Hepatobiliary Quiz Answers—19 (2016)

Answers to Multiple Choice Questions

Answers: A, C, and D

Normal liver has an excellent regenerative capacity. However, this ability is impaired significantly in conditions of hepatic injury—both acute and chronic. Most of our knowledge about hepatic regeneration is derived from animal models of rats, mice and zebrafish.¹ Regeneration occurs predominantly by replication of mature hepatocytes in the uninjured liver. In presence of liver injury where hepatocyte proliferation is affected, hepatocyte progenitor cells (HPC) too contribute to hepatocyte regeneration.² Hepatocytes can undergo trans-differentiation into ductular cells, and contribute to ductular regeneration.³

As the liver tissue regenerates after an injury, stellate cells and biliary cells proliferate in addition to hepatocytes. The hepatic lobules increase in size and complexity, forming double-celled plated between sinusoids, but their numbers remain the same.⁴

Animal models with extensive hepatectomy show an increase in systemic and portal endotoxemia. Use of gentamicin for bowel decontamination led to reduction in lipopolysaccharide levels as well as reduction in mortality. This finding has direct implication for humans, as gut related microbial sepsis is a major cause of death after large hepatic resection.

Bile acids have been shown to play an important role in liver regeneration. Lower levels of bile acids or their receptors impair regeneration. In fact, patients with external biliary drainage after liver resection were found to have poorer regeneration than those without external biliary drainage.

Answers: A, C, D and E

Many new techniques have emerged for non-invasive assessment of liver fibrosis over the last few years. Transient elastography (TE), point and 2D shear wave elastography (SWE), and magnetic resonance elastography are the best studied among the imaging based techniques. These methods have a high reproducibility and good intraobserver and interobserver concurrence.⁷ All ultrasound-based assessments occasionally tend to overestimate liver stiffness, and are better at ruling out rather than confirming the presence of cirrhosis or significant fibrosis.⁷ Studies comparing all three methods TE, point SWE and 2D SWE all have similar accuracy in detection of cirrhosis. 2D SWE performs slightly better in detecting intermediate fibrosis stages.⁸ This is probably due a difference in the assessed region of interest (ROI), which is the maximum in 2D SWE, followed by TE, and least in point SWE.⁷ FibroTest is based on 6 serum markers and is as accurate as TE in detecting cirrhosis, but better at detection of clinically significant fibrosis (METAVIR 2 or higher).⁹ Higher levels

of fibrosis as assessed with non-invasive methods have now been shown to correlate with development of complications like portal hypertension, variceal bleed, hepatocellular carcinoma, and even mortality.^{7,10,11}

Answers: A and C

Hepatic haemangiomas are the most common primary liver tumors, being present in around 5% cases in imaging series, and up to 20% in autopsy series. Most hemangiomas are small (<3 cm), and can be reliably diagnosed on ultrasound as homogenous hyperechoic lesions with sharp margins and posterior acoustic enhancement.^{12,13}

Magnetic resonance imaging (MRI) is the most reliable imaging modality in atypical cases, showing T1 hypointense and T2 hyperintense lesion. Upon dynamic imaging after contrast administration, a discontinuous peripheral nodular enhancement with progressive centripetal filling is diagnostic.^{14,15} In cases where imaging is not conclusive, a needle biopsy gives the diagnosis with a 96% accuracy.¹⁶ It can be done provided a cuff of normal hepatic parenchyma is interposed between the capsule and the margin of haemangioma.

Answers: B and C

Focal nodular hyperplasia (FNH) is a benign, polyclonal hepatocellular proliferation. It is a hyperplastic reaction to an underlying arteriovenous malformation.¹² The lesion is usually solitary, but may be multiple in 20–30% cases, esp. in patients with underlying vascular liver diseases viz. Budd–Chiari syndrome, sinusoidal obstruction syndrome and congenital disorders of vessels.^{17,18}

MRI has a sensitivity of 70–80%, with 100% specificity for the diagnosis of FNH. The sensitivity is lower especially in lesions <3 cm, which usually lack the typical central scar. These smaller lesions are better-identified by contrast enhanced ultrasound.¹⁹

Once the diagnosis is confirmed, no further follow-up imaging is needed for asymptomatic patients, including in pregnancy. A diagnosis of FNH does not warrant discontinuation of oral contraceptives.¹²

Answers: A, B, C and E

Bacterial infections are common in patients with cirrhosis, and lead to significant morbidity and mortality. Of all the cirrhotic patients admitted in hospital, 25–35% of patients with cirrhosis either have infection at admission or acquire one during hospitalization.²⁰ This number is higher (45–60%) for those admitted with variceal bleeding.²¹ Systemic inflammatory response syndrome (SIRS) is present in up to 30% of without underlying infection. Conversely, features of SIRS may be absent even in presence of infection. Still, presence of SIRS has a prognostic significance, being associated with higher probability of portal hypertension-related complications.²² However, diagnosis of sepsis is

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often difficult in these patients. Serum procalcitonin has emerged as a reliable marker of infection. In a meta-analysis of 10 studies, procalcitonin showed a sensitivity 79% and specificity of 89% in diagnosing bacterial infection.²³

Relative adrenal insufficiency is seen in up to 77% of patients with cirrhosis and sepsis, and is associated with impaired circulatory and renal function, as well as higher short-term mortality.²⁴

Albumin administration improves outcome in patients with spontaneous bacterial peritonitis. Importantly, survival benefit is seen only when its use is restricted to those with serum creatinine >1 mg/dl, blood urea nitrogen >30 mg/dl or bilirubin >4 mg/dl.²⁵

Answers: B, C and D

The liver is the major site for metabolism and clearance of many drugs. Thus, liver dysfunction leads to altered drug metabolism. Bioavailability of oral drugs is significantly increased as a result of reduced first-pass metabolism. This is due to decline in intrinsic drug clearance as well as portosystemic shunting.²⁶ Intrinsic drug clearance occurs through phase I (e.g., oxidation mediated by cytochrome pathway) or phase II (e.g., glucuronidation, sulfation) metabolism. Phase I metabolism is affected to a greater extent in patients with cirrhosis.²⁷ Fluid retention and ascites increase the volume of distribution of hydrophilic drugs and thus higher doses are required.²⁸ Drugs highly bound to plasma proteins have higher free plasma concentrations due to reduced synthesis of plasma proteins, as well as displacement by bilirubin.²⁹ Patients with cirrhosis may have delayed gastric emptying, delaying the absorption of medications by the small intestine. However, the extent of absorption is not affected.³⁰

Answers: A, C, D, and E

Metoprolol is extensively metabolized by the liver. In presence of hepatic insufficiency, its bioavailability is increased from 50% to 80% and its elimination is prolonged. Thus, doses should be reduced by a factor of 2–3. Liver too extensively metabolizes Amiodarone and diltiazem.³¹ Though specific data on amiodarone is not available, half life of diltiazem and its active metabolite is slightly prolonged, and a dose reduction to half is suggested.^{26,31} Cirrhotic cardiomyopathy is commonly associated QT interval prolongation, which worsens with severity of cirrhosis. QT prolongation may be seen in up to 60% patients with Child C cirrhosis. Thus, baseline and regular monitoring of QT interval is important in patients on antiarrhythmics.³³

In patients with distributive shock, noradrenaline is the vasopressor of choice, as it leads to peripheral vasoconstriction while preserving cardiac output. Dopamine may lead to splanchnic vasodilatation and thus worsen portal hypertension.³⁴

Answers: A, C and E

Early post-transplant period is marked by high serum transaminases due to reperfusion injury, with aspartate transaminase peaking at 24 h, followed by a rapid fall over 7 days. This is followed by a cholestatic phase, with a bilirubin peak by 7–10 days along with a rise in alkaline phosphatase. If there is a rise in the falling bilirubin or transaminases after 5–10 days post transplant, acute rejection should be ruled out.³⁵ The incidence of acute cellular rejection has reduced with the routine use of tacrolimus. It is less common among the critically ill and elderly recipients.³⁶ Neurological complication may be seen in up to 25% recipients in the early post-operative period, the most common being encephalopathy and seizures. Delayed awakening post anesthesia is common in those with pre-existing encephalopathy, the duration of which is proportional to the severity of the encephalopathy. Recipients who develop delirium are seen to have poorer outcomes.^{37–38} Post-operative hemorrhage requiring laparotomy within 48 h may be seen in 10% cases.³⁹ Common sources include vascular anastomoses, cystic bed and liver lacerations, however, a major source is not identified in most cases. Recipients of living donor or split grafts are said to be at a greater risk of bleeding because of the presence of large, raw surfaces.¹

Answers: A, B, D and E

Auxiliary liver transplant techniques allow placement of a graft liver in addition to the native liver. These include heterotopic auxiliary liver transplant (HALT) and auxiliary partial orthotopic liver transplantation (APOLT). HALT involves implanting the new liver graft in a nonanatomical location with minimal or no handling of the native liver. It is usually placed beneath the native liver. The advantage of this technique was minimal handling of native liver, which can worsen hemodynamics and raise intracranial pressure in patients with acute liver failure. However, this technique was associated with graft congestion, abdominal compartment syndrome, prolonged ventilation, and overall poor outcomes, and has now fallen out of favor.^{40,41} APOLT involves placement of a partial liver graft at the natural location of the liver, resecting out a native lobe, and leaving behind a part of the native liver. The advantage of this technique is that it allows withdrawal of immunosuppression once the native liver regenerates and takes over normal function. APOLT is suitable in patients with a good capacity of effective native liver regeneration. This includes those with hyperacute and acute forms of liver failure. However, hemodynamically unstable patients are not suitable candidates as this procedure is longer and requires more liver manipulation as compared to standard orthotopic liver transplantation, this leading to higher risk of perioperative mortality.⁴² Subacute liver failure has distorted reticulin framework, which leads to ineffective regeneration. The results are best in younger patients with

better regenerative capabilities. Up to 65% patients have been successfully taken off immunosuppression according to the recent series. The improvement in outcomes may be due to better patient selection and improving surgical techniques.^{43,44}

Answers: B and E

King's College criteria (KCC) is the most extensively used and validated criteria for prognostication of acute liver failure (ALF), and to assess need for liver transplantation. While the criteria are highly specific (79–95%), its sensitivity is much lower (58–69%). Thus, some patients who do not meet KCC may still be at a high risk of mortality without transplantation. A recent meta-analysis has found that MELD score predicts mortality better than KCC in non-paracetamol ALF patients (diagnostic odds ratio 4.2 vs 8.4). Addition of lactate to the KCC model significantly improves the accuracy in predicting mortality.^{45,46}

KCC is a dynamic model, and patients who fulfill the criteria should be re-evaluated daily. Those who show improvement may improve without liver transplantation. Over the last 4 decades, non-transplant survival has drastically improved. This is mainly due to improvement in intensive care and reduced incidence of cerebral edema, which is the most important cause of mortality in early ALF.^{47,48}

Conflicts of Interest

The authors have none to declare.

REFERENCES

- Forbes SJ, Newsome PN. Liver regeneration – mechanisms and models to clinical application. *Nat Rev Gastroenterol Hepatol*. 2016;13:473–485.
- Yanger K, Knigin D, Zong Y, et al. Adult hepatocytes are generated by self-duplication rather than stem cell differentiation. *Cell Stem Cell*. 2014;15:340–349.
- Lu WY, Bird TG, Boulter L, et al. Hepatic progenitor cells of biliary origin with liver repopulation capacity. *Nat Cell Biol*. 2015;17:971–983.
- Papp V, Dezso K, Laszlo V, et al. Architectural changes during regenerative and ontogenic liver growth in the rat. *Liver Transpl*. 2009;15:177–183.
- Friedrich-Rust M, Poynard T, Castera L. Critical comparison of elastography methods to assess chronic liver disease. *Nat Rev Gastroenterol Hepatol*. 2016;13:402–411.
- Gerber L, Kasper D, Fitting D, et al. Assessment of liver fibrosis with 2D shear wave elastography in comparison to transient elastography and acoustic radiation force impulse imaging in patients with chronic liver disease. *Ultrasound Med Biol*. 2015;41:2350–2359.
- Houot M, Ngo Y, Munteanu M, Marque S, Poynard T. Systematic review with meta-analysis: direct comparisons of biomarkers for the diagnosis of fibrosis in chronic hepatitis C and B. *Aliment Pharmacol Ther*. 2016;43:16–29.
- Foucher J, Chanteloup E, Vergniol J. Diagnosis of cirrhosis by transient elastography (Fibroscan): a prospective study. *Gut*. 2006;55:403–408.
- Akima T, Tamano M, Hiraishi H. Liver stiffness measured by transient elastography is a predictor of hepatocellular carcinoma development in viral hepatitis. *Hepatol Res*. 2011;41:965–970.
- Horta G, Lopez M, Dotte A, et al. Benign focal liver lesions detected by computed tomography: review of 1,184 examinations. *Rev Med Chil*. 2015;143:197–202.
- Gandolfi L, Leo P, Solmi L, Vitelli E, Verros G, Colecchia A. Natural history of hepatic haemangiomas: clinical and ultrasound study. *Gut*. 1991;32:677–680.
- EASL Clinical Practice Guidelines on the management of benign liver tumours. *J Hepatol*. 2016;65:386–398.
- O'Neill EK, Cogley JR, Miller FH. The ins and outs of liver imaging. *Clin Liver Dis*. 2015;19:99–121.
- Caldironi MW, Mazzucco M, Aldinio MT, et al. Echo-guided fine-needle biopsy for the diagnosis of hepatic angioma. A report on 114 cases. *Minerva Chir*. 1998;53:505–509.
- Brancatelli G, Federle MP, Grazioli L, Blachar A, Peterson MS, Thaete L. Focal nodular hyperplasia: CT findings with emphasis on multiphasic helical CT in 78 patients. *Radiology*. 2001;219:61–68.
- Sempoux C, Paradis V, Komuta M, Wee A, Calderaro J, Balabaud C, et al. Hepatocellular nodules expressing markers of hepatocellular adenomas in Budd–Chiari syndrome and other rare hepatic vascular disorders. *J Hepatol*. 2015;63:1173–1180.
- Soussan M, Aube C, Bahrami S, Boursier J, Valla DC, Vilgrain V. Incidental focal solid liver lesions: diagnostic performance of contrast-enhanced ultrasound and MR imaging. *Eur Radiol*. 2010;20:1715–1725.
- Nanchal RS, Ahmed S. Infections in liver disease. *Crit Care Clin*. 2016;32:411–424.
- Bunchorntavakul C, Chamroonkul N, Chavalitdharmrong D. Bacterial infections in cirrhosis: a critical review and practical guidance. *World J Hepatol*. 2016;8:307–321.
- Fernandez J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol*. 2012;56:S1–S12.
- Lin KH, Wang FL, Wu MS, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection in patients with liver cirrhosis: a systematic review and meta-analysis. *Diagn Microbiol Infect Dis*. 2014;80:72–78.
- Acevedo J, Fernandez J, Prado V, et al. Relative adrenal insufficiency in decompensated cirrhosis: relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. *Hepatology*. 2013;58:1757–1765.
- Poca M, Concepción M, Casas M, et al. Role of albumin treatment in patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol*. 2012;10:309–315.
- Gallagher J, Biesboer AN, Killian AJ. Pharmacologic issues in liver disease. *Crit Care Clin*. 2016;32:397–410.
- Rodighiero V. Effects of liver disease on pharmacokinetics. An update. *Clin Pharmacokinet*. 1999;37:399–431.
- Lin S, Smith BS. Drug dosing considerations for the critically ill patient with liver disease. *Crit Care Nurs Clin North Am*. 2010;22:335–340.
- Verbeeck RK, Horsmans Y. Effect of hepatic insufficiency on pharmacokinetics and drug dosing. *Pharm World Sci*. 1998;20:183–192.
- Delco F, Tchambaz L, Schlienger R, et al. Dose adjustment in patients with liver disease. *Drug Saf*. 2005;28:529–545.
- Klotz U. Antiarrhythmics: elimination and dosage considerations in hepatic impairment. *Clin Pharmacokinet*. 2007;46:985–996.
- Bernardi M, Calandra S, Colantoni A, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology*. 1998;27:28–34.
- Canabal JM, Kramer DJ. Management of sepsis in patients with liver failure. *Curr Opin Crit Care*. 2008;14:189–197.

35. Keegan MT, Kramer DJ. Perioperative care of the liver transplant patient. *Crit Care Clin*. 2016;32:453–473.
36. Aduen JF, Sujay B, Dickson RC, et al. Outcomes after liver transplant in patients aged 70 years or older compared with those younger than 60 years. *Mayo Clin Proc*. 2009;84:973–978.
37. Zivkovic SA. Neurologic complications after liver transplantation. *World J Hepatol*. 2013;5:409–416. Keegan & Kramer 470.
38. Lescot T, Karvellas CJ, Chaudhury P, et al. Postoperative delirium in the intensive care unit predicts worse outcomes in liver transplant recipients. *Can J Gastroenterol*. 2013;27:207–212.
39. Liang TB, Bai XL, Li DL, et al. Early postoperative hemorrhage requiring urgent surgical reintervention after orthotopic liver transplantation. *Transplant Proc*. 2007;39:1549–1553.
40. Mazariegos GV, Machaidze Z. Auxiliary liver transplantation: location, location, location. *Pediatr Transplant*. 2009;13:1–2.
41. van Hoek B, de Boer J, Boudjema K, Williams R, Corsmit O, Terpstra OT. Auxiliary versus orthotopic liver transplantation for acute liver failure. EURALT Study Group. European Auxiliary Liver Transplant Registry. *J Hepatol*. 1999;30:699–705.
42. Rela M, Kaliamoorthy I, Reddy MS. Current status of auxiliary partial orthotopic liver transplantation for acute liver failure. *Liver Transpl*. 2016;22:1265–1274.
43. Chenard-Neu MP, Boudjema K, Bernuau J, et al. Auxiliary liver transplantation: regeneration of the native liver and outcome in 30 patients with fulminant hepatic failure – a multicenter European study. *Hepatology*. 1996;23:1119–1127.
44. Weiner J, Griesemer A, Island E, et al. Longterm outcomes of auxiliary partial orthotopic liver transplantation in preadolescent children with fulminant hepatic failure. *Liver Transpl*. 2016;22:485–494.
45. McPhail MJ, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's College criteria and model for end-stage liver disease scores to predict mortality of patients with acute liver failure: a meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14:516–525.
46. Craig DG, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. *Aliment Pharmacol Ther*. 2010;31:1064–1076.
47. O'Grady J. Timing and benefit of liver transplantation in acute liver failure. *J Hepatol*. 2014;60:663–670.
48. Bernal W, Lee WM, Wendon J, Larsen FS, Williams R. Acute liver failure: a curable disease by 2024? *J Hepatol*. 2015;62:S112–S120.

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: rkpsdthiman@hotmail.com (R.K. Dhiman)