# Transplant Hepatology Board Review Course
# Practice Module Supplement
# ANSWERS & RATIONALES

## 1

**Correct answer: C**

**Rationale:**
This young patient has a large central lesion that does not appear to be entirely benign. The main question is if this is an adenoma (in which case there in an increased risk of rupture and transformation to HCC once > 5 cm) or a focal nodular hyperplasia (FNH), which is benign and does not have any malignant potential. Both appear very similarly on contrast-enhanced images except a FNH may have a central scar. Contrast with gadobenate dimeglumine or gadoxetate disodium can help detect the two lesions (adenomas do not take up the contrast, whereas FNH does) but this is not an option provided in the answer choices.

No further follow-up is not the right answer due to the size and characteristics of the lesion. Repeat imaging in 12 months is not the right answer because if this is an adenoma, something should be done now given its size and location. Surgical resection is not the right answer because if it is an FNH, it can be monitored as it does not have the risk of rupture or malignant transformation associated with adenomas. Transplant evaluation is rarely indicated for these large lesions unless the patient has a very large adenoma with associated portal hypertension or concern for malignant transformation to HCC.

**References:**
Cherqui D et al. Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological, and pathological correlations. Hepatology 1995;22:1674.

Lewis, R. Clinical Approach to Liver Mass Lesions. In: Mayo Clin Gastro and Hep Board Review, Hauser SC, ed. 2015, 5th ed, Ch 24: 252-264.

## 2

Correct answer: B

Rationale:
Patients with acute liver failure present with mental status changes and coagulopathy without preexisting liver disease. Choice A is wrong because although the majority of adults with hepatitis B experience spontaneous recovery with supportive care, 1% of patients present with acute liver failure and progressive hepatic deterioration despite antiviral therapy. Choice C is wrong because presentation of Wilson's disease with acute liver failure is almost uniformly fatal without a liver transplant. Choice D is wrong because although *Amanita phalloides* poisoning can be treated with penicillin G and N-acetylcysteine, liver transplantation is often the only lifesaving option. Choice B is the correct answer because patients with ischemic hepatitis or "shock liver" often recover with supportive care and stabilization of the circulatory dysfunction; two thirds of these patients suffer from cardiac disease.

References:
Lee WM, Larson AM, Stravitz RT. AASLD Position Paper: The Management of Acute Liver Failure: Update 2011. Hepatology 2011;1-22.

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## 3

Correct answer: A

Rationale:
Ipilimumab is an anti-CTLA4 monoclonal antibody that falls within the class of immune checkpoint inhibitors. Immune checkpoint inhibitors can initiate autoimmune side effects including autoimmune hepatitis. A liver biopsy is indicated to establish the diagnosis and rule out other causes of increased liver function tests. Histologic findings associated with liver injury from anti-CTLA4 mAbs have been recently described as granulomatous hepatitis, centrilobular necrosis, and central vein endotheliitis. Liver tests typically improve after stopping the drug and administering a course of steroids, although cases of spontaneous resolution have been described. The patient has significant elevation of LFTs and abnormal bilirubin; prompt discontinuation of drug is important; therefore, answers B and C are incorrect. Defibrotide is used to treat Budd-Chiari syndrome, which this patient does not have.

References:
Champiat S, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Annals of Oncology 2016 Apr;27(4):559-74.

De Martin E, Michot JM, Papouin B, et al. Liver injury from cancer immunotherapy using monoclonal immune checkpoint inhibitors. J Hepatol 2018.

Kleiner D, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci 2012;57:2233-2240.

Weber J et al, Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017;377:1824-1835.

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## 4

**Correct answer: D**

**Rationale:**
Calcineurin inhibitors (tacrolimus and cyclosporine) are the mainstay agents in prevention of allograft rejection. The mechanism of action is by blocking signal 1 activation by forming a complex with the phosphatase calcineurin. Tacrolimus blocks FKBP-12, whereas cyclosporine blocks cyclophilin. Answer A describes mechanism of mTOR inhibitors (sirolimus and everolimus), B describes mechanism of action of cell cycle inhibitors (mycophenolate mofetil, azathioprine), and answer E describes mechanism of action of prednisone. Answer C describes mechanism of action of T cell depleting agents (such as thymoglobulin), which are used for induction of immunosuppression and for steroid refractory rejection.

**References:**
Martinez O, Rosen H. Basic Concepts in Transplant Immunology. Liver Transplantation 2005;11(4):370-381.

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## 5

**Correct answer: D**

**Rationale:**
This patient has intrahepatic cholestasis of pregnancy (IHCP), and ursodeoycholic acid (UDCA) often improves symptoms, biochemical parameters, and potentially fetal outcomes. UDCA increases bile salt export pumps and increases placental bile transporters. This is a classic IHCP presentation of a pregnant woman in the second or third trimester with severe itching and elevated bile acids. Up to 25% can present with jaundice. Transaminases can be greater than 1000 U/L. Early delivery at 37 weeks (not at 34 weeks as in choice A) is recommended as intrauterine death is more common in the last month of pregnancy, but few deaths occur before 37 weeks. Cholestasis generally resolves with delivery. Testing for LCHAD deficiency is done when acute fatty liver of pregnancy is suspected (unlikely with normal renal function, normal mental status, normal glucose, and normal coagulation). Platelet transfusion with delivery should be considered for woman with HELLP syndrome not with IHCP. There is no indication for liver biopsy.

**References:**
Tran et al. ACG Clinical Guideline: Liver Disease and Pregnancy. Am J Gastroenterol 2016;111:176-94.

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## 6

Correct answer: D

Rationale:

The relative risk of de novo malignancies is increased in liver transplant recipients compared with age- and sex-matched non-transplant controls. Examples include skin cancers, lymphomas, oropharyngeal cancers, and kidney cancers. Squamous cell cancer of the skin is significantly increased in the liver transplant recipient with an estimated relative risk of 20% to 70%. While less common than squamous cell cancers of the skin, melanoma risk is also increased in liver transplant recipients with an estimated increase by 2% to 5%. Thus, significant proactive vigilance must be maintained for these patients. There is also an increased risk of lymphoma or post-transplant lymphoproliferative disorder likely related to EBV infection. Oropharyngeal and lung cancer risk are also increased especially in patients transplanted for alcoholic liver disease or those who have prior history of smoking. Attention should be paid to promote smoking cessation in the post-transplant patient.

References:

Lucey MR, et al. Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation, Liver Transplantation 2013;19:3-26.

## 7

Correct answer: B

### Rationale:

This patient's presentation with an episode of rejection, treated with corticosteroids, followed by viral syndrome with hepatitis and leukopenia between 1 and 6 months post-transplant is most consistent with human herpesvirus 6 (HHV-6) reactivation (potentially with concomitant CMV reactivation). HSV reactivation tends to occur very early post-transplant (first month) with severe acute hepatitis. Adenovirus infections are relatively common and may cause respiratory symptoms, gastroenteritis, hepatitis, and urinary tract infection. Severe anemia is typical of infection with Parvovirus B19. *P. jerovecii* pneumonia may account for her cough but is typically accompanied by significant dyspnea and hypoxemia.

During the period from 1 to 6 months, transplant recipients can develop opportunistic infections such as aspergillosis, cryptococcosis, or toxoplasmosis. Infections due to *Pneumocystis jirovecii* or herpesviruses are less likely to appear in transplant patients receiving prophylaxis. Viral pathogens and allograft rejection cause the majority of febrile episodes during this period.

CMV syndrome (fever, malaise, bone marrow suppression) accounts for the majority of CMV disease after liver transplantation, whereas tissue-invasive disease (eg, colitis, enteritis, esophagitis, gastritis, hepatitis, pneumonitis, encephalitis, retinitis) is less common. CMV can also cause indirect effects (allograft rejection, vanishing bile duct syndrome, chronic ductopenic rejection, hepatitis C recurrence, allograft hepatitis) as well as immunomodulatory effects, which can make patients more susceptible to developing opportunistic infections. HHV-6 can present with a febrile illness (sometimes associated with rash), myelosuppression, pneumonitis, neurologic diseases, and hepatitis. HHV-6 can predispose liver transplant recipients to certain infections such as CMV. This patient's constellation of symptoms in the first 6 months after transplant, associated with an episode of rejection, are evocative of HHV-6 infection, potentially with CMV reactivation.

### References:

Abdel Massih RC, Razonable RR. Human herpesvirus 6 infections after liver transplantation. World J Gastroenterol. 2009;15(21):2561-2569. Abdel Massih RC, Razonable RR. Human herpesvirus 6 infections after liver transplantation. World J Gastroenterol. 2009;15(21):2561-2569.

Lautenschlager I, Höckerstedt K, Linnavuori K, Taskinen E. Human herpesvirus-6 infection after liver transplantation. Clin Infect Dis. 1998;26(3):702-707.

## 8

Correct answer: D

Rationale:

Cryptococcosis is the third most commonly occurring invasive fungal infection (IFI) in solid organ transplant recipients after *Candida* and *Aspergillus*. CMV infection can increase risk of each of these IFIs (although identification of an IFI does not indicate need for CMV prophylaxis). Symptoms caused by cryptococcal infection develop at a mean of 30 months after transplant. Posttransplant cryptococcal infection can manifest as pneumonia (46%), isolated meningitis (36%), disseminated disease (11%), and less frequently, involvement of another single organ.

Lungs are the portal of entry for primary infection in most patients. Pulmonary infection ranges from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome. Among immunosuppressed patients with pulmonary cryptococcosis, CNS involvement must be ruled out with a lumbar puncture. Rapid reduction of immunosuppressive therapy in conjunction with initiation of antifungal therapy in solid organ transplant recipients may lead to the development of immune reconstitution inflammatory syndrome (IRIS), the clinical manifestations of which mimic worsening disease due to cryptococcosis.

References:

Baddley JW, Forrest GN; AST Infectious Diseases Community of Practice. Cryptococcosis in solid organ transplantation. Am J Transplant 2013;13(suppl 4):242-249.

## 9

Correct answer: D

Rationale:
This patient's clinical picture is consistent with primary non-function (PNF) of allograft liver. PNF is defined as poor initial graft function requiring re-transplantation or leading to death. PNF occurs within 2 to 7 days of transplant and has an incidence of 2% to 6%. Patients demonstrate features seen in acute liver failure including hemodynamic instability, encephalopathy, lactic acidosis, and hypoglycemia. While no uniform criteria exist, biochemical abnormalities include elevated AST and ALT levels (>1500 U/L) and elevated PT (>16 s) in conjunction with the presence of encephalopathy or elevated ammonia. Predictors of PNF include female donors, advanced donor age, pre-perfusion allograft steatosis, and cold ischemia time, factors present in this patient. Once identified, patients with PNF should be re-listed for liver transplant and meet UNOS criteria for Status 1A. The other options would be inappropriate given the patient's presentation.

References:
Ploeg RJ, D'Alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, et al. Risk factors for primary dysfunction after liver transplantation—a multivariate analysis. Transplantation 1993;55:807-813.

Nanashima A, Pillay P, Verran DJ, Painter D, Nakasuji M, Crawford M, et al. Analysis of initial poor graft function after orthotopic liver transplantation: experience of an Australian single liver transplantation center. Transplant Proc 2002;34:1231-1235.

Uemura T, Randall HB, Sanchez EQ, Ikegami T, Narasimhan G, McKenna GJ, et al. Liver Retransplantation for Primary Non-function: Analysis of a 20-year Single-Center Experience. Liver Transpl 2007;13:227-233.

# 10

Correct answer: C

Rationale:

This patient presents with classic symptoms of sinusoidal obstruction syndrome (SOS) after receiving high-intensity myeloablative conditioning therapy for hematopoietic stem cell transplant (HSCT). Busulfan and cyclophosphamide are both associated with higher risk of SOS compared with lower intensity, non-myeloablative conditioning regimens. SOS develops within the first month post-HSCT, and in the case of cyclophosphamide conditioning, typically within 20 days. This patient meets diagnostic clinical criteria based on Seattle Criteria (at least 2 of the following criteria within 20 days of HSCT: total bilirubin > 2 mg/dL, hepatomegaly or right upper quadrant pain, > 2% weight gain). In addition, HVPG greater than 10 mmHg is highly specific for SOS (91%) and histology is consistent showing classic early findings of zone 3 congestion and early collagen deposition that subsequently progresses to non-thrombotic occlusion of central veins and sinusoids.

Aside from diuretic therapy, treatment options are limited. Anti-coagulation alone or in conjunction with thrombolysis has been studied with high rates of bleeding and little clinical benefit (29% survival) and is not recommended. TIPS is effective for treating portal hypertension (mean reduction in HVPG from 20.2 mmHg to 6.4 mmHg) but does not improve survival (3-month mortality 87.5%) and is not recommend for severe SOS post-HSCT. There is limited evidence to support TIPS in SOS following solid organ transplant. Liver transplantation for SOS can be considered in patients with benign conditions or malignancy with favorable prognosis but would not be considered in this patient having just undergone therapy for AML. Defibrotide is a single-stranded polydeoxyribonucleic acid with fibrinolytic, anti-thrombotic, and anti-ischemic properties. Defibrotide (6.25 mg/kg) given for at least 14 days led to complete remission in up to 55% of patients and survival past post-HSCT day 100 of 43%, both significantly improved compared with historical controls. The FDA approved defibrotide for the treatment of severe SOS in April 2016. There is also data to support defibrotide for prophylaxis of HSCT though this is currently limited to the pediatric population.

References:

Azoulay D, Castaing D, Lemoine A, et al. Transjugular intrahepatic portosystemic shunt (TIPS) for severe veno-occlusive disease of the liver following bone marrow transplantation. Bone Marrow Transplant 2000;25:987-92.

Campos-Varela I, Castells L, Dopazo C, et al. Transjugular intrahepatic portosystemic shunt for the treatment of sinusoidal obstruction syndrome in a liver transplant recipient and review of the literature. Liver Transpl 2012;18:201-5.

DeLeve LD, Valla DC, Garcia-Tsao G, et al. Vascular disorders of the liver. Hepatology 2009;49:1729-64.

Fried MW, Connaghan DG, Sharma S, et al. Transjugular intrahepatic portosystemic shunt for the management of severe venoocclusive disease following bone marrow transplantation. Hepatology 1996;24:588-91.

McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med 1993;118:255-67.

Richardson PG, Murakami C, Jin Z, et al. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. Blood 2002;100:4337-43.

Shulman HM, Gooley T, Dudley MD, et al. Utility of transvenous liver biopsies and wedged hepatic venous pressure measurements in sixty marrow transplant recipients. Transplantation 1995;59:1015-22.

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## 11

**Correct answer: C**

**Rationale:**
IL-10 is a critical cytokine mediator of allograft tolerance. IL-10 is produced by dendritic cells, $T_{REG}$, liver sinusoidal epithelial cells, Kupffer cells, and hepatocytes. IL-10 leads to expansion of both $T_H2$ and $T_{REG}$ resulting in a cytokine milieu that promotes tolerance. IL-1β and IL-6 are cytokine mediators of acute inflammation (eg, ischemia-reperfusion injury) and lead to allograft immunity, favoring $T_H1$ responses and leading to increased expression of co-stimulatory molecules, further driving alloreactivity. IL-12 is the primary cytokine that drives differentiation of $T_H1$ $CD4^+$ T-cells, and baseline low levels of IL-12 are one of the key elements of the liver's baseline immunotolerant phenotype. IL-17 is associated with $T_H17$ cells and has been associated with allograft immunity, not tolerance.

**References:**
Niu J et al. Prevention of acute liver allograft rejection by IL-10-engineered mesenchymal stem cells. Clin Exp Immunol 2014:176;473-84.

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## 12

**Answer: B**

**Rationale:**

Hepatitis E virus (HEV) is a non-enveloped, positive-strand, RNA virus transmitted via fecal-oral transmission. The incubation time of the virus is 15 to 60 days and in immunocompetent hosts, typically causes a self-limited acute hepatitis. The diagnosis is confirmed with HEV IgM testing (typically positive for up to 12 weeks after exposure) and HEV RNA testing. Importantly, HEV rarely causes acute liver failure (ALF) with no confirmed RNA-positive reports of ALF due to HEV from the ALF Study Group, although acute HEV has been associated with increased incidence and mortality in pregnant women. Interestingly, in immunocompromised patients, HEV, specifically genotype 3, which is otherwise associated with zoonotic infections, can result in chronic infection with progression to cirrhosis reported. The first line of treatment for chronic HEV is immunosuppression reduction. In patients who fail to improve, ribavirin is recommended at a dose of 600 mg daily for 3 months. In retrospective analysis, this was associated with a sustained virologic response (SVR) in 78% of patients with chronic HEV. Pegylated interferon alpha does have some antiviral activity for HEV; however, its use in post-transplant patients is prohibited by the risk of rejection. Sofosbuvir and tenofovir have no known activity against HEV.

**References:**

Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. N Engl J Med 2012;367:1237-44.

Fontana RJ, Engle RE, Scaglione S, et al. The role of hepatitis E virus infection in adult Americans with acute liver failure. Hepatology 2016;64:1870-1880.

Kar P, Jilani N, Husain SA, et al. Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy? Am J Gastroenterol 2008;103:2495-501.

Kamar N, Mansuy JM, Cointault O, et al. Hepatitis E virus-related cirrhosis in kidney- and kidney-pancreas-transplant recipients. Am J Transplant 2008;8:1744-8.

Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. N Engl J Med 2008;358:811-7.

Kamar N, Izopet J, Tripon S, et al. Ribavirin for chronic hepatitis E virus infection in transplant recipients. N Engl J Med 2014;370:1111-20.

## 13

**Correct answer: D**

**Rationale:**
Hepatorenal syndrome is a pre-renal form of acute kidney injury caused by splanchnic vasodilation with no underlying intrinsic kidney disease.

**References:**
Runyon BA, AASLD, Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013;57:1651-3.

Salerno F, Gerbes A, et al. Diagnosis, prevention and treatment of the hepatorenal syndrome in cirrhosis: a consensus workshop of the international ascites club. Gut 2007;56:1310-1318.

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## 14

**Correct answer: B**

**Rationale:**
Portal hypertension (PH) is mechanistically important in driving many of the complications related to liver disease. The most common technique to quantify PH involves measurement and calculation of the hepatic venous pressure gradient (HVPG). Measurement involved advancing a catheter into a hepatic vein until wedged or by occlusion with a balloon catheter where the wedged hepatic vein pressure (WHVP) can be measured, the wedged and occluded pressures are essentially equal and represent the pressure within the sinusoid. With the balloon deflated or "free" position, the hepatic vein free pressure (HVFP) can be measured. The difference between WHVP and HVFP yields the HVPG (ie, HVPG = WHVP-HVFP). Classification of PH can be made through these measurements and calculation of these values. The following table is helpful in classifying varying forms of PH based on these parameters.

| | | Hepatic Vein Pressure Measurement | | |
|---|---|---|---|---|
| **Type of Portal Hypertension** | **Examples** | **Wedged (WHVP)** | **Free (FHVP)** | **Gradient (HVPG)** |
| Prehepatic | Portal vein thrombosis | Normal | Normal | Normal |
| Presinusoidal | Cirrhosis attributed to cholestatic liver disease, schistosomiasis, idiopathic portal hypertension | Normal | Normal | Normal |
| Sinusoidal | Cirrhosis attributed to alcohol/HCV/NASH | Increased | Normal | Increased |
| Postsinusoidal | Sinusoidal obstruction syndrome | Increased | Normal | Increased |
| Posthepatic | Right heart failure | Increased | Increased | Normal |

Adapted from Garcia-Tsao et al G. Hepatology 2017;65(1):310-335.

Portal vein thrombosis is a form of prehepatic PH wherein portal venous pressure proximal to the clot is markedly elevated. Pressure distal to the obstruction (WHVP and HVFP) is normal; therefore, HVPG is also normal.

HVPG is similarly normal in post-hepatic obstruction (eg, IVC web, CHF, constrictive pericarditis, or tricuspid insufficiency) owing to an elevation in both WHVP and FHVP (answer D). Intrahepatic forms of PH can be delineated to presinusoidal, sinusoidal (answer E), and postsinusoidal etiologies. Classic examples of each form can be found in the table.

### References:

Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2017;65(1):310-335.

Grozsmann RJ, Glickman M, Blei AT, Storer E, Conn HO. Wedged and free hepatic venous pressure measured with a balloon catheter. Gastroenterology 1979;76:254-258.

Grozsmann RJ, Atterbury CE. The Pathophysiology of Portal Hypertension: A Basis for Classification. Semin in Liv Dis 1982;2(3):177-186.

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## 15

### Correct answer: A

### Rationale:

There have been several studies examining risk factors contributing to post-liver transplant renal dysfunction. Several common factors have been identified across these studies with the strongest associations being increasing age and post-transplant creatinine levels. Notably, two studies have shown female sex to be a risk factor. Other clinical factors associated include pre-transplant hypertension, pre-transplant diabetes, pre-transplant renal dysfunction (Answer C), post-transplant renal dysfunction, pre-/post-dialysis, liver transplantation from a CMV positive donor, and hepatitis C (Answer B). Interestingly, when compared with cyclosporine in a study by O'Riordan et al., tacrolimus was shown to be protective against post-transplant renal dysfunction (Answer E).

### References:

Cabezuelo JB, Ramfrez P, Rios A, et al. Risk Factors of Acute Renal Failure after liver transplantation. Kidney International 2006;69:1073–1080.

Ojo AO, Held PJ, Port FK et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931–940.

O'Riordan A, Wong V, McCormick PA, et al. Chronic Kidney Disease Post-liver Transplantation. Nephrol Dial Tranpslant 2006;21:2630-2636.

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# 16

Correct answer: A

## Rationale:

This case represents an uncommon but potentially lethal complication of liver transplantation, graft-versus-host disease (GVHD). In a series of 1082 transplants among 1009 patients, Smith et al., identified 12 patients (~1% incidence) with clinical signs of GVHD. Despite its relative rarity, this presentation has an estimated mortality rate of greater than 90% making diagnosis essential.

Based on the work from Billingham, development of GVHD requires three basic conditions: (a) the graft must contain immunologically competent cells, (b) the host must be sufficiently different from the graft to be seen as antigenically foreign, and (c) the host must be incapable of mounting an effective rejection of the graft.

Clinical presentation typically presents within 2 to 6 weeks after transplant and typically start with fever and skin rash. Other signs and symptoms include GI complaints (eg, nausea, vomiting, abdominal pain, diarrhea) and cytopenias (predominantly neutropenia and thrombocytopenia). The differential diagnosis includes drug reaction and CMV infection, which may lead to a delay in diagnosis. Diagnosis can be made based on clinical presentation and confirmed through histological and immunohistochemical findings. In this case, no evidence of drug associated reaction (Answer B) was noted on biopsy.

In their series, Smith and colleagues determined risk factors associated with development of GVHD, which included both age-related factors and HLA A/B mismatches. Close matching of HLA types of donor and recipient were a significant risk factor, specifically 0-1 class 1 (HLA A/B) mismatches carried an odds ratio of more than 15. In contrast, neither 2 or more HLA class 1 mismatches nor HLA DR mismatches carried an increased risk (Answer D). That is, fewer HLA A/B mismatches are associated with an increased risk of GVHD. Additionally, recipient age 65 years or older and donor-recipient age difference of 40 or more years were associated with an odds ratio of 9.1 and 10.1, respectively. In this case, the age of the recipient and donor did not meet these criteria and are not associated with an increased risk of GVHD (Answer C). There are no data to suggest that sex of either recipient or donor confers an increased risk of GVHD (Answer E)

## References:

Billingham R. The biology of graft-versus-host reactions. Harvey Lect 1966-1967;62:21–78.

Peck GL, Elias PM, Graw RGJr. Graft-versus-host reaction and toxic epidermal necrolysis. Lancet 1972;2:1151–3.

Smith DM, Agura E, Netto G, Collins R, Levy M, Goldstein R, et al. Liver transplant-associated graft-versus-host disease. Transplantation 2003;75:118–26.

## 17

**Correct answer: D**

**Rationale:**
This liver biopsy shows venulitis, consistent with acute cellular rejection. Despite adequate immunosuppression, rejection can be encountered regularly. Treatment of mild-to-moderate rejection usually consists of corticosteroids or increased background immunosuppression. There is no evidence of cholangitis or biliary obstruction so ERCP would not be the first choice in management. Venulitis is not routinely observed in hepatic artery stenosis. There is no evidence of CMV on the biopsy. Biopsy features do not suggest alcoholic hepatitis.

**References:**
Banff Working Group, Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology 2006;44:489-501.

Lucey MR, Terrault N, Ojo L, et al. Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl 2013;19:3-26.

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## 18

**Correct answer: B**

**Rationale:**
Everolimus has been shown to delay wound healing in up to 35% of those taking the medication in combination with cyclosporine or tacrolimus. Immunosuppressants of the mTOR class can inhibit endothelial cell and fibroblast growth factors. Additionally, nitric oxide and vascular endothelial growth factor (VEGF) can be blocked leading to reduced angiogenesis and immune function within wounds. The other listed medications are not commonly thought to affect wound healing.

**References:**
Kaplan B, Qazi Y, Wellen JR. Strategies for the management of adverse events associated with mTOR inhibitors. Transplantation Reviews 2014;28(3):126-133.

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## 19

Correct answer: A

Rationale:
Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer, after hepatocellular carcinoma (HCC). Although much less common than HCC, its incidence has been rapidly increasing in the past few decades. It may develop in patients with normal liver or with underlying liver disease, and its risk factors are similar to HCC, including cirrhosis, chronic viral hepatitis, alcohol excess, diabetes, and obesity.

The diagnosis of iCCA can only be made definitively with pathology. PET scan is not accurate for early diagnosis of iCCA, and its role as a staging modality is still unclear. Assessment of resectability and/or intra- and extra-hepatic metastatic disease, as well as venous and arterial invasion, is best accomplished using radiographic studies such as CT and/or MRI. Tumor markers such as CA 19-9 are insensitive and insufficient to establish the diagnosis and may be elevated in biliary obstruction from non-malignant causes. It may, however, offer prognostic value to determine response to therapy. Surgical resection is the treatment of choice for iCCA in patients with single intrahepatic nodules and no evidence of disease dissemination, and regional lymphadenectomy provides prognostic value for staging. Patients demonstrating intrahepatic metastases, vascular invasion or obvious lymph node metastases, or those with advanced liver disease, should not undergo resection. For patients with unresectable disease, transarterial chemotherapy and radiotherapy have shown some anti-tumor effects, and ablation approaches may be considered for small, single lesions less than 3 cm if surgery is not an option. Cisplatin and gemcitabine is the systemic therapy practice standard for iCCA in patients with ECOG performance status 0 or 1, and there is no significant evidence that further chemotherapy beyond progression of first-line chemotherapy improves survival.

References:
Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014;60:1268-1289.

## 20

Correct answer: D

Rationale:
The histologic image shows moderate inflammation in the portal tracts with a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, and rare eosinophils. Foci of spillover into the hepatic parenchyma are present. These features are consistent with autoimmune hepatitis, which has developed in a patient with known primary sclerosing cholangitis by cholangiogram.

The diagnosis of autoimmune hepatitis is aided by the Autoimmune Hepatitis Scoring System, but this is more difficult in the setting of an overlap with a biliary disease such as primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC), which takes points away from the diagnosis. Autoimmune markers are also commonly present in the setting of other immune-mediated diseases such as PBC or PSC, and more reliance is placed on the histologic findings. The relatively acute rise in the serum transaminases out of proportion to the alkaline phosphatase, and the presence of plasma cells and interface hepatitis in this case support the diagnosis of autoimmune hepatitis. She was treated with prednisone and azathioprine, with resolution of the liver tests back to her baseline.

Cytomegalovirus hepatitis is histologically characterized by the presence of viral inclusions associated with mononuclear infiltrates and microabscesses. Ustekinumab use has been accompanied by mild-to-moderate elevations in serum AST and ALT in 0.5% to 1.4% of patients, but such elevations were self-limited and were no more frequent than those occurring with placebo. No cases of acute liver injury with severe aminotransaminase elevations or jaundice has been linked to ustekinumab therapy as of yet.

Primary biliary cholangitis is typically characterized by portal lymphocytic infiltrate with granulomas and presents with liver test elevations that are more of a cholestatic than a hepatitic pattern.

References:
Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E, on behalf of the International Autoimmune Hepatitis Group. Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. Journal of Hepatology 2011;54:374–385.

Livertox.org accessed at: https://livertox.nih.gov/php/searchchem.php

## 21

Correct answer: D

Rationale:

Specific clinical conditions are deemed to be appropriate for MELD exceptions based on the MELD Exceptional Case Guideline (MESSAGE) Committee Conference Document. There is inadequate evidence to support granting a MELD exception for ascites in adult candidates, as most of the excess mortality risk related to ascites is similar to portal hypertension and hepatorenal syndrome and will be accurately reflected in the lab values used to calculate the MELD score. There is also inadequate evidence to support granting a specific MELD exception for gastrointestinal bleeding in adult candidates who experience acute or chronic blood loss independent of their calculated MELD. Similarly, there is no evidence to show that candidates who require frequent blood transfusions develop antibodies while waiting for a liver transplant and warrant a MELD exception. Patients with Budd-Chiari syndrome can present as having acute liver failure or evolve to cirrhosis with portal hypertension. Available evidence suggests that factors that predict mortality in patients with chronic Budd-Chiari syndrome are aligned with the MELD score and that patients with acute liver failure can be prioritized according to the acute liver failure allocation policy. Hence, MELD exception points should not be necessary for Budd-Chiari syndrome. MELD exception for chronic rejection is also not recommended, as it is anticipated that progressive allograft dysfunction due to rejection will be appropriately reflected in the development of liver dysfunction, and prioritization by the calculated MELD score may be appropriate. In primary hyperoxaluria, progressive deposition of calcium oxalate leads to renal failure, which increases the pretransplant mortality risk. Thus, hyperoxaluria complicated by renal failure and proven by liver biopsy will qualify for automatic MELD/PELD exception award.

References:

Freeman Jr RB, Gish RB, Harper A, Davis GL, Vierling J, Lieblein L, Klintmalm G ,Blazek J, Hunter R, Punch J. Model for End-Stage Liver Disease (MELD) Exception Guidelines: Results and Recommendations From the MELD Exception Study Group and Conference (MESSAGE) for the Approval of Patients Who Need Liver Transplantation With Diseases Not Considered by the Standard MELD Formula. Liver Transplantation 2006;12:S128-S136.

## 22

**Correct answer: B**

**Rationale:**
The general approach to therapy of PTLD involves a step-wise strategy that starts with reduced immunosuppression, with plans for further escalation of treatment based largely on the clinical response and the histopathologic characteristics of the PTLD. Reported response rates to immunosuppression reduction have been highly variable (0–73%), likely reflecting the heterogeneity and size of the populations studied and the nonstandardization of immunosuppression reduction. Complete or partial surgical resection as well as radiation therapy have been used as adjunctive therapy for localized disease with reduction of immunosuppression. Antiviral agents such as acyclovir and ganciclovir, with or without immunoglobulin, have had variable results in the management of early PTLD, whereas combination of arginine butyrate with ganciclovir seems to be more promising. Cytotoxic chemotherapy such as CHOP, ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) and ProMACE CytoBOM (mechlorethamine, doxorubicin, cyclophosphamide, etoposide, vincristine, prednisone, procarbazine, methotrexate, cytarabine, bleomycin) was used as initial chemotherapy to treat PTLD, but its high rate of toxicity is allowing rituximab, an anti-CD20 humanized chimeric monoclonal antibody, to become a more preferred agent.

**Reference:**
Allen UD, Preiksaitis JK, the AST Infectious Disease Community, Epstein-Barr Virus and Post-transplant lymphoproliferative disorder in solid organ transplantation. Liver Transplantation 2013;13:107-120.

Dierickx D and Cardinaels N. Posttransplant lymphoproliferative disorders following liver transplantation: where are we now? World J Gastroenterol 2015;21(39):11034-11043

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## 23

**Correct answer: A**

**Rationale:**
Humoral or antibody-rejection may occur in ABO-compatible liver transplants and concomitantly with acute rejection. The histologic diagnosis is supported by the detection of C4d-positive staining. Treatment of humoral rejection is based on two complementary approaches: (1) the removal of harmful antibodies from the blood stream through plasmapheresis or immunoadsorption and (2) the modulation of various components of specific and/or innate immunity using strategies including intravenous immunoglobulin, anti-CD20 antibody (rituximab), anti-thymocyte globulin (ATG), proteasome inhibitor (bortezomib), or anti-C5 antibody (eculizumab). There is no role for belatacept, steroid boluses, mTOR inhibitor, or thymoglobulin therapy to treat humoral rejection.

**References:**
Cuadrado A, San Segundo D, Lopez-Hoyos M, Crespo J, Fabrega E. Clinical significance of donor-specific human leukocyte antigen antibodies in liver transplantation. World J Gastroenterol 2015 October 21; 21(39):11016-11026.

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## 24

**Correct answer: C**

**Rationale:**
Patients who have C282Y homozygous or compound heterozygous hemochromatosis with elevated liver enzymes or ferritin level greater than 1000 ng/mL are at increased risk of advanced liver fibrosis or cirrhosis. Therefore, it is recommended that these patients should undergo liver biopsy to grade and stage their liver disease before undergoing phlebotomy.

**References:**
Bacon et al. Diagnosis and Management of Hemochromatosis: 2011 Practice Guideline by the American Association for the Study of Liver Diseases. Hepatology 2011:54;328-43.

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## 25

**Correct answer: C**

**Rationale:**
Hepatitis B has a high rate of vertical (mother-to-child) transmission. In the absence of passive and active immunization, infants born to hepatitis B-infected mothers, especially those with active viral replication (high HBV DNA) have a high (>90%) chance of developing chronic HBV. This can be reduced to less than 5% with use of hepatitis C immunoglobulin (HBIG) and vaccine combination. This mother should also be treated with either tenofovir or telbivudine (both category B) starting in the third trimester to further reduce the risk of vertical transmission.

**References:**
Terrault et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: ASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-99.

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## 26

Correct answer: C

Rationale:

Patients with suspected alcoholic hepatitis should be admitted to the hospital to ensure complete infectious evaluation, support alcohol abstinence, provide nutrition support, and for consideration of medical therapy in severe cases. Severity and prognosis of alcoholic hepatitis should be assessed with a scoring system upon hospital admission. Data for the efficacy of glucocorticoids in severe acute alcoholic hepatitis have yielded conflicting results with some demonstrating improved 28-day survival among those with an Maddrey's Discriminant Function greater than 32 or MELD greater than 20, especially in those with encephalopathy. Glucocorticoid therapy could be considered in this patient after an assessment for infections. The potential improvement in early survival with glucocorticoids may be offset by increased infectious complications impacting 90-day and 1-year survival outcomes. The STOPAH clinical trial found no statistically significant improvement in survival at any time point (28-days, 90-days, or 1 year) with either prednisolone or pentoxifylline. The presence of systemic inflammatory response syndrome (SIRS) in acute alcoholic hepatitis is associated with increased risk of multiorgan failure and mortality; thus, this patient has multiple identifiers of poor prognosis. All patients admitted with jaundice and suspected alcoholic hepatitis should be evaluated for infection, regardless of fever, and a high index of suspicion for infection should remain even if initial infectious evaluation is negative. In this patient, presenting signs and symptoms for alcoholic hepatitis overlap significantly with those of sepsis. Alcohol abstinence, nutrition support, folic acid and B vitamin supplementation, and avoidance of nephrotoxins are mainstays of best supportive care for alcoholic hepatitis and have likely contributed to improved survival observed in placebo groups from more recent randomized controlled trials. Enteral nutrition therapy is the preferred route of support given favorable impact on intestinal barrier function and lower risk of infection. While the patient may be a reasonable candidate for diuretic therapy for his ascites and edema, this is best delayed to assess and manage infection and determine the trajectory of his kidney function. Given reported alcohol cessation 2 weeks ago and evidence of hepatic encephalopathy, benzodiazepine therapy may be both unnecessary and potentially harmful given risk of decline in his mental status. Close medical monitoring for signs and symptoms of withdrawal is appropriate.

References:

EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease. J Hepatol 2012;57:399-420.

Medical Management of Severe Alcoholic Hepatitis:Expert Review from the Clinical Practice Updates Committee of the AGA Institute Clinical Gastroenterology and Hepatology 2017;15:512.

Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619–1628.

## 27

**Correct answer: D**

**Rationale:**
Surgical resection is a curative option for HCC, but the patient is a poor candidate in view of portal hypertension, multifocal disease, and decompensated cirrhosis. The patient can be a candidate for liver transplantation as his HCC is within Milan Criteria. The patient does not have a class 5B lesion as his lesions are not greater than or equal to 2 cm and less than 5 cm. However, he does have 2 class 5A lesions as defined by a lesion greater than 1 cm and less than 2 cm with arterial enhancement, venous washout, and peripheral rim enhancement (pseudocapsule). Patients with 2 to 3 class 5A lesions can qualify for automatic upgrade with MELD exception points after 6 months as per UNOS policy. Sorafenib is not a curative option for patients with HCC.

**References:**
Martin P, et al. Evaluation for liver transplantation in adults: 2013 practice guidelines of the AASLD and the American Society of Transplantation. Hepatology 2014:59;1144-65.

UNOS Policy 9. Allocation of Livers and Liver-Intestines. Available at https://optn.transplant.hrsa.gov

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## 28

**Correct answer: B**

**Rationale:**
In a multicenter study of 663 Japanese patients who underwent ABO-incompatible living donor liver transplantation, only the absence of rituximab prophylaxis was a significant predictor of the risk of antibody-mediated rejection, which in turn was a significant risk for poor overall survival. There were no significant differences between the incidences of acute cellular rejection, bacterial infection, or CMV disease between the rituximab and non-rituximab groups, and the rate of fungal infection was significantly lower in the rituximab group than in the non-rituximab group.

**References:**
Egawa et al. Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation: A Japanese multicenter study. Am J Transpl 2014;14:102-114.

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## 29

**Correct answer: C**

**Rationale:**
His cirrhosis is advanced (as evidenced by the refractory ascites and high MELD-Na), and TIPS will likely cause his liver to decompensate further. Diuretics will likely exacerbate the hyponatremia. He does not have hepatorenal syndrome, although adding midodrine to the outpatient medications may be reasonable. A low salt diet should be part of the recommendation but will not control his tense ascites. This patient should be referred for liver transplant evaluation (although this was not an answer choice that was provided).

**References:**
Runyon et al. Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012 Hepatology 2013;57(4):1651-1653.

Salerno et al. Gastro 2007;133:825-834.

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## 30

**Correct answer: C**

**Rationale:**
Liver biopsy remains the gold standard for diagnosis of nonalcoholic steatohepatitis. Steatosis, lobular inflammation, and presence of ballooned hepatocytes are necessary features on liver biopsy that support a diagnosis of nonalcoholic steatohepatitis. While fibrosis is typically distributed in a perisinusoidal and/or periportal manner, presence of fibrosis is not necessary for establishing a diagnosis. Interface hepatitis and plasma cells are typically found in autoimmune hepatitis but not in NASH.

**References:**
Bedossa P; FLIP Pathology Consortium. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology 2014;60:565-575.

Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, et al. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Hepatology 2012;56:1751-1759.

Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-1321.

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## 31

Correct answer: A

Rationale:

Liver disease is commonly encountered in cystic fibrosis. The most common hepatic histologic manifestation of cystic fibrosis is hepatic steatosis. Hepatic steatosis in cystic fibrosis patients is reported to be seen in as many of 65% of cystic fibrosis patients. While cholestasis and neocholangiogenesis described as “focal biliary cirrhosis” is the classic histology, statistically, hepatic steatosis is most commonly encountered. Interface hepatitis describes autoimmune hepatitis, although this would be considered less likely given the clinical features. Microabscesses are described with infectious etiologies, especially cytomegalovirus infection. Hepatic sinusoidal dilation can be seen with hepatic outflow obstruction or cardiac dysfunction. Advanced cystic fibrosis can lead to cor pulmonale and portopulmonary hypertension.

References:

van Mourik IDM. Liver disease in cystic fibrosis. Paediatrics and Child Health 2017;27(12):552-555.

## 32

Correct answer: B

Rationale:
Steatosis lowers mitochondrial membrane potential and causes deterioration in mitochondrial function. Kupffer cell activity is increased and the sinusoidal lining is disrupted and narrowed. These changes enhance cell damage during cold ischemia and potentiate ischemia/reperfusion injury. Higher degrees of steatosis have been associated with primary non-function (PNF), graft failure, early renal failure, and biliary complications. However, good graft outcomes may be achieved by minimizing other risk factors such as donor age and longer cold ischemia time.

Hepatic artery thrombosis is associated with intraoperative factors, including duration of the hepatectomy, arterial reconstruction (aortic conduit use, in particular) and multiple transfusions. Other potential factors including episodes of acute rejection, hypercoagulable state, and CMV infection may also play a role.

Donor steatosis has not been associated with increased risk of acute or chronic rejection.

References:
Durand F, Renz JF, Alkofer B, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. Liver Transpl 2008;14:1694-707.

Fukumori T, Ohkohchi N, Tsukamoto S, et al. The mechanism of injury in a steatotic liver graft during cold preservation. Transplantation 1999;67:195-200.

Silva et al, Hepatic Artery Thrombosis Following Orthotopic Liver Transplantation: A 10 Year Experience from a Single Centre in the United Kingdom. Liver Transpl 2006;12:146 –151.

Spitzer AL, Lao OB, Dick AA, et al. The biopsied donor liver: incorporating macrosteatosis into high-risk donor assessment. Liver Transpl 2010;16:874-84.

## 33

**Correct answer: A**

**Rationale:**
Sofosbuvir/velpatasvir daily for 12 weeks (answer A) is one option for treatment of NS3 protease inhibitor (telaprevir, boceprevir, or simeprevir) + pegylated interferon/ribavirin treatment-experienced genotype 1 patients with compensated cirrhosis. Other recommended regimens include:

- Glecaprevir/pibrentasvir for 12 weeks
- Ledipasvir/sofosbuvir for 12 weeks
- Elbasvir/grazoprevir plus weight-based ribavirin for 12 weeks (genotype 1a patients without baseline NS5A RASs) or 16 weeks (genotype 1a patients with baseline NS5A RASs)

B is incorrect: The correct regimen that includes ledipasvir/sofosbuvir requires weight-based ribavirin and treatment for 12 weeks. C is incorrect: The correct regimen that includes elbasvir/grazoprevir would need the addition of weight-based ribavirin. D is incorrect: Glecaprevir/pibrentasvir requires 12 weeks of treatment

**References:**
AASLD-IDSA. NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients With Compensated Cirrhosis. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/treatment-experienced/gt1/ns3/compensated-cirrhosis.

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## 34

**Correct answer: B**

**Rationale:**
The risk difference is the decimal greater than or less than 1.0 in the hazard ratio (HR), with a HR greater than 1.0 meaning increased risk (+%) and HR less than 1.0 meaning reduced risk (-%). In this case, the point estimate HR is 1.18, which means that LDLT has an 18% higher risk of biliary complications in the adjusted model than DDLT.

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## 35

**Correct answer: D**

**Rationale:**

Although this patient has decompensated cirrhosis and would clearly benefit from liver transplantation, his MELD score is not competitive in his region. In the absence of a decompensating event or qualifying for MELD exception points, it is unlikely that he will receive a liver transplant in the near future. The development of HCC within Milan criteria does qualify for MELD exception points; however, a 1.8-cm HCC does not qualify for exception points, so answer A is incorrect. Patients with hepatopulmonary syndrome with room air PaO2 less than 60 mmHg qualify for MELD exception points; however, his room air PaO2 is 65 mmHg, so answer B is incorrect. Although agreeing to accept an anti-HBc positive donor, or other so-called “marginal” livers such as steatotic livers or livers from older donors can increase the pool of donor livers that patients are eligible to receive, these practices are common in high MELD regions and will not dramatically increase his chance for transplant. The median MELD score at transplant varies as much as 12 points between different regions. In some regions, a MELD score of 25 may be immediately competitive for transplant, so answer D is correct.

**References:**

OPTN/SRTR 2015 Annual Data Report: Liver. DOI: 10.111/ajt.14126

## 36

**Correct answer: B**

**Rationale:**

The correct answer is B, 4 cm. In December 2017, UNOS implemented a national hepatocellular carcinoma downstaging policy. Under this policy, patients with a tumor burden can be downstaged to within T2 (Milan Criteria) as long as the index tumor burden does not exceed defined criteria.

To be eligible for standard MELD exception, the criteria for maximum tumor burden are:

- One lesion greater than 5 cm and less than or equal to 8 cm
- Two or three lesions each less than 5 cm and total diameter of all lesions less than or equal to 8 cm
- Four or five lesions each less than 3 cm and total diameter of all lesions less than or equal to 8 cm

This tumor burden needs to be downstaged to within T2 (Milan Criteria) as defined by the below criteria:

- One lesion less than 5 cm
- Two or three lesions less than 3 cm

In the vignette, the patient has two lesions each measuring 2 cm in size, so the maximum size of the third lesion is 4 cm for a total tumor burden of 8 cm.

In addition to criteria for the size and number of liver tumors, criteria for alpha fetoprotein (AFP) are also used. Patients with AFP less than 1000 ng/mL are eligible for standard MELD exception. Patients with AFP exceeding 1000 ng/mL must have a reduction of AFP to less than 500 ng/mL to be eligible for standard MELD exception.

Patients are granted a standard MELD exception only after they have reached T2 (Milan Criteria) and AFP criteria. During the first 6 months, no additional MELD points are granted. After this 6-month waiting period, patients are granted 28 MELD exceptions points as long as tumor burden remains within T2 (Milan Criteria) and AFP criteria. Each subsequent 3-month interval, patients are eligible for an increase in MELD exception by 2 points; eg, 30, 32, then to a maximum score of 34.

**References:**

United Network for Organ Sharing policy 9. Available at http://optn.transplant.hrsa.gov

## 37

**Correct answer: D**

**Rationale:**
Transplant listing decisions can be contingent on the ability to pay. The likelihood of success is generally regarded as legitimate criterion for allocating scarce organs. If one cannot afford to pay for aftercare or medication, graft and patient survival will suffer. Charity care does not have infinite capacity with average billable charges for organ transplants approaching $1 million in the first year and $30,000 yearly thereafter. To continue to provide the service to the greatest number of people possible, ability to pay has to be considered. OPTN and NOTA expressly forbid discrimination or preference on the basis of race, citizenship, or celebrity status. ICU status may indicate that patient is too ill for transplant, but simply being in an ICU cannot be used as criterion to deny transplantation. Undocumented immigrants may receive transplants if they are able to pay for the care. They also can and do donate organs in the US, accounting for 3.3% of deceased donors. Most of the donated organs are transplanted into US citizens. Contribution to the donor pool means that undocumented immigrants do not count as "transplant tourists" by the Declaration of Istanbul.

**References:**
Grubbs V. Undocumented Immigrants and Kidney Transplant: Costs and Controversy. Health Aff 2014;33(2):332-335.

Wightman A, Diekema D. Should an Undocumented Immigrant Receive a Heart Transplant? AMA Journal of Ethics 2015;17(10):909-913.

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## 38

**Correct answer: D**

**Rationale:**
In A2ALL, at 5 years post-transplant, there were no significant differences in graft survival for left lobe recipients compared with right lobe recipients (86% [95% CI 74–93] vs 82% [95% CI 69–89]; *P*=0.85) or recipient survival (90% vs. 84%, *P*=0.44). Left lateral segments are generally too small for adult recipients.

**References:**
Braun HJ, Dodge JL, Roll GR, et al. Impact of Graft Selection on Donor and Recipient Outcomes Following Living Donor Liver Transplantation. Transplantation 2016;100(6):1244-1250.

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## 39

Correct answer: B

Rationale:
Tamoxifen therapy has been linked to the development of both nonalcoholic fatty liver and nonalcoholic steatohepatitis. Fatty liver is typically seen after 1 to 2 years of therapy and can progress.

Simvastatin may cause elevations in serum ALT during therapy. More significant injury can also occur and present with a variety of patterns, including hepatocellular, cholestatic, or mixed pattern. However, the development of fatty liver is not associated with this medication.

Etanercept has been associated with development of autoimmune hepatitis and induction of auto antibodies. Although the patient has elevated ANA and ASMA, the liver biopsy shows fatty liver, which is not typical of this drug.

Nitrofurantoin is one of the most common causes of drug inducted liver injury. Multiple patterns of injury have been reported, both in the acute and chronic form. Acute injury is typically hepatocellular. The chronic form typically presents during long term prophylaxis and can mimic autoimmune hepatitis. Fatty liver is not seen with either the acute or chronic form of injury.

References:
Bruno et al. Incidence and risk factors for non-alcoholic steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial. BMJ 2005;330:932.

LiverTox: Clinical and Research Information on Drug-Inducted Liver Injury. Available at https://livertox.nlm.nih.gov/

Yeh, et al. Pathology of Nonalcoholic fatty liver disease. Am J Clin Pathol 2007;128:837-847.

## 40

**Correct answer: C**

**Rationale:**
The two most important predictors of transplant-free survival are total bilirubin (TB) and alkaline phosphatase (ALP) response to ursodeoxycholic acid. These 2 factors are used in the 2 main predictions scores (GLOBE PBC Score and UB-PBC Score) and have been determined to be independently predictive of transplant-free survival in a very large database set of PBC patients. While the other answers (INR and variceal bleeding) are noted to be signs of advanced liver failure, TB is the only answer listed (ALP is not listed but is also correct) that has been shown to be predictive of transplant-free survival. Pruritis and other symptoms (eg, fatigue) do not correlate with stage of disease or outcomes. ALT has not been shown to be predictive of survival.

**References:**
Carbone, et al. Hepatology 2016;63(3) 930-950.

Lammers, et al. Gastro 2014;147(6):1338-1349.

Lammers, et al. Gastro 2015;149(7):1804-1812.