**Hepatitis B Infection**

**Epidemiology / risk factors:**

* Transmission: percutaneously, sexually, perinatally
* Affects 1.25 million persons in the US; 350-450 million worldwide
* Leads to 1 million deaths worldwide from cirrhosis, liver failure, HCC
* Symptoms: usually asymptomatic, especially in children
* Screen the following groups:
  + Signs and symptoms of acute hepatitis
  + Chronic liver disease (chronically elevated ALT or AST)
  + Persons born in countries with HBV prevalence >= 2% (asia, africa, south pacific, middle east, russia, eastern europe, and certain parts of latin america, inuit/eskimo)
  + Pregnant women \* *many people infected perinatally or in childhood!*
    - >90% infected infants develop lifelong infection
  + Those requiring immunosuppressive therapy \* *hep B reactives with immunosuppression (can be fatal): chemotherapy, anti-TNF therapy, steroids (Hep B reactivates upon withdrawal from steroids)*. Patients need to be prophylaxed during treatment with chemo and for at least 6 months afterwards
  + Patients born to parents from high risk / high prevalence areas
  + Injection drug users
  + Persons with HIV or HCV
  + Screen families!

**Natural Course:**

* **immune-tolerate phase:** most pts immune tolerant in first 2 decades of life. High levels of HBV in serum, very active viral replication, but normal transaminases. Low rate of spontaneous clearance.
* **immune-reactive phase:** *immune response leads to hepatocyte lysis* with flare in aminotransferase levels – can sometimes can see frank hepatic failure during immune reactivity.  Increased immune pressure on the virus suppresses viral DNA and accelerates clearance of HBeAg with seroconversion to anti-HBe Ab.  *Only approx 20% "clear" disease and become HepBsAg negative.*
* **low-replicative phase:** patient transitions to inactive carrier state. Serum HBV DNA levels are low, aminotransferase levels are not elevated, and anti-HBe usually has replaced HBeAg. Previously considered "healthy carrier" state, but pts still with risk for future flare and progression of fibrosis. Can be considered "inactive carrier" state with normal LFTs and viral load < 2,000. *Can reactivate at any time - and seems that 20% reactivate*
* **reactivation phase:** increased HBV viral load from spontaneous mutation in the core or core promotor or precode region of viral genome. In eAg negative patients, transaminases fluctuate but fibrosis accelerates and it's associated with an increased rate of HCC

**Diagnosis:**

* DNA virus with reverse transcription – incorporates into human DNA
* **HepBsAg:** serologic hallmark of HBV infection. Appears 1-10 weeks after exposure then usually undetectable after 4-6 months. Persistence after 6 months implies chronic infection. In pts with chronic infection, rate of clearance is approx 0.5% per year.
* **HepBsAb (anti-HBs):** disappearance of surface antigen is followed by appearance of surface Ab.
* **Hep B core Ag:** core antigen is intracellular, expressed in infected hepatocytes. NOT detected in serum.
* **Hep B core Ab**: IgG Ab against core antigen persists in patients who recover from acute hep B as well as those who progress to chronic infection
* **Hep B e Antigen:** secretory protein from precore protein. Marker of HBV replication and infectivity. Presence of this is usually associated with high levels of viral replication.
  + **Hep B e Ag negative:** truncated versions of virus that has evolved/mutated. This is a less antigenic form that's better able to avoid immune response, leading to preferential replication and expansion. Loss of HBeAg typically presents during later phases of chronic HBV infection and is associated with lower HBV DNA levels and higher prevalence of advanced fibrosis
* **Hep B e Antibody:** seroconversion usually occurs early in pts with acute infection, prior to development of antibody to surface antigen. Seroconversion to anti-HBe is usually associated with decreased in viral load and remission of liver disease, although some patients will continue to have active liver disease even with seroconversion.
* Biopsy: helpful to determine the degree of liver damage if it's not clear by labs. Biopsies have significant sampling error and may under read 1-2 degrees of cirrhosis

**Treatment:**

* Treatment: for most patients, treatment is only suppressive and pts relapse when medications are stopped (except for perinatal treatment, treatment is now considered lifelong)
* **Treatment indicated:**pts with *acute liver failure, cirrhosis and clinical complications*, *cirrhosis or advanced fibrosis* with HBV DNA in serum, or r*eactivation of chronic HBV after chemotherapy or immunosuppression*; *infants* born to women who are HBsAg-positive (give immunoglobulin and vaccination)
* Treatment **may** be indicated: pts in immune-active phase who do not have advanced fibrosis or cirrhosis
* Treatment **not** routinely indicated: pts with chronic hep B in immune-tolerant phase (with high levels of serum HBV DNA but normal serum ALT levels or little activity on liver biopsy); pts in inactive carrier state or low replicative phase (with low levels of or no detectable HBV DNA in serum and normal serum ALT levels); patients who have latent HBV infection (HBV DNA without HBsAg)
* Treatment is non-toxic, just expensive. Drugs of choice are **entecavir or tenofovir.** May take up to 6-12 months to have viral load undetectable and may never completely be undetectable.

**Follow up:**

* Continue to monitor LFTs, hep B DNA quant, pretty much FOREVER. Cannot predict who will reactivate - course is variable
* If pt has positive HBV quant, follow transaminases every 3 months for approx 2 years, then q6mo long term. Follow up hep B viral load every 6 months. Follow CBC and full LFTs every year to check for cirrhosis (low platelets, low albumin)
* **HCC surveillance:** AFP every 6 months, sono every 6-12 months for men > 40, women > 40-50, and if African **> 20.** Family history doubles the risk of HCC
* Counseling: partners/families need testing/vaccination. Encourage smoking/etoh cessation and weight management

**References:**

* Jan Diamond (I miss you! Thank you for so much of this information!)
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* Ganem and Pince (2004). Hepatitis B Virus Infection – Natural History and Clinical Consequences. NEJM (350); 11: 1118-1129.
* Uptodate: “Diagnosis of hepatitis B virus infection”