

# Viral Hepatitis, Non-alcoholic Fatty Liver Disease, Autoimmune Hepatitis

## Steven Herrine, MD

### Educational Goals

By the completion of this lecture you should be familiar with the:

1. Classification, nucleic acid and mode of transmission the six known hepatotropic viruses.
2. Incubation period and serologic profile in acute and chronic viral hepatitis.
3. Clinical course of acute and chronic viral hepatitis.
4. Identification, natural history and sequelae of fulminant viral hepatitis.
5. Classification, demographics and natural history of non-alcoholic fatty liver disease (NAFLD)
6. Approach to diagnosis and treatment of autoimmune hepatitis

### Key words:

- active immunoprophylaxis
- adefovir
- anti-HAV IgG, IgM
- anti-HBc IgG, IgM
- anti-HBs
- anti-HCV
- antinuclear antibody (ANA)
- anti-smooth muscle antibody (ASMA)
- autoimmune hepatitis
- azathioprine
- cerebral edema
- cirrhosis
- coinfection
- corticosteroids
- cryoglobulinemia
- end-stage liver disease
- extrahepatic manifestations
- fulminant hepatitis
- glomerulonephritis
- HBeAg
- HBsAg
- HBV DNA
- HCV RNA
- hepatocellular carcinoma
- hypergammaglobulinemia
- icteric phase
- immunoglobulin
- interferon
- lamivudine
- neutralizing antibody
- non-alcoholic fatty liver disease (NAFLD)
- passive immunoprophylaxis
- peginterferon
- porphyria cutanea tarda
- steatohepatitis
- steatosis
- superinfection
- sustained virologic response
- tenofovir
- vertical transmission

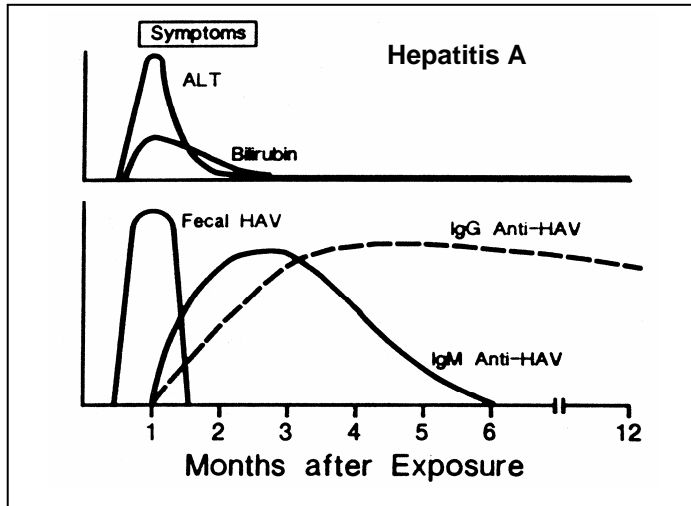
### I. Hepatotropic Viruses

Virus	Classification	Nucleic Acid	Transmission
A	Picornavirus	RNA	Enteral
B	Hepadnavirus	DNA	Parenteral
C	Flavivirus-like	RNA	Parenteral
D	Viroid-related	RNA	Parenteral
E	Calcivirus	RNA	Enteral
G	Flavivirus-like	RNA	Parenteral

### II. Acute Viral Hepatitis - clinical or biochemical evidence of liver disease of less than six months duration

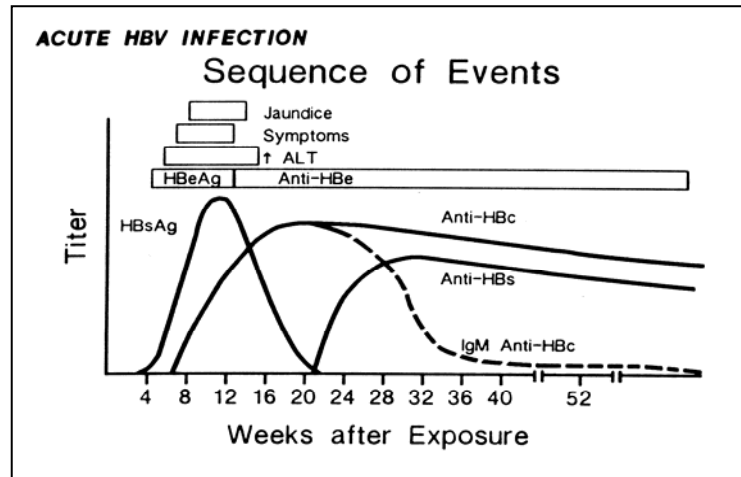
#### A. Hepatitis A

1. Incubation period of 15-45 days (mean 30 days)
2. Viral replication takes place in the liver. Virus is present in liver, bile, stool and blood during incubation. Virus is shed in the stool; shedding ↓ with onset of jaundice
3. Anti-HAV IgM present at onset of illness, **IgG is the persistent antibody, and is protective against future infection**



B. Hepatitis B

1. Incubation period of 30-180 days (mean 80 days)
2. HBsAg is the first serologic marker of infection
3. HBeAg and HBV DNA appear shortly after HBsAg
4. Disappearance of HBeAg and HBV DNA connotes a good prognosis
5. anti-HBc analogous to anti-HAV in that **IgM is a marker of acute infection**, IgG is the persistent antibody. However, anti-HBc is not protective
6. anti-HBs appears after clearance of HBsAg. **Anti-HBs is the protective ("neutralizing") antibody**



C. Hepatitis D (delta hepatitis agent)

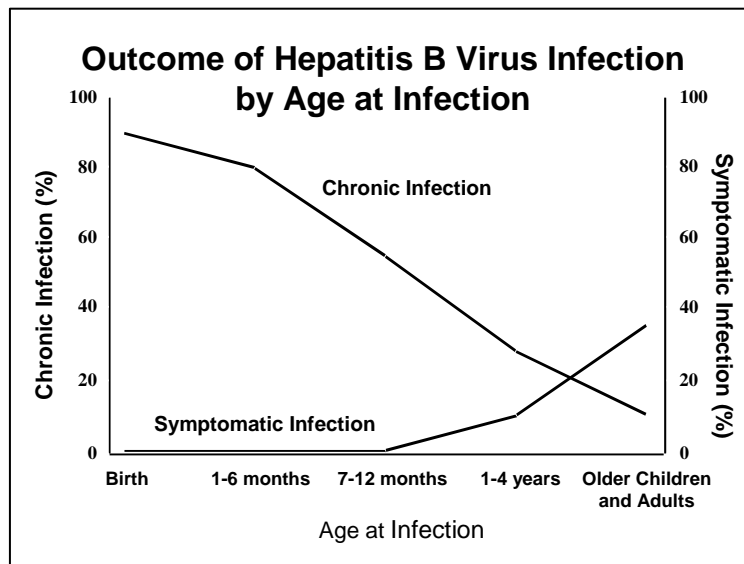
1. Requires presence of HBV (or other hapadnaviruses) for replication and expression
2. Can infect via coinfection or superinfection
  - a) Coinfection: clearance of HBsAg usually accompanied by clearance of anti-HDV
  - b) Superinfection: HDV infection usually becomes chronic

D. Hepatitis C

1. Incubation period of 15-160 days (mean 50 days)
2. HCV RNA is earliest marker of infection.
3. anti-HCV appears at 6-8 weeks, but is **not a neutralizing antibody**
4. The majority of acute HCV is subclinical and asymptomatic

E. Hepatitis E

1. Incubation period of 14-60 days (mean 35 days)
  2. Infection is enteric and usually from contaminated water. Usually occurs in India, Asia, Africa and Central America. Person-to-person spread is rare
  3. Recovery is the rule, except in pregnancy, where fulminant hepatitis occurs in 10-20%
- F. Hepatitis G
1. Member of the flaviviridae family, as is hepatitis C
  2. Risk of transmission similar to HCV (transfusion, IVDU)
  3. High prevalence among liver transplant recipients
  4. Not convincingly shown to be a cause of hepatitis in humans
- G. Clinical manifestations of acute viral hepatitis
1. Signs and Symptoms
    - a) Prodromal symptoms: anorexia, nausea, vomiting, fatigue, malaise, fever
    - b) Icteric phase: jaundice, right upper quadrant pain
    - c) Recovery phase: constitutional symptoms disappear, lab abnormalities improve
    - d) **Hospitalization is indicated** for inability to take oral fluids, synthetic dysfunction (coagulopathy) or encephalopathy
  2. Laboratory features
    - a) Serum aminotransferases (AST and ALT) often exceed 1000 IU
    - b) Bilirubin elevations follow and may persist despite fall in transaminases
    - c) Elevations of prothrombin time (PT) or International Normalized Ratio (INR) indicate synthetic dysfunction and poor prognosis
  3. Prognosis
    - a) Hepatitis A: Virtually all patients recover without sequelae. Variants include relapsing hepatitis and cholestatic hepatitis. Rarely causes fulminant hepatitis. **Chronic hepatitis A never occurs**
    - b) Hepatitis B: 95% recover without sequelae. Fulminant hepatitis seen in ~1%. Chronic hepatitis is estimated to occur in 1-10% of adults, but much more



commonly in infants with vertical transmission (see figure below)

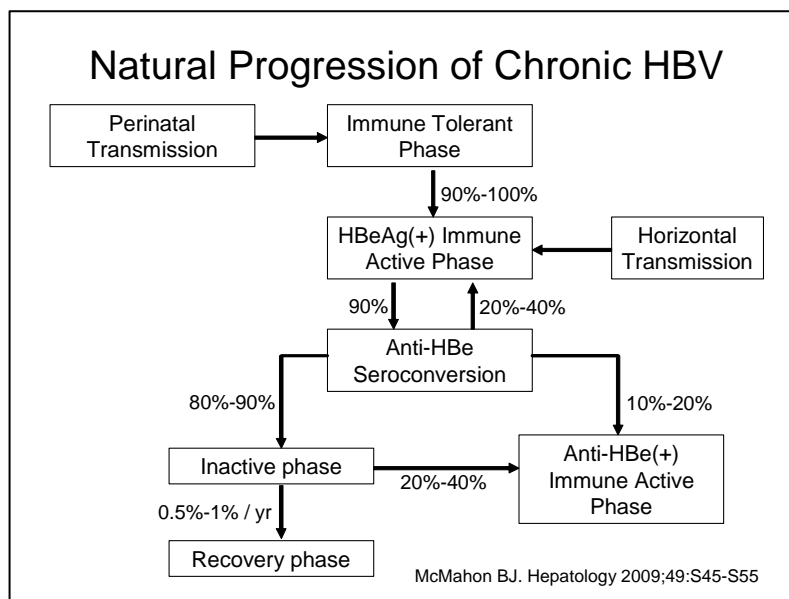
- c) Hepatitis C: An estimated **85% of cases become chronic**
  - d) Hepatitis D: In coinfection, prognosis similar to acute HBV alone, in superinfection, mortality appears increased
  - e) Hepatitis E: Prognosis is good **except in pregnant women**
  - f) Hepatitis G: does not appear to cause liver disease in humans
4. Passive and active immunoprophylaxis

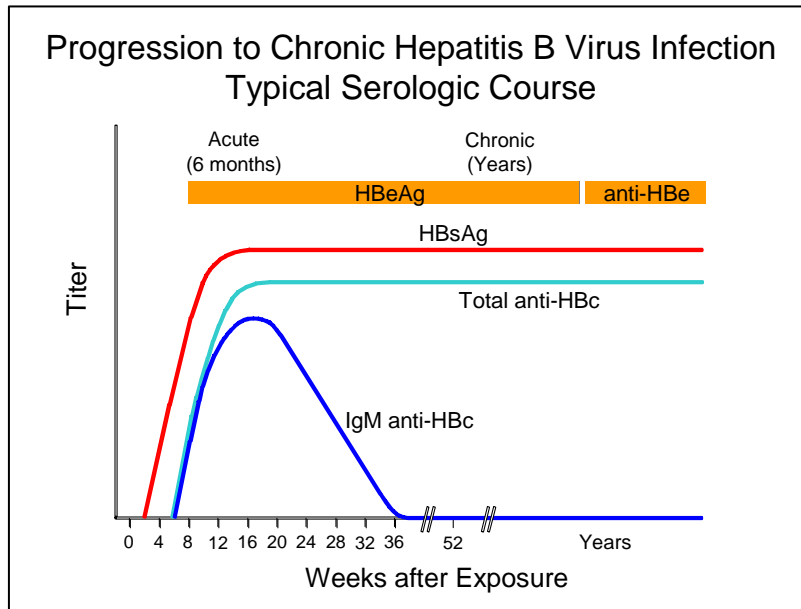
- a) Hepatitis A: Household and institutional contacts: immunoglobulin (IG). Highly effective vaccine is available
- b) Hepatitis B: preexposure prophylaxis: vaccine to individuals at risk (healthcare workers, hemodialysis patients, custodial institutional staff, inmates of long-term correctional facilities, promiscuous individuals, household and intimate contacts of chronic HBsAg carriers). Postexposure prophylaxis: combination of hepatitis B immune globulin (HBIG) and vaccine
- c) Hepatitis C: screening of blood donors. Use of IG for needle stick is not recommended
- d) Hepatitis D: prevention strategy is to immunize against HBV
- e) Hepatitis E: No data on use of IG. Vaccine under development

### III. Chronic Hepatitis - clinical or biochemical evidence of liver disease of at least six months duration

#### A. Hepatitis B - **persistent HBsAg is the *sine qua non* of chronic HBV**

1. Infection at birth (vertical transmission) becomes chronic in approximately 90% of infections
2. Adult acquired infection is estimated to become chronic in 1-10% of cases
3. **Phases of chronic hepatitis B infection**
  - a) Immune tolerant phase
    - Usually perinatal infection
    - Transaminases normal
    - HBV DNA high (> 200,000 IU/mL)
    - Mild histology
  - b) Immune active (clearance) phase)
    - a. Elevated ALT
    - b. HBV DNA > 20,000 IU/mL in HBeAg+
    - c. HBV DNA >2000 IU/mL in anti-HBe+
    - d. Active histology
  - c) Inactive phase
    - a. Anti-HBe+
    - b. ALT levels normal
    - c. HBV DNA low (< 2000 IU/mL)
  - d) Recovery phase
    - a. Clearance of HBsAg
    - b. HCC screening still recommended
4. Patients with chronic hepatitis B have an **increased risk of hepatocellular carcinoma**, even those without cirrhosis





## B. Hepatitis C

1. Chronicity (persistent viremia at least six months after transmission) estimated to occur in 85% of infections
2. **Progression to cirrhosis estimated to occur in 20-30%** over 10-30 years
3. Even with significant histologic hepatitis, infection can be asymptomatic
4. Chronic hepatitis C is the **most common indication for liver transplantation** in US
5. Chronic hepatitis C carries an increased risk of hepatocellular carcinoma, probably limited to those with cirrhosis (note difference with HBV, where HCC is seen prior to development of cirrhosis)

## C. Clinical Considerations in Chronic Hepatitis

1. Hepatitis B: ranges from asymptomatic to debilitating end-stage disease
  - a) Symptoms: fatigue, jaundice, anorexia, pruritis, cachexia
  - b) Signs of end-stage liver disease: ascites, edema, GI bleeding, coagulopathy, encephalopathy, hypersplenism
  - c) Exacerbations of acute hepatitis-like symptoms usually represent viral reactivation
  - d) Extrahepatic manifestations due to immune complex deposition: arthralgias, arthritis, leukocytoclastic vasculitis, glomerulonephritis, polyarteritis nodosa
2. Hepatitis C: Severe histologic activity and even cirrhosis can be present in asymptomatic infected individuals.
  - a) Symptoms: fatigue is common, jaundice is unusual
  - b) Signs of end-stage liver disease the same as in chronic hepatitis B
  - c) Extrahepatic manifestations: cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda

## D. Treatment of chronic viral hepatitis

1. Hepatitis B
  - a) Interferon
    - 1) used in immune active HBV infection
    - 2) 40% seroconversion rate from HBeAg(+) to HBeAg (-) and/or clear serum HBV DNA, 10% clear HBsAg
    - 2) Successful therapy is often accompanied by a transient increase in serum transaminases

- 3) Interferon side effects: "flu-like" symptoms, bone marrow suppression, irritability, thyroiditis. Suicide reported in previously depressed patients
  - 4) Interferon not recommended in clinically decompensated hepatitis B infection
  - b) **Nucleoside/nucleotide analogues**
    - 1) Lamivudine: Seroconversion in 30%-40%, but high viral mutation rate.
    - 2) Adefovir dipivoxil, approved in 2002: less mutations
    - 3) Entecavir, approved in 2005: more potent antiviral, few mutations to date
    - 4) Telbivudine, approved 2006, similar mutation pattern as lamivudine
    - 5) Tenofovir, approved 2008. Similar mutation pattern to adefovir
    - 6) New agents: clevudine, emtricitabine, valtorcitabine
  - c) Reinfection and decompensation is common after liver transplantation in those with chronic replicative hepatitis B. The use of nucleoside/nucleotide analogues and HBV immune globulin has allowed successful transplantation in this group
  - d) **Reactivation of HBV** can be seen in chronically infected patients undergoing immunosuppression of chemotherapy. Prophylaxis with nucleoside/nucleotide analogues is recommended
2. Hepatitis C
- a) Current standard of care: subcutaneous **peginterferon weekly plus oral ribavirin** for 6-12 months
  - b) Sustained virologic response (lack of detectable HCV RNA by PCR in serum six months after cessation of treatment) is seen in about 50%
  - c) Interferon not recommended in patients with decompensated liver disease
  - d) Reinfection with hepatitis C is common after liver transplantation. Approximately 20% of those reinfected with hepatitis C will develop cirrhosis in their graft within 5 years. Therapy in this group with interferon has met with limited success.
  - e) Interferon side effect profile similar to that in hepatitis B
  - f) Development of specific antivirals is in phase III (protease inhibitors)

#### IV. Fulminant Hepatitis

- A. Definition: Onset of encephalopathy within 6 weeks of onset of liver disease (usually identified by jaundice)
- B. Etiology
  1. Most common identified etiology of fulminant hepatitis is **acetaminophen toxicity**
  2. Most frequent identifiable etiology of **infectious** fulminant hepatic failure is HBV
    - a) Fulminant hepatitis is rare in hepatitis A (0.01-0.1% of cases). 40% survival rate is best among viral etiologies
    - b) Although hepatitis B is the most common cause of fulminant viral hepatitis, only 1% of cases of hepatitis B have a fulminant presentation
    - c) Fulminant hepatitis C has been described but is rare
    - d) Fulminant hepatitis is seen in both hepatitis D coinfection and superinfection
    - e) Hepatitis E infection in pregnancy: fulminant presentation in 10- 20% of cases
  3. There are numerous other causes of fulminant hepatic failure
    - a) Other viruses: Herpes Simplex Virus (HSV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV)
    - b) Toxins: acetaminophen, amanita mushrooms, chemicals, idiosyncratic
    - c) Miscellaneous: Wilson's disease, acute fatty liver of pregnancy, ischemia, hepatic vein thrombosis (Budd-Chiari syndrome), malignancy
- C. Clinical Manifestations
  1. **Onset of encephalopathy within 6 weeks of onset of liver disease**
  2. Lab features: high transaminases, synthetic dysfunction (prolonged prothrombin time, impaired gluconeogenesis), hypotension, renal failure, hypoxemia
  3. **Cerebral edema**: leading cause of mortality; bacterial infection is second
  4. Medical management is supportive: protect airway, treat infection, support blood pressure, decrease intracranial pressure
  5. Consideration for liver transplantation should begin immediately

## V. Non-alcoholic Fatty Liver Disease (NAFLD)

- A. Definition/Epidemiology
  1. NAFLD is a clinicopathological condition which histologically resembles alcoholic liver disease but occurs in patients that deny alcohol use. NAFLD is subdivided into **steatosis (no hepatocellular necrosis) and steatohepatitis**
  2. Associated with non-insulin dependent diabetes mellitus, obesity, hyperlipidemia
  3. Estimated to affect 10%-25% of the population, depending on the region. Incidence as high as 50%-75% in obese individuals
  4. The most common cause of abnormal serum aminotransferases in blood donors
  5. The most common cause of asymptomatic elevation of serum aminotransferases once other causes of liver disease are excluded
  6. NAFLD may be a leading cause of what is now termed "cryptogenic cirrhosis"
- B. Pathogenesis: Incompletely understood. Increasing amounts of clinical and laboratory evidence points to peripheral insulin resistance and its sequelae as an important cofactor in the development of NAFLD
- C. Clinical Features:
  1. The most common presentation of NAFLD is asymptomatic elevation of serum aminotransferases. Cholestatic liver chemistries are occasionally seen
  2. Patients with **NAFLD can progress to cirrhosis** and end-stage liver disease, although the incidence of such progression is a matter of controversy
- D. Diagnosis
  1. Hepatomegaly is commonly detectible on physical examination
  2. Ultrasound, CT and MRI are all fairly sensitive techniques to detect fat in the liver.
  3. Liver biopsy can differentiate simple steatosis from the more progressive steatohepatitis. Histologic findings are indistinguishable from alcoholic liver disease
- E. Treatment
  1. Because the cause of this disease is unclear, there is no **currently accepted pharmacologic therapy**. Management has been limited to control of the underlying risk factors, such as diabetes, hyperlipidemia and obesity
  2. Thiazolidinediones may emerge as useful pharmacologic therapy
  2. Anecdotal reports using gemfibrozil, betaine, metformin have been encouraging

## VI. Autoimmune Hepatitis

- A. Definition/Epidemiology
  1. A chronic inflammatory condition of the liver characterized by hepatocellular inflammation, necrosis and fibrosis
  2. Also known as chronic active hepatitis, lupoid hepatitis, plasma cell hepatitis
  3. Three types: (I, II, III) are defined; only **type I, by far the most common**, will be presented here
  4. A disease predominantly of young to middle-aged women
- B. Pathogenesis
  1. Liver injury is due to cell-mediated immune attack of hepatocytes
  2. Lymphocytes become sensitized to hepatocytes membrane proteins
  3. Humoral immunity may contribute to extrahepatic manifestations of autoimmune hepatitis by way of immune complex deposition
- C. Clinical Features
  1. Similar to presentation of viral hepatitis: can present insidiously or acutely
  2. Fatigue, myalgias, right upper quadrant pain, jaundice can be presenting features
  3. Rapid recognition and treatment is essential for good outcome. Autoimmune hepatitis can progress to cirrhosis in a matter of months. Untreated severe autoimmune hepatitis is associated with a mortality of 40%
- D. Diagnosis
  1. Because this disease causes hepatocellular injury, **elevated serum transaminases** are usually present. Transaminase elevation occasionally above 1000 U/L. Severe cases can present with elevations in bilirubin and alkaline phosphatase

2. **Antinuclear antibody (ANA) and anti-smooth muscle antibody (ASMA)** are often positive, sometimes in high titer
3. Hypergammaglobulinemia (>3.0 g/dL) is supportive of diagnosis
4. Liver biopsy is a useful adjunct in the diagnosis of autoimmune hepatitis. Features include portal inflammation, lobular inflammation, **plasma cell infiltration**, hepatocytes apoptosis. Severe cases may demonstrate bridging necrosis, periportal collapse, and fibrosis

#### E. Treatment

1. Most cases respond dramatically to **corticosteroid treatment**. In fact, response to corticosteroids is often used as part of the diagnostic criteria for the disorder
2. The disease can relapse with tapering or discontinuation of corticosteroids
3. Azathioprine can increase the chance of successful withdrawal of steroids

### VII. References

#### Viral Hepatitis

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#### Autoimmune hepatitis

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### VIII. Study Questions

1. A 25 year old woman presents to her family physician with 2 weeks of fatigue, followed by two to three days of nausea/vomiting, right upper quadrant abdominal pain and now, jaundice. She recently returned from a spring break vacation to Central America. On exam, she is dehydrated, lethargic, displays scleral icterus, tender hepatomegaly but no asterixis. Labs are notable for total bilirubin 5.1 mg/dL, direct bilirubin 3.4 mg/dL, alkaline phosphatase 260 U/L, AST 2900 U/L, ALT 3200 U/L, albumin 3.5 g/dL, INR 2.1. Serology: anti-HAV IgG(+), anti-HAV IgM(-), HBsAg(+), anti-HBc IgG(+), anti-HBc IgM(+), anti-HBs(-), anti-HCV(-).
    - What is the cause of her acute hepatitis?
    - Does she need to be admitted to the hospital?
    - What is the likely outcome of this infection?
    - Is she likely to be infectious?
    - What would a liver biopsy show?
2. An asymptomatic 58 year old woman with a history of hypothyroidism is found on routine laboratory evaluation to have the following results: total bilirubin 0.8 mg/dL, direct bilirubin 0.3 mg/dL, alkaline phosphatase 96 U/L, AST 460 U/L, ALT 670 U/L, albumin 3.8 g/dL, INR 0.9. her physical examination is unremarkable. Further evaluation reveals the following: Serology: anti-HAV IgG(+), anti-HAV IgM(-), HBsAg(-), anti-HBc IgG(+), anti-HBc IgM(-), anti-HBs(+), anti-HCV(-). Antinuclear antibody and anti-smooth muscle antibodies are detectable. Liver biopsy shows portal inflammation with a predominance of plasma cells.
    - What is the likely diagnosis?
    - What is the best treatment?
    - Does this patient require hepatitis A vaccination? Hepatitis B vaccination?