1. Correct answers: 1 and 3

Unlike the West where antibiotics are the most common cause of drug-induced liver injury (DILI) and paracetamol (acetaminophen) is the most common cause of acute liver failure (ALF), antitubercular drugs are the most common cause of both DILI and ALF in India. The degree of elevation of liver enzymes correlates poorly with severity of liver injury, but presence of clinical jaundice is a strong predictor of mortality, called the Hy’s law. Hy’s law has been now been modified by the Food and Drug Agency as bilirubin >2 mg/dL or and transamminases >3 upper limit of normal. The pattern of liver injury also dictates the outcomes, with cholestatic DILI having better prognosis than hepatocellular DILI, but with higher chance of protracted course, despite stopping the offending drug.

2. Correct answers: 1, 3 and 5

Both Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores have been evaluated in various studies and have been found to be useful for risk assessment for surgery in chronic liver disease patients. In one small study of 53 patients MELD was found to be superior to CTP score. Patients with MELD score of 10 or less can undergo elective surgery, in patients with MELD score of 10–15 elective surgery should be performed with caution and pre-operative optimization, and in patients with MELD score of >15 surgery should be avoided. Laparoscopic cholecystectomy is safer than open cholecystectomy and can be safely performed in compensated cirrhosis without portal hypertension. Umbilical hernia can get complicated and lead to leakage, ulceration, rupture, and incarceration. These complications can lead to high mortality after emergency surgery. Therefore, an umbilical hernia should be repaired electively in cirrhotics before they develop complications with an attempt to aggressively control ascites before and/or after repair. Inguinal hernia on the other hand has a lower risk of complications and a higher risk of recurrence after surgery. Hence, elective surgical repair of an inguinal hernia is not recommended in patients with cirrhosis. Isoflurane, desflurane, and sevoflurane have only minimal hepatic metabolism (<0.2%), which makes them, along with nitrous oxide, the best anesthetic choices for patients with liver disease. Propofol is preferred to benzodiazepines as a narcotic and among opioids, sufentanil and remifentanil are preferred. Contraindications to elective surgery in liver disease include: acute viral hepatitis, alcoholic hepatitis, acute liver failure, acute renal failure, severe coagulopathy, hypoxemia and cardiomyopathy.

3. Correct answers: 1, 4 and 5

Cardiorespiratory failure has been identified as the commonest cause for ICU readmission after liver transplantation (LT) and cardiovascular events are the leading cause of non-graft related death among LT recipients. Conventional coagulation tests (CCTs), even when put together, do not provide a complete picture of the coagulation status. Tests which assess the viscoelastic properties of whole blood, like thrombelastography (TEG), rotation thrombelastometry (ROTEM) and sonoclot overcome the limitations of CCTs and complement them. These tests are repeated frequently during the surgery for correction of coagulopathy and reduce blood loss and transfusions. Normal glucose metabolism, with increased insulin requirement, could be a sign of a well functioning allograft posttransplant, whereas hypoglycemia can be an ominous sign of compromised liver recovery. However, hyperglycemia can lead to increased risk of liver allograft rejection, surgical site infection and increased mortality. Hence, frequent glucose monitoring with modest target of blood glucose of <150 mg/dL is advised. Serum potassium levels are independent predictors of death after liver transplantation. Hypokalemia is often secondary to diuretic therapy whereas hyperkalemia is characteristically seen following organ reperfusion. Variables associated with clinically significant hyperkalemia include higher baseline potassium, amount of red cells transfused, organ recovery after cardiac death, longer warm ischemia time, and longer donor hospital stay. The most common acid–base disturbance in cirrhosis is respiratory alkalosis. The C-fibers located in alveolar epithelium respond to increased interstitial lung water by signaling the respiratory center to cause rapid shallow breathing. On the other hand lactic acidosis is common during transplantation. Loss of base equivalents starts during the dissection phase and accelerates during the anhepatic stage. A further rise in plasma lactate concentration occurs immediately after graft reperfusion. Maximal acidosis and base deficit are therefore seen in the first several minutes after graft reperfusion and the main consequence of metabolic acidosis is myocardial depression. Early recognition of metabolic disturbances and their subsequent treatment improves outcome and decreases perioperative mortality.

4. Correct answers: 2 and 3

Patients with chronic liver disease have 14–15 times higher incidence of tuberculosis. Also, they are more likely to have extra-pulmonary tuberculosis (TB) like TB peritonitis and disseminated TB. Diagnosis of TB in cirrhosis poses a challenge. Due to immune
dysfunction in cirrhosis tuberculin skin test can be falsely negative and is positive in only 20–25% of cases. Also, Adenosine deaminase level has only 30% sensitivity in TB peritonitis in patients with cirrhosis. Treatment of TB in cirrhosis is also difficult. In the presence of preexisting liver disease, the likelihood of drug-induced hepatitis may be higher. Secondly, the outcome of drug-induced hepatitis in patients with marginal hepatic reserve may be serious, even fatal. Thirdly, monitoring of drug-induced hepatitis may be confounded in the presence of underlying liver disease due to fluctuating liver function tests related to the preexisting liver disease. Isoniazid itself is not hepatotoxic; toxicity is mediated through its metabolite, hydrazine. Isoniazid is metabolized in the liver through two main pathways. Acetyl hydrazine, a non-toxic metabolite, is formed when metabolism proceeds along the N-acetyltransferase 2 (NAT 2) pathway while hydrazine, the toxic metabolite, is formed when it proceeds along the amidase pathway. Thus, slow acetylators have higher risk of isoniazid-induced hepatotoxicity.

5. Correct answers: 2 and 3

Up to 12% of patients receiving isoniazid may have transaminitis. Majority of these are self limited and asymptomatic. Age appears to be the most important factor in determining the risk of isoniazid-induced hepatotoxicity. Hepatic damage is rare in patients less than 20 years old; it is observed in 0.3% of those in the 20–34 years age group, increasing to 1.2% in the 35–49 years age group and 2.3% in those older than 50 years of age. Mechanism is idiosyncratic, and rechallenge with isoniazid can be tried once enzymes have returned to normal. Conjugated hyperbilirubinemia is seen with rifampicin due to inhibition of the major bile salt exporter pump, impeding secretion of conjugated bilirubin at the canalicular level. Occasionally rifampicin can cause hepatocellular injury although less commonly than isoniazid or pyrazinamide but importantly it can potentiate hepatotoxicity of other antitubercular drugs when given in combination. Hepatotoxicity is the most serious side effect of pyrazinamide and is usually dose dependent. When administered in a dose of 40–50 mg/kg orally, signs and symptoms of hepatic disease appear in about 15% of patients, with jaundice in 2–3% and death due to hepatic necrosis in rare instances. Lower doses employed currently (15–30 mg/kg per day) are much safer. Pyrazinamide may also exhibit idiosyncratic hepatotoxicity. Chronic hepatitis B, including inactive carriers are at a higher risk of antitubercular therapy (ATT) induced hepatotoxicity. Amongst 110 inactive HBsAg carriers and 97 controls without HBV infection, 38 inactive HBsAg carriers (35%) and 19 control subjects (20%) developed elevated liver enzyme levels during ATT (P = 0.016). A higher proportion of inactive HBsAg carriers who received ATT evidenced moderate-to-severe drug-induced hepatotoxicity and the liver injury was also more severe by histological assessment in the hepatitis B carriers when compared to controls.

6. Correct answers: 1, 3 and 4

Earlier it was believed that majority of cases in India are due to inferior vena cava (IVC) occlusion with membranous obstruction of IVC being the common cause. However, recent studies have shown that similar to the West, isolated HV thrombosis is most common followed by combined occlusion followed by isolated IVC obstruction and IVC thrombosis is more common than IVC membrane. A hypercoagulable state is identified in 86% cases and only 4% of cases are due to IVC membrane. The ascitic fluid analysis is similar to the composition of ascites seen in patients with cardiac or pericardial disease. The serum–ascitic albumin gradient is high reflecting portal hypertension, but the total protein level in the ascitic fluid is usually more than 2.5 g/dL, reflecting relatively preserved liver function compared to ascites in cirrhotics. Doppler of the hepatic venous outflow tract is the technique of choice for initial investigation with a sensitivity and specificity of 85% or more. Mere non-visualization of the hepatic veins is not diagnostic of BCS as it can be seen in advanced cirrhosis of any etiology. Absence of flow or retrograde flow in the hepatic veins and the presence of thrombosis within the hepatic veins or inferior vena cava suggest BCS. Other specific features are intrahepatic comma shaped or subcapsular collateral veins which can be seen in 80% cases of BCS, a spider-web appearance usually located in the vicinity of hepatic vein ostia, together with the absence of a normal hepatic vein in the area, an absent or flat hepatic vein waveform without fluttering and a hyperechoic cord replacing a normal vein. Transjugular intrahepatic portosystemic shunting (TIPS) is considered the standard mode of portosystemic shunting in those who do not improve or develop severe or recurrent complications despite medical treatment, angioplasty or stenting. If all hepatic vein ostia are blocked and inaccessible the shunt is directly placed between the retrohepatic vena cava and the portal vein, a procedure known as direct intrahepatic portosystemic shunt (DIPS). DIPS has shown 100% technical success rate and patency rates similar to TIPS.

7. Correct answers: 1 and 2

Oxidative stress, inflammation and neurosteroids have synergistic role in pathogenesis of hepatic
encephalopathy (HE). In the setting of intestinal barrier dysfunction and systemic inflammation, gut flora and their by-products such as ammonia, indoles, oxindoles and endotoxin play an important role in the pathogenesis of HE. Presence and severity of minimal HE in cirrhosis was not related to the severity of liver disease and plasma ammonia concentration but to markers of inflammation. A significant association between infection or systemic inflammatory response and grade 3/4 HE has also been demonstrated, while HE grade or coma score did not correlate with ammonia, biochemistry and model for end-stage liver disease (MELD) score.

Bacterial overgrowth and impaired intestinal barrier integrity results in endotoxemia, i.e. release of bacterial endotoxins in circulation, mainly consisting of lipopolysaccharides (LPS), flagellin, peptidoglycan, and microbial nucleic acids. They are also termed as ‘pathogen-associated molecular patterns (PAMPs)’. Endotoxemia initiates liver damage through its interaction with toll-like receptors (TLRs). Fecal microbiome differs significantly between cirrhotic patients and controls. There is a significantly greater abundance of Lachnospiraceae and Ruminococcaceae in the control group while Enterobacteriaceae, Fusobacteriaceae, Alcaligenaceae, Lactobacillaceae, and Leuconostocaceae are significantly lower in the controls compared with cirrhotic patients. Alcaligenaceae abundance was significantly associated with poor cognitive performance. The mechanism of action of lactulose is incompletely understood and it’s effect on gut microbiota is likely to be related, in part, to alterations in gut flora and their by-products. Gut bacterial function, rather than a change in the microbiome composition, may be responsible for the effects of lactulose, as lactulose withdrawal does not significantly change the gut microbiota composition.

In this study, a shift in choline metabolism from gut bacterial metabolism to the formation of glycine, creatinine and ammonia was associated with the recurrence of HE. Although HE is linked to substantial derangements in the gut microbiome, with significant fecal overgrowth of potentially pathogenic species, small intestinal bacterial overgrowth and a pro-inflammatory milieu, there is no significant difference in the fecal microbiome families between the HE and no-HE patients. Therefore, the colonic mucosal microbiome rather than stool microbiome may be associated with these derangements in cirrhotic patients with HE.

8. Correct answers: 2 and 5

Majority of the patients with primary sclerosing cholangitis (PSC) have both the intra- and extra-hepatic bile duct abnormalities. Twenty five percent may have only intrahepatic disease. Isolated disease of the extrahepatic ducts is seen in only about 5% cases. The gallbladder, cystic duct and pancreatic duct may also be involved. Magnetic resonance cholangiography (MRC) is non-invasive and avoids radiation exposure and is now the diagnostic imaging modality of choice for PSC. Sensitivity and specificity of MRC is 80% and 87%, respectively. Endoscopic retrograde cholangiography (ERC) is invasive procedure and has potentially serious complications like pancreatitis and bacterial cholangitis and is not used routinely for diagnostic purposes. ERC still has a useful role in excluding large duct PSC where MRC views may not be optimal in diagnosing PSC. A dominant stricture is a stenosis with a diameter of <1.5 mm in the common bile duct or <1 mm in the hepatic duct and is seen in 45–58% of patients on follow-up. It should raise the suspicion of the presence of a cholangiocarcinoma. Although cholangiocarcinoma develops in approximately 10%–15% of PSC patients, stenotic lesions are far more often benign than malignant in nature. Inflammatory bowel disease (IBD) is common in patients with PSC, seen in 60–80% patients of PSC. Ulcerative colitis is seen in 48–86%, and Crohn disease in 13% of patients with IBD. Although IBD can be diagnosed at any time during the course of PSC, in the majority diagnosis of IBD precedes that of PSC by even by several years. However, IBD can also occur some years after the diagnosis of PSC, even after liver transplantation for PSC. Mass lesions in the gallbladder are not uncommon in patients with PSC, occurring in 6–14% of cases, and 56–57% of these lesions prove to be malignant. In view of high-risk malignancies of gallbladder polyps in patients with PSC, cholecystectomy is recommended irrespective of size of the polyp.

9. Correct answers: 2 and 3

Antimitochondrial antibodies (AMA) are present in 90–95% patients with primary biliary cirrhosis (PBC) and are highly disease-specific, found in less than 1% of normal controls. Both immunofluorescence and enzyme-linked immunosorbent assays can be used to test for AMA. Patients who lack AMA but have clinical presentation and liver histology identical to patients with typical AMA-positive PBC are called AMA-negative PBC. Almost all will have antinuclear and/or antismooth muscle antibodies. These patients have similar course of illness and response to ursodeoxycholic acid (UDCA) as AMA-positive patients. High dose UDCA (13–15 mg/kg/day) is the only drug approved for the treatment of patients with PBC and several randomized trials and combined analyses have shown that UDCA improves biochemistry as well as delays histologic progression and improves transplant free survival. However, fatigue associated with PBC is not improved by UDCA and no therapy is approved for
the treatment of fatigue. Modafinil at doses of 100–200 mg/day improves fatigue as assessed by the PBC-40 questionnaire. Sjogren’s syndrome and Raynaud’s disease are significantly more common in PBC patients than age and gender-matched population. They may also have a higher chance of autoimmune thyroid disease, arthritis, scleroderma and renal tubular acidosis.

10. Correct answers: 1, 3 and 4

Overlap syndromes are autoimmune hepatopathies presenting with both hepatic and cholestatic pattern on biochemistry and histology. Overlap between autoimmune hepatitis and PBC is the most common occurring in about 10% of adults with AIH or PBC, whereas AIH-PSC overlap syndrome is seen in 6–8% of children and young adults with AIH or PSC. In a series of 55 children who had clinical, biochemical and histological features of AIH, 27 had cholangiographic findings suggestive of PSC. The term autoimmune sclerosing cholangitis was coined for this overlap of PSC and AIH. Existence of overlap of PSC and PBC is controversial and has been documented in one case. The components of the overlap syndrome may occur sequentially, even appearing years after one other. Due to low prevalence of overlap syndromes no randomized controlled trials have evaluated treatment regimens. An initial trial of high dose UDCA, with addition of steroids for non-responders seems to be a reasonable approach and has achieved biochemical response in up to 85% patients in one study.

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REFERENCES
Bajaj JS, Hylemon PB, Ridlon JM, et al. Colonic mucosal micro-

Bajaj JS, Hylemon PB, Ridlon JM, et al. Linkage of gut microbiome

Dhiman RK. Gut microbiota, in

Shawcross DL, Davies NA, Williams R, Jalan R. Systemic in

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