neurotransmitters (Cangiano et al., 1982), endotoxin (Nolan, 1981), impaired prostaglandin
synthesis or metabolism (Zipser et al., 1979) and the vasoactive properties of substance P (Hortnagel et al., 1984) causing inappropriately increased concentrations of adrenaline and noradrenaline. In addition to the systemic changes in cardiovascular function there is an increase in portal pressure in patients with FHF and small varices may form.

The result of these changes in cardiovascular function is the development of tissue hypoxia. Lactic acidosis develops and, despite a shift to the right in the haemoglobin-oxygen dissociation curve, oxygen extraction remains low—especially so in those patients who progress to the “multi-organ” failure so often seen in Grade IV encephalopathy (Bihari et al., 1984). Thus, if metabolically active tissues are unable to increase their oxygen extraction—possibly as a result of changes in the microcirculation—it is important to attempt to minimize the effects that disturbances in lung function may have on arterial oxygenation.

Treatment

**Volume replacement.** Optimal right and left heart filling pressures can be obtained only by suitable monitoring techniques. Infusion of plasma protein fraction to correct hypovolaemia may lead to marked increases in cardiac output and oxygen extraction in some patients. Patients who do not respond to such therapy have probably suffered severe loss of control of the microcirculation, and prognosis is poor.

**Vasoconstrictors and inotropes.** If such drugs have to be used during periods of marked hypotension to maintain cerebral perfusion, a short-term noradrenaline infusion is probably the treatment of choice. Tissue hypoxia, onset of renal failure and eventual prognosis have not been found to be influenced by the use of vasopressors.

**Vasodilators.** The role of prostacyclin infusions to encourage dilatation in the microcirculation in patients with FHF is as yet uncertain. Manipulation of the microcirculation to improve tissue oxygenation could be of considerable importance in preventing multi-organ failure and improving chances of survival.

**Lung problems.** As encephalopathy increases, endotracheal intubation is necessary both to provide for adequate chest physiotherapy and suction, and to prevent aspiration. As these patients may be restless the position of the tracheal tube should be verified by daily x-ray.

Arterial hypoxæmia as a result of ventilation: perfusion mismatches is common in FHF. On the whole, such changes are relatively easy to treat, and do not contribute to the tissue hypoxia described above. Low pressure pulmonary oedema is also a frequent occurrence in these patients (Trewby et al., 1978).

**IPPV.** Increasing the inspired oxygen fraction and artificial ventilation with or without PEEP usually corrects the arterial hypoxaemia. Both IPPV and PEEP and have quite marked depressant effects on cardiac output and hepatic blood flow (Bonnet et al., 1982).

The advantages of IPPV in these patients is control of blood-gas tensions and reduction in oxygen consumption, with perhaps a reduction in lactic acid formation. There is no advantage in long-term hyperventilation (see above) in terms of a reduction in ICP. It also leads to decreases in hepatic blood flow, and is not recommended.

**HAEMATOLOGICAL PROBLEMS**

Complex deficiencies of the haemostatic system can develop. This results mainly from deficient synthesis of coagulation factors—although inactivation of plasminogen activators may also be impaired. The prothrombin time and platelet count are good guides to haemostatic status. Spontaneous haemorrhage is unlikely to occur if platelet concentrations are greater than $30 \times 10^9$ litre$^{-1}$. More common causes of haemorrhage are anatomical lesions, such as peptic ulcers and, rarely, varices. The routine use of the H$_2$-antagonists given prophylactically was shown to reduce the frequency of subsequent gastrointestinal haemorrhage (MacDougall and Williams, 1978).

The use of stored blood is not recommended; less than 24 h old is to be preferred. If this is not available, 2 units of FFP should be administered for every 6 units of stored blood. Vitamin K and calcium gluconate should also be given. There appears, however, to be little benefit from replacement therapy before the haemorrhage occurring.

**Renal failure**

Renal failure is a common feature of FHF and, if obvious causes such as sepsis are excluded, occurs in up to 40% of patients. In most instances it accompanies severe FHF and is the result of intense vasoconstriction, but in 10% of patients renal failure is disproportionately severe. Endotoxaemia, imbalance of the renin-angiotensin
system and prostaglandin synthesis and metabolism have all been implicated (Wilkinson et al., 1974; Arroyo et al., 1983; Perez-Ayuso et al., 1984). It is important to differentiate pre-renal causes such as hypovolaemia early, as they are potentially reversible. A urinary sodium concentration of < 12 mmol litre\(^{-1}\) and a urine:plasma osmolality ratio > 1.15 would indicate hypovolaemia as the prime cause of the renal failure. Adequate haemodynamic measurements would confirm the diagnosis.

Treatment of the renal failure with haemodialysis is essential, for disturbances in electrolytes are too great for conservative management. Often the patient will require the use of dialysis and ultrafiltration techniques.

**Haemoperfusion**

Detailed consideration of this form of treatment is beyond the scope of this article. The rationale behind this form of therapy is that, if the circulating toxins that may be implicated in the aetiology of cerebral oedema, renal failure and cardiovascular instability can be removed either by dialysis or adsorption to some form of solvent, then the mortality associated with FHF may be reduced (Chang and Migchelson, 1973; Opolon et al., 1976). The use of prostacyclin infusions has reduced the incidence of profound hypotension from platelet damage seen in the earlier perfusions. Readers are referred to a more detailed article (Silk and Williams, 1984) for a fuller discussion of this subject.

**CHRONIC LIVER DISEASE**

**SIGNS AND SYMPTOMS OF HEPATIC DECOMPENSATION IN A PATIENT WITH CHRONIC LIVER DISEASE**

Progressive chronic liver disease is characterized in varying degrees by the presence of jaundice, ascites and encephalopathy, and patients may, in addition, present with acute episodes of hepatic decompensation superimposed on a gradual deterioration in liver function. This may be precipitated by viral hepatitis, the intake of sedative hypnotic drugs, acute intestinal haemorrhage from oesophageal varices, sepsicaemia or an acute alcoholic binge. The aim of treatment in these patients is to recognize the precipitating factors early, for if these can be treated, many patients can be restored to their previous state of relative well-being. Unlike FHF, liver function does not return to normal, but can be restored to the pre-episodic state with effective treatment of the precipitating factors. The development of a hepatoma may be a very unusual cause of hepatic decompensation in a patient with chronic liver disease, but it is certainly worthy of consideration because, if proven, and without systemic metastases, this could be a good indication for hepatic transplantation.

**Clinical presentation**

The most dramatic clinical presentation of these patients is with a massive gastrointestinal bleeding from oesophageal or gastric varices. Profound hypovolaemia and hypotension are early consequences. Associated liver function can deteriorate rapidly, as a result of poor hepatic perfusion. In addition, a high protein load will be presented to the gut (1 unit of blood approximates to 60 g of protein).

**Bacterial infection**

Patients suffering from cirrhosis are very susceptible to infection, and this in itself can be a cause of hepatic decompensation in patients with chronic liver disease. Spontaneous bacterial peritonitis (SBP) is the single most important bacterial infection to identify clearly in patients with cirrhosis. This syndrome occurs in 8-18% of cirrhotic individuals with ascites (Conn and Fessel, 1971; Kline, McCullum and Guth, 1976). Patients may present with a combination of pyrexia, abdominal tenderness and pain, although not uncommonly the condition is clinically silent, without any signs or symptoms referable to the abdomen (Hoefs et al., 1982). An otherwise unexplained deterioration in renal function may be the clue to the alert physician that SBP is present. Unless the diagnosis is made early and suitable antibiotic therapy instituted, mortality with this particular type of bacterial infection can approach 95%. Bearing in mind that 30% of such patients present with no symptoms referable to the abdomen (Hoefs et al., 1982), awareness of the likelihood of such a syndrome is clearly important.

**Hepatitis**

Patients with underlying chronic liver disease may acutely decompensate in response to hepatitis —either viral or acute alcoholic. If it results from viral infection, there may be a history of malaise, anorexia and abdominal pain. Such patients usually present with very high serum aminotrans-
ferase concentration, and rapidly develop jaundice. In addition to hepatitis B, Epstein–Barr virus and cytomegalovirus, the non-A non-B hepatitis virus can lead to this clinical syndrome (Dienstag, 1983). More recently it has been realized that infection with delta virus (Rizzetto, 1983) can be responsible for the deterioration in liver function in patients with proven HBs Ag-positive chronic liver disease. The presentation of a patient with alcoholic liver disease, suffering from a superimposed bout of acute alcoholic hepatitis can mimic an acute abdominal surgical emergency with acute upper right quadrant pain, abdominal guarding, tenderness, jaundice and fever with leucocytosis.

Exploratory laparotomy in these patients in the belief that one might be dealing with an intra-abdominal surgical emergency, is mistaken (Powell-Jackson, Greenway and Williams, 1982). A radioactive scan of the liver shows no uptake of isotope and, by careful questioning of the relatives and friends, a history of heavy drinking may be obtainable.

**EVALUATION—CLINICAL AND BIOCHEMICAL ASSESSMENT OF THE PATIENT**

Child proposed a grading for patients suffering from chronic liver disease which has stood the test of time and may be used either in its original form (Child, 1964; Christensen et al., 1984) (table III) or with the modification proposed by Pugh and colleagues (1973) (table IV). Although it was originally devised to assess the risk of portal-systemic shunting operations, it is widely used today to assess the outcome of any form of interventional therapy. Patients are graded A, B or C depending on the presence of encephalopathy, ascites, bilirubin concentrations, prothrombin time and serum albumin concentrations. Marked differences in prognosis related to Child’s grading are demonstrable. Thus, at King’s College Hospital only 30% of Grade C patients, 1 year after the initial variceal bleed, survived, compared with 75% in the Grade A group (Westaby et al., 1983). It is to be remembered that, with the grading system, patients suffering from primary biliary cirrhosis have a bilirubin concentration disproportionate to concurrent hepato-cellular damage. In general, so-called liver function tests reflect either hepato-cellular damage or defects in biliary excretion, either intra- or extra-hepatic. In the first group of tests are included the prothrombin time and serum albumin concentration (an indicator of chronic hepatic impairment). The second group includes alkaline phosphatase, γ-GT, transaminases and, to some extent, serum bilirubin concentrations. However, these various biochemical tests do not necessarily give an accurate clinical picture of the underlying pathological position.

Intra-hepatic cholestasis seen in some types of idiosyncratic drug reactions, viral hepatitis or septicaemia may easily be misdiagnosed as extra-hepatic biliary obstruction. The use of further diagnostic aids such as ultrasound makes the differential diagnosis easier. If intra-hepatic fibrosis is present, in addition to biliary obstruction, then the intra-hepatic duct dilatation is not seen on ultrasound.

**TREATMENT**

**Gastrointestinal haemorrhage**

Initial management of patients presenting with gastrointestinal haemorrhage requires attention to the following areas:

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### Table III. Child’s (1964) classification of functional hepatic reserve in patients with cirrhosis

<table>
<thead>
<tr>
<th>Test or clinical observation</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (μmol litre⁻¹)</td>
<td>&lt; 40</td>
<td>40–50</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Serum albumin (g litre⁻¹)</td>
<td>&gt; 35</td>
<td>30–35</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>None</td>
<td>Minimal</td>
<td>Advanced</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Excellent</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Risk of operation</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
</tbody>
</table>

### Table IV. Grading of the severity of liver disease according to Pugh and colleagues (1973)

<table>
<thead>
<tr>
<th>Biochemical and clinical indices</th>
<th>Points for increasing abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy (Grade)</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (μmol litre⁻¹)</td>
<td>&lt; 25</td>
</tr>
<tr>
<td>Albumin (g litre⁻¹)</td>
<td>35</td>
</tr>
<tr>
<td>Increase in prothrombin time (s)</td>
<td>1–4</td>
</tr>
</tbody>
</table>
(1) Control of haemorrhage, and if attributable to bleeding oesophageal varices, this usually entails the use of balloon tamponade or vasopressin, or both.

(2) Urgent attention to replacing the circulating volume, to maintain both hepatic and renal perfusion.

(3) Prevention of aspiration, since the results of this may be disproportionately devastating in these patients as they are particularly sensitive to infection.

(4) Early endoscopic examination to establish the precise location of the haemorrhage.

Although the initial bleed often stops spontaneously, there is a high incidence (60%) of a rebleed within 24–48 h. Thus, after the initial haemorrhage has been controlled and the circulating volume restored, the management of these patients requires an ITU approach involving the use of balloon tamponade, vasopressin and other vasoconstrictors, the maintenance of circulating volume as a result of both aggressive circulatory monitoring and infusion therapy, and the prevention of aspiration and infection.

In the longer term, injection sclerotherapy of the oesophageal and gastric varices would appear to be the treatment of choice. For a more detailed description of the acute and chronic management of variceal bleeding, readers are referred to Westaby and colleagues (1982).

Encephalopathy

The grading of hepatic encephalopathy initially proposed by Trey and Davidson (1970) for use in patients with fulminant failure has also been of use in assessment of the encephalopathy as a result of chronic liver disease. The details of grading encephalopathy 1–4 are shown in table II.

In earlier days, the EEG was much used to assess encephalopathy. However, it is costly in terms of staff and equipment and in the research environment has been replaced by the measurement of visual evoked potentials. Simple psychometric tests, such as the Reitans trial connection test, performed on the pre-coma patients have been found to be as useful as any of the more advanced psychomotor tests.

Of more practical import is the immediate differentiation of causes of hepatic encephalopathy from similar neurological sequelae resulting from other causes. In the elderly patient, the differentiation from a senile dementia can be difficult, and in patients suffering from alcoholic cirrhosis the presence of chronic subdural haematoma resulting in neurological deterioration should be seriously entertained. The most common neurological abnormality in early hepatic coma is asterixis (flapping tremor), which is accompanied by an intellectual deterioration, slurred speech, reversal of sleep rhythm, confusion, drowsiness and irritability (table II), which should make the diagnosis of hepatic encephalopathy relatively easy.

The aetiological factors in hepatic encephalopathy are diverse, and Zieve (1974) has demonstrated how synergism can occur between compounds such as ammonia and mercaptans and free fatty acids to produce coma in experimental animals. Secondary factors such as hypoxia, hypovolaemia, hypotension and hypoglycaemia are more amenable to treatment. Complicating these factors is the administration of sedatives to control the extreme restlessness often seen during the early stages of hepatic encephalopathy; this may induce deeper levels of coma. Distressing though it may be to both the patient and the attendants, physical restraint during the earlier stages of hepatic encephalopathy is preferable to sedation.

Protein restriction to prevent the production of potential neurotoxins from the metabolism of gut proteins is still the main area of therapy in the treatment of encephalopathy. Use may be made of the branched chain amino acids (BCAA) valine, leucine, isoleucine, which are preferentially metabolized in extrahepatic sites and thus, in situations where hepatic function is poor, plasma and CNS concentrations do not increase. BCAA may be involved in the active transport of potentially neurotoxic amino acids such as phenylalanine and tyrosine from the central nervous system, and an abnormal amino acid profile has been implicated in the development of encephalopathy.

These theoretical observations have been somewhat negated by controlled clinical trials (Erikson, Person and Wahren, 1982; Wahren, Denis and Desurmont, 1983) which investigated BCAA administered i.v. and by mouth and demonstrated no improvement in chronic encephalopathy, even though there was a reduction in the aromatic amino acid (AAA) plasma profile or a change in the BCAA:AAA ratio. Despite the disappointing results of BCAA manipulation in terms of
encephalopathy, they may well have a role in reversing the negative nitrogen balance seen in these patients without increasing the encephalopathy (Millikan, Henderson and Warren, 1983). Despite the commercial availability of these preparations they are expensive, and hyperosmolar, and further investigation in this area is clearly required. In addition to the use of BCAA, attempts have been made to manipulate intra-cranial neurotransmitters by the use of bromocriptine and L-dopa.

In Grade 1 coma it is normal to restrict protein intake to 40 g day\(^{-1}\) or less, but when coma deepens this must be discontinued and the bowel purged twice a day with 50% magnesium sulphate solution 80 ml instilled down a naso-gastric tube. In those patients suffering from acute decompensation, encephalopathy tends to be fairly short-lived, and then protein can be restarted on the basis of 20 g every 3 days up to 1 g/kg body weight. Rarely, long-term protein restriction, less than 50 g day\(^{-1}\), is required to control chronic encephalopathy. In these circumstances vegetable protein is better tolerated than animal protein. The patient compliance is low as a result of symptoms such as abdominal distension, diarrhoea and flatulence. Associated problems such as salt restriction and the extremely low variety of potential foods make expert dietary assistance very important.

In these patients the use of antibiotics and lactulose to inhibit and absorb toxins produced from gut flora is common. Neomycin has been extensively used (Crossley and Williams, 1984), but small amounts of neomycin may well be absorbed, leading to nephrotoxicity. Its use should really be restricted to 1–2 weeks and when associated with severe exacerbations of encephalopathy. As an alternative, Morgan, Read and Speller (1982) have been investigating the use of metronidazole 800 mg daily to control gram-negative anaerobes. More commonly, these patients are given lactulose administered by naso–gastric tube, the daily dose being 90 ml in divided aliquots. The purpose of giving lactulose is to induce catabolic repression, trapping potential toxins in the gut as a result of a pH gradient across the intestinal wall (Castell and Moore, 1971). In addition, bacterial deaminating enzymes may well be inhibited (Vince, Killingley and Wong, 1978). If intractable encephalopathy is a major problem, the patient should be considered for hepatic transplantation.

### Infection

In patients requiring the use of a Sengstaken tube for the control of variceal bleeding, it must be remembered that aspiration pneumonitis is common. It should be suspected if the patient becomes pyrexial, in which case blood and sputum should be cultured. Other rarer forms of infection may be bacterial endocarditis associated with i.v. drug abuse, septic arthritis or even tuberculosis. *Escherichia coli* and enteric bacteria can be isolated in approximately 75% of patients. *Pneumococcus* and anaerobic bacteria are the causal organisms in the remaining 25%. In the case of spontaneous bacterial peritonitis, the white cell count in the ascitic fluid is not a good guide to the presence of infection and, if this entity is suspected on clinical grounds, treatment should be instituted immediately with i.v. cefuroxime and metronidazole until specific bacterial sensitivities can be established. On the whole, antibiotics penetrate the ascitic fluid readily and, except in a severely ill patient, direct i.p. instillation of antibiotics is rarely necessary.

### Nutrition

Nutritional control of the patient with chronic liver disease can be complex as a result of the interplay of factors such as chronic sodium and protein restriction coupled with potential malabsorption and abnormal protein breakdown rates, such that these patients require, on the whole, a minimum protein intake of 50 g day\(^{-1}\). During periods of encephalopathy, supplementation of the conventional diet with protein is clearly impracticable, and, if gastrointestinal absorption is normal, attempts can be made to increase protein utilization by the use of high calorie preparations such as Hycal.

There has been interest in the use of alternative nitrogen sources such as branch chain amino acids, leucine, isoleucine and valine (see above). The attraction of their use is twofold: first, they may reduce muscle catabolism, which is a characteristic feature of poor hepatic function (probably as a result of the increased concentration of glucagon leading to muscle catabolism as a means of gluconeogenesis); and second, they are thought to play a role in the aetiology of encephalopathy, in that, in reduced hepatic function, the aromatic amino acid profile in plasma increases and this may lead to reduced transport out through the blood–brain barrier of the amino acids phenylala-
nine and tyrosine, with a potential change in the balance of cerebral neurotransmitters. Regardless of this theoretical advantage, studies to date suggest that, despite adequate alteration in the biochemical amino acid profile, use of branch chain amino acids does not improve the acute or chronic encephalopathy (Erikson, Person and Wahren, 1982; Wahren, Denis and Desurmont, 1983). Nevertheless, the other area of interest in their use in the suppression of muscle catabolism leading to a positive nitrogen balance has been investigated by Milikan, Henderson and Warren (1983) and, in their opinion, this aspect of the use of BCAA has been beneficial and has not led to an increased incidence or worsening of encephalopathy in their patients.

**Drug use**

Whilst it is advisable to reduce to the absolute minimum drugs administered to patients suffering from acute decompensation as an aspect of their chronic liver disease, there are situations arising in which sedatives, anti-depressants and other drugs are necessary. Clearly, these patients have an altered metabolism and response to drug therapy (Bircher, 1983) as a consequence of not only a reduced hepatocyte mass, but also the loss of the first-pass effect, probably as a result of spontaneous opening of portal-systemic shunts, increased end-organ sensitivity, and possibly hypoalbuminaemia leading to a dramatic decrease in the protein-bound fraction of administered drugs. If sedatives are required, oxazepam and lorazepam (Shull et al., 1976) seem to be safer than compounds such as diazepam and other tranquillizers, and the general maxim to give a small amount of the drug and observe the therapeutic effect is true in this situation. Pethidine, morphine and other narcotics readily produce encephalopathy in these patients. If their use is required for pain relief, very small initial doses are recommended. Other drugs which should be used with caution are the hypoglycaemic agents and beta-blockers. Propranolol, for example, is used to reduce portal pressure in these patients, but a much reduced dose is required.

**CONCLUSION**

Much can be done to increase the survival of patients in liver failure, especially FHF, but this requires early transfer to centres used to dealing with FHF, so that early charcoal haemoperfusion and aggressive treatment of cerebral oedema, including intracranial pressure monitoring, can be undertaken. Ideally, transfer should be made when the patient is in Grade II encephalopathy—preferably by helicopter. The question of paracetamol overdose should always be considered, as antidote treatment must be given within 14 h of ingestion.

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**REFERENCES**


