

Viral Hepatitis (2009)

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Hepatitis A (HAV)

- "Infectious Hepatitis"
- Picornavirus family (RNA)-cytopathic
- Developing vs. developed countries
- Travelers

Epidemiology of HAV in USA

- 35,000 non-hosp./13,000 hosp. cases/year
- 152 deaths due to HAV
- 76% non-hosp./88% hosp. cases > 14 years old

Clinical Features of HAV

- Fecal-oral (food, water)
- 2-4 weeks incubation
- Antibody to HAV (anti-HAV)
- Fever, abdominal pain, malaise, fatigue, N/V/D, jaundice, pruritus - gone by 2-4 weeks after onset-no carrier state
- Fulminant hepatic failure rare (0.14% fatal) but almost exclusively in >50 y.o. age group

Control of Hepatitis A

- Two-dose vaccine (HAVRIX or VAQTA) with doses separated by 6-12 months (adults)-peds = 3 doses (0, 1, 6-12 mo.)
- Especially for international travelers (military), Native Alaskans and Americans, others where endemicity rates are high (high-risk sexual activity [anal-receptive intercourse], illicit drug abusers, people with clotting factor disorders or chronic liver disease, handlers of primates)
- Combination vaccine - A + B (Twinrix®)
- Passive immunotherapy with IgG (ISG):
 - Pre-exposure: 0.05 mL/kg IM q 4-6 months
 - Post-exposure: 0.02 mL/kg IM w/n 2 weeks
- Environmental (sanitation)

Control of Hepatitis A (cont'd)

- Initial: Routine childhood vaccination where mean annual rate of disease \geq 2-fold national mean: AZ, AK, OR, NM, UT, WA, OK, SD, NV, CA, ID (optional where rate > national mean but < 2-fold above it: MO, TX, CO, AR, MT, WY)
- Today: Universal childhood vaccination

Hepatitis B

- "Serum Hepatitis"
- DNA-Nucleocapsid core surrounded by an outer lipoprotein coat containing the surface antigen
- Incubation period = 46-180 days
- Immune activation, not cytopathic

Hepatitis B Virus (HBV) in USA

- 0.3% overall incidence
- 1,500,000 with chronic infection (incr.)
- 200,000-300,000 new acute cases/year
- 1-10% become chronic (on average)
- 10,000-15,000 new cases chronic hepatitis/year

Epidemiology of HBV

- 200 million world wide - 25% will die of HBV sequelae (cirrhosis, primary liver cancer)
- 90% of babies born to mothers positive for HBsAg → infected and 90% carrier rate
- 20-30% young children infected → carriers
- Adults 5-10% → carriers

High Risk Groups for HBV

- Adolescents
- Residents/staff of homes for devel. challenged
- Hemodialysis patients
- Factor conc. recipients
- Household members/sex partners of HBV carriers
- Adoptees from countries where HBV is endemic

High Risk Groups for HBV (cont'd)

- Travelers (\geq 6 mo., endemic, close with locals)
- Travelers (even short-term if tx in local medical setting or sex with locals where endemic)
- Anal-receptive intercourse
- IVDA
- Prisoners
- Reactivation with cancer chemo, esp. rituximab and alemtuzumab (monoclonal antibodies)

Summary of HBV Markers

Marker	Characteristics
HBsAg	First serologic marker to appear; disappears with clinical improvement; presence with IgM anti-HBc indicates acute infection; persistence beyond 6 months indicates chronic infection (carrier state).
IgM Anti-HBc	Marker of recent acute infection: helps distinguish acute from chronic infection; usually present for up to 6 months, then becomes undetectable; simultaneous presence with HBsAg indicates acute infection.
HBeAg	Marker of infectivity: detectable in acute or chronic HBV infection; persistence beyond 10 weeks indicates likely chronic liver disease.

Summary of HBV Markers (cont'd)

Marker	Characteristics
Anti-Hbe	Conversion from HBeAg to anti-HBe usually points to a benign outcome.
Anti-HBc	Indicates current or previous infection: not associated with recovery or immunity.
Anti-HBs	Marker of recovery and immunity; detectable after HBsAg disappears and recovery is complete; indicates immunity after inoculation with HBV vaccine.

Prevention of HBV

- OSHA guidelines (healthcare workers)
- HBV vaccines: pre-exposure, post-exposure
- ACIP recommendations (universal childhood vaccination)
- Screen all pregnant women

Pre-exposure HBV Vaccination

- Infants/children (2-3 doses 11-20 y.o.):
 - 2, 4, 6 months
 - Birth, 1-2, 6-18 months
- Adults (3 doses)
 - 0, 1, 6 months (or 0, 1, 2, 12 months)
 - (use high dose vaccine in immunosupp., dialysis, severe liver disease)
- 5-10% healthy recipients don't respond adequately
- Response ↓ if > 40 y.o., male, obese, smoker

Pre-exposure HBV Vaccination (cont'd)

- Deltoid (adults) and anterolateral thighs (infants) ONLY (never into buttocks!)
- SC and ID - No!
- Need to revaccinate - if immunocompetent, NO ("Immunologic memory")
-if immunocompromised, YES (boost when level <10mIU/mL on annual testing)
- COMVAX = Hib + Hep. B (peds)
- TWINRIX = Hep. A + Hep. B

Post-exposure HBV Prophylaxis

- Risk of acquisition ranges from 20-66% from needle-stick injury, 90% mother → child
- HBV vaccine series PLUS HBIG 0.06 mL/kg
- May not need HBIG to prevent perinatal transmission (only vaccine) if mother is HBe Ag neg.
- Vacc. ↓ newborn risk by 72%, HBIG by 50%, vacc. + HBIG by 92%

When to Treat Chronic HBV

- Seropositive for HBsAg > 6 mo
- HBV DNA positive in serum
- Increased AST/ALT

(acute or chronic liver disease, reactivation after chemotx or immunosuppression)

DON'T treat if no evid. of tissue damage, inactive carriers, latent infection (i.e. HBV DNA + but HBsAg-)

Control of Chronic HBV

Alpha-interferon (2b) Monotherapy

- Adults: 5mU qd or 10 mU tiw X 4-8 months
- Children: 6mU/sq.m. BSA tiw X 4-8 months
- Don't use if decompensated liver disease
- If doesn't respond to course of IFN alone: retreat with IFN + nucleo(s)tide analogue, nucleo(s)tide analogue alone, 2 nucleo(s)tide analogues together

Control of Chronic HBV (cont'd)

Lami (Epivir, Epivir-HB) Monotherapy

- Adults: 100 mg qd (HIV-), 150 bid (HIV +)
- Children: 3 mg/kg/d
- Adjust for CrCl < 50 mL/min
- ↓ vertical transmission
- Well-tolerated
- Rebound in viral replication after withdrawal
- Treat until 6 months after becomes anti-Hbe positive
- Resistance becoming big issue!

Control of Chronic HBV (cont'd)

Adefovir (Hepsera®) Monotherapy

- Adults: 10 mg qd (no peds dosing yet)
- Effective vs. Lami-resistant strains
- Adjust dose for CrCl < 50 mL/min (q 2, 3, or 7d!)
- Nephrotoxin (pre-existing CRF, on other nephrotoxins) – safe post-renal transplant
- Rebound in viral replication after withdrawal
- Treatment duration as per lami
- ↓↓ resistance potential (now!) vs. lami
- This dose is not effective vs. HIV!

Control of Chronic HBV (cont'd)

Entecavir (Baraclude®) Monotherapy

- Adults: 0.5 mg qd (↑ to 1 qd if lami-resis.)
- Effective vs. Lami-resistant strains
- Adjust dose for CrCl < 50 mL/min
- Rebound in viral replication after withdrawal
- Treatment duration as per lami
- ↓↓ resistance potential (now!) vs. lami
- Not effective vs. HIV!

Control of Chronic HBV (cont'd)

Telbivudine (Tyzeka®) Monotherapy

- Adults: 600 mg qd
- Adjust dose for CrCl < 50 mL/min (400 or 200 mg qd)
- ? role vs. Lami – resistant strains
- Muscle toxicity (watch sx and CPK)
- Treatment duration as per lami
- Not effective vs. HIV!

Control of Chronic HBV (cont'd)

Tenofovir (Viread®) Monotherapy (Not FDA-Approved for HBV)

- Adults: 300 mg qd
- Effective vs. Lami-resistant strains
- Dose adjust for CrCl < 50 mL/min (q 2 d or twice weekly)
- Rebound in viral replication after withdrawal
- Insuff. data re propensity to develop resistance
- Effective vs. HIV

Control of Chronic HBV (cont'd)

- HDV coinfection-IFN (lami etc don't work)
- HIV coinfection-lami (use HIV dose), tenofovir
- HCV coinfection-HCV IFN combo regimens (see below) – may need to add lami, adef, entec, tenof, or telbiv
- Decompensated liver dz-lami, adef, entec, tenof, or telbiv only
- Follow viral nucleic acid levels to assess response

Still Experimental HBV Treatments

- Nucleosides/nucleotides + IFN
- Two or more nucleosides/nucleotides in combination
- Nucleosides/nucleotides + Ther. Vaccine
- IFN + Ther. Vaccine

Hepatitis C Virus (HCV)

- "Non-A, Non-B hepatitis" (10 types, 30 subtypes)
- Flavi-like virus (RNA) – 1988 - cytopathic AND immune activation
- 1.8% general population is anti-HCV-positive (3.9 million Americans)

Epidemiology of HCV

- Parenteral transmission (transfusion, IVDA)
- ? Sexual and perinatal (5%) transmission (inefficient)
- 85% cases → chronic (8-10,000 deaths/year in US)
 - Chronic hepatitis
 - Cirrhosis (hepatic failure)
 - Primary liver cancer
- Diagnosis
 - Anti-HCV (ELISA → RIBA)
 - HCV RNA by PCR (response to therapy)

Clinical Features of HCV

- Incubation period of 4-20 weeks
- Mild + subclinical course usually-40-75% asymptomatic or mild symptoms not leading to medical attention
- Fulminant hepatic failure rare

Prevention of HCV

- NO vaccination
- Immune serum globulin or interferon post-exposure no benefit
- Screen blood products: anti-HCV, ALT, Anti-HBc
- Autotransfusion (bank blood for elective surgery)

When to Treat Chronic HCV

- Seropositive for HCV antibody > 6 months
- Seropositive for HCV RNA
- Increased AST/ALT

Control of Chronic HCV

IFN alfacon-1, IFN alpha-2b, 2a Monotherapy

- Only use if stable liver dz
- High relapse rates post-tx
- Dosing
- Adults: alfacon-1, 9 mcg tiw sc, or 2a 3mU tiw sc, or 2b 3 mU tiw sc X 24 wk. (genotypes 2+3) or 48 weeks (genotype 1, 4, 5 + 6)
- Children: 2a or 2b 3 mU/sq.m. tiw sc X as per adults
- Remember: duration is genotype-dependent!!

Control of Chronic HCV (cont'd)

Pegylated IFN Monotherapy

- PEG increases T_{1/2} (4-6 h → 48-96 h), decreases CL (by 90%), q week dosing
- Increase biochemical/clinical response (initial and sustained)
- Alpha-2b (1.5 mcg/kg q wk) and Alpha-2a (180 mcg q wk) - durations as for std. IFN

Control of Chronic HCV (cont'd)

Interferon side effects

- Fever, HA, fatigue, arthralgias, myalgias common (pretx with acetaminophen)
- Depression, irritability, decr. blood counts
- Can induce autoimmune disease such as thyroiditis (hypothyroidism, hyperthyroidism) + aggravates other autoimmune disorders

Control of Chronic HCV (cont'd)

- **IFN + ribavirin** (800 mg/d in genotypes 2+3; 1000-1200 mg/d in genotypes 1, 4, 5, 6, 1000 ng/d if ≤ 75 kg, 1200 mg/d if > 75 kg)
- Tx of choice as initial tx today, esp. PEG IFN
- Ribavirin ADRs: dose-related hemolytic anemia (avoid in renal failure) and fetotoxic
- Receipt $< 60\%$ planned doses \downarrow response rates
- Jump on anemia early with small dose \downarrow 's \rightarrow return to target dose (max. cumulative exposure)

Control of Chronic HCV (cont'd)

- Stopping Rule - if haven't seen a 2 log \downarrow in HCV RNA by 12 wk., chance of response is only 1-3%
- Relapse after IFN alone stopped - retreat with \uparrow dose/duration, combo tx
- Relapse after std. IFN + Riba stopped - retreat with PEG IFN + Riba (≥ 48 wks)
- Relapse after PEG IFN + Riba stopped - retreat with same ≥ 48 wk., expt. tx

HCV Treatment Follow-up

- CBC with platelets (IFN, riba)
- INR, AST, ALT, Bili, Alk phos (Hep C)
- Glucose (IFN)
- Creatinine/UA (Hep C)
- TSH, ANA (IFN)
- HCG (preg. contraind.)

Control of Chronic HCV (cont'd)

- Avoid alcohol and other hepatotoxins
- Infected individuals should not donate blood, organs, tissues, or semen
- Use latex condoms to avoid possible sexual transmission
- ? Needle exchange programs to decrease IVDA transmission
- Don't share toothbrushes/razors with HCV + individuals

HCV-HIV, HBV-HIV, HBV-HCV, and HBV-HCV-HIV Coinfections

- Coinfections are rel. common in incarcerated
- Potentiate each other
- Treat HBV and HCV as early as possible (accel. ↓ liver fx)
- Poorer response if CD4 < 200 (may need to start HAART first)
- Strategies for tx being developed for agents to use and sequence of use
- For HBV-HCV, use HCV combo regimens (may need to add nucleo(s)tide for HBV)

Hepatitis D Virus (HDV)

- Delta agent (RNA)
- 1977
- Requires HBV to express pathogenicity
- Increased risk of fulminant hepatic failure (co-infection) + chronicity → cirrhosis (superinfection)

Epidemiology of HDV

- Parenteral and sexual transmission
- At-risk population same as for HBV
- HDV-positivity rates in USA:
 - HBsAg carriers with liver dz = 25%
 - Healthy HBsAg carriers = 1.4-8.0%
 - HBsAg-positive IVDA = 20-53%
- Prevent by preventing HBV (vaccine)
- NO vaccine for HDV
- Interferon alpha - 5 mU qd or 10 mU tiw X 12+ months
