Hepatobiliary Quiz Answers—17 (2016)

Answers to Multiple Choice Questions

1. Correct Answers: A, C, D, and E

Hepatorenal syndrome (HRS) represents a life-threatening form of renal failure in patients with decompensated cirrhosis. It occurs in 18% of patients with decompensated cirrhosis annually.¹ Terlipressin, along with volume expansion-using albumin, is one of the most effective forms of therapy, leading to a reversal in about a third of cases. Baseline serum creatinine is the strongest predictor of reversal of HRS. Patients with serum creatinine <3.0 mg/dl are most likely to benefit from treatment with terlipressin.² As their renal function worsens, their likelihood of benefiting from terlipressin declines. Terlipressin also decreases renal arterial resistance and plasma renin activity in patients with cirrhosis. However, there is also a modest reduction in cardiac output.³ There is evidence to suggest that continuous infusion of terlipressin may be more effective and better tolerated than intermittent boluses in the treatment of HRS.⁴ Dopamine alone has been ineffective in HRS, and has no effect on plasma renin activity in these patients.⁵ However, a recent study showed efficacy of dopamine both in lowering plasma renin activity and in treatment of HRS when used in combination with albumin and furosemide.⁶

2. Correct Answers: A, B, and E

Non-selective beta-blockers (NSBBs) are the first-line therapy for primary as well as secondary prophylaxis of esophageal variceal bleeding.⁷ NSBBs lead to blockade of β -2 receptors in the splanchnic vascular bed leading to vasoconstriction, and that of β -1 receptors in the heart leading to reduced cardiac output. This leads to reduction in portal flow and hepatic venous pressure gradient, thereby decreasing the chances of variceal bleeding. NSBBs also have non-hemodynamic effects, as they increase gut motility and reduce bacterial translocation, thereby limiting systemic inflammation.^{8,9} Anticarcinogenic effects have been described by virtue of reduction in bacterial translocation, thereby limiting the load of pro-inflammatory cytokines from the gut to the liver. NSBBs also inhibit catecholamine driven cancer cell migration, angiogenesis, invasiveness, and proliferation. However, there have recently been concerns regarding poor outcome in patients with decompensated cirrhosis with refractory ascites.^{10,11} A recent meta-analysis of twenty-three randomized trials revealed that NSBBs may decrease incidence of HCC with a risk difference of 2.6%. However, there was no effect of NSBB on HCC mortality or all-cause mortality.¹² Another meta-analysis of 3 randomized and 8 observational trials confirm the absence of an increased mortality with NSBBs in patients with decompensated cirrhosis, even with refractory ascites.¹³ Also, patients on treatment with NSBBs

when admitted with ACLF had a significantly lower mortality and a less severe inflammatory response.¹⁴ Thus, the existing evidence does not favor an adverse long-term outcome of NSBBs on patients with cirrhosis. However, evidence in this field is still evolving.

3. Correct Answers: A, B, and C

The appearance of the low molecular weight, Non-Transferrin Bound Iron (NTBI) in the blood is the primary pathogenic event resulting in iron overload. This results in oxidative damage, which is central in the pathogenesis of iron toxicity.¹⁵ Once the homeostatic antioxidant mechanisms are overwhelmed by the labile NTBI, oxidative stress arises, leading to lipid peroxidation of cell membranes and damage to proteins and DNA by adduct formation.^{16,17} Kupffer cells accumulate iron and lead to activation of stellate cells and myofibroblasts thereby promoting fibrogenesis.¹⁸ Iron overload also leads to necroinflammatory activity, interferes with immunologic tumor surveillance, and a direct mutagenic effect, predisposing to the development of Hepatocellular Carcinoma (HCC) even in the absence of cirrhosis.¹⁵ The pathophysiology of iron overload is primarily affected by the protein Hepcidin. Hepcidin is an antimicrobial peptide that evolved as part of the innate immune defense. Its main effect is to induce a state of iron lockdown, preventing pathogens from using iron to grow and proliferate during infection. It binds to ferroportin, a membrane protein responsible for making iron available into the bloodstream. Hepcidin leads to the degradation of ferroportin, blocking iron transfer to the circulation.¹⁹ Oxidative stress in the liver secondary to alcohol or chronic viral hepatitis can lead to suppression of hepcidin, leading to excess iron accumulation and progression of underlying disease.^{20,21}

4. Correct Answers: A, D, and E

Intrahepatic cholestasis of pregnancy (ICP) classically presents in the third trimester with pruritus, raised serum bile acids, and spontaneous resolution after delivery. The incidence of ICP varies widely (0.2–25%) with geographic location.²² Many large population-based studies describe ICP more frequently in patients with hepatitis C virus (HCV) infection. Such patients also have higher HCV viral load compared with those without ICP.^{23–25} It is also more common in women with prior history of ICP, multi-fetal gestation, and advanced age.²² Though classically a disease of the third trimester, it has been seen to occur as early as seventh weeks of gestation.²⁶ A marked increase in maternal serum estrogen levels (e.g., ovarian hyperstimulation) may trigger ICP in the first trimester.²⁷ Earlier occurrence of ICP is associated with a worse fetal outcome.²⁸

Serum bile acid level is the most sensitive and specific marker for the diagnosis of ICP, after exclusion of other causes of cholestasis. Higher bile acid levels (>40 mmol/L) correlate with higher rates of fetal complications,

including preterm delivery, meconium-stained liquor, and even perinatal death.²⁹ Maternal outcome is good, with symptoms rapidly subsiding after delivery and complete recovery. However, a recent large population based study showed a higher risk of hepatobiliary cancer, autoimmune diseases, and cardiovascular diseases in women with ICP.³⁰

5. Correct Answers: A, B, and E

Juvenile onset hemochromatosis is characterized by early onset and severe disease. It is usually due to mutations of HJV (Hemojuvelin gene) or loss of HAMP (Hepcidin gene), and is seen equally in both genders. These patients usually present in the second decade, typically with features of hypogonadism.¹⁵ Dilated cardiomyopathy is a common complication, which leads to death by the end of the third decade if untreated. The hepatic complications seem less common, probably because the dominant symptoms are secondary to endocrine and cardiac manifestations. However, there is profound hepatocellular damage, with cirrhosis developing in up to 40% of patients even at a young age.³¹

6. Correct Answers: A, C, and D

Primary Biliary Cirrhosis (PBC), now rechristened as Primary Biliary Cholangitis, is a chronic autoimmune cholestatic disease characterized by periportal inflammation and progressive destruction of the small and medium intrahepatic bile ducts, leading to cholestasis, fibrosis, and eventual progression to cirrhosis and end stage liver disease. 53% of patients with PBC had one other autoimmune condition, while 20% had 2 or more autoimmune conditions.³² Up to 6% cases may have an affected family member.³³ Ursodeoxycholic acid (UDCA) is the only drug approved by the Food and Drug Administration (FDA) for the treatment of PBC. However, about a third of the patients show an incomplete response. Response to UDCA (variably defined as reduction in alkaline phosphatase (ALP) to less than 1.67 to 3 times upper limit of normal in different studies) is a strong predictor of long-term outcome.³⁴ Bilirubin also has been evaluated as a prognostic indicator, and a recent meta-analysis indicated that high levels of bilirubin and ALP correspond to poorer long-term outcomes.³⁵ Pruritus is seen in 40–80% of patients with PBC.³⁶ Patients who present with pruritus early have poorer response to UDCA and a worse clinical outcome.³⁷

Budesonide, a non-halogenated glucocorticoid absorbed in the small bowel with a high first pass metabolism has been tried in PBC with encouraging results in pre-cirrhotic PBC as an add-on to UDCA. However, late stage PBC patients showed significant increase in budesonide plasma levels and developed serious side effects.³⁵

7. Correct Answers: C, D, and E

Direct-acting antiviral agents (DAAs) are associated with high rates of sustained virologic response in HCV infection. However, some patients still do not respond to DAAs. Risk

factors include advanced stages of liver fibrosis, previous antiviral therapy, and high baseline viral load. Presence of Resistance Associated Variants (RAVs) has also been associated with poorer response to treatment. However, presence of RAVs at baseline leads only to a small reduction in SVR, especially with DAAs, which have a high genetic barrier to resistance. Treatment failure usually occurs only if other negative predictive host or viral factors are present concomitantly. However, in patients with virologic breakthrough during treatment, RAVs are almost always observed.³⁸

Antiviral activity of DAAs in different genotypes is influenced by the naturally occurring RAVs, especially NS3 proteases. Simeprevir has poor response rates in genotypes 2 and 3 due to the presence of naturally occurring high level RAVs, which are absent in genotype 4 and 6.^{39,40} NS3 protease RAVs are commonly associated with replicative impairments, and thus are replaced rapidly by wild-type virus after stopping protease inhibitor based therapy. Conversely, NS5A RAVs are more durable and confer high level of resistance.^{41–43}

8. Correct Answers: A, C, and E

Hepatitis E virus (HEV) infection is classically an acute, self-limited hepatitis, which may lead to acute liver failure in 1–4% cases. Chronic hepatitis E (CHE) is rarely seen, mainly in immunosuppressed individuals after solid organ transplant, acquired immunodeficiency syndrome, and in patients on cancer chemotherapy.⁴⁴ CHE is almost exclusively reported with genotype 3, with a single case report of genotype 4.^{45,46} 60% of solid organ transplant recipients exposed to HEV develop CHE, and 10% progress to cirrhosis within 2 years.⁴⁷

CHE is diagnosed by demonstration of HEV RNA in the stool or serum by viral nucleic acid tests at least 3 months after the time of detection of HEV. Patients usually present with vague symptoms, fatigue being the commonest.^{48–51} Of the extrahepatic manifestations, neurological features are the most common, and include pyramidal signs, ataxia, proximal myopathy, encephalitis, cognitive dysfunction, and peripheral neuropathy. Renal manifestations include membranoproliferative glomerulopathy, membranous glomerulonephritis, IgA nephropathy and cryoglobulinemia. Many of these patients improve with ribavirin therapy.

9. Correct Answers: A, C, and E

Cytomegalovirus (CMV) is the most common viral infection after liver transplantation, seen in upto 50% of recipients. It is usually seen 1 to 4 months post transplant.^{52–55} Half of these cases will have symptomatic CMV disease. Patients present with fever and jaundice, and liver function tests show a cholestatic pattern. Liver biopsy shows cholestatic features, with microabscesses and typical intranuclear inclusion bodies.⁵⁶ CMV may also be a risk factor for vanishing bile duct syndrome and chronic liver graft rejection.^{57–59} Ganciclovir is used for treatment of established CMV infection.

10. Correct Answers: A and E

Features of metabolic syndrome are very common among post-transplant patients, with over two-thirds having at least one component, and over half fulfilling the criteria for metabolic syndrome as per National Cholesterol Education Program's Adult Treatment Panel III (ATPIII). Obesity is seen in over a third of transplant recipients. Most patients gain weight after the procedure, especially in the first 1–3 years.^{60–62} If lifestyle measures fail to bring about weight loss, medical or surgical options can be considered. Orlistat has been tried in liver transplant recipients with a good safety profile, but with no clear evidence of efficacy.⁶³ Other drugs for weight loss have not been evaluated. Surgical option may be considered in refractory cases, with restrictive procedures being favored over malabsorptive due to the need for continued access to the biliary tree and preventing malabsorption of drugs. The weight loss should be gradual, as rapid weight loss can adversely affect allograft function. One-third of liver transplant recipients develop long-term type 2 diabetes mellitus. These patients managed the same as non-transplant patients. Metformin remains the first-line therapy. In the immediate post-transplantation period, patients require insulin administration. However, as the patient transitions to the outpatient setting, they should be shifted to oral antidiabetics.⁶⁴ Management of hypertension includes the usual sodium restriction, exercise, smoking cessation, and avoidance of alcohol intake. A reduction of immunosuppression should be considered if feasible. Dihydropyridine calcium channel blockers are the first-line drugs as they ameliorate renal vasoconstriction of calcineurin inhibitors.⁶⁵ Angiotensin converting enzyme inhibitors and angiotensin receptor blockers might not be tolerated early after liver transplantation due to renal dysfunction and hyperkalaemia secondary to high-dose immunosuppression, but are better tolerated when reduced dose of immunosuppressants are used.

Conflict of Interest

The authors have none to declare.

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