ANAESTHESIA AND LIVER DISEASE

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Liver disease can vary in severity from sub-clinical to end-stage liver disease (ESLD), with life threatening, multi-organ multi-system failure. Anaesthetic and operative risks are related to the severity of liver dysfunction, so thorough pre-operative assessment is essential for safe peri-operative care. A good understanding of the pathophysiology of liver dysfunction is vital for assessment of operative risk.

PATHOPHYSIOLOGY OF ESLD

While the severity of liver dysfunction may vary widely, a limited review of the pathophysiology of severe disease is appropriate. The range of symptoms depends largely upon whether the disease presentation is acute or chronic. If chronic, features may be super-imposed on a background of poor nutrition and chronic ill health. The acute presentations have been subject to re-classification in recent times in order to take into account differing survival rates with medical treatment alone. The first formal definition was proposed by Trey and Davidson who defined fulminant liver failure (FHF) as the appearance of encephalopathy within eight weeks of onset of jaundice. The King's College group now recognises three levels of acute presentation within FHF (Table 1). Contrary to expectation, survival rates are better in the acute and hyper-acute groups on medical management alone. Gimson has written a useful review of fulminant hepatic failure.

Impaired liver function

Impaired liver function gives rise to effects directly attributable to the failing liver itself and also to indirect effects expressed via other organ systems. Effects directly attributable include hypoglycaemia, lactic acidosis, hypermetabolism, azotemia and impaired urea synthesis. Jaundice appears when serum bilirubin exceeds 35 µmol/l and defects in cholesterol metabolism together with intra-hepatic cholestasis may lead to production of poor quality bile and malabsorbtion of fat and fat-soluble vitamins. There is reduced synthesis of proteins such as albumin, clotting factors, thyroid binding globulin and pseudo-cholinesterase. Impaired hormone biotransformation, reduced production of modulator proteins and reduced protein binding lead to increased circulating levels of hormones such as insulin, thyroxine, T_3, aldosterone and oestrogen.

Impaired hormone modulation, failure to clear by-products of metabolism, activation of cytokines and release of vasoactive substances from the damaged liver result in patho-physiological changes in many organ systems. These indirect effects include:

Cardiovascular changes

Vasodilatation and vascular shunting are almost invariable in ESLD. Low systemic vascular resistance (SVR) results in high cardiac output and high mixed venous oxygen saturations. Pulmonary hypertension may develop, while portal venous hypertension can lead to varices, variceal bleeding and porto-systemic shunting. Low flow in the portal vein can result in portal venous thrombosis. Variceal bleeding may be life threatening.

Pulmonary changes

Pulmonary problems are both vascular and mechanical. Intra-pulmonary shunt dilatation (hepato-pulmonary syndrome), impaired hypoxic vaso-constriction and ventilation perfusion mismatch lead to arterial desaturation and clubbing if chronic. Pleural effusions together with ascites can cause considerable mechanical embarrassment of respiration and a reduction in functional residual lung capacity.

Electrolytes and Renal

There are numerous causes of renal impairment in liver failure, including hepato-renal syndrome, sepsis and renin-angiotensin activation. Hyponatraemia due to water retention and inhibition of membrane bound Na/K ATPase, hypoalbuminaemia and oedema are common. Saline should be avoided but hypomagnesaemia and hypo-phosphataemia should be corrected.

Neurological problems

Mechanisms leading to deepening encephalopathy, loss of vascular auto-regulation, cerebral oedema and death are incompletely understood. A number of processes may act in parallel, but can be summarised as the accumulation of neurotoxic compounds penetrating an impaired blood-brain barrier. At the same time, lack of nutrients and substrates may impair brain metabolism and alter neuro-transmitter synthesis. Of particular interest are a group of endogenous benzodiazepine-like

Table 1: Liver Failure: mode of presentation and survival

Presentation		Encephalopathy	Jaundice (Days)	Survival Rate (medical management only)
Chronic		No	+/-	-
FHF	Sub-acute	Yes	29-72	14%
	Acute	Yes	8-28	26%
	Hyper-acute	Yes	<7	36%

substances that are thought to act at a site closely linked to the g-amino butyric acid (GABA) receptor. Drowsiness can be transiently reversed by flumazenil, but not in all cases. Symptoms can occur in chronic as well as in acute disease, may be rapid in onset and may be precipitated by a gastrointestinal bleed, dietary protein overload or sepsis. Somnolence can be exacerbated by sedative drugs and narcotics.

Rapid correction of hyponatraemia can lead to osmotic demyelination and central pontine myelinolysis and should be avoided.

Haematological

Anaemia may be the result of nutritional deficiency, toxic bone marrow depression or gastrointestinal bleeding from varices or erosions. Coagulation defects arise from thrombocytopenia, platelet dysfunction and decreased levels of circulating clotting factors. Clotting factor levels fall because of impaired synthesis, vitamin K malabsorbtion and intravascular consumption. The short half-life of clotting factors means that INR or Prothrombin Ratio (PTR) can reliably be used to evaluate residual hepatic function.

Susceptibility to infection

There may be a wide variety of defects in host defences that can contribute to a substantial risk of sepsis, with up to 80% of patients with FHF developing bacterial sepsis (frequently Gram positive organisms) and 30% fungal sepsis. Clearly, particular attention must be paid to aseptic technique when inserting lines.

Drug disposition

There may be considerable derangement of drug handling in the patient with liver dysfunction. Aetiology may influence pharmacokinetics and the nature and extent of hepatocellular damage may alter drug metabolism. Cholestasis will reduce absorbtion of fat-soluble drugs after oral administration, while other drugs with limited systemic availability due to high hepatic extraction, may achieve high peak plasma concentrations if there is porto-systemic shunting. Compartment changes and altered protein binding will affect volume of distribution, clearance and re-distribution. Patients with liver dysfunction may be particularly sensitive to opiates and benzodiazepines due to altered end-organ sensitivity (see 'Neurological problems' above).

Causes of Liver Failure

The commonest causes of acute and chronic liver failure (ALF) are listed in Table 2. In the UK, paracetamol poisoning was until two years ago the most frequent cause of FHF. When a change in regulations reduced over-the-counter pack size of paracetamol to a maximum of 8 tablets, the incidence of paracetamol poisoning fell dramatically. Worldwide, by far the major cause of liver disease is viral infection, with Hepatitis B (HBV) and C (HCV) together accounting for 75% of all cases. The natural history of chronic infection with both HBV and HCV includes progression to cirrhosis and an increased risk of developing hepatocellular carcinoma (HCC).

Infection with HCV deserves special mention. The nature of HCV replication is such that during the course of a single infection, HCV frequently changes its antigenic signature. As a result of this and of other mechanisms, the virus is able to confuse host immune responses, with the result that 85% of HCV infections become chronic, as opposed to about 5% in the case of HBV. Chronic HCV infection is insidious and it may take up to 15 years for overt signs of liver failure to develop. Not only can apparently stable, asymptomatic patients decompensate acutely as a result of anaesthesia, but they can also represent a significant infection risk for the anaesthetist.

Risk and severity scoring

In 1964, Child and Turcotte classified risk for patients with liver cirrhosis undergoing porto-caval anastomosis for management of portal hypertension. Pugh et al at King's College Hospital published a severity scoring system for patients undergoing oesophageal transection for bleeding oesophageal varices. The two systems have been amalgamated and provide a disease severity assessment based on two clinical and three laboratory variables (Table 3).

Surgery in patients with liver dysfunction

The Child-Pugh classification is a useful method of staging the progress of liver decompensation. However, despite its surgical

Table 2: Causes of Liver Failure (UK)

CHRONIC		ACUTE	
Infection	*Viral*	Infection	*Viral A-E, Non A-E*
Biliary obstruction	*1°: PBC*	Drugs	*e.g. paracetamol, rifampicin, phenytoin, halothane*
	2°: Congenital, stone		
Alcohol		Toxins	*Amanita phalloides*
Toxins		Miscellaneous	*Wilson's disease*
Drugs			*Fatty liver of pregnancy*
Auto-immune			*HELLP*
Metabolic diseases			*Lymphoma*
Wilson's Disease			*Sepsis*
a_1-Antitrypsin deficiciency			*Reye's syndrome*
Veno-occlusive	*Budd-Chiari*		*Heatstroke*

Table 3: Child-Pugh Score

Clinical or biochemical measurement	Points scored		
	1	**2**	**3**
Encephalopathy grade	None	1-2	3-4
Ascites	Absent	Mild	Moderate to severe
Bilirubin	<35 μmol/l	36-60 μmol/l	>60 μmol/l
Albumin	>35 g/l	28-35 g/l	<28 g/l
PT (secs. prolonged)*	1-4 secs	4-6 secs	>6 secs
[INR]	[<1-7]	[1.7-2.3]	[>2.3]
*Score prothrombin time or INR			

Child-Pugh A Score $\leq$ 6,
Child-Pugh B Score 7-9,
Child-Pugh C Score $\geq$10

pedigree, it is of limited predictive value in anaesthesia and surgery, because **Group B and C patients all represent a high perioperative risk**. In general surgical practice, only emergency or life-saving procedures should be undertaken in these patients. In a unit where liver transplantation is an option, other procedures can be considered, particularly those intended to 'buy time' until a suitable donor organ is available. **Group A patients are lower risk** and with sufficient care can be considered as candidates for most types of surgery.

Hepatocellular carcinoma is a recognised complication in those with chronic HBV or HCV infection. Rates are reported to run between 800 and 2000 cases per year per 100,000 chronically infected. Even in Group A patients, operative mortality for hepatic resection of tumour runs at 5%-10%.

Group B/C patients present an extremely high operative risk and surgical procedures in these patients should be avoided if possible. Considerable morbidity and a high mortality rate invariably accompany all but minor surgery. Procedures that might be performed in these patients include:

- Laparotomy for perforation or bleeding - often following previous surgery
- Porto-systemic anastomosis for portal hypertension: includes meso-caval and distal lieno-renal anastomosis. Encephalopathy is a common post-operative complication.
- Peritineo-venous shunting for intractable ascites where liver transplantation is not an option.

Hepatic resection of tumour in Group B/C patients carries an operative mortality of about 50%.

Anaesthesia for patients with liver dysfunction

For the purposes of this presentation, the basic principles of peri-operative care of three types of 'liver' patient will be considered. They are:

1. Medium risk patients - Child-Pugh Group A
2. High risk patients - Child-Pugh Group B/C
3. Management of patients with bleeding varices

1) Anaesthesia in Child-Pugh Group A Patients
In general terms, these patients can be considered as 'normal' and, for minor procedures, anaesthetic technique can be dictated by personal preference. However, major procedures should be planned with care and even though tests of coagulation may prove to be unremarkable, major bleeding is a possibility and adequate venous access and blood products should be available.

As with any patient, there should be careful pre-operative assessment, with appropriate history, examination and investigations. Issues relevant to Child-Pugh A patients are shown in Table 4. The anaesthetist should be aware of aetiology, particularly in the case of viral hepatitis or drug idiosyncrasy. It is useful to know also whether the condition is chronic or whether the patient is convalescing from an acute episode. Patients with chronic liver dysfunction can run a remitting / relapsing course and previous episodes of encephalopathy or bleeding are relevant

Table 4: Peri-operative considerations in Child-Pugh A patients

Pre-operative	Aetiology of condition – virology, drug idiosyncrasy Blood count and platelets Clotting screen Assess renal function Previous anaesthetics
Per-operative	Consider drug bio-availability issues ? avoid drugs excreted via liver Regional techniques acceptable if clotting normal
Post-operative	Monitor for post-operative hepatic decompensation Possible prolonged duration of action in opiates HDU / ITU care

to patient management. Patients recovering from an acute condition, such as acute hepato-cellular damage secondary to drug idiosyncrasy may continue to have an underlying coagulopathy or may have impaired drug clearance. Drugs dependent upon the liver for clearance, such as vecuronium and rocuronium will have a prolonged duration of action.

Regional techniques may be used in the absence of coagulopathy and are particularly helpful in post-operative pain management. Propofol is a useful induction agent as it undergoes considerable extra-hepatic metabolism, similarly, atracurium clearance is independent of liver metabolism. Isoflurane preserves hepatic blood flow, but both sevoflurane and desflurane are acceptable. Since many patients may be managed in intensive care post-operatively, the merit of using short and ultra short- acting narcotic analgesics is debatable. Morphine and fentanyl are entirely acceptable.

Postoperative HDU or ITU admission should be considered for all Group A patients undergoing major surgery, in order to forestall coagulation, fluid management, renal and respiratory complications.

2) Child-Pugh Group B/C patient undergoing major surgery

Patients in this group are very ill and present a considerable anaesthetic challenge. There can be profound derangement of nearly every physiological system and anaesthesia in such patients should not be embarked upon lightly. Aspects of pre-operative assessment are detailed in Table 5. Previous upper abdominal surgery, portal hypertension and coagulopathy dramatically increase the potential for per-operative blood loss, which can further complicate critical physiological derangements. 8-12 units of blood, together fresh frozen plasma and platelets should be available. An exhaustive discussion of peri-operative management is beyond the scope of this paper, but the principal issues are listed below in note form.

Pre-medication

Sedative premedicants should be avoided in the encephalopathic patient. Other drugs may be needed pre-operatively and include antibiotics and H_2 receptor antagonists. Delayed gastric emptying is not uncommon. The oral or intravenous route should be used for administering drugs – intramuscular injections should be avoided. Coagulopathy may require correction with fresh frozen plasma and platelets and renal replacement therapy may need to be considered.

Induction and per-operative considerations

The comments on anaesthetic technique for Group A patients above apply equally in the case of Group B/C patients. Regional techniques need to be considered carefully as most patients will suffer some form of coagulopathy; and epidural varices can pose an additional risk. Other issues in the per-operative management of Group B/C patients include:

Vascular access with a multi-lumen central venous catheter together with at least one large bore central line (e.g., 8.5 FG Swan Sheath), is of paramount importance. Monitoring of arterial and central venous pressures is mandatory. Pulmonary artery, pulmonary capillary wedge pressure and cardiac output measurements may be necessary in the sick patient. The availability of techniques such as trans-oesophageal echocardiography and volumetric haemodynamic monitoring / pulse contour analysis can provide significant additional information for the strategic management of these patients.

Table 5: Pre-operative considerations in Child-Pugh B/C patients

History	Aetiology. Previous upper abdominal surgery. Anaesthetic history CVS: exercise tolerance, oedema, orthopnoea RS: dyspnoea, ascites, pleural taps GI: bleeding, haematemesis, maelaena, piles Sepsis / urine output Medication:diuretics / antibiotics
Examination	Usual PLUS muscle mass, cyanosis, clubbing, temperature CVS: pulse rate, venous pressure, BP, oedema RS: resp. rate, effusions, sputum Abdo: ascites, spleen, caput medusae CNS grade of consciousness (seeencephalopathy below) ICP: unconscious patient Venous access (existing + potential)
Encephalopathy	**Grade 1:** mild confusion, fully coherent when roused **Grade 2:** increasing confusion, rousable, able to be rational **Grade 3:** sleeping mostly, roused to command, may be agitated or aggressive **Grade 4:** unrousable, ± reacts to pain, ?signs of cerebral oedema
Investigations	ECG, CXR; Blood - electrolytes, sugar, albumin, creatinine, gas, SpO_2, lactate, Blood count, platelets, INR (PTR); Viral serology; Ultrasound - abdominal (portal flow, pressure, ascites) AND cardiac (myocard wall movement, pericardial effusion) ; endoscopy, microbiology

Although per-operative studies have yet to be undertaken, evidence is emerging that the use of these devices in ITU may significantly shorten ITU stay in the critically ill.

Coagulation and fibrinolysis are major concerns. The potential for large volume blood replacement means that temperature should be measured and a fluid warmer and warming mattress used. Cold patients do not clot. Regular per-operative estimation of INR/PTR may be necessary. Alternatively, thrombo-elastography provides useful intra-operative evaluation of coagulation.

Blood conservation Blood conservation with a 'cell saver' should be considered, particularly if the patient has had previous upper abdominal surgery or has portal hypertension and bleeding is likely to be heavy.

Preservation of hepatic function. N-acetylcysteine (NAC) is a sulphur-containing antioxidant that has been shown to benefit patients with fulminant hepatic failure. NAC appears to improve oxygen delivery and consumption, and reduce base deficit.

Renal Function

Renal function is often impaired in these patients, so peri-operative replacement therapy may be needed. Dopamine, in spite of doubts cast over its ability to influence long-term outcome, may be useful in preserving renal function. Appropriate inotropic support may also be needed.

Post-operative management

Patients will require post-operative admission to the intensive care unit for all but the most minor surgery, and should undergo elective ventilation until cardiovascular parameters are stable and there is no evidence of bleeding. Parameters monitored per-operatively should continue to be monitored in the post-operative phase, with regular review of blood count, clotting profile and blood gases, chemistry and sugar. Dopamine and inotropes should be continued as long as necessary. The principle complications are likely to be continued bleeding, sepsis and hepatic decompensation and a low index of suspicion should be entertained for all of these. Patients who continue to bleed despite adequate blood and blood product replacement must undergo urgent laparotomy to stop bleeding and evacuate clot. While intra-abdominal tamponade may be regarded as useful in reducing bleeding, there can be deleterious effects on the kidneys that may be only transiently reversible. Furthermore, a large clot can present an unacceptable protein load to an already impaired liver, precipitating encephalopathy, and can be a nidus for sepsis.

Analgesia and sedation

If neuraxial anaesthesia has been used, then appropriate analgesic regimes can be implemented, with light sedation while the patient is ventilated. Otherwise fentanyl or morphine can be given by infusion, together with propofol or midazolam for sedation

3) Bleeding oesophageal varices

The therapeutic pathway for the management of bleeding oesophageal varices is well established. As soon as the airway has been appropriately protected, adequate venous access and volume replacement obtained and blood cross-matched, the most common sequence is as follows:

1. Administration of a vaso-constrictor (e.g., vasopressin, glypressin or somatostatin) and balloon tamponade, for example, with a **Sengstaken Tube**. Balloon placement should be undertaken by an experienced clinician, as mal-positioning can result in oesophageal rupture, an invariably fatal complication.

2. Injection sclerotherapy can be used acutely, but is used also to prevent recurrence of bleeding.

3. If the preceding manoeuvres fail to arrest bleeding, then an aorto-portogram should be undertaken with a view to de-vascularisation or porto-systemic shunting.

4. In general, surgical de-vascularisation (oesophageal transection) is undertaken if the superior mesenteric vein or the portal vein is thrombosed, effectively ruling out shunt procedures. The procedure involves use of a staple gun and has a low operative mortality.

5. If the superior mesenteric vein or the portal vein is patent, then meso-caval or distal lieno-renal anastomosis can be attempted. Mortality is about 40%. Alternatively, the TIPS (Transvenous Intra-hepatic Porto-systemic Shunt) procedure may be used. This involves placement of an expandable metallic stent between the branches of the portal vein and systemic circulation within the liver parenchyma.

Principles of anaesthetic management

Bleeding oesophageal varices are a life-threatening complication of chronic liver disease and often occur against a background of abnormal clotting, thrombocytopenia, encephalopathy and ascites. Overall mortality is 30%. The anaesthetist may be involved in any or all of the stages listed above. The principles of anaesthetic management are as ever:

- Protect the airway.
- Establish good vascular access.
- Volume replacement - colloid, blood, fresh frozen plasma and platelets. Avoid saline.
- Check / correct clotting. Give Vitamin K, correct fibrinolysis and review blood chemistry.

Many aspects of management mentioned in connection with Child-Pugh Group B/C patients apply here, including post-operative care.