1. A 50 year old man is seen in the office for routine evaluation. He is asymptomatic. He acknowledges drinking one pint of liquor per day for many years. Physical examination reveals marked hepatomegaly, without splenomegaly. Liver enzymes include AST 65 and ALT 25 (normal for each less than 50). CBC, coagulation studies, bilirubin and albumin are normal. If this patient were to undergo liver biopsy, which of the following findings is MOST LIKELY to be present:

   A. Microvesicular steatosis
   B. Macrovesicular steatosis
   C. Macronodular cirrhosis
   D. Mallory’s hyaline
   E. Ballooning degeneration of hepatocytes with polymorphonuclear infiltrate

The recommended response is B.

Macrovesicular steatosis is virtually universal following heavy alcohol use. It is usually asymptomatic but commonly causes hepatomegaly. Microvesicular steatosis is characteristic of disorders of mitochondrial fatty acid oxidation and is a rare manifestation of alcoholic liver disease. Findings of alcoholic hepatitis, such as Mallory’s hyaline, cellular ballooning and polymorphonuclear infiltrate, occur in about 20% of heavy drinkers. Similarly only about 20% of chronic heavy users of alcohol
develop cirrhosis, typically micronodular. It should be noted that absence of findings to suggest alcoholic hepatitis or cirrhosis (leukocytosis, jaundice, splenomegaly, ascites, etc.) does not exclude these possibilities, as they are often insidious and subclinical.


2. In a patient hospitalized for severe alcoholic hepatitis, which of the following would be an indication to treat with methylprednisolone?

A. New onset of confusion and asterixis
B. Massive variceal hemorrhage
C. Ascites with spontaneous bacterial peritonitis
D. Albumin less than 3.0 g/dl
E. AST/ALT ratio greater than 2

The recommended response is A

The most reliable marker of poor short term prognosis in alcoholic hepatitis is the presence of hepatic encephalopathy. Severe jaundice and coagulopathy with a Maddrey discriminant function greater than 32 (calculated according to the formula Bilirubin (mg/dl) + 4.6 x [Prothrombin time – control] ) also identifies patients with high mortality. In these groups steroids appear to improve short term survival. Patients
lacking these findings have not been shown to benefit from steroids. Steroid use is relatively contraindicated in the setting of infection or gastrointestinal bleeding.


3. A 60 year old man is referred because of abnormal liver tests. He is obese (BMI 36) and has mild elevations of cholesterol and triglyceride, managed with diet and simvastatin. He takes hydrochlorothiazide for mild essential hypertension and acetaminophen 1 g twice daily for back pain. He denies alcohol use. Physical examination is unrevealing except for moderate abdominal obesity. Liver panel reveals AST 75, ALT 60 (upper limit of normal for each = 50) with normal alkaline phosphatase, bilirubin, albumin and INR. CBC is normal except for platelets 120,000. Fasting glucose is 160. Serological tests for hepatitis B and C are negative and ceruloplasmin, alpha-1-antitrypsin, anti-nuclear antibody and transferrin saturation are normal. Abdominal ultrasound reveals an echogenic liver. Of the following, the test most likely to lead to the correct diagnosis is:

A. Magnetic resonance imaging
B. Serum protein electrophoresis
C. Plasma acetaminophen level
D. Liver biopsy
E. Repeat liver tests following withdrawal of simvastatin

The recommended response is D.

This is a common clinical scenario describing the presentation of a patient with non-alcoholic steatohepatitis and early cirrhosis. The patient has multiple manifestations of the metabolic syndrome, including obesity, fasting hyperglycemia, hyperlipidemia, and hypertension and he is at very high likelihood of having non-alcoholic fatty liver disease. This possibility is supported by the finding of an echogenic liver. AST > ALT and thrombocytopenia are both subtle indicators of cirrhosis and suggest the presence of more aggressive non-alcoholic steatohepatitis. Magnetic resonance imaging can confirm hepatic fat, but the distinction between simple NAFLD, NASH and cirrhosis can only be made by liver biopsy. Serum protein electrophoresis showing elevated immune globulins might suggest a diagnosis of autoimmune hepatitis, but again a liver biopsy would be needed to distinguish this from NAFLD. Acetaminophen is not hepatotoxic at doses less than 2.5 g/d and plasma levels are only helpful in the setting of acute overdose toxicity. Simvastatin can cause low grade transaminase elevations but would not explain thrombocytopenia, AST > ALT or echogenic liver.

4. All of the following treatments are rational and appropriate in patients with non-alcoholic fatty liver EXCEPT:

A. Avoidance of iron supplements and alcohol  
B. Dietary weight loss  
C. Regular exercise  
D. Insulin sensitizing agents (metformin, pioglitazone)  
E. High carbohydrate, low fat diet

The recommended response is E.

Non-alcoholic fatty liver disease and steatohepatitis are thought to be caused by hyperinsulinism, which evolves in response to insulin resistance. Weight loss and exercise improve insulin sensitivity. Insulin sensitizing agents also are rationale and are under study. Though their benefits are not yet proven in NAFLD, it is reasonable to prefer these drugs in patients requiring drug therapy for control of type II diabetes. High carbohydrate diet increases insulin release and should be avoided in patients with the metabolic syndrome. Alcohol aggravates steatosis and iron may increase liver injury and inflammation in NAFLD.

5. Shortly after birth, an infant becomes jaundiced. Bilirubin is absent from the urine. Liver enzymes and albumin are normal and the liver is not palpable. Despite phototherapy the baby develops seizures and dies. Post mortem examination reveals kernicterus with bilirubin staining of the basal ganglia. Genetic analysis is most likely to reveal a hereditary disorder of:

A. The hepatic canalicular phospholipid transporter ABC B4
B. The hepatic canalicular bile acid transporter ABC B11
C. The hepatic mitochondrial fatty acid oxidizing enzyme LCADH
D. The hepatic bilirubin UDP-glucuronosyltransferase UTG1A1
E. The hepatic canalicular bilirubin transporter ABC C2

The recommended response is D.

The clinical scenario describes a patient with type 1 Criggler-Najjar syndrome. The otherwise normal liver tests suggest that the defect is an isolated bilirubin abnormality. The absence of bilirubin in urine and development of kernicterus are manifestations of unconjugated hyperbilirubinemia, which develops because deficient UGT1A1 prevents bilirubin glucuronidation. Conjugated hyperbilirubinemia is characteristic of the Dubin-Johnson syndrome caused by ABC C2 deficiency. Conjugated bilirubin is water soluble and appears in urine; it is not neurotoxic and does not cause kernicterus. The defects of the canalicular bile acid and phospholipid transporters are associated with progressive
familial intrahepatic cholestasis types 2 and 3, respectively; hyperbilirubinemia when it occurs is conjugated and is part of a more generalized cholestasis with progressive liver injury. Mitochondrial fatty acid oxidizing defects produce microvesicular steatosis and liver failure.


6. A 24 year old medical student is referred to you for evaluation of hyperbilirubinemia. He is asymptomatic. He denies drug or alcohol use. Liver tests previously have been normal and he has given blood several times over the past year without being refused. He is on no medications. He denies any family history of liver disease. Physical examination is normal. Fasting blood tests reveal total bilirubin of 2.1 (upper limit of normal 1.5) with direct bilirubin of 0.2. Liver enzymes, albumin and INR are normal, as are complete blood count and haptoglobin. The next step in management of this patient should be:

A. Liver imaging (ultrasound, CT or MRI)
B. Liver biopsy
C. Genetic testing for a hepatic transport defect
D. Genetic testing for a hepatic metabolic defect
E. Reassurance; no further testing

The recommended response is E.
This is a typical presentation of Gilbert’s syndrome, a very common condition in which a mild variation in the UGT1A1 promoter region leads to reduced activity of bilirubin UDP-glucuronosyltransferase, resulting in mild unconjugated hyperbilirubinemia. Genetic testing can confirm the gene abnormality (an elongated 7 TA repeat in the DNA polymerase binding region of the UGT1A1 gene promoter) but is expensive and unnecessary. About 15% of the U.S. population is homozygous for this abnormality. Liver function is normal and the defect is of no clinical significance. Liver biopsy and liver imaging would reveal only normal liver and would not be helpful.


7. Hepatic adenomas are a frequent complication in which of the following diseases?
   A. Wilson’s disease
   B. Type 1 glycogen storage disease
   C. Type 1 progressive familial intrahepatic cholestasis
   D. Nodular regenerative hyperplasia
   E. Primary biliary cirrhosis

The recommended response is B.
Patients with glycogen storage disease who survive to adulthood frequently develop multiple hepatic adenomas. The pathogenesis is unknown. Solitary hepatic adenomas are a rare complication of oral contraceptive use. They are not encountered in the other disorders listed.


8. A husband and wife seek your advice. Last year their daughter died of cirrhosis at the age of thirty. A nephew on the husband’s side also developed cirrhosis as a young adult. The couple’s older son, age 25, has recently been found to have a mild abnormality of serum transaminases with normal bilirubin. A younger son, age 20, has normal liver tests. None of the affected individuals uses alcohol, none is obese, and none is chronically infected with hepatitis B or C. The couple are in their mid-50’s and apparently healthy. You suspect a hereditary liver disease. Possibilities include mutations involving any of the following EXCEPT:

A. HFE
B. TfR2 (coding for the type 2 transferrin receptor)
C. ATP7B (coding for hepatic copper transporting p-type ATPase)
D. SERPINA1 (coding for alpha-1-antitrypsin)
E. UGT1A1 (coding for bilirubin UDP-glucuronosyl transferase)
The recommended response is E.

UGT1A1 defects, including Gilbert’s syndrome and Criggler-Najjar syndrome, lead to impaired bilirubin conjugation with indirect hyperbilirubinemia. Liver function is otherwise unimpaired and cirrhosis does not occur. HFE and TfR2 defects are associated with classical adult hemochromatosis. ATP7B defects cause Wilson’s disease. SERPINA1 mutations are responsible for alpha-1-antitrypsin deficiency. All can cause cirrhosis in young adults.


9. In the preceding case, with further testing, both sons are found to have fasting transferrin saturation greater than 90%. The older son’s circulating ferritin is 2,500, whereas the younger son’s ferritin is 400 (upper limit of normal = 200). You receive additional history that the daughter who died was found at autopsy to have a hepatic iron index of 3.5 and was homozygous for the HFE C282Y mutation. At this time you recommend all of the following EXCEPT:

A. The older son should be tested for the C282Y mutation of the HFE gene

B. For the older son, liver biopsy may be justified to rule out cirrhosis

C. The younger son should be tested for the C282Y mutation

D. For the younger son, liver biopsy may be justified to rule out cirrhosis
E. The father and mother should have transferrin saturation and ferritin measured.

The recommended response is D.

If transaminases are normal and ferritin is less than 1000 at the time of diagnosis of hereditary hemochromatosis, cirrhosis is rarely present and liver biopsy is not required. If there is evidence of liver disease or ferritin is greater than 1000, liver biopsy should be done to look for cirrhosis. Patients with cirrhosis at diagnosis have a lifelong risk of hepatocellular carcinoma despite phlebotomy and may benefit from cancer surveillance. Both sons have a high likelihood of hereditary hemochromatosis and the genotype should be confirmed. One or both of the parents may also have hemochromatosis and this possibility needs to be excluded; the absence of clinical manifestations in the sixth decade of life does not exclude this possibility, since rate of accumulation of iron is highly variable.


10. In the preceding case, in which the daughter who died was C282Y homozygous, what is the approximate probability that her mother carries at least one C282Y mutant HFE allele?

A. 100%
Critique: Classical HFE hemochromatosis is an autosomal recessive disorder. One allele is inherited from each parent. Therefore each parent is either heterozygous or homozygous for C282Y.

11. In the preceding case, the C282Y homozygous daughter who died of hemochromatosis had a child the year before she died. The baby’s father is of Irish descent. Given the prevalence of hemochromatosis, what is the approximate probability that the baby is homozygous for C282Y?

A. 0.1-0.2%
B. 0.5-1.0%
C. 4-8%
D. 40-60%
E. 80-100%

The recommended response is C.
About 1 of every 8 individuals of Northern European ancestry is heterozygous for C282Y (1 in 200 is homozygous). If a C282Y heterozygote marries a heterozygote, each child has a 50% likelihood of being C282Y homozygous. Without knowing the father’s genotype, the estimated risk for each child is about 1 in 16, or slightly more than 6%.


12. In the preceding case, the baby undergoes genetic testing and is found to be homozygous for C282Y. With appropriate management, what is the approximate lifetime risk that this child will die of complications of hemochromatosis?

A. Zero
B. 5%
C. 20%
D. 50%
E. 80%

The recommended response is A.

All manifestations of hemochromatosis are caused by excessive iron deposition in tissues. If the genotype is identified prior to iron accumulation, iron indices can be monitored,
phlebotomy can be initiated early, and hemochromatosis complications should be prevented. Unwillingness of insurers to provide life and health insurance coverage to C282Y homozygotes is irrational and inappropriate.


13. An autosomal dominant form of hemochromatosis accompanied by high levels of hepcidin production is associated with mutations of the gene coding for which of the following?

A. HFE protein  
B. Transferrin receptor type 2  
C. Hemojuvelin  
D. Hepcidin  
E. Ferroportin

The recommended response is E.

Ferroportin gene defects are thought to lead to hemochromatosis because the altered ferroportin does not recognize hepcidin. Unlike the forms of hemochromatosis associated with the other genes listed, the ferroportin defect is expressed in a dominant
manner. The liver mechanisms regulating hepcidin are intact, and hepcidin expression therefore increases in a futile attempt to suppress iron hyperabsorption. All of the other choices are genes associated with forms of hemochromatosis in which hepcidin expression is inappropriately reduced due to abnormalities either in the hepcidin gene itself or in regulation of hepcidin gene expression.


14. A 25 year old woman is referred to you by her psychiatrist because of abnormal liver tests. She has been exhibiting bizarre behavior for several months, complaining of difficulty speaking and swallowing, and has recently lost her job as an accountant because of inattentiveness. Routine screening laboratory studies revealed AST 150, ALT 110, alkaline phosphatase 40, albumin 3.0, and bilirubin 1.5. She was previously healthy, is not obese, and denies alcohol use. She is an only child and reports no family history of liver disease. Tests for hepatitis B and C have been negative. Physical examination is noteworthy for a hard nodular liver edge palpable at the costal margin and a palpable spleen tip. Based on the history and physical findings you suspect Wilson’s disease. All of the following would support this diagnosis EXCEPT:

A. Finding of corneal rings on slit lamp examination
B. Low serum ceruloplasmin
C. Low 24 hour urinary copper excretion
D. Presence of rhodamine positive granules in hepatocytes on liver biopsy
E. Homozygosity for the ATP7B defect H1069Q

The recommended response is C.

In Wilson’s disease, biliary copper secretion is impaired. Free copper increases in the circulation, as does urinary copper excretion. All of the other findings listed are typical of Wilson’s disease and are among the criteria used to establish a diagnosis. Corneal rings are a late finding, but usually are present by the time patients develop neurological manifestations.


15. In the preceding case, having established a diagnosis of Wilson’s disease, you should begin her immediately on which of the following oral mineral supplements:
A. Iron
B. Selenium
C. Copper
D. Zinc
E. Chromium

The recommended response is D.

Zinc induces intestinal metallothionein, which binds copper and prevents its transfer from the epithelial cell into the circulation.


16. In the preceding case, having established a diagnosis of Wilson’s disease in this patient, which of the following considerations regarding chelation therapy is TRUE?

A. Trientene is more toxic than D-penicillamine
B. Trientene is more effective than D-penicillamine
C. Neurological symptoms often worsen following initiation of D-penicillamine
D. Early liver transplantation is usually preferable to chelation
E. Treatment benefits of chelation will not become apparent for several years.
The recommended response is C.

One of the dangers of chelator therapy is the risk of causing acute neurological deterioration in as many as half of patients. Trientine is less toxic than D-penicillamine but also is a less potent chelator. Liver transplantation usually is unnecessary. Chelation leads to normalization of liver tests within months and improvement of neurological symptoms over 1-2 years; additional improvement after 2 years is unlikely.


17. The alpha-1-antitrypsin (protease inhibitor) genotype associated with the highest risk of cirrhosis is:

A. ZZ
B. SS
C. MM
D. MS
E. MZ

The recommended response is A.
The Pi (protease inhibitor) ZZ genotype of alpha-1-antitrypsin is the most severe form associated with liver disease. The SS form is milder and rarely causes liver disease. MM is normal. MS and MS heterozygotes are at low risk of liver disease, though there is some evidence that they may be more susceptible to autoimmune and other forms of liver injury.


18. A 40 year old man, not previously known to have liver disease, is found incidentally on abdominal ultrasound to have a solitary 3 centimeter liver mass. Biopsy reveals hepatocellular carcinoma and cirrhosis. Staging studies show no evidence of vascular invasion or metastasis. He is referred to you for consideration of liver transplantation. He acknowledges prior alcohol abuse but has been sober for three years and is committed to sustained sobriety. He is not infected with hepatitis B or C or with HIV. He is otherwise healthy except for mild obesity. He has no significant lung disease, heart disease or neurological findings on pretransplant evaluation. Of the following possible etiologies of his liver disease, which is associated with the WORST prognosis for one year post-transplant survival?

A. Wilson’s disease
B. Alcoholic cirrhosis
C. Non-alcoholic steatohepatitis
D. Alpha-1-antitrypsin deficiency
E. Hereditary hemochromatosis

The recommended response is E.

Patients with hereditary hemochromatosis have unusually poor survival after transplantation with one year mortality on the order of 30-40%. This is related at least in part to risk of infections and congestive cardiomypathy. The cardiomyopathy often is not clinically apparent prior to transplantation. All of the other conditions are associated with one year post-transplant mortality of no more than 10-20% in well selected patients.


19. A newborn child at age six weeks is found to be jaundiced with marked bilirubinuria. Hepatomegaly is present on physical examination and transaminases are elevated. Complete blood count is normal. Which of the following hereditary disorders is most likely to be the cause of this clinical presentation?

A. Wilson’s disease
B. Criggler-Najjar syndrome
C. Alpha-1-antitrypsin deficiency
D. Hereditary hemochromatosis due to ferroportin gene defect
E. Hereditary hemochromatosis due to HFE gene defect (C282Y homozygous)

The recommended response is C.

Alpha-1-antitrypsin deficiency is the most common cause of neonatal hepatitis. Wilson’s disease can present at any age but is rare in the neonatal period. In Criggler-Najjar syndrome, bilirubin-UDP-glucuronosyl transferase deficiency produces unconjugated hyperbilirubinemia and does not cause bilirubinuria, transaminase elevations or hepatomegaly. Hereditary hemochromatosis caused by HFE does not become manifest until iron accumulates and is not encountered during the first year of life. Ferroportin gene defects produce mild iron overload in adults.


20. A previously healthy 40 year old woman presents to you complaining of fatigue and dark urine for several weeks. She denies alcohol use and is on no medications. She is jaundiced. The liver is mildly enlarged and slightly tender on physical examination. Neurological examination is normal. Laboratory tests are noteworthy for AST 1000 ALT 1500 and alkaline phosphatase 350. Bilirubin is 10 mg/dl and INR is 1.3. Serological tests of hepatitis A, B and C are negative. Anti-smooth muscle antibody is positive at 1:320 and levels of immunoglobulin G are twice normal. Ultrasound reveals diffuse hepatomegaly, normal bile ducts and
normal gallbladder. Liver biopsy would be expected to show which of the following findings?

a. Perivenular polymorphonuclear inflammation with ballooning of hepatocytes and Mallory bodies
b. Infiltration of portal tracts with lymphocytes and plasma cells; interface hepatitis with piecemeal necrosis along limiting plate
c. Infiltration of portal tracts with lymphocytes and destruction of interlobular bile ducts
d. Noncaseating granulomas in hepatic parenchyma and portal tracts
e. Ground-glass hepatocytes with lobular inflammation, diffuse apoptosis and Councilman bodies.

The recommended response is B.

This is a typical acute presentation of type 1 autoimmune hepatitis. Liver biopsy demonstrates lymphocytes and plasma cells infiltrating the portal tracts and causing piecemeal necrosis of hepatocytes along the limiting plate, a phenomenon termed interface hepatitis. There is relative preservation of bile ducts. This is in contrast to primary biliary cirrhosis, in which interlobular bile ducts are the target for autoimmune injury and liver parenchyma is relatively spared. Noncaseating granulomas can be seen in a number of conditions but are characteristic of hepatic sarcoidosis; autoimmune markers typically are absent and liver enzymes have a more cholestatic pattern.
Pericentral polymorphonuclear inflammation, ballooning and Mallory bodies are typical findings of alcoholic hepatitis; this condition rarely produces transaminase elevations over 500, and the ratio of AST to ALT is almost always greater than 1. Ground glass hepatocytes, lobular inflammation and apoptosis are typical findings of hepatitis B infection.


21. A 40 year old woman is referred to you because of elevated alkaline phosphatase of 350 iu/ml with normal transaminases. She acknowledges being troubled by itching and fatigue for the last year or two but has otherwise been healthy. Physical examination is noteworthy for xanthelasmas above the eyes. She is not icteric and the liver is not palpable. Laboratory testing is noteworthy for elevated antimitochondrial antibody and increased serum level of immunoglobulin M. Liver biopsy reveals mononuclear portal infiltration with destruction of interlobular bile ductules. Which of the following therapies should be initiated?

A. Prednisone alone
B. Prednisone plus azathioprine
C. Azathioprine alone
D. Ursodeoxycholic acid
E. Methotrexate
The recommended response is D.

This is a typical case of primary biliary cirrhosis. Ursodeoxycholic acid therapy improves cholestasis and may retard progression of fibrosis and delay time to transplantation in this disorder. Prednisone and/or azathioprine are employed in autoimmune hepatitis but are ineffective in primary biliary cirrhosis, and the steroids may worsen osteopenia. Methotrexate in randomized clinical trials has also been shown to be ineffective for treatment of PBC.


22. A 40 year old woman with chronic severe rheumatoid arthritis develops upper gastrointestinal hemorrhage. Physical exam reveals splenomegaly but no stigmata of cirrhosis. Endoscopy reveals esophageal varices. Liver enzymes, bilirubin, albumin and INR are persistently normal. On CT and ultrasound the portal and hepatic veins and their tributaries appear patent and the liver appears diffusely nodular. Percutaneous needle liver biopsy is unremarkable; in particular, no significant fibrosis is present. This constellation of findings is most consistent with which of the following diagnoses?
   a. Nodular regenerative hyperplasia
   b. Primary biliary cirrhosis
   c. Primary sclerosing cholangitis
d. Hepatic venoocclusive disease

e. Autoimmune hepatitis

The recommended response is A

Nodular regenerative hyperplasia is a rare complication of systemic autoimmune diseases in which immune complex deposition in small portal and hepatic venules leads to venular obliteration, ischemic atrophy of perivenular hepatocytes and compensatory hypertrophy of periportal hepatocytes. While most patients are asymptomatic, a few develop complications of portal hypertension. Liver function is normal. Inflammation and hepatic fibrosis are absent and the diagnosis often is not possible on needle biopsy; larger wedge biopsy is usually required. The other disorders listed produce portal hypertension only in the context of progressive fibrosis leading to cirrhosis; liver tests and biopsy are almost always abnormal in patients with these conditions by the time they have developed portal hypertension.


23. A 30 year old man without prior history of liver disease undergoes myeloablative therapy for acute myelogenous leukemia, followed by bone marrow transplantation. Two weeks later he develops jaundice, tender hepatomegaly, ascites and edema. AST is
elevated at 500 IU/ml and alkaline phosphatase is mildly elevated. The most likely explanation for his liver disease is:

A. Septic phlebitis of the portal vein (pylephlebitis)
B. Hepatic veno-occlusive disease
C. Acute viral hepatitis from blood products
D. Acute acalculous cholecystitis
E. Budd-Chiari syndrome

The recommended response is B.

Hepatic veno-occlusive disease is a common complication of bone marrow transplantation, usually seen within the first 4 weeks. It occurs when myeloablative treatment with chemotherapeutic drugs and radiation damages sinusoidal and venular epithelium. Septic portal phlebitis is a rare condition associated with intra-abdominal infections such as appendicitis. Acute viral hepatitis from blood product transfusion is rare today, has a minimum incubation of 4 weeks, and would not cause ascites. Acalculous cholecystitis can occur in this setting but would not produce ascites and usually would not cause jaundice. Budd Chiari syndrome results from thrombosis of large hepatic veins, especially in patients with hypercoagulable states; jaundice occurs relatively late.