

Part III: Gastroenterological Disorders

Chapter 33: Hepatic Failure

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Fulminant Hepatic Failure

Fulminant hepatic failure (FHF) is defined as liver failure complicated by encephalopathy occurring within 8 weeks of the onset of illness. Histologically, the liver shows massive necrosis of hepatocytes, often with preservation of the reticular framework. In broad terms, the clinical features of FHF are presumed to result from acute failure of the normal functions of the liver: synthesis, storage and detoxification.

Aetiology

1. Viral Hepatitis

Acute viral hepatitis accounts for approximately 70% of patients with FHF.

(a) *Acute hepatitis A (HAV)* is diagnosed by the presence of IgM antibody to hepatitis A virus. It accounts for 2-30% of patients with FHF.

(b) *Acute hepatitis B (HBV)* is diagnosed by the presence of the IgM antibody (HBcAb) to hepatitis B core antigen, with or without hepatitis B surface antigen (HBsAg). Up to 50% of patients with negative HBsAg are IgM anti-core antigen positive. It is the major cause of FHF and accounts for 25-75% of cases. Co-infection with hepatitis D (delta) virus, increases the risk of FHF in patients with acute HBV.

(c) *Acute non-A, non-B hepatitis* is diagnosed by the absence of serological evidence of recent infection with HAV, HBV, and other viruses, no history of exposure to drugs and toxins, and the absence of autoantibodies. There are three types of non-A, non-B hepatitis viruses; epidemic or enterally transmitted (A-type), post transfusion (B-type) and sporadic. Sporadic non-A, non-B hepatitis infection accounts for 23-44% patients with FHF. Characteristically, there is a long interval between the onset of jaundice and development of encephalopathy (more than 3 weeks) and a very high mortality (90%).

(d) *Other viruses*, such as herpes simplex 1 and 2, varicella zoster virus, cytomegalovirus (CMV) and Epstein Barr (EB) virus can produce severe liver cell necrosis.

2. Acute Drug-Induced Hepatitis

Drug-induced hepatitis is responsible for approximately 15% of cases of FHF. Many drugs have been implicated. However, isoniazid, sodium valproate, anti-depressants, nonsteroidal antiinflammatory drugs, and halothane have been reported most frequently. The risk of developing FHF in patients with drug-induced hepatitis and jaundice is 20%, whereas the risk is less than 1% with viral hepatitis and jaundice.

3. Acute Hepatitis due to Poisoning

(a) *Paracetamol overdose*. Since the mechanism of paracetamol hepatotoxicity is known, treatment of paracetamol overdose with N-acetylcysteine has decreased the incidence of subsequent FHF. In Britain, paracetamol poisoning is second only to viral hepatitis as a cause of FHF. However, in other countries, as few as 2% of FHF are due to paracetamol poisoning. FHF is also a complication of acute yellow phosphorus poisoning.

(b) *Amanita mushrooms*, particularly *amanita phalloides*, are toxic through heat stable amanatoxins, which cause hepatic necrosis. The lethal dose is 50 g.

(c) *Industrial solvents*. Carbon tetrachloride ingestion, chloroform inhalation and xylene (in glue sniffers) are very rare causes of FHF.

4. Miscellaneous

Miscellaneous causes account for approximately 10% of FHF. They include Wilson's disease, microvesicular steatosis (Reye's syndrome, acute fatty liver of pregnancy), ischaemic liver cell necrosis, hepatic venous obstruction, malignant infiltration of the liver, auto-immune chronic active hepatitis, reactivation of chronic hepatitis B, hyperthermia, complication of liver transplantation and partial hepatectomy.

Clinical Features

There may be a history suggestive of a cause. However, in many cases such a history may not be available. The disease typically evolves over several days, but deep coma can occur in hours or may develop over months in subacute or "late onset hepatic failure". Most patients become deeply jaundiced. A sickly sweetish breath (hepatic foetor) is characteristic of FHF. This is probably due to a mixture of volatile compounds, methethiol, dimethyl sulphide and dimethyl disulphide (mercaptans) which are excreted in breath. The liver is usually small and impalpable. Abdominal pain may occur.

Signs of chronic liver disease, such as palmar erythema, spider naevi, ascites, splenomegaly and hypoalbuminaemia, are not usually present on admission. Acute portal hypertension commonly develops after 3 weeks and may result in bleeding from oesophageal varices.

1. Encephalopathy

By definition, encephalopathy is always present in FHF. It is classified, by severity, into 4 grades (Table 1). One of the earliest signs of encephalopathy in FHF is a generalized increase in muscle tone, which may progress to full decerebrate posturing with trismus and opisthotonus. Cerebral oedema is present in over 80% of patients with grade IV encephalopathy, and is the major cause of death. It is heralded by spontaneous hyperventilation, followed by dysconjugate eye movements and dilatation of the pupils which react only sluggishly to light. Papilloedema is unusual. Unless treatment is successful at this stage, respiratory arrest and brain stem coning ensue.

Table 1. *Stages of Encephalopathy*

O	Normal awareness
I	Mood change and confusion
II	Drowsiness, inappropriate behaviour
III	Stuporose but rousable
IV	Unrousable to minimal stimuli or no response to noxious stimuli

The cause of encephalopathy in FHF is unknown. It is generally attributed to accumulation of toxic substances in the circulation which damage the blood brain barrier (BBB), inhibit Na-K ATPase (the sodium pump) and impair neuronal function. Substances arising from the gut, such as ammonia, mercaptans, fatty acids and phenols can act alone or synergistically to produce coma. They have been shown experimentally to both increase BBB permeability and to inhibit Na-K ATPase.

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in normal brain and may be important in hepatic encephalopathy. Most circulating GABA arises from the gut flora. In health, GABA is cleared from the portal circulation by the liver. Hepatic extraction is reduced in liver failure, and high circulating concentrations have been observed in animal models of acute hepatic encephalopathy. GABA normally penetrates BBB slowly, but in the presence of circulating toxins which increase BBB permeability, its neuroinhibitory effects might be facilitated. Other neurotransmitters such as octopamine, serotonin, histamine, phenylethanolamine and catecholamines are also implicated. Amino acids, such as glutamine (which, with alpha-ketoglutarate, interacts with ammonia in the brain), methionine (which is metabolized to mercaptans), and tryptophan all have neurotoxic potential.

The relative contributions of vasogenic oedema (in increasing BBB permeability) and cytotoxic oedema (in Na-Ka ATPase inhibition) to acute hepatic encephalopathy are even less clear. Clinically, mannitol infusion can decrease intracranial pressure (ICP) in hepatic encephalopathy, suggesting that the BBB remains intact (at least) in some regions. An increase in cerebral blood flow of up to 3 times normal has been observed in Grade IV encephalopathy, contributing to raised ICP. Hypoglycaemia, electrolyte and acid-base disturbances, renal failure, sepsis and hypoxia may also contribute to cerebral dysfunction.

2. Bleeding Diathesis

Signs of bleeding may be present on admission or develop subsequently. Bleeding from the gastrointestinal tract (GIT), nasopharynx, respiratory tract or into the retroperitoneal space may occur. Intracerebral haemorrhage is unusual.

The prothrombine time (PT) is always prolonged and is used as a prognostic index and to chart the course of the disease. Liver synthesis of fibrinogen and factors V, VII, IX, X is impaired. The production of factors VIII, XI and XII may also be impaired.

Alterations in platelet count, morphology and function have all been described in FHF. About 2/3 patients have platelet counts less than $100,000 \times 10^6$ cells/L. The platelet count tends to decrease progressively during the course of FHF, and is lower in patients who die.

There is increased platelet adhesion but decreased platelet aggregation. Low grade disseminated intravascular coagulation (DIC) may occur.

3. Respiratory Failure

The airway may be compromised because of the decreased level of consciousness. Hyperventilation leading to respiratory alkalosis is probably mediated by the central nervous system. Lactic acidosis may also be responsible for hyperventilation late in the course of FHF. Apart from centrally mediated abnormalities of respiratory control, hypoxia is commonly seen and is the indication for ventilation in approximately 1/3 of patients. This may represent intrapulmonary shunting and histological studies have confirmed diffuse dilatation of the pulmonary vascular bed, with pleural spider naevi in some cases. Complications of coma, such as bronchopneumonia, aspiration or atelectasis also contribute.

Around 30% patients have non cardiogenic pulmonary oedema confirmed by chest X-ray and lung water measurements. Pulmonary oedema is more common with extreme prolongation of the PT and therefore tends to occur in the sickest patients. No mechanism has been proven, but it is suggested that it may be either neurogenic, or the result of a common factor producing both cerebral and pulmonary oedema. This factor might possibly be an endogenous inhibitor of Na-K ATPase.

4. Cardiovascular Disturbances

In FHF there is a severe circulatory disturbance characterized by a low systemic vascular resistance with a compensatory increase in cardiac output. Hypotension is common, even in the absence of hemorrhage and sepsis, and carries a poor prognosis. It has been suggested that, as in sepsis, there is maldistribution of blood flow in the microcirculation leading to covert tissue hypoxia. No mediator has been identified that can account for these circulatory changes.

5. Renal Failure

Renal insufficiency occurs in approximately 50% of patients with FHF, and usually indicates a poor prognosis. Renal failure may be due to acute tubular necrosis or more commonly, to *hepatic nephropathy*, also known as the *hepatorenal syndrome* or *functional renal failure*. In this condition there is a decline in the glomerular filtration rate but tubular function is preserved. The biochemical features are similar to prerenal renal failure with urinary sodium concentration < 10 mmol/L, urine osmolality > 1000 mOsm/kg and a urine to plasma creatinine ratio of > 10 . However, renal failure cannot be reversed by volume replacement. There are no morphological changes in the kidney to explain these observations, and such kidneys resume normal function when transplanted to recipients without liver disease. It is believed that hepatic nephropathy is due to intense renal vasoconstriction, but the exact mechanisms remain unknown.

6. Metabolic Disturbances

Fever develops in most patients with fulminant hepatitis. Hypothermia may develop in the late stages, and may indicate hypoglycaemia or progression of cerebral oedema with

poor prognostic significance. Severe hypoglycaemia occurs in 25% of patients. Hypokalaemia is common early in disease. Hyponatraemia, oedema and ascites reflect sodium and water overload.

Respiratory alkalosis is common. Metabolic alkalosis may also occur, probably as a result of hypokalaemia and defective urea synthesis. In the later stages, over 50% of patients have high mixed venous lactate concentration associated with metabolic acidosis. Mortality is high in this group. Lactic acidosis is most likely related to underlying tissue hypoxia combined with a failure of lactate clearance by the liver.

7. Infective Complications

In 20-36% of patients, the course is further complicated by bacterial and sometimes fungal infections, especially septicaemia, pneumonia, urinary tract infections and infected ascites. This high incidence is probably related to low serum complement concentrations, impaired neutrophil function, and decreased humoral opsonizing activity in FHF.

8. Impaired Drug Metabolism

Patients with FHF are unduly sensitive to the depressant effects of sedative and analgesic drugs. This is chiefly due to impaired drug breakdown, but increased cerebral sensitivity and changes in plasma protein binding contribute.

9. Pancreatitis

Acute haemorrhagic pancreatitis is found at postmortem in 10% of patients dying from FHF. The aetiology is unknown.

10. Rare Complications

Rare complications of viral hepatitis include myocarditis, atypical pneumonia, aplastic anaemia, transverse myelitis and peripheral neuropathy.

Monitoring and Investigations

1. *Vital Observations* - Temperature, heart rate and rhythm and arterial blood pressure should be monitored continuously, and central venous pressure and urine output measured hourly.

2. *Pulmonary Artery Catheter* - Indications for insertion of a Swan-Ganz catheter are controversial. Optimization of oxygen delivery may benefit outcome, but coagulopathy and susceptibility to infection increase the risk of complications. It is prudent to reserve its use for situations where haemodynamic data are likely to lead to major management changes.

3. *Intracranial Pressure (ICP) Monitoring* - should allow early recognition and treatment of intracranial hypertension. However, experienced clinicians have been shown to be capable of detecting episodes of raised intracranial pressure and ICP monitoring is associated with an increased risk of intracerebral haemorrhage. At present, ICP monitoring

should be reserved for the evaluation of new treatments or when cerebral oedema is likely to be prolonged as in Reye's syndrome.

4. *Laboratory Investigations* - should indicate serological investigations for hepatitis (hepatitis A and B, CMV, EB virus and herpes simplex) and a drug screen, specifically for paracetamol, to determine the cause of FHF. Plasma caeruloplasmin concentration and 24 hour urinary copper excretion exclude Wilson's disease.

5. *Coagulation Studies* - are a sensitive index of liver function and should be performed daily.

6. *Liver Functions Tests* - should also be performed daily. Both conjugated and unconjugated fractions are usually elevated. Bilirubin concentrations greater than 300 micromol/L and persistent are likely to be associated with severe disease. Plasma aminotransferase concentrations (alanine transferase (ALT) and aspartate aminotransferase (AST)) show variable increases in FHF, and peak levels vary from 400-4000 IU/L. Plasma concentrations of these enzymes do not correlate well with the degree of liver cell damage, and relatively normal levels in association with deep jaundice and a small liver, usually signify massive liver cell necrosis. Plasma alkaline phosphatase concentration (ALP) is rarely elevated above 3 times normal in the acute phase, but shows variable increases during recovery where there may be a cholestatic picture. Plasma alpha foetoprotein, pre-albumin and factor V concentrations have been used as prognostic indicators. Plasma albumin and globulin concentrations are usually normal on presentation.

7. *Other Investigations* - Blood glucose levels should be measured 4 hourly. Plasma electrolytes, urea, creatinine and albumine should be measured at least daily. Arterial blood gases should be measured daily or more frequently if indicated.

Specimens of sputum and urine should be cultured regularly, and blood taken for culture if there are signs of sepsis.

Chest X-rays and 12 lead ECG should be performed daily.

An electroencephalogram (EEG) may be helpful in the assessment of encephalopathy.

Liver biopsy may rarely be necessary to exclude underlying cirrhosis or malignancy. If indicated, the transjugular route is preferred, because of a decreased risk of haemorrhagic complications.

Managament

The mainstay of treatment in FHF is support, with accurate fluid balance, maintenance of the circulation and ventilation, control of bleeding, correction of hypoglycaemia and treatment of complications in anticipation of liver regeneration. As cerebral oedema is the major cause of death, treatment should be focused on preventing or minimizing this complication. Other major complications such as renal failure, haemorrhage and sepsis further compromise cerebral status. Where FHF is possibly due to drug administration, all medication should be ceased.

1. Management of Cerebral Oedema

Patients should be nursed with the head elevated to 30 degrees; with venous return from the head unimpeded by malpositioning or tapes.

The decision to intubate and ventilate is often difficult. The airway is often well maintained due to increased muscle tone associated with hepatic encephalopathy. A degree of spontaneous hyperventilation is common. Patients in stage III coma who appear unresponsive may become extremely irritable when an endotracheal tube is inserted. Sedative drugs should be avoided if possible, because of their unpredictably and prolonged effects, and neurological assessment is important to follow the course of the disease. Nevertheless, mechanical ventilation should be instituted when airway compromise, hypoxia, hypercarbia, or intracranial hypertension are present. Cerebral blood flow is increased in hepatic encephalopathy, and moderate hyperventilation can decrease intracranial pressure in the *short term* (although ineffective long term). Mechanical ventilation, however, decreases liver blood flow (see below), as does respiratory alkalosis.

The mainstay of treatment of cerebral oedema in FHF is mannitol. Infusion of 20% mannitol (1 g/kg) reversed clinical signs of cerebral oedema, reduced ICP by a mean of 22 mm Hg (2.9 kPa) and increased survival. In patients with renal failure, mannitol should only be used in conjunction with haemodialysis or haemofiltration, since fluid overload may exacerbate cerebral oedema.

Frusemide may be useful in FHF to maintain the initial osmotic gradient established by mannitol and normovolaemia during infusions of albumin and clotting factors, and to inhibit CSF secretion by the choroid plexus.

Perfect control of fluid balance is necessary. Hypervolaemia increases the risk of cerebral oedema, and hypovolaemia may result in hypotension, decreasing cerebral perfusion pressure. Hypertension is almost always secondary to increased ICP. If hypertension occurs, measures to decrease ICP (hyperventilation and mannitol infusion) should be instituted. Antihypertensive drugs may precipitate brainstem coning.

There is no evidence that lactulose administration will delay or prevent the development of grade III or IV encephalopathy. Nevertheless, it is widely used in a dose of 30 mL tds via nasogastric tube, to reduce ammonia production and to reduce the volume of colonic contents. Use of neomycin is not recommended because of its nephrotoxicity and ototoxicity.

Corticosteroids do not influence the incidence and severity of cerebral oedema. Barbiturates are not recommended because of cardiovascular depression.

Clinical and EEG improvement with a benzodiazepine antagonist (which acts as the GABA receptor) has been noted in a case report. However, therapeutic benefits are not proven.

2. Maintenance of Circulation

Relative hypovolaemia is common in FHF and has been observed in 76% of ICU admissions. It is likely due to inappropriate vasodilation and generalized capillary leak. If there is coexisting hypotension or oliguria, volume deficits should be corrected with blood or components depending on haematological parameters. Hypervolaemia must be avoided. A pulmonary artery catheter may be necessary to optimize fluid replacement.

Although inotrope infusion is indicated if hypotension persists despite normovolaemia, there is no evidence that any inotrope improves tissue perfusion or overall survival, and the requirement for vasopressor support is associated with increased mortality. However, rapid elevation of blood pressure with a noradrenaline infusion may be transiently lifesaving when a hypotensive patient develops signs of imminent brainstem coning.

3. Coagulopathy and Bleeding

Severe bleeding occurs in approximately 1/3 of patients. Prophylactic use of H₂-antagonists is recommended which may decrease the incidence and severity of GIT bleeding. Blood losses should be replaced by blood transfusion. Administration of fresh frozen plasma (FFP) is indicated to replace coagulation factors in the presence of bleeding, but its prophylactic use without bleeding does not influence morbidity or mortality. Vitamin K should be administered daily. Administration of Factor IX concentrates (eg, prothrombines) is contraindicated, as massive intravascular coagulation may result.

Platelet transfusions are indicated if the platelet count falls below 50.000 x 10⁶ cells/L. Administration of FFP and platelets is indicated before surgical procedures and catheterisation of central veins.

4. Renal Management

The development of renal failure in FHF has mortality rates approaching 100%. Prevention of renal failure is therefore of prime importance. Hypotension and hypovolaemia should be treated promptly and potentially nephrotoxic drugs avoided. Low dose dopamine has not been shown to prevent acute renal failure. Despite the high mortality, recovery from FHF and renal failure may occur, particularly when both are due to paracetamol poisoning. Haemodialysis or continuous haemofiltration may be indicated if renal failure is due to nephrotoxic agents or ATN, but do not improve survival in the hepatorenal syndrome.

5. Nutrition

Most patients with FHF have normal nutritional status before their acute illness. Fluid restriction (for cerebral oedema) together with the requirement for blood components preclude giving large volumes of nutrient solutions. Consequently, nutritional support is neither necessary nor practical early in illness. Glucose 10% infusions to prevent hypoglycemia serve as a source of energy. If illness is prolonged, balanced feeding solutions, preferably enteral, should be administered. Branched chain amino acid (BCAA) solutions have not been demonstrated to improve encephalopathy or overall mortality. Hypoglycaemia is treated with

5 or 10% dextrose. However, if profound, 50% dextrose allows smaller volumes to be infused and has less effect on plasma sodium concentration.

6. Measures to Improve Liver Function

There are no drugs which reverse the effects of hepatic failure. Corticosteroid drugs have no place in treatment of FHF and their use has been associated with increased mortality. Beneficial effects of prostacyclin and fibronectin have not been demonstrated.

Maintenance of liver blood flow may theoretically prevent further damage and allow rapid recovery of hepatocytes, although effects are unproven. Hepatic blood flow is adversely affected by ventilation (flow is reduced by approximately 50%) and PEEP. Low dose dopamine increases splanchnic blood flow, although a benefit in FHF has not been investigated. Oxygen content should be maintained with an adequate Hb concentration and oxygen saturation.

7. Artificial Liver Support

Exchange transfusion, plasma exchange, human cross circulation, porcine liver cross perfusion, haemofiltration through large pore membranes and haemoperfusion have not improved survival.

8. Liver Transplantation

Recent results of liver transplantation in FHF have been encouraging, with survival rates of 60%. As survival with medical therapy alone is approximately 20%, liver transplantation is increasingly indicated in FHF. (See Chapter 34, Liver Transplantation.)

Prognosis

The strongest determinant of survival in FHF is the grade of coma. Survival is approximately 70%, 40% and 20% with grade II, III and IV encephalopathy respectively. If convulsions occur, survival is only 5%. Age also influences survival, and young patients have a better prognosis. When the time between onset of symptoms and encephalopathy is short, prognosis appears to be improved. With viral hepatitis, survival rates are poorest in non-A, non-B FHF, intermediate in hepatitis B, and best in hepatitis-A disease. The presence of alpha-foetoprotein in plasma suggests an improved prognosis, particularly in hepatitis B disease. Sex of the patient and duration of jaundice or coma have not been shown to be consistent prognostic indicators.

Extreme prolongation of the PT carries a bad prognosis, but plasma concentration of transaminases and ammonia do not discriminate survivors from nonsurvivors. The occurrence of complications, particularly renal failure, hypotension and haemorrhage adversely affects survival.

Precautions Against Hepatitis

All ICU staff should be vaccinated against HBV. AIDS cannot be spread by HBV vaccination. The majority of vaccinated individuals have circulating antibody for about 4 years, although protection is likely to be lifelong. There is no vaccine against either HAV or non-A, non-B hepatitis. All patients with FHF should be initially regarded as infectious. They should be barrier-nursed unless an alternative non-infectious diagnosis is proven. Vaccination should not lead to complacency. Disposable gloves and gowns should be worn and incinerated after use. Hands should be washed regularly and any spilt blood removed immediately. The bed area and related equipment are disinfected with glutaraldehyde, formaldehyde or hypochlorite. These have been shown to inactivate HBV, but their effect on non-A, non-B agents have yet to be conclusively demonstrated. Blood, urine, faeces and other biological samples should be handled carefully and labelled prominently. All precautions should be taken to avoid puncture by contaminated needles or other sharp instruments.

The procedure for needlestick or permucosal exposure to blood or high-risk body fluids depends on whether the exposed individual has antibodies (HBs-Ab) HBV surface antigen (HBs-Ag). These may be acquired by vaccination or by previous subclinical infection. If HBs-Ab is present no further action is necessary. If HBs-Ab status is unknown, hepatitis B immune globulin (HBIG) (0.06 mL/kg) should be administered as early as possible within 7 days and the person tested for HBs-Ab. If HBs-Ab is negative, vaccination should also be started immediately, and the first dose of HBV vaccine (20 microg IM at a different site) should be given within 7 days of exposure and repeated 1 and 6 months later. Passively acquired HBs-Ab does not interfere with the immune response to the vaccine.

For HAV, immune globulin markedly reduced attack rate both pre- and post-exposure. A single IM dose of 0.02 mL/kg is advised within 2 weeks of exposure.

Hepatic Failure in Chronic Liver Disease

Chronic liver cell failure is usually the result of cirrhosis (alcoholic, chronic active hepatitis, postnecrotic, primary biliary, sclerosing cholangitis, metabolic disease) or infiltrative processes (neoplasia or metabolic). It is characterized by jaundice, ascites and encephalopathy, which may be present singly or in combination. Spider angiomas and palmar erythema are usually present. Acute episodes of decompensation may be caused by additional insults, such as GIT bleeding, sepsis or large alcohol intake. It is therefore important to recognize and treat these precipitants if possible. Unlike FHF, patients with chronic liver disease have minimal potential for hepatic regeneration. ICU admission of these patients is dependent on a reversible component or consideration for liver transplantation. If these patients deteriorate sufficiently to need respiratory support, survival is unusual. In chronic liver failure, coagulopathy, cardiovascular and renal dysfunction are similar to those in FHF discussed above.

Encephalopathy

In chronic liver disease, the presumed mechanism of encephalopathy are similar to those described in FHF. However, the clinical picture typically develops more slowly and cerebral oedema is rare. Portal hypertension and the development of portal-systemic collaterals

(shunts) are usual. Hence the failing liver cells are unable to metabolize circulating toxins from the GIT which gain access to the systemic circulation. Thus encephalopathy in chronic liver disease is often called portal-systemic encephalopathy (PSE). Surgical manoeuvres (eg, portacaval shunt) which decompress the portal venous system may precipitate PSE in this way.

The most usual precipitating factor is nitrogenous overload, particularly due to GIT haemorrhage. This results in excess ammonia and mercaptan production from blood protein breakdown in the gut, and is commonly associated with shock, which augments the predisposition to PSE. In addition, ammonia is present in transfused blood. Increased dietary protein, uraemia, constipation and hypokalaemia (by increasing renal veni ammonia output) also increase ammonia production. Sedative or analgesic drugs, fluid and electrolyte abnormalities, sepsis and surgery can also precipitate PSE.

The early stages of encephalopathy comprise personality changes with irritability, intellectual deterioration, slurred speech, reversal of sleep rhythm, confusion, drowsiness and later coma. There is characteristically a flapping tremor of the outstretched hand (asterixis). This disappears when coma supervenes. In coma, there is initially increased muscle tone with hyperreflexia, but later tendon reflexes are lost and the patient becomes flaccid.

Treatment of encephalopathy in chronic liver disease involves aggressive treatment of precipitating factors and full supportive care. Dietary protein should be ceased initially and calories provided as glucose (300-500 g/day). Lactulose should be given orally (30 mL tds) or by retention enema. Although the data are conflicting, it is unlikely that branched chain amino acids are useful.

Ascites

Ascites is a common complication and is almost invariably present in patients with bleeding varices or advanced encephalopathy. Portal hypertension, hypoalbuminaemia, excessive hepatic lymph formation and abnormalities of sodium and water balance all contribute to its pathogenesis.

Diagnostic paracentesis should be performed to exclude bacterial peritonitis (SBP), which occurs in 4-15% of cirrhotic patients with ascites. Treatment with parenteral broad spectrum antibiotics should be commenced if the ascitic fluid neutrophil count is $> 250 \times 10^6$ cells/L, organisms are seen on Gram stain or subsequently cultured. Mortality from SBP approaches 70%.

Treatment of ascites includes salt restriction (40 mmol/day), fluid restriction (1500 mL/day) and diuretic therapy. However, these measures are not advised in cardiovascular instability. Up to 50% of cirrhotic patients develop complications with diuretic therapy. These include hypovolaemia, electrolyte disturbances, encephalopathy and renal failure. There is no evidence that paracentesis is an excellent adjunct to diuretic therapy and shortens hospital stay. However, if volume is not replaced similar complications may occur.

Oesophageal Varices

Portal hypertension, oesophageal varices and the treatment of variceal bleeding are discussed elsewhere. Variceal haemorrhage is the major cause of acute decompensation in chronic liver disease.

Liver Dysfunction in the ICU

Critically ill patients admitted to the ICU with primarily non-hepatic disease frequently develop liver dysfunction. There may be:

(a) direct hepatocellular damage (hepatitis-like pattern) with a marked rise in plasma ALT and AST, a prolonged PT, and variable elevations of both conjugated and unconjugated bilirubin, with only mild elevations of ALP; or

(b) intrahepatic cholestasis, where there is elevation of ALP and conjugated bilirubin, with relatively normal plasma ALT and AST.

Multiple aetiological factors may be present, and hepatocellular damage and intrahepatic cholestasis may coexist. It is likely that a decreased hepatic perfusion plays a role in many cases, as both hepatocytes and Kupffer cells are extremely sensitive to hypoxia. In patients with unexplained jaundice associated with a cholestatic picture, ultrasonography of the liver should be performed to exclude extrahepatic bile duct obstruction.

1. Circulatory Failure

Hepatic changes are common in shock due to acute heart failure, trauma, burns, haemorrhage or sepsis. Changes are due to cellular hypoxia and can be related to the duration of shock; if longer than 24 hours a degree of hepatic necrosis is almost always present, but unusual if less than 10 hours. Plasma ALT and AST rise rapidly to 8-10 times normal. This is known as ischaemic hepatitis. These may improve within 24 hours if shock is reversed. There may be mild jaundice and the PT frequently rises. In congestive heart failure, the increased pressure in the right atrium is transmitted to the hepatic veins. Mild jaundice is common and the elevation in plasma bilirubin is proportional to the degree of cardiac failure. The low cardiac output is probably a contributing factor. Plasma ALT, AST and ALP concentrations are mildly elevated. There is tender hepatomegaly which may be associated with ascites and splenomegaly. The prognosis is that of the underlying heart disease.

2. Sepsis and Multiple Organ Failure

Hepatic dysfunction develops in a variable proportion of patients with sepsis and is associated with increased mortality. Jaundice develops 2-3 days after the onset of infection and is associated with hepatomegaly in 50% of patients. Plasma bilirubin is usually 100-200 micromol/L and ALP 2-3 times normal. Plasma ALT and AST are normal in 70% of patients. Occasionally, increased plasma bilirubin may be an isolated finding. Liver histology shows intrahepatic cholestasis with little hepatic necrosis, unless there is coexisting hypoperfusion.

Circulating endotoxin can produce cholestasis experimentally, but as hepatic dysfunction is similar in sepsis and in trauma, inflammatory mediators probably contribute. It is likely that metabolic dysfunction of hepatocytes mediates the characteristic changes of hypermetabolism and hypercatabolism observed in sepsis and multiple organ failure. Management is aggressive treatment of the precipitating infection. (See Chapter 63, Severe Sepsis.)

3. Drugs

Jaundice and liver dysfunction has been associated with many drugs (Table 2). Drugs may impair metabolism of bilirubin or may be hepatotoxic (directly or due to metabolites).

Hypersensitivity reactions may also cause hepatocellular dysfunction, and occasionally, massive liver cell necrosis. In such cases there may be other allergic manifestations such as fever, arthralgia, urticaria and eosinophilia. Drugs may cause hepatocellular necrosis or intrahepatic cholestasis (Table 2).

Table 2. *Adverse Hepatic Drug Reactions*

Type	Examples	Comments
Central (Zone III) Necrosis	Carbon tetrachloride Paracetamol Halothane	Dose dependent, multi-organ failure
Hepatitis-like	Alpha methyl dopa Nitrofurantoin Isoniazid, Halothane	Chronic active hepatitis Massive hepatic necrosis in severe cases
Cholestatic hepatitis	Chlorpromazine Tolbutamide, Chlorpropamide Erythromycin	
Cholestasis without hepatitis	Anabolic steroids	Often some increase AST
Fibrosis	Methotrexate Hypervitaminosis A	Portal hypertension, cirrhosis
Vascular abnormalities	Anabolic androgens Oral contraceptives	Sinusoid dilation, veno-occlusive
Granulomatous reactions	Hydrallazine Allopurinol	Often some cholestasis, lobular hepatitis
Neoplasms	Sex hormones	Some benign.

4. Total Parenteral Nutrition (TPN)

Elevation of plasma AST, ALP and bilirubin concentration may occur with TPN, particularly if excessive calorie intake is prolonged (eg, over 17200 kJ (4.000 kcal)/day for over 6 weeks). Histologically, there is fatty infiltration of the liver, associated with cholestasis and periportal inflammation. When energy intake is high, it is likely that fatty acid synthesis outstrips the ability of the liver to secrete lipid. Essential fatty acid deficiency is a rare cause of hepatomegaly with fatty infiltration.

5. Hepatitis

Exposure to viral or non-A, non-B hepatitis may have occurred. The clinical picture and management are as discussed above.

6. Benign Postoperative Intrahepatic Cholestasis

In this condition, jaundice typically appears on the first postoperative day, and both conjugated and unconjugated fractions are increased. Plasma ALT, AST and ALP concentrations are normal or only slightly elevated. Liver histology shows intrahepatic cholestasis, with dilated bile canaliculi and casts, with minimal liver cell damage. In most circumstances, there is an increased bilirubin load (from blood transfusion or resolving hematomas), and liver dysfunction may be due to a reduced ability to transport conjugated bilirubin. Although described as benign, mortality is 50%.