Hepatobiliary Quiz (Answers)—16 (2015)

Answers to Multiple Choice Questions

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

Liver transplant recipients are twice as prone to develop malignancies as compared to the general population.¹⁻⁴ The risk is most in patients transplanted for alcohol-related liver disease or primary sclerosing cholangitis (PSC).³⁻⁵ The most common malignancies in this population include dermatological cancers, post-transplantation lymphoproliferative disease and gastrointestinal, lung, oropharyngeal and gynecological solid tumors.

Screening strategies recommended for early detection are mostly similar to that in general population. Exceptions include an annual dermatological screening, as the risk of skin cancers up to 20-fold higher than general population,⁵ and annual colonoscopies in patients with PSC and inflammatory bowel disease, as they may have a 10 times higher risk compared to other liver transplant patients.⁶ In some patients with post-transplantation lymphoproliferative disease, reduction of immunosuppression alone might lead to regression of malignancy.⁷

2. Correct Answers: A, B, and E

Vascular invasion is an important feature of advanced hepatocellular carcinoma (HCC). Microvascular invasion cannot be visualized on imaging. However, macrovascular invasion is often seen as a malignant thrombus, and precludes transplantation as well as locoregional therapies.⁸⁻¹⁰ Portal vein invasion is more common, though hepatic veins may also be involved.

Due to the coagulation abnormalities and slow flow in the portal circulation in patients with cirrhosis, bland thrombi are also common. They may even arise superimposed on malignant thrombus, complicating the imaging picture.¹¹

Tumor thrombus may expand the vein, and are likely to be contiguous with the source HCC. There is streak-like enhancement within the thrombus in the arterial-phase owing to arterial neovascularity. Enhancement of tumor thrombus often follows enhancement of the source HCC.¹¹

3. Correct Answers: B and C

In transplant recipient patients, any pregnancy is deemed as high-risk pregnancy. They are more prone to develop pre-eclampsia and hypertension, and are more likely to deliver pre-term.¹²

Conception should be delayed till after the first year of transplant so that the patient is on the lowest dose of immunosuppression with stable allograft function. Steroid doses >20 mg/day of prednisolone have been associated with higher incidence of cleft palate.¹³ However, the

overall risk of structural malformations in liver transplant recipients remains similar to the general population.^{12,14}

Calcineurin inhibitors are considered to be low risk when used at the lowest possible dose.¹⁵ While they may be associated with low birth weight and renal impairment in the baby, no structural abnormalities in the fetus have been documented. They are also acceptable during breastfeeding.¹⁶⁻¹⁸ Mycophenolate mofetil is contraindicated during pregnancy and must be discontinued before conception.¹⁸ Oral contraceptives may be safely used in liver transplant recipients with good allograft function.^{14,19}

4. Correct Answers: B, C and E

Hepatitis C virus core-antigen (HCV-Ag) may be an alternative for diagnosis of hepatitis C, and monitoring of therapy.²⁰ HCV-Ag protein has a highly conserved sequence, which can be detected using enzyme-immunoassays.²¹ The assay is cheap, simple, and does not require skilled manpower, thereby enabling small laboratories where HCV RNA testing may not be feasible, to detect active HCV infection. Commercial automated platforms like Abbott Architect[®] are available which can perform both anti-HCV and HCV-Ag together.²⁰⁻²²

HCV-Ag is valuable in detection of HCV infection in seronegative hemodialysis patients, early treatment monitoring and as a cost-effective alternative to nucleic acid technology for the identification of blood donors in the pre-seroconversion window.²²⁻²⁷ However, the test needs further evaluation before it can replace the need for HCV RNA testing.^{28,29}

5. Correct Answers: A, C and E

Bilirubin encephalopathy, also known as kernicterus, is a syndrome of jaundice and encephalopathy in infants. It involves the deposition of unconjugated bilirubin into the cortical gray matter, predominantly the basal ganglia.^{30,31} Most common cause is a hemolytic anemia, usually due to Rh or ABO incompatibility. The risk of developing bilirubin encephalopathy is higher in neonates with low birth weight, hypothermia, anoxia, acidosis, sepsis, hypoalbuminemia, and meningitis.³²

The infants initially present with somnolence and hypotonia. Over several days, they develop the irreversible stage characterized by spasticity. Patients who survive the neonatal period may also develop choreoathetosis, sensorineural hearing loss, dental dysplasia, gaze abnormalities (particularly vertical gaze palsy) and mild mental retardation.³³

6. Correct Answers: A, B, C and E

Hemophagocytic lymphohistiocytosis (HLH) is characterized by fever, splenomegaly, cytopenias, jaundice, and hemophagocytosis in bone marrow, lymph nodes, liver and

other tissues.^{30,34} It may be primary (genetic), or secondary (acquired) to viral infections, autoimmune diseases or malignancies. It occurs secondary to excessive inflammation by a lack of normal downregulation of activated macrophages and lymphocytes.³⁵ Excessive cytokine production is a primary mediator of tissue damage and leads to multiorgan dysfunction. Immune activation is commonly initiated by an infection both in primary and secondary cases. The most common infectious trigger is viral infection, especially Epstein-Barr virus.³⁰

Clinically, the patients present with fever, hepatosplenomegaly, lymphadenopathy, jaundice (in more than 2/3 cases), and maculopapular rash. Neurological manifestations are seen in nearly half of the cases: encephalopathy, meningismus, and seizures are the most common.^{36,37} Laboratory abnormalities include cytopenias, hyperbilirubinemia, hypertriglyceridemia and hyperferritinemia. Serum fibrinogen levels are typically low. Histological evidence of hemophagocytosis is typically seen in bone marrow, spleen, and lymph nodes and even in the liver. Lymphocytic portal tract infiltration is also commonly seen.³⁸

7. Correct Answers: A, B, C and E

Cardiovascular manifestations of cirrhosis stem from involvement of both the heart as well as the vascular system. Cirrhosis leads to peripheral vasodilatation and hyperdynamic circulation. In response, the renin-angiotensin system is activated, leading to Na⁺ retention and volume overload. In order to maintain blood pressure, the cardiac output also rises.

Almost half of the patients with cirrhosis develop at least mild diastolic dysfunction. Though the mechanisms of myocardial stiffness and remodeling are unclear, it occurs more commonly in patients who have more advanced liver disease with higher MELD and Child-Pugh scores.³⁹⁻⁴¹

Patients with cirrhosis are also more likely to have a prolonged QT interval, independent of other known risk factors for this condition.^{39,42,43}

Hereditary hemochromatosis often involves the heart, and can lead to congestive heart failure, conduction abnormalities, and, rarely, a restrictive cardiomyopathy. In patients who develop heart failure, cardiac function improves with therapeutic phlebotomies.⁴⁴

Non-alcoholic fatty liver disease (NAFLD) may be considered a hepatic manifestation of the metabolic syndrome, and a risk factor for coronary artery disease. Institution of statin therapy in patients with abnormal liver enzyme levels attributable to NAFLD may reduce cardiovascular morbidity.^{45,46}

8. Correct Answers: B, C, D and E

Hepatopulmonary syndrome (HPS) is characterized by right-to-left shunting of blood within the pulmonary

vasculature via intrapulmonary vascular dilatations (IPVDs) leading to ventilation perfusion mismatch. Shunting occurs due to precapillary and postcapillary dilatation of the pulmonary microvasculature, as well as by the formation of new blood vessels.^{39,47,48}

HPS may occur in at least 10% of all patients with cirrhosis and portal hypertension, and in one third of patients evaluated for liver transplantation.⁴⁷⁻⁴⁹

HPS is a diagnosis of exclusion, and none of the tests are specific for its diagnosis. Presence of IPVDs may be seen in up to 60% of patients with cirrhosis, and their presence without hypoxemia is not associated with adverse events.⁴⁸⁻⁵¹

Spider angiomas are more common in patients with HPS.³⁹

9. Correct Answers: A, D and E

Antimicrobials are the commonest cause of idiosyncratic drug induced liver injury (DILI) worldwide. In Europe and USA, amoxicillin-clavulanate is the most common, in contrast to antituberculosis drugs in India.⁵²⁻⁵⁷ Idiosyncratic DILI is not dose dependent per se, however, most cases occur at a dose of more than 50 mg DILIs. Drugs that undergo over 50% hepatic metabolism are also more likely to lead to hepatotoxicity.⁵⁸

Age is a risk factor for specific drugs.⁵⁹ Children generally have a lower risk for DILI except from aspirin used during viral illnesses and valproate.⁶⁰⁻⁶² Women do not seem to be at an increased overall risk for DILI, however, they are more likely to progress to acute liver failure.^{59,63,55}

10. Correct Answers: B and E

Amoxicillin-clavulanate is the most frequent cause of idiosyncratic DILI in several European and American series.⁶⁴⁻⁶⁷ The incidence of DILI is much higher with the amoxicillin-clavulanic acid combination than with amoxicillin alone.^{68,69} The risk increases with age, and males are at a slightly greater risk. Presence of HLA DRB1*15 and DQB1*06 and double-null heterozygosity for glutathione S-transferase (GSTT1/GSTM1) is also associated with a higher risk.⁷¹ Young patients are more likely to have a hepatocellular pattern of DILI, while older patients are more likely to have a cholestatic or mixed pattern. Most patients recover within 4-6 months following DILI.^{65,71,72}

REFERENCES

1. Watt KD. Keys to long-term care of the liver transplant recipient. *Nat Rev Gastroenterol Hepatol*. 2015;12:639-648.
2. Fung JJ, Jain A, Kwak EJ, Kusne S, Dvorchik I, Eghtesad B. De novo malignancies after liver transplantation: a major cause of late death. *Liver Transpl*. 2001;7(11 (suppl 1)):S109-S118.
3. Schrem H, Kurok M, Kaltenborn A, et al. Incidence and long-term risk of de novo malignancies after liver transplantation with implications for prevention and detection. *Liver Transpl*. 2013;19:1252-1261.

4. Watt K, Pedersen R, Heimbach J, et al. Probability and mortality of de novo malignancy after liver transplantation: results of the multi-centered, prospective NIDDK long term database. *Gastroenterology*. 2009;137:2010–2017.
5. Herrero JI, España A, Quiroga J, et al. Nonmelanoma skin cancer after liver transplantation. Study of risk factors. *Liver Transpl*. 2005;11:1100–1106.
6. Singh S, Edakkanambeth Varayil J, Loftus Jr EV, Talwalkar JA. Incidence of colorectal cancer after liver transplantation for primary sclerosing cholangitis: a systematic review and meta-analysis. *Liver Transpl*. 2013;19:1361–1369.
7. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. *Crit Rev Oncol Hematol*. 2005;56:155–167.
8. Chandarana H, Robinson E, Hajdu CH, et al. Microvascular invasion in hepatocellular carcinoma: is it predictable with pretransplant MRI? *AJR Am J Roentgenol*. 2011;196:1083–1089.
9. Jhaveri KS, Cleary SP, Fischer S, et al. Blood oxygen level-dependent liver MRI: can it predict microvascular invasion in HCC? *J Magn Reson Imaging*. 2013;37:692–699.
10. Xu P, Zeng M, Liu K, et al. Microvascular invasion in small hepatocellular carcinoma: is it predictable with preoperative diffusion-weighted imaging? *J Gastroenterol Hepatol*. 2014;29:330–336.
11. Bashir MR, Hussain HK. Imaging in patients with cirrhosis: current evidence. *Radiol Clin N Am*. 2015;53:919–931.
12. Blume C, Pischke S, von Versen-Hoyneck F, Gunter HH, Gross MM. Pregnancies in liver and kidney transplant recipients: a review of the current literature and recommendation. *Best Pract Res Clin Obstet Gynaecol*. 2014;28:1123–1136.
13. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology*. 2000;62:385–392.
14. Watt KD. *Nat Rev Gastroenterol Hepatol*. 2015;12:639–648.
15. Jain A, Venkataramanan R, Fung JJ, et al. Pregnancy after liver transplantation under tacrolimus. *Transplantation*. 1997;64:559–565.
16. Armenti VT, Ahlswede KM, Ahlswede BA, Jarrell BE, Moritz MJ, Burke JF. National transplantation Pregnancy Registry—outcomes of 154 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation*. 1994;57:502–506.
17. Kainz A, Harabacz I, Cowrick IS, Gadgil SD, Hagiwara D. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation*. 2000;70:1718–1721.
18. Hoeltzenbein M, Elefant E, Vial T, et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. *Am J Med Genet*. 2012;158A:588–596.
19. Krajewski C, Sucato G. Reproductive health care after transplantation. *Best Pract Res Clin Obstet Gynaecol*. 2014;28:1222–1234.
20. Puri P, Anand AC, Saraswat VA, et al. Indian National Association for Study of the Liver (INASL) Guidance for Antiviral Therapy Against HCV Infection in 2015. *J Clin Exp Hepatol*. 2015;5:221–238.
21. Tanaka E, Ohue C, Aoyagi K, et al. Evaluation of a new enzyme immunoassay for hepatitis C virus (HCV) core antigen with clinical sensitivity approximating that of genomic amplification of HCV RNA. *Hepatology*. 2000;32:388–393.
22. Chakravarti A, Chauhan MS, Dogra G, Banerjee S. Hepatitis C virus core antigen assay: can we think beyond convention in resource limited settings? *Braz J Infect Dis*. 2013;17(3):369–374.
23. Cresswell FV, Fisher M, Hughes DJ, et al. Hepatitis C core antigen testing: a reliable, quick, and potentially cost-effective alternative to hepatitis C polymerase chain reaction in diagnosing acute hepatitis C virus infection. *Clin Infect Dis*. 2015;60:263–266.
24. Moini M, Ziyaeyan M, Aghaei S, et al. Hepatitis C virus (HCV) infection rate among seronegative hemodialysis patients screened by two methods; HCV core antigen and polymerase chain reaction. *Hepat Mon*. 2013;13(6):e9147.
25. Mixson-Hayden T, Dawson GJ, Teshale E, et al. Performance of architect HCV core antigen test with specimens from US plasma donors and injecting drug users. *J Clin Virol*. 2015;66:15–18.
26. Vermehren J, Susser S, Berger A, et al. Clinical utility of the architect HCV Ag assay for early treatment monitoring in patients with chronic hepatitis C genotype 1 infection. *J Clin Virol*. 2012;55:17–22.
27. Daniel HDJ, Vivekanandan P, Raghuraman S, Sridharan G, Chandy GM, Abraham P. Significance of the hepatitis C virus (HCV) core antigen as an alternative plasma marker of active HCV infection. *Int J Med Microbiol*. 2007;25:37–42.
28. Tillmann HL. Hepatitis C virus core antigen testing: role in diagnosis, disease monitoring and treatment. *World J Gastroenterol*. 2014;20(22):6701–6706.
29. Reyes-Mendez MA, Juarez-Figueroa L, Iracheta-Hernandez P, Medina-Islas Y, Ruiz-Gonzalez V. Comparison of two diagnostic algorithms for the identification of patients with HCV viremia using a new HCV antigen test. *Ann Hepatol*. 2014;13:337–342.
30. Anand AC, Garg HK. Approach to clinical syndrome of jaundice and encephalopathy in tropics. *J Clin Exp Hepatol*. 2015;5:S116–S130.
31. Connolly AM, Volpe JJ. Clinical features of bilirubin encephalopathy. *Clin Perinatol*. 1990;17:371–379.
32. Gould CF, Lowe JD, Richardson RR, Ly JQ, Campbell SE, Beall DP. Bilirubin encephalopathy. *Appl Radiol*. 2004;33:37–40.
33. Maisels MJ, Baltz RD, Bhutani VK, et al. Neonatal jaundice and kernicterus. *Pediatrics*. 2001;108:763–765.
34. Larroche C. Hemophagocytic lymphohistiocytosis in adults: diagnosis and treatment. *Jt Bone Spine*. 2012;79:356–359.
35. Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into pathophysiology and practical guidelines. *Biol Blood Marrow Transplant*. 2010;16:S82–S89.
36. Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118:4041.
37. Henter JL, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. *Semin Oncol*. 1991;18:29–33.
38. Fisman DN. Hemophagocytic syndromes and infection. *Emerg Infect Dis*. 2000;6(6):601–608.
39. Goldberg DS, Fellon MB. The Art and science of diagnosing and treating lung and heart disease secondary to liver disease. *Clin Gastroenterol Hepatol*. 2015;13:2118–2127.
40. Krag A, Bendtsen F, Henriksen JH, et al. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut*. 2010;59:105–110.
41. Nazar A, Guevara M, Sitges M, et al. LEFT ventricular function assessed by echocardiography in cirrhosis: relationship to systemic hemodynamics and renal dysfunction. *J Hepatol*. 2013;58:51–57.
42. Bal JS, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. *Liver Int*. 2003;23:243–248.
43. Zambruni A, Di Micoli A, Lubisco A, et al. QT interval correction in patients with cirrhosis. *J Cardiovasc Electrophysiol*. 2007;18:77–82.
44. Bacon BR, Adams PC, Kowdley KV, et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54:328–343.
45. Wong VW, Wong GL, Yip GW, et al. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. *Gut*. 2011;60:1721–1727.

46. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study: a post-hoc analysis. *Lancet*. 2010;376:1916–1922.
47. Krowka MJ, Wiseman GA, Burnett OL, et al. Hepatopulmonary syndrome: a prospective study of relationships between severity of liver disease PaO₂ response to 100% oxygen, and brain uptake after (99m)Tc MAA lung scanning. *Chest*. 2000;118:615–624.
48. Fallon MB, Krowka MJ, Brown RS, et al. Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. *Gastroenterology*. 2008;135:1168–1175.
49. Krowka MJ. Hepatopulmonary syndrome versus portopulmonary hypertension: distinctions and dilemmas. *Hepatology*. 1997;25:1282–1284.
50. Schenk P, Schoniger-Hekele M, Fuhrmann V, et al. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology*. 2003;125:1042–1052.
51. Gomez FP, Martinez-Palli G, Barbera JA, et al. Gas exchange mechanism of orthodeoxia in hepatopulmonary syndrome. *Hepatology*. 2004;40:660–666.
52. Lewis JH. The art and science of diagnosing and managing drug-induced liver injury in 2015 and beyond. *Clin Gastroenterol Hepatol*. 2015;13:2173–2189.
53. Fisher K, Vuppalanchi R, Saxena R. Drug-induced liver injury. *Arch Pathol Lab Med*. 2015;139:876–887.
54. Chalasani N, Bonkovsky HL, Fontana RJ, et al. Drug-induced liver in the USA: a report of 899 instances assessed prospectively. *Gastroenterology*. 2015;148:1340–1352.
55. Andrade RJ, Lucena MI, Fernandez MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005;129:512–521.
56. Bjornsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology*. 2005;42:481–489.
57. Devarbhavi H, Dierkhising R, Kremers WK, et al. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol*. 2010;105:2396–2404.
58. Vuppalanchi R, Gotur R, Reddy KR, et al. Relationship between characteristics of medications and drug-induced liver disease phenotype and outcome. *Clin Gastroenterol Hepatol*. 2014;12:1550–1555.
59. Chalasani N, Bjornsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology*. 2010;138:2246–2259.
60. Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service study of Reye's syndrome and medications: report of the main study. *JAMA*. 1987;257:1905–1911.
61. Hurwitz ES. Reye's syndrome. *Epidemiol Rev*. 1989;11:249–253.
62. Scheffner D, Konig S, Rauterberg-Ruland I, et al. Fatal liver failure in 16 children with valproate therapy. *Epilepsia*. 1988;29:530–542.
63. Lucena MI, Andrade RJ, Kaplowitz N, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. *Hepatology*. 2009;49:2001–2009.
64. Timbo BB, Ross MP, McCarthy PV, Lin CT. Dietary supplements in a national survey: prevalence of use and reports of adverse events. *J Am Diet Assoc*. 2006;106:1966–1974.
65. Hussaini SH, O'Brien CS, Despot EJ, Dalton HR. Antibiotic therapy: a major cause of drug-induced jaundice in southwest England. *Eur J Gastroenterol Hepatol*. 2007;19:15–20.
66. Pillans PI. Drug associated hepatic reactions in New Zealand: 21 years experience. *N Z Med J*. 1996;109:315–319.
67. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology*. 2002;36:451–455.
68. Garcia Rodriguez LA, Stricker BH, Zimmerman HJ. Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. *Arch Intern Med*. 1996;156:1327–1332.
69. Salvo F, Polimeni G, Moretti U, et al. Adverse drug reactions related to amoxicillin alone and in association with clavulanic acid: data from spontaneous reporting in Italy. *J Antimicrob Chemother*. 2007;60:121–126.
70. O'Donohue J, Oien KA, Donaldson P, et al. Co-amoxiclav jaundice: clinical and histological features and HLA class II association. *Gut*. 2000;47:717–720.
71. Larrey D, Vial T, Micallef A, et al. Hepatitis associated with amoxicillin-clavulanic acid combination report of 15 cases. *Gut*. 1992;33:368–371.
72. Hautekeete ML, Brenard R, Horsmans Y, et al. Liver injury related to amoxicillin-clavulanic acid: interlobular bile-duct lesions and extra-hepatic manifestations. *J Hepatol*. 1995;22:71–77.

Sahaj Rathi
Radha K. Dhiman*

Department of Hepatology, Postgraduate Institute of
Medical Education and Research, Chandigarh 160012,
India

*Address for correspondence: Radha K. Dhiman, Department
of Hepatology, Postgraduate Institute of Medical
Education and Research, Chandigarh 160012, India
E-mail address: rkpsdhiman@hotmail.com (R.K. Dhiman)