Monitoring and managing hepatic disease in anaesthesia

D. Kiamanesh, J. Rumley and V. K. Moitra*

Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, NY, USA
* Corresponding author. E-mail: vm2161@columbia.edu

The liver metabolizes drugs, food, and toxins; synthesizes procoagulants and anticoagulants; and regulates temperature, glucose, and metabolism. When patients with liver disease need surgery, anaesthesiologists face several perioperative challenges. Patients with liver disease have physiological perturbations that range from mild hyperbilirubinemia of no clinical consequence to severe coagulopathy and metabolic disarray (Fig. 1). This article reviews the current body of knowledge of perioperative assessment, monitoring, and management of hepatic disease in patients who will undergo surgery.

Perioperative risk assessment

Patients with liver disease who undergo non-hepatic surgery have greater transfusion requirements, high infection risk, cardiac compromise, longer hospital stays, and increased operative mortality.1–6 Patient-specific risk factors, various scoring systems, and surgical procedures stratify risk for these patients.6–9 Independent risk factors for complications and mortality are outlined in Table 1.

The Child–Turcotte–Pugh (CTP) classification system, originally devised in 1964 to predict outcomes in cirrhotic patients undergoing portosystemic surgery, assesses perioperative risk for patients with liver disease who undergo hepatic or nonhepatic surgery.8 10 Scores are calculated from five variables: serum albumin, serum bilirubin, ascites, prothrombin time (PT), or INR (modified CTP score), and grade of encephalopathy to stratify patients into three groups (Class A = score 5–6; Class B = score 7–9; Class C = score 10–15).11 This scoring system relies on a subjective assessment of ascites and encephalopathy and does not consider preoperative infection, aetiology of cirrhosis, or surgery type.6 Original studies suggested high mortality rates in Class A patients (10%), Class B patients (82%), and Class C patients (82%) who undergo abdominal surgeries.12 13 A newer study reports lower mortality rates after abdominal operations: Class A = 2%; Class B = 12%; Class C = 12%.14 Improvements in surgical technique, anaesthetic management, and perioperative care might explain the difference in these findings.

The model for end-stage liver disease (MELD) score is a validated and prognostic tool that estimates disease severity and survival in patients with liver disease. The MELD score is objective, ranges from 6 to 40 points, and is calculated from the serum bilirubin, serum creatinine, INR, and aetiology of liver disease.15 The MELD score has been validated across a number of liver diseases (alcoholic hepatitis and variceal bleeding)16 and surgeries (abdominal, orthopaedic, and cardiovascular).5 8 17–19 In patients who have undergone abdominal surgery, an elevated MELD score was a better predictor of poor perioperative outcome than CTP classification.17 Patients with MELD scores > 15 should avoid elective surgery.20 In 2002, the United Network for Organ Sharing adopted the MELD score as a method of allocation of organs to estimate survival. The incorporation of hyponatraemia, an important prognostic factor in patients with cirrhosis, into the MELD score might improve risk stratification among patients awaiting liver transplantation.21

The type of surgical procedure influences perioperative outcomes in patients with hepatic disease. During abdominal surgery, reflexive systemic hypotension from visceral traction and blood loss can reduce hepatic arterial blood flow.22 23 Patients with extensive liver disease who undergo abdominal surgery have a mortality rate of 30%.12 24 Mortality rates in cirrhotic patients who undergo open cholecystectomy are 23–50%; cardiac surgery, 16–31%; laparotomy for trauma, 45%; and oesophageal surgery, 17–26%.25–33 Patients with

Summary. Patients with liver disease have multisystem organ dysfunction that leads to physiological perturbations ranging from hyperbilirubinemia of no clinical consequence to severe coagulopathy and metabolic disarray. Patient-specific risk factors, clinical scoring systems, and surgical procedures stratify perioperative risk for these patients. The anaesthetic management of patients with hepatic dysfunction involves consideration of impaired drug metabolism, hyperdynamic circulation, perioperative hypoxaemia, bleeding, thrombosis, and hepatic encephalopathy.

Keywords: liver; liver, cirrhosis; liver, disease; liver, function; liver, metabolism
coagulopathy or CTP Class C cirrhosis are at even higher risk during open cholecystectomies, abdominal surgeries, and cardiovascular procedures. Contraindications to elective surgery include fulminant hepatic failure, acute viral or alcoholic hepatitis, chronic active symptomatic hepatitis, CTP Class C cirrhosis, severe coagulopathy (platelet count, 50,000 \( \mu \text{L}^{-1} \), uncorrectable PT > 3 s above control), hypoxaemia, heart failure, and acute kidney injury.

**Management of anaesthetic medications and metabolism**

The metabolic activity and clearance of anaesthetic medications is impaired in patients with liver disease. Without adjusted doses of medications, duration of drug action is extended and toxic levels can result. Emergence from anaesthesia can be delayed.

Hepatic metabolism takes place via two pathways: phase 1, biotransformation via the cytochrome P450 system (which requires delivery of oxygen via hepatic perfusion); and phase 2, glucuronide conjugation. The first is decreased in liver disease; the second is relatively spared when dysfunction begins.
Many anaesthetic drugs (i.e. opioids, barbiturates) bind to albumin in the circulation. Low albumin levels increase the free fraction of drug and can theoretically exaggerate pharmacological effect. End-stage liver disease alters hepatic extraction, renal excretion, and levels of serum proteins in addition to albumin. The net effect of these changes is unpredictable, making general recommendations for drug administration difficult. For safety, drugs are titrated to desired effect.

Patients with hepatic dysfunction can be sensitive to sedatives such as midazolam and diazepam. In contrast, the pharmacokinetics of lorazepam, which undergoes glucuronidation, is less likely to be affected by liver disease. Benzodiazepines can precipitate hepatic encephalopathy, and flumazenil can reverse this condition. Conversely, patients who have a history of alcohol abuse can require large doses of benzodiazepines. Rapid redistribution of bolused propofol determines its duration of action, which is not affected by impaired liver metabolism. In a small study of cirrhotic patients, propofol infusions did not increase termination half-life or clearance to a clinically significant degree.

The adverse effects of morphine can be more pronounced in patients with severe liver disease. Morphin metabolism by glucuronidation in the liver, and its intermediate metabolites are eliminated renally. Although the pharmacokinetics of morphine can be unaltered in patients with mild hepatic disease, a prolonged half-life is associated with a prolonged PT, hypobalbuninaemia, encephalopathy, ascites, and jaundice. The elimination of morphine metabolites can be prolonged in patients with hepatorenal syndrome (HRS). Metabolism of fentanyl, sufentanil, and morphine, which have a high hepatic extraction ratio, is slowed by impaired hepatic blood flow.

In patients with liver disease and oedema, neuromuscular blocking agent doses must be augmented because fluid retention increases the volume of distribution. Neuromuscular blocking agents that are metabolized by the liver, such as vecuronium and rocuronium, have a slower onset and longer duration of action. Liver disease reduces plasma cholinesterase activity, and prolonged neuromuscular block after succinylcholine has been reported. Acute kidney injury with elevated potassium levels or immobilization for long periods might preclude the use of succinylcholine.

Vasodilating anaesthetic agents such as propofol and volatile anaesthetics cause hypotension if intravascular volume is depleted (i.e. by overdiuresis or gastrointestinal losses), and reduce liver perfusion. In addition to perioperative haemorrhage and hypotension, volatile anaesthetic agents can reduce hepatic blood flow and hepatic oxygen uptake. Compared with the vasoconstrictive effects of halothane, isoflurane and desflurane can improve hepatic blood flow and splanchnic perfusion via hepatic vasodilation.

Patients with end-stage liver disease often exhibit coagulation disorders. The presence of a coagulopathy is a contraindication to regional anaesthesia, particularly epidural anaesthesia. In patients without a preoperative disorder of coagulation, intraoperative or postoperative coagulopathy from hepatic ischaemia, insufficient residual hepatic parenchyma, and dilution can develop. Delayed epidural catheter removal has been suggested in patients who undergo hepatectomy.

Organ response, assessment, and management

Hepatic response

Laboratory tests, such as albumin and bilirubin, are non-specific and can be affected by other diseases and medications. Even with hepatic disease, patients can have normal liver function and laboratory values because the liver, the largest organ and gland in the body, has a large reserve capacity. Albumin, produced exclusively in the liver, has been used to assess hepatic synthetic function. Low levels of this non-specific marker are also found in patients with malnutrition, renal disease, and capillary leak syndrome. This prognostic marker in hospitalized patients is a negative acute phase reactant because the production of albumin decreases during states of inflammation with cytokine release and surgical tissue trauma. Albumin, with a long half-life of 20 days, can be normal even in acute liver failure.

The breakdown of red blood cells within the reticuloendothelial system forms unconjugated ('indirect') bilirubin. Unconjugated bilirubin is transported to the liver to be conjugated and secreted into bile. Increased production, decreased hepatic uptake, and decreased conjugation of bilirubin cause unconjugated hyperbilirubinaemia. The most common causes of unconjugated hyperbilirubinaemia are haemolysis, resolution of haematomas, inborn errors of bilirubin conjugation (Gilbert’s syndrome and Crigler–Najjar syndrome), or portal hypertension. Under normal circumstances, levels of conjugated bilirubin in serum are negligible after rapid excretion into the biliary system. Conjugated hyperbilirubinaemia can indicate intrinsic liver disease, especially in conjunction with elevated aminotransferase levels, a sign of hepatocellular injury. Conjugated hyperbilirubinaemia with elevated alkaline phosphatase and minimal increase in aminotransferase levels is consistent with a purely cholestatic process and can result from numerous causes, including cholestatic drug reactions or obstructive jaundice.

The normal portosystemic arterial pressure gradient between the portal vein and hepatic vein is <5 mm Hg. Intrahepatic vascular resistance and portal venous blood flow increase the gradient, characteristic of portal hypertension. Vascular resistance in the liver can result from several factors: liver fibrosis, regenerative nodules, collagen deposits in the space of Disse, endothelial dysfunction, imbalance between endogenous vasoconstrictors (i.e. norepinephrine, thromboxane A, endothelin I, angiotensin II, and leukotrienes) and vasodilators (nitric oxide), and contraction of portal and septal myofibroblasts and smooth muscle cells. As the pressure gradient between the portal vein and the hepatic vein increases, gastrointestinal and haemorrhoidal varices develop to decompress the portal system. Portal hypertension produces endogenous vasodilators that cause splanchnic vasodilation.
Complications of portal hypertension include gastrointestinal bleeding from varices and abdominal ascites, intraoperative bleeding from intra-abdominal collaterals, and formation of ascites and pleural effusions.68 72 Almost half of patients with cirrhosis have oesophageal varices at the time of diagnosis, with the 1 yr risk of variceal haemorrhage at 12% and a 1 yr rate of recurrent haemorrhage at 60%. The 6 wk mortality with each episode of variceal haemorrhage is between 15% and 20%.73 In patients with acute upper gastrointestinal bleeding, a restrictive transfusion strategy (transfusion when the haemoglobin is <7 g dl−1) can decrease subsequent bleeding and prevent an increase in the portal-pressure gradient.74 Patients who have received multiple previous transfusions, such as patients with a history of gastrointestinal bleeding, should be evaluated in advance for cross-matching large quantities of blood products possibly required for a procedure.

Before operation, ascites is initially managed with a low sodium diet and diuretic therapy. Patients with ascites refractory to treatment with diuretics require large-volume paracentesis and albumin replacement to prevent hypotension and HRS.75 76 Large-volume abdominal ascites can lead to a lower venous return and, in conjunction with pleural effusions, can decrease pulmonary reserve and prevent patients from lying flat. If there is evidence of tense ascites, recent food ingestion, or a propensity for delayed gastric emptying, a rapid-sequence induction of general anaesthesia with tracheal intubation should be considered.

A transjugular intrahepatic portosystemic shunt (TIPS) prevents recurrent variceal bleeding and manages refractory ascites.76 During the procedure, an expandable stent is placed into the liver parenchyma for portosystemic exchange to decrease portal hypertension. The procedure is performed under local or general anaesthesia as a ‘bridge’ to liver transplantation in patients with severe liver disease.77 General anaesthesia might be preferred because of the duration of the procedure and the potential for a life-threatening event such as bleeding, infection, haemobilia, arrhythmias, liver ischaemia, and stent migration.78 Preoperative evaluation of cardiac function (particularly right ventricular function) is essential because stent placement can rapidly increase venous return and cardiac output to unmask underlying cardiomyopathy.79 80 Encephalopathy can worsen from enhanced systemic delivery of biogenic amines normally cleared by the liver.

Cardiovascular response

The systemic response of patients with end-stage liver disease mimics the hyperdynamic circulatory changes in patients with sepsis. Tachycardia, elevated cardiac output, low arterial pressure, and low systemic vascular resistance are characteristic.81 82 Enhanced endogenous production or diminished hepatic clearance of vasodilating substances (nitric oxide, carbon monoxide, and endogenous cannabinoids, tumour necrosis factor-α, adrenomedullin, and hydrogen sulfide) and the inflammatory response to bacterial translocation cause splanchnic arterial vasodilation (Fig. 2).81 82 These changes have been reversed with liver transplantation.81 83 In response to splanchnic vasodilation and decreased systemic vascular resistance, the body retains sodium and water, which increases plasma volume. An increase in cardiac output and heart rate follow.81 84 Venous capacitance increases from formation of portosystemic shunts with portal hypertension to contribute to a hyperdynamic circulation.

Management of vasodilatory hypotension focuses on expanding the intravascular volume, administering a vasocostricting agent such as norepinephrine or vasopressin, and determining the underlying cause of vasodilation to target. Aggressive fluid resuscitation without assessment of fluid responsiveness should be avoided because excessive i.v. fluid administration to a non-fluid-responsive patient can increase cardiac filling pressures, which can cause hepatic congestion, pulmonary oedema, and resulting respiratory failure.

Systemic conditions such as haemochromatosis (ventricular hypertrophy with increased end-diastolic and end-systolic volumes), amyloidosis (restrictive cardiomyopathy), Wilson’s disease (supraventricular extrasystolic beats), and alcoholism (systolic and diastolic dysfunction) can affect liver and cardiac function.85 During the perioperative period, the circulatory system can be challenged with shunt insertion or greater afterload from surgical stress, unmasking underlying cardiomyopathy. Echocardiography shows impaired myocardial function similar to that found in sepsis.86 This condition is also characterized by QT prolongation and systolic and diastolic dysfunction.87 Reduced β-adrenoceptor function might explain these findings.88 Cirrhotic cardiomyopathy is often reversible and requires inotropic and diuretic support to prevent elevation of central venous pressure and hepatic congestion.

Patients with portal hypertension can develop portopulmonary hypertension (PPHTN) and right ventricular dysfunction. While the exact pathogenesis of PPHTN remains unclear, histopathological findings are indistinguishable from those observed in idiopathic pulmonary artery hypertension (medial hyper trophy, concentric intimal proliferation, plexiform lesions, in situ thrombosis, and fibrotic changes).88 89 A hyperdynamic circulation might increase shear stress on the pulmonary vasculature to cause remodelling and pulmonary hypertension.90 91 The mean pulmonary artery pressure >25 mm Hg at rest and pulmonary vascular resistance >240 dyn s cm−5 define PPHTN. PPHTN has been reported in 6–9% of patients with advanced liver disease.91 92 In a retrospective study of patients who underwent orthotopic liver transplantation (OLT), mortality was 50% in patients with the mean pulmonary artery pressures between 35 and 50 mm Hg and 100% in patients with pressures >50 mm Hg.93 Calcium channel blockers, which can be used in patients with pulmonary arterial hypertension, are not recommended in PPHTN because they produce mesenteric vasodilatation and worsen portal hypertension. β-Blocker therapy, which is often used in patients with portal hypertension to reduce the risk of variceal bleeding, is contraindicated in patients with PPHTN because its negative inotropic effect decreases exercise tolerance.94 95 Finally, while liver transplantation is a tempting option to reduce PPHTN, moderate or severe uncontrolled PPHTN is associated with significant mortality risk and is a contraindication to OLT.93–95 Intraoperative management
is targeted to prevent increases in pulmonary vascular resistance by controlling hypoxia, hypercarbia, acidosis, pain, and hypothermia.

Because of these cardiovascular changes, invasive monitors usually are used during the perioperative period. Beat-to-beat arterial pressure is monitored and blood is sampled frequently via a radial artery catheter. Pulse pressure variation, calculated from the invasive arterial tracing, assesses fluid responsiveness. Peripheral arterial pressure measurements can be unreliable in patients with severe vasoconstriction or vasodilation. Central venous access is established to measure right atrial pressure and to administer drugs. Monitoring central venous pressure does not reliably measure blood volume or change in blood volume. Echocardiography assesses ventricular filling, contractility, and function. Myocardial ischaemia, pulmonary embolism, pleural effusion, and inadequate inferior vena cava reconstruction can be observed with transoesophageal echocardiography (TOE). The risk of rupture of oesophageal varices with TOE is rare. Bladder pressures should be measured if intra-abdominal hypertension from ascites is suspected.

**Pulmonary response**

Up to 70% of patients with end-stage liver disease complain of dyspnoea. Potential causes of preoperative hypoxaemia and respiratory failure in patients with cirrhosis include atelectasis from the compressive effects of ascites, hepatic hydrothorax, hepatopulmonary syndrome (HPS), underlying chronic pulmonary disease and occasionally acute respiratory distress syndrome. Chest radiography rules out pulmonary oedema, pleural effusions, or cardiomegaly in patients with symptoms of dyspnoea. Muscle wasting and intra-abdominal hypertension from ascites increase the work of breathing. Ascites fluid can enter the pleural space through small channels in the diaphragm to cause a hepatic hydrothorax (usually on the right side). Compressive atelectasis from ascites and pleural effusions reduce functional residual capacity and decrease the time to oxygen desaturation. Lung recruitment and pleural fluid drainage can improve pulmonary mechanics. Respiratory alkalosis can be observed in patients with a high respiratory drive from liver dysfunction. The use of positive-pressure mechanical ventilation and PEEP can lead to an increased average intrathoracic pressure, which decreases venous return from the inferior vena cava and hepatic veins and can lead to congestion of the liver. This concern remains controversial, as studies with PEEP of up to 10 cm H₂O have shown no adverse effects on hepatic arterial, portal venous, or hepatic venous flow.

A diagnosis of HPS is considered in patients without cardiopulmonary disease who have a $P_{aO_2} < 8.0$ kPa. The triad of liver disease and/or portal hypertension, widened age-corrected alveolar–arterial oxygen gradient ($\geq 2–2.7$ kPa) while breathing room air, and documented intrapulmonary vascular dilation (IPVD) define HPS. Enhanced production or impaired hepatic clearance of endogenous vasodilators (i.e. nitric oxide, vasodilator prostaglandins, substance P), or inhibition of vasoconstrictive substances (i.e. tyrosine, serotonin, and endothelin) by a
damaged liver can cause IPVD. IPVD causes hypoxaemia via ventilation and perfusion mismatching, intrapulmonary shunt physiology, and diffusion limitation. Patients with HPS often complain of dyspnoea and fatigue; they can have clubbing and spider angiomas. They may experience platypnoea (dyspnoea in the upright position relieved by recumbency) or have orthodeoxia (arterial oxyhaemoglobin desaturation in the upright position). Preferential perfusion of IPVDs with the patient upright might cause these clinical manifestations.

**Contrast-enhanced echocardiography** or perfusion lung scanning with technetium-99m-labelled macroaggregate albumin detects intrapulmonary shunting suggestive of IPVD. Resolution of this syndrome after transplant has been reported.

Medical therapy for HPS has, to date, been relatively ineffective. Currently, the only known treatment option for patients with HPS is liver transplantation.

### Renal, electrolyte, and glucose response

Acute kidney injury commonly occurs in patients with chronic liver disease and is present in up to 20% of patients hospitalized with decompensated liver cirrhosis. Patients with acute kidney injury and cirrhosis have more complications and greater risk for mortality after liver transplantation than those without renal failure. Gastrointestinal bleeding, diarrhoea from infection or lactulose administration, and diuretic medications change circulatory function via hypovolaemia and can cause pre-renal injury. This injury rapidly reverses with correction of the underlying pathophysiology and volume resuscitation. As cirrhosis progresses, reduction in systemic vascular resistance activates the renin–angiotensin and sympathetic nervous systems, which leads to ascites, oedema, and vasoconstriction of the intrarenal circulation and renal hypoperfusion. Ischaemic events and medications such as non-steroidal anti-inflammatory drugs or aminoglycosides cause intrinsic renal damage.

Managing kidney injury, low urine output, and electrolyte abnormalities in patients with hepatic disease is challenging. Prerenal kidney injuries reverse with enhanced renal perfusion or removal of the obstruction, respectively. Optimizing renal perfusion and avoidance of nephrotoxic drugs are also important in these patients.

Continuous renal replacement therapy can be used perioperatively to manage volume shifts, acid–base balance, and electrolyte disturbances. Placement of a TIPS can improve serum creatinine, with more profound effects on those patients with higher baseline levels.

HRS is caused by functional renal vasoconstriction (via activation of the renin–angiotensin system, the sympathetic nervous system, and arginine vasopressin) in response to splanchnic arterial vasodilatation. Although histological findings and diagnostic tests for HRS are lacking, diagnostic criteria are used to categorize two types of HRS. Criteria for HRS include (i) cirrhosis with ascites, (ii) serum creatinine >1.5 mg dl\(^{-1}\), (iii) no improvement of creatinine after 2 days of diuretic withdrawal and volume expansion with albumin, (iv) absence of shock, (v) no current or recent treatment with nephrotoxic drugs, and (vi) absence of parenchymal kidney disease. In type I HRS, renal function is impaired rapidly and progressively with a doubling of the initial serum creatinine to >2.5 mg dl\(^{-1}\) or a 50% reduction in the 24 h creatinine clearance to <20 ml min\(^{-1}\) in <2 weeks. Patients with type II HRS have impaired renal function and a serum creatinine >1.5 mg dl\(^{-1}\) and do not meet the criteria for type I HRS. Compared with patients diagnosed with prerenal failure, patients with HRS lack a renal response to a 1.5 litre volume challenge. Distinguishing between HRS and acute tubular necrosis is difficult. Fractional excretion of sodium <1% suggests tubular function and favours a diagnosis of HRS. The presence of renal tubular epithelial cells in urinary sediment favours a diagnosis of acute tubular necrosis.

Medical management of HRS is marginally effective, but liver transplantation usually reverses HRS.

Hyponatraemia from accumulated secretion of anti-diuretic hormone acts on vasopressin-2 receptors of the renal tubular collecting duct to impair excretion of solute-free water. When extracellular volume expands, ascites and oedema can result. Patients with hyponatraemia have loss of extracellular fluid from the kidneys (overdiuresis) or gastrointestinal tract, ascites or oedema is rare. These patients can have prerenal failure from low circulating volume or hepatic encephalopathy from rapid reduction in serum osmolality. Distinguishing between hypovolaemic and hyponatraemic hyponatraemia guides treatment. Hyponatraemia is managed with fluid restriction (1–1.5 litre day\(^{-1}\)) and withholding of diuretics. Vaptans, medications that block the V2 receptor, increase solute-free water excretion dose-dependently and might preclude water restriction so that diuretics can be continued. Patients with hyponatraemia are not given diuretics; instead, saline is administered to increase plasma volume.

Patients with preoperative hyponatraemia are at risk for central pontine myelinolysis (CPM) perioperatively. CPM is a neurological condition characterized by symmetric non-inflammation demyelinating lesions in the basis pontis. The aetiology of CPM is uncertain, but osmotic stress on central nervous system cells has been suggested, and CPM correlates with rapid correction of hyponatraemia.
Disorders of glucose metabolism are observed in patients with chronic liver disease and cirrhosis. Multiple factors affect glucose levels, including the inflammatory response to surgery, steroid administration, hepatic dysfunction, altered glycogen stores, and insulin resistance in liver failure. Episodes of hypoglycaemia are observed in patients with end-stage liver disease.

**Haematological response**

In patients with hepatic disease, haemostatic changes promote both bleeding and thrombosis. Inadequate synthesis of all coagulation factors (except for von Willebrand’s factor and factor VIII), thrombocytopenia, platelet function defects, dysfibrinogenaemia, and elevated tissue plasminogen activator (tPA) levels cause bleeding. Elevation of von Willebrand’s factor and Factor VIII and decreased levels of ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), protein C, protein S, antithrombin, α 2-macroglobulin, plasminogen, and heparin cofactor II favour thrombosis.

Factors VII, X, V, II (prothrombin), and I (fibrinogen) have a short half-life (hours to days) and are synthesized solely by hepatocytes, making possible a ‘semi real-time’ evaluation of hepatic synthetic function. Although patients with liver disease can have abnormal PT from decreased production of pro-coagulant factors, the rebalanced state of pro- and anti-coagulants in patients with liver disease makes the PT an unreliable tool for evaluating tendency to bleed or clot. Levels of fibrinogen, an acute phase reactant, are normal or increased in mild-to-moderate liver disease. In patients with severe hepatic dysfunction, however, fibrinogen is poorly synthesized and dysfunctional, which increases the risk of bleeding. Although hyperfibrinolysis (from increased levels of tPA and reduced levels of thrombin-activatable fibrinolysis inhibitor and plasmin inhibitor) has been observed in cirrhotic patients, its association with bleeding is unclear. Hypofibrinolysis (from increased levels of plasminogen activator inhibitor and reduced levels of plasminogen) can restore the balance of fibrinolysis.

Thrombocytopenia and platelet dysfunction are characteristic of end-stage liver disease. Thrombocytopenia results from several factors: portal hypertension with hypersplenism, which sequesters platelets; consumption of platelets during systemic intravascular coagulation; and impaired hepatic synthesis of thrombopoietin, which stimulates platelet production in the bone marrow. Defective signal transduction; uraemia from acute kidney injury; and intrinsic defects of ADP, arachidonic acid, collagen, and thrombin prevent platelet aggregation.

Patients with active sites of bleeding should be transfused with fresh-frozen plasma, packed red blood cells, cryoprecipitate, or platelets as dictated by clinical assessment and laboratory tests. In addition, desmopressin can be considered for patients with concomitant renal dysfunction and uraemic bleeding. Coagulation status should always be monitored by inspection of the surgical field. Measurements from thromboelastography or rotational thromboelastometry assess the viscoelastic properties of a whole blood sample as a function of time to reflect the function and interaction of plasma, blood cells, and platelets. These measurements detect a hypercoagulable state and distinguish hyperfibrinolysis from other causes of coagulopathy, such as factor depletion or thrombocytopenia to offer a composite picture of the clotting cascade. Although both have been used to guide haemostatic management during liver transplantation, there are no studies evaluating these tests as predictors of intraoperative bleeding in patients with hepatic disease.

Uncontrolled haemorrhage and massive transfusion in the operating theatre or the intensive care unit can cause the lethal triad of acidosis, coagulopathy, and hypothermia. Left uncorrected, each of these abnormalities can exacerbate the others, creating a ‘bloody vicious cycle’. Additional early complications of massive transfusion include (i) acute haemolytic transfusion reactions, (ii) febrile non-haemolytic transfusion reactions, (iii) transfusion-related acute lung injury (TRALI), (iv) transfusion-associated circulatory overload, (v) allergic reactions, (vi) bacterial sepsis, (vii) hypocalcaemia, and (viii) hyperkalaemia (see Pham and Shaz, this issue).

Warming the room, applying forced warming systems, administering blood products and fluids through a fluid warmer, and heating and humidifying inspired gases reduce the risk of hypothermia. Dilutional coagulopathy and thrombocytopenia may be prevented by transfusing packed red blood cells, fresh-frozen plasma, and platelets in a 1:1:1 ratio. Occasionally, recombinant Factor VIIa is administered. Factor VIIa has not been shown to decrease red blood cell transfusion requirements during hepatotomies. Potassium, magnesium, and calcium levels are frequently monitored to correct abnormal levels. Improving haemodynamic parameters, adjusting minute ventilation, or administering sodium bicarbonate or tromethamine manage metabolic acidosis. The risk of TRALI can be reduced by minimizing transfusions and transfusing packed red blood cells with a short storage time (see Cohen and Matot, this issue) and fresh-frozen plasma from men or nulliparous women.

**Neurological response**

Patients with liver disease can have encephalopathy before operation or after operation. Brain dysfunction manifests in acute or chronic liver failure or after a spontaneous or surgical porto-systemic shunt. Hepatic encephalopathy is a neuropsychiatric complication of acute and chronic liver disease with features that range from mild confusion to cerebral oedema with intracranial hypertension. Patients have disturbances in consciousness, cognitive abilities, behaviour, fine motor skills, concentration, reaction time, memory, and/or electroencephalogram. The pathogenesis of hepatic encephalopathy is not understood, but most theories implicate elevated levels of ammonia, a gut-derived neurotoxin, which is shunted to the systemic circulation from the portal system. Bacteria in the intestinal tract produce ammonia, which crosses the blood–brain barrier into...
astrocytes that detoxify it to glutamine. An increased concentration of intracellular glutamine leads to swollen astrocytes with reduced ability to regulate neurotransmission. High serum ammonia levels are present in patients with hepatic encephalopathy, even though the degree of elevation of ammonia does not correlate with neurological dysfunction. Other factors, such as hyponatraemia, gastrointestinal bleeding, and infection, may contribute to the development of hepatic encephalopathy. Left untreated, cerebral oedema can progress to intracranial hypertension and brain herniation. Multiple grading scales assess the severity of hepatic encephalopathy. The most common scales are the West Haven Criteria (Conn Score) which has grades 0 through 4 and the Glasgow coma score.

Initial therapy for hepatic encephalopathy identifies and treats reversible triggers (i.e. gastrointestinal bleeding, hypokalaemia, alkalaeemia, hypoglycaemia, hypovolaemia, and infection) of this neuropsychiatric syndrome and considers minimizing benzodiazepine medications. While there is no evidence of a direct correlation between the degree of elevation of ammonia and severity of hepatic encephalopathy, it is well accepted that ammonia is a factor. Non-absorbable disaccharides such as lactulose acidify the gut environment to decrease absorption of ammonia from the gut via catharsis. Excessive dosing of lactulose causes dehydration however. Oral antibiotics (rifaximin, neomycin, vancomycin, paramomycin, or metronidazole) reduce ammonia-producing enteric bacteria. Rifaximin, in combination with lactulose, might reduce episodes of hepatic encephalopathy.

Patients who develop fulminant hepatic failure are at risk for hepatic encephalopathy, cerebral oedema with increased intracranial pressure (ICP), and herniation. In cases of altered mental status, a head CT scan is often indicated to evaluate intracranial bleeding, herniation, the extent of cerebral oedema, or both. ICP monitoring should be seriously considered for patients with fulminant hepatic failure and encephalopathy, even given the bleeding risks associated with invasive monitors. Bleeding risk seems to be the greatest deterrent to ICP monitoring.

ICP elevations to > 25 mm Hg should be treated with mannitol to achieve hyperosmolarity. Preoperative hyperventilation has not been shown to improve outcome and corticosteroids are not indicated. Pentobarbital coma can be used for patients unresponsive to mannitol, but can worsen cerebral hypoperfusion by causing systemic hypotension. Many centres consider sustained cerebral hypoperfusion (cerebral perfusion pressure < 40 mm Hg) a contraindication to transplant because of the high risk for brain death. In the future, transcranial Doppler ultrasonography, near-infrared spectrophotometry, and measurements of extracellular lactate via cerebral microdialysis could offer means of monitoring for elevated ICP in these patients.

For anaesthesia, drugs or conditions that exacerbate elevations in ICP should be avoided. Recent evidence shows that moderate hypothermia (32–33°C) can reduce cerebral oedema and intracerebral hypertension; however, the side-effects of these manoeuvres are greater risk of infection, cardiac dysrhythmias, and coagulopathy.

Conclusions
Patients with hepatic disease are at high risk for poor perioperative outcomes. Assessment of the severity of liver dysfunction and consideration of type of surgery stratifies risk and delays elective surgery in patients with significant hepatic disease (CTP Class C cirrhosis). Managing surgical patients with hepatic disease considers anesthetic dose adjustment and monitoring the multisystem organ responses to liver dysfunction.

Authors’ contributions
All authors participated in literature search, writing of first draft, editing, and final approval.

Acknowledgement
The authors would like to thank Sally Kozlik for her invaluable editorial assistance.

Declaration of interest
None declared.

References


22 Gelman SL. Disturbances in hepatic blood flow during anesthesia and surgery. *Arch Surg* 1976; **111**:881–3


24 Neeff H, Mariaskin D, Spangenberg HC, Hopt UT, Makowiec F. Early and late outcome of cardiac surgery in patients with liver cirrhosis. *Arch Surg* 1985; **120**:555–64


34 Neeff H, Mariaskin D, Spangenberg HC, Hopt UT, Makowiec F. Early and late outcome of cardiac surgery in patients with liver cirrhosis. *Arch Surg* 1985; **120**:555–64
patients with hepatic cirrhosis. *Br J Clin Pharmacol* 1997; **44**; 139–44


57 O’Riordan J, O’Beirne HA, Young Y, Bellamy MC. Effects of desflurane and isoflurane on splanchnic microcirculation during major surgery. *Br J Anaesth* 1997; **78**:95–6

58 Borromeo CJ, Stix MS, Lally A, Pomfret EA. Epidural catheter and increased prothrombin time after right lobe hepatectomy for living donor transplantation. *Anesth Analg* 2000; **91**:1139–41


61 Tsui SL, Yong BH, Ng KF, Yuan TS, Li CC, Chui KY. Delayed epidural catheter removal: the impact of postoperative coagulopathy. *Anaesth Intensive Care* 2004; **32**:630–6


67 Rochling FA. Evaluation of abnormal liver tests. *Clin Cornerstone* 2001; **3**:1–12


70 Shibayama Y, Nakata K. Localization of increased hepatic vascular resistance in liver cirrhosis. *Hepatology* 1985; **5**:643–8


77 DeGasperi A, Corti A, Corso R, et al. Transjugular intrahepatic portosystemic shunt (TIPS): the anesthesiological point of view after 150 procedures managed under total intravenous anesthe-


81 Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology* 2006; **43**:5121–31


83 Vaughan RB, Angus PW, Chin-Dusting JPF. Evidence for altered vascular responses to exogenous endothelin-1 in patients with advanced cirrhosis with restoration of the normal vasoconstrictor response following successful liver transplantation. *Gut* 2003; **52**:1505–10

84 Hall TH, Dhir A. Anesthesia for liver transplantation. *Semin Cardiothorac Vasc Anesth* 2013; **17**:180–94

85 Moller S, Hove JD, Dixin U, Bendtsen F. New insights into cirrhotic cardiomyopathy. *Int J Cardiol* 2013; **167**:1101–8


87 Biancofiore G, Mandell MS, Rocco GD. Perioperative considerations in patients with cirrhotic cardiomyopathy. *Curr Opin Anaesthesiol* 2010; **23**:128–32


89 Stauber RE, Olschewski H. Portopulmonary hypertension: short review. *Eur J Gastroenterol Hepatol* 2010; **22**:385–90


95 Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. *Liver Transpl* 1997; **3**:494–500


100 Fallon MB, Abrams GA. Pulmonary dysfunction in chronic liver disease. *Hepatology* 2000; **32**: 859–65


107 Hartlieb M, Gutkowski K. Kidneys in chronic liver diseases. *World J Gastroenterol* 2012; **18**: 3035–49


114 Gluud LL, Christensen K, Christensen E, Krag A. Terlipressin for hepatorenal syndrome. *Cochrane Database Syst Rev* 2012; **9**: CD005162


123 Nordlie RC, Foster JD, Lange AJ. Regulation of glucose production by the liver. *Annu Rev Nutr* 1999; **19**: 379–406


135 Martinez J, MacDonald KA, Palascan JE. The role of sialic acid in the dysfibrinogenemia associated with liver disease: distribution of sialic acid on the constituent chains. *Blood* 1983; **61**: 1196–202


137 Colucci M, Binetti BM, Branca MG, et al. Deficiency of thrombin-activatable fibrinolysis inhibitor in cirrhosis is associated with increased plasma fibrinolysis. *Hepatology* 2003; **38**: 230–7

138 Lisman T, Leebeek FW, Mosnier LO, et al. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. *Gastroenterology* 2001; **121**: 131–9


142 Pham HP, Shaz BH. Update on massive transfusion. *Br J Anaesth* 2013; 111 (Suppl. 1): i71–i82


150 Cohen B, Matot I. Aged Erythrocytesa fine wine or sour grapes?. *Br J Anaesth* 2013; 111 (Suppl.): 162–170

151 Teperman LW, Peyregne VP. Considerations on the impact of hepatic encephalopathy treatments in the pretransplant setting. *Transplantation* 2010; 89: 771–8


165 Dmello D, Cruz-Flores S, Matuschak GM. Moderate hypothermia with intracranial pressure monitoring as a therapeutic paradigm for the management of acute liver failure: a systematic review. *Intensive Care Med* 2010; 36: 210–3