Hepatitis B Virus Infection

Case: A healthy 38-year old man presents with jaundice and is found to have acute icteric hepatitis B virus infection despite no obtainable history of exposure and the belief that he was vaccinated in the past.

Epidemiology and transmission
- U.S. is considered a low prevalence (0.1–2%) area; in low-prevalence areas, predominant modes of transmission are sexual intercourse and IVDU.
- In SE Asia, China, Africa prevalence is 10-20%; worldwide prevalence largely reflects high incidence of vertical transmission (40-50% of women of reproductive age are HbeAg+) and ~90% rate of progression to chronicity of perinatal infection.
- Infection rate of infants born to HBeAg+ mothers is 90%.
- HBV survives long periods outside the body, so it is postulated (without firm evidence) that transmission between breaks in the skin via close bodily contact, toothbrushes, razors, tattooing, body piercing, even children’s toys (?) can occur.
- Transfusion-related HBV has decreased dramatically (to 1 in 63,000) with donor screening, which uses HbsAg, and anti-HBe Ab (for detection of window period and low level chronic HBV infection); in U.S. survey, 0.4% of blood donors admitted to high-risk behavior within 3 months before donation.
- Nosocomial infection – HBV is the most commonly transmitted blood-borne virus, but transmission is still very rare; exposures are associated with needle sticks, surgery, pathology, hemodialysis, oncology units, and organ transplants.

Pathogenesis and mechanism of liver injury
- Liver injury is immune-mediated (rather than viral cytotoxicity), via cytotoxic T-cell lysis of infected hepatocytes; this is likely why individuals are observed to have exacerbations of liver disease at times of immune clearance.

Clinical presentation and lab findings
- Acute hepatitis
  - Incubation period is 1-4 months; during this time there may be a serum sickness-like prodrome of fever, rash, arthralgia.
  - May be followed by constitutional symptoms, anorexia, nausea, jaundice, RUQ discomfort.
  - Transaminases range up to 1000-2000, with ALT>AST.
  - 70% have anicteric hepatitis, in which bilirubin may be normal, while 30% develop icteric hepatitis; fulminant hepatic failure occurs in 0.1-0.5%, and may show no evidence of HBV replication at presentation.
  - In HIV-negative adult-acquired cases, ~95% clear the virus; in those who recover, transaminases normalize within 4 months.

- Chronic hepatitis
  - It is rare to obtain a history of acute hepatitis, and most are asymptomatic.
  - Markers of progression to cirrhosis: decreased WBC and platelets (suggesting hypersplenism), laboratory indices of decreased synthetic function (↓ albumin, ↑ bilirubin, ↑ PT).
  - Extrahepatic manifestations (10-20%)
    - polyarteritis nodosa – mononeuritis multiplex, vasculitic rash, renal artery disease/infarction +/- HTN, mesenteric arteritis.
    - membranous nephropathy – nephrotic syndrome with low complement levels; more common in pediatric HBV; steroids are contraindicated.
  - Two phases of infection: replicative (early) and nonreplicative (late)
    - Replicative phase is believed to correspond to immune tolerance
      - High levels of HBV DNA, HbeAg+
      - No symptoms, normal ALT, minimal change on biopsy.
• Poor response to interferon therapy
  - Transition period of immune clearance (often 2nd-3rd decade)
  - Clearance of HbeAg (10-20%/year) and HBV DNA with seroconversion
  - Exacerbations of liver disease – most are asymptomatic, detected as ↑ ALT on routine follow-up
    - ↑ anti-HBc IgM can lead to misdiagnosis of acute HBV
    - ↑ AFP can lead to misdiagnosis of HCC
• Nonreplicative phase
  - HbeAg-negative, antiHBe +; undetectable HBV DNA (PCR detects low levels in some, generally insignificant)
  - Normal ALT, resolution of necroinflammation on biopsy

Natural history of chronic HBV infection
- Prognosis is relatively good in non-endemic areas: in 16-yr follow-up of HBsAg+ Canadians, only 3 of 317 died of HBV cirrhosis, none had HCC
- In endemic areas, 5-year progression of chronic HBV to cirrhosis 12-20%, with 20-23% of those progressing to decompensated cirrhosis within 5 years
- Survival rate of compensated cirrhosis 85% at 5 yrs, decompensated 14-35% at 5 yrs
- Poor prognostic factors: prolonged replicative phase and failure to clear HBeAg, older age, lab evidence of cirrhosis (↓ albumin, ↓ platelets, ↑ spleen, ↑ bilirubin)
  - Alcohol accelerates liver injury, but there is no evidence it increases risk of chronicity
  - Coexistent HCV infection leads to more severe liver disease, but it is believed HCV is dominant in this and that the HBV course is actually milder
  - HBV/HDV coinfection is more likely to lead to fulminant hepatitis
  - HDV superinfection is associated with accelerated progression to cirrhosis
  - HAV immunization is recommended by ACIP for all individuals with chronic liver disease, but available evidence does not indicate much benefit, particularly in HBV

Serologic diagnosis
- See the figures from UpToDate
- HBsAg – hallmark of infection; appears in 1-10 wks, prior to symptoms or ↑ALT
  - Usually undetectable in 4-6 months; persistence after 6 mos implies chronic infection
- Anti-HBs Ab – first appears after disappearance of HBsAg, generally persists for life, conferring long-term immunity
- Window period – anywhere from several weeks to months after exposure, during which neither HBsAg nor anti-HBs Ab is detectable
- HBeAg is intracellular and not detectable in blood; however, anti-HBc IgM Ab is detectable early (~2 wks) and is the basis of diagnosis during the window period; after ~ 6 mos, IgM goes away and anti HBe IgG Ab becomes detectable
  - Initially we generally order an anti-HBc total Ab and fractionate it only if positive
- HBeAg – appears early; marker of HBV replication and infectivity
  - In most acute HBV cases, seroconversion to anti-Hbe Ab is rapid and indicates disappearance of HBV DNA and remission of liver disease
  - In chronic HBV, this seroconversion may be delayed for decades (or not happen at all), and serum HBV DNA and active liver disease thus persist
  - In some individuals, there is a mutant HBeAg that is undetectable despite viral replication (+ HBV DNA), this is known as a “precore mutant”
- HBV DNA – clinical roles
  - Diagnosis of fulminant liver disease (which is often HBsAg-negative) – rare
  - Viral load assessment in evaluating candidacy for antiviral therapy
  - Viral load assessment as endpoint of antiviral therapy – but usually HBeAg is used
Some serologic scenarios
- When HBsAg and anti-HBs Ab coexist (24%), the antibodies are unable to neutralize the viral particles – hence individual is a HBV carrier
- In cases of isolated positive anti-HBc total Ab – DDx is 1) window period of acute hepatitis B – fractionation will reveal anti-HBc IgM+ in this scenario alone), 2) recovery from acute HBV in which anti-HBs Ab has waned below detectable level, and 3) chronic HBV in which anti-HBs Ab has waned
- DDx of HBsAg+ with acute hepatitis – acute HBV, exacerbation or reactivation of chronic HBV, HBV carrier superinfect with HCV or HDV, HBV carrier newly exposed to a drug or toxin

Treatment of chronic HBV infection (the basics)
- Decisions about which patients to treat and which drug(s) to use are very complicated, and are generally made at the subspecialty level
- Ultimate goal is to reduce infectivity, induce remission of liver disease, and prolong survival
- Endpoints monitored are HBeAg, HBV DNA, HBsAg (as indices of eradication), ALT, and liver biopsy; generally patients with ALT < twice upper limit are observed
- **Interferon-alpha** – 16 weeks treatment (5MU SC QD or 10MU SC 3/wk) in placebo-controlled meta-analysis is shown to increase clearance of all of the above serologic markers
  - Most responses are durable, especially if no relapse after 1 year
  - Survival benefit in studies with short-term follow up
  - Costly; contraindicated in decompensated cirrhosis; requires parenteral dosing; can have severe side effects (flu-like, etc.)
  - Peg-interferon initially showing promise; larger trials are needed
  - Hepatitis flares can occur with induction of therapy
- **Lamivudine** (3TC) – 100mg PO QD, lower dose in renal insufficiency, higher in HIV
  - Treatment for 12 mos is efficacious in clearing HBeAg, normalizing ALT, improving liver biopsy; similar efficacy to interferon
  - Better tolerated, less costly, oral administration, can be used in decompensated cirrhosis
  - Major problem with monotherapy is resistant (YMDD) mutants (24%), especially with longer course of therapy – however, even with breakthrough infection, some people realize benefit in ALT, biopsy with continuation of the drug
  - Hepatitis flares are associated with cessation of treatment
  - HIV patients should undergo immune reconstitution with a full HAART regimen before HBV treatment
- **Adefovir dipivoxil** – 48 wks of 10mg PO QD
  - Second line drug – efficacious, but less available evidence than other drugs; also appears to have lower eradication rate
  - Important side effect is renal toxicity
  - Promises to play important role in YMDD mutants; resistance has not yet been observed
- Combination therapy is the logical next step, and clinical trials are underway
- Treatment outcomes are generally less favorable for Asian patients, patients with lesser ALT elevations (<2x normal)
- In the patient awaiting transplantation, timing of treatment is controversial; some recommend early lamivudine in hope of stabilizing liver disease, others recommend waiting until just before transplant to avoid development of resistant mutants and post-transplant recurrence

Vaccination and post-exposure prophylaxis
- Vaccine currently used is a thimerosal-free recombinant HBsAg
- Indicated for all neonates, individuals with high-risk sexual behavior, IVDU, household contacts of HBV patients, healthcare workers, and chronic hemodialysis patients
- In endemic areas, as many as 50+% have already been exposed, so prevaccination screening with a single anti-HBc Ab test is done to prevent wasting the vaccine
- Standard dosing is 10µg IM in deltoid at months 0, 2, and 6; the second dose can be given up to 3 months late, the third dose can be given up to 1 year late; if later than this, the series must be repeated; neonates also get HBIG with the first dose
- Generally well-tolerated (25% have arm soreness); at least six studies have failed to show any association with multiple sclerosis
- Efficacy is >90%, but dialysis patients have a lower response rate (50-60%); certain HLA haplotypes also can be nonresponders, and gluteal injection and inappropriate storage also can lead to nonresponse; in these situations, recommendation is to give one or more additional doses
- Post-vaccination testing is recommended to document seroconversion in HD patients, IVDU, high-risk sexual behaviors, 1-2 months after series completed
- Combination vaccines with HAV and Hib have been made without compromising efficacy
- Single-dose vaccine using polymers has yet to undergo testing in humans
- Oral vaccine consists of avirulent Salmonella strain that produces HBsAg, still in development
- Worldwide, the problem is that endemic areas are underfunded and lack infrastructure, while many well-developed countries do not have vaccination policies, citing their low prevalence of disease; even in Taiwan where there is active universal vaccination program, coverage only 87%
- Post-exposure prophylaxis: first dose of vaccine, along with HBIG, given within 12 hours of exposure; other two doses according to standard schedule