Hepatobiliary Quiz (Answers)—13 (2015)

Answers to Multiple Choice Questions

1. Correct answers: A, C and D

Liver cells are the sole site of synthesis of albumin. Usual daily production is about 10–15 g per day, which may be increased 3–4 fold when required. Of the total body albumin, 30%–40% is retained in the intravascular compartment, while the rest 60–70% remains in the interstitial spaces.¹ The half-life of albumin is 12.7–18.2 days in a young healthy adult. However, circulatory half-life of albumin is approximately 16–18 h as about 5% of albumin is exchanged between intravascular and interstitial spaces every hour. Degradation of albumin is predominantly in the muscles, liver and kidneys.² The oxidative forms of albumin—non-mercaptalbumin 1 and non-mercaptalbumin 2 increase with increasing severity of liver failure.³

2. Correct answer: A

According to the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines,⁴ all patients who develop SBP should be treated with broad spectrum antibiotics and intravenous albumin. However, this is most advantageous in patients with bilirubin >4 mg/dL and serum creatinine >1 mg/dL at the time of diagnosis.

Post-paracentesis circulatory dysfunction (PPCD) is an important concern in managing patients with refractory ascites. Various plasma expanders and vasoconstrictors have been tried in an effort to prevent this complication, but albumin is the one to have shown the most clinical benefit.⁵ 8 g of albumin per liter of ascites removed is the treatment of choice to prevent PPCD in patients undergoing large volume paracentesis (>5 L).

There has been some evidence that albumin administration in patients with hepatic encephalopathy may show improvement in hepatic encephalopathy.⁶ However, these findings were not confirmed by a more recent multicenter trial.⁷

Effective hypovolemia has the central role in the pathophysiology of complications of cirrhosis.¹ Thus, the major aim in management is to preserve intravascular volume. Correction of hypoalbuminemia is not the goal, and therefore serum albumin levels cannot be used to guide intravenous albumin therapy.⁸ There has been some evidence on use of albumin in non-SBP sepsis having a beneficial effect on survival. However, this was not found to be significant, and is not currently recommended.

3. Correct answers: D and E

Prevalence of portal vein thrombosis (PVT) in liver cirrhosis ranges from 1% to 28% of patients in various studies.⁹ The prevalence is found to be higher in patients with more advanced cirrhosis.^{10–13} All patients of cirrhosis must be screened for presence of PVT. Doppler

ultrasonography and computed tomography (CT) are both sensitive and specific for its detection.^{14,15} Magnetic resonance imaging can be used as an alternative, especially in patients having renal failure. However, it has a lower resolution than CT.¹⁶

Patients of cirrhosis with PVT have higher morbidity than those without PVT. These patients are also more likely to have refractory bleed, as well as higher likelihood of rebleeding.¹⁷

Patients with PVT undergoing liver transplantation are more likely to have postoperative complications and higher mortality. This is related to a more complex surgical procedure, greater requirement of blood transfusions, increased risk of complications such as primary non-function or dysfunction, hepatic artery thrombosis, re-laparotomy, postoperative pancreatitis, sepsis, and renal failure.^{18–20} The mortality rate also increases with the extent of PVT.²¹

4. Correct answers: C and E

It is still unclear whether it is beneficial to routinely anticoagulate all patients with cirrhosis who are incidentally found to have PVT on imaging. However, those patients who are on the waiting list for liver transplantation should be given anticoagulation. Patients who achieve even partial recanalization have a higher survival rate after liver transplantation. Over 80% patients who achieve recanalization survive at 2 years post-transplantation as opposed to about half of those with complete PVT.¹³

Both low molecular weight heparin (LMWH) and vitamin K antagonists (VKAs) seem to be equally effective in treatment of PVT. LMWH has the advantage of not affecting INR values and therefore does not interfere with MELD or Child scoring. However, there is limited information on the pharmacodynamic profile of LMWH in cirrhotic individuals and hence it is difficult to determine the optimal dose of LMWH. Also, monitoring of anti-Xa activity to guide therapy is unreliable in cirrhosis. It requires daily subcutaneous injections. On the other hand, VKAs are convenient as they are given orally. However, defining adequate anticoagulation in already altered INR is difficult. There is a potential risk of further lowering of protein C and they are associated with extensive drug interactions.^{22–25}

The aims of anticoagulation are to achieve recanalization of the portal vein and to prevent extension of the thrombus to the splenic and superior mesenteric vein. A recanalized portal vein allows a conventional end-to-end portal venous anastomosis without adding to the complexity of orthotopic liver transplantation (OLT). Therapy with anticoagulation has neither been associated with increased blood loss during liver transplantation nor found to precipitate variceal bleeding.¹³ However, it can make the bleeding more severe.

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5. Correct answers: B and D

In patients with compensated cirrhosis, there is a balanced reduction in both pro- and anticoagulant proteins. Thus there is only a little change in hemostatic potential. During decompensation, this balance may get skewed to either side. Among the procoagulant factors, levels of factor VIII and vWF increase, while the remaining are reduced. Apart from abnormalities of the coagulation cascade, these patients also have defective platelet function and number which may lead to a bleeding tendency. However, this gets counterbalanced by higher concentration of factor VIIIa/vWF, which increases platelet adhesion.^{26–28}

A thrombophilic genotype may be identified in up to 70% of patients with cirrhosis and PVT. The most common abnormalities found in these patients were polymorphisms of methylene-tetrahydrofolate reductase and prothrombin gene.^{29–31}

6. Correct answers: B, D and E

Sinusoidal obstruction syndrome (SOS) is an obliterative venulitis of the terminal hepatic venules. It is commonly seen in patients undergoing Hematopoietic Stem Cell Transplantation (HSCT), chemotherapy for liver metastasis/acute myeloid leukemia, radiation induced liver injury, herbal medications, liver transplantation, and in patients with veno-occlusive disease with immunodeficiency syndrome.³² HSCT is one of the most common causes of SOS. It was previously thought to occur in up to 60% patients,³³ but the overall incidence is now found to be 13.7%.³⁴ The incidence has declined over the years due to reduction in intensity of conditioning regimens for HSCT, and reduction in use of unrelated donors.³⁵ Among these patients, higher risk is seen in those patients who undergo transplantation for malignancy, are over 15 years of age, have abnormal pretransplant serum levels of liver enzymes and have lymphomas or solid tumors with hepatic metastasis.^{35–39}

7. Correct answers: A and B

Experimental animal studies have shown that sinusoidal endothelial cell (SEC) swelling is one of the initial changes in the pathogenesis of SOS. There is increased adhesion of leucocytes and red blood cells dissect beneath the endothelial cells into the space of Disse and parenchyma. Kupffer cells are lost and replaced with influx of monocytes. Together these factors compromise the sinusoidal lumen and leads to a sluggish flow in the sinusoids. The lumen gets occluded by aggregation of sinusoidal lining cells, red blood cells, and adherent monocytes thus eventually leading to SOS.⁴⁰

Glutathione depletion seems to play the central role in the pathogenesis of SOS. Other important factors are nitric oxide depletion, vasoconstriction, increased expression of matrix metalloproteinase-9 (MMP9) and vascular endothelial growth factor and activation of clotting cascade.^{40–43} Increased expression and release of MMP9 is an early

change in the pathogenesis of SOS. MMP9 inhibitors have been found to prevent SOS in animal models.⁴¹

8. Correct answers: C and E

Of all the patients who undergo OLT, up to 80% of patients develop infections within one year.⁴⁴ Of these, bacterial infections are most common, accounting for about 70%, followed by viral (20%) and fungal infections (8%). Bacterial infections are the most frequent and dangerous complication among OLT patients and generally occur within 2 months of transplantation, most frequently in the abdominal cavity, surgical sites, blood stream, and urinary tract and respiratory infections.^{44–47}

The risk of infections depend on two major factors-the level of immunosuppression and the exposure to infectious agents. Immunosuppressants blunt the adaptive immune response, making the recipient heavily dependent on the innate immunity. Thus any genetic defects in innate immune system like toll like Receptors and lectin pathway make the patient highly vulnerable to infections.^{48–50}

MELD >20 is a significant risk factor for developing infection within the first 30 days after OLT. Other risk factors include albumin level <2.8 g/dL, intraoperative erythrocyte transfusion more than 6 units, intraoperative fresh frozen plasma transfusion more than 12 units, bilioenteric anastomosis, postoperative intensive care unit stay more than 6 days, and postoperative length of hospital stay more than 21 days.⁵¹

Overall infectious complications are similar between deceased and live donor liver transplantation (LDLT). However, intra-abdominal infections seem to be more frequent in the LDLT group.⁵² Pulmonary infections are also found to be more common in LDLT patients.⁵³

9. Correct answers: A and C

Tuberculosis may occur within 2 weeks in patients undergoing solid organ transplantation. Post OLT, tuberculosis involve the lungs in 51–64% patients. Of the extrapulmonary sites, gastrointestinal tract is involved most often. Other sites involved include muscle, joints, skin, and central nervous system, and lymph nodes.^{54–56} Reactivation of latent infection is the most common mechanism of developing tuberculosis in this population. Non-tubercular mycobacterial infections are less common in post-OLT patients. When present, they most commonly manifest as pulmonary and multifocal cutaneous infections.⁵⁷

Treatment of tuberculosis in this population has its own concerns. Rifampicin is a strong enzyme inducer and may increase metabolism of cytochrome P-450 significantly. This may increase the dose requirement of calcineurin inhibitors by 2–5 times. Rifabutin may be considered, as it is a weaker inducer of the cytochrome P-450 enzymes. However, data on the use of this drug in transplant recipients remains limited.⁵⁸

10. Correct answers: A, C and D

After OLT the most frequently encountered fungal infection is candidiasis. It is the leading cause of invasive fungal infection. The most commonly isolated species are *Candida albicans* followed by *Candida glabrata* and *Candida tropicalis*. The gastrointestinal tract is often colonized with candidal species and is the most likely portal of entry, via translocation through the intestinal walls to extraluminal locations or due to spillage from bowel anastomosis.^{59,60} *Candida* may cause intra-abdominal abscesses, peritonitis, or may disseminate hematogenously to other organs. Need of hemodialysis post-operatively, prophylaxis for spontaneous bacterial peritonitis, and retransplantation are important risk factors for invasive candidiasis.^{61,62}

Cytomegalovirus (CMV) infections are common in post-OLT patients. Patients who develop CMV disease are at a higher risk for invasive candidal infections. Prophylaxis of patients at high risk for CMV disease, such as CMV antibody negative recipient receiving organ from an antibody positive donor, decreases the incidence of invasive candida infection.⁶³

Routine antifungal prophylaxis has been shown to decreased incidence of fungal infections, and mortality attributable to fungal infection in most studies. It is now routine practice among transplant centers to give antifungal prophylaxis post OLT.⁶⁴

Aspergillus is the next most common fungal infection in this patient population, of which *Aspergillus fumigatus* is the most common culprit.⁶⁵ The portal of entry is pulmonary, from where it may spread hematogenously to other organs in 50–60% cases.^{66,67} Diagnosis may be difficult and may require invasive investigations like bronchoscopy and bronchoalveolar lavage. High resolution CT of the chest may show 'halo sign' in early infection. Molecular tests like aspergillus galactomannan, 13-b-glucan, and aspergillus polymerase chain reaction aide the diagnosis.^{65,68–70}

Antifungal therapy for aspergillus should be started early as soon as there is a clinical suspicion. For treatment of invasive aspergillosis, voriconazole is the drug of choice. Other triazoles-itraconazole and posaconazole, caspofungin, or amphotericin B can also be considered.^{44,71}

Conflicts of interest

All authors have none to declare.

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